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Investigating the Interplay of Psychological Interventions and Mental and Organic Disorders.

Thesis' author: Francesca Malandrone

Supervisor: Prof. Luca Ostacoli

PhD Programme Coordinator: Prof. Pasquale Pagliaro

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1. Introduction

1.1. Psychological interventions and their effects.

Psychological interventions are a systematic set of treatments carefully designed to address a variety of psychological and emotional issues and they could be defined as activities or groups of activities aimed at changing behaviors, feelings, and emotional states (Hodges et al., 2011). These interventions, often delivered by trained mental health professionals, include a wide range of approaches such as psychotherapy, cognitive behavioral interventions, and trauma-focused therapies (Cristea et al., 2021; Fonagy, 2010). The overall goal of these interventions is to reduce symptoms, improve coping, and promote overall mental well-being, reflecting ongoing research and clinical efforts to elucidate the mechanisms and outcomes of various therapeutic approaches. As described by Taylor and colleagues (Taylor et al., 2010), psychological interventions can be divided into top-down and bottom-up approaches. In the top-down category, interventions are designed based on an individual's ability to consciously engage with and alter their thoughts. Bottom-up interventions, on the other hand, focus on the individual's use of bodily sensations and/or movements, providing an alternative avenue for therapeutic engagement. Top-down interventions represent a class of psychological therapies or techniques that are rooted in cognitive processes initiated at the level of the cerebral cortex (Craig, 2002; Holmes et al., 2018). In contrast, bottom-up interventions focus on mechanisms thought to underlie symptoms and aim to modify them. This approach identifies potentially modifiable target processes based on existing theories of etiological or maintenance factors (Lemmens et al., 2016; Macleod et al., 2019). In most psychological interventions, especially when it comes to psychotherapy, there is a continuous integration and alternation between top-down and bottom-up techniques and processes. Notable examples include Eye Movement Desensitization and Reprocessing (EMDR) and Mindfulness-Based Interventions (MBIs). EMDR, a therapeutic technique effective for trauma-related disorders, involves the use of bilateral stimulation, often through guided eye movements, to process distressing memories (Shapiro, 1989). MBIs, on the other hand, incorporate mindfulness practices such as meditation and present-moment awareness to alleviate various psychological conditions (Kabat-Zinn, 1990). This framework emphasizes the dynamic interplay between top-down and bottom-up interventions and recognizes the intricate relationship between conscious cognitive processes and

physiological influences. As the field of psychological interventions continues to evolve, incorporating new techniques and approaches, ongoing research contributes to a more nuanced understanding of their mechanisms and enhances their effectiveness in addressing a wide range of mental health challenges.

Psychological interventions play a crucial role in enhancing both physical and mental health outcomes. These interventions have shown significant effectiveness across various organic illnesses, contributing to improved well-being and overall health. For example, in the context of cardiovascular diseases (CAD), Magán and colleagues (Magán et al., 2021) found a broad impact of psychological interventions on mental health in CAD patients, which is vital given the recognized role of psychological factors as risk factors for recurrent cardiac events or increased mortality. Another study highlighted that psychotherapy interventions were comparably effective to Selective Serotonin Reuptake Inhibitors (SSRIs) reinforcing the role of psychological interventions in addressing mental health concerns in individuals with cardiac conditions, where the impact on psychological well-being is crucial for overall health (Zambrano et al., 2020). Richards et al. (Richards et al., 2018) found that psychological interventions were associated with a reduction in the risk of cardiac deaths and participant-reported symptoms of depression, anxiety, and stress. Psychological interventions were also found effective in improving physical function and pain intensity in people with chronic, non-specific low back pain (LBP) ((Ho et al., 2022). Similarly, Swainston and colleagues (Swainston et al., 2023) highlighted the effectiveness of psychological interventions in reducing somatic and depression symptoms in patients with persistent physical symptoms (PPS). Black and colleagues (Black et al., 2020) found the efficacy of various psychological therapies in improving Irritable Bowel Syndrome (IBS) symptoms, a chronic gastrointestinal condition. Considering immune- and inflammation-related health outcomes, psychological interventions have emerged as positive influential (Moore et al., 2013; Slavich & Cole, 2013; Sternberg, 2006). From stress to negative emotions, these psychosocial elements can significantly influence immunologic activity, as evidenced by studies exploring the association between life stress, emotions, and social support (Fagundes & Way, 2014; Irwin, 2008; Kiecolt-Glaser et al., 2002; Rohleder, 2019). Recently, Shields and colleagues (Shields et al., 2020) extended this understanding by demonstrating that psychosocial interventions were significantly associated with enhanced immune system function, as indicated by decreases in proinflammatory cytokines and increases in immune cell counts over time.

Cancer emerges as a focal point among medical conditions with compelling evidence supporting the efficacy of psychological interventions. The integration of pharmacological treatment or chemotherapy with psychological interventions is increasingly acknowledged as a vital component in cancer care (Semenenko et al., 2023). Notably, they help in effectively addressing depressive and anxious states, enhancing the quality of life and reducing the fear of cancer recurrence (Grimmett et al., 2022) and managing diverse mental and physical conditions such as nausea, dyspnoea, fatigue, chronic pain, and pain severity (A-Tjak et al., 2015; Getu et al., 2021; Hughes et al., 2017; Park & Lim, 2022; Warth et al., 2020). According to Ruano et al. (Ruano et al., 2022), employing psychological strategies proves beneficial in reducing pain among individuals who have undergone chemo/radiotherapy or oncological surgery with a lasting impact that persists until the completion of therapy. Among the numerous psychological interventions, MBIs such as Mindfulness-Based Cognitive Therapy (MBCT) emphasizes awareness and relaxation, mitigating depressive and fatigue episodes, and reducing the fear of cancer recurrence (Park & Lim, 2022). Studies underscore MBIs effectiveness in providing coping strategies to reduce stress, anxiety, and depressive mood, ultimately contributing to an improved overall quality of life (Carlson, 2016; Hoffman et al., 2012; Shennan et al., 2011). A recent systematic review from Paley and colleagues (Paley et al., 2023) found that MBIs show similar efficacy also in advanced cancer and in palliative care. The field of cancer care is witnessing a growing focus on Post-Traumatic Growth (PTG), with research revealing the positive impact of psychosocial factors, coping strategies, and social support on enhancing PTG in cancer patients (Tomita et al., 2017). Psychosocial interventions not only positively influence PTG levels but also impart essential skills, including relaxation techniques, stress management, and coping strategies. These interventions alleviate self-rated pain severity, contributing to an enhanced overall quality of life for cancer patients (J. Li et al., 2020; Warth et al., 2020). Furthermore, psychological interventions demonstrate their capability to mitigate cancer-related anxiety and depression, potentially facilitating PTG by improving neuroendocrine functioning (Dunigan et al., 2007; Fu et al., 2016). Psychological interventions have shown potential benefits in easing distress and enhancing the quality of life for cancer patients (Murray, 2016). Recent findings indicate that EMDR therapy holds promise as a supportive treatment for individuals affected by cancer, aiding patients, their families, and professional caregivers (Faretta & Borsato, 2016). Moreover, a comprehensive review by Dimitrov and colleagues (Dimitrov et al., 2019) presents evidence

supporting the effectiveness of trauma-focused interventions, including EMDR and CBT, in addressing symptoms of cancer-related Post-Traumatic Stress Disorder (PTSD). A recent systematic review (Portigliatti Pomeri et al., 2021)reported that EMDR interventions were linked to significantly reduced psychological distress and post-treatment mood disorder spectrum symptoms in cancer patients.

Psychological interventions can lead to improvements in mental wellbeing as well as mental illness. A recent systematic review conducted by van Agteren and colleagues (van Agteren et al., 2021), aimed to synthesize the current scientific evidence on distinct psychological interventions in both clinical and non-clinical populations to improve mental states of wellbeing. The review's findings underscore the substantial potential for improving mental wellbeing through a diverse range of psychological interventions. Notably, positive psychological interventions (PPIs) and MBIs consistently demonstrated positive outcomes across various populations. The meta-analyses further underscored the effectiveness of interventions grounded in Acceptance and Commitment Therapy (ACT), cognitive therapy, or CBT, as well as singular PPIs and interventions emphasizing reminiscence. Additionally, the review's results advocate for the preference of higher-intensity multi-component programs over singular activities and exercises, providing valuable insights for the optimization of mental health interventions. Regarding bottom-up approaches, Rosendahl and colleagues (Rosendahl et al., 2021) provided a comprehensive summary of the available randomized controlled trials on body psychotherapy. The results indicate moderate effect sizes on primary outcomes such as psychopathology and psychological distress, with nearly all studies reporting favourable effects for body psychotherapy with studies focusing on depression and anxiety disorders tended to show a more pronounced improvement consistently with previous literature (Kvam et al., 2016). As regards depressive disorder treatment, psychotherapy holds a crucial position alongside pharmacotherapy. Approximately 280 million individuals worldwide suffer from depressive disorders, imposing significant distress on patients and their families (WHO, 2022). These disorders are associated with increased mortality and morbidity rates (Cuijpers et al., 2014) and substantial economic costs (König et al., 2020). Furthermore, they represent the second leading cause of years lived with disability on a global scale (WHO, 2022). Psychotherapy, along with pharmacotherapy, emerges as the primary intervention for depressive disorders. Cuijpers and colleagues have conducted extensive research on the effectiveness of psychotherapies in treating depression (Cuijpers et al., 2023). Their analysis, encompassing over 850 randomized controlled trials (RCTs), explored

diverse psychotherapy types across age groups, settings, and target populations with varying controls, durations, and formats (individual, group, telephone, guided self-help, digital). Comparative trials evaluated psychotherapies against each other, pharmacotherapy, and combined treatment. Effectiveness was evident in individual, group, telephone, and guided self-help formats, with diminished efficacy when lacking human support. Therapeutic benefits extended to diverse groups, including college students, postpartum women, and patients with medical disorders, albeit with smaller effects in children and adolescents compared to adults. Overestimation of psychotherapy effects was noted due to low trial quality and publication bias. Psychotherapies demonstrated comparable short-term effects with pharmacotherapy but likely greater long-term effectiveness. Combined treatment outperformed either psychotherapy or pharmacotherapy in both short and long terms, emphasizing the pivotal role of psychotherapies in depression treatment and their potential to reduce the disease burden. Consistently with a previous systematic review (Cuijpers et al., 2020), among various therapeutic approaches, none demonstrated superior efficacy in reducing depression. Furthermore, psychological interventions have proven effective in averting the onset of depression, thereby reducing its incidence over time (Cuijpers et al., 2021).

Extending the evidence seen in depression, psychological interventions play a crucial role in addressing and managing symptoms in other mental health conditions, such as Attention-Deficit/Hyperactivity Disorder (ADHD). ADHD is a prevalent neuropsychiatric condition affecting around 5% of school-aged children globally. The estimated prevalence of ADHD in adults is approximately a 3–5% prevalence of ADHD in adults (Fayyad et al., 2017). While pharmacological interventions, primarily medication, are the mainstay for adult ADHD treatment, showing safety and efficacy with a reported 70% improvement (Fields et al., 2017; Spencer et al., 2001), various psychological interventions have demonstrated significant efficacy in alleviating ADHD symptoms (Fullen et al., 2020). Non-pharmacological interventions exhibit superior outcomes compared to inactive control conditions, particularly in managing the core behavioural symptoms of ADHD. Active control conditions, while yielding mixed results, underscore the potential impact of non-pharmacological interventions, emphasizing their role in assisting adults with ADHD. Meta-analyses highlight the moderately positive impact of CBT interventions on ADHD symptom severity compared to other active interventions (Lopez et al., 2018; Scholz et al., 2023; Young et al., 2020). The sustained effects on symptom reduction for at least 12 months

(Lopez et al., 2018) emphasize the enduring benefits of CBT. While existing reviews predominantly focus on CBT, evidence suggests its effectiveness in reducing inattention symptoms in adults with ADHD, especially in group sessions and briefer interventions in outpatient care settings. Although psychoeducation evidence is limited, incorporating educative elements may prove beneficial and feasible in outpatient care (Scholz et al., 2023).

As far as available in literature, psychological interventions emerge as effective not only clinically but also as drivers of neurobiological changes. The literature concerning the neurobiological effects of psychological interventions is vast and uneven (Beauregard, 2014; Mancke et al., 2018; Scult et al., 2019). Studies revealed the potential of psychotherapy to modulate brain function across various psychopathological conditions, leading to a normalization of brain function, especially in disorders like Obsessive-Compulsive Disorder (OCD), depression, and schizophrenia. The effects are comparable to medication, with indications of measurable changes in brain structure (Barsaglini et al., 2014). Recent research points to the genetic dimension, as CBT for depressive and anxiety disorders induces gene expression changes related to symptomatology (Kahl et al., 2016; Roberts et al., 2014, 2015; Schiele et al., 2018; Ziegler et al., 2016, 2019). Epigenetic regulation is observed in subjects with PTSD and alterations in the Brain-Derived Neurotrophic Factor (BDNF) gene after Dialectical Behavioral Therapy (DBT) in those with Borderline Personality Disorder (BPD) (Perroud et al., 2013; Thomas et al., 2018). Notably, psychological interventions impact DNA methylation status, with changes associated with treatment outcomes. The exploration extends to Mind-Body Therapy and MBIs, showcasing promising outcomes and epigenetic changes related to inflammation and immune function biomarker genes (Cozzolino et al., 2017; Kaliman et al., 2014). Pellicano and colleagues (Pellicano et al., 2022) emphasize, in a systematic review, that psychological interventions are associated with significant and favourable epigenetic changes only when concomitant clinical improvement occurs. It is interesting to note that the outcome of therapy would seem to correspond both positively and negatively to an associated epigenetic response (Franco, 2017). This aspect could be also considered as a risk factor for subsequent adherence and prognosis to a treatment.

1.2. Exploring the impact that adverse events have on physical and mental health.

Psychological distress and organic diseases exhibit a mutual relationship, impacting each other. This reciprocal interaction extends to organic illnesses, functioning as stressors and affecting mental health through variables like social isolation, stigma, lifestyle adjustments, and interference in relational domains.

Resuming the cancer-related topic, the prevalence of depressive and anxiety disorders or symptoms is higher among individuals with cancer than the general population. However, these issues are often overlooked (Pitman et al., 2018). The coexistence of cancer and mental health conditions may lead to higher comorbidity rates with conditions such as diabetes, cardiovascular disease, and musculoskeletal conditions (Proctor et al., 2003). Emotional distress is prevalent among cancer patients due to the life-threatening nature of the disease, aggressive medical treatments, lifestyle changes, and the direct effects of the tumor (Bultz & Holland, 2006; J. C. Holland et al., 2007; Zabora et al., 2001). For instance, in prostate cancer, the causes of distress go beyond the psychosocial impact of the diagnosis, involving complex hormonal, physical, and psychological consequences of both the cancer and its treatments (Dickey & Grayson, 2019; Fervaha et al., 2019; Nead et al., 2017). Brunckhorst and colleagues (Brunckhorst et al., 2020) emphasizes the common mental health-related complications of prostate cancer, with a high prevalence of depressive and anxiety symptoms and an increased risk of suicidal ideation. Integrating mental health care into urological and oncological follow-up is crucial for early identification and treatment. Similarly, bladder cancer has significant effects on mental health, with changes apparent soon after diagnosis and independent associations with worsened morbidity and mortality rates (Pham et al., 2019). Another example of the impact of cancer diagnosis on mental health is breast cancer, a diagnosis which is particularly distressing for women, leading to a range of emotional responses, including anger, anxiety, despair, helplessness, fear of death, and suicidal thoughts (Mohammed et al., 2009; Schubart et al., 2014). Clinically relevant symptoms of anxiety and depression are common during treatment, with persistent depressive symptoms observed in one in five women for at least two years after diagnosis (Avis et al., 2015). Adverse mental health outcomes, such as sleep disturbance, persist during and after cancer treatment (Savard et al., 2001). Williams and colleagues (Williams et al., 2018) highlight that breast cancer survivors are more prone to adverse mental health outcomes, including anxiety, depression, neurocognitive dysfunction, sexual dysfunction, and suicide, compared to non-cancer groups. In general, approximately one-third of cancer survivors, are diagnosed with mental health conditions (Earle et al., 2007; Mitchell et al., 2011). Common mental health

disorders among cancer survivors include major depression, generalized anxiety disorder, adjustment disorder, panic disorder, or post-traumatic stress disorder (Fox et al., 2013). These evidence underscores the importance of addressing mental health concerns in cancer patients and survivors to improve overall well-being.

Along similar lines, the intricate relationship between psychological distress and organic diseases, influencing and shaping each other, finds resonance in the broader health landscape, notably in the context of the unique challenges posed by the COVID-19 pandemic. The impact of the COVID-19 pandemic extends beyond physical health, significantly affecting individuals' mental well-being. Patients, both confirmed and suspected cases of COVID-19, faced psychological pressure, health-related problems, and fears of severe consequences and contagion, leading to loneliness, denial, anxiety, depression, insomnia, and despair (W. Li et al., 2020; Xiang et al., 2020). The psychological toll was not confined to those with confirmed cases; even suspected cases might grapple with anxiety, manifesting in repeated temperature checks and sterilization behaviours (W. Li et al., 2020). The interplay between immune mechanisms and infections introduces another layer of complexity. Chronic inflammation triggered by infections can detrimentally impact cognitive function, increasing the risk of major mood disorders in patients hospitalized for autoimmune or infectious diseases (Pape et al., 2019). The immune system's response to SARS-CoV-2 infection results in inflammation, potentially affecting mental health (Tay et al., 2020). Even after recovering from COVID-19, patients may continue to experience anxiety and depression post-discharge (Yuan et al., 2020). Individuals with pre-existing mental health disorders faced heightened vulnerability to poor COVID-19 outcomes due to comorbidities, such as diabetes and hypertension, associated with severe cases (Williams et al., 2020). The pandemic's initial wave, marked by social isolation measures, closures, and fear, witnessed a surge in mental health problems, persisting at higher levels than pre-pandemic times (Cénat et al., 2022; Prati & Mancini, 2021; Robinson et al., 2022). A meta-review revealed substantial psychophysiological stress during the pandemic, with prevalence rates of insomnia, psychological stress, and overall stress at 32%, 28%, and 36%, respectively (Sousa et al., 2021). Psychopathological concerns, including anxiety, depression, and PTSD, were prevalent at 26% overall (Sousa et al., 2021). Comparisons with previous viral outbreaks showed varying patterns, with lower proportions of depression but higher proportions of anxiety during the COVID-19 pandemic (Serrano-Ripoll et al., 2020). A meta-analysis by

Wu and colleagues underscored the widespread mental health challenges posed by the pandemic, revealing pooled prevalence rates of depression (31.4%), anxiety (31.9%), distress (41.1%), and insomnia (37.9%) across different populations (Wu et al., 2021). Subgroup analyses highlighted elevated prevalence among non-infectious chronic disease patients, quarantined individuals, suspected cases, physicians, and nurses, emphasizing the need for tailored mental health support in various affected groups.

When discussing infections, considerable attention in recent years has focused on examining the impact of early childhood infections on neurodevelopment and mental health. The role of infectious diseases, atopies, and inflammatory conditions in contributing to the risk of neurodevelopmental disorders (ND) and common mental disorders (CMD) has gained increasing recognition (Ajdacic-Gross et al., 2016). The immune system plays a pivotal role in this vulnerability-trigger model, with early-life factors such as infections, atopies, and inflammatory processes establishing a lasting vulnerability for CMD (Ajdacic-Gross et al., 2016). Notably, the Paediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections (PANDAS) model exemplifies this early vulnerability, linking streptococcal infections to autoimmune disorders like ADHD, OCD, and tic disorders (TD) such as Gilles de la Tourette Syndrome (GTS) (Martino et al., 2009; Murphy et al., 2012). The associations between early infections and ND and CMD extend beyond PANDAS to encompass various autoimmune processes like NMDA receptor encephalitis (Kayser & Dalmau, 2016). For instance, the link between Epstein-Barr virus (EBV) infections in childhood and the risk of psychotic experiences in adolescence highlights the broad impact of infections on mental health (Khandaker et al., 2014). Studies by the Goodwin group further suggest that respiratory diseases and severe infections in childhood increase the risk of mental disorders such as depression, anxiety disorders, and oppositional defiant disorder later in life (Goodwin, 2011; Goodwin & Buka, 2008). Atopic and inflammatory diseases emerge as crucial risk factors for ND and CMD, contributing independently of major factors like childhood adversities, traumatic experiences, and familial aggregation (Ajdacic-Gross et al., 2016). Early life immune challenges associated with prenatal infection increase the risk of neuropsychiatric disorders later in life, with evidence linking early-life infection exposure to adult mental disorders (Brown & Meyer, 2018). Reports also indicate associations between childhood mental disorders, including Autism Spectrum Disorder (ASD), ADHD, and depression and anxiety in adolescence, following prenatal or early childhood infection exposure (Brown & Meyer, 2018; Goodwin,

2011; Hagberg et al., 2012; Zhou et al., 2015). Biological studies revealed elevated proinflammatory markers in children with various psychiatric conditions (Belem da Silva et al., 2017; Jyonouchi et al., 2001; Malik et al., 2011; Nadeem et al., 2020; Tang et al., 2019) while epidemiological studies exploring the underlying mechanisms of associations between infections and neurodevelopmental disorders revealed connections with bacterial, viral, fungal, and parasitic infections. A large-scale study by Debost and colleagues underscores the dose-dependent relationship between childhood infections and the hazard of ADHD, ASD, major depressive disorder, and schizophrenia (Debost et al., 2022). Genetic and psychosocial confounding did not fully explain the association, suggesting a complex interplay between genetic susceptibility, environmental factors, and psychiatric disorders. Specifically, Group-A Streptococcus (GAS) infections are linked to the acute-onset and exacerbation of OCD and tic disorder symptoms in prepubertal individuals, leading to the proposal of the PANDAS syndrome (Köhler-Forsberg et al., 2019; Swedo et al., 1998; Wang et al., 2016). Prenatal maternal infections, particularly bacterial ones, are associated with an increased risk of OCD and TD/GTS (Zhang et al., 2023). Familial factors and defects in immunity contribute to the association between early-life infections and the risk of OCD and TD/GTS, suggesting a double-hit scenario. Chaplin and colleagues' findings emphasize that common early-childhood infections, particularly a high infection burden, are associated with the risk of depressive symptoms and suspected/definite psychotic experiences up to the age of 17 and 12, respectively (Chaplin et al., 2022). Notably, childhood infections are not associated with the risk of depressive symptoms or psychotic experiences at age 18/19. In the last two decades, the role of infections, especially GAS, in determining acute movement and psychiatric disorders, including OCD, TD, and ADHD, has gained attention (Dale et al., 2004; Dale & Brilot, 2012; Mercadante et al., 2000; Swedo et al., 1998). A proposed molecular mimicry mechanism explains enduring symptoms post-GAS infection remission (Cunningham, 2019; Kirvan et al., 2006). High titers of GAS infection markers, including Anti-Streptolysin O (ASO) and Anti-DNase B, and Anti-Basal Ganglia Antibodies (ABGA), are found in these disorders (Church et al., 2002; Kiessling et al., 1993; Martino et al., 2007). Notably, ADHD plays a significant role in post-streptococcal basal ganglia disorder, with higher titers of GAS infection markers found in children with ADHD compared to those with OCD or TD (Peterson et al., 2000).

Recognizing the impact of organic diseases on mental health is imperative, as it allows for the identification of unmet needs among patients and caregivers. This consideration not only has the potential to reduce care costs and treatment periods but also enables the implementation of preventive interventions and facilitates a deeper understanding of psychological and illness-related phenomena.

One population where this intersection is evident is among cancer patients and survivors. Addressing the mental health needs of this growing group can significantly enhance their quality of life, mental and physical health outcomes, and potentially alleviate the economic burden on the healthcare system (J. Holland & Weiss, 2008). Mental health conditions contribute substantially to hospital, long-term care, and ambulatory care costs among cancer survivors, surpassing other chronic conditions (Rim et al., 2016). Khushalani and colleagues (Khushalani et al., 2018) emphasize that mental health conditions escalate healthcare costs across all phases of care and service types for cancer survivors. For cancer patients, co-existing depression and anxiety disorders influence treatment choices, adherence, functional outcomes, and even mortality (Dall'Era, 2015; Prasad et al., 2014; Sciarra et al., 2018). Suicidal ideation and suicide mortality are elevated in cancer patients, persisting even after accounting for the level of psychiatric care received precancer diagnosis, with a prominent increase in the first 50 months post-diagnosis (Klassen et al., 2019). Routine screening for psychological distress emerges as a beneficial practice among cancer patients, improving psychosocial outcomes. It enhances communication between patients and healthcare providers, stimulating discussions about psychosocial and mental health issues (Bidstrup et al., 2011; Carlson et al., 2009, 2012; Meijer et al., 2013).

In the context of the COVID-19 pandemic, a preliminary meta-analysis concludes that patients with mental health disorders face an increased risk of COVID-19 mortality (Toubasi et al., 2021). Mental health disorders are associated with increased COVID-19–related mortality across diverse populations and continents (Fond et al., 2021). Meta-analyses across different populations reveal that mental health problems, including depression, anxiety, PTSD, psychological distress, sleep problems, and substance use disorders, have surged during the pandemic (Cénat et al., 2021; Pappa et al., 2020; Prati & Mancini, 2021; Sideli et al., 2021).

Regarding ADHD, undiagnosed adults with ADHD are more likely to encounter difficulties at work, substance abuse, or increased medical incidents and injuries (Asherson et al., 2012; Folgar et al., 2018; Kittel-Schneider et al., 2019; Swensen et al., 2004). Substance abuse in this context has been hypothesized as a form of self-medication for those with undiagnosed or untreated ADHD (Gudjonsson et al., 2012; Wilens et al., 2007). Undiagnosed parental ADHD can significantly impact parenting quality and increase chaos in the home environment (Chronis-Tuscano et al., 2008). The impact of a lack of ADHD diagnosis on mental health, substance abuse, and education/work is further highlighted by French and colleagues (French et al., 2023). Health risks, both mental and physical, are associated with a lack of ADHD diagnosis. Mental health difficulties, including depression, anxiety, psychiatric inpatient admissions, and suicidality, are recurrent findings across studies. The late diagnosis not only poses mental health risks but also manifests in day-to-day challenges, encompassing social difficulties, relationship issues, financial challenges, and obstacles in education, work, and driving. These insights underscore the importance of early diagnosis and intervention in addressing the multifaceted impact of organic diseases on mental health.

2. Aim of the study

The overarching goal of this PhD thesis is twofold. Firstly, it aims to scrutinize the state of the art and effectiveness of psychological interventions in the domains of cancer, depression, and ADHD. Through an extensive exploration of existing literature and empirical evidence, this research seeks to provide a comprehensive understanding of the methodologies and outcomes associated with these interventions. Simultaneously, the study aims to investigate the intricate interplay between organic pathology and psychological distress, delving into how this interaction influences both physical and mental health. By elucidating the dynamic relationship between these factors, the research aims to contribute valuable insights that can inform holistic approaches to healthcare and intervention strategies.

In addition to these primary objectives, a secondary aim of this research is to validate a psychological assessment tool to facilitate the observation and measurement of changes resulting from psychological interventions. Moreover, the tool would be useful to deepen knowledge related to various psychopathological frameworks, providing a nuanced understanding of the diverse manifestations of mental health challenges.

Collectively, this work aims to advance the knowledge in the field of psychology, fostering a deeper understanding of effective interventions and the complex interplay between psychological and organic factors.

3. Results

A Brief Narrative Summary of Randomized Controlled Trials Investigating EMDR Treatment of Patients With Depression

Francesca Malandrone
Sara Carletto
University of Turin, Turin, Italy

Michael Hase
Lüneburg Center for Stress Medicine, Lüneburg, Germany

Arne Hofmann
EMDR Institut Deutschland, Bergisch Gladbach, Germany

Luca Ostacoli
University of Turin, Turin, Italy

Depression, one of the most common mental disorders, is characterized by enormous social costs and limited rates of treatment success, even though psychotherapeutic and pharmacological treatments currently contribute to an increase in the remission rate. In light of recent studies that have shown that traumas and adverse life experiences may represent risk factors for the onset of depression, the therapeutic approach of eye movement desensitization and reprocessing (EMDR) therapy has been seen as potentially effective in the treatment of depression. The purpose of the present brief narrative review is to summarize the current literature on the efficacy of EMDR in patients with depression, in particular by referring to randomized controlled clinical trials (RCTs) that examined depression as a primary outcome. The data examined are updated to March 2019 and count seven RCT studies covering the years from 2001 to 2019. They are heterogeneous by type of intervention and demographic characteristics of the sample. Although the selected studies are few and with different methodological critical issues, the findings reported by the different authors suggest in a preliminary way that EMDR can be a useful treatment for depression.

Keywords: eye movement desensitization and reprocessing; EMDR; depression; review; randomized controlled trial

Depression is a common mental disorder and one of the leading causes of disability worldwide, with huge individual and societal costs (World Health Organization, 2017). Given the tremendous disease burden, different treatment options for this disorder are available. They range from low-intensity psychosocial interventions to high-intensity psychological interventions integrated with pharmacotherapy, depending on symptom severity (National Institute for Health and Care Excellence, 2018). Among psychological interventions, cognitive behavioral therapy (CBT), interpersonal psychotherapy, problem-solving therapy, behavioral activation, and short-term psychodynamic therapy have been found to be equally effective in treating depressive disorders (Barth, Michlig, & Munder, 2014; Cuijpers, Van Straten, Andersson, & Van Oppen, 2008). Nevertheless, the proportion of patients who recover after treatment is still limited, with relapse rates estimated around 50% after 2 years (Hollon et al., 2002; Vittengl,

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Clark, Dunn, & Jarrett, 2007). Therefore, it is essential to identify how to improve treatment outcomes.

In recent years an important correlation between exposure to adverse experiences during childhood and the development of depression in adulthood has been highlighted (Li, D'Arcy, & Meng, 2016; Nemeroff, 2016; Norman et al., 2012), suggesting that trauma-focused treatments may contribute to the treatment of this disorder. Eye movement desensitization and reprocessing (EMDR) is an evidence-based therapy for the treatment of psychological trauma *sequelae* and could represent a valid therapeutic option for the treatment of patients suffering from depression, either as a stand-alone treatment or as an add-on to other interventions. The first report of patients with depressive disorder treated with EMDR was described in the late 1990s (Manfield, 1998). In the following years, several other case and uncontrolled studies were published. The results of these studies have been summarized by two recent reviews (Carletto et al., 2017; Wood & Ricketts, 2013). In their review, Wood and Ricketts (2013) described the historical development of clinical and research applications of EMDR therapy for the treatment of depression as a primary diagnosis, reporting the results of the first case and uncontrolled studies; in the second review, Carletto et al. (2017) summarized the results of only controlled studies, also adding an evaluation of the study quality. Both reviews concluded that EMDR should be considered a promising approach, even though they highlighted several limitations that were mainly related to the small number of randomized controlled studies at that time. In recent years the interest of researchers and clinicians has continued to grow and several other controlled and randomized studies have been conducted.

The aim of this brief narrative review is to provide a summary presenting the results of the randomized controlled studies currently available in the literature on this topic. Literature search was carried out by searching "EMDR" or "Eye Movement Desensitization and Reprocessing," and "depress*" as keywords in principal databases (e.g., PubMed, PsychINFO) and in the Francine Shapiro Library; studies with a randomized controlled trial (RCT) design which investigated depression as primary outcome were included with no limitations related to type of population, age, comorbidity with organic disease, or pharmacotherapy.

To the best of our knowledge, seven RCTs have been conducted for the evaluation of the efficacy of EMDR therapy in treating depressive symptoms as a primary diagnosis. Characteristics of those studies are shown in Table 1. All studies included adult patients. Studies had samples composed from 22 to 82 participants who had a depression diagnosis only in six studies, whereas in one study patients had a concurrent general medical condition. Five studies specified the concomitant use of antidepressant therapies, while in the others it was not specified or it was an exclusion criterion. The number of sessions of EMDR treatment ranged from 3 to 24. A variety of measures were applied to evaluate depressive symptoms: four studies used the Beck Depression Inventory (BDI), one study employed the Hamilton Depression Scale, one study used both the Symptom Checklist-90 (SCL-90) and the BDI-II, and one study used both the Montgomery-Asberg Depression Rating Scale (MADRS) and the BDI-II.

Summary of Findings

In two studies EMDR was compared with no treatment, that is, waiting lists or no-intervention. Behnam Moghadam (2015) conducted a study involving patients with myocardial infarction to evaluate EMDR in treating depression. The control group received no intervention. The experimental group reported, compared to the control group, a significant reduction in depressive symptoms with depressive symptomatology levels below the clinical threshold following treatment. Mauna Gauhar (2016) administered EMDR to patients with major depression who showed a significant improvement in symptoms compared to the control group (waiting list). This improvement was also identified at the 3-month follow-ups.

Three studies evaluated EMDR in comparison with another active intervention. In his unpublished dissertation, Hogan (2001) investigated the efficacy of a single session of EMDR or CBT. Although no significant differences were observed between the two groups, which proved to be equally effective in treating depressive symptoms, it is possible to differentiate them by analyzing the data of individual participants. In fact, four people belonging to the EMDR group show an almost complete remission of depressive symptoms. In comparison, it was not possible to observe such a symptom reduction in the CBT group. In addition, patients reported that EMDR treatment was less negative than CBT "primarily due to the increased awareness of negative thoughts common to CBT but not experienced in EMDR treatment" (Hogan, 2001). Ostacoli et al. (2018) published the first RCT comparing EMDR with CBT in patients with recurrent depressive episodes and reported that both interventions were effective in reducing clinical levels of depression, although a statistically significant

increase in EMDR treatment was observed at the end of the intervention phase. Minelli et al. (2019) compared EMDR with trauma-focused cognitive behavioral therapy (TF-CBT) in patients with treatment resistant depression treated with different types of psychosocial and/or pharmacological therapies. EMDR was shown to be as effective as TF-CBT in reducing depression symptoms during hospitalization; however, at the follow-up visit, only EMDR maintained this amelioration.

Finally, EMDR was evaluated as an adjunctive treatment in two studies. In the research conducted by Lei and Zhen-Ying (2007), an intervention involving the addition of EMDR sessions to therapy with sertraline was compared with the administration of sertraline alone. Although the data collected showed no statistically significant differences between the two groups, the combination of EMDR with sertraline appears to have produced a more rapid effect, contributing to greater safety and better compliance with therapies. Hase et al. (2018) compared the efficacy of EMDR combined with psychoeducation to psychoeducation alone in patients with depression, showing a significant improvement in those patients who received adjunctive EMDR.

As regards EMDR protocols used to treat patients, four studies (Behnam Moghadam, 2015; Hogan, 2001; Lei & Zhen-Ying, 2007; Minelli et al., 2019) referred to the standard EMDR protocol of Shapiro (1995; Shapiro, 2001). One study (Mauna Gauhar, 2016) used the Shapiro's standard protocol but with a slight modification in Phase 3 during target assessment: patients were asked to first identify the negative cognition most strongly associated with reduced functions and then to identify the related disturbing event. In the other two studies (Hase et al., 2018; Ostacoli et al., 2018) the EMDR treatment followed the DeprEND protocol: that is, the manual for EMDR in the treatment of depressive patients (see Hofmann et al., 2016 for a detailed explanation).

Discussion

Most research on the application of EMDR for treating depressive disorders carried out in the last 18 years investigated the use of the Shapiro standard protocol (Shapiro, 2001). In 2016 the DeprEND protocol was published to define a specific protocol for this kind of population, thus addressing different types of memories such as traumatic memories or depressive and suicidal states (Hofmann et al., 2016).

RCTs that have evaluated EMDR efficacy on the improvement of depressive symptoms are few and

TABLE 1. Characteristics of Seven Randomized Controlled Clinical Trials

Author (Year)	N	Treatments/WL	Number of Sessions	Findings
Hogan (2001)	30	EMDR versus CBT	4	EMDR = CBT
Lei and Zhen-Ying (2007)	64	Sertraline + EMDR versus Sertraline	6	Sertraline + EMDR = Sertraline
Behnam Moghadam (2015)	60	EMDR versus TAU (no intervention)	3 (45–90 minutes)	EMDR > TAU
Mauna Gauhar (2016)	26	EMDR versus WL	6 to 8 (1 hour)	EMDR > WL
Ostacoli et al. (2018)	82	EMDR versus CBT	15 ± 3	Posttreatment: EMDR > CBT; Follow-up: EMDR = CBT
Hase et al. (2018)	30	EMDR + TAU versus TAU	1 or 2 EMDR sessions/week. Minimum 4 sessions, maximum 12.	EMDR + TAU > TAU
Minelli et al. (2019)	22	EMDR versus TF-CBT	24 (three 1-hour sessions/week, for 8 weeks)	Posttreatment: EMDR = TF-CBT; Follow-up: EMDR > TF-CBT

Note. CBT = cognitive behavioral therapy; TF-CBT = trauma-focused cognitive behavioral therapy; WL = waiting list; TAU = treatment as usual.
> indicates significantly better than.

with some methodological concerns. However, the findings of these studies suggest that EMDR could be a compelling option for the depression treatment. In particular, greater evidence of effectiveness in the treatment of depressive symptoms was found when EMDR was compared with inactive control groups (e.g. waiting list). When EMDR was administered as an add-on to other treatments (e.g. sertraline or psychoeducation), authors reported the potentiality of boosting and strengthening the effects of the standard treatments.

Lastly, a direct comparison with CBT (Ostacoli et al., 2018) found that EMDR seemed to be comparable or slightly superior to CBT, which is considered the gold standard intervention for the treatment of depression, according to clinical guidelines (National Collaborating Centre for Mental Health (UK), 2010). Moreover, results of the follow-up analysis suggest that EMDR improvements may have more potential to remain stable and maintained over time.

It is possible to identify some limitations concerning the studies in this field. Current evidence is heavily influenced by methodological flaws, including randomization details not reported and small sample size, and only two studies cited the DeprEND protocol. In fact, almost no information has been provided about treatment conceptualization nor the type of targets, making it difficult to compare the studies and to derive important clinical information. Therefore, findings are tentative and need to be supported by larger and more robust evaluations. Clinical interviews conducted by independent assessors must be used in the future. The main results available to date, in fact, are the result of self-reported measures, which have in themselves the risk of poor objectivity in measuring the effectiveness of the intervention (such as the potential overestimation). Only few studies included follow-up assessments, which are fundamental to evaluate long-term effects. Therefore, better designed research is needed to confirm the available findings.

The dissemination of the DeprEND protocol among clinicians and researchers is of the utmost importance, in order to obtain more comparable data and to increase the information about the effectiveness of this specific EMDR protocol. More broadly, beyond the methodological aspects, more information about treatment conceptualization, targets, and stabilization, as well as resources installation techniques should be provided. These recommendations have a repercussion at clinical and research levels, allowing to make the most of the potential of the EMDR treatment. Moreover, in order to expand the framework of knowledge on this topic, a systematic review and meta-analysis on the effects of EMDR treatment on depressive symptoms, both as primary and secondary outcome in controlled studies, is in progress by our research group (PROSPERO Register for Systematic Reviews registration number: CRD42018090086). In conclusion, even though more research is needed, EMDR could be considered a useful therapy to treat depression, as an alternative to gold standard treatments or in addition to routine clinical tools.

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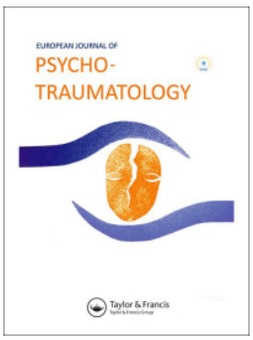
Correspondence regarding this article should be directed to Sara Carletto, Department of Clinical and Biological Sciences, University of Turin, Regione Gonzole 10, 10043 Orbassano (TO), Italy. E-mail: sara.carletto@unito.it



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Eye movement desensitization and reprocessing for depression: a systematic review and meta-analysis

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REVIEW ARTICLE

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Eye movement desensitization and reprocessing for depression: a systematic review and meta-analysis

Sara Carletto [a,*], Francesca Malandrone [b,*], Paola Berchialla [b], Francesco Oliva [b], Nicoletta Colombi [c], Michael Hase[d], Arne Hofmann[e] and Luca Ostacoli [b]

[a]Department of Neurosciences, University of Turin, Turin, Italy; [b]Department of Clinical and Biological Sciences, University of Turin, Turin, Italy; [c]Biblioteca Federata di Medicina "Ferdinando Rossi", University of Turin, Turin, Italy; [d]Lüneburg Centre for Stress Medicine, Lüneburg, Germany; [e]EMDR-Institute, Bergisch Gladbach, Germany

ABSTRACT

Background: In recent years, eye movement desensitization and reprocessing (EMDR) has been applied to different psychiatric conditions beyond post-traumatic stress disorder (PTSD), and an increasing number of studies have evaluated its effect on depression. To date, no quantitative synthesis of the efficacy of EMDR on depression has been conducted.
Objective: To meta-analytically review the studies on EMDR for depression as the primary target for treatment.
Method: Studies with a controlled design evaluating the effect of EMDR on depression were searched on six electronic databases (PubMed, Embase, CINAHL, PsycINFO, Cochrane database, and Francine Shapiro Library) and then selected by two independent reviewers. A systematic review and meta-analysis was conducted.
Results: Eleven studies were included for qualitative synthesis. Nine studies were included in the meta-analysis, involving 373 participants. The overall effect size of EMDR for depressive symptoms is large (n = 9, Hedges' g = – 1.07; 95%CI [–1.66; – 0.48]), with high heterogeneity (I^2 = 84%), and corresponds to a 'number needed to treat' of 1.8. At follow-up (range 3–6 months), the effect remains significant but moderate (n = 3, Hedges' g = – 0.62; 95%CI [–0.97; – 0.28]; I^2 = 0%). The effect of EMDR compared with active controls is also moderate (n = 7, g = – 0.68; 95%CI [–0.92; – 0.43]; I^2 = 0%). No publication bias was found, although the results are limited by the small number and poor methodological quality of the included studies.
Conclusions: Review findings suggest that EMDR may be considered an effective treatment for improving symptoms of depression, with effects comparable to other active treatments. However, findings need to be interpreted in light of the limited number of the studies and their quality. Further research is required to understand the longer-term of effects EMDR in treating depression and preventing depression relapse.
Protocol registration: PROSPERO (CRD42018090086).

Desensibilización y reprocesamiento por movimientos oculares para la depresión: una revisión sistemñtica y meta-análisis

Antecedentes: En los últimos años, la desensibilización y reprocesamiento por movimientos oculares (EMDR) se ha aplicado a diferentes condiciones psiquiátricas más allá del trastorno de estrés postraumático (TEPT), y un número creciente de estudios ha evaluado su efecto en la depresión. Hasta la fecha, no se ha realizado ninguna síntesis cuantitativa de la eficacia de la EMDR en la depresión.
Objetivo: Revisar meta-analíticamente los estudios de EMDR para la depresión como objetivo principal del tratamiento.
Método: Se buscaron estudios con un diseño controlado que evaluaran el efecto de la EMDR en la depresión en seis bases de datos electrónicas (PubMed, Embase, CINAHL, PsycINFO, base de datos Cochrane y Francine Shapiro Library) y luego fueron seleccionados por dos revisores independientes. Se realizó una revisión sistemática y un metanálisis.
Resultados: Se incluyeron once estudios para la síntesis cualitativa. Se incluyeron nueve estudios en el meta-análisis, con 373 participantes. El tamaño del efecto global de la EMDR para los síntomas depresivos es grande (n = 9, g de Hedges = –1,07; IC del 95% [–1,66; –0,48]), con alta heterogeneidad (I^2 = 84%), y corresponde a un 'número necesario a tratar' de 1,8. En el seguimiento (rango 3-6 meses), el efecto sigue siendo significativo pero moderado (n = 3, g de Hedges = –0,62; IC del 95% [–0,97;-0,28]; I^2 = 0%). El efecto del EMDR en comparación con los controles activos también es moderado (n = 7, g = –0,68; IC del 95% [–0,92;-0,43]; I^2 = 0%). No se encontró ningún sesgo de publicación, aunque los

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关键词
眼动脱敏和再加工; EMDR; 抑郁;系统综述;元分析;创伤;心理治疗。

HIGHLIGHTS

- This review summarizes the current evidence on the effects of EMDR for depression.
- Findings show that one-third of people with depression could benefit from EMDR.
- EMDR could be considered as an alternative to first-line treatments for depression, pending further research.

CONTACT Luca Ostacoli luca.ostacoli@unito.it Department of Clinical and Biological Sciences, University of Turin, Regione Gonzole 10, Orbassano, Turin 10043, Italy

*These authors contributed equally to this work

Supplemental data for this article can be accessed here.

resultados están limitados por el pequeño número y la pobre calidad metodológica de los estudios incluidos.
Conclusiones: Los resultados de la revisión sugieren que la EMDR puede considerarse un tratamiento eficaz para mejorar los síntomas de la depresión, con efectos comparables a los de otros tratamientos activos. Sin embargo, los hallazgos deben interpretarse a la luz del número limitado de los estudios y su calidad. Se requiere investigación adicional para comprender los efectos a largo plazo de la EMDR en el tratamiento de la depresión y la prevención de la recaída de la depresión.
Registro del protocolo: PROSPERO (CRD42018090086).

抑郁的眼动脱敏和再加工:系统综述和元分析

背景:近年来, 眼动脱敏和再加工 (EMDR) 已被应用到创伤后应激障碍 (PTSD) 以外的不同精神疾病中, 并且越来越多的研究评估了其对抑郁的影响。至今尚未对EMDR对抑郁症疗效进行定量综合分析。
目的:以元分析方法综述以抑郁症为主要治疗目标的EMDR研究。
方法:在六个电子数据库 (PubMed, Embase, CINAHL, PsycINFO, Cochrane数据库和Francine Shapiro库) 中搜索包含评估EMDR对抑郁症影响的对照设计的研究, 然后由两名独立的审阅者进行选择。进行了系统综述和元分析。
结果:纳入了11项定性综合研究。元分析包括九项研究, 共373名参与者。 EMDR对抑郁症状的总体效应量较大 (n = 9, Hedges' g= −1.07; 95%CI [−1.66; −0.48]), 异质性较高 (I^2 = 84%), 对应于1.8的'需要治疗的数量'。在随访时 (3-6个月), 效果仍然显著但中等 (n = 3, Hedges' g= −0.62; 95%CI [−0.97; −0.28]; I^2 = 0%) 。与主动对照组相比, EMDR的作用也中等 (n = 7, g= −0.68; 95%CI [−0.92; −0.43];I^2 = 0%) 。没有发现发表偏倚, 尽管结果受限于纳入研究的数量较少和方法质量较差。
结论:综述结果表明, EMDR可以被认为是一种有效改善抑郁症状的治疗方法, 其效果可与其他主动疗法相比较。但是, 结果需要在依据有限数量的研究及其质量的前提下解释。需要进一步的研究来了解EMDR在治疗抑郁和预防抑郁复发方面的长期作用。
协议注册:PROSPERO (CRD42018090086) 。

1. Introduction

Depression is widespread in the world with a prevalence that ranges between 2.6% (among males in the Western Pacific Region) and 5.9% (among females in the African Regions), with a peak in late adulthood and a higher rate for women than for men (World Health Organization, 2017). This disease impacts on people's quality of life and functioning. In this regard, in 2017 the World Health Organization identified depression as one of the major causes of reduced life years due to mortality and disability (James et al., 2018). According to the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5), depression assumes clinical relevance when it leads to significant distress or impairment in social, occupational, or other important areas of functioning and meets the diagnostic criteria for an episode of major depressive disorder (American Psychiatric Association, 2013).

The treatment of depression has greatly evolved over the last few years and there are now various therapeutic options that combine pharmacology and psychotherapy (National Institute for Health and Care Excellence, 2009, 2018). However, less than half of the treated patients (Johnston, Powell, Anderson, Szabo, & Cline, 2019) show a positive response to drug therapy (i.e. a reduction in depressive symptoms) and, although the introduction of cognitive behavioural therapy (CBT) has allowed a doubling of the percentage of responders (Hofmann et al., 2014), recurrence rates at 1 and 2 years remain high at 29% and 54%, respectively (Vittengl, Clark, Dunn, & Jarrett, 2007).

Among the main risk factors for depression, traumatic events play a crucial role. This seems particularly evident when considering that psychiatric patients show an 89.9% prevalence of early traumatic experiences compared to 50% for the general population (Schalinski et al., 2016). The causal relationship between traumatic events and the onset of a depressive disorder is complex and has yet to be fully outlined. However, it is likely that the impact of traumatic experiences is mediated by an individual's epigenetic, immunological, endocrine (Caldji et al., 1998; Huot, Plotsky, Lenox, & McNamara, 2002; Ladd et al., 2000; Liu, 1997; Meaney et al., 1996; Plotsky & Meaney, 1993), neurobiological (Andersen et al., 2008; Davey, Yücel, & Allen, 2008; Ernst, Pine, & Hardin, 2006) and psychological modifications (Aldao, Nolen-Hoeksema, & Schweizer, 2010a; Courtney, Kushwaha, & Johnson, 2008; Crow, Cross, Powers, & Bradley, 2014; Maciejewski & Mazure, 2006; Wright, Crawford, & Del Castillo, 2009). Exposure to adverse events during childhood and adolescence is not only a significant risk factor for developing a depressive disorder but also influences the course, prognosis, and response to treatments. Indeed, this exposure has been shown to be one of the main factors in recurrence, persistence, and resistance to the treatment of depression (Nanni, Uher, & Danese, 2012; Nelson, Klumparendt, Doebler, & Ehring, 2017). Furthermore, it seems to increase the individual sensitivity of the disorder to psychotherapeutic interventions, which in these cases are more effective than drug therapy (Nemeroff et al., 2003). Relying on these

findings, some authors proposed considering trauma-associated depression as a particular subtype, which would require a different approach compared to the traditional one proposed by the guidelines (Minelli et al., 2019; Nanni et al., 2012; Nelson et al., 2017; Paterniti, Sterner, Caldwell, & Bisserbe, 2017).

Eye movement desensitization and reprocessing (EMDR) is a first-choice therapy in post-traumatic stress disorder (PTSD) and is based on the adaptive information processing (AIP) model proposed by Shapiro (Shapiro, 2018). Such a model proposes the influence of dysfunctional memories that have not been completely processed underlying various psychiatric disorders (such as PTSD, mood disorders, chronic pain, and drug addiction). These memories could be triggered by internal or external stimuli, thus assuming an intrusive nature and accompanying appearance of PTSD symptoms and other disorders (Hase et al., 2018). According to Barry and collaborators (Barry, Naus & Rehm, 2006), dysfunctional memories are characterized by a lack of 'memory awareness' as a consequence of their incomplete processing. EMDR therapy targets this lack of awareness by reprocessing such pathogenic memories with the use of alternate bilateral stimulations (e.g. eye movements), thus enabling their transformation and integration into already existing semantic links (Hase, Balmaceda, Ostacoli, Liebermann, & Hofmann, 2017; Solomon & Shapiro, 2008).

Recently, a specific EMDR therapy protocol for the treatment of depressive disorders (DeprEND®) has been published (Hofmann et al., 2016). Research findings have shown that EMDR could contribute to a significant reduction of depressive symptoms associated with PTSD when compared to waitlist/usual care or non-trauma-focused CBT. However, these findings are supported by very low-quality evidence (Bisson, Roberts, Andrew, Cooper, & Lewis, 2013; Cuijpers, van Veen, Sijbrandij, Yoder, & Cristea, 2020).

Moreover, in recent years EMDR has been applied to the treatment of psychiatric disorders beyond PTSD, such as depression, although it is not currently recommended by the guidelines (Cuijpers et al., 2020; Valiente-Gómez et al., 2017). Therefore, it is essential to determine whether EMDR is an evidence-based treatment for depression.

Previous reviews addressing this topic have been published (Carletto et al., 2017; Malandrone, Carletto, Hase, Hofmann, & Ostacoli, 2019; Wood & Ricketts, 2013), suggesting the potentiality of EMDR for depression but also highlighting the paucity of methodologically sound studies conducted until then. As other studies have been conducted in recent years, including some randomized controlled trials (RCTs), the present systematic review and meta-analysis aims to update and add a quantitative analysis on the efficacy of EMDR for the treatment of depression.

2. Methods

2.1. Protocol registration

The review protocol was registered in the PROSPERO repository (CRD42018090086). The original protocol recorded on PROSPERO has undergone some variations. In particular, the search has been updated and the meta-analysis focused on depression considered as a primary diagnosis and outcome.

The systematic review and meta-analysis was carried out following the PRISMA statement and the PRISMA checklist (Moher, Liberati, Tetzlaff, & Altman, 2010) and it was drafted following the Cochrane Handbook Guidelines (Higgins et al., 2019).

2.2. Search strategy for identification of studies

Searches were conducted in the following databases on 30 September 2020: PubMed, Embase, CINAHL, PsycINFO and the Cochrane Central Register of Controlled Trials. Moreover, we performed a search with the keyword 'depress' in the Francine Shapiro Library, which is an online compendium of conference presentations, scholarly articles, and other important grey literature related to EMDR. From selected studies, cross-references were checked manually (see Supplementary Material S1 for details of the search strategy).

2.3. Eligibility criteria

2.3.1. Design

We included studies with a controlled trial design, either randomized or not. No year or language restrictions were applied.

2.3.2. Population

Trials included patients of any age with depression as a primary diagnosis and primary outcome of the study. Depression is defined as either major depressive disorder or depressive symptoms (above or below a predefined cut-off on the questionnaires employed in each study). There was no restriction by concurrent organic disease.

2.3.3. Intervention and comparison

We included studies that evaluated EMDR intervention alone or in addition to another treatment in comparison with no intervention, waiting list, treatment as usual, or other types of intervention (e.g. antidepressant medication, CBT, psychodynamic therapy).

2.3.4. Outcome

We included studies with depression as a primary outcome. Studies were supposed to include quantitative data on depressive scores, as measured by standardized

psychometric scales, before and after the intervention/s. Finally, in order to be included in the meta-analysis, studies also had to provide enough data to calculate effect sizes.

2.4. Data collection and analysis

2.4.1. Study selection and appraisal

Two authors (S.C. and F.M.) independently conducted standardized assessments to determine study eligibility according to the inclusion criteria. They screened the abstracts and then retrieved and analysed the full texts for all material deemed relevant. Any disagreement was discussed with a third author (L.O.) before agreement was reached.

2.4.2. Data extraction

Data from the selected studies were inserted into a standard template by two independent researchers (S.C. and F.M.). Extracted data covered publication year, publication type, language, study design, population, primary diagnosis, sample size (for both experimental and control groups), duration and type of intervention, duration and type of comparator, depression measure and length of follow-up. Article authors were contacted via email for missing information.

2.4.3. Risk of bias in individual studies

The internal validity of the RCTs was assessed using Version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB 2) (Sterne et al., 2019), which consists of five domains (randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, selection of the reported result) and a categorization of the overall risk of bias. Risk of bias of controlled studies was assessed using the MINORS scale (Slim et al., 2003; Zeng et al., 2015). For all included studies, quality was also assessed using the platinum standard (PS) (Hertlein & Ricci, 2004), which was specifically designed to evaluate effectiveness in EMDR research. Assessment of the risk of bias was made by two independent coders (S.C. and F.M.) and any disagreements were discussed and resolved with a third reviewer (L.O.).

2.4.4. Summary measures

For each study, the mean change from baseline (post-score – baseline score) was computed. Because the included studies used different scales for measuring depression, effect sizes were computed as the standardized mean difference based on Hedges' *g* method (Hedges & Olkin, 1985). Moreover, as the correlation coefficient between the post- and baseline scores is needed for computing the standard error, the value of 0.7 was assigned, as suggested by Rosenthal (1991).

The DerSimonian and Laird random-effects model was used to pool estimates across studies (DerSimonian & Laird, 1986). Average effect size and 95% confidence interval (95%CI) were computed using the Jackson method. The number needed to treat (NNT) was calculated with the formulae provided by Kraemer and Kupfer (2006). To estimate heterogeneity between studies, Cochran's Q test and the Higgins I^2 statistic were used. Similarly, subgroup analyses were carried out using random-effects models by considering the risk of bias. The extent to which different treatment doses affect the effect size was examined by applying a univariate meta-regression. To identify influential studies that resulted in variation, a sensitivity analysis was carried out using GOSH (graphical display of study heterogeneity) plots, which fit the same meta-analysis model for all the possible study combinations and look for specific patterns by performing clustering with *k*-means, DBSCAN (density-based spatial clustering of applications with noise) and Gaussian mixed models (Olkin, Dahabreh, & Trikalinos, 2012). Publication bias was examined by visual inspection of funnel plots and using Egger's test (Egger, Smith, Schneider, & Minder, 1997). Analyses were carried out using R version 3.6.1 (R Development Core Team, 2019).

3. Results

3.1. Study selection and study characteristics

The PRISMA flowchart describing the selection process, including reasons for exclusion, is presented in Figure 1. The search retrieved 11 studies: 10 articles on adult patients and one on adolescents (Table 1). Meta-analysis included 9 studies, as two studies (Lei & Zhen-Ying, 2007; Tang et al., 2015) was excluded due to there being no usable data for calculating the effect sizes.

The meta-analysis involved 373 participants, with 177 allocated to EMDR treatment and 196 controls.

Ten studies were published in journals and one was a PhD dissertation thesis. All except one were in English. The first published study dates back to 2007 and the last in 2020. Regarding the study design, eight studies were RCTs and three were controlled studies (CS). None of the studies included patients with a PTSD diagnosis. The presence of traumatic experiences was considered as an inclusion criterion in only one of the studies (Minelli et al., 2019), whereas in the other studies it was assessed among other variables. Concerning the use of medication, one study considered it to be an exclusion criterion, one study reported no information, and nine studies chose to keep stable or not exclude the use of antidepressants. In five studies, the efficacy of EMDR was investigated as an add-on to other

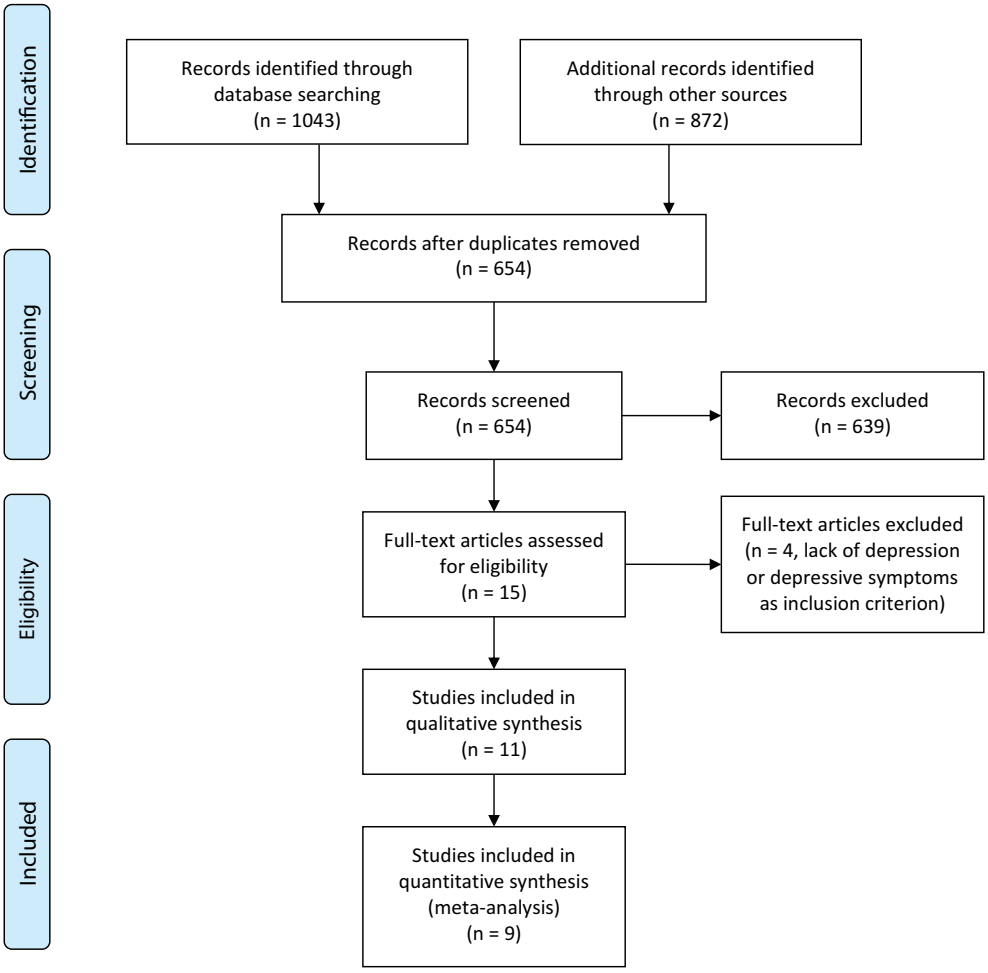

Figure 1. PRISMA flow diagram.

psychotherapies, medications, or psychoeducation, and six studies compared EMDR as a stand-alone treatment. When EMDR was investigated as a stand-alone treatment, two studies compared EMDR with a waiting list/no treatment control group, whereas four studies compared EMDR with an active control. Among the latter, all studies compared EMDR with CBT. The average amount of EMDR therapy administered is 16.97 hours (SD = 16.53) and the average amount of control treatment is 19.08 hours (SD = 15.94). Although six studies planned a follow-up evaluation, only four studies provided data for including in the meta-analysis.

3.2. Risk of bias within studies

The risk of bias for each study is reported in Table 2 and Figure S2. Eight RCTs were assessed with RoB 2. The quality of the included studies was not optimal: the overall risk of bias was rated as low in only 22.2% of the studies. The major issues identified were related to deviation from the intended intervention, in particular the lack of intention-to-treat analysis and inadequate reporting of allocation concealment.

The three controlled studies showed a high risk of bias, mainly related to missing methodological information. Quality assessment according to the PS is reported in Supplementary Material S3. The total PS score for each study ranged from 6.5 to 11.5 (maximum of 13), with a mean of 8.73 (SD = 1.63). Almost all studies were judged to have clearly defined target symptoms, reliable and valid measures and used a control or comparison group. Moreover, almost all studies reported the level of therapist(s) training and applied a manualized, replicable, specific EMDR treatment. The lowest PS scores are mainly related to not reporting information regarding the assessors' training, effect size and level of treatment adherence. Finally, in only two studies was the treatment length 11 or more sessions, which is considered the threshold to achieve an effect according to the PS guidelines (Hertlein & Ricci, 2004). Overall, the PS scores were largely consistent with the judgement of risk of bias provided by RoB 2/MINORS.

3.3. Synthesis of results

The forest plot of the overall effect of EMDR is reported in Figure 2. EMDR results in a large significant effect on depressive symptoms (n = 9, Hedges' g = – 1.07; 95%CI [–1.66, – 0.48]), with high heterogeneity (I^2 = 84%). The effect size corresponds to an NNT of 1.8. Exclusion of one outlier

Table 1. EMDR for depression or depressive symptoms as a primary outcome.

Study	Type	Language	Design	Population	Primary diagnosis measure	Depression measure	Medications	Comparison	EMDR sessions	Control sessions	Follow-up	Main results
Behnammoghadam et al. (2015)	Published article	English	RCT	Patients with myocardial infarction	BDI (>17)	BDI	ND	EMDR (n = 30) vs. TAU (n = 30)	3 (45–90 min per session)	No intervention	ND	EMDR>TAU
Dominguez et al. (2021)	Published article	English	RCT	Patients with depressive disorder	DSM-5	DASS-21 depressive scale	Yes	Group CBT+individual EMDR (n = 16) vs. group CBT +individual assertiveness training (n = 17) vs. group CBT alone (n = 16)	3 (90 min)	3	6 and 12 weeks	Post-treatment: Group CBT +EMDR = group CBT +assertiveness training = group CBT alone Follow-up: Group CBT+EMDR > group CBT +assertiveness training Group CBT+EMDR > group CBT alone
Gauhar (2016)	Published article	English	RCT	Patients with MDD	DSM-IV-TR	BDI-II	No (exclusion criteria)	EMDR (n = 13) vs. WL (n = 13)	6/8 (1 hour weekly)	No intervention	No	EMDR>WL
Hase et al. (2015)	Published article	English	CS	Adult in-patients with mild-to-moderate depressive episode	SCL-90-R depression scale (ICD-10)	SCL-90-R; BDI	9 in EMDR and 10 in control group were on antidepressant medication at time of admission	TAU (psychodynamic psychotherapy) +EMDR (n = 16) vs. TAU (n = 16)	5.6 (SD = 2.4) individual and 7.6 (SD = 4.5) group + 4.6 (SD = 2.4)	6.5 (SD = 2.5) individual and 7 (SD = 3.9) group	12/16 months but no data	EMDR+TAU>TAU
Hase et al. (2018)	Published article	English	RCT	Patients with depression	BDI-II (>12) (ICD-10 F32.x and F33.x)	SCL-90-R; BDI-II	Yes	EMDR+TAU (n = 14) vs. TAU (psychoeducational group, n = 16)	8.5 of EMDR (60 min)	Twice a week (90 min)	1 and 2 years after but no data	EMDR+TAU>TAU
Hofmann et al. (2014)	Published article	English	CS	Patients with unipolar primary depression	SCID-I; BDI-II	BDI-II	Yes	CBT+EMDR (n = 21) vs. CBT (n = 21)	44.48 of CBT + 6.9 of EMDR	47.11 CBT	No	CBT+EMDR>CBT
Hogan et al. (2001)	Dissertation thesis	English	RCT	MDD or another depressive disorder such as dysthymia or adjustment disorder with depressed mood	SCL-90-R	BDI-II	Medications were allowed if the response had been stabilized prior to initiation of the study	EMDR (n = 15) vs. CBT (n = 15)	4	4	3 months but no data	EMDR = CBT
Lei & Zhen-Ying (2007)	Published article	Chinese	RCT	Patients with depression	HDRS>17; CGI>3; CCMD-3	HDRS	Yes	Sertraline (n = 32) vs. sertraline+EMDR (n = 32)	6	Only medication	No	Sertraline +EMDR = sertraline
Minelli et al. (2019)	Published article	English	RCT	In-patients with TRD with at least three traumatic experiences.	SCID-I	BDI-II; MADRS	Yes	EMDR (n = 12) vs. TF-CBT (n = 10)	24	24	3 months	Post-treatment: EMDR = TF-CBT Follow-up: EMDR>TF-CBT
Ostacoli et al. (2018)	Published article	English	RCT	Patients with recurrent depressive episodes	MINI-Plus; BDI-II (scores >13)	BDI-II	Yes	EMDR+TAU (n = 40) vs. CBT+TAU (n = 42)	15.1	14.6	6 months	EMDR = CBT
Tang et al. (2015)	Published article	English	CS	Taiwanese adolescents who experienced Typhoon Morakot diagnosed with MDD and suicide risk	Mandarin Chinese version of the CES-D	CES-D	Yes	EMDR (n = 41) vs. TAU-psychoeducation (n = 42)	4 (60, 40, 40, 40 minutes)	Weekly group psychoeducation session	No	EMDR>TAU

BDI-II = Beck Depression Inventory, Version II; CBT = cognitive behavioural therapy; CCMD-3 = Chinese Classification of Mental Disorders, Version 3; CES-D = Center for Epidemiologic Studies Depression Scale; CGI = Clinical Global Impression Scale; CT = controlled study; DASS-21 = Depression Anxiety Stress Scale, 21 items; DSM (-IV and −5) = Diagnostic and Statistical Manual of Mental Disorders (Editions IV and 5); EMDR = eye movement desensitization and reprocessing; HDRS = Hamilton Depression Rating Scale; ICD-10 = International Classification of Diseases, 10th Edition; MADRS = Montgomery–Asberg Depression Rating Scale; MDD = major depressive disorder; MINI-Plus = Mini International Neuropsychiatric Interview-Plus; ND = not defined/not reported; RCT = randomized controlled trial; SCID-I = Structured Clinical Interview for DSM-IV Axis I Disorders; SCL-90-R = Symptom Checklist-90-Revised; SD = standard deviation; TAU = treatment as usual; TF-CBT = trauma-focused cognitive behavioural therapy; TRD = treatment-resistant depression; WL = waiting list.

Table 2. Risk of bias.

RCT	Study	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	RoB 2 overall bias
	Behnammoghadam et al. (2015)	Some concerns	Some concerns	Low	Some concerns	High	High
	Dominguez et al. (2021)	Low	Low	Low	Low	Low	Low
	Hase et al. (2018)	Some concerns	Some concerns	Low	Low	Some concerns	Some concerns
	Hogan et al. (2001)	High	Some concerns	Low	Low	Some concerns	High
	Lei & Zhen-Ying (2007)	Some concerns	High	Low	High	Some concerns	High
	Gauhar (2016)	Some concerns	High	High	Some concerns	Some concerns	High
	Minelli et al. (2019)	Some concerns	Some concerns	Low	Low	Low	Some concerns
	Ostacoli et al. (2018)	Low	Low	Low	Low	Low	Low

Controlled	Study	A clearly stated aim	Inclusion of consecutive patients	Prospective collection of data	Endpoints appropriate to the aim of the study	Unbiased assessment of the study endpoint	Follow-up period appropriate to the aim of the study	Loss to follow-up less than 5%	Prospective calculation of the study size	An adequate control group	Contemporary groups	Baseline equivalence of groups	Adequate statistical analyses	MINORS total score	MINORS overall risk of bias
	Hase et al. (2015)	2	0	1	2	1	2	2	0	2	2	2	1	17	High
	Hofmann et al. (2014)	2	0	1	2	0	1	2	0	2	0	2	1	13	High
	Tang et al. (2015)	2	1	1	1	0	1	2	0	2	2	1	1	14	High

Randomized controlled trials (RCTs) were evaluated with the Cochrane risk-of-bias tool for randomized trials (RoB 2). The proposed judgement about the risk of bias arising from each domain is generated by an algorithm and is expressed as low, high or some concerns.

Controlled studies were evaluated using the MINORS scale, with items scored as: 0, not reported; 1, reported but inadequate; 2, reported and adequate. The global ideal score is 16 for non-comparative studies and 24 for comparative studies: low risk of bias was considered for studies fulfiling all the MINORS criteria with a score of 2; 'some concerns' was rated when studies were judged to raise some concerns in at least one domain but judged not to be at high risk of bias for any domain; and high risk of bias was applied to all other studies.

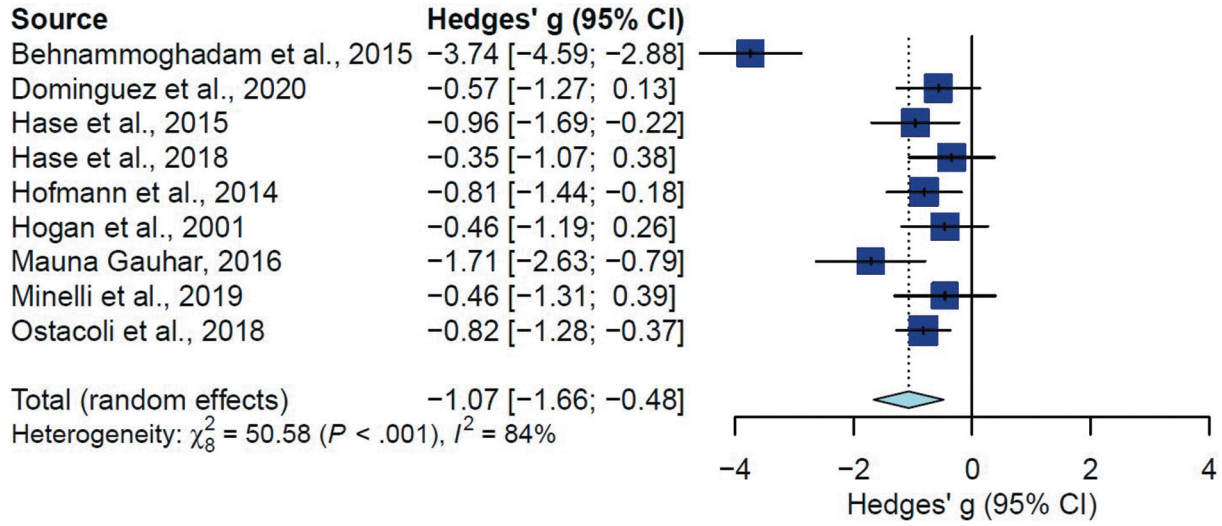

Figure 2. Overall effect of EMDR for depression: forest plot.

resulted in a smaller but still moderately significant effect size for post-treatment (n = 8, g = – 0.75; 95% CI [–0.99, – 0.50], NNT = 2.5; forest plot S5), with low heterogeneity (I^2 = 2%). At follow-up, the effect is still significant (n = 3, g = – 0.62; 95%CI [–0.97, – 0.28]; forest plot S6) with no heterogeneity (I^2 = 0%). As can be seen in Figure 3, low-quality studies showed a higher effect size than those of high quality. Considering only the latter, EMDR showed a moderate effect (n = 2, g = – 0.75; 95% CI [–1.13, – 0.37]) with no heterogeneity (I^2 = 0%; Figure 3). The effect of EMDR was compared with an active control group in seven studies, showing a moderate effect (n = 7; g = – 0.68; 95%CI [–0.92, – 0.43]; forest plot S7) with no heterogeneity (I^2 = 0%). In three studies, EMDR was compared to CBT, resulting in a still significant moderate effect size (n = 3, g = – 0.68; 95%CI [–1.03, – 0.33]; forest plot S8) with no heterogeneity (I^2 = 0%). In four studies, EMDR was an add-on to

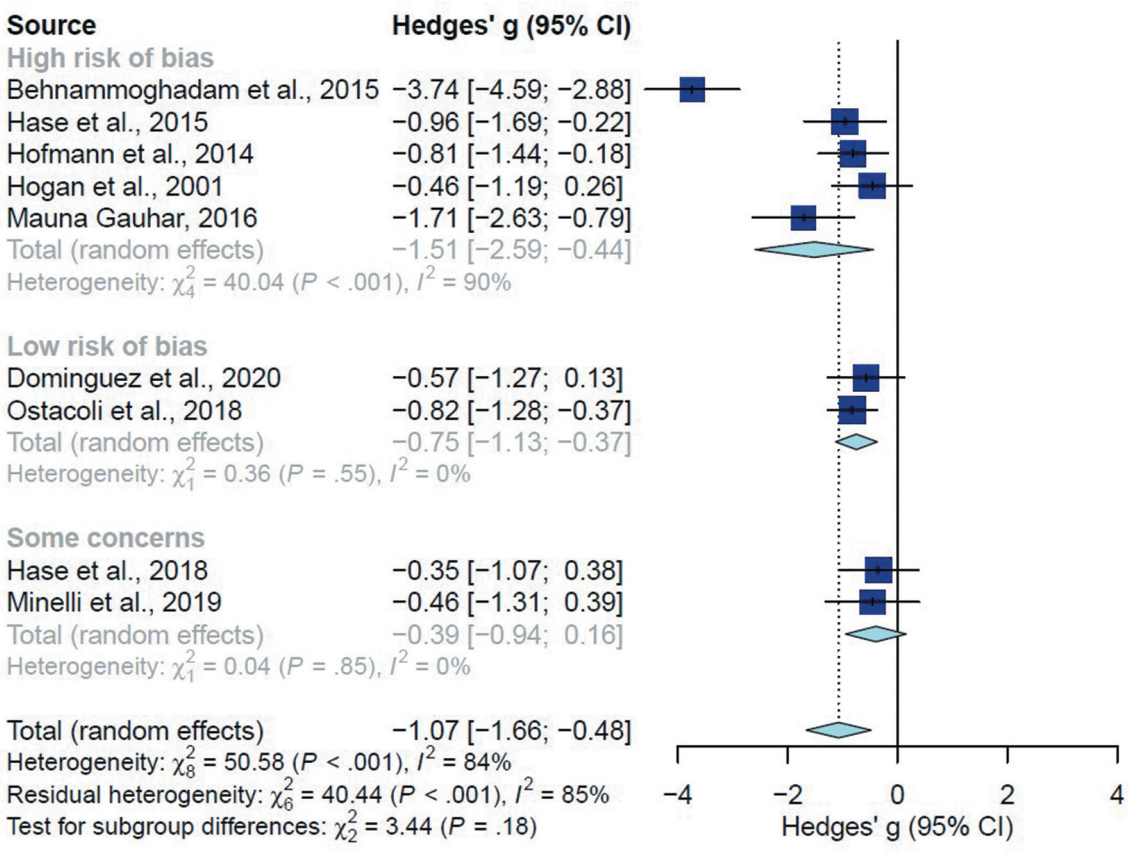

Figure 3. Overall effect with risk of bias: forest plot.

another treatment, showing a moderate effect (g = – 0.68; 95%CI [–1.02, – 0.33] with no heterogeneity (I^2 = 0%). The forest plot is reported in Supplementary Material S9. A dose–response effect on EMDR effect size at post-treatment was not observed (n = 7, β = 0.0003; p = 0.4231).

3.4. Risk of bias across studies

Neither visual inspection of funnel plots nor Egger's test showed any evidence of publication bias (Figure 4 Figure 5).

4. Discussion

The aim of this systematic review and meta-analysis was to update the state of the art and add a quantitative analysis on EMDR therapy for depression as the primary target for treatment.

To our knowledge, this is the first meta-analysis on this topic. Although EMDR is typically associated with the treatment of PTSD, the AIP model (Shapiro, 2001) opens up the possibility to treat other mental health conditions with a trauma-focused approach (Hase et al., 2017).

The results from the nine studies included in the present meta-analysis show that EMDR has a large effect, although high heterogeneity was found and only two studies present a low risk of bias. The statistical effect also reflects clinical significance, as one-third of people with depression benefit from EMDR therapy. In the limited number of studies where follow-up data was available positive effect of EMDR treatment were maintained but with a smaller effect. It should be noted that this latter finding is based on only three studies, so future studies are needed. The effect was moderate even when EMDR is compared with active controls and when compared directly with CBT. These results

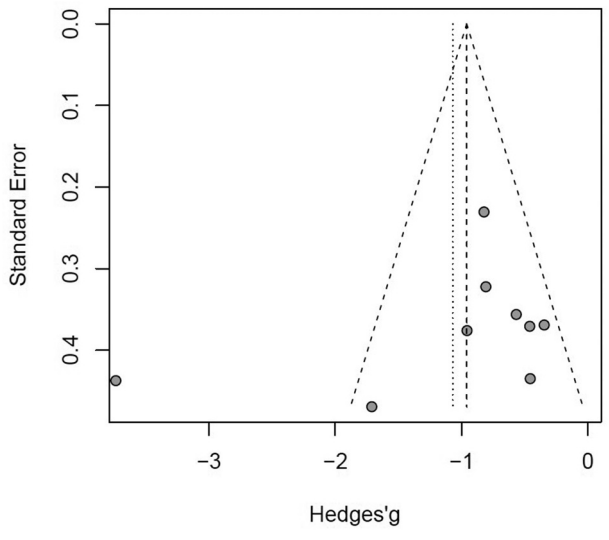

Figure 4. Funnel plot.

are strengthened by the absence of heterogeneity, therefore EMDR could be considered as an effective trauma-focused treatment for depression. The effectiveness of EMDR appeared not to be related to the treatment dose received. This is in line with previous studies, which showed no psychotherapy dose–response relationship for depression (Barth et al., 2013; Stulz, Lutz, Kopta, Minami, & Saunders, 2013). Furthermore, it is important to consider the limited range of EMDR sessions in the studies conducted so far. The effect sizes obtained in this meta-analysis are similar or superior to other meta-analyses evaluating the effects of CBT and other psychotherapies for depression (Cuijpers, Huibers, Daniel Ebert, Koole, & Andersson, 2013; Cuijpers, Van Straten, Andersson, & Van Oppen, 2008) that are currently recommended as effective treatments for depression in the clinical guidelines (National Institute for Health and Care Excellence, 2018; Parikh et al., 2009). This finding is in line with evidence showing that different types of psychotherapies have comparable effects (Barth et al., 2013; Cuijpers, Quero, Dowrick, & Arroll, 2019; Cuijpers et al., 2008). However, our meta-analysis included only 9 studies, compared to more than 100 studies in other meta-analyses, thus highlighting the need for high-quality studies to further evaluate the effect of EMDR for depression.

4.1. Strengths and limitations of the studies

In general, the studies have several limitations. As expected from studies in a field that is still in its infancy, several methodological limitations were found, such as small sample size, high risk of bias, and high heterogeneity. Less than half of the studies evaluated the long-term effect of EMDR on depression. Treatment fidelity was independently checked and considered as adequate in only three studies.

The studies also have some strengths. In most articles, the outcome evaluation criteria were well explained and the assessment tools were all validated. Furthermore, in recent years an increasing number of RCTs addressing the effectiveness of EMDR in treating depression as a primary outcome have been published, along with an increase in their methodological quality. A manualized treatment protocol was applied in the great majority of studies and data on the competence of the therapists were provided in all but one of the studies.

4.2. Strengths and limitations of this review

To our knowledge, this is the first meta-analysis on the effectiveness of EMDR in the treatment of depression as a primary outcome, going beyond previous research that evaluated its effect as an associated symptom in patients with PTSD (Bisson et al., 2013; Cuijpers et al., 2020). Moreover, the Francine Shapiro

Library was consulted to retrieve grey literature, thus conducting a comprehensive review as suggested in the Cochrane handbook (Higgins et al., 2019). This meta-analysis does have some limitations. First of all, the number of included studies is small, indicating that the interest in research on the application of EMDR for depression is still in its infancy. Secondly, the majority of the studies were characterized by low methodological quality and only a few studies examined long-term effects, thus limiting interpretation of the results of this meta-analysis. Finally, another limitation was represented by the impossibility of retrieving data for two studies, which therefore were not included in our quantitative synthesis.

4.3. Implications for clinical practice and research

The results of this study can inform clinical practice by considering EMDR effective at reducing depression, thus adding an additional therapeutic option for clinicians treating this disorder. The increase of therapeutic strategies for depression is of particular importance as it allows better personalization to be provided according to patients' preferences. In fact, studies have shown that receiving a preferred treatment is associated with stronger therapeutic alliance, lower dropout rates, and positive treatment outcomes (Lindhiem, Bennett, Trentacosta, & McLear, 2014; Swift, Callahan, Cooper, & Parkin, 2018; Windle et al., 2020). It is also essential to routinely evaluate the presence of adverse childhood experiences and traumatic events in people with depression in order to identify if trauma-focused psychotherapies such as EMDR could be more effective for patients with a history of maltreatment. Previous studies have shown that exposure to childhood maltreatment predicts a poorer response to drug treatment (Nanni et al., 2012; Williams, Debattista, Duchemin, Schatzberg, & Nemeroff, 2016) and a better response to psychotherapy (Nemeroff et al., 2003) in patients with depression. Therefore, trauma-focused therapies could represent a valid option for patients with depression, who are less likely to respond to usual treatments and may require specific interventions focused on their maltreatment history. It may also be useful to consider whether different types of adverse childhood experiences play a role in predicting the outcome of treatment, in line with findings supporting a significant association of childhood maltreatment, especially emotional abuse and neglect, with depression (Humphreys et al., 2020; Mandelli, Petrelli, & Serretti, 2015; Nelson et al., 2017).

Among EMDR clinicians, evaluation of the type and sequence of treatment targets (e.g. current episode trigger; event(s) that gave rise to the series of recurring depressive episodes; belief system related to attachment history events) could be useful for improving therapeutic outcomes. More studies should also consider adopting the DeprEnd® protocol (Hofmann et al., 2016) as an EMDR intervention specific for depression, or at least report a more specific description of the intervention offered to patients, in line with current checklists such as the template for intervention description and replication (Hofmann et al., 2014). As effect sizes could be inflated by the inclusion of low-quality studies, further studies with better methodological quality are needed to obtain more reliable effect estimates. Future studies should include longer-term follow-up (i.e. after 1 and 2 years). This would make it possible to investigate whether EMDR could be effective not only for reducing depressive symptoms but also preventing relapses, particularly in comparison with other interventions already recommended by clinical guidelines. Although treatment duration was not identified as a potential moderator of intervention efficacy either in this study or in previous reviews on CBT (Barth et al., 2013; Santoft et al., 2019), further studies should try to identify the ideal number of sessions to achieve a successful outcome. As emotional dysregulation is a common clinical feature in patients with depression (Aldao et al., 2010a; Sloan et al., 2017), and previous research has found that this association is mediated by the exposition to traumatic events (Christ et al., 2019), it would be interesting for future research to explore the impact of EMDR on emotional regulation. Furthermore, no study has been conducted so far to evaluate the neurobiological effects of EMDR in depression.

To date, there is preliminary evidence on the effects of EMDR therapy on adolescents with depression (Bae, Kim, & Park, 2008; Paauw, De Roos, Tummers, De Jongh, & Dingemans, 2019). Previous reviews have shown encouraging, although limited, results on the effectiveness of EMDR in reducing depressive symptoms secondary to PTSD in children and adolescents (Manzoni et al., 2021; Moreno-Alcázar et al., 2017). Future controlled studies are needed to further evaluate the effects of EMDR for depression as a primary target of the treatment among children and adolescents. Future studies should analyse possible adverse effects and rates of attrition from EMDR treatment, as these aspects are essential to inform clinical practice. Finally, it would be interesting to investigate the impact on the economic and social costs of treating depression with EMDR compared to other psychotherapies or pharmacotherapy.

5. Conclusion

The findings from this review suggest EMDR can be considered as an effective trauma-focused treatment for reducing symptoms of depression, although several methodological weaknesses were found in the

included studies. Further studies are required in order to replicate these findings, improve methodological quality, and evaluate longer-term effects.

Data availability

The data that support the findings of this study are openly available in the GitHub repository at https://github.com/berkeley3/Eye-movement-desensitization-and-reprocessing-for-depression.

Data transparency statement

The authors declare that there are no previously published or in press works stemming from this same dataset.

Disclosure statement

M.H., A.H. and L.O. are EMDR supervisors, M.H. and A.H. are EMDR trainers, S.C., M.H., A.H. and L.O. have been invited speakers at national and international EMDR conferences and S. C., M.H., A.H. and L.O. are the authors of four of the included studies. F.M., P.B., F.O. and N.C. declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Ethic statement

No institutional review board approval and informed consent were obtained as the study did not involve participants.

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ORCID

Sara Carletto http://orcid.org/0000-0002-4951-7479
Francesca Malandrone http://orcid.org/0000-0002-9438-8637
Paola Berchialla http://orcid.org/0000-0001-5835-5638
Francesco Oliva http://orcid.org/0000-0002-1939-552X
Nicoletta Colombi http://orcid.org/0000-0001-6870-5590
Luca Ostacoli http://orcid.org/0000-0002-6874-1396

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Research paper

Restoring bottom-up communication in brain-heart interplay after trauma-focused psychotherapy in breast cancer patients with post-traumatic stress disorder

F. Malandrone [b,1], V. Catrambone [a,1], S. Carletto [b,*], P.G. Rossini [b], M. Coletti Moja [c], F. Oliva [b], M. Pagani [d], G. Valenza [a,1], L. Ostacoli [b,1]

[a] NeuroCardiovascular Intelligence Lab, Department of Information Engineering & Research Centre "E. Piaggio", School of Engineering, University of Pisa, Italy
[b] Department of Clinical and Biological Sciences, University of Turin, Italy
[c] Neurology Department, Ospedale degli Infermi, Ponderano, Italy
[d] Institute of Cognitive Sciences and Technologies, Consiglio Nazionale delle Ricerche, Rome, Italy

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ABSTRACT

Background: The psychological impact of breast cancer (BC) is substantial, with a significant number of patients (up to 32 %) experiencing post-traumatic stress disorder (PTSD). Exploring the emotional aspects of PTSD through the functional brain-heart interplay (BHI) offers valuable insights into the condition. BHI examines the functional interactions between cortical and sympathovagal dynamics. This study aims to investigate changes in functional directional BHI after trauma-focused (TF) psychotherapy, specifically Eye Movement Desensitization and Reprocessing (EMDR), in comparison to treatment as usual (TAU) among BC patients with PTSD. To our knowledge, this study represents the first examination of such changes.

Methods: We enrolled thirty BC patients who met the criteria for a PTSD diagnosis, with fourteen receiving EMDR and fifteen receiving TAU over a two- to three-month period. We analyzed changes in the emotional response during a script-driven imagery setting. Quantification of the functional interplay between EEG and sympathovagal dynamics was achieved using the synthetic data generation model (SDG) on electroencephalographic (EEG) and heartbeat series. Our focus was on the difference in the BHI index extracted at baseline and post-treatment.

Results: We found statistically significant higher coupling in the heart-to-brain direction in patients treated with EMDR compared to controls. This suggests that the flow of information from the autonomic nervous system to the central nervous system is restored following EMDR-induced recovery from PTSD. Furthermore, we observed a significant correlation between improvements in PTSD symptoms and an increase in functional BHI after EMDR treatment.

Conclusions: TF psychotherapy, particularly EMDR, appears to facilitate the restoration of the bottom-up flow of interoceptive information, which is dysfunctional in patients with PTSD. The application of BHI analysis to the study of PTSD not only aids in identifying biomarkers of the disorder but also enhances our understanding of the changes brought about by TF treatments.

1. Introduction

Breast cancer (BC) is one of the most common oncological diseases among women worldwide (Momenimovahed and Salehiniya, 2019). It entails significant psychological consequences, including anxiety, depression (Goerling et al., 2020) and traumatic stress (Cordova et al., 2017). Reports show that up to 32 % of women suffering from BC may experience post-traumatic stress disorder (PTSD) (Arnaboldi et al., 2017), with symptoms that include hyper-arousal, emotional numbness, intrusive thoughts, and flashbacks when asked to recall their diagnosis and cancer memories (Arnaboldi et al., 2014; O'Connor et al., 2011). This underscores the traumatic potential of a BC diagnosis as well as its

* Corresponding author.
E-mail address: sara.carletto@unito.it (S. Carletto).
[1] These authors contributed equally.

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possible impact on the course of the disease and the related treatments.

The literature on the neurobiological mechanisms of PTSD has grown rapidly over the last decade. At the level of the central nervous system (CNS), activity in the medial prefrontal cortex (mPFC) decreases, whereas it increases in the amygdala due to activation of the innate alarm system evoked by trauma-related stimuli or conditions (Lanius et al., 2020). Baek et al. (2019) highlighted the involvement of the superior colliculus (SC)-medio dorsal thalamus (MDT) pathway in mice. The SC is involved in visual-attentional processes and plays a crucial role in inner fear regulation (Evans et al., 2018; Wei et al., 2015). This structure targets the MDT, regulating emotional activity through a loop that involves the prefrontal cortex and the amygdala. The brainstem has also been suggested to play a crucial role (Felmingham et al., 2008) as has the midbrain periaqueductal grey (PAG) (Rabellino et al., 2017; Terpou et al., 2020) considering its functional connectivity to the default mode network (DMN), mediating high-order, self-related processing and innate and defensive responses (Lanius et al., 2020). These structures are involved in the central autonomic network (CAN), which integrates central (CNS), peripheral and autonomic (Autonomic Nervous System; ANS) functions and regions of the nervous system. The most studied index to investigate the ANS functions is heart rate variability (HRV). A pivotal meta-analysis (Chalmers et al., 2014) revealed reduced resting HRV in PTSD patients, and a recent study (Thome et al., 2017) revealed a lack of the CAN's regulatory capacity on ANS functioning at rest in people with PTSD, which could help explain some of the negative alterations in cognition and mood associated with this condition. Thome et al. (2017) also found that HRV values in the PTSD group were unrelated to functional connectivity within CAN-related brain regions, suggesting an uncoupling of the ANS from the CAN related to the failure of the top–down control of cardiac activity by higher-order brain regions. According to these authors, the lack of HRV-CAN covariation at rest may indicate that autonomic responses are not being regulated by the CAN in a top-down manner in PTSD. Furthermore, in the PTSD group, they found widespread resting state functional connectivity between CAN-related regions and other brain regions associated with emotional reactivity, motor readiness, self-referential processing, and sensory salience detection. The authors speculated that this may reflect the neurological correlates of a response pattern, indicating difficulty in differentiating between threat and safety situations and in developing context-appropriate responses. Given the widespread enhanced PAG resting functional connectivity seen in PTSD patients, it is even more likely that this pattern reflects a hypersensitive affective system at rest (Panksepp and Biven, 2012). In line with these findings, Rabellino et al. (2017) observed that the individual's ability to adaptively adjust parasympathetic outflow during exposure to stressful stimuli, either subliminal or supraliminal, via critical hubs of the CAN decreases with the severity of PTSD symptomatology.

A recent publication (Harricharan et al., 2021) proposed that traumatized individuals may have a limited capacity to perform multisensory integration, this contrasts with the experience of healthy individuals who are able to combine multiple sources of raw sensory information from their internal and external worlds to develop a unified coherent perception of a multimodal sensory experience. This limitation in trauma patients could be linked to an impairment in sensory processing, the ability to register, modulate and organize interoceptive and exteroceptive stimuli and, in turn, guiding adaptive and goal-oriented behavioural responses (Atick and Atickt, 2009; Baker et al., 2008; Chun et al., 2010; Gilbert and Sigman, 2007). An extremely stressful event in which one's health and integrity are perceived to be severely endangered can lead an individual's system to selectively focus attention on stimuli that are reminiscent of the traumatic event (Harricharan et al., 2021). In PTSD, this results in hypersensitivity to internal and external stimuli, increasing emotional and behavioural reactivity even to non-threatening stimuli. When the person's experience during the traumatic event is closer to the feeling of death and helplessness, the consequence may be a hyposensitivity, as in the dissociative subtype of PTSD.

To elicit and, thus, investigate emotional reactions in people with PTSD, the well-known "script-driven imagery" paradigm, which uses a participant's neutral and traumatic narratives (Orr et al., 1993), has been used to great effect. While the participants listen to their scripts, neurophysiological response data such as HRV (Bujarski et al., 2015) are recorded. The autonomic data obtained from the HRV index can be combined with neural response data provided by electroencephalography (EEG) to deepen our understanding of the role of functional brain-heart interplay (BHI) in the emotional processing of several psychiatric conditions (Catrambone et al., 2021a, 2021b, 2021c). Analysis of the coupling of brain and heart dynamics provides one potential route to revealing the complexities of the brain regions and functionalities involved in the autonomic control of the heart. In other words, the study of BHI offers a new perspective on the functioning of the CAN (Beissner et al., 2013; Benarroch, 1993; Valenza et al., 2016). Functional BHI analysis provides a more integrated description of two traditionally separate physiological systems in mediating both neurological and psychiatric disorders (Catrambone and Valenza, 2021). In addition to disclosing the underlying mechanisms of PTSD, neurobiological indices (such as BHI markers, or measures from EEG and HRV) can help optimise psychological treatments by emphasising the processes underlying the relationship between clinical improvement and neurobiological aspects.

Eye Movement Desensitization and Reprocessing (EMDR) therapy is a well-established psychological intervention used to address traumatic conditions and emotional dysregulation, including those experienced by cancer patients (Portigliatti Pomeri et al., 2021), and it is considered one of the elective treatment for PTSD (National Institute for Clinical Excellence, 2018; World Health Organization, 2013). Several studies have investigated the neurobiological correlates of EMDR showing morphometric changes in both limbic and cortical structures (Landin-Romero et al., 2018; Pagani et al., 2021; Trentini et al., 2021). Moreover, changes in brain activity have been shown after EMDR therapy, with an increase in brain activity in the frontal regions and a decrease in the limbic regions after treatment (Landin-Romero et al., 2018; Pagani et al., 2021; Trentini et al., 2021). Preliminary data showed that the high frequency (HF) components of HRV (i.e., parasympathetic activity) increased following EMDR sessions (Farina et al., 2015).

Previous research has evaluated the neurobiological impact of trauma-focused (TF) psychotherapy on people with PTSD. However, to date, no study has taken a perspective that integrates top-down processes, typically centred on the CNS, with bottom-up processes, which usually take into account the ANS. To fill this gap, the present study aimed to investigate the differences in functional BHI by comparing the effects of a TF psychotherapy - such as EMDR - with those of a treatment as usual - such as supportive therapy - (TAU) for the treatment of PTSD in BC patients.

2. Materials and methods

This study used data from a previous study (Carletto et al., 2019), which evaluated the effect of EMDR therapy compared to usual treatment (TAU) on PTSD symptoms in patients with BC and identified associated neurophysiological changes by only EEG. A full description of the study methods is provided in Carletto et al. (2019).

Women with BC and diagnosis of PTSD were recruited at the Breast Unit Service of the University Hospital "Città della Salute e della Scienza "in Torino (Italy) between September 2016 and November 2017. The study was approved by the local Research Ethics Committee. Informed written consent was obtained from all participants. Eligible patients underwent a three-step screening. Those who identified the illness as the traumatic event completed the Impact of Event Scale-Revised (IES-R; Weiss and Marmar, 1997) questionnaire. Patients with IES-R scores $\geq$33 received a PTSD diagnosis confirmation using the Structured Clinical Interview for DSM-5 (SCID-5; Weathers et al., 2018). The Clinician-

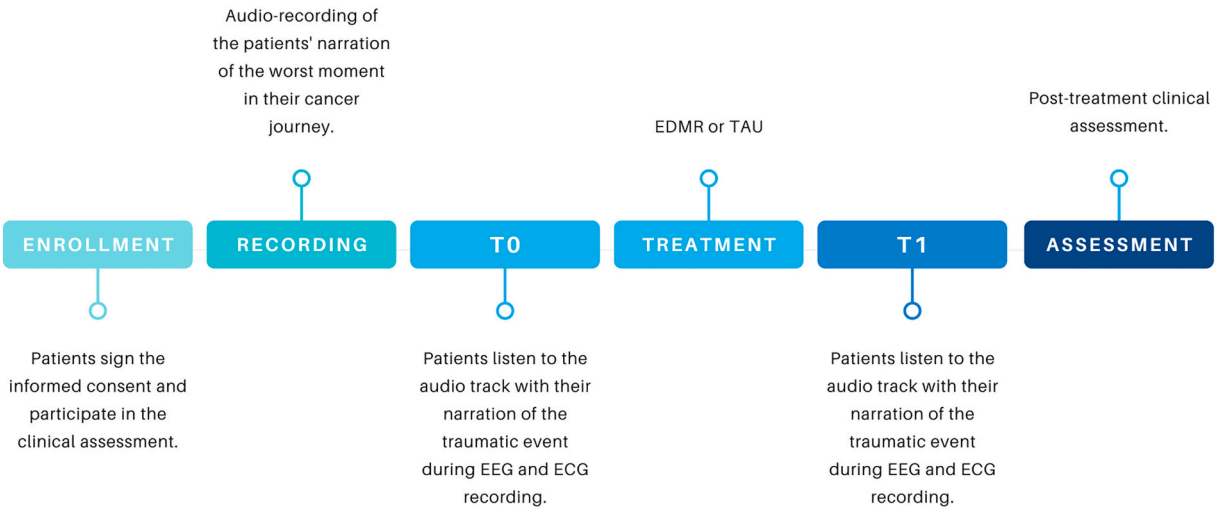

Fig. 1. EEG recording timeline at T0 and T1.

Administered PTSD Scale (CAPS-5; Weathers et al., 2018) assessed PTSD severity. A total of 30 BC patients met the criteria for PTSD diagnosis. Consecutive patients diagnosed with PTSD were asked whether they were willing to receive EMDR other than TAU. On reaching the maximum number of patients in the EMDR group, the remaining patients were assigned to the TAU group.

The TAU group received four supportive therapy sessions over two months, one session every other week. The therapy aimed to help patients cope with psychological symptoms related to BC. Two experienced psychotherapists provided the therapy and received supervision throughout the study.

The EMDR group received ten EMDR sessions over 2–3 months. EMDR followed Shapiro's protocol for traumatic events (Shapiro, 2001) and used a specific protocol for oncological patients (Faretta and Borsato, 2016). The first two sessions focused on stabilisation techniques, while the rest addressed trauma reprocessing. Three experienced practitioners provided EMDR with supervision from a certified senior EMDR supervisor.

The mean age was 55.47 (SD 7.64) in the EMDR group and 48.40 years (SD 9.42) in the TAU group. Except for a slightly higher age in the EMDR group, no significant demographic differences were observed between the two groups at the baseline. The pre- and post-treatment clinical results are presented in Carletto et al. (2019).

2.1. Estimation of functional BHI

EEG recordings were collected using a Galileo system (EBNeuro, Florence, Italy) while patients seated on a comfortable chair in a quiet room. Thirty-seven active electrodes were applied to the scalp using a pre-cabled electrode cap. Data were collected and digitised at a sampling rate of 1024 Hz. Participants were assessed by EEG at two separate time points: at baseline (T0) – all participants underwent two resting state EEG measurements, with eyes open and eyes closed before and after an EEG measurement during script-driven imagery; and post treatment (T1) – after the last session of EMDR or TAU treatment the EEG procedure was repeated. The EEG recordings were pre-processed using the so-called HAPPE pipeline, extensively explained in Gabard-Durnam et al. (2018). Fig. 1 shows the EEG recording timeline at T0 and T1. In brief, the pre-processing pipeline rejects as bad channels the 1 % tail electrodes external to the distribution built through the average log-power normalised joint probability and replaces them through a spherical interpolation algorithm applied to neighbouring channels. Frequencies below 1 Hz and the main electrical frequency noise at 50 Hz were filtered out exploiting a multitaper regression algorithm (Gabard-Durnam et al., 2018). Muscular and ocular artefacts and discontinuities were detected and rejected implementing a wavelet-enhanced independent component analysis (ICA)-based algorithm. A further fast-ICA algorithm was applied, and the extracted components were fed through a machine learning algorithm able to recognise artefact components (Gabard-Durnam et al., 2018). Finally, a common re-referencing procedure was employed (Candia-Rivera et al., 2021).

Table 1
BHI indices extracted through the model.

Index	From	Band	To	Band
$C_{Brain_j \to Heart_{B_C}}$	Brain	δ, θ, α, β	Heart	LF, HF
$C_{Heart_{B_C} \to Brain_j}$	Heart	LF, HF, HT	Brain	δ, θ, α, β

For the electrocardiographic (ECG) series, a MP160 research system by BIOPAC Systems was employed for the recording, using a 3-lead montage with a sampling frequency of 500 Hz. The well-known Pan-Tompkins algorithm (Pan and Tompkins, 1985) was used to detect R-peak events, and the series of time intervals between subsequent R-peaks were constructed and defined as RR-series. Possible physiological or algorithmic artefacts in the RR-series (such as ectopic beats or peak misdetections) were detected and corrected through the use of Kubios software (Tarvainen et al., 2014). A visual inspection assured the final quality of the retained recordings (i.e., EEG and RR series).

2.2. Spectral analysis

For the EEG, the power spectral density (PSD) was estimated using Welch's method, with a Hamming window of 2048 samples (2 s) with 1792 samples of overlap (1.75 s, 87.5 % of the Hamming window). The PSD was integrated in four classical EEG frequency bands: $\delta \in [1-4\ Hz)$, $\theta \in [4-8\ Hz), \alpha \in [8-12\ Hz), and\ \beta \in [12-30\ Hz)$.

For the HRV, the smoothed pseudo-Wigner-Ville distribution method (SPWVD) was employed (Orini et al., 2012). It estimates the PSD with a relatively low variance, and it has independent control of filtering in the temporal and frequency domains (Pola et al., 1996).

2.3. Quantification of functional BHI

The functional directional BHI was estimated using the synthetic data generation model (SDG) designed in Catrambone et al. (2019). In brief, the EEG series is modelled using a multiple-oscillator model (one for each considered frequency band), in which amplitudes of all oscillators are shaped using a first order exogenous autoregressive model.

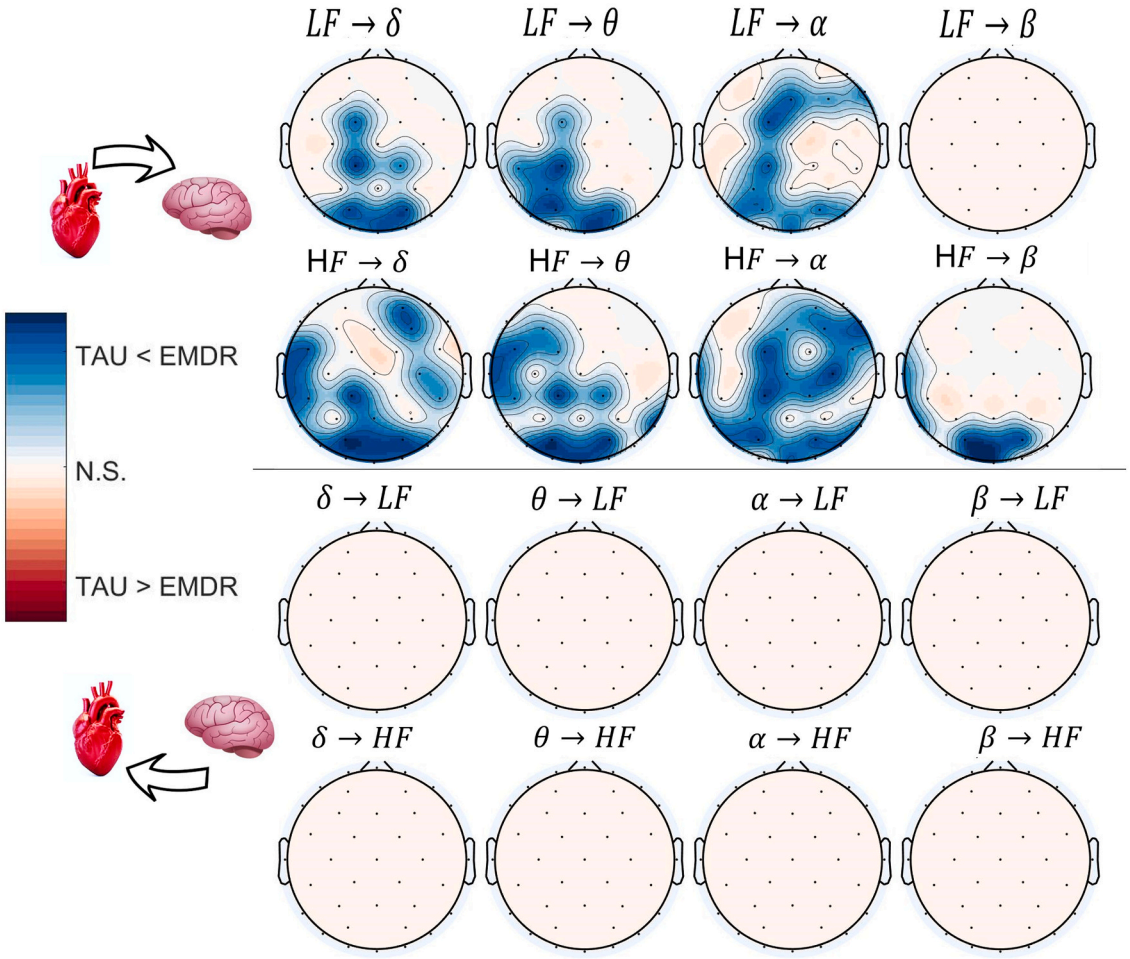

Fig. 2. *P*-value topographic maps from non-parametric Mann-Whitney tests for unpaired samples between $|BHI(T_0 - T_1)|$ during script experimental phases in TAU subjects versus those receiving EMDR. White areas indicate that changes between groups are not significant, whereas blue areas indicate that BHI changes in the EMDR group are significantly higher than those in the TAU group, and red areas indicate the opposite.
The statistical test compared the absolute difference between T0 and T1 during the script phase for the two experimental groups. Significant brain regions ($p < 0.05$, corrected through permutation test for multiple comparisons) are highlighted with respect to the green areas, which indicate no significant changes between conditions. Blue regions represent a BHI that is significantly higher in EMDR subjects with respect to the TAU group; reference regions represent the opposite. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

The exogenous term accounts for the heart-to-brain interplay and it is specific for EEG and HRV frequency bands. It quantifies the strength of the coupling from a specific HRV frequency range to a specific EEG frequency range. Conversely, the model shapes the RR series with an integral pulse frequency modulation model, in which the autonomic activity accounts for low frequency (LF) and HF oscillations separately, the amplitudes of which are modelled to be influenced by brain activity through the brain-to-heart interplay term. This term quantifies the strength of the coupling from a specific EEG frequency band to a specific HRV frequency band. According to this model, both the electrophysiological dynamics (i.e., EEG and HRV series) are mutually dependent, and their interaction is modulated by the introduced coupling terms. In summary, a positive $C_{\delta \to LF}(t_k)$ indicates that the EEG-δ band, at time t_k, leads to a linearly proportional increase (i.e., it exerts a positive influence) in the HRV-LF band PSD time course. Employing the inverse model formulation, described in detail in Catrambone et al. (2021a, 2021b, 2021c, 2019), leads to the derivation of an entire family of BHI biomarkers. Through this framework, the directional BHI indices listed in Table 1 were derived. To implement the model, an easy-to-use MATLAB (Mathworks Inc., freely available online.[2]) implementation tool was exploited. In brief, the model quantifies the functional brain-to-heart directional interplay as well as the heart-to-brain directional interplay throughout the EEG oscillations in different frequency bands (i.e., δ, θ, α and β) and the HRV power in the LF and HF bands. Following recent evidence on autonomic dynamics, HRV-LF power was considered a marker of sympathovagal activity in this study, and the HF power a marker of vagal activity (Hopf et al., 1995; Pinna and Edwards, 2020; Reyes del Paso et al., 2013). To avoid confounding factors and to focus on the effect that the EMDR treatment might evoke, we considered the difference between BHI indices extracted during the first and second treatment (T0-T1) during the script-driven imagery sessions.

2.4. Statistical analyses

Intra-subject time-varying BHI estimates were condensed using the median value extracted in a specific experimental window (e.g., T0-

[2] https://github.com/CatramboneVincenzo/Brain-Heart-Interaction-Indexes and https://it.mathworks.com/matlabcentral/fileexchange/72704-brain-heart-interaction-indexes?s_tid=srchtitle

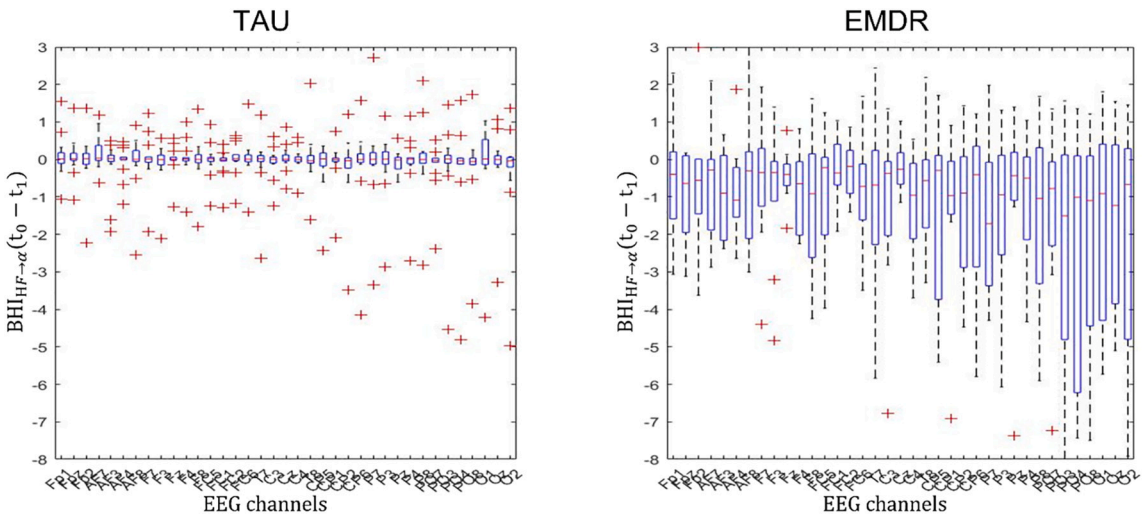

Fig. 3. Boxplots associated with the BHI index (HF → α) from the 37 EEG channels for the TAU group (left panel) and EMDR group (right panel).

script), and between-group statistical differences are shown as *p*-value topographic maps obtained from a non-parametric Mann-Whitney test for independent samples.

The group differences being statistically compared (i.e., EMDR vs TAU) involved functional BHI measurements in the following cases: i) script phase before treatment T0 (BHI_{T0}); ii) script phase after treatment T1 (BHI_{T1}); and iii) absolute difference between script phases at T1 and T0 (i.e., $|BHI_{T1} - BHI_{T0}|$). Moreover, Pearson's correlation coefficient analysis was performed to investigate whether functional BHI estimations were linearly correlated with the clinical parameters obtained through screening questionnaires (described in Carletto et al., 2019) before and after treatment (i.e., correlation between $|BHI_{HF\to\alpha}(T_0)|$ and $Q_{T0}|$). The statistical significance threshold was chosen to be $\alpha = 0.01$, and *p*-values were adjusted for multiple comparisons through permutation tests with 1000 permutations. A spatial cluster-mass permutation correction was applied to assess the physiological plausibility of the results (Friston et al., 1994): it assesses that when an electrode is found as significant it is enclosed in a larger group of significant electrodes, thus avoiding to consider spurious channels.

3. Results

No statistically significant differences were found between BHI estimations at time T0 (i.e.,$|BHI(T_0)|$) between the EMDR and TAU groups, in any scalp locations or frequency bands considered (Fig. S1 in Supplementary Material). At the post-treatment time point (T1), the EMDR group showed remission of PTSD in all treated patients, while no remission was observed in the TAU group (Fig. S2 in Supplementary Material).

The results show functional BHI changes in patients recovering from PTSD after EMDR therapy in the script phase after treatment (BHI_{T1}) with respect to the TAU group. To this end, the BHI SDG model (Catrambone et al., 2021a, 2021b, 2021c, 2019) was applied using the EEG and HRV series. The results from the statistical analysis of the SDG model output are depicted in Fig. 2. The white areas indicate that the differences between the groups are not significant, whereas the blue areas indicate that the BHI changes in the EMDR group are significantly higher than those in the TAU group. Red areas indicate that the BHI changes in the EMDR group are significantly lower than those in the TAU group. Fig. 2 reports the statistical analysis performed on the absolute value of the difference between the functional BHI indices extracted during the script-T0 phase and the BHI index extracted during the script-T1 phase (e.g., $|BHI_{HF\to\alpha}(T_0 - T_1)|$). Fig. 2 shows that almost all the combinations of heart-to-brain interactions (i.e., the first two rows) are diffusively significant, with the exception of the $BHI_{LF\to\beta}$ combination, whereas no significant differences were found in the opposite direction (i.e., brain-to-heart). More specifically, a central and dorso-parietal left region, together with a bilateral occipital one, are highlighted in the BHI indices from the sympathovagal LF band to the δ and θ EEG band, which is added a prefrontal right region in the $BHI_{LF\to\alpha}$ case. Considering the vagal HF band, a broader region, involving the posterior hemisphere and the temporal left lobe, is enhanced in the $BHI_{HF\to\delta,\theta,\alpha}$ statistics, with some peculiarity for each EEG band. In particular, a prefrontal right region is shown as statistically significant for the δ and α bands, and the latter also involves a broader central and parietal right region. A small significant group of electrodes is highlighted by the statistical analysis in the $BHI_{HF\to\beta}$ index, involving the occipital and left-temporal regions. It should also be noted that in all the aforementioned $BHI_{heart\to brain}$ significant analyses, the functional indices were higher in patients treated with EMDR than those receiving TAU.

To understand the differences between the EMDR and TAU groups better, in terms of absolute values of the differences in BHI indices

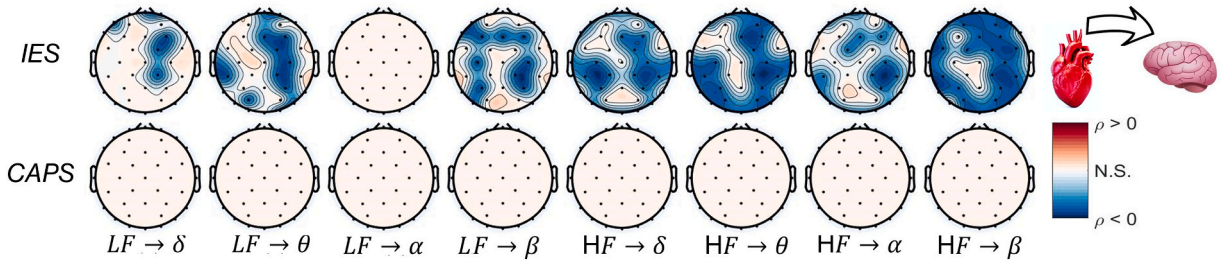

Fig. 4. Topographical representation of Pearson's correlation analysis of clinical parameters obtained using screening questionnaire results (i.e., IES-R and CAPS-5) and $BHI_{heart\to brain}$ indices at script-T1 phase in the EMDR group.

extracted before and after the treatment, Fig. 3 shows the boxplots associated with each of the 37 EEG electrodes. The TAU group shows values in a small interval, and close to zero, suggesting that the BHI indices extracted at T1 do not differ remarkably from those extracted at T0. Conversely, compared with the TAU group, the EMDR group has a more widespread distribution, with numeric values presenting a negative sign almost everywhere, thus suggesting that the BHI indices extracted at T1 are higher than those extracted at T0.

The results of the correlation analysis are shown in Fig. 4, and in the Supplementary Materials in Figs. S3, S4 and S5. To ensure statistical power robustness, we limited the correlation analysis to screening the questionnaires and BHI indices which resulted as being significantly affected by EMDR treatment. In particular, the IES-R (Weiss and Marmar, 1997) and the CAPS-5 clinical questionnaires and BHI indices in the heart-to-brain direction were explored. Fig. 4 depicts diffuse significant linear correlation in the EMDR-T1 phase, involving IES-R responses and all the EEG frequency bands and HRV bands (with the exception of the $BHI_{LF\rightarrow\alpha}$ indices). The highlighted scalp region spread from a centro-parietal right region for the $BHI_{LF\rightarrow\delta}$ to an almost ubiquitous significant correlation employing the $BHI_{HF\rightarrow\beta}$ indices. No significant correlation was detected for the CAPS-5 singular subscale scores. Notably, no significant correlation was detected in the T0 phase in either group; the associated results are reported in the Supplementary Material, in Figs. S3, S4 and S5.

4. Discussion

This study represents a pioneering attempt to evaluate the functional BHI in individuals with PTSD, along with the subsequent improvements observed following TF intervention when compared to TAU. Statistically significant higher coupling, in the heart-to-brain direction, was found in patients treated with TF psychotherapy (EMDR) compared with controls (TAU). Such a higher coupling occurred considering both the HRV-LF and -HF bands, at the heartbeat level, and different frequency bands at the central level, being the central axis between the hemispheres, from the midline frontal to occipital cortex, the most activated. Thus, it is plausible that the heart-to-brain interplay and communication empowerment is associated with the resolution of PTSD symptoms. This phenomenon, at this level, appeared to be quite generalised and not frequency specific.

The results of this study are consistent with the linear correlations observed in the clinical data of our previous study (Carletto et al., 2019), which show an improvement in PTSD symptoms accompanied by an increase in functional BHI after EMDR treatment. Comparing the two studies further, these findings are also coherent with the EEG results which highlighted the significant differences in delta and theta bands in the left angular and right fusiform gyri only in the group treated with EMDR, implying better communication between different brain regions (Carletto et al., 2019). Moreover, our findings appear to be in line with improved bottom-up and top-down regulation in response to successful treatment as highlighted in a systematic review on the neurobiological correlates of the psychotherapeutic treatment of PTSD (Malejko et al., 2017). Furthermore, our findings highlight the importance of bottom-up processes in TF psychotherapies.

Recent studies found that psychiatric, neurological and developmental disorders involving emotional dysregulation show altered interoceptive processing (Bonaz et al., 2021; Khalsa and Lapidus, 2016). The interoceptive system is a large collection of neural structures that cooperate to produce a real-time map of the body's homeostatic state (Carvalho and Damasio, 2021). Interoception entails signals moving from the non-neural interior of the organism to its neural central core – a bottom-up process – as well as broad reactions and control from the CNS to the periphery (Chen et al., 2021). This latter top-down component is assumed to incorporate cortically produced interoceptive predictions based on past experience (Carvalho and Damasio, 2021; Chen et al., 2021; Khalsa and Lapidus, 2016; Petzschner et al., 2021). According to Carvalho and Damasio (2021) "the interoceptive system monitors the state of the body and orchestrates automatic responses thereto". The results of the present study show that interoception increases after EMDR, whereas interoception in the TAU group seems to be reduced, probably because of the activation of traumatic processes. In the TF psychotherapy group, the consequence is a decrease in the automatic and undifferentiated responses typical of PTSD, with an increase in the flow of bottom-up information and a recovery of the ability to discriminate the danger level of incoming stimuli.

Previously, Thome et al. (2017) described that, compared with healthy subjects, patients with PTSD show an uncoupling between ANS and CAN with a non-functional top-down regulation of autonomic responses. Thanks to the opportunity offered by the innovative BHI methodology, it is possible to assess CAN internal functioning. In their study of healthy subjects, Candia-Rivera et al. (2021) found that emotional processing is sustained by a bidirectional BHI. In particular, these authors hypothesise that emotional activation originates from the ascending flow of information starting in the ANS and integrates with the CNS (heart-to-brain), which triggers a cascade of neural activations that modulate central control over the periphery (brain-to-heart). Our results show that the flow of information in the direction from the ANS to the CNS appears to be restored following recovery from PTSD after TF psychotherapy (EMDR). It is possible to speculate that the reopening of the bottom-up communication flow (heart-to-brain) has cascading effects on emotional regulation mechanisms modulated by top-down processes (brain-to-heart), restoring the coupling between ANS and CAN found to be dysfunctional in PTSD patients in Thome et al. study (Thome et al., 2017), and thus associated with PTSD recovery.

The application of BHI could bring new life to studies on the neurobiology of psychological disorders as it offers a novel way of interpreting the data arising from existing assessment techniques (such as EEG, HRV, etc.), thereby providing additional information related to the communication flow (i.e., the exchange and integration of information) underlying emotional regulation (Candia-Rivera et al., 2022). BHI analysis offers the opportunity to delve into the mechanisms underlying psychological disorders by adopting a relational perspective between systems that will make it possible to identify markers linked to different mental disorders, which may favour earlier and more precise diagnoses in the future. BHI could facilitate the identification of treatment outcome markers, with the possibility of comparing different interventions, studying their effectiveness and investigating their mechanisms of action. Moreover, this methodology emphasises the important role of the ANS, supporting the idea of a visceral origin of the emotions (Candia-Rivera et al., 2022).

Due to its preliminary nature, this study has several limitations. First of all, the number of patients involved was low, and no control group, involving healthy subjects without PTSD, was employed. Another limitation is represented by the lack of a specific assessment of dissociative symptoms. Future studies should consider evaluating possible differences in the BHI between patients with PTSD and patients with the dissociative subtype (Nicholson et al., 2017) and include a follow-up investigation of the functional BHI to observe its correlation with how clinical changes are maintained or modified over time. Finally, the BHI methodology would also benefit from including an investigation of the role of the enteric system, which would expand our knowledge of the microbiota-gut-brain axis in different psychiatric disorders (Leclercq et al., 2016; Socała et al., 2021).

In conclusion, functional BHI analysis provides a novel approach to the study of PTSD, for identifying biomarkers of the disorder and for understanding the changes produced through TF psychotherapy. The results suggest that TF psychotherapy (EMDR) may favour a restoring of the bottom-up flow of interoceptive information that is dysfunctional in PTSD patients.

Statement of ethics

The authors assert that the study was approved by the local Research Ethics Committee (University Hospital "Città della Salute e della Scienza" of Turin, Italy) and that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. Written informed consent was obtained from participants to participate in the study.

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This research received a grant from EMDR International Association.

CRediT authorship contribution statement

F. Malandrone: Investigation, Data curation, Writing – original draft. **V. Catrambone:** Formal analysis, Data curation, Writing – original draft. **S. Carletto:** Investigation, Writing – review & editing, Supervision. **P.G. Rossini:** Data curation. **M. Coletti Moja:** Investigation. **F. Oliva:** Validation. **M. Pagani:** Methodology, Resources, Project administration. **G. Valenza:** Conceptualization, Writing – review & editing, Supervision. **L. Ostacoli:** Conceptualization, Writing – review & editing, Supervision, Project administration.

Declaration of competing interest

LO, SC and MP have been invited speakers at EMDR conferences. The other authors declare no potential conflicts of interest.

Data availability statement

Data are available at https://github.com/CatramboneVincenzo/Brain-Heart-Interaction-Indexes and https://it.mathworks.com/matlabcentral/fileexchange/72704-brain-heart-interaction-indexes?s_tid=srchtitle.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2024.01.172.

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Review Article

The Neural Signature of Psychological Interventions in Persons With Cancer: A Scoping Review

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Pierre Gilbert Rossini, MSc[1], Luca Ostacoli, MD[1,2], Marco Pagani, MD, PhD[3], Francesca Malandrone, PsyD[1], Francesco Oliva, MD[1], Luca Cominu, MSc[2], Maria Chiara Annetta, MSc[2], and Sara Carletto, PhD[4]

Abstract

Objective: People diagnosed with cancer have to deal with the debilitating psychological implications of this disease. Although the clinical efficacy of psychological interventions is well documented, relatively little has been written on the neural correlates of these treatments in the context of oncology. The present work is the first to provide an overall perspective of the existing literature on this topic. It also considers the potential directions for future research. **Methods:** This scoping review was carried out across 5 databases (EMBASE, PsycINFO, OVID MEDLINE, CINAHL, COCHRANE CENTRAL), from conception dates until 3 December 2021. **Results:** From an initial set of 4172 records, 13 papers were selected for this review. They consisted of 9 randomized controlled studies (RCTs), 1 quasi-experiment, 2 single case studies, and 1 secondary quantitative analysis. The studies were also heterogeneous in terms of the patient and control populations, psychological interventions, and neuroimaging methodologies used. The findings from these few studies suggest that psychological interventions in oncology patients may modulate both cortical and subcortical brain activity, consistent with the brain areas involved in distress reactions in general and to cancer specifically. The implications of this scoping review in terms of future research are also discussed. **Conclusions:** The literature on the neural correlates of psychological interventions in cancer patients is very limited, and thus requires further exploration. The provision of psychological interventions offers cancer patients a more integrated approach to care, which may in turn help preserve both the physical and the psychological wellbeing of individuals with cancer.

Keywords

cancer, neural correlates, neural signature, neuroimaging, oncology, psycho-oncology, psychological interventions, scoping review

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Background

As stated by the World Health Organization,[1] the global cancer burden is increasing with major personal and social consequences. Treatment of the physical aspects of cancer generally takes center stage in the care of cancer patients; however, accumulating evidence is also starting to recognize the importance of considering the psychological implications of oncological disease. Between 30% and 45% of cancer patients experience high levels of health-related emotional distress,[2] as well as several physical and psychological issues that severely affect their quality of life. According to a recent review of epidemiological studies concerning psychiatric disorders in cancer patients, depression, anxiety, trauma or stress-related, somatic, neurocognitive disorders, and other subthreshold symptoms (such as an irritable mood, demoralization, or a sense of hopelessness) are the most common psychiatric conditions affecting cancer patients.[3] In particular, major depressive disorders and minor depressive episodes are very common in cancer

[1]Department of Clinical and Biological Sciences, University of Turin, Turin, Italy
[2]Clinical Psychology Unit, University Hospital "Città della Salute e della Scienza", Turin, Italy
[3]Institute of Cognitive Sciences and Technologies – CNR, Rome, Italy
[4]Department of Neuroscience "Rita Levi Montalcini", University of Turin, Turin, Italy

Corresponding Author:
Francesca Malandrone, Department of Clinical and Biological Sciences, University of Torino, Regione Gonzole, 10, 10043, Orbassano, Torino 10124, Italy.
Email: francesca.malandrone@unito.it

patients, mainly related to pain and fatigue. Furthermore, phobias related to chemotherapy anticipatory nausea and vomiting are the most widespread anxiety issues, together with stress-related post-traumatic stress disorder (PTSD) sub-syndromic symptoms, which are estimated to affect 15% of cancer patients. Finally, the disease or its treatment (ie, chemotherapy) often impact several neurocognitive domains, including memory, attention, concentration, learning functions, calculation, and visual-spatial perception.[3] The concurrence of stress-related symptoms and disorders has been found to have a significant impact on a patients' quality of life, and, as a consequence, on their global health outcomes.[4] Psychological distress in cancer patients can be reduced using psychosocial interventions,[5] although little has been written about the neurobiological mechanisms (such as brain networks, regions, or circuits involved) underpinning the clinical enhancements. One recent review, in addition to presenting the evidence on the effects of psychological interventions on clinical outcomes in cancer patients, reported on neuroimaging studies which correlate the negative psychological effects of cancer with major changes in brain activity.[2] Concerning the first point, the authors report on a number of stress management interventions (such as cognitive-behavioral approaches) which may reduce anxiety and depression, and in turn improve both quality of life and disease outcomes. Regarding the second point, they found that the distress states (mainly anxiety, depression, and PTSD) may be related to structural and functional alterations in the brain regions usually involved in emotional regulation, such as the amygdala (Amy), anterior cingulate cortex (ACC), hippocampus (Hy), hypothalamus (Hip), insula (Ins), prefrontal cortex (PFC), and thalamus (Th). It is noteworthy that neuroimaging studies have also indicated many of these areas (ie, ACC, PFC, Hy, and Amy) as being affected by psychotherapeutic interventions in depressed and PTSD patients.[6,7] This is consistent with the idea that emotional dysregulation and abnormal brain activity, mainly within the cortico-limbic networks, are directly associated.[8] Investigations into the neural substrate of clinically observed changes may shine some light on the biological processes underpinning psychosocial interventions. The insights obtained may, in turn, help direct the further development of such interventions, and even establish why some patients respond to treatments better than others, as in the case of Cognitive Behavioral Therapy (CBT[8,9]) and Neurofeedback.[10] This is particularly relevant in the setting of cancer therapy, where acute and chronic stress can impact the onset of the disease as well as its progression.[11-13]

Thus, based on the findings of Reis and colleagues',[2] who provide the neural description of psychological suffering within cancer patients, our work is a major stepping stone in the field which will ground the basis for future research. We propose that greater knowledge of the brain regions or circuits targeted by psychosocial interventions will be fundamental in paving the way to more targeted and effective treatments. For instance, describing the neural changes before and after a psychological treatment may overcome the intrinsic subjectivity of self-report measures and behavioral measures of psychopathology,[14] and this may help identify the specific factors of distinct interventions (eg, target brain area, duration of treatment, etc.) key to determining their clinical efficacy. Such evidence would undoubtedly support and promote the wider application of an integrated and comprehensive approach to cancer care as advocated by clinicians and researchers in the field of psycho-oncology.[4]

The primary aim of this scoping review was to evaluate and summarize the available literature on the neural correlates of psychological interventions in the adult cancer population. Moreover, it aims to provide evidence on whether these structural and functional changes actually correlate with psychological outcome, as assessed using standardized and validated questionnaires.

Methods

Given that little has been written on the neurobiological correlates of psychological interventions in cancer patients, we adopted the scoping approach. This approach is designed to inform about the available evidence in a given field, the ways in which research has been conducted on a specific topic, and about the primary gaps in the current knowledge.[15] The scoping review framework set out by Arksey and O'Malley,[16] and formally reviewed by the Joanna Briggs Institute (JBI),[17] was used to guide the process. The 5 stages of the framework were: (i) identifying the research question(s); (ii) identifying the relevant studies; (iii) selecting the studies; (iv) extracting the data; (v) summarizing and discussing results. As suggested in the scoping framework of Sucharew and Macaluso,[18] a risk of bias appraisal regarding studies included is also provided.

Identifying relevant studies

A comprehensive research strategy was adopted in order to retrieve both published and unpublished studies. Electronic searches were performed on July 27, 2020, on 5 bibliographic databases (EMBASE, PsycINFO, OVID MEDLINE, CINAHL, COCHRANE CENTRAL) to identify potentially eligible studies. The search was updated on 3 December 2021, to identify and incorporate and further publications (see Supplemental Material). No restrictions were applied on language, gender, age, or publication date. The inclusion criteria are specified in Table 1. We targeted all forms of psychological intervention, including all forms of psychological, psychotherapeutic, or psychosocial intervention. Consistent with the inclusion criteria, we searched

Table 1. Study Inclusion and Exclusion Criteria.

	Inclusion	Exclusion
Design	Randomized and non-randomized controlled studies, case study/report, observational, case series, quasi-experiment, pre–post tests	Systematic reviews, trial protocols
Publication type	Peer-reviewed articles published in any language with available full text, conference proceedings, published abstracts, posters	
Participants	Adults aged ≥18, any cancer diagnosis and treatment phase	Participants <18, any other diagnosis
Interventions	Any psychological intervention	Any other type of intervention
Outcome	Any neurobiological technique	Any other technique

the oncology population as a whole. We confined our retrieval to a specific outcome, defined as any neuroimaging technique able to outline the neural correlates of the intervention's effects.

Study Selection and Appraisal

Once all duplicates had been removed, the remaining titles were screened and studies with no clear relevance to the research topic were removed by 2 independent reviewers (PGR, LC), using a conservative approach as described by Higgins and colleagues.[19] The inclusion and exclusion criteria (Table 1) were then applied to the remaining abstracts in order to identify the eligible studies, for which the full-text papers were subsequently retrieved. If the full text was not available, the first or correspondence author was contacted. If no agreement could be reached regarding the inclusion of a study, even after full-text consultation, a third review author (FM) was involved to resolve the disagreement.

Two independents reviewers (PGR, FM) assessed the quality of the randomized controlled trials (RCTs) using the Cochrane RoB 2 Tool,[20] which can estimate the methodological weaknesses (risk of bias) on 5 specific domains: the randomization process (D1), the deviation from the intended intervention (D2), the missing outcomes data (D3), the measurement of the outcomes (D4), and the selection of reported results (D5) (Figure 2). An overall judgment of each RCT was thus obtained.

The quality of the quasi-experimental study was assessed using the Cochrane ROBINS I Tool,[21] which can estimate the methodological weaknesses (risk of bias) on 7 specific domains: the confounding variables (D1), the selection of participants in the study (D2), the classification of interventions (D3), deviation from the intended interventions (D4), the missing outcomes data (D5), the measurements of outcomes (D6), and the selection of the reported results (D7) (Figure 2). An overall judgment of the quasi-experimental study was thus obtained.

The quality of case report studies was assessed using the only tool available: the JBI checklist for case reports,[22] which provides a quality assessment based on the patient's demographic and history, the description of the current clinical condition, the treatment procedure explanation, the post-intervention outcomes reporting, the adverse events indication, and the presence of any takeaway lessons. An overall judgment of each case report regarding their inclusion or exclusion was thus obtained.

Data Extraction

After carefully reading the full-text versions of each study included in the scoping review, 2 reviewers (PGR, MCA) independently extracted the following data:

- Population: geographical location, sample size, and cancer type.
- Intervention/comparator: a short description of the psychological interventions and the control/comparator procedure used.
- Outcomes: the neuroimaging technique used to obtain the primary outcome; the name of the psychological distress assessment instruments used to obtain secondary clinical outcomes.
- Study design: a short description of the data collection procedures used.

Data were aggregated to answer the following scoping questions:

1. What are the most recurrent study designs?
2. What are the most recurrent oncological populations?
3. What are the most applied psychological interventions and comparators?
4. Which neuroimaging techniques are implemented the most to quantify the intervention outcomes?
5. What are the main intervention effects on neural outcome and clinical outcome, respectively?
6. Was it possible to correlate the neural and the clinical outcomes?

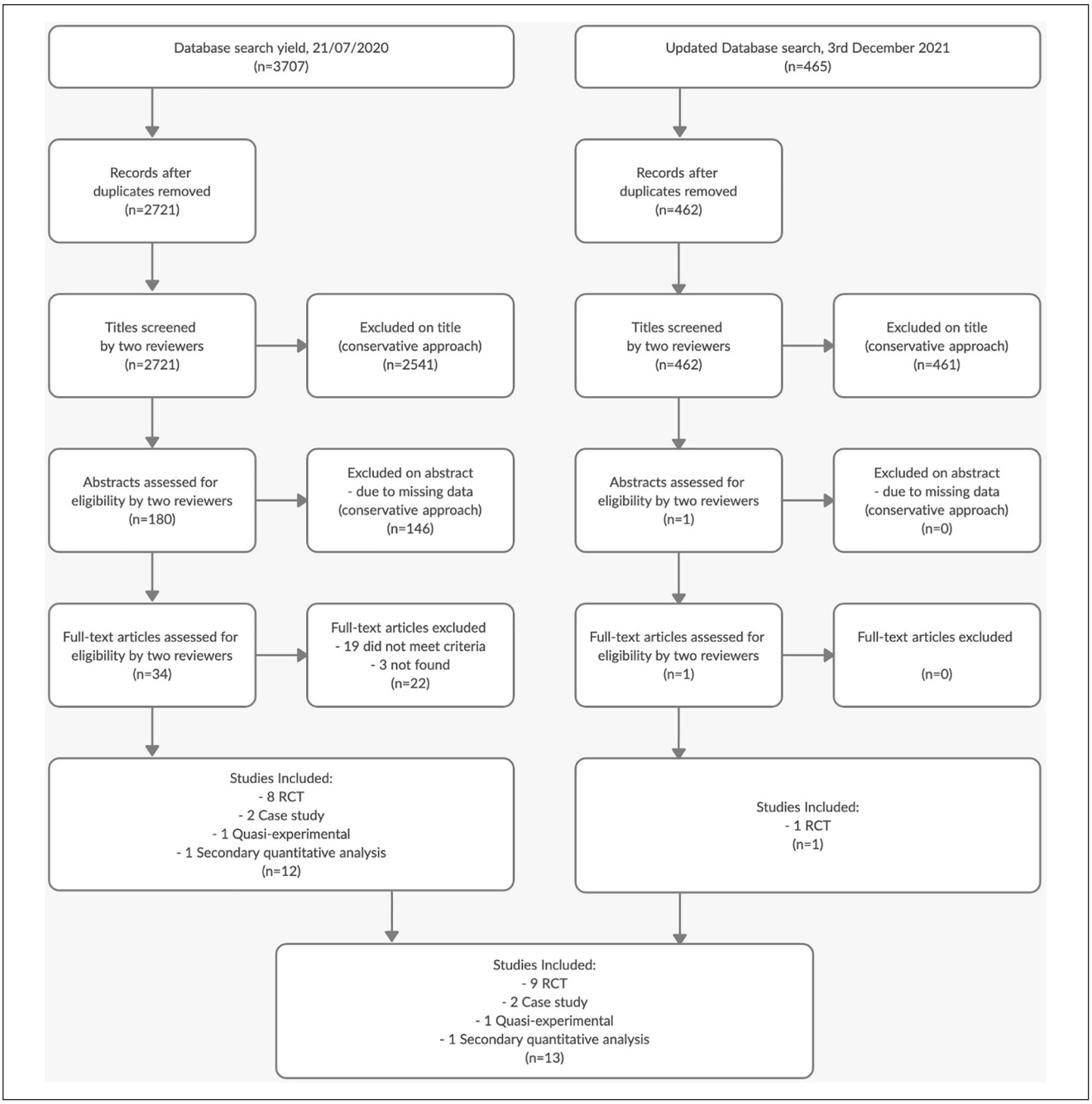
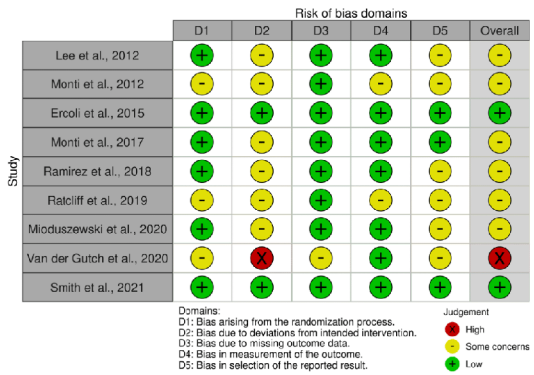


Figure 1. PRISMA flow chart of the studies selection process.

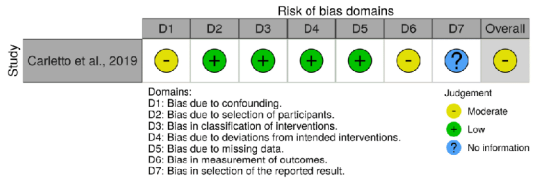
Results

Overview of the Included Articles

The study selection process is outlined in Figure 1 as a PRISMA flow diagram.[23] Thirteen manuscripts were considered eligible for inclusion in this review, and their characteristics are summarized in Table 2. All 13 records are articles published in journals and written in English. All studies were carried out in either North America or Europe. The oldest publication dated back to 2012, whereas the latest were published in 2021. The intervention groups of these studies amounted to a total of 182 patients, whereas the active control/waiting list group comprised 163 individuals. Neural data was obtained from a total of 148 patients, compared with 143 in the control/waiting group. Out of the 13 studies, 9 were randomized controlled trials, 1 was a quasi-experiment, 2 were single-case studies, and 1 constituted a quantitative secondary analysis of



RoB 2



ROBINS 1

	Gawrysiak et al. 2012	Gawrysiak et al. 2013
Were patient's demographic characteristics clearly described?	Yes	Yes
Was the patient's history clearly described and presented as a timeline?	No	No
Was the current clinical condition of the patient on presentation clearly described?	Yes	Yes
Were diagnostic tests or assessment methods and the results clearly described?	Yes	Yes
Was the intervention(s) or treatment procedure(s) clearly described?	Yes	Yes
Was the post-intervention clinical condition clearly described?	Yes	Yes
Were adverse events (harms) or unanticipated events identified and described?	No	No
Does the case report provide takeaway lessons?	Yes	Yes
Overall appraisal:	Included	Included

JBI Checklist

Figure 2. Risk of bias assessment resume. The left-sided traffic light plots (ROB 2, ROBINS 1) provide an overview of the RCTs and quasi-experimental methodological quality, the right-sided table informs on the quality of single case studies.

previously published data. In all studies, the neural and the clinical results for those in the experimental group are post-intervention compared to baseline. For studies with control conditions, there were no significant neural changes at post-study compared to baseline, with 1 exception.[24]

RCT Studies

Lee and colleagues[24] carried out an RCT to describe the relaxation effect of 30 minutes of monochord sounds (MC) on the power spectral density of the electroencephalography (EEG) signal and anxiety in gynecologic cancer patients during chemotherapy compared with a well-established relaxation technique (Progressive Muscular Relaxation [PMR]). The authors found increased posterior θ power and decreased midfrontal β2 power in response to the sound. However, the same effect was found in the control group treated with PMR. Both groups showed a reduction in anxiety level and an improved psychological state. A decrease in α power was observed in the MC intervention group only. No correlations or associations between neural and clinical outcomes were reported.

Monti and colleagues[25] evaluated changes in functional brain activation, using functional magnetic resonance imaging (fMRI), and anxiety scores following an 8-week mindfulness-based art therapy (MBAT) intervention in patients with breast cancer. Results were compared with those obtained in an educational control group, provided with support and resources to maximize QoL. The MBAT technique entails expressive art tasks and aims to enable self-expression and regulation. Changes in brain activation were assessed when the patients were in 5 different states: at rest (initial and final; no task demanded), during meditation (body scan, similar to those learnt during MBAT training), during a neutral task (passive listening), and during a stressful task (ie, counting backwards from 1000 for 7 minutes). The authors reported higher CBF (cerebral blood flow) signals in the left insula cortex, right amygdala, right hippocampus, and bilateral caudate nucleus during the initial rest period and during meditation compared to baseline (ie, brain activity pre MBAT intervention) in the experimental group. Furthermore, in the experimental group, the CBF signals detected during the final rest period and during the stressful task showed a tendency to be lower, although statistical significance was not achieved. Furthermore, a significantly lower CBF signal was found over the posterior cingulate in response to the stressful task, with a subsequent reduction in reactivity. Finally, the higher CBF signal detected during the initial rest period was correlated ($r = .90$; $P < .002$) with lower anxiety levels in the MBAT group. These results were not found in the educational control group.

Ercoli and colleagues[26] evaluated the effects of 5 weeks of cognitive rehabilitation (CR) for attention, executive,

Table 2. General Characteristics of the Included Studies.

Authors	Study design	Population	Intervention (n) vs comparator (n)§	Length of interventions	Neural outcome	Clinical outcome	Main results	Neural and clinical outcome correlations
Lee et al.[24]	RCT	Gynecologic cancer undergoing the first chemotherapy	MC (18); (16) vs PMR (19); (14)	MC: 34 min PMR: 34 min	EEG: PSD	STAI-G, FB_1	MC and PMR: < anxiety and improved psychological states during chemotherapy + > posterior θ, < midfrontal β2 band MC: <α band posterior activity compared with PMR	Not reported
Monti et al.[25]	RCT	Patients with breast cancer	MBAT (8) vs EC (10)	MBAT: 8-wk program	fMRI: CBF (rest, meditation, stress task)	SCL-90 (anxiety sub-scale)	MBAT: < anxiety + > CBF in left insula, right amygdala, right hippocampus, bilateral caudate during rest and meditation Stress task: < posterior cingulate	MBAT: * > CBF left caudate and < anxiety score during rest condition
Ercoli et al.[26]	RCT	Breast cancer survivors + cognitive complaints	CR (29); (20) vs WL (16); (9)	CR: 5-wk, 2 h per wk	qEEG: PSD	PAOFI, BDI-II, cognitive $batteries_3$	CR: > PAOFI, RAVLT scores + <δ global power > frontal distribution of α power	Not reported
Monti et al.[27]	RCT	Cancer patients + PTSD symptoms	NET (11) vs WL (12)	NET: 3 to 5 × 1-h sessions for ~1 mo	fMRI: BOLD (neutral, stress condition)	STAI, PTCI, BSI-18, IES	NET: < distress, anxiety and traumatic stress + < BOLD in right parahippocampus, brainstem, right anterior cingulate, left insula during stress condition (< reactivity)	Not reported
Monti et al.[28]	RCT (secondary quantitative analysis of Monti et al.[27])	Cancer patients + PTSD symptoms	NET (11) vs WL (12)	NET: 3 to 5 × 1-h sessions for ~1 mo	fMRI: FC + HR (stress condition)	STAI, PTCI, BSI-18, IES	NET: > functional connectivity between cerebellum and amygdala, parahippocampus, brainstem, < HR in response to distressing memories	NET: * < HR and < IES values

(continued)

Table 2. (continued)

Authors	Study design	Population	Intervention (n) vs comparator (n)§	Length of interventions	Neural outcome	Clinical outcome	Main results	Neural and clinical outcome correlations
Ramirez et al.[29]	RCT	Terminally ill patients	MT (20) vs CG (20)	MT: 1 session ~30 min	EEG: PSD	ESAS	MT: < anxiety, tiredness, breathing difficultness, > well-being + > valence and $arousal_4$	Not reported
Ratcliff et al.[30]	RCT	Women undergoing SBB (partly breast cancer)	GM (30); (8) vs FB_2 (30); (13) vs SC (16); (5)	GM: ~35 min FB_2: ~35 min	EEG: CSD	STAI, BPI, VAS	GM: >β activity during biopsy insula and ACC+ steeper reduction in anxiety during the biopsy compared with control groups (group × time effect on VAS anxiety ratings). FB_2: similar trend to GM with >β during biopsy in insula and ACC GM, FB_2: non-significant δ decrease precuneus	* <δ precuneus and < VAS anxiety (not associated with groups)
Mioduszewski et al.[31]	RCT	Breast cancer survivors + CNP	MBSR (13) vs WL (10)	MBSR: 1-2.5-h sessions for 8 wk + 1 full day session during the fifth week	MRI: DTI-FA	BPI, FFMQ	MBSR: < pain severity and interference + > FA left uncinatum and fronto-occipital fasciculi, left amygdala, left hippocampus, left external capsule, left sagittal striatum	MBSR: * > FA values and < BPI scores
Van der Gucht et al.[33]	RCT	Breast cancer survivors + cognitive impairment	MBI (12) vs WL (13)	MBI: 4 × 3-h sessions over 8 wk	fMRI: FC	DASS, CIS (fatigue subscale), CIM, CFQ	MBI: < cognitive impairments on subjective measures, emotional distress, fatigue + > connectivity between IPS and ACC networks	MBI: * > connectivity ACC-lIPS and < emotional distress

(continued)

Table 2. (continued)

Authors	Study design	Population	Intervention (n) vs comparator (n)§	Length of interventions	Neural outcome	Clinical outcome	Main results	Neural and clinical outcome correlations
Smith et al.[32]	RCT	Breast cancer survivors + CNP	MBSR (13) vs WL (10)	MBSR: 1 × 2.5-h sessions for 8 wk + 1 full day session at the end	fMRI: FC	BPI, FFMQ	MBSR: < pain severity and interference + > FC PCC and ACC/medial PFC (FC1) + < FC PCC and bilateral precentral gyrus, right superior frontal gyrus and pons (FC2)	MBSR: * > FC1 and < Ps scores + * < FC2 and < Ps scores
Gawrysiak et al.[34]	Case report	Patient with breast cancer and depression	BATD (1)	BATD: 8 × 1-h sessions	fMRI: BOLD response (neutral, preferred music; music, silence)	BDI II, HRSD, EROS, BIS, BAS	BATD: < depression + preferred music, music > BOLD rdlPFC, rmoPFC, neutral music > BOLD subgenual cingulate cortex	Not reported
Gawrysiak et al.[35]	Case report	Patient with breast cancer and depression	PPP (1)	PPP: 8 × 1-h sessions over 13 wk	fMRI: BOLD response (neutral, preferred music)	BDI II, BAI, MSPSS, HRSD, EROS	PPP: < depression + preferred music > BOLD vmPFC and loPFC	Not reported
Carletto et al.[36]	Quasi Exp	Patients with breast cancer + PTSD	EMDR (14) vs TAU (15)	EMDR: 10 sessions over 2 to 3 mo	EEG: PSD	IES-R, SCID-5, CAPS-5, STAI-Y, BDI-II	EMDR: < depressive symptoms + > δ and θ power, left angular and right fusiform gyri	EMDR: * < clinical symptoms and > δ, θ bands

Abbreviations: <: decrease; >: increase; *: correlation; §: when multiple sample size numbers are provided, the first indicates the total number of participants, while the second refers to the number of participants with analyzable neural outcome data; ACC: anterior cingulate cortex; $Arousal_4$: ratio of β on α power over the prefrontal cortex; BADT: behavioral activation treatment for depression; BAI: beck anxiety inventory; BAS: behavioral activation scale; BDI II: beck depression inventory-II; BIS: behavioral inhibition scale; BOLD: blood oxygenation level dependence; BPI: brief pain inventory; BSI-18: brief symptom inventory; CAPS-5: clinician-administered PTSD scale; CBF: cerebral blood flow; CFQ: cognitive failure questionnaire; CG: control group; CIM: comprehensive inventory of mindfulness experiences; CIS: checklist individual strength; CNP: chronic neuropathic pain; $cognitive\ batteries_3$: (brief visual memory test-revised) − (verbal fluency tests) − (paced auditory serial addition test) − (trail making tests) − (computerized CNS vital signs) − (WTAR: Wechsler test of adult reading); CR: cognitive rehabilitation; CSD: current source density; DASS: depression anxiety stress scales; DTI: diffusion tensor imaging; EC: educational control group; EEG: electroencephalography; EMDR: eye movement desensitization and reprocessing therapy; EROS: environmental reward observation scale; ESAS: Edmonton symptom assessment system; FA: fractional anisotropy; FB_1: questionnaire about physical and psychological states and perception of the relaxation treatments; FB_2: focused breathing; FC: functional connectivity; FFMQ: five facet mindfulness questionnaire; fMRI: functional magnetic resonance imaging; GM: mindfulness-based meditation; HR: heart rate; HRSD: Hamilton rating scale for depression; IES: impact of event scale; IES-R: impact of event scale-revised; IPS: intraparietal sulcus; lIPS: left intraparietal sulcus; loPFC: left orbital prefrontal cortex; MBAT: mindfulness-based art therapy; MBI: mindfulness-based intervention; MBSR: mindfulness-based stress reduction; MC: monochord (sounds); MR: magnetic resonance; MSPSS: multidimensional scale of perceived social support; MT: music therapy; NET: neuro emotional technique; Ps: pain severity; Pi: pain interference; PAOFI: patient's assessment of own functioning inventory; PCC: posterior cingulate cortex; PFC: prefrontal cortex; PMR: progressive muscle relaxation; PPP: pragmatic psychodynamic psychotherapy; PSD: power spectral density; PTCI: post-traumatic cognitions inventory; PTSD: post-traumatic stress disorder; qEEG: quantitative electroencephalography; RAVLT: Rey auditory verbal learning test; RCT: randomized controlled trial; rdlPFC: dorsolateral prefrontal cortex (right-side); rmoPFC: medial orbital prefrontal cortex (right-side); rs: resting-state; SBB: stereotactic breast biopsy; SC: standard care; SCID-5: structured clinical interview for DSM-5; SCL-90: symptoms checklist-90-revised; STAI: state trait anxiety index; STAI-G: German version of the state anxiety inventory; STAI-Y: state-trait anxiety inventory Y; TAU: treatment as usual; $Valence_4$: computed as the difference between the right and left frontal α power, that is αF4–αF3; VAS: visual analogue scales; vmPFC: ventral medial prefrontal cortex; WL: waiting list.

and memory functions on cognitive complaints and EEG signals in breast cancer survivors. The authors reported improved subjective measures of cognitive complaints and objective cognitive performance indexes. Furthermore, these improvements were accompanied by overall decrease in δ "slow-wave" power and an increase frontal distribution of α power with respect to baseline in the experimental group, which were not observed in the waiting list group (WL). These changes in α power were significantly associated with reduction in cognitive complaints as assessed 2 months after the rehabilitation program. Notably, the benefits of the interventions lasted up to 2 months.

Monti and colleagues[27] performed an RCT to evaluate the effect of a 1-hour Neuro Emotional Technique (NET) on functional brain activity, using fMRI, and traumatic stress symptoms in cancer patients (various diagnoses) with symptoms of PTSD, related to distressing memories (ie, the diagnosis itself, painful medical procedures, etc.). Importantly, since a full PTSD diagnosis occurs in just 3% to 10% of cancer cases, only patients with subsyndromal PTSD cancer-related symptoms were included in the study. NET is a form of complementary and alternative medicine (CAM). Its aim is to regulate the hyperactivation of the autonomic nervous system, reducing the impact of traumatic stress-related symptoms. To assess the effects of NET on traumatic stress responses, neutral and traumatic auditory stimuli (self-generated scripts related to the individual's morning routine and to a distressing cancer-related event, respectively) were delivered to patients while fMRI assessments were performed. Patients who had undergone the NET intervention showed a decrease BOLD signal in the right parahippocampus, brainstem, right anterior cingulate gyrus, and left insula during the stress condition (ie, less reactivity to the distressing stimuli) compared to baseline together with a reduction in the clinical level of distress, anxiety, and traumatic stress. These results were not found in the waiting list control group. The reduction in neurophysiological reactivity was not significantly associated with clinical improvement. Moreover, secondary functional connectivity and autonomic reactivity (heart rate [HR]) analyses were performed in the same sample[28] in order to outline the neural correlates of the NET intervention better. The analysis revealed greater functional connectivity between the cerebellum and the amygdala and the parahippocampus and the brain stem in response to NET, together with a smaller rise in HR in response to distressing stimuli. This last decrease was correlated ($r = .45$; $P = .047$) with a smaller impact of the trauma.

Ramirez and colleagues[29] carried out an RCT to investigate the effect of 30 minutes of both active and receptive music therapy (MT) on the brain oscillatory activity (as assessed via EEG) and the emotional states (anxiety, anger, depression, stress) in terminally ill cancer patients. MT relies on the therapeutic effects of listening to sound on emotional, attentional, and cognitive regulation. The results reported an increased arousal state together with a more positive emotional valence in response to listening to music. MT was also found to decrease anxiety, tiredness, and the level of breathing difficulty and to increase well-being. These effects were not observed in the control group provided with company. No correlations or associations between neural and clinical outcomes were reported.

Using EEG current source density (CSD) analysis, Ratcliff and colleagues[30] compared the effect of 35 minutes of mindfulness-based guided meditation (GM), which entails an increase of self-awareness and regulation, with the effects of guided focused breathing (FB) and standard care (SC) control groups on cortical brain rhythms and levels of anxiety and pain in women scheduled for stereotactic breast biopsy (SBB). The results show greater values of β band power in the Ins (Cohen's $d = 1.4$) and the ACC ($d = 1.0$) in the GM group compared with subjects in the SC group, together with lower anxiety levels. Notably, the authors report a group × time effect/interaction for visual analogue scale (VAS) anxiety ratings during the biopsy procedure compared with the control groups. The active control group (FB_2) showed an increase in β band power in the Ins ($d = 1.6$) and the ACC ($d = 0.70$) similar to that observed in the GM group. Moreover, a non-significant δ band power decrease in the precuneus was found in both the GM and the FB group. Finally, the decrease in δ power in the precuneus was associated with decreased anxiety during the biopsy (VAS; $r = .51$, $P = .009$), although this was not associated with any specific group.

Mioduszewski and colleagues[31] used diffusion tensor imaging (DTI) to investigate the effects of an 8-week mindfulness-based stress reduction (MBSR) program on white matter integrity and pain levels in breast cancer patients. MBSR programs consist of training in self-awareness and stress management and are believed to help reduce chronic neuropathic pain. The MBSR training increased the fractional anisotropy (FA) in the left uncinatum and frontooccipital fasciculus, left amygdala, left hippocampus, left external capsule, and left sagittal striatum as compared with the pre-MBSR scan. This was correlated with a decrease in the pain severity ($r = -.49$; $P < .05$) and pain interference scores ($r = -.436$; $P < .05$). This result was not found in the waiting list control group.

Smith and colleagues[32] used resting state fMRI to investigate the impact of an 8-week MBSR program on functional connectivity (FC), pain severity, and pain intensity in breast cancer survivors with comorbid chronic neuropathic pain as compared with a WL control group. In the MBSR group, FC was increased between the posterior cingulate cortex (PCC) and the ACC/medial prefrontal cortex and decreased between the PCC and the bilateral precentral gyrus, right superior frontal gyrus and pons. Moreover, the increase in FC was correlated with decrease in pain severity

scores ($r=-.57$; $P<.0005$), and the decrease in FC was correlated ($r=-.51$; $P=.014$) with greater pain severity. These results were not found in the waiting list control group.

Finally, Van der Gucht and colleagues[33] used fMRI to compare the impact of an 8-week mindfulness-based intervention (MBI) on FC, emotional distress, and fatigue in breast cancer survivors with cognitive impairments with the same measures assessed in a WL control group. The fMRI routine was performed before commencing the intervention (T1), at the end of the 8-week treatment (T2), and 3 months post-intervention (T3). Increased connectivity was found between the ACC and both the left and the right intraparietal sulcus (IPS) networks at T2, along with improvements in distress, fatigue, and emotional distress symptoms. Moreover, the amelioration in distress symptoms was correlated ($r=-.57$; $P=.004$) with the increase in FC between the ACC and left IPS.

Non RCT Studies

Gawrysiak et al.[34,35] reported on 2 cases of breast cancer patients with depression, where an fMRI music-based paradigm was applied to assess reward responsiveness in response to psychotherapies. Reward responsiveness is believed to be low in depressed individuals and may be involved in causing and maintaining the depressed state. Thus, the rationale behind Gawrysiak's approach was to assess the impact of psychotherapies believed to reinforce the ability to react and enjoy positive experiences on the functional activation of several brain regions involved in reward responsiveness and on clinical symptoms.

In the first case study, following 8 sessions of behavioral activation treatment for depression (BATD), which aims to increase and reinforce healthy and positive behaviors,[34] brain activity was found to increase over the right dorsolateral prefrontal cortex (dlPFC) and medial orbital prefrontal cortex (moPFC) when the patient listened to either preferred or neutral music, whereas it decreased in response to neutral music over the subgenual cingulate cortex. The second case study[35] used fMRI to assess the effects of 8 sessions of pragmatic psychodynamic psychotherapy (PPP), which involved the identification of key relational and conflictual themes. The study revealed increased brain activity over the ventromedial prefrontal cortex (vmPFC) and the left orbital prefrontal cortex (loPFC) during preferred music listening. Both studies reported improvements in depressive symptoms, which were not correlated with changes in neural activity.

Finally, Carletto and colleagues,[36] in a quasi-experimental design study, compared the efficacy of 10 sessions of eye movement desensitization and reprocessing (EMDR) with 4 sessions of EMDR treatment in reducing PTSD symptoms in breast cancer patients. The impact of the 2 treatments on brain cortical oscillations (as assessed with EEG power spectral density) was also described. The authors reported an increase in δ and θ powers of the left angular and the right fusiform gyri in response to EMDR only. Moreover, authors reported significant correlations ($P<.05$) between δ power changes and decreases in clinical scores of depression and traumatic stress.

Risk of Bias Assessment

The result of the risk of bias appraisal is shown in Figure 2. In terms of methodology, RCT studies show a medium overall risk of bias, mainly due to participants' non-adherence to their assigned intervention or a failure in observing the protocol. Results were partially selected according to their direction, magnitude, or statistical significance. Furthermore, subjects were often aware of the forthcoming treatment as often happens in psychological settings, where it is hard to leave the participant blind to procedures. Finally, major differences in equipment and methods were observed, leading to inconsistent results (this applies above all to EEG data). The quasi-experiment is marked by a moderate overall risk of bias, especially around the confounding variables domain, where the patients' prognostic factor can predict their allocation; moreover, the outcome measure is at moderate risk due to the assessor's awareness of the nature of the intervention. Finally, the case report studies were included in this scoping review since the JBI checklist highlighted methodological in 2 criteria only (patient's history, adverse events identification).

Discussion

To the best of our knowledge, the present scoping review is the first to address the neural correlates of psychological interventions in the oncological population. Due to the detailed search strategy and the conservative screening approach applied, only 13 original studies were identified on this topic. Furthermore, the current literature is very heterogeneous with respect to intervention protocols and the types of neuroimaging methods adopted, the patient's disease stage and type of cancer, the types of oncological treatments received, patient gender, the time elapsed since cancer diagnosis, and the concurrent assumption of psychoactive drugs, all of which this might contribute to inconsistent results. Moreover, our findings are mostly based on small and low powered samples, which does not allow us to draw any objective conclusions about the actual effects of the psychological interventions. Furthermore, most of the studies did not specify the duration of the observed effects, which is relevant for determining which interventions can exert long-lasting benefits. Finally, the majority of the studies (expect for Ratcliff et al.[30]) quantify the impact of interventions in terms of *P*-values, rather than effect size.

The following discussion questions will address the scoping questions in order to give a broad appreciation of the available evidence.

What Are the Most Recurrent Study Designs?

Although the total number of studies considered was only 13, the majority of them were RCT's ($n=9$). The remaining studies adopted weaker methodologies, such as the quasi-experiment ($n=1$), single case studies ($n=2$), and secondary quantitative analysis ($n=1$). More research adhering to methodologically strong approaches is essential to be able to draw more robust conclusions.

What Are the Most Recurrent Oncological Populations?

The most studied population consisted of breast cancer patients (9 studies): 7 studies reported on the neural correlates of psychological interventions and their effect on the clinical outcomes of various comorbid conditions (PTSD, cognitive complaints, cognitive impairments, chronic neuropathic pain, and depression); 1 study combined EEG studies with the assessment of parameters linked to anxiety and pain in women scheduled for medical procedure (stereotactic breast biopsy); and one did not address comorbidities at all. Regarding other patient populations, 1 study enrolled women with gynecological cancer (ovarian or cervical carcinoma), and another study enrolled terminally ill oncological patients. Finally, the remaining 3 studies enrolled patients with different forms of cancer and comorbid PTSD.

Since the majority of the studies were focused on breast cancer patients or survivors, the results obtained from the individual studies and scoping review cannot be generalized across oncological populations.

Which Are the Most Applied Psychological Interventions and Comparators?

Five studies applied a mindfulness-based technique to address anxiety, pain, and cognitive impairments. One study, which applied quantitative secondary analysis, implemented NET to regulate the hyperactivation of the autonomic nervous system and reduce the impact of PTSD symptoms. Two studies employed an intervention involving sound to impact anxiety and pain. Three studies applied structured psychotherapeutic interventions, namely an EMDR protocol, a form of psychodynamic therapy (PPP), and a behavioral therapy (BATD), to reduce depressive and PTSD symptoms. Finally, 1 study applied a form of cognitive rehabilitation with the aim of ameliorating cognitive complaints. Looking at the comparators, most of the studies included a WL control group. Other studies entailed support, company (ie, conversation), FB, SC, and PMR control groups.

Which Neuroimaging Techniques Are Implemented the Most to Quantify the Intervention Outcomes?

The literature considered in this scoping review mainly focused on EEG indexes and MRI measures. The *power spectral density* and the *current source density*, both of which estimate the frequency distribution of the EEG signal, were the measures most implemented to evaluate the cortical response to treatments. In relation to MRI imaging, on the other hand, and consistent with current trends in psychological research, 2 main pathways were followed[2]: the functional pathway, which was the most reported approach (7 studies), based on the role of local hemodynamic responses linked to changes in neural activity; and the structural pathway, such as diffusion tensor imaging (1 study) which provides a measure of the integrity of white matter between brain regions and their communication. Some of the key neurobiological outcomes assessed in the context of psychotherapy research are thought to seem to relate to spatial and temporal correlations between brain regions which may outline the modulation of large-scale brain networks, such as default, affective, and attentional networks.[6] In the oncological context, this indeed may prove to be a promising route of investigation; in fact, the present review revealed several studies that addressed measures of connectivity between brain regions. Furthermore, 1 study[28] assessed *heart rate* as a parameter of autonomic arousal and stress outcome. An alternative measure of this outcome could be *heart rate variability* (HRV; a measure of the fluctuation in the length of heartbeat intervals), shown to be a reliable bottom-up indicator of psychological distress[37] and ANS (autonomous nervous system)-heart interplay.[38] Finally, other biomarkers of treatment efficacy have been proposed, such as the output measures generated from the combination of EEG with transcranial magnetic stimulation (TMS), which may directly and reliably assess cortico-cortical excitability and connectivity, in a non-invasive way, in the context of psychological research.[39]

What Are the Main Intervention Effects on Neural Outcome and Clinical Outcome, Respectively?

The main neural effects of treatments are illustrated in Figure 3. The results are discussed according to the type of psychological intervention and refer to the brain areas most involved (Table 3). The impact of mindfulness practices on neural activity is outlined in relation to several brain regions involved in high-level brain processes, such as attentional

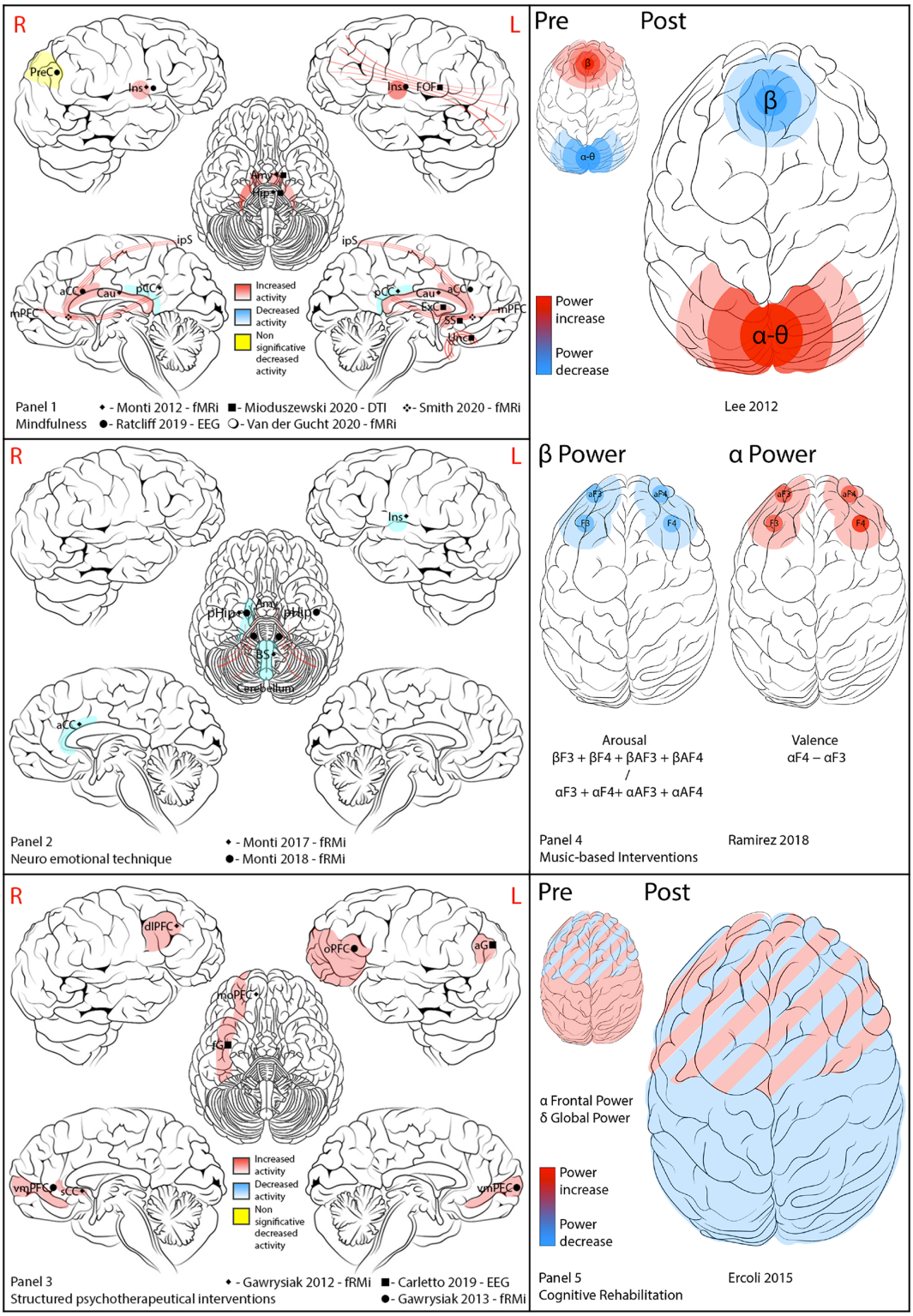


Figure 3. Overview of the psychological interventions' neural correlates. Each panel focuses on a specific intervention type.
Abbreviations: aCC, anterior cingulate cortex; aG: angular gyrus; Amy: amygdala; BS: brain steam; Cau: caudate; dlPFC: dorsolateral prefrontal cortex; ExC: external capsule; fG: fusiform gyrus; FOF: fronto-occipital fasciculus; Hip: hypothalamus; Ins: insula; iPS: intraparietal sulcus; moPFC: medial orbital prefrontal cortex; oPFC: orbital prefrontal cortex; pCC: posterior cingulate cortex; pHip: parahippocampus; PreC: precuneus; sCC: subgenual cingulate cortex; SS: sagittal striatum; Unc: uncinatum; vmPFC: ventromedial prefrontal cortex.

Table 3. Overview of the Brain Regions Impacted by Each Intervention.

Authors	Intervention	Brain areas
	Mindfulness-based interventions	
Monti et al.[25]	Mindfulness-based art therapy	↑ Subcortical regions (insula, right amygdala, right hippocampus, bilateral caudate)
Ratcliff et al.[30]	Guided meditation Focused breathing	↑ Subcortical regions (insula, ACC) ↓ Precuneus
Mioduszewski et al.[31]	Mindfulness-based stress reduction	↑ Left subcortical regions (uncinate fasciculus, amygdala, hippocampus, external capsule)
Van der Gucht et al.[33]	Mindfulness-based intervention	↑ Salience network (ACC), dorsal attention network (left and right IPS)
Smith et al.[32]	Mindfulness-based stress reduction	↑↓ Default mode network: AAC, PCC
	Neuroemotional technique	
Monti et al.[27]	Neuroemotional technique	↓ Subcortical regions (parahippocampus, brainstem, anterior cingulate, insula)
Monti et al.[28]	Neuroemotional technique	↓ Subcortical regions (amygdala, parahippocampus, brain stem)
	Structured psychotherapeutical interventions	
Gawrysiak et al.[34]	Behavioral activation treatment for depression	↑ Prefrontal regions (rmoPFC, rdlPFC), subgenual cingulate
Gawrysiak et al.[35]	Pragmatic psychodynamic psychotherapy	↑ Prefrontal regions (loPFC, vmPFC)
Carletto et al.[36]	Eye movement desensitization and reprocessing therapy	↑ Subcortical regions Left angular and right fusiform gyri
	Music-based interventions	
Lee et al.[24]	Monochord sound	↑ Occipital, ↓ Frontal regions
Ramirez et al.[29]	Music therapy	↑ Prefrontal regions
	Cognitive rehabilitation	
Ercoli et al.[26]	Cognitive rehabilitation	↓ Generalized slow waves decrease; ↑ Frontal regions

Abbreviations: ACC: anterior cingulate cortex; IPS: intraparietal sulcus; PCC: posterior cingulate cortex; rmoPFC: medial orbital prefrontal cortex (right-sided); rdlPFC: dorsolateral prefrontal cortex (right-sided); loPFC: left orbital prefrontal cortex; vmPFC: ventral medial prefrontal cortex.

control and emotional regulation. In particular, the studies considered in this review looked at activity in the Ins, the ACC, and the PFC to investigate the impact of mindfulness practices at the neurobiological level.[40] Their results provide evidence that mindfulness strengthens prefrontal cognitive control mechanisms, with a concomitant down-regulation of activity in regions relevant for affect processing, such as the amygdala and subcortical regions.[41] Conversely, the included studies report activation of both limbic and cortical brain regions in breast cancer patients treated with mindfulness,[25,30-33] which is typical in untrained meditators.[42] Thus, although limbic activation is consistent with other fMRI studies, it needs to be further explored as these structures are expected to be less active in relaxation paradigms.[25] In this respect, future studies should consider the "expertise" variable, as the activation pattern in expert meditators entails cortical/prefrontal activation at the expenses of limbic components, which are primarily involved in emotional processing.[42]

Although research into the effects of NET is still in its early days,[27,28] the evidence obtained thus far support the potential of this tool for investigating the subsyndromal traumatic stress symptoms reported by cancer patients and survivors. This may be done by investigating the role of the cerebellar functional pathway to the brainstem and limbic areas (mainly the parahippocampus, Ins, and ACC) in mediating the traumatic response to cancer. NET (as well as other mind-body therapies) seems to normalize the reactivity of these regions, enhancing self-regulation and favoring less-aroused states.[43] In particular, the involvement of these structures seems to be consistent with the findings from investigations into the neural features of PTSD in cancer patients,[37] and certainly needs to be investigated further.

Evidence from psychotherapeutic interventions are scarce. The 2 case studies of patients with both depression and cancer[34,35] report that BATD and PPP trigger the hyperactivation of areas of the PFC (dlPFC, moPFC, oPFC) and cingulate cortex. This is consistent with other studies that investigated the neurobiological outcomes of therapeutic interventions in anxiety and depression disorders, and which reported neural activity changes in the cortico-limbic brain regions implicated in emotion regulation.[8] Similarly, EMDR seems to increase activation of associative cortical areas at the expense of the limbic components, which might

be considered a neural correlate of improvements in PTSD symptomatology.[44-47] The role of each PFC area in mediating the beneficial effects of psychotherapy in cancer patients remains to be clarified, which will require the implementation of more methodologically robust study designs (such as RCTs).

Studies looking at the effects of music therapy on brain activity revealed a pattern of posterior θ and α modulation.[29] This prompts the hypothesis that the effects of music therapy on patterns of brain cortical oscillations are similar to those obtained with meditation, which similarly leads to an increase in δ rhythms.[48] Moreover, evidence suggests that β rhythm asymmetry in frontal regions may be a sign of a more positive emotional state.[49] Furthermore, music seems to determine more sustained arousal (ie, less depressed mood) and more positive emotions, which is relevant within the context of palliative care.[29] However, larger sample sizes are needed to describe this effect in more detail.

Just 1 study[26] addressed cognitive complaints in breast cancer patients undergoing cognitive rehabilitation. Chemotherapy is often associated with cognitive dysfunctions (the so-called "chemobrain"), which can negatively impact the quality of life.[50] The reported overall reduction in δ power at 2 months after the intervention may reflect an improvement in cognition since slow EEG waves are associated with mild cognitive impairments.[51] However, these are preliminary outcomes only, and therefore need be replicated in further, more powerful studies. It is also highly noteworthy that all the included studies reported improvements in clinical psychological measures, showing treatments to be effective in reducing anxiety, depression, stress-induced pain, fatigue, and cognitive complaints in people dealing with cancer.

Overall, it is interesting that most of the areas targeted by psycho-oncological interventions are coherent with those found to be involved in distress reactions to cancer,[2] such as the ACC, prefrontal cortices, Hy, Amy, and Ins. This may mean that different psychological interventions share a common neural mechanism of action, where the higher-level areas modulate the hyperactivation of subcortical regions, leading to better emotional regulation and balance.[41,47] Future studies should consider each area's role in mediating the beneficial effect of several therapies, especially from a functional point of view.

Was It Possible to Correlate the Neural and the Clinical Outcomes?

Seven studies reported a significant positive or negative correlation between neurobiological effects and clinical outcome. Only statistically significant correlations are reported herein. Inconsistencies in the results may be due to low sample sizes and differences in the statistical power. Investigating the correlations between observed neurobiological changes and clinical outcome is essential in order to be able to understand what changes in neural activity may underlie the clinical effect of an intervention. Thus, future studies investigating the effectiveness of psychological interventions in cancer patients should also endeavor to gather data on the neural correlates of their treatments, such that new insights may come to light.

Study Strengths and Limitations

This present review adhered to the established guidelines for a scoping review[17,18] and adopted a comprehensive search strategy involving 5 databases. The study design stages were carried out by at least 2 independent reviewers to ensure the highest degree of objectiveness and to be as inclusive as possible. An important strength lies in the fact that the review overviewed the existing evidence on a barely investigated topic. Moreover, this work followed a study protocol established a priori but which is not registered, since this is not a requirement for scoping reviews. However, this work is not exempt from limitations. Firstly, despite our attempts to be as comprehensive as possible, it is not impossible that gray literature published outside the standard channels exists and was missed by the review. Secondly, this study is significantly limited in that it does not provide any concrete guidance from a clinical or policy-making point of view; however, this is not the objective of a scoping review. Thirdly, for the same reason, the present work does not infer the effect size of interventions from the original studies. Finally, the review is not reporting all statistically non-significant ($P < .05$) results from primary studies, which may also be considered to generate additional hypothesis in future studies.

Clinical Implications and Future Directions

The limited and heterogeneous nature of the results does not allow us to provide any recommendations regarding specific treatments or protocols for specific conditions, which again was not an aim of this scoping review. Despite this, the observed improvement of distress symptoms following psychological interventions is notable and of great value as it shows that such treatments are able to positively impact upon quality of life in these patients as well as oncological disease outcomes.[4] Furthermore, although psychopharmacology options are valuable tools for treating symptoms of distress related to oncological disease, several papers have called for the need for more integrated cancer care, including psychosocial/psychotherapeutic, psychopharmacological, and complementary therapies.[52] In order for such strategies to become endorsed, determining

whether non-pharmacological treatment options can exert significant changes on clinical symptoms and on brain activity is fundamental. Indeed, several studies have reported the effectiveness of psychotherapy in modulating the brain functioning across psychopathological conditions,[8,53,54] and the same might be true for psychological interventions in the oncological context, where the distress burden has been shown to worsen the prognosis.[11-13] Before recommending psychological interventions as evidence-based treatment options, much more research will be required in order to systematically assess their clinical and neural efficacy. Moreover, future studies should compare the aforementioned neural correlates with those found to underlie psychopharmacological treatments for emotional distress in cancer, as suggested by the literature on the effectiveness of psychotherapy.[53] Also, future research should include a follow-up assessment to describe the long-term effects of treatments, to control for covariates such as gender, cancer treatment type, and cancer stage, and provide a methodologically sound estimation of sample size to obtain sufficient power. Finally, since the *P*-value is hugely impacted by the sample size,[55] future studies should consider estimating the effect of intervention in terms of effect size.

Conclusions

The aim of this scoping review was to provide an early overview of the available evidence on the neural correlates of treatments for psychological distress in cancer patients. These preliminary findings indicate that the cortical and limbic areas targeted by psychological interventions may be coherent with those involved in the individual's distress reaction to cancer. Furthermore, the evidence supports the use of both the neural and clinical outcomes for assessing the impact of a psychosocial treatment. Further research with larger and more heterogeneous populations is needed to draw stronger conclusions.

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ORCID iDs

Francesca Malandrone https://orcid.org/0000-0002-9438-8637

Maria Chiara Annetta https://orcid.org/0000-0003-3112-421X

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The efficacy of mindfulness-based interventions in attention-deficit/hyperactivity disorder beyond core symptoms: A systematic review, meta-analysis, and meta-regression.

Francesco Oliva [a,*], Francesca Malandrone [a], Giulia di Girolamo [b], Santina Mirabella [b], Nicoletta Colombi [c], Sara Carletto [b], Luca Ostacoli [a]

[a] Department of Clinical and Biological Sciences, University of Turin, Italy
[b] Department of Neuroscience "Rita Levi Montalcini", University of Turin, Italy
[c] Biblioteca Federata di Medicina "Ferdinando Rossi", University of Turin, Italy

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ABSTRACT

Background: Mindfulness-Based Interventions (MBIs) have been increasingly proposed as treatment in patients with Attention-Deficit/Hyperactivity Disorder (ADHD), showing promising results on different proposed outcomes, in both children and adults.
Objectives: To systematically review and meta-analyse studies concerning the effects of MBIs on either ADHD and associated features, associated clinical conditions, neurocognitive impairments, mindfulness skills, global functioning and quality of life.
Methods: Searches were conducted on five databases, including controlled and observational studies on both adults and children populations. The review process was compliant to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA). Meta-analyses and meta-regression models were conducted.
Results: Thirty-one full-texts were included. In both adults and children, MBIs showed to be more effective than waiting lists in improving ADHD symptoms and some other outcomes. In adults, a medium pooled effect size was shown by meta-analysis for ADHD symptoms but in some cases a publication bias was detected. Subgroup analysis and meta-regression confirmed the gap detected by our systematic review between the medium/large effect size of inactive-controlled studies and the low/negligible one of active-controlled studies. In children, no active-controlled studies have been conducted. Mindfulness Awareness Practice (MAP) and Mindfulness Based Cognitive Therapy (MBCT) were the most used protocols in adult studies, whereas a combination of MBCT and Mindfulness Based Stress Reduction (MBSR) was more preferred for children and adolescent patients.
Conclusions: Even if further studies with a better methodology are needed, we can suggest the MBIs may be useful as complementation and not as replacement of other active interventions.

1. Introduction

Attention-Deficit/Hyperactivity Disorder (ADHD) is a highly heritable neurodevelopmental disorder (Faraone et al., 2005; Faraone and Doyle, 2001; Levy et al., 1997; Rietveld et al., 2004; Sprich et al., 2000). The onset of ADHD takes place during childhood (American Psychiatric Association, 2013) with a prevalence of 5.3 (95% CI=5.0–5.6, Polanczyk et al., 2007) and it persists into adulthood in two-thirds of the cases (Faraone et al., 2006) affecting 2.5% of the adult population (Simon et al., 2009). The clinical presentation of ADHD may vary between patients, as inattention or hyperactivity/impulsivity could prevail or both of them could be equally represented (Faraone et al., 2015; Franke et al., 2018; Kooij et al., 2019).

ADHD treatment is multimodal, consisting of pharmacological and non-pharmacological approaches always associated with punctual psychoeducation (Kooij et al., 2019). The first-line medications are stimulants, i.e., methylphenidate (MPH) and amphetamines (Dalrymple et al., 2019). Non-pharmacological approaches (i.e., cognitive-behavioral

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* Corresponding author.
E-mail address: francesco.oliva@unito.it (F. Oliva).

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therapy - CBT, and coaching) complement medications addressing not only ADHD symptoms but also DSM-5 associated features (e.g., emotional dysregulation), neuropsychological dysfunction (Willcutt et al., 2005), delayed sleep onset (Kooij and Bijlenga, 2013; Wynchank et al., 2018), and anxiety/depression (Fayyad et al., 2017; Katzman et al., 2017).

Growing interest has been given to Mindfulness-Based Interventions (MBIs) since they have been increasingly used in combination with conventional treatments in mental health (McClintock et al., 2016). MBIs could play a role as augmentation strategies in ADHD since they have shown they can improve attention, awareness, sense of self and executive functions, and reduce impulsivity, emotional dysregulation, and stress levels (Baijal and Gupta, 2008; Hylander et al., 2017; Kozasa et al., 2012; Krisanaprakornkit et al., 2010; Lutz et al., 2008; Rapport et al., 2002; Schonert-Reichl et al., 2015; Tang et al., 2014, Tang et al., 2007; Tsai and Chou, 2016), ameliorating also some comorbid psychiatric conditions such as anxiety, depression, and substance abuse (Bueno et al., 2015; Cole et al., 2016; de Lisle et al., 2012; Gu et al., 2016; Hesslinger et al., 2002; Hofmann et al., 2010; Philipsen et al., 2007; van de Weijer-Bergsma et al., 2012; Vøllestad et al., 2012; Witkiewitz et al., 2013; Zylowska et al., 2008), even in patients with bipolar disorder (Chu et al., 2018; Lovas and Schuman-Olivier, 2018; Xuan et al., 2020).

Some systematic reviews of studies on MBIs and ADHD have already been conducted with promising, albeit still not definitive, conclusions (Cairncross and Miller, 2016; Chimiklis et al., 2018; Evans et al., 2018; Lee et al., 2017; Poissant et al., 2019; Tercelli and Ferreira, 2019; Xue et al., 2019). Overall, existing reviews have mainly focused on the effectiveness of mindfulness (or related interventions, such as meditation and yoga) in improving ADHD symptoms. The evidence of MBIs efficacy among adult patients (Lee et al., 2017) seems to be stronger than that detected in children (Chimiklis et al., 2018). Age and type of control condition seemed to affect the overall effect size on ADHD symptoms according to a prior meta-regression analysis (Xue et al., 2019). Moreover, the majority of these reviews claimed for the necessity of further investigations, pointing out the low quality and heterogeneity (Chimiklis et al., 2018; Evans et al., 2018; Lee et al., 2017; Poissant et al., 2019).

The aim of the present review was to evaluate the efficacy of MBIs in improving not only ADHD symptoms but also diagnostic associated features (i.e., emotional dysregulation, neuropsychological function impairment, circadian rhythm disorder with delayed sleep onset), health status and quality of life, and other associated conditions (e.g., anxiety and depression), focusing on the contribution of different control conditions to the overall effect.

2. Methods

2.1. Protocol registration

The review protocol was registered in the PROSPERO repository (CRD42019130639).

2.2. Search strategy for identification of studies

A literature search was performed on PubMed, Embase, CINAHL, PsycINFO, the Cochrane Central Register of Controlled Trials from the earliest dates available to June 25th, 2020 using keywords and text words for ADHD and MBIs. Moreover, we performed a search with the keywords 'ADHD', 'mindfulness' and 'attention deficit hyperactivity disorder' in Google Scholar in order to screen books and book chapters, scholarly articles, and other important grey literature related to the topic. From selected studies, cross-references were checked manually. The search strings are described in Supplementary material (S1.1).

2.3. Eligibility criteria

We included studies concerning patients with a diagnosis of ADHD. There was neither restriction by concurrent organic disease nor limit in terms of participants' gender or age (i.e., children, adolescents, and adults).

We included studies that evaluated MBIs alone or in addition to another treatment in a pre-post design, in comparison with no intervention, Waiting List (WL), Treatment As Usual (TAU) or other types of intervention (e.g. antidepressant medication, CBT, psychodynamic therapy). We included studies that provided quantitative data, as measured by standardized psychometric scales, before and after the intervention/s.

Any type of health-related outcome was included. The reasons for exclusion were: 1) qualitative studies, 2) systematic reviews, 3) case reports. No year or language restrictions were applied.

2.4. Data collection

Two authors (FO and FM) independently conducted standardized assessments to determine study eligibility, according to the inclusion criteria. First, they screened the abstracts and then retrieved and analyzed the full-texts for all the records deemed relevant. Any disagreement was solved involving a third author (LO).

Data from the selected studies were inserted in a standard template by two independent researchers (FO and FM). Article authors were reached via email for any missing information.

2.5. Quality assessment

The internal validity of the Randomized Controlled Trials (RCTs) and the quality of non-RCT studies were assessed by the Version 2 of the Cochrane risk-of-bias tool for RCTs (Sterne et al., 2019) and the MINORS Scale (Slim et al., 2003; Zeng et al., 2015), respectively. Both quality assessment tools were used according to instructions provided by authors.

The risk of bias was assessed by two independent coders (FO and FM) and any disagreements were discussed and resolved with a third reviewer (LO).

2.6. Statistical analysis

All meta-analysis procedures were performed using meta (Balduzzi et al., 2019), metafor (Viechtbauer, 2010), and dmetar (Harrer et al., 2019b) packages of R (R Core Team,2020).

We followed the same procedure for each eligible outcome (i.e., at least three controlled studies should have counted the outcome among those considered).

A random-effect-model based on inverse variance method with Hartung-Knapp-Sidik-Jonkman adjustment (Hartung, 1999) was performed to pooling effect sizes from post-intervention mean, standard deviation, and sample size of two compared groups (meta package). Hedges' g with 95% confidence interval (95%CI) and prediction interval with 95% confidence interval (95%CI) were calculated. Sidik-Jonkman method was used to estimate $\tau 2$ (Sidik and Jonkman, 2007). Heterogeneity was also assessed by Cochran's Q-statistic and Higgin's & Thompson's I^2 estimation (Higgins et al., 2003). No, low, moderate, and high heterogeneity were defined by 25%, between 25% and 50%, between 50 and 75%, and >75% I^2 values, respectively. Forest plots were used to present the model results.

Outliers were detected by checking for lack of overlap between studies and pooled confidence intervals using the dmetar package. Then, a conventional leaved-one-out (Viechtbauer and Cheung, 2010) with Baujat's graphical methods and, when possible, a more sophisticated Graphic Display of Heterogeneity (GOSH) plots with diagnostic methods (Harrer et al., 2019a; Olkin et al., 2012) were used for the influence

analysis. Finally, an adjusted model and the respective forest plot were performed excluding outliers and influential studies for a sensitivity analysis.

A contour-enhanced funnel plot and the Egger's test were used to detect publication biases (Egger et al., 1997; Peters et al., 2008). The contour-enhanced funnel plots included three shaded contours marking areas, one for each different significance level of effect size (dark blue, $0.025<p<0.05$; blue, $0.01<p<0.025$; light blue, $p<0.01$) into which the effects size of each study falls. The Duval and Tweedie's trim-and-fill procedure (Duval and Tweedie, 2000) was adopted to calculate the bias-corrected effect size (meta package).

A subgroup analysis using a mixed-effects model (i.e., random-effects model without Hartung-Knapp-Sidik-Jonkman adjustment within subgroups, and fixed-effects model between subgroups) was conducted to evaluate the impact of the type of control condition on pooled effect size. A meta-regression model with control condition was performed and then it was compared through ANOVA test with a multiple meta-regression model using all possible dummy variables that can define subgroups (metafor package). ANOVA test included Akaike's Information Criterion with small sample adjustment (AICc) and Likelihood Ratio Test (LRT) calculations.

3. 3. Results

3.1. Study selection and study characteristics

The PRISMA flowchart describing the selection process, including reasons for exclusion, is presented in Fig. 1. The search retrieved 31 articles: 16 conducted on adults, 14 on children, and one study on a mixed sample of adolescents and adults.

3.2. Adults

All the details about included studies involving adult patients are summarized in Supplementary material S3.1.

Overall, the studies involved a sample of 1336 patients, 1040 (77.84%) of whom completed the study. The age ranged from 18 to 68 years.

The most employed MBIs protocols were MBCT, MAP and DBT.

3.3. Controlled studies on adults with ADHD

3.3.1. ADHD symptoms

All twelve controlled studies investigated the effects of MBIs on ADHD symptoms. Two of them (Cole et al., 2016; Groß et al., 2017) did not provide the required data for the computation of effect sizes and therefore were not included in the meta-analysis. Since not all the

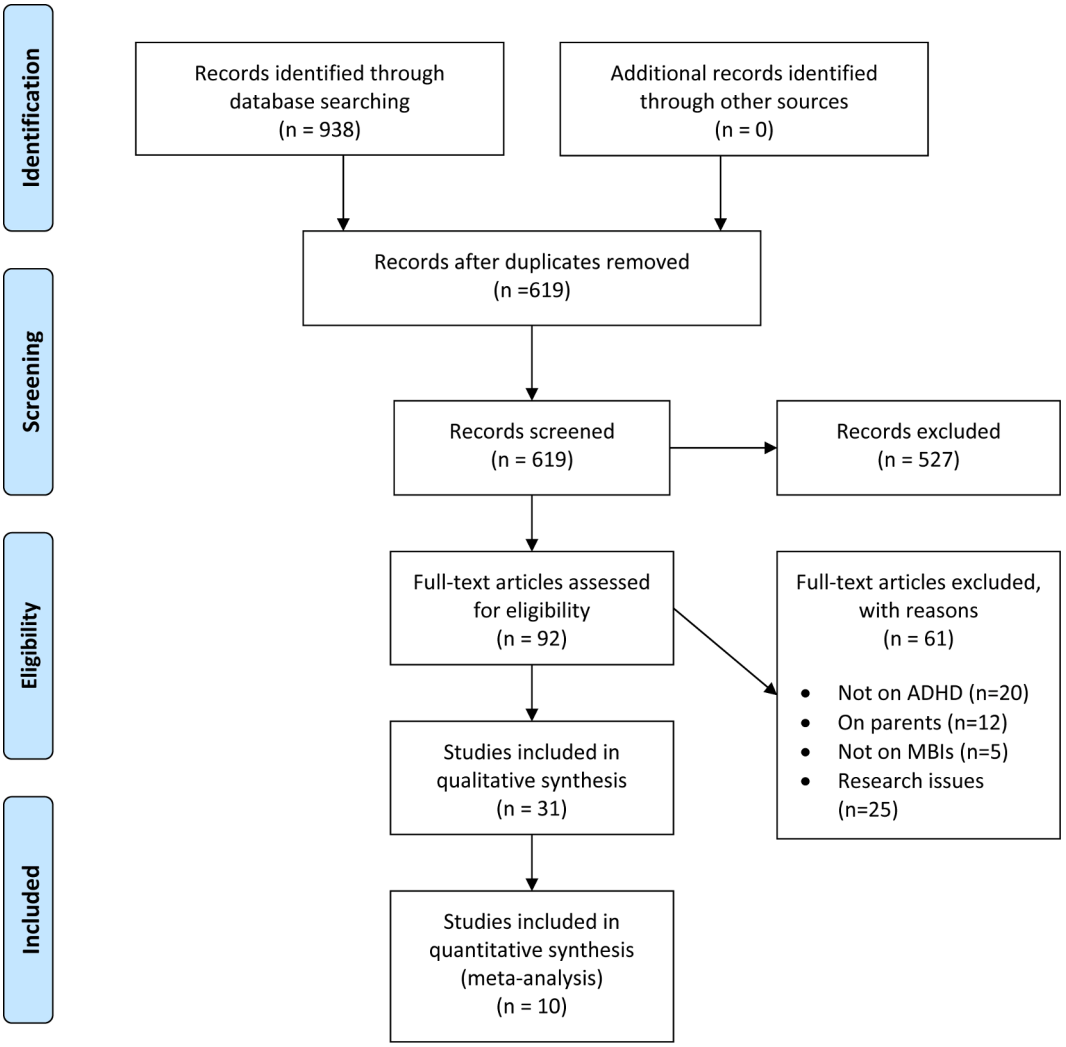

Fig. 1. PRISMA 2009 flow diagram.

eligible studies have reported results on both inattention and hyperactivity symptoms as well as ADHD total symptoms, we built three different models to include the maximum possible number of studies. All respective forest plots, influential and sensitivity analyses, and funnel plots were presented in the Supplementary material S2 (S2.1-S2.36).

The pooled effect size of MBIs on inattention (g=-0.69, 95%CI=-1.13/-0.25, p=0.006) was higher than either that on hyperactivity/impulsivity symptoms (g=-0.46, 95%CI=-0.80/-0.11, p=0.015) and that on ADHD total symptoms (g=-0.52, 95%CI=-0.96/-0.09, p=0.025)

Moderate and significant level of heterogeneity was detected for all three effect sizes (total symptoms, I^2=67.7%, Q=18.59, p=0.005; inattention, I^2=72.6%, Q=32.87, p<0.001; hyperactivity/impulsivity, I^2=57.1%, Q=18.67, p=0.017). No outliers were found in all three meta-analysis models, whereas some influential studies were identified. Sensitivity analysis excluding influential studies successfully reduced heterogeneity of each outcome (total symptoms, I^2=57.5%, Q=11.76, p=0.038; inattention, I^2=69.5, Q=26.24, p=0.001; hyperactivity/impulsivity, I^2=0.0%, Q=3.59, p=0.609) without any change in term of effect size of MBIs on inattention symptoms (g=-0.60, 95%CI=-0.99/-0.20, p=0.008) and with a great reduction of the effect size on ADHD total symptoms (g=-0.42, 95%CI=-0.82/-0.01, p=0.046) and hyperactivity/impulsivity symptoms (g=-0.38, 95%CI=0.61/0.15, p=0.008). A certain skewness for small-sized impacting studies could be noticed at funnel plots beyond not significant Egger's tests (total, Egger's test=-1.78, 95%CI=-9.23/-5.67, p=0.657; inattention, Egger's test=-4.02, 95%CI=-7.94/-0.10, p=0.074; hyperactivity/impulsivity symptoms, Egger's test=-2.90, 95%CI=-6.82/-1.02, p=0.183), suggesting possible publication biases. The effect size obtained by controlling for selective publication according to the trim-and-fill procedure was unchanged for total (g=-0.52, 95%CI=-0.96/-0.09, p=0.025), medium for inattention symptoms (g=0.50, 95%CI=-0.96/-0.04, p=0.035), and under significance level for hyperactivity/impulsivity (g=-0.30, 95%CI=-0.70/0.09, p=0.114).

Subgroup analysis underlined the impact of control conditions on between-studies heterogeneity for all three ADHD symptoms outcomes. Heterogeneity in both active and inactive control subgroups was null for total (Fig. 2) and attention symptoms (Fig. 3), and really low for hyperactivity/impulsivity (Fig. 4). Moreover, significant differences were found between studies with active and those with inactive control conditions in terms of effect size on total (χ2(1)=11.84, p<0.001), inattention (χ2(1)=15.99, p<0.001), and hyperactivity/impulsivity symptoms (χ2 (1)=7.79, p=0.005).

Multiple meta-regression model including both control conditions (active and inactive) and rater (patient, clinician, observer) did not outperform that with control condition alone in explaining ADHD symptoms heterogeneity of total ADHD symptoms (AICc control+rater=122.19, AICc control=11.57, LRT=1.38, p=0.846), inattentive (AICc control+rater=38.96, AICc control=11.06, LRT=2.10, p=0.552) and hyperactivity/impulsivity (AICc control+rater=53.19, AICc control=12.15, LRT=2.17, p=0.539). Indeed, the model with control condition only explained 100% of the heterogeneity and showed a significant moderation effect for total symptoms (F(1,5)=17.79, p=0.008), inattention (F(1,8)=28.54, p<0.001) and hyperactivity/impulsivity (F(1,7)=9.62, p=0.017). Among all the investigated predictors, inactive control only had a significant predictive value for both inattention (b=-0.898, t=-5.34, p<0.001) and hyperactivity/impulsivity (b=-0.578, t=-3.10, p=0.017) as well as total ADHD symptoms (b=-0.722, t=-4.22, p=0.008).

3.4. Neuropsychological functions

Overall eight studies (Bachmann et al., 2018; Fleming et al., 2015; Gu et al., 2018; Hepark et al., 2019; Hoxhaj et al., 2018; Janssen et al., 2018; Mitchell et al., 2017; Schoenberg et al., 2014) investigated neuropsychological functions. A meta-analysis on the effect of MBIs on neuropsychological functions was not conducted because of the extreme between-study difference in assessment tools and outcomes (See supplementary materials S3.1). However, four controlled studies (Fleming et al., 2015; Hepark et al., 2019; Janssen et al., 2018; Mitchell et al., 2017) have properly assessed pre-post intervention variations of executive functions with consistent tools and thus were meta-analytically investigated. All respective forest plots, influential and sensitivity analyses, and funnel plots were presented in the Supplementary material S2 (S2.37-S2.45). Pooled effect size was medium (g=-0.65, 95% CI=-1.24/-0.06, p=0.038) with low and non-significant heterogeneity (I^2=55.4%, Q=6.73, p=0.081). No outliers were detected and one

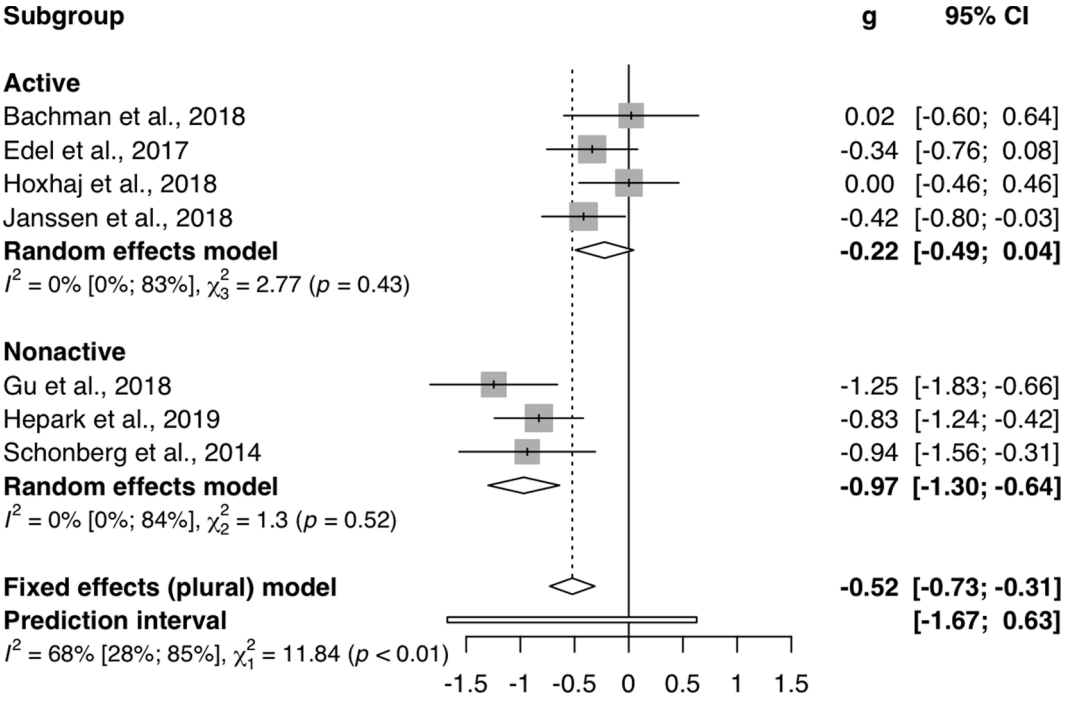

Fig. 2. Subgroup analysis for total ADHD symptoms (by control condition).

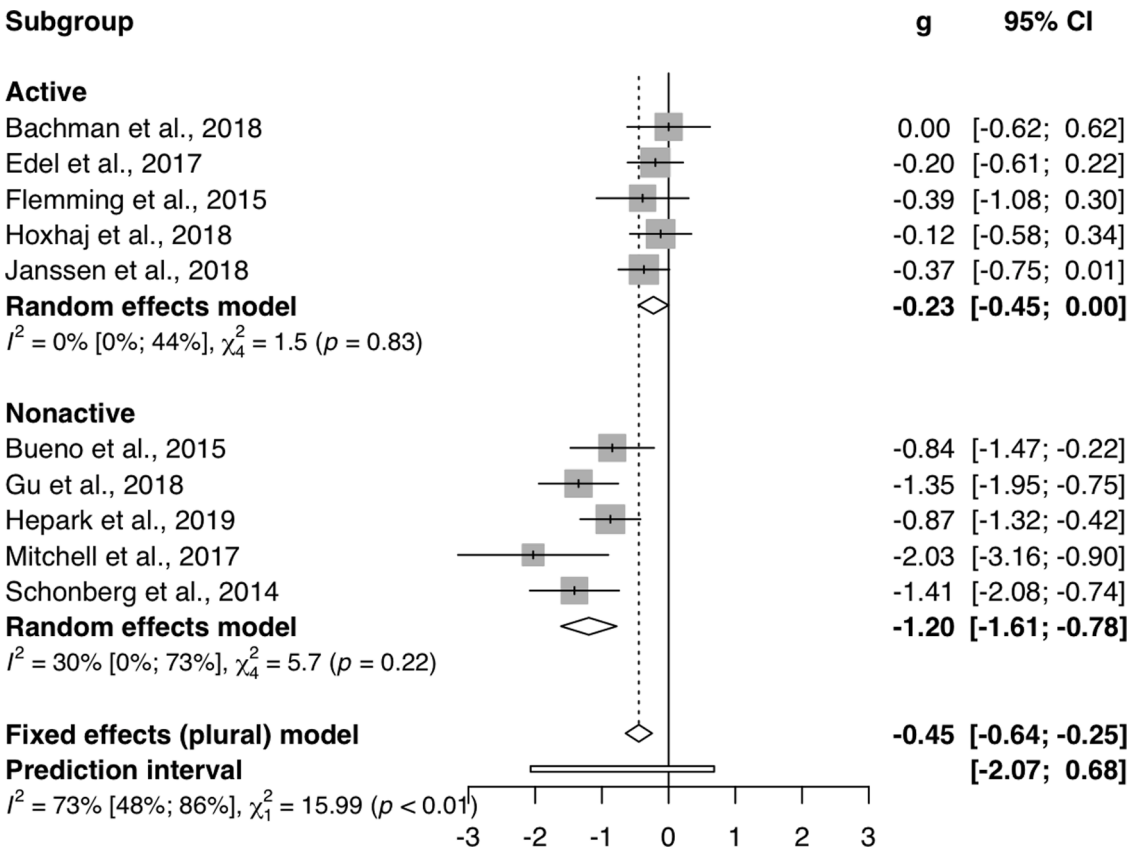

Fig. 3. Subgroup analysis for attention symptoms (by control condition).

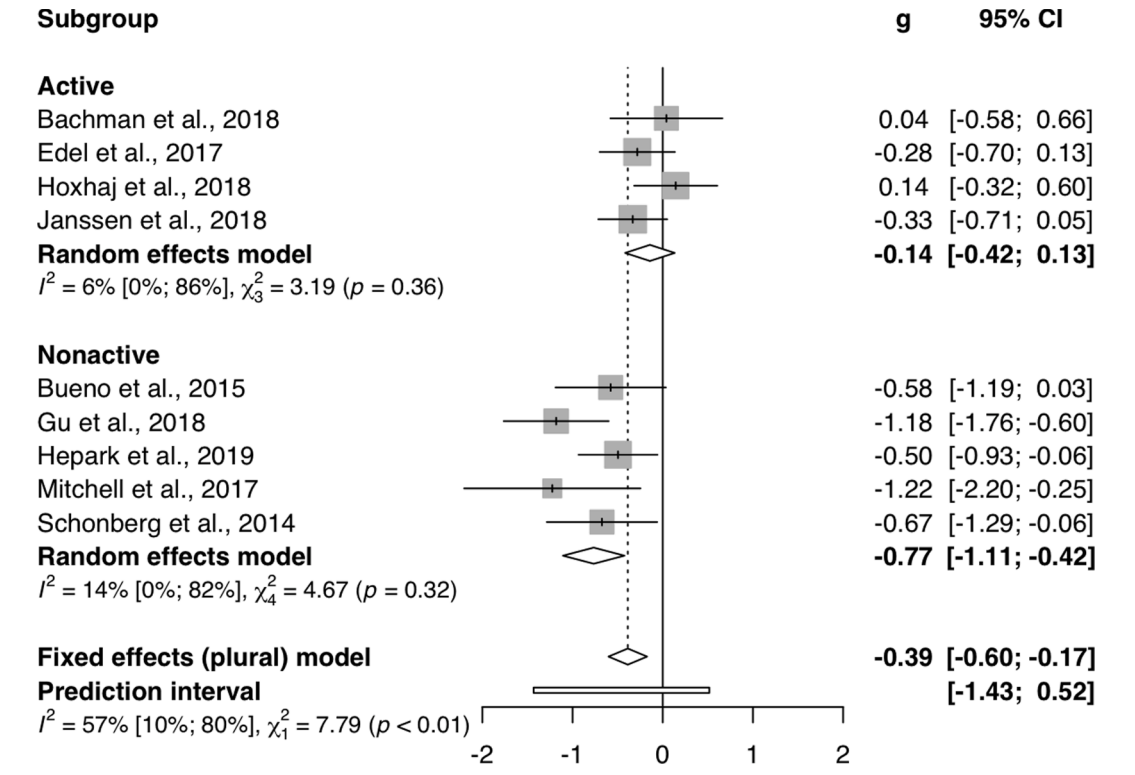

Fig. 4. Subgroup analysis for hyperactivity/impulsivity symptoms (by control condition).

influential study was identified and excluded in the sensitivity analysis, which showed a null heterogeneity (I^2=0.0%, Q=0.36, p=0.836) and an increased effect size (g=-0.89, 95%CI=-1.20/-0.57, p=0.007). However, a publication bias was detected and the model corrected according to trim-and-fill analysis presented a small effect size (g=-0.38, 95% CI=-0.97/0.22, p=0.164) and considerable heterogeneity (I^2=75.6%, Q=20.51, p=0.001).

Subgroup analysis showed a higher effect size for studies comparing MBI with inactive control conditions (χ2(1)=6.18, p=0.013; Fig. 5). The two groups presented a negligible heterogeneity (Fig. 5).

The meta-regression model with control conditions (active, inactive) fully explained the heterogeneity of effect size, but did not find any significant moderator effect (R^2=100.0%, F(1,4)= 7.90, p=0.107). No other models could be built with the available variables.

3.5. Associated conditions

Anxiety and depression were the only two associated conditions, which were investigated by at least three controlled studies.

The meta-analysis on five studies (Bueno et al., 2015; Fleming et al., 2015; Gu et al., 2018; Hepark et al., 2019; Hoxhaj et al., 2018) investigating the efficacy of MBIs on depression showed a small effect size (g=-0.35, 95%CI=-0.64/-0.06, p=0.028) without between-studies heterogeneity (I^2=0.0%, Q=3.06, p=0.548). No outliers were detected and one possible influential study was found. Sensitivity analysis without the influential study showed a smaller effect size (g=-0.26, 95% CI=-0.43/-0.09, p=0.028) while maintaining null heterogeneity (I^2=0.0%, Q=0.55, p=0.90).

As regards anxiety, four studies (Bueno et al., 2015; Fleming et al., 2015; Gu et al., 2018; Hepark et al., 2019) were pooled showing a medium effect size (g=-0.61, 95%CI=-0.87/-0.35, p=0.005) without heterogeneity (I^2=0.0%, Q=1.08, p=0.782). No outliers were detected and one possible influential study was identified and excluded in sensitive analysis. The resulting model confirmed a moderate effect size (g=-0.53, 95%CI=-0.61/-0.46, p=0.001) without heterogeneity (I^2=0.0%, Q=0.02; p=0.988). No publication biases were found for both anxiety and depression meta-analyses. All respective forest plots, influential and sensitivity analyses, and funnel plots were presented in the Supplementary material S2 (S2.46-S2.63).

No subgroup analyses and meta-regressions were conducted considering the lack of between-study heterogeneity.

Anger and hopelessness (Cole et al., 2016), health status (Janssen et al., 2018), emotional dysregulation (Mitchell et al., 2017), and perceived stress (Schoenberg et al., 2014) were investigated in one study each. All authors reported a better outcome for MBIs than for control conditions.

3.6. Mindfulness related outcome

Two controlled studies (Cole et al., 2016; Edel et al., 2017) and six RCTs (Fleming et al., 2015; Gu et al., 2018; Hepark et al., 2019; Hoxhaj et al., 2018; Janssen et al., 2018; Schoenberg et al., 2014) investigated mindfulness related outcomes. A meta-analysis was conducted on seven controlled studies (see Supplementary material S2.64-S2.72 for details) as the study by Cole et al. (Cole et al., 2016) did not provide the necessary data. A medium effect size (g=0.58, 95%CI=0.25/.91, p=0.03) with a certain heterogeneity (I^2=56.5%, Q=13.78, p=0.032) was estimated. No outliers were found and one possible influential study was identified. Sensitive analysis without the influential study showed a similar effect size (g=0.66, 95%CI=0.37/0.95, p=0.002) with a not significant heterogeneity (I^2=313.9%, Q=7.34, p=0.196). A publication bias was detected and the model adjusted according to trim-and-fill procedure showed a low effect size (g=0.51, 95%CI=0.18/0.84, p=0.008) with significant heterogeneity (I^2=60.1%, Q=17.56, p=0.014).

Subgroup analysis focusing on control conditions showed a significantly high effect size for studies comparing MBI with inactive control condition (χ2(1)=4.91, p<0.026; Fig. 6). This subgroup analysis really impacted on between-studies heterogeneity as both groups presented low and not significant heterogeneity (Fig. 6).

The meta-regression model with control conditions (active, inactive) fully explained the heterogeneity of effect sizes, without showing a significant moderator effect (R^2=100.0%, F(1,5)= 4.88, p=0.078). The full model including also assessment tool and intervention as factors did not outperform that with control condition alone in explaining effect size heterogeneity (AICc control+assessment+intervention=119.29 AICc control=13.73, LRT= 6.45, p=0.168) and in revealing significant predictors.

3.7. General functioning and quality of life

Two controlled studies (Bueno et al., 2015; Cole et al., 2016) and

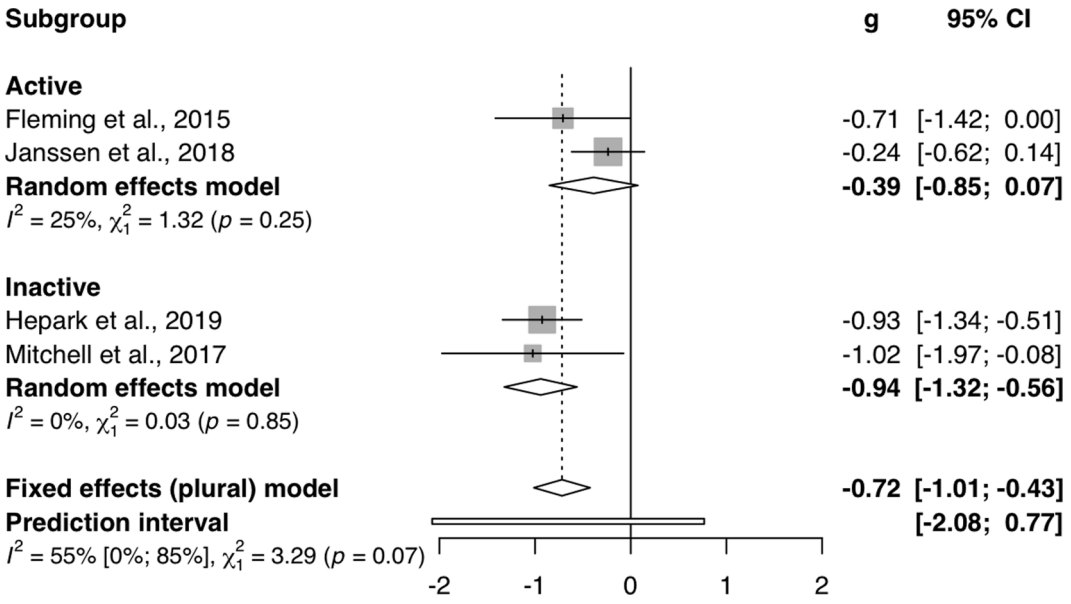

Fig. 5. Subgroup analysis for executive functions (by control condition).

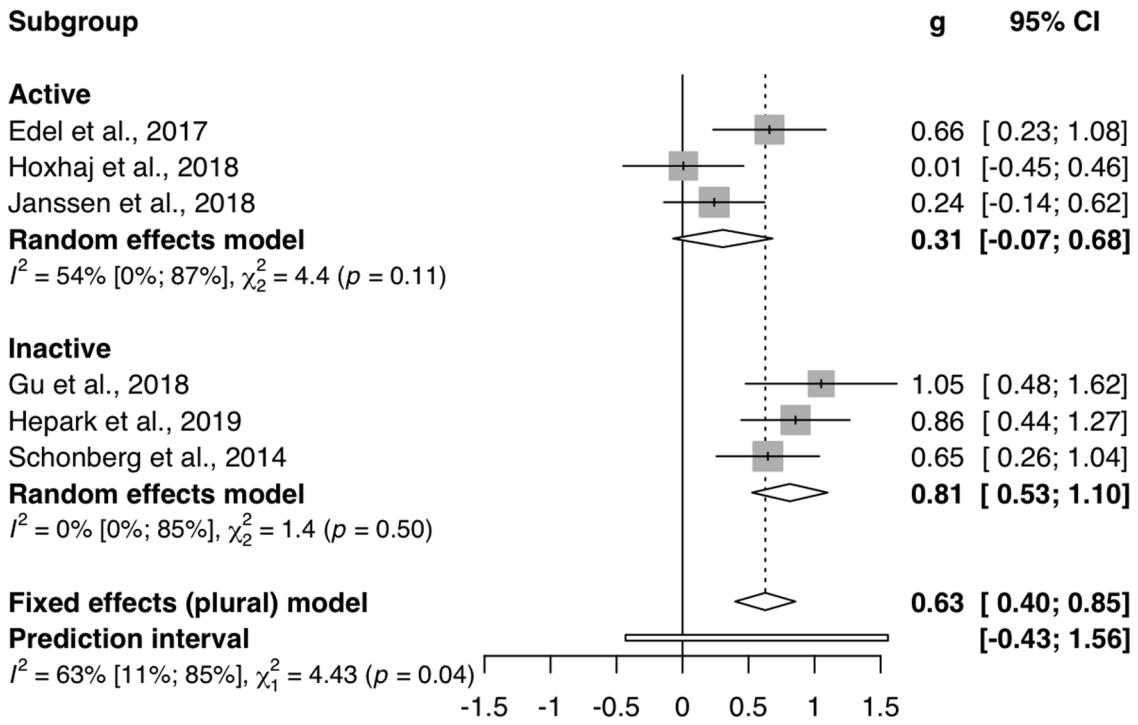

Fig. 6. Subgroup analysis for mindfulness skills (by control condition).

four RCTs (Hepark et al., 2019; Hoxhaj et al., 2018; Janssen et al., 2018; Schoenberg et al., 2014) also included these two outcomes.

A meta-analysis was conducted despite the low number of studies showing data on changes of quality of life and global functioning after MBI (see Supplementary material S2.73-S2.85 for details). The pooled effect size of the three studies considering quality of life was large (g=0.86, 95%CI=-0.59/2.31, p=0.125) and with considerable heterogeneity (I^2=75%, Q=8.06, p=0.018). No outliner was detected and one influential study was excluded. Sensitive analysis showed a large and significant effect size (g=1.24, 95%CI=0.46/2.01, p=0.031) without heterogeneity (I^2=0.0%, Q=0.06, p=0.809). A publication bias was detected and the trim-and-fill adjusted model had a small but not significant effect size (g=0.26, 95%CI=-0.94/1.46, p=0.579) with a considerable heterogeneity (I^2=86.7%, Q=30.02, p<0.001).

The pooled effect size of the three studies considering global functioning was low and not significant (g=-0.28, 95%CI=-0.82/0.26, p=0.156) and no heterogeneity was found (I^2=0.0%, Q=1.70, p=0.428). No outliner was identified and one influential study was excluded from the sensitive analysis model, which showed a large but not significant effect size (g=-0.40, 95%CI=-2.26/1.47, p=0.225) without heterogeneity (I^2=0.0%, Q=0.65, p=0.421). A publication bias was detected and the trim-and-fill adjusted model had a negligible effect size (g=-0.12, 95%CI=-0.52/0.28, p=0.449) with a certain heterogeneity (I^2=31.3%, Q=5.83, p=0.213).

No subgroup analysis and meta-regression were conducted considering the number of studies and the lack of between-study heterogeneity.

Lastly, only one study considered self-efficacy (Edel et al., 2017) finding no significant differences between MBI and control conditions in improving this outcome.

3.8. Observational studies on adults with ADHD

3.8.1. ADHD symptoms

All five studies found improvement in ADHD symptoms, reporting a significant reduction in both attention deficit and hyperactivity/impulsivity after MBIs (Hepark et al., 2014; Janssen et al., 2018; Philipsen et al., 2007; Tarrasch et al., 2016; Zylowska et al., 2008). One study specified the effect size to be large for both the symptoms domains (Hepark et al., 2014).

3.8.2. Neuropsychological functions

Two studies considered neuropsychological functioning (Janssen et al., 2017; Zylowksa et al., 2008) finding a significant enhancement of executive functions.

3.8.3. Associated conditions

Three studies (Philipsen et al., 2007; Tarrasch et al., 2016; Zylowska et al., 2008) reported a significant improvement in depressive symptoms, whereas anxiety responded to MBIs only in one out of three studies (Zylowska et al., 2008).

Two studies investigated health status (Janssen et al., 2017; Philipsen et al., 2007), finding significant improvements.

Other associated conditions were investigated in single studies (supplementary materials S3.1)

3.8.4. Mindfulness related outcomes

Two studies (Janssen et al., 2017; Tarrasch et al., 2016) observed a significant improvement in mindfulness related outcomes after MBI.

3.8.5. General functioning and quality of life

Quality of life (Hepark et al., 2014), general functioning (Janssen et al., 2017), and satisfaction with life (Tarrasch et al., 2016) were investigated in single studies (supplementary materials S3.1).

3.9. Risk of bias and quality of the studies on adults with ADHD

Nine RCTs were assessed with RoB2 (Supplementary material S1.2). As can be seen in Supplementary material S1.3, several methodological weaknesses were found. No study reached an overall low risk of bias.

Similarly, all eight observational and controlled studies showed a high risk of bias (Supplementary material S1.4).

3.10. Children and adolescents

Fifteen studies were included on children and adolescents with ADHD (see Supplementary material S3.2 for details). The whole population was composed by 412 children and adolescents, 384 (93.2%) of whom completed the study. The age ranged from seven to 16 years.

The most adopted protocol was a combination of MBSR and MBCT.

3.11. Controlled studies on children and adolescents with ADHD

3.11.1. ADHD symptoms

ADHD symptoms were measured in seven (Huguet et al., 2019; Muratori et al., 2020; Sidhu 2015; Rynczak, 2013; van der Oord et al., 2012; Vanzin et al., 2020a, Vanzin et al., 2020b) out of the eight controlled studies included. Two studies (Rynczak, 2013; Muratori et al., 2020) also considered impulsivity as a separate outcome, whereas Sibalis et al. (Sibalis et al., 2019), Sidhu (Sidhu 2015), and Vanzin et al. (Vanzin et al., 2020b) measured attention alone. In particular, the latter investigated focused and sustained attention, attention inhibition and flexibility. MBI outperformed any control condition, the only two exceptions being Vanzin et al. (Vanzin et al., 2020a; Vanzin et al., 2020b) who did not find any difference between ACT and placebo drugs.

3.11.2. Associated conditions

Only one controlled study considered emotion dysregulation as its outcome and found MBI significantly outperformed control condition in improving emotional dysregulation (Huguet et al., 2019).

3.11.3. Mindfulness related outcomes

Mindfulness level among children was measured in two studies (Muratori et al., 2020; van der Oord et al., 2012).

3.12. Observational studies on children and adolescents with ADHD

3.12.1. ADHD symptoms

Overall, these were the most investigated outcomes. Inattention was considered in seven studies (Haydicky et al., 2015; Huguet et al., 2017; van de Weijer-Bergsma et al., 2012; Vanzin et al., 2020b; Worth, 2014; Zhang et al., 2017; Zylowska et al., 2008) whilst hyperactivity/impulsivity was investigated only in four of them (Haydicky et al., 2015; Huguet et al., 2017; Worth, 2014; Zylowska et al., 2008). ADHD symptoms were always reduced after MBIs, only in one study the control condition outperformed MBI in ameliorating hyperactivity/impulsivity (Haydicky et al., 2015).

3.12.2. Neuropsychological functions

Executive functions were investigated in four studies (Huguet et al., 2017; van de Weijer-Bergsma et al., 2012; Worth, 2014; Zhang et al., 2017). Only Worth (Worth, 2014) did not find MBI outperforming the control condition.

Behavioral problems were considered in three studies (Carboni et al., 2013; van de Weijer-Bergsma et al., 2012; Zhang et al., 2017), however, only one of them found this outcome to significantly respond to MBI (Carboni et al., 2013).

3.12.3. Associated conditions

Three studies evaluated anxiety response to MBI (Haydicky et al., 2015; Huguet et al., 2017; Zylowska et al., 2008). Post-treatment anxiety levels were lower only in one study (Zylowska et al., 2008) as Huguet et al. (Huguet et al., 2017) noticed a statistically significant reduction of parent-reported but not of self-reported anxiety symptoms and Haydicky et al. (Haydicky et al., 2015) did not find any change from baseline.

The same three studies also evaluated depressive symptoms and again only Zylowska et al. (Zylowska et al., 2008) did find a significant pre-post intervention reduction.

Fatigue was considered in a single study (van de Weijer-Bergsma et al., 2012), which did not find any improvement after MBI (van de Weijer-Bergsma et al., 2012).

3.12.4. Mindfulness related outcomes

Mindful skills (Worth, 2014), acceptance level (Haydicky et al., 2015), and mindfulness awareness (van de Weijer-Bergsma et al., 2012) were considered in one study each, with conflicting results.

3.13. Risk of bias and quality of the studies on children and adolescents with ADHD

Three RCTs were assessed with RoB2 (Supplementary material S1.2). The study showed a high risk of bias. Conversely, two studies showed some concerns only (Huguet et al., 2019; Muratori et al., 2020). All eleven observational and controlled studies showed a high risk of bias (Supplementary material S1.4).

4. Discussion

Consistently with previous systematic reviews and meta-analysis (Cairncross and Miller, 2016; Chimiklis et al., 2018; Evans et al., 2018; Lee et al., 2017; Poissant et al., 2019; Tercelli and Ferreira, 2019; Xue et al., 2019) ADHD symptoms are confirmed to be the most studied outcomes. As regards adults, the highest efficacy of MBIs was detected on attention symptoms and total ADHD symptoms (medium effect size). The small effect on hyperactivity-impulsivity disappeared when publication bias adjustment was applied as well as sensitivity analysis greatly reduced the effect size on hyperactivity-impulsivity and even that on total ADHD. Overall, MBIs confirmed their efficacy on ADHD symptoms regardless of the different adjustments, though its effect seems to be higher on attention symptoms.

Subgroup analysis and meta-regression were consistent in supporting a significantly higher efficacy of MBIs vs. inactive controls than vs. active controls, which seemed to fully explain the pooled effect size heterogeneity. According to our findings in the majority of active-controlled studies, MBIs failed to outperform psychoeducation and skills training groups. The confidence interval of pooled effect size of studies with active controls included the null value in total ADHD symptoms and hyperactivity/impulsivity subgroup analysis, but not in that of attention symptoms. This small advantage of MBIs on psychoeducation should be confirmed by future and better designed RCTs, however, MBIs option should be taken into account in patients with predominantly inattentive presentation or if residual attention symptoms persist after psychoeducation or skills training. Among the inactive-controlled RCTs, three studies stood out for their large effect size on attention and total symptoms (Gu et al., 2018; Mitchell et al., 2017; Schoenberg et al., 2014), which was greater than that reached by the most efficacious stimulant treatments (see Cortese et al., 2018 for a comprehensive meta-analysis). Quality and size mainly explain this results, but differences between control groups (i.e., WL for aforementioned MBIs' studies and placebo drugs for stimulants RCTs) should be also taken into account, since some studies have reported a considerable pre-post effect of placebo drug at least in children (Sandler et al., 2010; Sandler and Bodfish, 2008). It could be suggested that any intervention seems to have a significantly higher effect than WL in improving ADHD symptoms.

Beyond ADHD symptoms, mindfulness skills, neuropsychological performance, and depression were the most studied outcomes in the adult ADHD population.

Concerning mindfulness skills, a medium effect size was estimated by meta-analysis that persisted after sensitivity analysis and publication bias adjustment, but it was affected by heterogeneity due to control conditions: MBIs showed a large effect size when compared to inactive control, whereas had no effect when compared to active control. Future studies should investigate this aspect, also evaluating the actual amount of mindfulness daily practice.

Only half of active-controlled studies found MBIs more effective in

improving executive functions. Meta-analysis partially solved this issue as both of those active-controlled studies had a confidence interval of effect size that included the null value. Overall sample size was medium without heterogeneity but both sensitivity analysis and publication bias adjustment really affected this estimation. Subgroup analysis found a large effect size for inactive-controlled studies, which contributed significantly to the overall effect size. Conversely, active-controlled studies did not show any effect. Meta-regression did not confirm a moderator effect of control condition on heterogeneity. Further studies are needed to confirm MBIs efficacy in ameliorating this outcome, regardless of the control condition. Moreover, a possible latency of the response could be involved as in a longitudinal study MBI showed a positive effect on executive functions only at follow-up but not at post-treatment. Only one study considered working memory, revealing that MBI and psychoeducation are similarly effective.

The poor performance of MBIs on depression levels suggested by our systematic review was confirmed by meta-analysis conducted on controlled studies that found a small and homogeneous effect size, regardless of sensitivity analysis and without publication bias. Conversely, anxiety levels seemed to remarkably improve according to meta-analysis conducted on controlled studies, which showed a medium effect size without heterogeneity and publication bias, which persisted after sensitivity analysis. Further active-controlled studies should include this outcome to provide data on the efficacy size of MBIs on anxiety in ADHD patients.

According to our findings, MBIs seemed not to confirm in ADHD patients the efficacy found in other clinical populations in reducing depressive and anxiety symptoms (Hofmann and Gómez, 2017).

Global functioning and quality of life are both improved by MBIs in all observational studies and once again MBIs were more effective than inactive but not than active controls. A meta-analytic subgroup analysis to confirm systematic review findings was not allowed due to the paucity of studies for either quality of life and global functioning. The meta-analysis showed a large effect size on quality of life with a lot of heterogeneity due to low effect reported by one active-controlled study, that was greatly reduced after publication bias adjustment, confirming the need for further controlled studies investigating this outcome. As regards global functioning, no effect of MBI was detected by meta-analysis even after publication bias adjustment.

Particularly noteworthy is that few authors have studied emotional dysregulation (Mitchell et al., 2017; Philipsen et al., 2007), anger outbursts (Cole et al., 2016), and delayed sleep onset (Tarrasch et al., 2016).

No study has considered self-esteem as an outcome, which is instead a common condition in ADHD, and can also lead to misdiagnosis (i.e., dysthymia, depression), significantly affecting patients' functioning and quality of life (Kooij et al., 2019).

As regards children and adolescents, the number of studies and the overall sample was really smaller than those including adults and no active-controlled studies have been conducted yet. As with adults, ADHD symptoms confirmed to be the most studied outcome. All the controlled and about half of observational studies found significant improvements. Notably, MBIs showed to be more effective on inattention than on hyperactivity/impulsivity. A meta-analytic investigation on children studies could not be performed because of the low number of studies.

With regard to other outcomes, really few observational studies considered depression, anxiety (in one study reported as internalizing symptoms), mindfulness related outcomes, and executive functions, whereas no controlled studies have investigated neuropsychological functions, general functioning and quality of life.

The most relevant finding regarding children and adolescents is that only one RCT considered emotional dysregulation, whereas none have evaluated the effect of MBIs on the other ADHD diagnostic-associated features, i.e., working memory and sleep quality.

The included studies had several limitations. The risk of bias assessment revealed that 75% of the RCTs have at least some concerns and that all controlled or observational studies have a high risk of bias. Only few studies performed a follow-up and the sample size was small in almost all of the included studies. Ad-hoc mindfulness protocols have often been used instead of already validated protocols to fit the studied populations (e.g., protocols adapted to children, to the school context or, more generally, to ADHD) without providing sufficient details on the adopted interventions and that reduces the methods reproducibility.

No studies compared mindfulness different protocols with each other or focused on the efficacy of mindfulness single components (self-judgment, self-compassion, participatory attention and observation, non-judgmental labeling, acceptance, etc.). Moreover, the number and the duration of sessions varied considerably across the studies. Few studies reported data on acceptability rate and adherence. Altogether, these limitations have important consequences on the possibility to draw a solid conclusion regarding the effectiveness of MBIs in ADHD and on the estimation of a true effect size during meta-analytic evaluation.

The selected studies also had some strengths. In most of the articles the outcome evaluation criteria were well explained and the assessment tools were validated. Furthermore, each study investigated a wide variety of outcomes, offering an overview of the potential that MBIs could have in treating patients with ADHD.

4.1. Limitations and strengths of this review

To our knowledge, this is the first systematic review that included any type of study design, MBI protocol, outcome, and age of the population. According to previous reviews findings about age, data were collected separately for adults and children, and subgroup analysis and meta-regression were performed to evaluate the impact of the type of control population on effect size. Moreover, unlike prior meta-analyses (Xue et al., 2019), influential studies were detected using different levels of methods (leave-one-out, Baujat's graphical method, and GOSH method).

4.2. Implications for clinical practice and research

This systematic review offers new perspectives for future research. The low general methodological quality highlights the need to conduct more active-controlled studies, on larger sample sizes with measurement at follow-up. Future studies should choose validated mindfulness protocols in order to reduce the heterogeneity and increase replicability and comparability.

Concerning outcomes, the systematic review highlights the importance of a deeper investigation on the most common ADHD associated features (i.e., emotional dysregulation, executive functions and working memory, delayed sleep onset). Future studies should also include among their outcomes the commonly present low self-esteem, especially when anxiety and depression are investigated.

From a clinical standpoint, according to the poor available evidence, we cannot conclude that MBIs are superior to other active interventions in ameliorating all the considered outcomes, suggesting a role as complementation and not as replacement of the psychoeducation in the management of patients with ADHD, consistently with some current guidelines' recommendations (Kooij et al., 2019).

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CRediT authorship contribution statement

Francesco Oliva: Conceptualization, Formal analysis, Project administration, Resources, Supervision, Validation, Writing - review & editing. **Francesca Malandrone:** Writing - review & editing, Investigation, Methodology, Visualization, Writing - original draft, Writing -

original draft, Writing - review & editing. **Giulia di Girolamo:** Data curation, Writing - review & editing. **Santina Mirabella:** Data curation, Writing - original draft. **Nicoletta Colombi:** Methodology, Resources, Validation. **Sara Carletto:** Investigation, Supervision, Writing - review & editing. **Luca Ostacoli:** Conceptualization, Project administration, Supervision, Validation.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2021.05.068.

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RESEARCH ARTICLE

Psychometric validation of the Italian version of the Emotional Style Questionnaire

Francesca Malandrone[1], Alberto Catalano[1], Federica Carfì[1], Claudio Gentili[2], Silvia Bianchi[3], Francesco Oliva[1], Fulvio Ricceri[1], Luca Ostacoli[1]*, Pelin Kesebir[4], Richard J. Davidson[4], Sara Carletto[5]

1 Department of Clinical and Biological Sciences, University of Torino, Torino, Italy, **2** Department of General Psychology University of Padova, Padova, Italy, **3** Private Psychotherapist, Palermo, Italy, **4** Center for Healthy Minds, University of Wisconsin–Madison, Madison, Wisconsin, United States of America, **5** Department of Neuroscience "Rita Levi Montalcini", University of Torino, Torino, Italy

* luca.ostacoli@unito.it

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Abstract

Emotional styles concern the ways in which individuals adapt and respond to the world and can be defined using six dimensions: outlook, resilience, social intuition, self-awareness, sensitivity to context and attention. The Emotional Style Questionnaire (ESQ) assesses how people vary across the dimensions and gauges an individual's overall level of emotional health. An Italian version of the ESQ (ESQ-ITA) could favour the understanding of cultural characteristics concerning emotions and personality within the Italian population, with both clinical and social implications. The aim of the present study is to validate the ESQ in the Italian language and to assess its psychometric properties. Two studies were conducted. Study 1 examined construct validity, internal consistency, and test–retest reliability, through Exploratory Factor Analysis (EFA) and Confirmatory Factor Analysis (CFA), Cronbach's alpha estimates, and by estimating the Spearman's rank correlation Study 2 examined construct validity and internal consistency through the CFA and Cronbach's alpha estimates and investigated criterion validity by correlating the ESQ-ITA dimensions with the corresponding scales or subscales used for the validation estimating, again, the Spearman's rank correlation coefficient Study 2 also examined the criterion validity of the validated scales and the ESQ-ITA overall score to assess its suitability as an indicator of emotional health. ESQ-ITA was confirmed to be reliable and stable. The correlation between the ESQ-ITA overall score and the other scales and questionnaires supports the use of ESQ-ITA to measure emotional health. The Italian version of the ESQ opens up the possibility to enrich the research landscape with new knowledge that will be useful for advancing the pathogenetic and therapeutic aspects of psychological distress and emotional dysregulation.

Introduction

Emotions play an extremely significant role in the human experience. The differences in the way each one of us lives, perceives, and reacts can be attributed to our unique emotional experience of life, and they are closely related to individual and social psychological well-being.

Considering the available literature, Davidson [1,2] proposed the concept of "emotional styles" with the aim of identifying the components that contribute to the emotional life of an individual. Emotional styles represent the way in which an individual adapts and responds to the world, and they can predict the probability that a person may feel certain emotions or experience certain moods. According to Kesebir and colleagues [3], each person has their own Emotional Style, one which is governed by specific brain circuits, identifiable using neuroimaging techniques. As such, our unique Emotional Style reflects the kind of emotional states we experience, as well as their intensity and duration[3]. It can, therefore, be defined as the "atom of our emotional life" [4]. Emotional Style is defined using six dimensions: outlook, resilience, social intuition, self-awareness, sensitivity to context and attention. Outlook refers to the ability to sustain positive emotions over time. The ability to sustain the experienced positive emotions is what distinguishes non-depressed individuals from depressed ones, characterized by high and low levels of activity in the nucleus accumbens, respectively [5]. Resilience, like the outlook dimension, describes a quality of affective chronometry, namely the time course of emotional responding [6]. It refers to the ability to recover from negative emotions or events. Resilience is important because emotional well-being is not only defined by the magnitude of one's initial emotional reaction to an event, but also by how long the emotional response is sustained [7,8]. Social intuition refers to one's degree of attunement to nonverbal social cues (voice tone, body language, facial expressions). Sensitivity to context refers to how much our emotional and behavioural responses consider our social context. Self-awareness refers to the ability to perceive one's bodily signals that reflect emotions. Finally, Attention refers to the ability to focus on something, screening out distractions and staying focused.

Recently, Kesebir et al. [3] validated the Emotional Style Questionnaire–ESQ, an easily implementable, 24-item self-report measure which provides a means to assess how people vary across the six dimensions and to generate a measure of emotional health. The Emotional Style construct was assimilated to the framework on personality set out by Davidson [1] and then further elaborated by Kesebir [3]. Indeed, they state that "each individual personality and temperament reflects a different combination of the six dimensions of Emotional Style" [4], and in their validation study the authors found a significant correlation between the ESQ and the Big Five Inventory, which was also recently associated with adaptive and maladaptive emotion regulation [9]. Therefore, the ESQ is appropriate for both research and clinical settings, both as a stand-alone measure of psychological well-being as well as a tool to investigate each of the six dimensions. The ESQ allows us to identify the strengths and weaknesses of an individual's Emotional Style, thus enabling psychological interventions which exploit the plasticity of brain structures to recover from any dysfunction with the aim of generating a healthy emotional life.

Due to its characteristics, the ESQ can also be a brief and effective tool for investigating emotional and personological aspects in other cultural and linguistic contexts. To date, the ESQ has been translated into Persian [10], Polish [11] and German [12], and its psychometric properties tested; each validation process yielded reliability and validity coefficients similar to that of the original version. An Italian version of the ESQ could offer interesting implications for future research as well, to deepen our understanding of cultural characteristics concerning emotions within the Italian population, with both clinical and social implications. The aim of the present study was to validate the ESQ in the Italian language and to assess its psychometric properties using a study sample recruited from the general population.

Methods

The research was approved by the authors of the original validation of the questionnaire. The research methodology includes two studies. Both study 1 and 2 were conducted at the

University of Turin, Italy. The study was conducted in accordance with the Declaration of Helsinki, and the research protocol was approved by the Ethics Committee of the University of Turin (prot. number 251935). Electronic informed consent was obtained by asking all participants to click a button at the beginning of the online survey consenting to their participation. Participation was voluntary and anonymous, and participants received no compensation.

Participants

Two different recruitments were conducted, and, for both studies, the inclusion criterion was that individuals were aged between 18 and 75 years. Symptoms related to anxiety, depression and stress were also recorded, not with the aim of excluding participants but to be able to carry out separate analyses by symptom level.

Participants were recruited by sharing the questionnaire link via mailing lists and social networks. The questionnaire provided a description of the project, listed its research objectives and requested that informed consent be given in order to participate in accordance with the criteria set out by the University of Turin's Bioethics Committee. Informed consent was obtained by asking all participants to click a button at the beginning of the online survey which gave their consent to participate in the study.

Study 1

The aim of Study 1 was to examine the construct validity, internal consistency and test–retest reliability of the Italian version of the ESQ (ESQ-ITA).

In the first phase, the ESQ was adapted linguistically and culturally into Italian, after which the psychometric properties were investigated following the protocol described in Kesebir et al [3]. The questionnaires were administered to a group of healthy volunteers, stratified by age, at baseline (TIME 1) and at 4 weeks (TIME 2) to evaluate test-retest reliability.

Translation and cultural adaptation

The Italian adaptation of the ESQ was carried out following the steps of the Cross-Cultural adaptation process recommended by Guillemin et al., to obtain a semantic, idiomatic, experiential, and conceptual equivalence [13,14]. The translation of the ESQ from English into Italian was conducted by an Italian native speaker. Then, a bilingual Italian-English person (a native English speaker blind to the original version of the ESQ), performed a back-translation. Comparing the original items with the back-translated items, further changes were made in the Italian translation, after which a second back-translation was performed. The consensus between the two sets of forward-backward translations was established through a discussion between two psychologists from our research group and the native speaker. To verify that the translation was adequate not only from a linguistic but also from a cultural point of view, its face validity was established with the assistance of 20 voluntary subjects, who provided useful feedback to improve some lexical and syntactic nuances through individual interviews in which the meaning of each questionnaire item was discussed with each volunteer.

Data analysis

Quantitative data are presented as median values plus the interquartile range, whereas quantitative data are presented as frequencies and percentages. The distribution of the quantitative variables was tested using the Shapiro-Wilk test, which showed almost all distributions to deviate from normality. The validation of the Italian version of the Emotional Style Questionnaire

consisted of a four-step process, using four successive analyses conducted in R software (version 4.0.2) [15].

First, in order to conduct a cross-cultural validation by examining the six dimensions identified in Kesebir et al. [3], an Exploratory Factor Analysis (EFA) was performed to identify the items contributing to each of these factors. This was done after checking the suitability of the data for factor analysis by means of the Kaiser-Meyer-Olkin (KMO) test to measure the sampling adequacy (MSA), and the Bartlett's test of sphericity to test whether the correlation matrix was significantly different from an identity matrix. Since the data were not normally distributed, principal axis factoring (PAF) was used as the extraction method of choice as it does not assume the data to be normal. As for the rotation method, both varimax and oblimin were used; however, as they led to the same conclusions, only the results for the varimax method are presented.

Second, we estimated the internal consistency of the factors extracted in the EFA as well as that of the ESQ-ITA's overall score using Cronbach's alpha. Due to inconsistencies in the results, we conducted parallel analysis (n = 5) in order to identify the most suitable number of factors, and then re-ran the EFA using five factors. The results obtained collapsed the outlook and resilience dimensions into a single dimension, thus the four items related to this dimension with the lowest factor loadings were excluded and the EFA was re-run.

Later, a Confirmatory Factor Analysis (CFA) was conducted considering the original six factors. To assess the goodness of fit, we estimated and reported different statistics: the Comparative Fit Index (CFI), the Akaike Information Criterion (AIC), the Root Mean Square Error of Approximation (RMSEA), and the Standardized Root Mean Square Residual (SRMR).

Finally, the test-retest reliability of the questionnaire over time was tested. The test-retest reliability was investigated by estimating the Spearman's rank correlation coefficient between each item response at Time 1 and the same response at Time 2. The same type of analysis was also performed for the ESQ-ITA overall score and for the dimensions detected and investigated in this study.

Results

The sample characteristics are described in Supplementary Material 2 (S2A Table in S2 File). The sample was composed of 208 participants with a median age of 43.00 years (IQR = 30.00–58.00). Of the 208 participants, 119 (57.2%) filled out the questionnaire in Time 1 and Time 2.

Before conducting the factor analysis, we performed the KMO test and the Bartlett's test of sphericity to establish the data's suitability for this type of analysis. The overall MSA was 0.75 and Bartlett's test was statistically significant at a 95% confidence level ($\chi 2 = 1281.18$), thus we concluded the data to be suitable.

S2B Table in S2 File shows the factor loadings related to the EFA conducted at Time 1, which considered the six factors described in Kesebir et al. [3]. From the loadings, it emerged that the first principal axis (PA1) extracted identified two dimensions (outlook and resilience even if one question is missing), while PA2, PA3, PA4, and PA5 each identified a single dimension, namely sensitivity to context, attention, social intuition and self-awareness, respectively. Finally, PA6 did not identify any dimension. For this reason, this factor analysis did not seem to identify the six dimensions correctly. In total, the extracted factors explained 41.6% of the total variance. Next, we determined the internal consistency of each dimension and that of the ESQ-ITA overall score by estimating Cronbach's alphas. The values are summarised in S2C Table in S2 File. Some low values of the Cronbach's alphas, such as that associated with social intuition ($\alpha = 0.57$), were at the limit of acceptability. Since the factor analysis with six factors

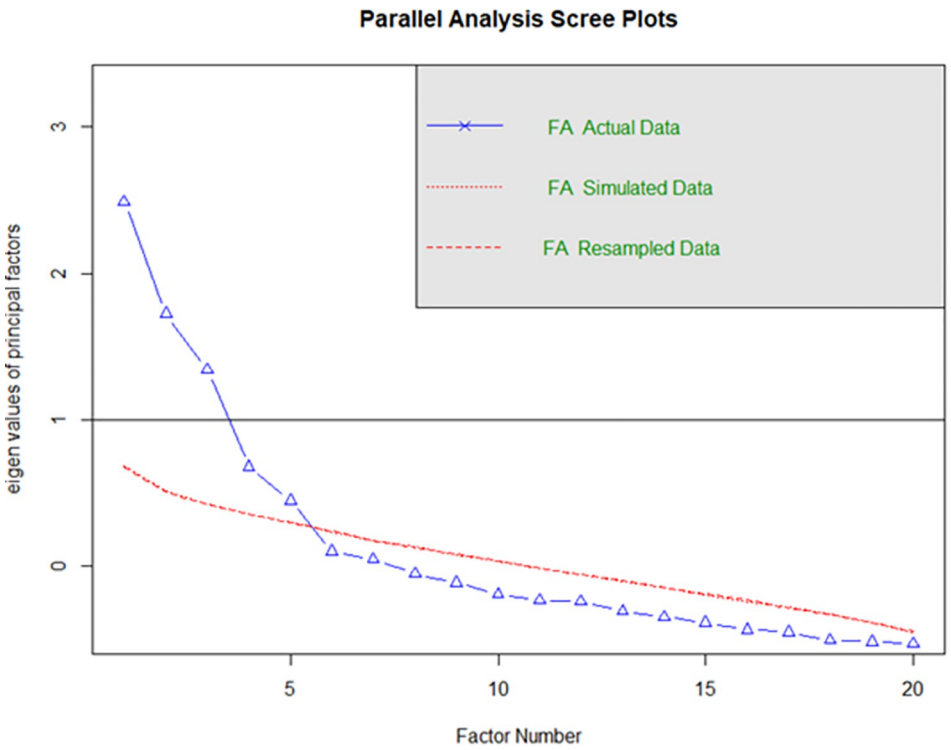

Fig 1. Study 1 scree plot on the entire population.

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did not identify the six dimensions correctly, we conducted the same analysis excluding the items relating to the outlook and resilience dimensions with the lowest factor loadings (i.e., items 1, 2, 8 and 14). Therefore, we ran a new EFA considering the remaining 20 items only. The results of the KMO test (overall MSA = 0.71) and the Bartlett's test of sphericity (χ^2 = 999.18) revealed that the data had become more suitable for factor analysis. We then identified the most suitable number of factors by means of parallel analysis. The resulting scree plot is shown in Fig 1 which shows the most suitable number of factors to be five; for this reason, we ran an EFA extracting five factors only. S2D Table in S2 File in summarises the factor loadings. Each factor extracted identified a single dimension. The four items related to the dimensions outlook and resilience were identified by the first factor, and together form the first dimension, which we call "outlook/resilience"; PA3 clearly identified the dimension "sensitivity to context", PA4 identified the dimension "attention", "social intuition" was identified by PA2, and finally PA5 identified the dimension "self-awareness" dimension. In total, the extracted factors explained 41.1% of the total variance.

Regarding the internal consistency, S2E Table in S2 File shows the values of Cronbach's alpha for the five dimensions and the ESQ-ITA overall score. As the table shows, the alpha values related to the first dimension were greater with respect to the previous values.

The CFA, whose results are shown in S2F Table in S2 File, confirmed the six-factor structures (Outlook, Resilience, Social Intuition, Self-Awareness, Sensitivity to Context, and Attention) identified in the original validation. The CFI was 0.893 and AIC was 16823.612. With regard to the RMSEA and SRMR, they were 0.047 (90% Confidence Interval (CI): 0.036–0.058) and 0.068, respectively.

Finally, to assess the test-retest reliability of the questionnaire over time, we estimated the correlation coefficients between the response to each item at Time 1 and Time 2, and between

the score for each of the six dimensions investigated in this study at the two different times. The results are summarized in S2G Table in S2 File. All correlations were positive and statistically significant ($p < 0.01$). Therefore, across an interval of 4 weeks, the test-retest results indicate very good reliability, and show that the questionnaire was reliable at both the item and dimension level. Compared with the original validation data published by Kesebir et al. [3], the factor coefficients are slightly lower, although they remain positive and statistically significant ($p<0.01$). In conclusion, the validation results show the Emotional Style Questionnaire and extracted dimensions in the Italian version to be as reliable as in the original version.

Study 2

As the EFA conducted in Study 1 produced different results with respect to the original validation study conducted by Kesebir et al. [3], and some items had relatively poor factor loadings, a number of linguistic changes were made to the questionnaire items to improve comprehensibility and new study with a new recruitment was conducted. In particular, we held a focus group in which two psychologists from our research group and five volunteers from the 20 who had participated in face validation took part. Within the focus group, the possible culturally mediated interpretation of the outlook and resilience items were questioned and reformulated once unanimous agreement was reached. The final Italian version of the Emotional Style Questionnaire (ESQ-ITA) is provided in S1 File. In terms of its readability, the Gulpease Index [16] for the final scale was 86 (84 in Study 1), meaning that it would be easily understood by a person with about 5 years of formal education and very easily understood by a person with more than 5 years of formal education.

In accordance with the original validation study [3], Study 2 aims: 1) to examine the construct validity and internal consistency of the final version of the ESQ-ITA; 2) to investigate the criterion validity correlating the ESQ-ITA dimensions and the corresponding scales or subscales used for validation; and 3) to examine the criterion validity of the validated scales or subscales and the ESQ-ITA overall score to assess whether it could be considered an indicator of emotional health (healthy emotionality).

Validation protocol

In order to examine the criterion validity of the individual subscales and the ESQ-ITA overall score (healthy emotionality), the following questionnaires and scales validated in the Italian language were selected.

Emotional Style Questionnaire—Italian Version (ESQ-ITA). The Emotional Style Questionnaire (ESQ) [3] is a 24-item self-report measure that evaluates people's responses across six dimensions and provides an overall score on healthy emotionality. Participants completed the ESQ, responding to 24 statements using a scale ranging from 1 (strongly disagree) to 7 (strongly agree). The original validation study reported the Cronbach's alpha values for the finalized 24-item scale and for each of the dimensions. They were: 0.93 for the overall scale, 0.87 for outlook, 0.91 for resilience, 0.84 for social intuition, 0.81 for self-awareness, 0.82 for sensitivity to context and 0.84 for attention; all values indicate good internal consistency.

Depression, Anxiety and Stress Scale (DASS-21). DASS-21 is a 21-item scale consisting of 3 subscales which assess the respondent's levels of depression, anxiety and stress [17,18]. Participants indicated the extent to which each statement applied to their inner state experienced over the course of the past week, on a scale ranging from 1 (strongly disagree) to 7 (strongly agree). Cronbach's alpha was 0.91 for the depression subscale, 0.88 for the anxiety subscale, 0.83 for the stress subscale, and 0.92 for the DASS-21 total score.

Mindful Attention Awareness Scale (MAAS). The MAAS is a 15-item scale (Cronbach's alpha, 0.84) which aims to investigate an individual's awareness of and attention paid to what

is taking place in the present [19,20]. Participants choose their response on a scale from 1 (almost never) to 6 (almost always).

Multidimensional Assessment of Interoceptive Awareness (MAIA). The MAIA is a multidimensional measure of interoceptive body awareness [21,22]. Its 32 items assess eight concepts related to interoceptive awareness (e.g., awareness of body sensations, and awareness of the connection between body sensations and emotional states). Participants respond to this measure using a 7-point Likert scale (1 = strongly disagree; 7 = strongly agree). Cronbach's alpha for the internal consistency in the emotional awareness dimension was 0.86 [23]. The MAIA scale was used to provide a score against which the outcome of the self-awareness subscale of the ESQ-ITA could be compared.

Resilience Scale for Adults (RSA). The Resilience Scale for Adults [24,25] is a 33-item self-report instrument (Cronbach's alpha ranges from 0.67 to 0.81) for evaluating the six dimensions of resilience in adults: (1) perception of the self, (2) planned future, (3) social competence, (4) family cohesion, (5) social resources, and (6) structured style.

Life Orientation Test–Revised. The LOT-R scale, developed by Scheier et al. [26,27], measures people's expectations regarding the favourability of future outcomes (Cronbach's alpha, 0.81). On a 7-point scale ranging from 1 (strongly disagree) to 7 (strongly agree), participants indicated the level to which they agreed with each statement. The LOT-R scale was used to provide a score against which the outcome of the outlook subscale of the ESQ-ITA could be compared.

Autism Spectrum Quotient (AQ-10). The AQ-10 scale, developed by Allison et al. [28,29], measures autism level. Participants express their agreement with each sentence on a 7-point Likert scale ranging from 1 (strongly disagree) to 7 (strongly agree). Cronbach's alpha coefficients demonstrated fair internal consistency (0.76 for AQ total, 0.64 for communication, 0.68 for social skills, 0.52 for imagination, 0.58 for local details, 0.54 for attention switching). The AQ-10 scale was used to provide a score against which the outcome of the social intuition subscale of the ESQ-ITA could be compared.

Data analysis

As in Study 1, data are presented as median frequencies and percentages plus the interquartile range; the distribution of the quantitative variables was tested using the Shapiro-Wilk test. After checking the data's suitability for factor analysis using the KMO test and Bartlett's test of sphericity, we ran a CFA on the new version of the questionnaire, in order to verify whether this tool is exactly as functional as the original one. The CFI, AIC, RMSEA, and SRMR were reported to assess the goodness of fit. Then, we estimated Cronbach's alpha for each dimension identified as well as for the ESQ-ITA overall score. This was done both on the entire sample and on subjects who reported a DASS Depression subscale score ≤ 13 and a DASS Anxiety subscale score ≤ 9.

Finally, we evaluated whether the criterion validity converged or diverged from its construct estimating the correlation between the six dimensions and the ESQ-ITA overall score and the validated scales and subscales. We used Spearman's rank correlation coefficient given the non-normality of data. The analyses were conducted both on the entire sample and on subjects who reported a DASS depression subscale score ≤ 13 and a DASS anxiety subscale ≤ 9.

Results

Table 1 summarises the sample characteristics and shows the median age of the participants to be 33 years (IQR = 26.00–53.00). Out of the 261 subjects recruited onto the study, 197 reported a DASS Depression subscale score ≤ 13 and a DASS Anxiety subscale score ≤ 9.

Table 1. Study 2 sample characteristics.

Variable	Freq.	Perc.
Entire population		
Education		
5 years of secondary school education	9	3.45
13 years of secondary school education	61	23.37
University degree	154	59.00
Post-graduate degree	37	14.18
Age	33.00 (26.00–53.00)*	
Sample characteristics following the exclusion of subjects with anxiety and depression cut-offs greater than 10 and 14, respectively.		
Education		
5 years of secondary school education	6	3.05
13 years of secondary school education	45	22.84
University degree	115	58.38
Post-graduate degree	31	15.73
Age	33.00 (26.00–53.00)*	

* Median (interquartile range).

Descriptive statistics related to the entire sample and following the exclusion of subjects with anxiety and depression scores greater than 10 and 14, respectively. Quantitative data reported as median values plus the interquartile range (IQR); qualitative data are reported as frequencies and percentages.

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Before running the CFA, we performed the KMO test and the Bartlett's test of sphericity. Considering the entire sample, the overall MSA was 0.86 and Bartlett's test statistic significant for a 95% confidence level ($\chi^2 = 2870.67$), thus supporting the data's suitability for factor analysis. S2H Table in S2 File reports the results related to the CFA, which confirmed the six-factor structures originally identified. Regarding the goodness of fit statistics, the CFI and AIC were 0.899 and 20585.349, respectively. In addition, RMSEA was 0.066 (90% CI: 0.058–0.074) and SRMR was 0.071 The estimates related to the Cronbach's alpha coefficients are summarised in S2I Table in S2 File. Since all values of Cronbach's alpha were greater than 0.71, we can conclude that the questionnaire identified six consistent dimensions. Similar results were obtained for the CFA conducted on the subjects who reported a DASS Depression subscale score ≤ 13 and a DASS Anxiety subscale ≤ 9. The overall MSA was 0.78, the Bartlett's test of sphericity was statistically significant for a 95% confidence level ($\chi^2 = 1893.54$). All overall MSA and $\chi 2$ estimates related to the Study 1 and Study 2 are summarised in S2L Table in S2 File. Once again, from the results it emerged that CFA confirmed the original six-factor structures (Table 2). In this case, the CIF was equal to 0.877 and AIC was 15016.439. In addition, the RMSEA was 0.067 (90% CI: 0.057–0.076) and SRMR was 0.070. Regarding internal consistency, Table 3 shows the Cronbach's alpha values related to the six dimensions and to the ESQ-ITA overall score. As the estimates show, the values were slightly lower compared with those for the entire sample.

Finally, given the non-normality of the data, Spearman's rank correlation coefficients were calculated to estimate the extent to which each of the dimensions and the ESQ-ITA overall score correlated with the validated scales and subscales. The Spearman's rank correlation coefficients are summarised in Table 4. As the results show, almost all correlations were statistically significant, considering a 95% confidence level showing that the criterion validity converges from its constructs.

Table 2. Study 2 results related to the Confirmatory factor analysis (CFA) after exclusion of subjects with anxiety and depression cutoffs greater than 10 and 14 respectively.

Dimension	Item	Factor loadings	p-value
Outlook			
	Item 1	0.588	< 0.001
	Item 7	0.823	< 0.001
	Item 13	0.655	< 0.001
	Item 19	0.760	< 0.001
Resilience			
	Item 2	0.696	< 0.001
	Item 8	0.690	< 0.001
	Item 14	0.655	< 0.001
	Item 20	0.714	< 0.001
Social Intuition			
	Item 3	0.717	<0.001
	Item 9	0.733	< 0.001
	Item 15	0.671	< 0.001
	Item 21	0.631	< 0.001
Self-Awareness			
	Item 4	0.764	< 0.001
	Item 10	0.791	< 0.001
	Item 16	0.745	< 0.001
	Item 22	0.463	< 0.001
Sensitivity to the Context			
	Item 5	0.894	< 0.001
	Item 11	0.633	< 0.001
	Item 17	0.680	< 0.001
	Item 23	0.214	0.016
Attention			
	Item 6	0.792	< 0.001
	Item 12	0.726	< 0.001
	Item 18	0.717	< 0.001
	Item 24	0.700	< 0.001

Factor loadings and p-value related to Confirmatory factor analysis (CFA) performed in Study 2 after exclusion of subjects with anxiety and depression cutoffs greater than 10 and 14, respectively, implemented on the new Italian version of the ESQ questionnaire. The results confirmed the six-factor structures originally identified and proposed by Kesebir et al., 2019.

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Discussion

This study aimed to validate the Italian version of the ESQ [3], an easily implementable self-report instrument which reveals how people vary across six dimensions (outlook, resilience, social intuition, self-awareness, sensitivity to context, and attention), identifies their Emotional Style, and provides an overall measure of emotional health.

The final version of the ESQ in the Italian language (ESQ-ITA) is composed of 24 items which allow the identification of six subscales (namely, outlook, resilience, context sensitivity, social intuition, attention, and awareness). The questionnaire is reliable, as confirmed by Cronbach's alpha coefficients greater than 0.60, and stable, as shown by the test-retest analysis, with satisfactory psychometric properties. The correlation between the ESQ-ITA overall score

Table 3. Study 2 Cronbach's alpha values following the exclusion of subjects with anxiety and depression cut-offs greater than 10 and 14, respectively.

Dimension	*Alpha*	*Mean*	*SD*
Outlook	0.80	4.9	1.10
Resilience	0.78	4.2	1.10
Social Intuition	0.78	5.5	0.86
Self-Awareness	0.78	5.4	1.10
Sensitivity to Context	0.69	5.4	1.10
Attention	0.82	4.7	1.20
ESQ-ITA Overall Score	0.84	5.0	0.65

Cronbach's alpha estimates for each dimension identified and the total score following the exclusion of subjects with anxiety and depression cut-offs greater than 10 and 14, respectively. The mean value plus standard deviation (SD) for the items that made up each dimension and the ESQ-ITA overall score were also calculated.

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and other scales and questionnaires suggests that, as for the original version, the Italian version similarly provides a valid measure of emotional health. In fact, the ESQ-ITA overall score positively correlated with optimism, resilience, attention, self-awareness and interoceptive awareness, whereas it negatively correlated with autistic traits, depression and anxiety symptoms, and stress.

As in the original validation study [3], a strong correlation between the outlook and resilience dimensions (0.79 with $p < 0.01$) was found, suggesting them to be two overlapping constructs. The same conclusion was arrived at in the German validation study [12]; the authors suggested that outlook could constitute an aspect of resilience, and advised that further studies would be needed to examine the differences between the two constructs at both the psychometric level and underlying neural level. The possibility also remains that in the Italian and German versions of the questionnaire, a cultural influence may be in effect. Indeed, Cameron and colleagues [30] suggested a strong role of culture in the determination of resilience, together with the social environment and psychological and physiological processes. Other authors have similarly suggested resilience to be deeply correlated with the ability to experience a sense of satisfaction and positive emotions, thereby identifying resilience not only as the ability to overcome adversity but also as the ability to increase positive affectivity [31–35].

The main limitation of this study is that education level was not uniformally distributed across the sample, which contained a high number of university graduates. Although education level as a modifying factor has never been specifically investigated in the validation studies performed to date, the possibility remains that education level may influence the questionnaire's comprehension. In the present study, it was not possible to do a stratified analysis due to the limited sample size, which would not have allowed us to obtain consistent results. However, as other authors have done, we specifically performed a readability assessment to address this issue using the Gulpease Index [16]–an index similar to the Gunning Fog Index which was purposely built to analyse the Italian language–the results of which concluded our study to be adequately readable. Finally, another limitation is the possible under-powered sample in Study 1. However, because the estimates were statistically significant both in the CFA and EFA, the under-powered sample did not influence our results in the Study 1.

The Italian version of the ESQ offers interesting implications for future research; for instance, future studies will be able to assess whether differences exist between subgroups of respondents divided according to education level. By using this tool, future studies will be able to deepen our understanding of cultural characteristics concerning emotions within the Italian population, with both clinical and social implications.

Table 4. Study 2 Spearman's rank correlation coefficients.

Scale	Outlook	Resilience	Social Intuition	Self-Awareness	Sensitivity to Context	Attention	Total Score
			Entire population				
LOTR	0.59***	0.45***					0.49***
RSA PS	-0.33***	-0.35***					-0.37***
RSA PF	0.60***	0.52***					0.57***
RSA CS	0.07	0.01					0.04
RSA SS	-0.03	-0.05					-0.03
RSA CF	0.44***	0.32***					0.45***
RSA RS	0.47***	0.27***					0.40***
RSA TOT	0.58***	0.41***					0.52***
ASQ			-0.28***				-0.52***
MAAS				0.43***	0.35***	0.57***	0.63***
MAIA NOT				0.38***			0.22***
MAIA NOT DIST				0.11			-0.02
MAIA NOT WORR				0.07			0.27***
MAIA ATTREG				0.38***			0.44***
MAIA EMAW				0.36***			0.25***
MAIA SELF-REG				0.37***			0.49***
MAIA BODYLIST				0.45***			0.38***
MAIA TRUST				0.45***			0.51***
	Subjects after exclusion of subjects with anxiety and depression cutoffs greater than 10 and 14 respectively						
LOTR	0.50***	0.33***					0.38***
RSA PS	-0.24***	-0.25***					-0.24***
RSA PF	0.48***	0.42***					0.42***
RSA CS	0.05	-0.03					0.01
RSA SS	-0.01	-0.02					-0.01
RSA CF	0.38***	0.24***					0.39***
RSA RS	0.35***	0.09					0.25***
RSA TOT	0.50***	0.31***					0.42***
ASQ			-0.28***				-0.53***
MAAS				0.39***	0.33***	0.56***	0.58***
MAIA NOT				0.40***			0.26***
MAIA NOT DIST				0.11			-0.01
MAIA NOT WORR				0.09			0.25***
MAIA ATTREG				0.36***			0.40***
MAIA EMAW				0.29***			0.24***
MAIA SELF-REG				0.33***			0.43***
MAIA BODYLIST				0.33***			0.35***
MAIA TRUST				0.39***			0.41***

*** $p < 0.01$

** $p < 0.05$

* $p < 0.1$.

Correlations between the factors extracted from the factor analysis or the total score and other scales/subscales already validated in the literature. Correlations were estimated using the Spearman's rank correlation coefficient. The correlation coefficients were calculated both on the entire sample and following the exclusion of subjects with anxiety and depression cut-offs greater than 10 and 14, respectively.

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More and more studies are attempting to identify the factors able to moderate or predict the effects of psychological interventions [34–36]. The ESQ could be used as an outcome predictor of psychological interventions, such as mindfulness-based interventions. In addition, it would allow for the tailoring of therapeutic strategies based on Emotional Style characteristics; for example, by studying the effects of individual mindfulness practices on the different dimensions. Future studies should also validate the ESQ-ITA in clinical samples to identify possible correlations with psychological symptoms. The Italian version of the ESQ opens up the possibility to enrich the research landscape with new knowledge that will be useful for advancing the pathogenetic and therapeutic aspects of psychological distress and emotional dysregulation.

In conclusion, the aim of the present study was to validate the ESQ in the Italian language and to assess its psychometric properties using a study sample recruited from the general population. The results of the present study show that ESQ-ITA is a reliable and stable measure which also provides quantitative data on emotional health.

Supporting information

S1 File. Supplementary material 1: S1 Table. Final Italian version of the Emotional Style Questionnaire.
(PDF)

S2 File. Supplementary material 2: Adjunctive results.
(PDF)

Author Contributions

Conceptualization: Francesca Malandrone, Claudio Gentili, Silvia Bianchi, Luca Ostacoli, Pelin Kesebir, Richard J. Davidson, Sara Carletto.

Data curation: Alberto Catalano, Federica Carfì, Francesco Oliva, Fulvio Ricceri.

Formal analysis: Alberto Catalano, Fulvio Ricceri.

Investigation: Francesca Malandrone, Federica Carfì, Fulvio Ricceri, Luca Ostacoli.

Methodology: Francesca Malandrone, Alberto Catalano, Claudio Gentili, Francesco Oliva, Fulvio Ricceri, Luca Ostacoli.

Project administration: Francesca Malandrone, Luca Ostacoli, Sara Carletto.

Supervision: Luca Ostacoli, Sara Carletto.

Validation: Pelin Kesebir, Richard J. Davidson.

Writing – original draft: Francesca Malandrone, Alberto Catalano, Federica Carfì, Claudio Gentili, Fulvio Ricceri.

Writing – review & editing: Francesca Malandrone, Alberto Catalano, Francesco Oliva, Fulvio Ricceri, Luca Ostacoli, Pelin Kesebir, Richard J. Davidson, Sara Carletto.

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Systematic Review

Factors Associated with Post-Traumatic Growth during the COVID-19 Pandemic: A Systematic Review

Andrea Bovero [1], Sarah Balzani [1], Gabriela Tormen [1], Francesca Malandrone [2,*] and Sara Carletto [1,2]

[1] Clinical Psychology Unit, University Hospital "Città della Salute e della Scienza di Torino", 10123 Torino, Italy; abovero@cittadellasalute.to.it (A.B.); sarah.balzani@edu.unito.it (S.B.); gabriela.tormen@edu.unito.it (G.T.); sara.carletto@unito.it (S.C.)
[2] Department of Clinical and Biological Sciences, University of Turin, 10043 Turin, Italy
* Correspondence: francesca.malandrone@unito.it

Abstract: The COVID-19 pandemic was an unprecedented event that further stimulated the debate on the concept of trauma. To increase knowledge about the traumatic potential of the pandemic, the main objective of this study was to identify, through a systematic literature review, the main factors associated with the adaptive outcome of post-traumatic growth caused by COVID-19. Studies were selected from the PsychInfo, Embase, and PubMed databases, and 29 articles were included at the end of the screening process. The identified factors are of different natures, including personal variables such as personality traits, coping, and cognitive strategies used to face adversity, and interpersonal variables, one of the most important of which is the level of social support. In addition, several results confirmed a relationship between post-traumatic growth and post-traumatic stress symptoms, as well as indices related to psychological well-being. Finally, the results are discussed by comparing them with those already present in the literature, as well as with some of the main explanatory models of post-traumatic growth. In this regard, some of the factors identified, such as maladaptive coping, avoidance symptoms, optimism, and low-stress tolerance, suggest the possibility that the process of post-traumatic growth may also be characterized by an illusory dimension.

Keywords: COVID-19; post-traumatic growth; trauma; protective factors; systematic literature review

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1. Introduction

The COVID-19 pandemic was an unprecedented event that further broadened the trauma debate. Due to the simultaneity and multiplicity of stressors, its effects may represent a unique type of trauma that has not yet been represented within the main paradigms [1]. The main sources of stress were economic uncertainty, fear of contagion, grief, and lockdown, which resulted in the greatest psychological distress [1]. The lockdown represented a strong psychological stress factor that increased social isolation, loneliness, anxiety, boredom, insomnia, and depression [2]. Many studies have focused on the negative effects of trauma caused by the pandemic [2–13]. These effects concern both the direct impact on people's mental health and the indirect impact that changes in lifestyle, including increased sedentariness and reduced sleep quality [8,9], have had on well-being.

Other studies have examined the presence of positive changes that occurred in people's lives as they attempted to cope with this adverse event [14–16]; these positive changes can be identified with the process of post-traumatic growth (PTG). According to Tedeschi and Calhoun's model [17], post-traumatic growth is an individual's experience of significant positive change arising from the struggle with a major life crisis. These changes result from the attempt to cope with a seismic event that has resulted in the shattering of one's cognitive schemas [18]. People who go through this type of traumatic experience develop beyond their previous level of adaptation or psychological functioning and therefore experience growth [17]. These authors explore personality traits related to growth, emphasizing creativity in problem-solving and the ability to regulate behavior in the external environment [19].

Following a challenging event, individuals undergo emotional, cognitive, and behavioral shifts, enteing a phase of rumination and adopting emotion-based coping strategies, leading to eventual growth marked by improved discomfort management, serenity, self-awareness, increased life appreciation, and enhanced creativity in behavior [19]. In the 'Janus Face of Self-Perceived Growth' model [20], also based on the work of Taylor et al. [21], it is hypothesized that, in addition to this dimension of real growth, there may also be illusory growth, which can be both functional and dysfunctional in relieving the stress caused by trauma [20].

For the purposes of this study, it is important to clarify the concept of trauma in the pandemic context, and in particular its meaning within the notion of PTG, as opposed to the meaning it assumes in relation to other trauma outcomes, such as PTSD. The latter is based on a conceptualization of trauma that requires "actual or threatened death, serious injury, or sexual violence" [22]. In contrast, Tedeschi et al. [23] merge the construct of PTG with a notion of trauma that focuses on the individual's subjective reaction rather than the characteristics of the event itself. Indeed, according to the authors, the traumaticity of an event would be a function of the destructuring effect it has on the individual's cognitive schemas. Therefore, when comparing these types of trauma-related outcomes, it is important to consider that they are based on trauma constructs with significant differences.

Several studies have investigated the factors associated with PTG caused by different types of traumas, such as in breast cancer patients, college students abused in childhood, and male rectal cancer patients [24–26]. The analysis of sociodemographic factors can also help to understand how people in more vulnerable groups, ethnic minorities, and people with mental disorders or other chronic illnesses, respond to trauma in terms of adaptive mechanisms, such as post-traumatic growth [27]. Prior research has highlighted that individuals from minority backgrounds tend to express higher levels of post-traumatic growth than their counterparts in majority groups [28,29]. Earlier studies have demonstrated that minority groups often report more adverse effects in the context of COVID-19 when compared to majority groups [30,31]. Vulnerability can also play a role in fostering positive outcomes. To put it differently, navigating the challenges of the current crisis from a standpoint of vulnerability might present an opportunity to uncover personal and environmental resources, ultimately promoting growth [23].

Regarding COVID-19 trauma, a systematic review of the literature was conducted to identify the factors associated with PTG in healthcare workers [32]. This population was one of the most vulnerable during the pandemic due to their exposure to direct and indirect trauma.

To increase knowledge of the traumatic effects of COVID-19 and to examine the protective factors associated with the adaptive outcome of post-traumatic growth, this systematic literature review aimed to synthesize studies investigating the factors associated with COVID-19-induced PTG in the general population; the only subpopulation that was excluded was that of healthcare providers, as they have already been studied [32]. Furthermore, given the duration of the pandemic, individuals may also have experienced stressors unrelated to the pandemic context, such as illness or the loss of a loved one. For this reason, only studies that used a measure of PTG that was able to capture the positive changes that individuals reported as directly related to the pandemic context were included in this review.

This review addresses a significant gap in the scientific literature on the impact of the COVID-19 pandemic on mental health. While other systematic reviews and metanalyses [13,33,34] have focused on summarizing the factors associated with adverse COVID-19 outcomes, such as PTSD, this review broadens the perspective by compiling the factors associated with the adaptive outcome of pandemic-induced PTG. Furthermore, investigating these factors in the wider population allows for the identification of a plethora of data that greatly aid the comprehension of the PTG process, as well as the wider effects of trauma. Understanding these data is crucial due to the complexity and diversity of factors associated with this positive outcome, which makes developing protocols for the active

promotion of PTG challenging. Thus, it is imperative to undertake research to comprehend these factors and facilitate the implementation of practices that mitigate the adverse effects of trauma and encourage positive changes.

2. Materials and Methods

This systematic review was carried out following the PRISMA Statement. The protocol was registered on the PROSPERO database (Record ID: CRD42023398006).

2.1. Search Strategy

Searches were conducted in the following databases on 23 December 2022: PubMed, PsychInfo, and Embase. The keywords and text words used in the search for each of the considered databases were "posttraumatic growth", "positive change", "PTG" and "stress-related growth". See Supplementary Material S1 for details of the search strategy. Reference lists of included articles and previous reviews were also searched.

2.2. Eligibility Criteria

All studies that investigated any factor associated with PTG caused by COVID-19 in the general adult population (18+) were included. The PTG scale had to be validated, standardized, and adapted to the context of COVID-19. Scale adaptation required that questionnaire instructions or items were modified to capture the positive changes that individuals reported as a result of the specific context of COVID-19. Studies had to have been published in English or Italian during the pandemic period and have a cross-sectional, longitudinal, or RCT design. Studies not meeting these criteria were excluded. Studies conducted on healthcare workers were also excluded.

2.3. Study Selection

Two authors (S.B. and G.T.) independently conducted standardized assessments to determine study eligibility according to the inclusion criteria. The abstracts were first screened, and all the full texts of all potential contributions were analyzed. Any disagreement was discussed with the other two authors (S.C. and A.B.) before agreement was reached. See Supplementary Material S2 for the study selection flowchart.

2.4. Data Extraction

Data from the selected studies were inserted into a standard template. Extracted data covered the year of publication, study design, population type, nationality, sample size, data collection period, mean age, sex, PTG assessment measure, instruments used to measure the associated factors, and the main outcomes related to PTG. Where available, information on COVID-19 prevention and control measures in place at the time of data collection was also included.

2.5. Quality Assessment

To assess the methodological quality and the internal validity in terms of the risk of bias (ROB) of the included studies, the Joanna Briggs Institute (JBI) critical appraisal checklist for analytical cross-sectional study was used [35]. The JBI checklist is composed of eight items regarding inclusion criteria, an adequate description of the subject and setting, appropriate measurement of exposure, criteria for measurement of the condition, the identification of confounding factors and strategies to deal with, the reliability of outcomes measures, and the appropriateness of the statistical analysis, with each item answered as "yes", "no", "unclear" or "not applicable". For classification purposes, when the total number of "yes" ranged from 0 to 2, the study was classified as having high ROB; from 3 to 5, the study was classified as having a moderate ROB; and when this number was at least 6, the study was classified as having a low ROB. Two independent researchers of the review team assessed ROB, and differences were resolved through discussion among all the authors.

2.6. Study Synthesis

The results of the evidence found are presented as a narrative synthesis. After reading and thoroughly examining the main associations reported in the included studies, several key themes were identified, which supported the organization and comparison of the results.

3. Results

The PRISMA flowchart describing the selection process, including reasons for exclusion, is presented in Supplementary Material S2. The initial search retrieved 866 articles after duplicate removal. Of these, only 29 articles were considered eligible for inclusion in this review. Table 1 provides an overview of the main data extracted from the studies. Of the 29 articles included, 18 were cross-sectional, 9 were longitudinal, and 2 were prospective cohort studies with cross-sectional data. All the articles included were written in English. Seventeen articles used the PTGI-21 measurement scale, eight used the PTGI-SF scale, two used the PTGI scale, one used the PTGI-13 scale, and one used the PTGI-S scale. The studies used samples from different populations, including workers, students, people with psychiatric diagnoses, veterans, people infected with COVID-19, pregnant women, and people who had experienced bereavement due to COVID-19. The factors associated with PTG examined in the studies are multiple and heterogeneous and were therefore divided into five categories: sociodemographic factors, COVID-19-related factors, individual factors, relational factors, and factors related to psychological well-being or distress.

Table 1. Overview of the main data extracted from the studies.

Authors	Study Design	Sample	Period of Data Collection	Mean Age	Gender	PTG Instrument	Associated Factors Instruments	Main Results on PTG	PTG Prevalence
Bayless (2021) [36]	cross-sectional study	US, Amazon Mechanical Turk (MTurk, N = 150) and undergraduate students (N = 16)	from 19 May 2020 (the US had 23,405 new COVID-19 cases per day) to 30 June 2020 (the US had 43,644 new cases per day)	35.8	38.6% females 61.4% males	PTGI 21-item COVID-19-adapted	Patient Health Questionnaire-2 (PHQ-2); Event-Related Rumination Inventory (ERRI); Form A of the Multidimensional Health Locus of Control scale (MHLC-A); PTSD Checklist for DSM-5 (PCL-5)	There was not a significant interaction between internal and external health-related locus of control domains in relation to PTGI scores; PTSS and rumination were associated with positive growth scores.	not reported
Casali et al. (2022) [37]	longitudinal study	Italy, general population (N = 254)	T1: April 2020 (first national lockdown) T2: December 2020 to January 2021 (second wave of the pandemic)	36.1	78.75% females 21.25% males	PTGI 21-item COVID-19-adapted	General health questionnaire-12 (GHQ-12); Values in action inventory of strengths-120 (VIA-IS-120)	Character had a significant direct effect on mental health at Time 2, and an indirect effect through the mediation of PTG (small); humanity was significantly related to PTG; no significant age or gender-related differences emerged in relation to PTG.	not reported
Celdrán et al. (2021) [38]	cross-sectional study	Spain, senior (55+) university students (N = 1009)	from 8–24 May 2020 (immediately after the forced lockdown in Barcelona)	66	61.7% females 38.3% males	PTGI-SF COVID-19-adapted	Series of questions regarding the Impact of COVID-19 (yes/no) and social resources (increase, no change, or decrease)	PTG was significantly associated with the experience of COVID-19, but only those who had been infected by it scored significantly higher on the PTGI-SF; age (being younger) was related to PTG; the presence of significant conversations and changes in loneliness (either an increase or a decrease) were related to PTG.	From moderate to high PTG in 20.5% of the sample
Chasson et al. (2022) [39]	cross-sectional study	Israel, Jewish, and Arab pregnant women (N = 916)	5 July to 7 October 2020 (second wave of the pandemic)	28.2	100% females	PTGI 21-item COVID-19-adapted	Intolerance of Uncertainty Scale-Short Form (IUS-12); The Life Orientation Test (LOT); The Self-Compassion Scale-Short Form (SCS-SF); COVID-19-related anxieties were measured by means of 2 items	Higher optimism and self-compassion were related to higher PTG; younger age and greater COVID-19-related anxieties were associated with higher PTG: higher fear of being infected and concern for the economic damage both significantly associated with higher PTG; being primiparous contributed to higher PTG; a positive association between intolerance of uncertainty and PTG was found among Jewish, but not Arab women; positive association between intolerance of uncertainty and PTG was stronger among women reporting higher self-compassion.	not reported

Table 1. *Cont.*

Authors	Study Design	Sample	Period of Data Collection	Mean Age	Gender	PTG Instrument	Associated Factors Instruments	Main Results on PTG	PTG Prevalence
Chen and Tang (2021) [40]	cross-sectional study	China, people bereaved due to COVID-19 (N = 422)	September and October 2020 (because of restrictions in social contact, after a person died from COVID-19, family members were usually not able to gather together to attend the wake preceding the funeral)	32.7	44.5% females 55.5% males	PTGI 21-item COVID-19-adapted	International ICD-11 Prolonged Grief Disorder Scale (IPGDS); Post-Traumatic Stress Disorder Checklist for DSM-5 (PCL-5)	Four profiles of prolonged grief, post-traumatic stress, and PTG were identified; those who were bereaved of an older loved one were more likely to be in the growth group rather than the moderate-combined group vs. death of a younger person was more likely to cause a moderate-combined than a growth profile; a closer relationship perceived by the bereaved increased the likelihood of being in the high-combined group and conflicts in the relationship decreased the chance of ending up in the most adaptive group of growth.	from moderate to high PTG in 90% of the sample
Ellena et al. (2021) [41]	cross-sectional study	Italy, young adults (N = 2000)	between 27 and 31 March 2020 (during the peak of the COVID-19 crisis in Italy)	27.1	49% females 51% males	PTGI COVID-19-adapted	In-Group Identification Scale adapted; A single item adapted from Zmerli and Newton (2008) was used to measure levels of interpersonal trust: "Since the start of COVID-19 emergency, how has your attitude toward this statement changed? Most people are trustworthy " (10-point Likert); Trust in institutions was measured by asking: "Since the beginning of COVID-19 emergency how has your confidence in these institutions changed ?" (5-point Likert)	National identity scores were positively related to interpersonal trust and the five PTG dimensions; each PTG dimension was positively associated with interpersonal trust; PTG "relating to others", perceptions of having new possibilities, and spiritual change dimensions mediated the positive relationship between national identity and interpersonal trust, whereas personal strength and appreciation of life did not.	not reported
Fino et al. (2022) [42]	cross-sectional study	Albania, general population (N = 231)	from 16 to 30 December 2020 (lockdown)	39.9	73.2% females 26.8% males	PTGI 21-item COVID-19-adapted	Coping Strategies Inventory Short-Form (CSI–SF); Hospital Anxiety and Depression Scale (HADS); Single items asking respondents to indicate their level of fear on a Likert scale; Adaptation of 8 items from the SARS Fear Scale (SFS)	Fear of COVID-19 was associated with both stress and growth outcomes, and this relationship was moderated by trait resilience; engagement coping was the only significant mediator of the relationship between COVID-19 fear and PTG.	not reported
Goutaudier et al. (2022) [43]	longitudinal study	France, general population (N = 1075)	T1: March to May 2020 (first lockdown) T2: March to May 2021	47.5	62.4% females 37.6% males	PTGI 21-item COVID-19-adapted	Beck Depression Inventory Short Form; Spielberger State–Trait Anxiety Inventory; Affective states were assessed with one item per affective state: fear, happiness, and anger (7-point Likert)	The highest level of PTG was found in participants who reported negative–moderate feelings (moderate levels of anger, fear, and happiness) during the first lockdown.	not reported

Table 1. *Cont.*

Authors	Study Design	Sample	Period of Data Collection	Mean Age	Gender	PTG Instrument	Associated Factors Instruments	Main Results on PTG	PTG Prevalence
Hyun et al. (2021) [44]	longitudinal study	US, young adults (N = 805)	T1: April to August 2020 T2: September 2020 to March 2021	24.8	84.8% females 11.3% males 3.9% other	PTGI-SF COVID-19-adapted	Connor–Davidson Resilience Scale (CD-RISC-10); Distress Tolerance Scale (DTS); Family Connectedness Scale (FCS); Patient Health Questionnaire (PHQ-8); Generalized Anxiety Disorder Scale (GAD-7); PTSD Checklist—Civilian Version (PLC-C); developed 6-item measure for pandemic-related worry (5-point Likert)	PTSD symptoms and COVID-19-related worries significantly predicted higher levels of PTG, while depression symptoms predicted lower levels of PTG; resilience and family connectedness significantly predicted higher levels of PTG; distress tolerance significantly predicted lower levels of PTG; Asians were less likely to report PTG.	not reported
Hyun et al. (2023) [45]	longitudinal study	US, young adults (N = 661)	T1: April to August 2020 T2: September 2020 to March 2021 T3: April to May 2021	25.4	85.3% females 14.7% males	PTGI-SF COVID-19-adapted	Pandemic-related distress measure consisted of 14 items capturing four areas of distress: financial stress, COVID-19 health risk, COVID-19-related worries, COVID-19-related grief; Patient Health Questionnaire (PHQ-8); seven-item Generalized Anxiety Disorder Scale (GAD-7)	At low levels of pandemic-related distress, depressive symptoms were similar for young adults with low, moderate, or high PTG; at high levels of pandemic-related distress, young adults with low PTG had the highest levels of depressive symptoms, and young adults with high PTG had the lowest levels of depressive symptoms; PTG at T2 buffered the effect of COVID-19-related distress from 2020 on depressive symptoms in 2021 among US young adults.	not reported
Ikizer et al. (2021) [46]	cross-sectional study	Turkey, general population (N = 685)	between 17 June and 21 August 2020 (new cases in Turkey had plateaued between June and August at around 1000 a day)	34.6	63.6% females 34.6% males 1.8% other	PTGI 21-item COVID-19-adapted	Six questions were administered to assess the severity of COVID-19 exposure; The Event-Related Rumination Inventory (ERRI); 10-item Perceived Stress Scale (PSS); PTSD Checklist for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (PCL-5); Post-Traumatic Growth Inventory-42 (21 items for Post-Traumatic Depreciation)	Positive correlation between PTS and PTG; positive correlation between PTG and PTD higher PTG was associated with lower levels of education and anticipating financial risks as a result of the pandemic; engaging in deliberate rumination emerged as another predictor of PTG.	not reported

Table 1. *Cont.*

Authors	Study Design	Sample	Period of Data Collection	Mean Age	Gender	PTG Instrument	Associated Factors Instruments	Main Results on PTG	PTG Prevalence
Kalaitzaki and Tamiolaki (2022) [47]	cross-sectional study	Greece, general population (N = 1361)	5–30 April 2020 (during the first COVID-19 lockdown) and 15 November to 12 December 2020 (during the second lockdown)	35.7	77.6% females 22.4% males	PTGI 21-item COVID-19-adapted	Post-Traumatic Stress Disorder Checklist for DSM-5 (PCL-5); Brief Coping Orientation to Problems Experienced Inventory (COPE); The ENRICHD Social Support Instrument (ESSI)	PTG did not significantly increase during the second lockdown; PTG was associated with PTSS during the first lockdown and with perceived stress during the second one; both adaptive and maladaptive coping strategies predicted PTG during the first lockdown, whereas only adaptive coping strategies predicted PTG during the second lockdown; perceived social support, emotional during the first lockdown, and instrumental during the second one, predicted PTG during the two lockdowns, respectively.	more than half of the participants displayed PTG during both lockdowns, with a trend of higher rates in the second lockdown (from 52.7% to 55.1%)
Landi et al. (2022) [48]	longitudinal study	Italy, general population (N = 382)	T1: 9–19 July 2020 (three months after the first national Italian lockdown, a period of better control of the pandemic in which all restrictions were lifted) T2: 9–19 October 2020 (the number of new COVID-19 cases started to increase again but with no corresponding restrictions)	40.5	77.5% females 22.5% males	PTGI-SF COVID-19-adapted	30-item Multidimensional Psychological Flexibility Inventory (MPFI); Impact of Event Scale-Revised (IES-R)	Time 1 PTG exhibited a significant small correlation with Time 1 PTS and a strong correlation with Time 2 PTG; Time 2 PTS was significantly and positively correlated with Time 2 PTG; being older was negatively correlated with Time 2 PTG while being infected with COVID-19 over the study period was positively associated with Time 2 PTG; higher PTG scores emerged in the high-PTS group; higher psychological flexibility at Time 1 and four of its subprocesses (present moment awareness, defusion, values, and committed action) were associated with higher PTG at Time 2 among people in the high-PTS group (but not in the low PTS group).	most (69.01%) participants did not report moderate-to-high PTG in any domain in the low PTG group, while in the high PTG group, 53.14% and 28.14% reported growth on at least one or two PTGI-SF domains, respectively.
Laslo-Roth et al. (2022) [49]	cross-sectional study	Israel, general population (N = 275)	from 15 March to 15 April 2020 (participants were subjected to social-distancing regulations during this period)	33.4	78.2% females 21.8% males	PTGI 21-item COVID-19-adapted	Questionnaire by the National Organization on Disability (NOD) with five items representing social participation: interactions with friends and family, religious activity, participating in social events in the community, volunteer activities or public activities, and going out to parks in the community; Adult state hope scale 6-items; Multidimensional scale of perceived social support 12 items; Cognitive reappraisal subscale of the Emotion Regulation Questionnaire (ERQ)	Agency thinking predicted PTG only indirectly, through social support and cognitive reappraisal; perceived social support was identified as a mediating factor between social participation and PTG; the perception of oneself in ordinary times as being socially engaged played a major role in the perception of psychological growth during the pandemic, and social participation was found to be linked directly and indirectly, through hope, to PTG.	not reported

Table 1. *Cont.*

Authors	Study Design	Sample	Period of Data Collection	Mean Age	Gender	PTG Instrument	Associated Factors Instruments	Main Results on PTG	PTG Prevalence
Lau et al. (2021) [50]	longitudinal study	China, general population (N = 327)	T1: from 12 March to 8 April 2020 (first major wave of a local outbreak in Hong Kong; mandatory closure of premises and businesses, and catering restrictions in restaurants: reduced service capacity and mandatory intertable distance in late March) T2: from 24 April to 12 May 2020 (palliation of the outbreak, only one case per day)	35	71.9% females 28.1% males	PTGI 21-item COVID-19-adapted	The perceived severity of the COVID-19 outbreak was measured by two items (10-point Likert); 13-item SOC (SOC-13); 22-item Impact of Event Scale-Revised (IES-R)	Having an above-sample-median monthly household income (HKD 40,000), being tertiary educated, and being with a family member or close friend who has experienced medical quarantine or having tested positive for COVID-19 were related to a higher likelihood of PTG; PTG was more likely to emerge in participants with high levels of both SOC and PTS: the interaction between the SOC and PTS mediated the relationship between Time 1 perceived outbreak severity and Time 2 PTG, such that PTG was more likely among participants with higher PTS and SOC; PTG was also associated with a weaker contingency between Time 1 and Time 2 perceived outbreak severity.	1.8% attained substantial PTG; 18.0% reported significant PTG in at least one domain in Time 2
Lewis et al. (2022) [51]	longitudinal study	England and Wales, adults with lived experience of a psychiatric disorder (N = 1424)	T1: June to July 2020 T2: November 2020 to January 2021	46.7	75.3% females 21.9% males 2.3% other	PTGI-SF COVID-19-adapted	COVID-19-related information and social support were measured by asking participants whether they or anyone close to them had experienced symptoms of COVID-19 and whether they had tested positive (“yes” or “no”); Participants were asked how socially supported they felt by friends and family in the past 2 weeks (5-point Likert); COVID-19-related trauma exposure was measured by asking participants if they found any aspect of the COVID-19 crisis traumatic (“yes” or “no”). If they answered “yes,” they were prompted to give a free-text description of their most troubling COVID-19-related experience; International Trauma Questionnaire (ITQ); WHO-5 Well-Being Index (WHO-5)	Higher PTGI-SF scores were most strongly associated with increased perceived social support, and perception of the pandemic as being traumatic; in the subsample of participants who perceived the pandemic as traumatic and completed the ITQ, higher PTGI-SF scores were most strongly associated with higher levels of psychological well-being and more severe PTSD symptoms.	not reported

Table 1. *Cont.*

Authors	Study Design	Sample	Period of Data Collection	Mean Age	Gender	PTG Instrument	Associated Factors Instruments	Main Results on PTG	PTG Prevalence
Li and Hu (2022) [52]	cross-sectional study	China, college students from universities (N = 463)	between 18 May and 22 July 2021	not reported	78.8% females 21.2% males	PTGI 21-item adapted	Connor–Davidson Resilience Scale (CD-RISC); Simplified Coping Style Questionnaire (SCSQ); Emotion Regulation Questionnaire; Awareness and impact of COVID-19 were collected through three questions (5-point Likert)	Psychological Resilience (PR), Positive Coping (PC), Cognitive Reappraisal (CR), and PTG were positively correlated with each other; PTG had a direct and positive association with PR, PC, and CR, respectively, mediated the relationship between PTG and PR; students with high-level PTG tended to report increased use of PC, which further facilitated their CR and, subsequently, promoted their PR.	not reported
Matos et al. (2021) [53]	cross-sectional study	21 countries worldwide (Europe, North America, South America, Asia, Oceania, Middle Est), general population (N = 4057)	between mid-April and mid-May 2020 (early months of the COVID-19 pandemic)	41.5	80.8% females 18.2% males 0.4% other 0.6% preferred not to report their gender	PTGI 21-item COVID-19-adapted	Social Connection: Compassionate Engagement and Action Scales (CEAS) and Social Safeness and Pleasure Scale (SSPS); Social Disconnection: Fears of Compassion Scales (FCS) and UCLA Loneliness Scale (UCLA LS); Perceived Coronavirus Risk Scale (PCRS); Impact of Event Scale-Revised (IES-R)	Higher perceived threat of COVID-19 predicted greater PTG; social connection (compassion and social safeness) received from others was a significant predictor of PTG; the interaction effect of perceived threat of COVID-19 and the social connection component was significant and positive, indicating that the three flows of compassion and social safeness significantly moderate (magnify) the impact of fear of contraction on PTG; that fears of compassion and loneliness significantly moderate (reduce) the impact of fear of contraction on PTG.	not reported

Table 1. *Cont.*

Authors	Study Design	Sample	Period of Data Collection	Mean Age	Gender	PTG Instrument	Associated Factors Instruments	Main Results on PTG	PTG Prevalence
Na et al. (2021) [54]	prospective cohort study (with cross-sectional data)	US, military veterans (N = 3078)	Wave 1: median completion date on 21 November 2019 (pre-pandemic survey, before the first documented COVID-19 case in the U.S) Wave 2: median completion date: 14 November 2020 (peri-pandemic survey)	63.3	8.4% females 91.6% males	PTG-SF COVID-19-adapted	Responses on the two depressive symptoms of the PHQ-4; responses on the two generalized anxiety items of the PHQ-4; Life Events Checklist for DSM-5; Adverse Childhood Experiences Questionnaire; sum of the number of medical conditions endorsed in response to two questions; 10-Item Personality Inventory; endorsement of current treatment with psychotropic medication and/or psychotherapy or counseling in response to two questions; Duke University Religion Index; Medical Outcomes Study Social Support Scale-5; Connor-Davidson Resilience Scale-10; Number of close friends and family members; Secure attachment: response to one question; Purpose in Life Test-Short Form; a single-item measure of optimism from Life Orientation Test-Revised; single-item measure of gratitude from Gratitude Questionnaire; 5-item version of the Medical Outcomes Study Social Support Scale; single-item from Curiosity and Exploration Inventory-II; Perceived level of community integration (one question, 7-point Likert); Change variables from pre-pandemic to peri-pandemic; 4-item PTSD Checklist for DSM-5; total count of past-year potentially traumatic events	Female gender, non-white ethnicity, agreeableness, and protective psychosocial characteristics (purpose in life, religiosity/spirituality, and PTG in relation to earlier trauma) were related to PTG; pandemic-related factors associated with PTG included pandemic-related worries (physical health, mental/emotional health), social restriction stress, stress related to changes in family contacts, stress related to changes in social contacts, financial difficulties, stability of living situation, and PTSD symptoms; worries about the effect of the pandemic on one's physical and mental health, PTG in response to pre-pandemic traumatic life events, and greater severity of pandemic-related avoidance symptoms were the strongest correlates of pandemic-related PTG.	not reported

Table 1. *Cont.*

Authors	Study Design	Sample	Period of Data Collection	Mean Age	Gender	PTG Instrument	Associated Factors Instruments	Main Results on PTG	PTG Prevalence
Northfield and Johnston (2022) [55]	cross-sectional study	US, general population (N = 296)	August 2020	39.7	58.8% females 41.2% males	PTGI 21-item COVID-19-adapted	The Impact of Event Scale-Revised (IES-R); Multidimensional Scale of Perceived Social Support	A strong positive relationship was found between psychological distress and growth; this relationship was moderated by social support such that the relationship was stronger at higher levels of social support; perceived social support from significant others was not a strong predictor of PTG; however, perceived support from family and friends were; age significantly predicted PTG, with those younger in age reporting higher levels of PTG.	33.4% of the sample scored 63 or higher which is indicative of a moderate growth
Pietrzak et al. (2022) [56]	prospective cohort study (with cross-sectional data)	US, military veterans (N = 3078)	Wave 1: between 18 November 2019 and 8 March 2020 Wave 2 (1-year follow-up): between 9 November and 19 December 2020	63.3	8.4% females 91.6% males	PTGI-SF COVID-19-adapted	Survey with pandemic-associated risk factors (also PTSD symptoms), background characteristics (also suicidal ideation)	Veterans who screened positive for COVID-19-associated PTSD symptoms had a markedly higher prevalence of PTG; greater COVID-19-associated improvements in appreciation of life and social relationships were associated with a significant reduction in the odds of suicidal ideation.	43.3% reported moderate or greater levels of PTG
Sandrin et al. (2022) [57]	cross-sectional study	France, working population (N = 2004)	October 2020 (prior to the second confinement in France)	range: 18–60+	48% females 52% males	PTGI 21-item COVID-19-adapted	Psychosocial safety climate was measured with four items (5-point Likert); Performance was measured by responses to the following question: "Over the past week, how would you rate your performance at work on a scale of 0–100%? "; Kessler Psychological Distress Scale (K6)	Mediation analyses indicate that the psychosocial safety climate at work place has a direct and positive influence on PTG and performance, as well as a direct negative influence on psychological distress.	not reported
Shigemoto (2022) [58]	longitudinal study	US, Amazon's Mechanical Turk (N = 71)	the daily survey started on 3 May and ended on 31 May 2020 (at that time, in the U.S, there have been 1,150,000 cases of COVID-19 and 67,000 deaths, and each day, 30,000 new cases of COVID-19 have been reported)	41.9	46.5% females 53.5% males	PTGI-SF COVID-19-adapted	Event-Related Rumination Inventory (ERRI)	No significant relation was found between intrusive rumination and PTG, but there was a statistically significant positive association between deliberate rumination and PTG.	not reported

Table 1. *Cont.*

Authors	Study Design	Sample	Period of Data Collection	Mean Age	Gender	PTG Instrument	Associated Factors Instruments	Main Results on PTG	PTG Prevalence
Wall et al. (2023) [59]	cross-sectional study	UK, general population (N = 440)	May and June 2020 (during lockdown)	not reported	91.8% females 7.7% males 0.5% unknown	PTGI 21-item COVID-19-adapted	Impact of event scale-revised (IES-R); Brief COPE scale; Multidimensional Scale of Perceived Social Support (MSPSS); Connor-Davidson Resilience Scale-10 (CD-RISC-10); Life Orientation Test-Revised (LOT-R); Event-Related Rumination Inventory (ERRI)	Centrality of event, deliberate rumination, and social support were significant predictors of PTG.	49.5% of the sample scores of 45 or above on the PTGI (high levels of PTG)
Wang and Huang (2022) [60]	cross-sectional study	China, college students from a university (N = 690)	not reported	not reported	64.5% males 35.5% females	PTGI-13 item COVID-19-adapted	Self-efficacy scale comprising four dimensions and 15 items: tolerance ambiguity self-efficacy, opportunity-identification self-efficacy, relationship self-efficacy, and managerial self-efficacy (5-point Likert); Prosocial tendency Scale revised; Entrepreneurial intention scale comprising two dimensions (namely, goal intentions and implementation intentions) and 10 items (7-point Likert)	PTG significantly and positively affects the entrepreneurial intention of Chinese college students who have experienced trauma due to the COVID-19 pandemic; entrepreneurial self-efficacy and prosocial tendencies have a chain mediating effect on the relation between PTG and entrepreneurial intention.	not reported
Xiao et al. (2022) [61]	cross-sectional study	China, patients recovered from COVID-19 who were discharged from hospitals (N = 199)	from August to September 2020, discharged patients with COVID-19 are centralized and quarantined for 14 days in designated facilities and then quarantined for another 14 days at home	42.7	53.3% females 46.7% males	PTGI COVID-19-adapted	Questionnaire developed for this study: Demographic and Pre-hospitalization variables, Hospitalization variables, Post-hospitalization variables, Perceived Discrimination (nine questions, "yes"/"no"), Perceived Affiliate Stigma (seven questions, 4-point Likert), Perceived Impact of being Infected with COVID-19 (three questions, 10-point Likert), Social support (four questions, 10-point Likert); Patient Health Questionnaire (PHQ-15); Self-Stigma Scale; 2-item Connor–Davidson Resilience Scale (CD-RISC2); Patient Health Questionnaire (PHQ-9); 7-item Generalized Anxiety Disorder (GAD-7)	Having children, receiving mental healthcare services during hospitalization, clinical classification of COVID-19 at entry, self-stigma, and social support were significantly associated with PTG.	not reported

Table 1. *Cont.*

Authors	Study Design	Sample	Period of Data Collection	Mean Age	Gender	PTG Instrument	Associated Factors Instruments	Main Results on PTG	PTG Prevalence
Xie and Kim (2022) [62]	cross-sectional study	Mainly Sweden and China (other countries 16.6%), general population (N = 181)	from 25 April to 5 May 2021	24.7	70.2% females 29.8% males	PTGI-S COVID-19-adapted	Multidimensional Scale of Perceived Social Support (MSPSS); Ten-Item Personality Inventory (TIPI); Brief COPE Questionnaire	Perceived social support, personality traits (extraversion, emotional stability, agreeableness, and conscientiousness), and coping strategies (problem-focused coping, emotion-focused coping, and social support coping) were positively correlated with PTG; coping strategies (problem-focused coping, emotion-focused coping, and avoidance coping) mediated the relations between perceived social support, personality traits, and PTG	60.8% of participants with scores of 32 points or higher demonstrated personal growth
Xie et al. (2022) [63]	longitudinal study	China, self-quarantined college students (N = 226)	T1: 27 February 2020, with a 1-week duration (the peak phase of the COVID-19 in China, all universities in China have suspended offline classes and students have been asked to stay confined at home T2: 5 May 2021, with a 2-week duration (the post-pandemic phase in China)	19.6	41.2% females 58.8% males	PTGI 21-item COVID-19-adapted	Satisfaction with Life Scale (SWLS); Personal Values Questionnaire (PVQ)	PTG at the peak phase of the COVID-19 pandemic was positively associated with subsequent LS (Life Satisfaction). One year later, the association between COVID-19-related PTG at Time 1 and LS at Time 2 was partially mediated by ST (self-transcendence) and SE (self-enhancement) values at Time 2: PTG at Time 1 was positively related to ST value while negatively related to SE value at Time 2.	moderate to high levels of PTG; 65.4% of participants experienced at least medium levels of positive changes
Yan et al. (2021) [64]	cross-sectional study	China, discharged COVID-19 patients (N = 140)	February 2020	43.5	53.6% females 46.4% males	PTGI 21-item adapted	Profile of Mood Status (POMS); Post-Traumatic Stress Disorder Self-Rating Scale (PTSD-SS); Simplified Coping Style Questionnaire (SCSQ); Multidimensional Scale of Perceived Social Support (MSPSS)	Lower levels of mood disturbance, more severe PTSD, more positive coping style, and more perceived social support were associated with a higher level of PTG; PTG was negatively related to anger and time from onset to diagnosis in discharged COVID-19 patients; self-esteem showed a significant correlation with PTG.	not reported

Legend. CR: cognitive reappraisal; ITQ: International Trauma Questionnaire; LS: life satisfaction; PC: positive coping; PR: psychological resilience; PTD: post-traumatic depreciation; PTG: post-traumatic growth; PTGI-SF: Post-Traumatic Growth Inventory—Short Form; PTS: post-traumatic stress; PTSD: post-traumatic stress disorder; PTSS: post-traumatic stress symptoms; SE: self-enhancement.

3.1. Association between PTG and Sociodemographic Factors

A relationship between PTG and ethnicity has been found in several studies [39,44,54,58]. In particular, Asians were less likely to report PTG [44], whereas in a sample of Arab and Jewish women living in Israel, Arab women experienced higher levels of growth [39]. Finally, Caucasian/European Americans reported lower levels of growth [58]. In contrast, another study measured higher levels of PTG in the non-white ethnic group [54]. Also, in Northfield and Johnston's study [55], although ethnicity was not a significant predictor of PTG, a group difference was evident between African American and Caucasian participants, with African American participants reporting higher levels. Considering age and sex/gender, no significant differences in relation to PTG were reported in some studies investigating these variables [37,40,46,49,50,59,62,63]. In contrast, in the study by Celdrán et al. [38] and Fino et al. [42], women reported higher levels of growth, but of all the sociodemographic variables considered in the study by Celdrán et al. [38], only younger age significantly correlated with higher PTG, and the same was found in the study by Northfield and Johnston [55]; by contrast, in the study by Na et al. [54], being female was associated with pandemic growth. In the study by Ikizer et al. [46], only the level of education was a predictor of PTG, as higher levels of education were associated with lower levels of PTG, while being younger was only associated with negative outputs, such as higher levels of pandemic-related stress. In contrast, in the study by Lau et al. [50], having a university degree was associated with higher odds of PTG, as was having a higher monthly household income than the sample mean. In the longitudinal study by Landi et al. [48], being older was negatively correlated with PTG. In the study by Yan et al. [64], of all sociodemographic variables, only patients grouped based on their place of residence had a significant difference in PTG, i.e., those living in non-urban areas had higher levels than participants living in urban areas. Finally, in the study by Xiao et al. [61], having children was significantly associated with PTG, and in particular in the study by Chasson et al. [39], being primiparous was associated with higher PTG.

3.2. Association between PTG and COVID-19-Related Factors

In the study conducted by Celdrán et al. [38] and Hyun et al. [44], PTG showed a significant association with COVID-19 experience. However, only individuals who were infected with COVID-19 demonstrated significantly higher scores on the PTGI-SF. Anxieties and worries related to COVID-19 were associated with higher PTG [39,44], as was fear of contracting COVID-19 [53]. Similarly, in the study by Na et al. [54], most of the variance in pandemic-related PTG was explained by concerns about the effect of the pandemic on one's physical and mental health. In the study by Fino et al. [42], fear of COVID-19 was associated with both positive mental health outcomes (post-traumatic growth) and negative outcomes (depression and anxiety), and these relationships were mediated by the type of coping strategy used. In the longitudinal study by Landi et al. [48], COVID-19 infection during the study period was positively associated with PTG at time 2 (9–19 October 2020) but not at Time 1 (9–19 July 2020). In the study by Lewis et al. [51], higher PTGI-SF scores were strongly associated with the perception of the pandemic as traumatic. Specifically, being with a family member or close friend who experienced quarantine or who tested positive for COVID-19 was correlated with a higher likelihood of PTG [50]. In the study by Xiao et al. [61] involving adult patients cured of COVID-19 and discharged from the hospital between 1 February and 30 April 2020, significant protective factors of PTG included the clinical classification of COVID-19 infection at hospital admission. Consistent with this result, in Yan et al.'s study [64], the time from onset to diagnosis was negatively correlated with PTG, indicating that shortening this process could help improve patients' PTG. Finally, a study examined the relationship between prolonged grief (PG), post-traumatic stress (PTS), and PTG in individuals who have suffered bereavement due to COVID-19 [40]. The results showed that when the deceased was older, individuals were more likely to report high levels of PTS and PG. In contrast, conflicts in the relationship with the deceased person led to a lower likelihood of being in the group with high levels of growth and low levels of

PTS and PG. At the same time, the loss of a younger loved one and the presence of a close relationship with the deceased increased the likelihood of experiencing moderate or high levels in all three dimensions.

3.3. Association between PTG and Individual Factors

Regarding the association between PTG and individual characteristics, several studies have revealed a significant association with the process of deliberate rumination [36,46,58,59]. A relationship was also found between the employment of cognitive reappraisal and cognitive flexibility with PTG [48,49,52]. Specifically, the connection between PTG and cognitive flexibility was solely detected in those who have reported high levels of post-traumatic stress [48]; cognitive reappraisal, coupled with social support, mediated the relationship between agency thinking and PTG [49]; and cognitive reappraisal, together with positive coping, mediated the relationship between psychological resilience and PTG [52]. In this regard, another study has also confirmed the relationship between resilience and growth [44]. Another important individual characteristic that interacts with PTG is the type of coping strategy used. In the study by Kalaitzaki et al. [47], during the first lockdown in Greece, PTG was associated with both adaptive coping strategies, i.e., positive reframing, religious coping, and the use of emotional support, and maladaptive coping strategies, i.e., self-blame, denial, and substance use; in contrast, during the second lockdown, this association was observed only with adaptive coping strategies. In contrast, in Fino et al.'s study [42], the use of a positive coping strategy (engagement coping) positively mediated the effect of fear of COVID-19 on PTG, whereas negative coping (disengagement coping) mediated the effect of fear of COVID-19 on anxiety and depression. Also, in the study by Yan et al. [64], the use of positive coping strategies was associated with higher PTG levels. Finally, in the study by Xie and Kim [62], a correlation was found between PTG and problem-focused coping, emotion-focused coping, and social-support coping while avoidance coping mediated the relationship between conscientiousness, agreeableness, and PTG. Regarding other personality traits, the study by Casali et al. [37] revealed that out of the six character-related virtues (wisdom and knowledge, courage, humanity justice, temperance, and transcendence), only humanity was significantly associated with PTG. Optimism and self-compassion [39], self-transcendence [63], agreeableness [54,62], self-esteem [64], and sense of coherence [50] were also associated with higher levels of PTG. Other personality traits associated with PTG were extraversion, conscientiousness, and emotional stability [62]. Protective psychosocial characteristics associated with PTG included religiosity/spirituality, purpose in life, and PTG compared to previous trauma [54]. The study by Shigemoto et al. [58] also revealed that those who identified as religious tended to experience higher levels of PTG. Wang and Huang's study [60] showed that PTG significantly and positively influenced university students' entrepreneurial intention and that self-efficacy and prosocial tendencies mediated this relationship. In the study by Xie et al. [63], the results showed that COVID-19-related PTG was a positive factor in university students' life satisfaction and that personal values played a mediating role in this relationship. Among the predictors of PTG, the centrality of the event was found to be a significant factor [59]. Regarding the variables most related to the pandemic, the study by Xiao et al. [61], conducted among patients hospitalized for COVID-19, revealed an association between self-stigmatization and PTG. Finally, intolerance of uncertainty was associated with higher levels of PTG only in Jewish women (but not in Arab women) and in women with higher levels of self-compassion [39], whereas tolerance of distress was associated with lower levels of PTG [44].

3.4. Association between PTG and Relational Factors

With regard to interpersonal variables, in the studies by Wall et al. [59] and Xiao et al. [61], social support was found to be a significant protective factor for the development of PTG. The role of social support in the ability to cope with trauma and bring about positive change was also confirmed in a sample of people discharged from the hospital after

hospitalization for COVID-19 [64]. In Kalaitzaki et al.'s study [47], perceived emotional social support during the first lockdown and perceived instrumental social support during the second lockdown were predictive of growth during both lockdowns. However, the results of Celdrán et al. [38] showed that a state of increased contact with others was not necessarily associated with PTG. In fact, both increased and decreased perceived loneliness were significantly associated with PTG. In addition, the authors found that an increase in meaningful conversations was associated with growth. In the study by Northfield and Johnston [55], only social support from family or friends was associated with PTG, whereas this relationship was not observed for other significant others. Hyun et al. [44] also found a positive association between PTG and family connectedness. In the study by Matos et al. [53], social connectedness, in terms of compassion and perceptions of social safety, predicted higher levels of PTG. The impact of the social dimension is manifested not only in the level of support received but also in how socially active one feels; indeed, an association was found between social engagement before and during the pandemic and perceptions of growth [49]. Interpersonal trust, i.e., rating others as trustworthy, was also associated with all dimensions of PTG [41]. Only one of the included studies focused on the relationship between work context and PTG [57]. The results showed that perceptions of the psychosocial safety climate had a positive and direct effect on PTG. Finally, at the macro-social level, the "social" dimension of growth (i.e., relating to others) fully mediated the national identity–interpersonal trust association [41].

3.5. Association between PTG and Factors Related to Psychological Well-Being and/or Distress

Regarding the relationship between PTG and mental health outcomes, the study by Hyun et al. [44] showed that PTSD symptoms were significant predictors of higher PTG levels; the study by Na et al. [54] revealed that pandemic-related PTSD avoidance symptoms explained a significant proportion of the variance in pandemic-related PTG; and the study by Yan et al. [64] revealed a positive correlation between PTG and PTSD in discharged COVID-19 patients, and patients with high PTSD exposure had higher PTG. In general, several studies have confirmed an association between post-traumatic stress symptoms (PTSS) and PTG experienced during the pandemic [36,46–48]; in addition, the study by Ikizer et al. [46] revealed an association between post-traumatic depreciation and PTG. The relationship between PTSS and PTG also appears to be influenced by other factors. Northfield and Johnston [55] found a strong positive relationship between psychological distress and growth that was mediated by social support, such that the relationship was stronger at higher levels of social support. Lau et al. [50] found that PTG was more likely in participants with high levels of post-traumatic stress but also a high sense of coherence. The results of the study by Chen and Tang [40] identified four profiles of prolonged grief, post-traumatic stress, and post-traumatic growth in people who had suffered bereavement due to COVID-19; two of these profiles were characterized by moderate and high levels of both PTG and PTS. The study by Pietrzak et al. [56] showed that the prevalence of PTG was higher in veterans with PTSD symptoms and that positive changes in appreciation of life and social relationships (two dimensions of PTG) related to the pandemic were associated with a significant reduction in the likelihood of suicidal ideation. In the study by Lewis et al. [51], higher scores on the PTGI were associated with higher levels of psychological well-being, and in the subsample of participants who perceived the pandemic as traumatic, PTG was associated with higher PTSD scores. Casali et al. [37] also confirmed the role of PTG in mental health, as it mediated the relationship between positive personality traits and psychological well-being. Furthermore, depressive symptoms were predictors of lower levels of PTG in the study by Hyun et al. [44], whereas in the study by Hyun et al. [45], it was observed that at low levels of pandemic-related stress, depressive symptoms were similar for young adults with low, moderate, or high levels of PTG. However, at high levels of pandemic-related stress, young adults with low PTG had the highest levels of depressive symptoms, whereas those with high PTG had the lowest levels of depressive symptoms. In addition, PTG appeared to play a protective role against depressive symptoms, as it

attenuated the effect of COVID-19-related stress in 2020 on depressive symptoms in 2021. Finally, in the study by Goutaudier et al. [43], the highest levels of PTG were found in participants who reported moderate levels of anger, fear, and happiness during the first lockdown, whereas in the study by Yan et al. [64], a negative association was observed between PTG and anger.

3.6. Quality Assessment of the Included Studies

Notably, 3 studies (10.34%) had a low ROB, while 26 studies (89.65%) had a moderate ROB. None of the studies demonstrated a high ROB. Regarding study participants' recruitment and sampling procedures, 12 studies (41.37%) did not report enough information. Three studies (10.34%) did not appropriately describe the study subjects and research setting. In all studies, adequate data analyses were carried out. Details about the results concerning the ROB assessment of the included studies are summarized in Table 2.

Table 2. Risk of bias (ROB) assessment of the included studies.

Author	Were the Criteria for Inclusion in the Sample Clearly Defined?	Were the Study Subjects and the Setting Described in Detail?	Was the Exposure Measured in a Valid and Reliable Way?	Were Objective Standard Criteria Used for Measurement of the Condition?	Were Confounding Factors Identified?	Were Strategies to Deal with Confounding Factors Stated?	Were the Outcomes Measured in a Valid and Reliable Way?	Was Appropriate Statistical Analysis Used?	Number of YES	ROB
Bayless (2021) [36]	Yes	Yes	Yes	Not Applicable	Yes	Yes	Yes	Yes	7	Low
Casali et al. (2021) [37]	No	Yes	Yes	Not Applicable	Yes	Yes	Yes	Yes	6	Low
Celdrán et al. (2021) [38]	No	Yes	Yes	Not Applicable	No	No	No	Yes	3	Moderate
Chasson et al. (2022) [39]	Yes	Yes	Yes	Not Applicable	No	No	No	Yes	4	Moderate
Chen and Tang (2021) [40]	Yes	Yes	Yes	Not Applicable	No	No	Yes	Yes	5	Moderate
Ellena et al. (2021) [41]	No	Yes	Yes	Not Applicable	No	No	No	Yes	3	Moderate
Fino et al. (2022) [42]	Yes	Yes	Yes	Not Applicable	Yes	Yes	Yes	Yes	7	Low
Goutaudier et al. (2022) [43]	Yes	Yes	Yes	Not Applicable	No	No	Yes	Yes	5	Moderate
Hyun et al. (2021) [44]	No	No	Yes	Not Applicable	No	No	Yes	Yes	3	Moderate
Hyun et al. (2023) [45]	Yes	Yes	Yes	Not Applicable	No	No	Yes	Yes	5	Moderate
Ikizer et al. (2021) [46]	No	Yes	Yes	Not Applicable	No	No	Yes	Yes	4	Moderate
Kalaitzaki and Tamiolaki (2022) [47]	No	Yes	Yes	Not Applicable	No	No	Yes	Yes	4	Moderate
Landi et al. (2022) [48]	Yes	Yes	Yes	Not Applicable	No	No	Yes	Yes	5	Moderate
Laslo-Roth et al. (2020) [49]	No	Yes	Yes	Not Applicable	No	No	Yes	Yes	4	Moderate
Lau et al. (2021) [50]	Yes	Yes	Yes	Not Applicable	No	No	Yes	Yes	5	Moderate
Lewis et al. (2022) [51]	Yes	Yes	Yes	Not Applicable	No	No	Yes	Yes	5	Moderate
Li and Hu (2022) [52]	Yes	Yes	Yes	Not Applicable	Unclear	Unclear	Yes	Yes	5	Moderate
Matos et al. (2021) [53]	No	Yes	Yes	Not Applicable	No	No	Yes	Yes	4	Moderate
Na et al. (2021) [54]	No	No	Yes	Not Applicable	No	No	Yes	Yes	3	Moderate
Northfield and Johnston (2021) [55]	Yes	Yes	Yes	Not Applicable	No	No	Yes	Yes	5	Moderate
Pietrzak et al. (2022) [56]	No	No	Yes	Not Applicable	Unclear	Unclear	Yes	Yes	3	Moderate
Sandrin et al. (2022) [57]	Yes	Yes	Yes	Not Applicable	No	No	Yes	Yes	5	Moderate
Shigemoto (2022) [58]	Yes	Yes	Yes	Not Applicable	No	No	Yes	Yes	5	Moderate
Wall et al. (2023) [59]	No	Yes	Yes	Not Applicable	No	No	Yes	Yes	4	Moderate
Wang and Huang (2022) [60]	Yes	Yes	Yes	Not Applicable	No	No	Yes	Yes	5	Moderate
Xiao et al. (2022) [61]	Yes	Yes	Yes	Not Applicable	Unclear	Unclear	Yes	Yes	5	Moderate
Xie and Kim (2022) [62]	Yes	Yes	Yes	Not Applicable	No	No	Yes	Yes	5	Moderate
Xie et al. (2022) [63]	No	Yes	Yes	Not Applicable	No	No	Yes	Yes	4	Moderate
Yan et al. (2021) [64]	Yes	Yes	Yes	Not Applicable	No	No	Yes	Yes	5	Moderate

4. Discussion

To the best of our knowledge, this is the first systematic literature review that has synthesized studies investigating the factors associated with PTG induced by COVID-19. Among the sociodemographic variables, the synthesis of the studies showed already known associations, including those with young age [65] and ethnic minority status [28,29]. With regard to age, the fact that being younger is associated with higher levels of growth is also consistent with the model proposed by Tedeschi and Calhoun [18], according to which young people may be more open than older people to the learning and change that enables the growth process. Notably, one study found that the Asian American population was less likely to develop PTG than the American population [44]. This finding can be interpreted in the specific context of COVID-19, where people of Asian origin have experienced stigma and discrimination, which may have affected their mental health and ability to seek help [66], and consequently, their ability to experience positive change. The synthesis of studies on the association between PTG and income and education levels showed contradictory results. Ikizer et al. [46] found that PTG was linked to lower educational attainment and anticipation of financial risk, and higher education to lower levels of PTG, PTS, and PTD. By contrast, Lau et al. [50] found that PTG was linked to tertiary education and higher economic income, and on this basis, they suggest that education and higher income may serve as practical coping resources, in addition to psychological ones, and may mediate the relationship between stress and PTG. These disparities may be clarified by Tedeschi and Calhoun's model [18]. If the process of PTG necessitates a "seismic" event that impacts individuals' lives, leading to the questioning of significant mental patterns, it may be hypothesized that, while higher education and its work-related implications may have corresponded to reduced stress and mitigated the effect of the pandemic on mental health during COVID-19, the level of education was not always a protective factor due to the numerous stressors caused by the pandemic. In this regard, one of the factors associated with PTG is the centrality of the event, i.e., how critical a particular event is to a person's identity and life story; the greater the centrality, the greater the level of growth [59]. Considering the interplay of these sociodemographic variables, it is crucial to highlight that numerous factors need to be considered to comprehend the varied reactions toward extremely demanding circumstances, such as the pandemic context.

Another interesting finding in the context of the pandemic is the association between PTG and increased loneliness [38]. Despite many studies confirming the importance of social support in supporting the growth process, as discussed by the authors, this finding opens the possibility that a change in the relational dimension, whether in terms of increased or decreased loneliness, could stimulate growth. Such a change could challenge one's schemas and support the growth process.

In addition to the social dimension, many individual factors have been associated with PTG. Understanding these factors has important clinical implications for trauma interventions. This knowledge enables the advancement of strategies and procedures aimed at fostering PTG within the therapeutic alliance, a factor that research has demonstrated to be closely linked to psychological well-being. In this regard, the study by Pietrzak et al. [56] revealed that although the prevalence of PTG was higher in veterans with PTSD symptoms, positive changes in life evaluation and social relationships related to the pandemic were associated with a significant reduction in the likelihood of suicidal ideation. The association with PTSS and psychological distress is consistent with the possibility that the process of PTG requires a significant threat or the shattering of fundamental schemas, often accompanied by significant psychological distress [18]. Indeed, the association observed across multiple studies between PTG and concerns related to COVID-19 underscores the traumatic impact of the pandemic and the unsettling influence it exerted on individuals' mental well-being. Furthermore, the context of COVID-19 has accentuated the range of reactions to trauma, including those that may initially seem contradictory to one another. Indeed, the study by Ikizer et al. [46] showed an association between PTG and post-traumatic depreciation. Existing literature data indicate that this aspect may manifest separately from

PTG and within the same domains [67,68]. Such an association in the pandemic context suggests that the complexity of trauma may lead to both positive and negative changes in the same dimensions, which are related to each other. Nevertheless, more data are needed to clarify the relationships between these forms of trauma.

Furthermore, as a speculative hypothesis, we suggest that some factors emerging from the synthesis of the studies indicate the potential presence of an illusory dimension within PTG, consistent with the concept of the "Janus Face of Self-Perceived Growth" [20]. In particular, the literature underlines a positive association between PTG and maladaptive coping, avoidance symptoms, avoidant coping, and optimism traits, and a negative association with distress tolerance. Although these factors may represent initial attempts to alleviate the stress caused by a sudden event without negative consequences, the association with avoidance symptoms and coping may have negative effects on individual adjustment [20].

Finally, it is important to consider that few studies have reported clear data on the prevalence of PTG, which complicates the interpretation of the results. A comparison of the studies that have reported these data reveals that the prevalence of this phenomenon does not seem to be uniform across the samples studied.

This systematic literature review has several limitations that need to be considered when evaluating the results. Firstly, all studies used a self-report scale to measure PTG; therefore, there is a risk that participants may have under- or overestimated the information. At the same time, some studies used non-standardized measures for the associated factors, which are less sensitive in capturing the phenomenon of interest and hinder an accurate comparison of the factors related to PTG, as well as a clear understanding of the variables associated with the growth process. Therefore, there is a need to use more standardized measurement tools that can effectively capture the desired outcome. Secondly, the data collection process required participants to complete the PTG questionnaire with a focus on positive changes because of the pandemic. Although this criterion allowed for a better understanding of the specific effects of COVID-19, participants may have found it difficult to distinguish between specific changes caused by the pandemic and other positive developments in their lives not related to the pandemic. In addition, it is important to consider the limitations of the cross-sectional nature of most of the selected studies, including the difficulty of interpreting the associations identified and the inability to examine the temporal relationship between outcomes and other factors [69]. Finally, although all included studies were conducted during the pandemic, there were periods of heightened crisis due to increased contagion and restrictions, alternating with periods of lower tension. This may make it difficult to compare and interpret results, especially when considering PTG as a process and therefore sensitive to trauma exposure times. In this respect, most studies did not use time-sensitive measures of adverse experiences related to COVID-19. The limitations highlighted in this review underscore the importance of adopting an end-to-end research approach, emphasizing the need for a meticulous consideration of measurement tools, data collection methods, and the temporal dynamics of trauma exposure to ensure more standardized and robust analyses in future investigations of post-traumatic growth associated with the COVID-19 pandemic.

5. Conclusions

This systematic literature review provides important data for understanding the effects of the COVID-19 pandemic and, more generally, the effects of trauma and their association with PTG. This review suggests important future research directions for understanding the phenomenon of PTG. It is fundamental to investigate whether the currently available measures can detect real rather than illusory growth, and how different forms of response to trauma interact with each other. Finally, the synthesis of the studies showed a wide heterogeneity of protective factors that should be considered when implementing interventions to support people with traumatic experiences.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jcm13010095/s1, S1: Search strategies; S2: PRISMA flow diagram.

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Psychosocial factors associated with postpartum psychological distress during the Covid-19 pandemic: a cross-sectional study

Luca Ostacoli[1,2], Stefano Cosma[3], Federica Bevilacqua[3], Paola Berchialla[1], Marialuisa Bovetti[3], Andrea Roberto Carosso[3], Francesca Malandrone[1], Sara Carletto[2,4*] and Chiara Benedetto[3]

Abstract

Background: Trauma, natural and man-made catastrophic events can be predictors of postpartum psychological distress. In a public health response due to coronavirus disease 2019 outbreak, the Italian government imposed a lockdown from March 9 to May 3. This extraordinary situation may have been challenging for maternal psychological health. The aim of this study was to investigate the prevalence of depressive and post-traumatic stress symptoms in women giving birth during the Covid-19 pandemic and its associations with quarantine measures, obstetrical factors, and relational attachment style.

Methods: Women who gave birth in a high-volume obstetric/gynaecological medical centre located in an epidemic area during the Covid-19 pandemic (March 8 to June 15) were asked to complete an online survey about their childbirth experience and the perceived effect of the pandemic. The Edinburgh Postnatal Depression Scale (EPDS), the Impact of Event Scale-Revised (IES-R), and the Relationship Questionnaire (RQ) were administered to assess levels of postpartum depressive and post-traumatic stress symptoms (PTSS) and relational style of attachment, respectively. Multivariate analysis was applied to identify associations between quarantine measures, childbirth experience, attachment style, and EPDS and IES-R scores.

Results: The survey was completed by 163 women (response rate 60.8%). The prevalence of depressive symptoms was 44.2% (EPDS cut-off score ≥ 11) and the PTSS rate was 42.9% (IES-R cut-off score ≥ 24). Dismissive and fearful avoidant attachment styles were significantly associated with the risk of depression and PTSS, respectively. Perceived pain during birth was a risk factor for postpartum depression. Perceived support provided by healthcare staff was a protective factor against depression and PTSS. Another protective factor against PTSS was quiet on the ward due to the absence of hospital visitors.

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* Correspondence: sara.carletto@unito.it
[2]Clinical Psychology Service, City of Health and Science, Torino, Italy
[4]Department of Neuroscience "Rita Levi Montalcini", University of Torino, Torino, Italy
Full list of author information is available at the end of the article

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Conclusion: This study reports a high prevalence of postpartum depressive and PTSS in women who gave birth during the Covid-19 pandemic. Postnatal psychological distress seemed to be associated more with the prenatal experience and other individual factors than with the pandemic hospital restrictions. Early detection during pregnancy of an insecure attachment style is fundamental to provide targeted preventive and therapeutic psychological interventions.

Keywords: Depression, PTSD, Mental health, COVID-19, Pandemic, Pregnancy, Postpartum, Quarantine, SARS-Cov-2

Background

Being female is the foremost risk factor for developing post-traumatic stress symptoms (PTSS) and depressive symptoms among adults and adolescents. Major stressors (e.g., health crises and natural disasters) can increase prenatal stress and make pregnant women particularly vulnerable [1, 2]. Mental health disorders are a common cause of morbidity during pregnancy, with approximately 12% of women experiencing depression and up to 22% experiencing high levels of anxiety in late pregnancy [3, 4]. Maternal distress during pregnancy has been associated with serious negative outcomes, including maternal psychosocial functioning, parenting difficulties, and offspring psychopathology [5, 6]. Childbirth can be experienced as a traumatic event owing to the presence of objective (e.g., obstetric complications) and subjective (e.g., loss of control, fear and pain during birth, lack of support) factors [7].

Previous studies reported that trauma, natural and man-made catastrophic events can be predictors of postpartum depression symptoms [8–14]. In February 2020, Italy became the epicentre of the coronavirus disease 2019 (Covid-19) outbreak in Europe. In a public health response, the Italian government imposed a lockdown (March 9 to May 3) and implemented restrictive measures such as social distancing, shutdown of activities, schools, and public places [15, 16].

Hospitals instituted visitor restriction policies that did not allow support persons, including the woman's partner, to be physically present in obstetric maternity units, even during labour, except in the birth room. Pregnant women were no less affected than the general population; Covid-19 infection in epidemic areas was detected in about one out of ten women, regardless of the trimester of pregnancy [17, 18].

This extraordinary situation of isolation, loss of freedom, concern about the impact of Covid-19 on pregnancy or the possible vertical transmission of infection [19], and unfavourable obstetric outcomes may be challenging for maternal psychological health [20, 21]. Recent literature regarding the Covid-19 outbreak has largely focused on mental health and psychological needs during pregnancy. Following official statements on human-to-human transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), there was a clinically significant rise in the prevalence of depressive and anxiety symptoms among pregnant women in their third trimester [22–24].

The aim of the present study was to assess the prevalence and associated factors of postpartum depressive and PTSS during the Covid-19 pandemic. Our hypothesis was that specific factors related to the current pandemic may be associated with the rise in the incidence of depressive and PTSS.

Methods

Design and participants

For this cross-sectional study, the sample was composed of women who gave birth at the Obstetrics and Gynecology Unit 1, Sant'Anna Hospital, City of Health and Science, Torino, Italy during the hospital restrictions imposed by the Covid-19 pandemic. Study inclusion criteria were having given birth between March 8 and June 15 and age ≥ 18 years. The exclusion criterion was the inability to read/write Italian. The women were contacted either by telephone after discharge or in person while in hospital and asked for their email address by a resident in obstetrics and gynaecology. Those who agreed to participate in the study received an email with a link to a Google Form survey. All the questions in the survey were mandatory, in order to avoid missing data. Data were collected between June 15 and June 29. The study was conducted in accordance with the Declaration of Helsinki, and was approved by the Research Ethics Committee of the City of Health and Science, Torino, Italy. Informed consent was obtained by asking all participants to click a button at the beginning of the online survey to consent to participate.

Study measures

The questionnaire contained items investigating sociodemographic factors (age, education, work status, living condition, nationality), obstetric factors (previous pregnancies, fertility treatments), their childbirth experience (level of pain experienced during childbirth, perceived level of support from health care staff during childbirth), and potential Covid-19 exposure, fear of contracting the virus, and discomfort/quiet experienced in the absence of their partner and other hospital visitors due to the restrictions in force (see Supplementary file 1 and 2).

To assess levels of postpartum depressive and PTSS and relational style of attachment, the following validated self-report questionnaires were administered:

- The Edinburgh Postnatal Depression Scale (EPDS) [25], a 10-item, four-point Likert-like scale questionnaire that assesses pregnancy and postpartum depression. The total score ranges from 0 to 30, with higher scores indicating more severe depression. A score between ≥11 and ≥ 13 is considered optimal for screening and detection of depressive symptoms, respectively [26–28].
- Impact of Event Scale-Revised (IES-R) [29], a 22-item questionnaire consisting of three subscales (8 items for intrusions, 8 for avoidance, and 6 for hyperarousal). The scale assesses subjective distress caused by traumatic events. For the present study, the women were asked to refer to their recent birth when responding. A score ≥ 33 is the best cut-off to identify moderate PTSS, while a score ≥ 24 indicates mild PTSS [30, 31].
- The Relationship Questionnaire (RQ) [32] is a single-item measure with four short paragraphs designed to measure adult attachment style. Each item describes a prototypical attachment pattern (secure RQ1, dismissive-avoidant RQ2, preoccupied RQ3, and fearful-avoidant RQ4) rated on a 7-point Likert-type scale. The dismissive avoidant, preoccupied, and fearful avoidant patterns are considered different forms of insecure attachment. The secure attachment pattern (RQ1) is described as: "It is easy for me to become emotionally close to others. I am comfortable depending on them and having them depend on me. I don't worry about being alone or having others not accept me." The dismissive-avoidant pattern (RQ2) is described as: "I am comfortable without close emotional relationships. It is very important to me to feel independent and self-sufficient and I prefer not to depend on others or have others depend on me." The preoccupied attachment pattern (RQ3) is described as: "I want to be completely emotionally intimate with others, but I often find that others are reluctant to get as close as I would like. I am uncomfortable being without close relationships, but I sometimes worry that others don't value me as much as I value them." The fearful-avoidant attachment pattern (RQ4) is described as: "I am uncomfortable getting close to others. I want emotionally close relationships, but I find it difficult to trust others completely, or to depend on them. I worry that I will be hurt if I allow myself to become too close to others." The highest score of the four attachment prototype ratings is used to classify individuals as having a predominant attachment style.

Statistical analysis

Continuous variables are expressed as the mean ± standard deviation (SD) or median and interquartile range (IQR) when appropriate, while categorical variables are expressed as frequency and percentage. The Mann-Whitney or Student's t test, Chi-square and Fisher's exact tests were used to compare continuous and categorical variables. Multivariate analysis was carried out to identify associations with EPDS and IES-R. EPDS was dichotomized as 0 (absence of postpartum depressive symptoms) or 1 (presence of postpartum depressive symptoms) using a cut-off of 11 points. IES-R was categorized as 0 (absence of post-partum PTSS) or 1 (presence of PTSS) using a cut-off of 24 points. A multivariate model was developed based on statistical selection procedures. Variables were: pain level, support provided by healthcare staff during birth, attachment style, discomfort due to the absence of the partner, quiet on the ward due to hospital restrictions on visitors, days between and the date of birth and of questionnaire completion, discomfort due to Covid-19 before hospital admission, and if this was the first pregnancy. Model selection was performed using an automatic approach based on the Akaike information criteria (AIC) method. Given the large number of covariates, a genetic algorithm was employed to explore the candidate set of models. Model goodness of fit was evaluated with reference to the Brier score (the closer to 0, the better) and Somers' Dxy Index, which indicates the ability of the model to discriminate. Odds ratios (ORs) and 95% confidence intervals (95% CIs) are reported. The significance level was set at $p < 0.05$. Statistical analysis was performed using R version 4.0.0.

Results

Overall, 268 women were invited to participate in the online questionnaire; 163 of which completed the survey (60.8% response rate). Tables 1 and 2 present the sociodemographic and clinical characteristics of the sample, stratified by IES-R and EPDS. Regarding the RQ, it was not possible to determine the predominant style of attachment for five women. No differences were found between IES-R and EPDS categories, except for age. Women with postpartum post-traumatic and depressive symptoms were younger: the mean age of those with and those without distress was 33.6 and 35.7 years, respectively ($p = 0.01$); the mean age of those with and those without depression was 33.7 and 35.6 years, respectively ($p = 0.015$).

Symptoms of postpartum depression were present in 72 (44.2%) women (EPDS cut-off ≥11) and in 50 (30.7%) (EPDS cut-off ≥13). Overall, symptoms of postpartum PTSS were present in 70 (42.9%) women (IES-R cut-off ≥24) and in 48 (29.4%) (IES-R cut-off ≥33). The RQ revealed that the

Table 1 Distribution of cohort demographics, overall and by presence of symptoms

	Overall	IES-R < 24	IES-R ≥ 24	*p-value*	EPDS < 11	EPDS ≥ 11	*p-value*
	N = 163	*n* = 93	*n* = 70		*n* = 91	*n* = 72	
Age (years, mean ± SD)	34.77 (5.01)	35.65 (5.14)	33.61 (4.62)	0.010	35.62 (4.96)	33.71 (4.90)	0.015
Marital status (%)				0.100			0.164
Single	10 (6.1)	3 (3.2)	7 (10.0)		3 (3.3)	7 (9.7)	
Married/cohabitant	152 (93.3)	90 (96.8)	62 (88.6)		87 (95.6)	65 (90.3)	
Separated/divorced	1 (0.6)	0 (0.0)	1 (1.4)		1 (1.1)	0 (0.0)	
Level of education (%)				0.449			0.548
Low secondary school	16 (9.8)	8 (8.6)	8 (11.4)		7 (7.7)	9 (12.5)	
High secondary school	54 (33.1)	28 (30.1)	26 (37.1)		32 (35.2)	22 (30.6)	
University	93 (57.1)	57 (61.3)	36 (51.4)		52 (57.1)	41 (56.9)	
Employment status (%)				0.214			0.567
Unemployed	25 (15.3)	16 (17.2)	9 (12.9)		16 (17.6)	9 (12.5)	
Employed	135 (82.8)	77 (82.8)	58 (82.9)		74 (81.3)	61 (84.7)	
Student	1 (0.6)	0 (0.0)	1 (1.4)		0 (0.0)	1 (1.4)	
Partially employed	2 (1.2)	0 (0.0)	2 (2.9)		1 (1.1)	1 (1.4)	
Nationality (%)				0.135			0.162
Italian	148 (90.8)	86 (92.5)	62 (88.6)		82 (90.1)	66 (91.7)	
European	7 (4.3)	5 (5.4)	2 (2.9)		6 (6.6)	1 (1.4)	
non-European	8 (4.9)	2 (2.2)	6 (8.6)		3 (3.3)	5 (6.9)	

IES-R denotes Impact of Event Scale-Revised, *EPDS* Edinburgh Postnatal Depression Scale.

majority reported an insecure attachment style: dismissive-avoidant in 60 (38%); fearful avoidant in 25 (15.8%); and preoccupied attachment pattern in 8 (5.1%) (Table 2).

Multivariate analysis of the EPDS (Table 3) showed a significant role for perceived pain: the risk of depression rose more than twice (OR 2.25, 95% CI 1.35–3.75; $p = 0.002$) for each 5-point increase on the scale assessing the level of pain experienced during childbirth. The relational attachment style was also found to be significantly associated with the risk of depression: women with an RQ2 attachment pattern had a significantly higher risk to develop depression than those with an RQ1 (OR 2.45, 95% CI 1.13–5.32; $p = 0.024$). Finally, the perceived support provided by healthcare staff during birth was a protective factor (OR 0.46, 95% CI 0.29–0.73; $p = 0.01$), indicating a risk reduction of depression of 54% for each 3-point increase on the perceived support scale. No significant association was observed between depressive symptoms and the quiet on the ward related to the absence of hospital visitors and the distress due to absence of the woman's partner.

The IES-R (Table 3) showed a significant association between the risk of developing postpartum PTSS and the attachment style. Women with an RQ4 attachment pattern had a higher risk than those with an RQ1 pattern. Finally, associated protective factors were the quiet on the ward because of the absence of visitors during hospitalization (OR 0.53, 95% CI 0.31–0.90; $p = 0.018$) and support by the healthcare staff during birth (OR 0.59, 95% CI 0.38–0.92; $p = 0.019$). The number of days between birth and questionnaire completion was included in the model as an adjusted covariate but had no significant association with depressive and post-traumatic symptoms.

Discussion

The present study findings show that the prevalence of postpartum depressive and post-traumatic stress symptoms among the women experiencing childbirth during the Covid-19 pandemic was higher than that reported in previous studies before the pandemic. Literature data report that approximately 10–16% of women met major depression's criteria at 3 months postpartum [24, 33–36]. The findings for our cohort (30.7%) are shared by a recent study that reported that 30% of the mothers who gave birth during the Covid-19 pandemic had a global EPDS score > 12 compared with 11.9% in an antecedent matched group of postpartum women [36]. An EPDS score > 13 was self-identified by another online survey in 15% of women before and in 40.7% during the outbreak for the same cohort of women who were pregnant or within the first year after birth [35].

Moreover, in our cohort 42.9% referred mild PTSS and 29.4% moderate symptoms. Previous studies investigating post-traumatic stress disorder (PTSD) rates after childbirth reported a prevalence rate of 3–4% in

Table 2 Clinical data of the cohort, overall and by presence of symptoms

	Overall	IES-R < 24	IES-R ≥ 24	*p-value*	EPDS < 11	EPDS ≥ 11	*p-value*
	N = 163	*n* = 93	*n* = 70		*n* = 91	*n* = 72	
First pregnancy (%)	74 (45.4)	37 (39.8)	37 (52.9)	0.134	36 (39.6)	38 (52.8)	0.127
Type of birth (%)				0.577			0.353
Vaginal	78 (47.9)	45 (48.4)	33 (47.1)		43 (47.3)	35 (48.6)	
Planned caesarean section	43 (26.4)	27 (29.0)	16 (22.9)		26 (28.6)	17 (23.6)	
Urgent caesarean section	32 (19.6)	17 (18.3)	15 (21.4)		19 (20.9)	13 (18.1)	
Forceps/vacuum	10 (6.1)	4 (4.3)	6 (8.6)		3 (3.3)	7 (9.7)	
Perceived support by healthcare staff during childbirth (median [IQR])	9 [7, 10]	10 [8, 10]	8 [6, 10]	0.002	10 [8, 10]	8 [6, 10]	0.002
Pain level during childbirth (median [IQR])	8 [2, 9]	7 [1, 9]	8 [5, 10]	0.156	7 [0.5, 9]	8 [5, 10]	0.036
Breastfeeding (%)	144 (88.3)	82 (88.2)	62 (88.6)	1.000	81 (89.0)	63 (87.5)	0.958
Confirmed diagnosis of Covid-19 (%)	5 (3.1)	3 (3.2)	2 (2.9)	1.000	1 (1.1)	4 (5.6)	0.237
Contact with Covid positive people (%)	8 (4.9)	7 (7.5)	1 (1.4)	0.156	5 (5.5)	3 (4.2)	0.980
Relatives/loved ones with a confirmed Covid-19 diagnosis (%)	21 (12.9)	13 (14.0)	8 (11.4)	0.807	11 (12.1)	10 (13.9)	0.916
Perceived safety during hospitalization (median [IQR])	8 [6;9]	8 [7, 9]	7.5 [6, 9]	0.385	8 [7, 9]	8 [6, 9]	0.340
Discomfort due to absence of partner	10 [8, 10]	10 [8, 10]	10 [9, 10]	0.009	10 [8, 10]	10 [8,75, 10]	0.315
Quiet on the ward related to the absence of visitors	7 [5, 8.5]	7 [6, 9]	6 [4, 8]	0.005	7 [5,9]	7 [5,8]	0.42
Time between childbirth and questionnaire completion ≤15 days (%)	25 (15.3)	15 (16.1)	10 (14.3)	0.917	15 (16.5)	10 (13.9)	0.812
Attachment style (%)				0.083			0.044
RQ1	65 (41.1)	42 (45.7)	23 (34.8)		44 (50.6)	21 (29.6)	
RQ2	60 (38.0)	37 (40.2)	23 (34.8)		30 (34.5)	30 (42.3)	
RQ3	8 (5.1)	4 (4.3)	4 (6.1)		3 (3.4)	5 (7.0)	
RQ4	25 (15.8)	9 (9.8)	16 (24.2)		10 (11.5)	15 (21.1)	

IES-R denotes Impact of Event Scale-Revised, *EPDS* Edinburgh Postnatal Depression Scale, *RQ* Relationship Questionnaire, *IQR* Interquartile range

Table 3 Factors associated with postpartum depression and post-traumatic stress symptoms

EPDS (cut-off score ≥ 11)	**OR**	**95% CI**		***p-value***
Pain level during childbirth	2.254	1.354	3.754	0.002
Perceived support by healthcare staff during childbirth	0.460	0.289	0.730	0.001
RQ2 (vs. RQ1)	2.450	1.128	5.323	0.024
RQ3 (vs. RQ1)	3.680	0.728	18.607	0.115
RQ4 (vs. RQ1)	2.372	0.837	6.725	0.104
IES-R (cut-off score ≥ 24)	**OR**	**95% CI**		***p-value***
Distress related to the absence of partner	1.459	0.988	2.155	0.057
Quiet on the ward related to the absence of visitors	0.525	0.308	0.896	0.018
Perceived support by healthcare staff during childbirth	0.589	0.379	0.915	0.019
Time between childbirth and questionnaire completion	1.617	0.893	2.926	0.113
Pain level during childbirth	1.983	0.965	4.076	0.062
Fear of contracting Covid-19	1.484	0.989	2.225	0.056
First pregnancy	2.042	0.959	4.347	0.064
RQ2 (vs. RQ1)	1.273	0.556	2.917	0.568
RQ3 (vs. RQ1)	1.334	0.256	6.944	0.732
RQ4 (vs. RQ1)	3.651	1.188	11.219	0.024

IES-R denotes Impact of Event Scale-Revised, *EPDS* Edinburgh Postnatal Depression Scale, *RQ* Relationship Questionnaire, OR odds ratio, CI confidence interval.

community samples and 15.7–18.9% in high-risk samples [37, 38]. Loss of control of oneself and excessive pain are the two most general elements of childbirth that make it potentially traumatising [39]. However, the psychological impact of the Covid-19 outbreak on pregnancy might explain the reported increase in PTSS also during the postpartum period.

The health status of the unborn child during the pandemic, the consequences of preventive measures, and the unmotivated fear of receiving less support and care during labour, birth or the pre and the post-natal period can all increase psycho-emotional distress. According to a recent survey, up to 95% of pregnant women reported mild PTSS and 61% moderate PTSS. More than two-thirds of the women also reported higher-than-normal anxiety, which was higher during the first trimester of pregnancy [23]. Data on the impact of coronaviruses on the first trimester of pregnancy are scarce; although no significant difference in the early abortion rate has been observed [40], viral infection at this stage could potentially affect embryogenesis and organ development.

In the present study, factors associated with postpartum depressive and post-traumatic symptoms were also investigated. Postpartum depressive symptoms were found to be associated with a high level of pain experienced during childbirth and an insecure dismissive-avoidant attachment pattern, while postpartum PTSS was associated with a fearful avoidant attachment style. The perceived level of support from the healthcare staff during childbirth was found to be a protective factor against the development of postpartum depressive and post-traumatic stress symptoms. Prior to the Covid-19 pandemic, the level of pain and perceived support were associated with postpartum depressive and post-traumatic symptoms [37, 41, 42]. An insecure attachment style was found to be significantly associated with depression and PTSD [43, 44], also in the perinatal period [45–50]. In our sample, a dismissive-avoidant attachment pattern was found to be significantly associated with postpartum depressive symptoms, while the fearful avoidant pattern was associated with PTSS. The dismissive-avoidant attachment pattern is characterized by a relational style that tends towards independence and autonomy. Individual and relational changes emerging during the perinatal period can conflict with the need for autonomy and the emotional difficulty to ask for relational (and psychological) support and the development of mother-infant bonding, which is an additional risk factor for postpartum depression [48]. The fearful avoidant attachment pattern is characterized by a combination of avoidant and anxious tendencies, low self-esteem, and the active search for intimate relationships and emotional closeness, without being able to trust other people.

The fearful avoidant profile seems to be more related to postpartum PTSS, as this attachment pattern is often present in people who have experienced previous relational trauma. Stress during the perinatal period might trigger a reactivation of traumatic memories, thus fostering the development of PTSD. Our findings are shared by a previous study that found fearful attachment to be associated with anxiety but not depressive symptoms in the immediate postpartum period [47]. Previous studies have also reported an association between the preoccupied attachment pattern and perinatal distress symptoms [50] which were absent in our study sample probably because of the few women in our cohort with this attachment style. An early evaluation of attachment style, which can be done during the prenatal period, could provide an additional strategy to identify women at are at higher risk to develop postpartum psychological distress and to offer them preventive interventions [45].

In our sample, the only Covid-19 related factor found to be significantly associated with symptoms during the postnatal period was the level of quiet on the ward due to the absence of visitors, which was a protective factor against the development of PTSS. The level of distress related to the absence of partners and the fear of contracting the virus approached statistical significance and so were not associated with depressive or post-traumatic symptoms. These findings may be interpreted in light of the higher prevalence of perinatal distress found in our and other studies conducted during the Covid-19 pandemic [22–24, 36]. The increase in postnatal distress seems to be related to symptoms present already during pregnancy. We may speculate that the increase in depressive and post-traumatic symptoms in women who gave birth during the Covid-19 outbreak may be related more to a general climate of alarm and concern about the pandemic than to specific factors with a direct impact on the childbirth experience. Future studies are needed to elucidate these associations and to evaluate the long-term impact of Covid-19 on the emotional distress of mothers and their relationship with children.

To our knowledge, this is the first study to evaluate depressive and PTSS and associated psychosocial factors during the postnatal period in women who experienced childbirth during the Covid-19 pandemic. The study has also some limitations. The lack of a pre-Covid-19 control group and of a psychological assessment during pregnancy may limit the generalization of postpartum prevalence data. Nevertheless, these factors do not seem to affect the primary aim of the study, which was to evaluate associated factors. Moreover, the potential bias of a retrospective survey was mitigated by including the variable “time since childbirth” as a covariate in the analysis.

Conclusion

The study findings indicate a high prevalence of depressive and post-traumatic symptoms in the post-partum period in women who gave birth at a hospital located in an epicentre of the Covid-19 outbreak. Psychological distress was mainly associated with risk factors that are commonly reported in the literature, such as the level of pain experienced during birth, perceived support from healthcare staff, and attachment styles. The factors specifically related to the Covid-19 pandemic seemed to play an indirect role in increasing psychological distress. A future area of focus is to investigate their role.

Early detection of distress, which includes evaluation of psychological factors such as the attachment style, is fundamental for specific and targeted psychological interventions to contrast the negative impact that postpartum depression and PTSD can have on women's psychosocial health, mother-infant bonding, and child development.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12884-020-03399-5.

Additional file 1: Supplementary file 1. Survey developed for the study – English language version.

Additional file 2: Supplementary file 2. Survey developed for the study – Original language version (Italian).

Abbreviations

PTSS: Post-traumatic stress symptoms; Covid-19: Coronavirus disease 2019; SARS-COV-2: Severe acute respiratory syndrome coronavirus 2; EPDS: Edinburgh Postnatal Depression Scale; IES-R: Impact of Event Scale-Revised; RQ: Relationship Questionnaire; SD: Standard deviation; IQR: Interquartile range; AIC: Akaike information criteria; ORs: Odds ratios; 95% CIs: 95% confidence intervals; PTSD: Post-traumatic stress disorder

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Authors' contributions

CB, SCa and LO conceived the study idea. All authors contributed to the study design. FB, MB and ARB performed the data collection. PB performed the statistical analyses. PB, FB, MB, SCa, and SCo drafted the first version of the manuscript. All authors have discussed the results and revised this manuscript critically for important intellectual content. All authors have read and approved the final version.

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Availability of data and materials

The datasets generated during and/or analysed during the current study are openly available in the GitHub repository (https://github.com/berkeley3/covid19_SantAnna).

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki, and was approved by the Research Ethics Committee of the City of Health and Science, Torino, Italy. Written informed consent (by clicking a button at the beginning of the online survey) was obtained from all participants.

Consent for publication

Not applicable.

Competing interests

The authors report no conflict of interest.

Author details

[1]Department of Clinical and Biological Sciences, University of Torino, Torino, Italy. [2]Clinical Psychology Service, City of Health and Science, Torino, Italy. [3]Gynecology and Obstetrics 1, Department of Surgical Sciences, City of Health and Science, University of Torino, Torino, Italy. [4]Department of Neuroscience "Rita Levi Montalcini", University of Torino, Torino, Italy.

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Publisher's Note

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Review

The Impact of Vulvar Cancer on Psychosocial and Sexual Functioning: A Literature Review

Francesca Malandrone [1], Federica Bevilacqua [2], Mariagrazia Merola [3,4,*], Niccolò Gallio [2], Luca Ostacoli [1,3], Sara Carletto [3,4,†] and Chiara Benedetto [2,†]

[1] Department of Clinical and Biological Sciences, University of Torino, 10043 Torino, Italy; francesca.malandrone@unito.it (F.M.); luca.ostacoli@unito.it (L.O.)
[2] Gynaecology and Obstetrics 1, Department of Surgical Sciences, University of Torino, City of Health and Science, 10126 Torino, Italy; federica.bevilacqua@unito.it (F.B.); niccolo.gallio@unito.it (N.G.); chiara.benedetto@unito.it (C.B.)
[3] Clinical Psychology Service, City of Health and Science, 10126 Torino, Italy; sara.carletto@unito.it
[4] Department of Neuroscience "Rita Levi Montalcini", University of Torino, 10126 Torino, Italy
* Correspondence: mariagrazia.merola@unito.it
† These authors contributed equally to this work.

Simple Summary: The diagnostic and therapeutic pathway of vulvar cancer impacts severely on the psychosocial and psychosexual equilibrium of women affected by it. The current literature shows the presence of depressive and anxious symptoms in association with physical, psychological and behavioural alterations in sexuality as well as deterioration of partner relationship. The aim of this article is to highlight the difficulties and challenges faced by women diagnosed and treated for vulvar cancer to provide early recognition and appropriate assistance. By implementing an integrated care model, it should be possible to detect unmet needs and improve the quality of life of these women.

Abstract: Women who are diagnosed and treated for vulvar cancer are at higher risk of psychological distress, sexual dysfunction and dissatisfaction with partner relationships. The aim of this article is to provide a review of the psychological, relational and sexual issues experienced by women with vulvar cancer in order to highlight the importance of this issue and improve the quality of care offered to these patients. A review of the literature was performed using PubMed, CINAHL, PsycINFO, and the Cochrane Library. The results are presented as a narrative synthesis and highlight the massive impact of vulvar cancer: depressive and anxiety symptoms were more frequent in these women, and vulvar cancer may have a negative effect on sexuality from a physical, psychological and behavioural point of view. Factors that may negatively affect these women's lives are shame, insecurity or difficulties in self-care and daily activities. This review highlights the psychosocial and psychosexual issues faced by women diagnosed and treated for vulvar cancer, although more studies are needed to better investigate this field of interest and to identify strategies to relieve their psychological distress. Care providers should implement an integrated care model to help women with vulvar cancer recognise and address their unmet needs.

Keywords: vulvar cancer; anxiety; depression; distress; sexual functioning; quality of life

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1. Introduction

Vulvar cancer is a rare malignancy with an incidence of 2.5–4.4 per 100,000 persons per year, making it the fourth most common gynaecological malignancy in Europe [1]. The most common type is vulvar squamous cell carcinoma (VSCC), followed by basal cell carcinoma, extramammary Paget's disease and vulvar melanoma. The median age at diagnosis is 69 years [2]. Risk factors for the development of VSCC include increasing age, human papilloma virus (HPV) infection, immunodeficiency, smoking and vulvar inflammatory conditions [3]. Notably, in recent decades, the incidence of vulvar intraepithelial neoplasia

(VIN), the precursor to VSCC, has doubled for all age groups, increasing the most for patients under the age of 50 [4].

VSCC has two precursor forms: (1) vulvar intraepithelial neoplasia (VIN) HPV-related (i.e. vulvar high-grade squamous intraepithelial lesion, VHSIL) and (2) HPV-unrelated, also known as differentiated VIN (dVIN), typically related to chronic vulvar inflammatory conditions (e.g., lichen sclerosus or lichen planus). These two different biological entities also have a differing epidemiology, characteristics, and prognosis [5–8]. The diagnosis of vulvar cancer is often delayed, as there is not adequate awareness among women: the majority of women feel embarrassed to ask their physicians about vulvar health and vulvar symptoms [9]. VSCC is often asymptomatic for a long period of time, or it can present with pruritus, irritation, or pain. Late-presenting symptoms include bleeding, pain, vaginal discharge, and urinary- or bowel-related symptoms. Clinically, VSCC can present as an erythematous patch, plaque, ulcer, or mass.

Staging is based on a vulvar biopsy to determine stromal invasion, which represents an important prognostic factor, then a clinical assessment of tumour size, groin lymph nodes and eventual distant metastases [10]. The treatment of stage I disease is surgical excision with adjuvant radiation (RT) in cases with high-risk factors. Stages II–IVA vulvar cancer, locally advanced disease, is usually treated with radical surgery and adjuvant chemoradiation. In selected cases, neoadjuvant chemoradiation can be used to reduce tumour size to facilitate surgical resection in an attempt to avoid a pelvic exenteration. For stage IVB, palliation with chemotherapy (CT) and/or RT is recommended [10].

The various surgical options have different impacts on the quality of life of the patients. A wide local excision is a simple excision of a vulvar tumour, a procedure reserved for preinvasive disease and stage IA vulvar cancers; this is the most conservative vulvar surgery in cases of malignancy. A modified radical vulvectomy combines the excision of the primary tumour and bilateral groin dissection [11]. On incision at the primary vulvar tumour site, the surgeon should try to spare the vital organs (e.g., urethra, clitoris and anal sphincter) [12]. Reconstructive surgery may be needed during this procedure [13]. Wound dehiscence and infection are common after radical vulvectomy. The most radical surgery is total pelvic exenteration, which is reserved exclusively for carefully selected patients with malignancy extended to other organs (e.g., urethra, anus and vagina). Despite its large impact on the patient's quality of life, pelvic exenteration can be a potentially curative option. Surgical morbidity is high and includes infections, wound dehiscence, and urinary- and gastrointestinal-related complications. Inguinofemoral lymph node dissection is indicated when stromal invasion is >1 mm, and it is burdened with many postoperative complications including a significantly increased risk of lymphedema and wound breakdown [14]. For this reason, sentinel lymph node biopsy should be considered in pT1 vulvar cancers [15].

Although vulvar surgery and treatment has become more targeted and less radical over the decades, it may still cause scarring and mutilation of the external genitalia, and it also may affect various nerves and blood vessels involved in sexual, anal and/or urinary functions [16]. Women who undergo surgical treatment for vulvar cancer or VIN are at high risk of psychological distress, sexual dysfunction and dissatisfaction with partner relationships [17]. Factors associated with post-treatment sexual dysfunction include history of depression or anxiety, patient's increased age and the excision size of the vulvar cancer. Interest in the QoL of women with vulvar cancer has increased in recent years [18–20]. Most studies on QoL after vulvectomy are, however, focused on postoperative complications and long-term side effects [21–23], whereas the impact that surgery may have on sexual health and on a patient's relationships have not been properly investigated. Despite the first paper on post-surgical sexual function following vulvar cancer being published almost 40 years ago [24], the true impact of the different types of vulvectomies on the sexual health of vulvar cancer survivors has been poorly investigated.

The aim of this literature review is to provide a comprehensive synthesis of the psychological, relational and sexual issues experienced by women with vulvar cancer in order to inform both researchers and clinicians of the steps needed to advance knowledge in this area and to improve the quality of care offered to these patients.

2. Material and Methods

The search was conducted in the following databases on 14 July 2021: PubMed, CINAHL, PsycINFO and the Cochrane Library. Keywords included: vulvar malignancy, vulvar neoplasms, vulvar cancer, vulva *, vulvectomy, gynaecologic *, gynecologic *, cancer *, tumor *, cancer survivors/psychology, psychological adaptation, quality of life, psychological distress, stress, anxiety, depression, sexuality, sexual dysfunction, partner and sexual partner. Primary research studies that investigated psychological, psychosocial and/or sexual consequences of vulvar cancer in adult women were included with no limitations related to publication date. Studies on gynaecological cancer not focusing specifically on vulvar malignancy were excluded. Only studies in the English language were included. The references of the identified studies and relevant reviews were manually searched to identify other relevant articles. The results of the evidence found are presented as a narrative synthesis.

3. Results

The initial search retrieved 1715 articles after duplicates removal. Of these, only 30 articles were considered eligible for inclusion in the review. The details of the included studies are described in Table 1, while a summary of the results is given in Figure 1.

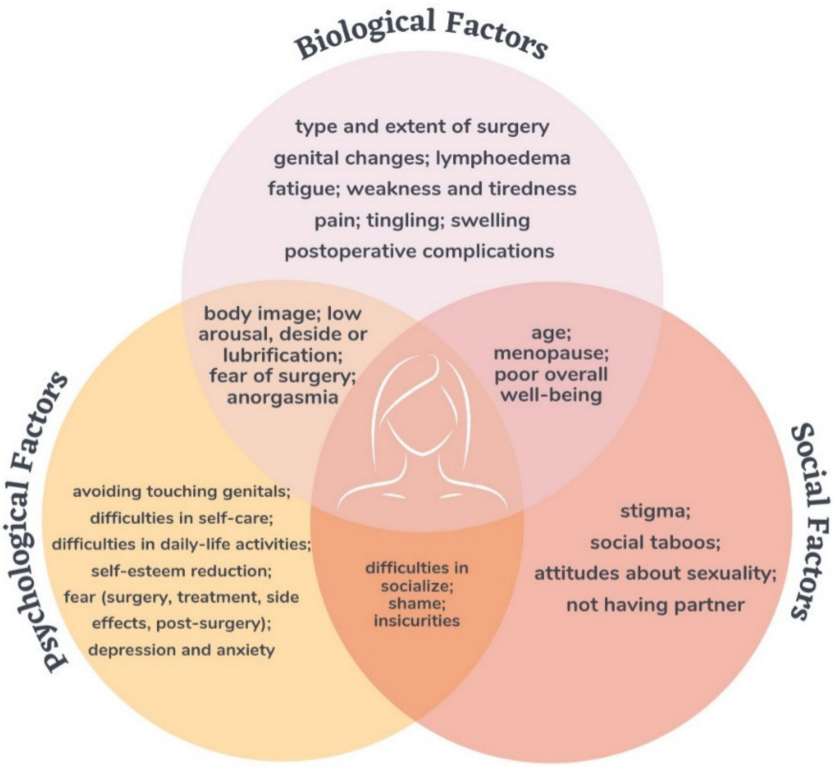

Figure 1. Summary of the results. This figure shows the main bio–psycho–social factors that impact the psychosocial and sexual well-being of women with vulvar cancer.

Table 1. Overview of the included studies.

Category	Studies	Country	Mean Age	Type of Surgery	Measures	Results
Quality of life	Blbulyan et al., 2020 [25]	Russia	56.3	-	EORTC; FACT-G	Lower overall quality of life. Restrictions in physical activity, poorer social interaction and emotional sphere. Worse global health status.
	de Melo Ferreira et al., 2012 [26]	Brazil	66.9	Vulvectomy + IFL	EORTC	
	Farrel et al., 2014 [27]	Australia	63	IFL	UBQC	
	Gane et al., 2018 [28]	Australia	57	Vulvectomy with or without SNB or IFL	FACT-G	
	Günther et al., 2014 [29]	Germany	63 WLE–59 RV	WLE or radical vulvectomy with or without IFL	EORTC	
	Hellinga et al., 2018 [30]	Netherlands	65.5	WLE/radical vulvectomy/pelvic exenteration + reconstruction with lotus petal flap	EORTC	
	Janda et al., 2004 [18]	Australia	68.8	WLE or radical vulvectomy with or without IFL	ECOG-PSR; FACT-G	
	Jones et al., 2016 [31]	UK	59.9	WLE or radical vulvectomy with or without IFL	EORTC	
	Likes et al., 2007 [32]	USA	47.5	WLE	EORTC	
	Oonk et al., 2009 [20]	Netherlands	69	WLE or radical vulvectomy with SNB or IFL	EORTC	
	Novackova et al., 2012 [33]	Czech Republic	66.5 CONS–73.8 RAD	WLE or radical vulvectomy with SNB or IFL	EORTC	
	Senn et al., 2013 [34]	Germany	18 (VIN) 42 (K)	Laser vaporisation/WLE/vulvectomy/radical vulvectomy/exenteration with or without SNB or IFL	WOMAN-PRO	
	Weijmar Schultz et al., 1990 [35]	Netherlands	55	WLE or radical vulvectomy with or without IFL	ad hoc questionnaire	
	Trott et al., 2020 [36]	Germany	63	Unspecified vulvar surgery with or without SNB or IFL with or without reconstruction	EORTC	
Partner relationship	Aerts et al., 2014 [37]	Belgium	57.4	Vulvectomy with or without SNB	DAS	Lower quality of partner relationship, marital satisfaction and dyadic cohesion.
	Barlow et al., 2014 [38]	Australia	58	Radical partial or total vulvectomy with or without IFL	clinical interview	
Sexual Functioning	Aerts et al., 2014 [37]	Belgium	57.4	Vulvectomy with or without SNB	SFSS; SSPQ	Worse sexual functioning. Disruption and reduction in sexual activity.
	Andersen et al., 1983 [24]	USA	55	WLE or radical vulvectomy	SCL-90	
	Andersen et al., 1988 [39]	USA	50.3	Laser vaporisation/WLE/vulvectomy	DSFI; SAI	
	Andreasson et al., 1986 [40]	Denmark	45.8	Vulvectomy	ad hoc questionnaire	
	Barlow et al., 2014 [38]	Australia	58	Radical partial or total vulvectomy with or without IFL	clinical interview	
	Blbulyan et al., 2020 [25]	Russia	56.3	-	FSFI	
	Farrel et al., 2014 [27]	Australia	63	IFL	clinical information	
	Green et al., 2000 [41]	USA	60	Vulvectomy with or without IFL	ad hoc questionnaire	
	Grimm et al., 2016 [42]	Germany	51.5	Laser vaporisation/WLE/radical vulvectomy	FSFI	
	Hazewinkel et al., 2012 [43]	Netherlands	68	WLE or radical vulvectomy with or without SNB or IFL	FSFI; BIS	
	Hellinga et al., 2018 [30]	Netherlands	65.5	WLE/radical vulvectomy/pelvic exenteration + reconstruction with lotus petal flap	FSFI; BIS	
	Jones et al., 2016 [31]	UK	59.9	WLE or radical vulvectomy with or without IFL	clinical interview	
	Weijmar Schultz et al., 1990 [35]	Netherlands	55	WLE or radical vulvectomy with or without IFL	ad hoc questionnaire	
	Likes et al., 2007 [32]	USA	47.5	WLE	FSFI	
Psychological health	Aerts et al., 2014 [37]	Belgium	57.4	Vulvectomy with or without sentinel node dissection	BDI	Presence of depressive and anxious symptoms, worsened by altered body image and sexual difficulties. Impact on general well-being, quality of life, and relationship with partner and families.
	Avery et al., 1974 [44]	USA	NA	Vulvectomy	clinical information	
	Andersen et al., 1983 [24]	USA	55	WLE or radical vulvectomy	BDI	
	Andreasson et al., 1986 [40]	Denmark	45.8	Vulvectomy	ad hoc questionnaire	
	Corney et al., 1992 [45]	UK	71% >65	Radical vulvectomy, Wertheim's hysterectomy or pelvic exenteration	HADS; clinical interview	
	Green et al., 2000 [41]	USA	60	Vulvectomy with or without IFL	PRIME-MD	
	Janda et al., 2004 [18]	Australia	68.8	WLE or radical vulvectomy with or without IFL	FACT-G; HADS	
	Jefferies and Clifford, 2012 [46]	UK	>50	-	clinical interview	
	McGrath et al., 2013 [47]	Australia	NA	-	clinical interview	
	Senn et al., 2011 [48]	Germany	55	Laser vaporisation/WLE/radical vulvectomy with or without SNB or IFL	clinical interview	
	Senn et al., 2013 [34]	Germany	18 (VIN) 42 (K)	Laser vaporisation/WLE/vulvectomy/radical vulvectomy/exenteration with or without SNB or IFL	WOMAN-PRO	
	Stellman et al., 1984 [49]	USA	53.4	Vulvectomy or radical vulvectomy	SQ	
	Tamburini et al., 1986 [19]	Italy	51.7	Vulvectomy with or without IFL	clinical interview	
	Thuesen et al., 1992 [50]	Denmark	41.4	WLE	clinical interview; ad hoc questionnaire	

BDI = Beck Depression Inventory; BIS = Body Image Scale; ECOG-PSR = ECOG Scale of Performance Status; CONS = sentinel lymph node biopsy; DAS = Dyadic Adjustment Scale; DSFI = Derogates Sexual Functioning Inventory; EORTC = European Organization for Research and Treatment of Cancer; FACT-G = Functional Assessment of Cancer Therapy—General; FSFI = Female Sexuality Index; GSI = Global Severity Index; HADS = Hospital Anxiety and Depression Scale; IFL = inguinofemoral lymphadenectomy; NA = not available; PRIME-MD = Primary Care Evaluation of Mental Disorders; RAD = inguinofemoral lymphadenectomy; RV = radial vulvectomy; SAI = Sexual Arousability Index; SCL-90 = Symptoms Checklist-90; SFSS = Short Sexual Functioning Scale; SNB = sentinel node biopsy; SSPQ = Specific Sexual Problems Questionnaire; SQ = Kellner Symptom Questionnaire; UBQC = Utility-Based Questionnaire-Cancer; WLE = wide local excision.

3.1. Psychological Impact

Vulvar cancer is a rare condition. Due to the lack of studies regarding the impact of the disease, little is known about the specific emotional, social and psychological impacts on these patients. Diagnosis and treatment, primarily consisting of surgery ranging from local excision to radical vulvectomy and clitoris removal, may have a significant negative psychological effect on these women. Symptoms may range from anxiety and sexual dysfunction to major depressive disorders. Depending on the extent of surgery, participants' self-perception of being a woman has been reported to be influenced in at least four dimensions: the appearance of post-surgical female genitals, sexuality, attractiveness and self-confidence [48].

The need for emotional support from the preoperative phase to follow-up care has already been recognised by Avery et al. in 1974 [44]. The first systematic review was carried out by Jefferies and Clifford [51], who examined the psychological, physical and sexual consequences for women following diagnosis and treatment for cancer of the vulva. Eight out of the 14 studies analysed reported psychological changes as a result of the diagnosis and surgery for vulvar cancer [19,24,39–41,45,49,50]. Only a few of these authors used validated measurement tools to record levels of depression and anxiety [18,24,37,41,45,49].

In terms of psychological distress and/or depression, in the study by Andersen [24], women affected by vulvar cancer experienced substantial and significant levels of distress in comparison to healthy women. Nearly 50% of the patients interviewed by Andreasson et al. [40] had an altered sense of their body image, describing feelings of "not being the same woman". This finding was later supported by Andreasson et al. [40], Stellman et al. [49], and Thuesen et al. [50].

Stellman and colleagues [49] reported that four out of nine women were unable to name the anatomic area surgically removed. This may have increased the women's feelings of isolation and embarrassment. The study also reported that six out of nine women were depressed and anxious. Loss of self-confidence and self-esteem, also associated with depression, were noted.

The study by Tamburini et al. [19] revealed that 72% of the sample showed symptoms on the hypochondria scale, 63% on the depression scale, 63% on the hysteria scale and 18% on the psychotic scale (paranoia, schizophrenia). These results, both for "neurotic" (hypochondria, hysteria and depression) and, to a lesser extent, the "psychotic" scales (paranoia, schizophrenia) tended to be more pathological than in patients undergoing the same radical surgery for carcinoma of the uterine cervix. This may be explained by the feeling of awkwardness or loss of self-esteem resulting from external genital mutilation and by severe sexual difficulties.

In a retrospective study by Corney et al. [45], women who underwent major gynaecological surgery (vulvectomy, hysterectomy and pelvic exenteration) for carcinoma of the cervix and vulva were interviewed to evaluate postoperative psychosocial and psychosexual problems, revealing that 21% of the women suffered from anxiety and 14% from depression.The study also tried to assess the relationship between the level of distress and the different clinical phases, finding that the period of highest distress or worry usually coincided with the period of most uncertainty. For 39% of women, the most distressing time was between the first medical indication of clinical problems and the diagnosis of cancer, and an additional 37% felt that it was the period between diagnosis and the operation. Moreover, this study showed that the presence of sexual problems was significantly associated with the women's level of anxiety. However, it was difficult to ascertain whether the sexual problems were making the women more anxious or whether their anxiety was affecting their sexual behaviour, cognition or emotions.

Green [41] detected symptoms of depression in 31% of women treated with vulvar surgery, but only 14% were taking antidepressant medication. Women with higher depression scores had greater sexual aversion disorder and experienced higher levels of body image disturbance and global sexual dysfunction. Janda et al. [52] showed that 21.8% of patients in the sample were affected by severe anxiety and 6.3% by depression.

The study by Senn et al. [48] focused on the symptoms of women during the first 6 months following surgical treatment for vulvar neoplasia. Using narrative interviews, the study showed eight interrelated psychological themes: delayed diagnosis, disclosed disease, disturbed self-image, changed vulva care, experienced wound-related symptoms, evoked emotions, affected interpersonal interactions and feared illness progression. The unknown diagnosis, surgery, location, changed female genitals and experienced symptoms evoked feelings of embarrassment, uncertainty, fear, sadness and tiredness. Senn et al. [34] tried to measure these symptoms with the WOMAN-PRO instrument, developed by them in 2013. The results showed that the three most prevalent psychosocial symptoms/issues were "tiredness" (95.4%), "insecurity" (83.1%) and "feeling that my body has changed" (76.9%). Despite physical symptoms occurring more frequently, in this sample they were less distressing than difficulties in daily life and psychosocial symptoms/issues.

Through a phenomenological study, Jefferies and Clifford [46] gave a voice to women regarding the stories of their illness, their feelings and their thoughts about diagnosis and treatment for cancer of the vulva. This study was an overview of their lived experience described using the concept of invisibility in the context of four existential dimensions: body, relationship, space and time.

The findings of the study by McGrath et al. [47] demonstrated that the challenges in relation to the diagnosis and treatment of vulvar cancer are exacerbated by concerns about privacy, shame and fear. Because of the private nature of the disease, the women from the sample tended to keep the condition a secret once diagnosed; the feeling of shame was as powerful as the sense of privacy. These feelings were so strong that even when a woman died of this cancer, the type of cancer was not revealed to avoid shame. Lastly, it was common for the women to feel scared and worried about the cancer, especially when first diagnosed.

In the study by Aerts et al. [37], women with a diagnosis of vulvar malignancy were compared to healthy controls. When compared with the situation before surgery, no significant differences in depressive symptoms, general well-being and quality of partner relationship were found after surgery. However, in comparison with healthy controls, women with vulvar malignancy reported significantly lower levels of psychological functioning both before and after treatment.

Finally, the review of the literature by Boden et al. [53] highlighted important psychosocial issues that women diagnosed and living with cancer of the vulva have to face. Challenges include social stigma surrounding the vulva and the diagnosis of vulvar cancer, feeling unprepared both physically and psychologically and a lack of information and support.

The literature, although poor, shows the massive impact of vulvar cancer, both in psychological and social dimensions. Through different means of investigation, the presence of depressive and anxiety symptoms in women has been demonstrated in every phase, from diagnosis to postoperative follow up. Moreover, the altered body image due to the surgical treatment and the presence of sexual difficulties can lead to deterioration in the emotional state. All of these elements can influence the women's general well-being, quality of life and their relationship with partners and families.

In conclusion, the review of the literature reveals the paucity of current studies regarding women who are suffering from cancer of the vulva today. Clearly there is a need for more research into the special needs of this small group of women.

3.2. Quality of Life, Sexuality and Partner Relationship

Several studies [18,27,28,31–33,36] reported an overall worsening of quality of life. Three studies [25,29,30] explored this aspect further, noting that the worsening of quality of life was related to a decrease in physical and cognitive functioning, social interactions and an increase in physical and emotional symptoms. The study by de Melo Ferreira and colleagues [26], going into more detail, found a negative correlation between quality of life and the severity of lymphoedema of the lower extremities.

Only two studies investigated partner relationships [37,38]. Aerts and colleagues [37] observed that poorer quality of partner relationship, marital satisfaction and dyadic cohesion were more common in women with preoperative vulvar malignancy. Dissatisfaction with partner life was also maintained at 6 months and 1 year after the operation. In this respect, Barlow and colleagues [38] found that conservative surgery led to no negative impact on couples' relationships.

Sexual functioning in this disease has been investigated but most frequently from a physiological perspective. However, some studies have intersected biological function with more psychosocial components. Aerts and colleagues [37] found that there is a correlation between psychosocial well-being and sexual dysfunction in patients with vulvar cancer. In general, it seems that vulvar cancer has a negative effect on sexuality not only from a physical point of view, for example, due to the fact of presenting with anorgasmia, difficulty in lubrication or pain, but also from a psychological and behavioural point of view, e.g., due to the fact of reporting reduced desire, reduced satisfaction, reduced sexual activity, fear of penetration or avoidance behaviour [24,25,27,30–32,35,38,40,41,43]. Of interest are the results presented in the study by Andersen and colleagues [24], which showed that while there was a deterioration in sexual functioning from a physiological point of view, there was little negative impact on sexual life. However, there was a reluctance to enter into relationships with new partners for those who did not have any before the illness.

Related Bio–Psycho–Social Factors

Several factors are responsible for the deterioration of quality of life, sexual functioning and partner relationships. In general, studies have considered the various factors, often incorporating the collection of these data into clinical interviews or using generic, albeit validated, assessment instruments. Although pre-existing problems have been shown to play an important role [32,33,36], several studies have reported that treatments and surgeries are crucial to patients' physical, mental and social health. Three studies [24,41,42] pointed out that outcomes seem to be correlated with the magnitude of surgical intervention. Aerts and colleagues and Likes and colleagues [32,37] found a negative correlation between quality of life and the excision size of the vulvar malignancy, meanwhile Gunther et al. [29], Barlow et al. [38] and Hazewinkel et al. [43] identified radical vulvectomy and clitoral removal as determinants of worsening quality of life, sexual functioning and partner life. Inguinofemoral lymphadenectomy also appears to negatively impact the lives of vulvar cancer patients as was found by Novackova and colleagues [33].

Some authors have observed that in connection with surgery, important impacting factors are fear of possible removal of their clitoris and fear of pain on resumption of sexual intercourse [38]. In general, it seems that aesthetic and functional changes of the genitals [39] and having undergone multiple vulvar procedures [38] have a significantly negative impact on well-being during the postoperative period. The postoperative period itself is not without risk due to the possibility of incurring postoperative wound-healing complications [36] that not only slow down the healing process but also hinder the recovery of normal biological, social and psychological functions. Factors associated with post-treatment sexual dysfunction include older age, poor overall well-being and history of depression and anxiety [37,42].

Regarding therapies, two studies found that radiotherapy or adjuvant inguinal radiotherapy [33,43] have a negative impact on patients' lives, mainly due to the associated side effects. The most impactful side effect seems to be lymphoedema, considered globally [20,29,31,33,38] or specifically of the lower extremities [18,26]. Lymphoedema causes patients pain, changes in sleep, fatigue, reduced movement amplitude and financial costs [26]. It is a tiring and energy-reducing condition, as it requires constant attention in terms of wearing compression stockings, performing massages and undergoing other treatments. It can reduce a patient's ability to work, perform household duties and socialise as well as negatively affecting the patients' body image and self-esteem [18]. Other side

effects that affect patients' lives are pain [28–31] and leg pain [27], persistent swelling of the lower limbs or vulva and/or pelvic/abdominal region [28], tingling [28] and fatigue [31,33].

From a psychological and behavioural point of view, factors such as body image disruption [24,34,38,41], feelings of weakness and fatigue [28,31,34] and avoidance behaviours regarding sexual intercourse and touching the genital area [38] seem to be decisive in worsening quality of life, quality of relationships and sexuality.

In addition to the psychological aspects of vulvar cancer, social, cultural and interpersonal aspects negatively affect patients' quality of life, sexuality and relationship with their partners. Studies have shown that age can modulate a person's response to the disease and treatment. On the one hand, younger women show more distress because of the greater proximity to the onset of menopause [24] and the impediments in the activities of daily living: the younger the patients are, the more they feel they should and would like to have more active lives with a greater number of relationships and a more active sex life [34]. On the other hand, it has been observed that with advancing age, patients experience greater suffering related to difficulties in investing in new romantic relationships and taking care of themselves [32,33,36]. Older patients also have prevalent attitudes about sexuality in later life such as those indicating that such activity is inappropriate, unimportant or readily expendable [24]. More generally, factors that negatively impact the lives of women with vulvar cancer are shame or insecurity [33,34], difficulties in self-care [48] and in daily activities such as homecare [34] and not having a sexual partner [33]. Stigma and social taboos also seem to play a key role [48].

4. Discussion

Despite covering a large time span—from the 1983 study by Andersen and colleagues to the 2020 study by Blbulyan et al.—the impact of vulvar cancer on mental health, quality of life, sexuality and relationships has been little investigated. The aim of this narrative review was to update the knowledge on these themes and suggest future directions for clinical practice and research.

Regarding quality of life, studies have often focused on well-being in general or global health; however, specific aspects of quality of life, emotional regulation and the ability and willingness to take care of oneself would also be of interest. Vulvar cancer seems to also have a role in worsening sexual functioning with a disruption and reduction in sexual activity. Similarly, the included studies observed lower quality of partner relationships, marital satisfaction and dyadic cohesion.

Regarding mental health issues, depressive and anxiety symptoms were prevalent among women affected by vulvar neoplasia at every step of the diagnostic and therapeutic pathway. Different factors can contribute to the onset of these symptoms. Psychological distress may be related to the altered body image due to the aftermath of the surgery. The results of the studies, although scarce, demonstrate that women may experience feelings of shame and embarrassment related to strong social stigma, which may lead to feelings of isolation and a loss of self-esteem. Moreover, sexual dysfunction is strongly associated with anxiety and depressive symptoms, which are often clinically significant, with a mutual influence.

Depression and cancer risk seem to be linked by a mutual relationship. The experience of receiving a cancer diagnosis can be a significant source of distress, with the onset of anxiety and/or depressive symptoms that can lead to sleep disturbance which may, in turn, increase the risk of depression. Major depressive disorder (MDD) is common among cancer patients with prevalence rates up to four-times higher than the general population [54]. Conversely, depression confers worse outcomes in oncological settings including non-adherence to treatment and increased mortality [55]. According to a study by Wang et al. [56], the estimated absolute risk increases (ARIs) associated with depression and anxiety are 34.3 events/100,000 person years for cancer incidence and 28.2 events/100,000 person years for cancer-specific mortality. Several mechanisms could explain this reciprocal influence [56]. Psychosocial stressors in cancer promote inflammation and oxidative/nitrosative

stress, with alterations in cytokine secretion and regulation (TNF-a or Il-6) [57]; decreased immunosurveillance; dysfunctional activation of the autonomic nervous system and hypothalamic–pituitary–adrenal axis. Given the high prevalence of depression and anxiety in the general population, particularly among cancer patients, and in consideration of the bidirectional link between the neuroendocrine and immune systems, the screening and intervention of underlying depressive and anxiety symptoms has significant repercussions both on clinical practice and public health regarding cancer prevention and treatment.

The studies included in this review have several limitations. First, most of the studies use non-validated tools such as clinical interviews or data taken from medical records. While these have made it possible to obtain qualitative insight into patients' experiences, there is less scope for distinguishing between areas and isolating the factors that impact on them. Sexual function has often been addressed on a physiological level via the maintenance of sexual activity or physical dysfunction (e.g., orgasm, pain on penetration and lubrication). Sexual satisfaction cannot be reduced simply to the extent of physical impairment, the presence of symptoms or the ability to perform a sexual task considered normal [35]. The fact that sex life is scarcely investigated from a psychological point of view may be due not only to the limitations of the studies but also to social and cultural issues surrounding the perception of the possibility for women to desire an active and satisfying sex life after the age of 50. A healthy sex life has been shown to play a key role in maintaining mental and physical health.

4.1. Implications for Future Research

Future studies with better methodological quality are needed to obtain more reliable data. In particular, controlled studies are needed. Given the high survival rate of vulvar cancer patients [58], quality of life, sexuality and psychological well-being are key areas for investigation, along with the long-term consequences of the disease and treatment pathways. These areas are crucial not only due to the high prevalence of psychological distress among cancer patient but also due to the consequences of such disorders on overall health [59]. In fact, considering breast cancer, a much more widespread, well-known and well-studied type of cancer among women, a large volume of literature is available on quality of life [60], sexuality [61,62] and partner relationships [63,64]. Furthermore, future studies should investigate the psychological aspects of sexual experience, shame, body image, desire and avoidance of desire as well as considering the sexual orientation of patients and the specific needs related to it that may emerge. It would also be useful to consider sexuality as a subjective, personal and individual dimension and not only within the context of the couple. Regarding the relationship with a partner, it would be interesting in the future to investigate not only the level of satisfaction and sexual activity but also other factors such as attachment.

With regard to the impact of different medical treatments, the approach to vulvar cancer has changed considerably over time, with a succession of different surgical procedures and pharmacological treatments. In light of this, it would be interesting to assess how different types of intervention may have different impacts on psychological, social and sexual outcomes. Future studies could compare different treatment pathways to explore this further.

4.2. Implications for Clinical Practice

The impacts of vulvar cancer on psychosocial- and sexuality-related areas highlight the importance of implementing effective strategies in both primary and secondary prevention. The ideal goal should be early recognition and appropriate treatment of the elements of psychosexual and psychosocial distress. These approaches should lead to an improvement in general well-being, a healthier sex life and more stable and supportive relationships.

Firstly, healthcare professionals should be adequately trained to help women to understand the basics of female external genital anatomy, so that they can learn the difference between physiological and pathological features. Very few women engage in vulvar self-

examination, and few women who identify abnormalities seek appropriate medical care. Vulvar self-examination may allow women to have a healthier relationship with their genitals, overcoming the obstacles due to the feelings of shame, judgment and embarrassment. In fact, this is an easy procedure that takes only a few minutes and could change the clinical course of some pathologies and, in some cases, could save lives [9].

The National Comprehensive Cancer Network has recognised psychological distress as the sixth vital sign in cancer care [65]. For this reason, it may be useful to facilitate its early detection using screening tests in a very early phase of the diagnostic and therapeutic pathways. This kind of test should be approved and validated so that it can determine clinical risk categories and assign the most effective interventional treatment. The importance of the role of psycho-oncologists in the treatment of vulvar cancer should be emphasised for proposing and offering psychological support and psychoeducational interventions. These kinds of interventions could be useful not only for sustaining women's sexual health [66] and their emotional condition but also for supporting the familial network. Moreover, evaluation by a psychiatric specialist may be useful in order to provide possible psychopharmacological therapy in the presence of severe depressive–anxiety symptoms, analysing the risk factors and any pharmacological interactions with chemotherapy treatments. This may be useful in improving the detection and treatment of psychosexual and psychosocial distress. The ideal goal could be the integration of a psycho-oncologist and/or psychiatrist in the multidisciplinary team for the treatment of vulvar cancer with the aim of addressing both the physical and psychosocial needs of these women [67].

5. Conclusions

This review highlights the psychosocial and psychosexual issues faced by women diagnosed with and treated for vulvar cancer. Many questions regarding the detection and management of psychological distress, sexual dysfunction and relational problems remain open, mainly due to the limited research into this area and the scarce integration of psycho-oncological knowledge in routine care. Care providers should implement an integrated care model to help women with vulvar cancer to recognise and address their still unmet needs, working within a bio–psycho–social framework.

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Early childhood infections, antistreptococcal and basal ganglia antibodies in adult ADHD: a preliminary study

Francesco Oliva[1*], Giulia di Girolamo[2], Francesca Malandrone[1], Noemi Iaia[1], Fiorella Biasi[1] and Giuseppe Maina[2]

Abstract

Background: To explore the relationship between adult Attention Deficit/ Hyperactivity Disorder (ADHD), antistreptococcal titers, ABGA, and recurrent infections during early childhood.

Method: Childhood history of recurrent infections and a blood sample were collected in a sample of DSM-IV adult outpatients with ADHD. The anti-streptolysin O (ASO), anti-deoxyribonuclease B (anti-DNase B), and anti-basal ganglia antibodies (ABGA) titers were determined in patient plasma by enzyme-linked immunosorbent assay (ELISA). Titers positivity was evaluated following manufacturer's specifications. Absolute titers were also collected as continuous variables.

Results: Fourteen out of 22 (63.6%) have had recurrent infections in childhood (i.e., seven, 31.8%, have had tonsillitis or adenoiditis and seven, 31.8%, have had any other infections). Eighteen patients (81.9%) were positive for anti-DNase B, five (22.7%) for ASO, and 4 (18.2%) were positive for both of them. Five participants (22.7%) were ABGA positive, whereas only two (9.1%) were positive for all three antibodies.

Conclusions: patients with ADHD might be more prone to infections during childhood and subclinical streptococcal infections during adulthood. Moreover, they seem to have an increased risk for basal ganglia autoimmunity in adulthood. Both infections and the ensuing acquired autoimmunity could influence the neurodevelopmental process, by contributing, at least in part, to the ADHD pathogenesis.

Keywords: ADHD, Group a streptococcus, Anti-streptolysin O, Anti-deoxyribonuclease B, ABGA, Basal ganglia, Adult

Background

ADHD is one of the most prevalent neurodevelopmental disorders and it is characterized by a persistent pattern of inattention and/or hyperactivity and/or impulsivity, leading to functional impairment [1] and several lifetime consequences [2]. Despite ADHD arises in childhood, it can persist in adulthood in about half of patients as a full-criteria disorder (45–57%) [3, 4], whereas a further 37% can show impairing symptoms or a subthreshold disorder at the 10 years after follow-up [3]. Neuroimaging and neurophysiological studies have consistently documented that improvement with age in core symptoms are accompanied by functional changes in cortical (right inferior frontal and inferior parietal/precuneus) and cerebellar regions [5, 6], whereas basal ganglia anomalies (i.e., right caudate) seem to be a peculiar lifetime feature of ADHD, regardless of adult remission [6, 7]. Studies on structural anomalies and age-by-diagnosis

* Correspondence: francesco.oliva@unito.it
[1]Department of Clinical and Biological Science, University of Turin, Orbassano (TO), Italy
Full list of author information is available at the end of the article

interaction in the caudate and putamen have also supported the pivotal role of subcortical basal ganglia anomalies in the pathophysiology of ADHD [8, 9].

Although the etiopathogenesis of ADHD is still unclear, a gene by environment model has been proposed to explain the high family history of the disorder [2, 10, 11]. Probably, a variable and complex interaction between predisposing genetic and environmental factors during the early months or years of life could affect the normal path of neurodevelopment. Considering the above-mentioned structural and functional evidences, environmental factors influencing basal ganglia development should be worthy of investigation. For instance, a specific vascular vulnerability of the striatum due to its positioning in a border zone of arterial supply has already been suggested by a case-control study reporting on hypoxic and other perinatal complications [12] and by a review of some in vivo studies [13]. A more recent study has documented the negative impact of exposure to polycyclic aromatic hydrocarbons on the caudate nucleus, even below the legislated annual target levels established in the European Union [14].

Over the last 20 years, the recognition of the role of some infections (e.g., group A streptococcus - GAS) in determining acute, somewhat mixed, movement (i.e., Sydenham's chorea) and psychiatric disorders (i.e., obsessive-compulsive disorders, tic disorder, ADHD), have increased the attention to infective agents as possible causes of childhood neurodevelopmental disorders, involving basal ganglia [15–18]. A molecular mimicry mechanism has also been proposed to explain the enduring symptoms subsequent to GAS infection remission [19, 20]. Moreover, high titers of GAS infection markers, i.e., anti-streptolysin O (ASO) and anti-deoxyribonuclease B (anti-DNase B), and anti-basal ganglia antibodies (ABGA) were found in this type of disorders [21–23].

Since Kiessling and colleagues [22] have reported a higher prevalence of distractibility and hyperactivity among patients with post-streptococcal movement disorders than in controls, a growing number of subsequent studies have specifically investigated, in different ways, the relationship between GAS infections, basal ganglia autoimmunity and ADHD with conflicting results [24–28].

ADHD appears to play an important role in post-streptococcal basal ganglia disorder at least as much as obsessive-compulsive and tic disorders even when considered alone: higher titers of GAS infection markers were found in children with ADHD than in those with obsessive-compulsive or tic disorder; ADHD and even more hyperactivity symptoms significantly predicted anti-DNase B titer; and ASO titers were correlated with basal ganglia volume in children with ADHD [26].

More recently, three case-control studies have focused on GAS infection and ABGA titers of children with ADHD and without comorbid obsessive-compulsive/tic disorders [24, 27, 28]. Only one study found higher ABGA titers among children with ADHD than controls (30% vs. 15%, [28]), whereas higher titers of ASO and anti-DNase B were reported in children with ADHD by two out of three studies [27, 28]. All those inquiring about GAS infection collecting pharyngeal swabs reported higher rates of positive culture among children with ADHD than controls [24, 27]. Regardless of the specific strengths and limitations, they all were conducted on child populations and, taken together with above-mentioned studies, they suggest a possible predisposition of patients with ADHD to be infected by GAS, involving basal ganglia development.

To the best of our knowledge, no studies have assessed GAS antibodies and ABGA titers in adult patients with ADHD in an attempt to confirm the lifespan vulnerability of this population to GAS infection, which could also, in some cases, involve basal ganglia autoimmunity.

The aim of the present preliminary study was to explore ASO, anti-DNase B, and ABGA titers in a sample of adult outpatients with ADHD.

Methods

This preliminary study was conducted at the adult ADHD outpatient center of the San Luigi Gonzaga University Hospital (Orbassano, Turin, Italy), between July 1, 2019 and September 1, 2019, on a consecutive sample of patients newly diagnosed with adult ADHD according to DSM-IV-TR criteria (age > 18 years). According to the outpatient service routine, all patients had been screened for adult ADHD using the Adult ADHD Self Reporting Scale (ASRS-1.1) screener, and then the DSM-IV ADHD diagnosis was confirmed through the Diagnostic Interview for Adult ADHD (DIVA 2.0). The severity of ADHD symptoms was rated by Adult ADHD Investigation Rating Scale (AISRS).

All patients were asked to participate in the study signing a written informed consent and a unique identification code was assigned to each patient, in order to maintain data anonymity and patient confidentiality. The research protocol of the present observational study was approved by the Research Ethics Committee of the San Luigi Gonzaga University Hospital (Orbassano, Turin, Italy), therefore the study was conducted in accordance with the Helsinki Declaration.

During the assessment process, information about the history of both infections and psychiatric disorders were collected and patients were also assessed for other psychiatric disorders through an in-depth psychiatric interview. Recurrent infections in childhood (i.e., under 12) were defined as at least three symptomatic episodes of infection with fever (e.g., tonsillitis, adenoiditis, glomerulonephritis, or others) per year for at least 1 year.

Blood samples from patients were collected in potassium ethylenediaminetetraacetic acid (EDTA) - containing tubes (BD Vacutainer® spray-coated K2EDTA, Becton, Dickinson and Company, Franklin Lakes, NJ, USA) at the end of each recruitment. Plasma was separated by centrifugation at 24,104 x g at 4 °C for 10 min and immediately stored at − 80 °C ready for analyses.

Commercial, ready-to-use, microwell ELISA kits were used for the quantitative determination of plasma concentration of ASO (Cat. No MBS038268, MyBioSource Inc., San Diego, USA), anti-DNase B (Cat. No MBS7226468, MyBioSource Inc., San Diego, USA), and ABGA (Cat. No MBS706650, MyBioSource Inc., San Diego, USA). Sample absorbance values were detected in a 96-multiwell plate reader (Model 680 Microplate Reader, Bio-Rad, Milan, Italy) using dual-wavelength recording modes at 450 nm and 655 nm (the latter used as reference). ELISA protocols instructions, and threshold values for adults provided by the manufacturer were adopted. . Thereby, the following values defined patient positivity: ASO > 200 U/ml; anti-DNase B > 86 ng/ml; ABGA > 1.18 (as the ratio referred to the negative control optical density) but absolute titers values were also collected as continuous variables.

Clinical assessment tools

The ASRS 1.1 [29] is a six-item self-report screener for adult ADHD, based on the DSM-IV-TR criteria. It was developed by the World Health Organization (WHO) and then validated internationally [30]. The screening is considered positive when at least four answers are above cut-off value.

The DIVA 2.0 [31] is a validated [32] semistructured interview to assess the adult patients, according to the DSM-IV criteria. It investigates DSM-IV inattentive and hyperactivity/impulsivity symptoms (criterion A) in both childhood and adulthood, using several real-life examples to support each question inquiring about 18 DSM-IV criteria. It also includes explicit questions for age at onset (i.e., the presence of symptoms before the age of 7 years, criterion B) and other primary psychiatric and/or substance use disorders (which could better explain the reported symptoms, criterion E). The last section consists in an in-depth evaluation of the main areas of functioning impacted by ADHD symptoms (criteria C and D). Furthermore, the collateral information should be reported in both content and source (i.e., the presence of parents/third parties; school reports).

The AISRS is a validated [33] 18-item scale matching the DSM-IV criteria. It is divided into two subscales of nine items each, investigating inattentive and hyperactivity/impulsivity, respectively. The items are provided with examples to minimize interrater variability. The scoring system ranges from zero (none) to three (severe). The maximum score for each subscale is 27 points, with a maximum total score of 54.

Statistical analysis

All analyses and calculations were performed using RStudio for MAC OS (Version 1.1.383, RStudio Inc., Boston, MA).

The positivity rate for every titer was calculated. The distributions of continuous variables were tested by Shapiro-Wilk's test. A p-value of 0.05 was used to designate statistical significance. Mean and standard deviation (SD) were used to report normally distributed variables, whereas median (Mdn) and interquartile range (IQR) were used for nonnormally distributed ones.

Results

A sample of 22 adult outpatients with ADHD was recruited. The sociodemographic and clinical features of the sample are summarized in Table 1. Little more than half of the patients were male. The age was not normally distributed (Shapiro-Wilk's test $W = 0.868$, $p < .001$). Most of the patients have reached a middle or high school diploma, but more than a fifth of them have got a degree. Although the majority of the sample referred from GPs, psychiatrists, or child neuropsychiatrists, less than half accessed the adult ADHD center on their own (Table 1). .

Little more than half of the sample had a predominantly inattentive subtype ADHD. The rate of psychiatric comorbidity was high but no patient has ever suffered from tic disorder, obsessive-compulsive disorder or Sydenham's chorea (Table 1).

Little more than a third of the sample has had recurrent infections with fever in childhood (Table 1)).

As regards antistreptococcal antibodies, 18 patients (81.9%) had positive anti-DNase B titer, five (22.7%) had positive ASO titer, four (18.2%) had them both positive. Five (22.7%) patients were ABGA positive, whereas only two (9.1%) resulted positive for all three titers. All titers were nonnormally distributed in the examined population (ASO, Median = 114.5, IQR = 82.2, Shapiro-Wilk's test $W = .792$, $p < .001$; anti-DNase B, Median = 95, IQR = 17, Shapiro-Wilk's test $W = .915$, $p = .049$; ASO, Median = .54, IQR = .17, Shapiro-Wilks W test = .661, $p < .001$). Within sample subgroups comparison could not be performed due to low numerosity.

Discussion

This is the first report on anti-GAS antibodies and ABGA titers in adult patients with ADHD. Although it is a preliminary study, the magnitude of GAS infections and basal ganglia autoimmunity in adult patients with ADHD cannot be considered negligible as a large proportion of the sample was anti-DNase B positive (index

Table 1 Sociodemographic and clinical features of the sample ($N = 22$)

Features	Value
Male, n (%)	12 (54.5%)
Age (years), Mdn ± IQR	30 ± 12
Education, n (%)	
Middle school diploma	9 (40.9)
High school diploma	8 (36.4)
Bachelor's degree	2 (9.1)
Master's degree	3 (13.6)
Occupational status, n (%)	
Employed	11 (50)
Unemployed	6 (27.3)
Students	5 (22.7)
Reference to ADHD outpatient center, n (%)	
Autonomous	10 (45.5)
General Practitioner	4 (18.2)
Child neuropsychiatrist	2 (9.1)
ADHD subtype, n (%)	
Predominantly inattentive	12 (54.5)
Predominantly hyperactive/impulsive	0 (0)
Combined	10 (45.5)
Positive family history of psychiatric disorders, n (%)	8 (36.4)
Positive family history of ADHD, n (%)	6 (27.3)
Psychiatric comorbidity, n (%)	8 (36.4)
Recurrent infections during childhood, n (%)	14 (63.6%)
Tonsillitis or adenoiditis	7 (31.8)
with Surgical removal	3 (13.6)
Rheumatic fever	3 (13.6)
Otitis	1 (4.5)
Mixed upperway infection	1 (4.5)
Glomerulonephritis	1 (4.5)
Pneumonia	1 (4.5)

of prior GAS infections), more than a quarter of the sample still showed ASO titer positivity (index of recent GAS infection) and the same amount presents ABGA positivity (index of acquired autoimmunity). The comparison with previous studies conducted on children with ADHD is challenging because of methods heterogeneity, albeit they all excluded patients with tics, obsessive-compulsive disorder, and Sydenham's chorea. On average, the positivity rate of ASO titers reported by previous studies (ranging from 50 to 60%, [24, 28]) doubled that detected in the present preliminary investigation, even considering the well-recognized age-related decrease of the threshold value [34]. Conversely, the positivity rate of anti-DNase B in our adult sample was higher than that reported by a prior study on children with ADHD (81.3% vs. 60%, [24]). The elevation of both ASO and anti-DNase B above the threshold was found in less than half proportion of patients than that reported by two of the prior studies (ranging from 50 to 60%, [24, 27]).

All patients were recruited and tested for titers during summer, the season having the fewest GAS outbursts [34]. On the one hand, this can partially explain the lower proportion of positive ASO titers (index of recent infection) than that registered in previous studies enrolling child patients during all seasons [24, 27, 28]. On the other hand, it provides further support to our findings because they should be considered an underestimation of the actual scenario. Retrospectively collected data on childhood history of infection suggest a distinctive immune vulnerability of ADHD as almost two-thirds of the sample showed a variety of recurrent infections, half of which were tonsillitis or adenoiditis. To our knowledge, this is the first report on the history of recurrent infection in adult ADHD. Only a previous study collected this data in children with ADHD, finding that 18% ($n = 7$) of the sample had a history of GAS infections [24]. All participants of the present preliminary study were non-remitter adult ADHD, thus adults who have had ADHD in childhood but not having current ADHD were not enrolled (i.e., remitters and subthreshold ADHD patients). Bearing in mind the ADHD remission rate from childhood to adulthood (45–57%, [3, 4]), we can suppose that a history of infections and thus a possible vulnerability to them might be a common feature of persistent adult ADHD. Future studies comparing remitters and non-remitter adults should be conducted to confirm this suggestion. Furthermore, the poor reliability of retrospective data collection could partially explain this considerable discrepancy in rate history of infections between adults and children and can not allow to discern streptococcus-related from other infections.

Even more emerged about basal ganglia autoimmunity as over a fifth of the sample had positive ABGA titers, consistently with a previous report regarding Italian children with ADHD (25%, [28]). This rate was also in line with that found in adults affected by obsessive-compulsive disorder (19.8%, [35]), which represents one of the most known neuropsychiatric manifestation of post-streptococcal autoimmune basal ganglia disorders [36]. ADHD seems to be even more prevalent than obsessive-compulsive disorder in adult populations (2.8% vs. 1.2%, [4, 37]) and, as mentioned above, the implication of structural and functional anomalies of basal ganglia in its pathophysiology has been well-recognized by neuroimaging studies [5, 6, 8, 9]. However, the relationship between ADHD and post-infective basal ganglia disorders is little investigated, especially during adulthood, when the neurodevelopment is expected to be complete,

thus neither infections nor the autoimmunity process can longer affect its course.

The main aim of the present study was to provide preliminary findings on the usefulness of ASO, anti-DNase B, and ABGA titers measurement in adult patients with ADHD. In this respect, we used easily available, standard, ready-to-use ELISA kit tests for the quantitative determination of blood titers that increased the reproducibility of our research and findings.

Nevertheless, different limitations should be taken into account. First of all, the sample size of the present study was small, although it was not so far from those of some clinical groups of previous case-control studies conducted on children ($n = 20$, [28] and $n = 22$, [27]), which however included a more or less appropriate control group (i.e., healthy children or patients with neurological disorders). In this regard, a noteworthy concern for future studies could be establishing the right eligibility criteria for a control group, given the impressive high psychiatric comorbidity rate of ADHD in adulthood (i.e., non-ADHD patients matched for comorbidity, enrollment season and age?). Another limitation can be recognized in current GAS infection detection because the inclusion of a rapid strep test or a pharyngeal swab culture would have been highly recommended to reach a more informative assessment.

Further studies including appropriate controls should be conducted on wider samples to confirm our preliminary findings, providing more solid evidence to support the already suggested vulnerability of patients with ADHD to some type of infections in childhood and perhaps also in adulthood [26, 28]. Nevertheless, to evaluate the trajectories of the relationship between childhood infections and ADHD development, further studies might consider ADHD remitters (i.e., adults without current ADHD but who have had ADHD in childhood). Notably, future studies may focus on a potential genetic predisposition to infection or other environmental factors affecting the neurodevelopment of the basal ganglia.

Conclusion

According to the present preliminary study, patients with ADHD might be prone to infections during childhood, subclinical streptococcal infections in adulthood, and they seem to have a high risk for basal ganglia autoimmunity as adults. Both infections and the ensuing acquired autoimmunity may influence the neurodevelopmental process, by contributing, at least in part, to the ADHD pathogenesis. ASO, anti-DNase B and ABGA titers seem to be easy to determine by using specific ELISA kits. It may be possible that a childhood predisposition to infection, which persists into adulthood as antistreptococcal titer positivity, might also contribute to the pathogenesis of ADHD and even to its persistence. Future controlled studies should confirm on wider samples our findings on streptococcal infections, autoimmunity, and ADHD. As for some other neuropsychiatric disorders, ADHD may be related to streptococcal infections or basal ganglia autoimmunity and this could have implications on pharmacological treatment.

Abbreviations

ADHD: Attention Deficit/ Hyperactivity Disorder; ASO: Anti-streptolysin O; anti-DNase B: Anti-deoxyribonuclease B; ABGA: Anti-basal ganglia antibodies; EDTA: Ethylenediaminetetraacetic acid; ASRS-1.1: Adult ADHD Self Reporting Scale; DIVA: Diagnostic Interview for Adult ADHD; AISRS: Adult ADHD Investigation Rating Scale; ELISA: Enzyme-linked immunosorbent assay

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Authors' contributions

FO and Gd conceived the study and drafted the manuscript. Gd collected blood samples and managed the recruitment process. NI and FB conducted laboratory analyses. FM collected and analyzed data. GM coordinated times and stages of the study. All authors read and approved the final manuscript.

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Availability of data and materials

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Ethics approval and consent to participate

The research protocol of the present observational study was approved by the Research Ethics Committee of the San Luigi Gonzaga University Hospital (Orbassano, Turin, Italy), therefore the study was conducted in accordance with the Helsinki Declaration.

Consent for publication

Not applicable.

Competing interests

The authors declare no potential conflicts of interest with respect to the research, authorship, or publication of this article.

Author details

[1]Department of Clinical and Biological Science, University of Turin, Orbassano (TO), Italy. [2]Department of Neurosciences "Rita Levi Montalcini", University of Turin, Turin, Italy.

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Diagnostic delay in ADHD: Duration of untreated illness and its socio-demographic and clinical predictors in a sample of adult outpatients

Francesco Oliva[1] | Francesca Malandrone[1] | Santina Mirabella[1] | Paolo Ferreri[2] | Giulia di Girolamo[2] | Giuseppe Maina[2]

[1]Department of Clinical and Biological Sciences, University of Turin, Turin, Italy

[2]Department of Neurosciences "Rita Levi Montalcini", University of Turin, Turin, Italy

Correspondence
Francesco Oliva, Department of Clinical and Biological Sciences, University of Turin, Regione Gonzole 10, Orbassano (TO), 10043 Turin, Italy.
Email: francesco.oliva@unito.it

Abstract

Aim: To investigate the Duration of Untreated Illness (DUI) and its socio-demographic and clinical predictors in a sample of adult ADHD outpatients.

Methods: The DUI of 150 adult outpatients with a confirmed diagnosis of DSM-IV ADHD was calculated. Non-parametric tests were used to evaluate differences in DUI among subgroups and to build a correlation matrix. Subsequently, a multiple linear regression model was performed.

Results: The median DUI was 17 years (interquartile range [IQR] = 14). DUI was longer in employed patients, those with a family history of ADHD, those with a history of major depressive disorder and those who had predominantly inattentive ADHD in childhood. The current age, age at administration of the first proper treatment and education level were correlated with DUI. Current age (63.3% of total variance), family history of ADHD and the presence of a predominantly inattentive type in childhood (together, 2.6% of total variance) were all predictors of DUI.

Conclusions: Information programmes for caregivers and training for health care professionals should be promoted to foster the early recognition of covert inattentive symptoms and shorten DUI.

KEYWORDS

ADHD, adult, diagnostic delay, duration of untreated illness, early treatment, underdiagnosis

1 | INTRODUCTION

Attention Deficit-Hyperactivity Disorder (ADHD) is one of the most common neurodevelopmental disorders and is characterized by different combinations of attention deficit, hyperactivity and/or impulsivity symptoms, which outline three subtypes (DSM-IV-TR, American Psychiatric Association, 2000) or clinical presentations (DSM-5, American Psychiatric Association, 2013) of ADHD, that is, predominantly inattentive, predominantly hyperactive and combined. However, the clinical manifestation of ADHD is actually heterogeneous, with different levels of severity and prevalences of each core symptom (Faraone et al., 2015; Franke et al., 2018; Kooij et al., 2019).

ADHD has been worldwide recognized as a lifespan disorder that over time interferes with functioning and development (American Psychiatric Association, 2013), leading to serious medical conditions and long-term consequences (Fayyad et al., 2007; Hodgkins et al., 2011; Kooij et al., 2019; Shaw et al., 2012) with severe functional impairment (Agnew-Blais et al., 2016; Faraone, Biederman, & Mick, 2006) and multiple psychiatric comorbidities (Franke et al., 2018; Furczyk & Thome, 2014; Jacob et al., 2007).

Among the long-term outcomes, we could include some harmful behaviours such as self-medication with alcohol, cigarettes, cannabis and stimulants (Franke et al., 2018; Jacob et al., 2007; Wilens et al., 2011); gambling (Waluk, Youssef, & Dowling, 2016); higher

speeding ticket rate (Vaa, 2014); delinquency and crime (Lichtenstein et al., 2012; Shaw et al., 2012); and incorrect use of contraceptives resulting in unplanned pregnancies (Hosain, Berenson, Tennen, Bauer, & Wu, 2012; Skoglund et al., 2019) and sexually transmitted diseases (Barkley, Fischer, Smallish, & Fletcher, 2006). Obesity and overeating (Hodgkins et al., 2011; Kaisari, Dourish, & Higgs, 2017; Shaw et al., 2012), as well as multiple divorces (Wasserstein, 2005), job-hopping, and unemployment (Barkley et al., 2006; Biederman et al., 2006) are also frequent in ADHD patients, being an expression of impulsivity.

These long-term outcomes reduce the self-esteem of untreated patients, increasing suicide ideation or the risk of attempts (Balazs & Kereszteny, 2017; Hodgkins et al., 2011; Shaw et al., 2012). Suicide is the third most frequent cause of death among 15 to 24 year old ADHD patients (Chronis-Tuscano et al., 2010).

A recent epidemiological study confirmed higher mortality rates among ADHD patients, not only because of suicide but also due to other unnatural causes, especially accidents (Dalsgaard, Østergaard, Leckman, Mortensen, & Pedersen, 2015). Other authors detected a higher prevalence of injuries (Amiri, Sadeghi-Bazargani, Nazari, Ranjbar, & Abdi, 2017), vehicle crashes (Vaa, 2014) and bone fractures (Chou, Lin, Sung, & Kao, 2014) among ADHD patients, which seemed to be reverted by pharmacological treatment (Surman, Fried, Rhodewalt, & Boland, 2017).

ADHD patients are more likely to develop mood, sleep, somatic, anxiety and cluster B/C personality disorders (Fayyad et al., 2017; Franke et al., 2018; Katzman, Bilkey, Chokka, Fallu, & Klassen, 2017; Oliva, Mangiapane, Nibbio, Portigliatti Pomeri, & Maina, 2018), thus worsening their clinical burden (Katzman et al., 2017).

Early intervention appears crucial in order to prevent such poor outcomes, because they improve or may even disappear with the appropriate pharmacological and non-pharmacological treatment (Dalsgaard et al., 2015; Katzman et al., 2017; Shaw et al., 2012). Therefore, a correct and prompt diagnosis is needed in order to start effective treatment. The time-lag between first ADHD symptoms and their recognition, however, may be long (Shelton et al., 1998). This delay is a relevant item for ADHD (Shaw et al., 2012), as well as for other psychiatry disorders. In particular, over the past 30 years increasing attention was paid to the duration of untreated psychosis—that is, the period between the onset of psychotic symptoms and the initiation of pharmacological treatment—and the duration of untreated illness or DUI—that is, the interval between the onset of a specific psychiatric disorder and the administration of the first appropriate pharmacological treatment (Altamura et al., 2015; Dell'Osso et al., 2016; Murru & Carpiniello, 2018)—to underline the impact of early pharmacological intervention on the distinctive functional and cognitive deterioration of schizophrenia spectrum disorders (Murru & Carpiniello, 2018; Palazzo et al., 2016). More recently, some authors have applied the concept of DUI from schizophrenia to other psychiatric disorders (Altamura et al., 2010), studying the impact of late recognition and treatment on the most important disorder-specific outcomes (Albert et al., 2019; Altamura et al., 2015; Fritz et al., 2017).

Although, to our knowledge, there are no prior studies concerning DUI among adult ADHD patients, a few have investigated similar aspects in children with ADHD (Ghanizadeh, 2007; Purper-Ouakil et al., 2007; Yamauchi, Fujiwara, & Okuyama, 2015).

Purper-Ouakil et al. (2007) reported that the mean diagnostic delay for ADHD (the period between first consultation for impairing symptoms and the time of definitive diagnosis) in a consecutive sample of children and adolescents referring to a French University-Hospital outpatient service was around 2.8 years and it was not associated with the severity, subtype or family history of ADHD. They also stressed that co-occurrence of internalizing or externalizing symptoms and of any comorbid psychiatric disorders seemed to increase the diagnostic delay. Ghanizadeh (2007) investigated some characteristics of young ADHD patients and their mothers and found a mean time-lag of 1.5 years from the parents' first suspicion of ADHD and the first ADHD assessment, mainly explained by parents as due to a lack of knowledge about where and how ADHD could be assessed.

More recently, Yamauchi et al. (2015) focused their attention on the time-lag between early symptoms and first clinical evaluation in young patients who were then diagnosed with ADHD and on its predictors. This time-lag was not predicted by a family history of ADHD, gender or the severity of impairment; however, some socio-economic conditions involving children and their parents, the lack of information about specific mental health services and the presence of behavioural problems were shown to be predictors of the time lag (mean time-lag of 2.6 years).

The aims of the present study were to estimate the DUI in a sample of adult ADHD outpatients and to evaluate the role of some socio-demographic and clinical features as its predictors.

2 | METHODS

2.1 | Study design and sample

The present study was conducted on a sample of adult patients with a diagnosis of ADHD according to the DSM-IV-TR. All patients accessing the adult ADHD outpatient centre of the "San Luigi Gonzaga" University Hospital (Orbassano, Turin, Italy), between January 2015 and December 2018, was informed about the procedures and purpose of the study and asked to participate in the research. All participants signed an informed consent form. The study inclusion criteria required participants (a) to be age ≥ 18 years and (b) to have a confirmed diagnosis of ADHD according to DSM-IV-TR criteria.

2.2 | Assessment

Since patients were usually referred to the adult ADHD outpatient centre by their psychiatrist, child neuropsychiatrist or general practitioner, according to the assessment protocol of the centre, at the first clinical examination they were checked for DSM-IV-TR criteria for other psychiatric disorders by a psychiatrist trained in adult ADHD

diagnosis. Patients were then screened for adult ADHD through the administration of the Adult ADHD Investigatory Symptoms Related Scale (ASRS 1.1) and questioned about socio-demographic and clinical features (ie, age, gender, education level, employment status, actual and lifetime psychiatric and medical comorbidity, family history of psychiatric and medical conditions). Subsequently, the same psychiatrist administered the Diagnostic Interview for ADHD in Adults (DIVA 2.0) to patients with the help of at least one parent, or a person who had known the patient well during childhood, in order to confirm the DSM-IV-TR ADHD diagnosis and to establish the age of onset, the ADHD type during childhood, and even the domains involved in the functional impairment. The severity of ADHD symptoms was, eventually, estimated through the administration of the ADHD Investigator Symptom Rating Scale (AISRS).

The DUI was calculated as the difference between the age at first proper treatment administration and the age of onset.

2.3 | Assessment tools

The ASRS 1.1 (Kessler et al., 2005) is a self-report screening questionnaire for adults, based on the DSM-IV-TR criteria. It was developed by the World Health Organization (WHO) and then validated internationally (Adler et al., 2006). It consists of a six-item checklist and the scoring system refers to the frequency of occurrence of each symptom. The result is considered positive when at least four answers are above the cut-off value.

The DIVA 2.0 (Kooij, 2013) is a validated (Ramos-Quiroga et al., 2019), semi-structured interview to assess adult ADHD patients, according to the DSM-IV criteria. It consists of a two-section interview each composed of nine questions. The first section evaluates in attentive symptoms, whereas the second concerns the hyperactivity/impulsivity domain. It investigates the presence of DSM-IV symptoms (criterion A) in both childhood and adulthood, and requires real-life examples supporting the answers. It also includes explicit questions about the age of onset (ie, the presence of symptoms before the age of 7 years, criterion B) and the presence of other psychiatric disorders or substance use which could better explain the reported symptoms (criterion E). A third section consists of an in-depth evaluation of the main areas of functioning impacted by ADHD symptoms (criteria C and D). Furthermore, all the collateral information should be reported, in terms of both content and source (ie, the presence of parents/third parties; school reports).

According to DSM-IV, a diagnosis can be approved in the presence of at least six out of nine symptoms in adulthood and in childhood, in one or both of the two domains (inattention and/or hyperactivity/impulsivity). Moreover, the functioning impairment criterion must be met (ie, the symptoms must impact at least two of the following: education/work, family and/or relationships; social contacts; free time/hobbies; self-esteem/self-image).

The AISRS is a validated (Spencer et al., 2010), 18-item scale matching the 18 DSM-IV criteria. It is divided into two subscales of nine items each, one investigating inattentive symptoms and the other about hyperactivity/impulsivity. The items are provided with examples to minimize interrater variability. The scoring system ranges from 1 (none) to 3 (severe). The maximum score for each subscale is 27 points, with a maximum total score of 54.

2.4 | Statistical analysis

The distribution of DUI and other continuous variables was tested using the Shapiro-Wilk test. As DUI was non-normally distributed ($W = 0.957$, P value < .001), non-parametric tests were used for the comparisons and the correlation matrix. The Mann-Whitney U test was adopted to compare the DUI distribution in subgroups defined by dichotomous variables (ie, gender, ADHD type in childhood and in adulthood, psychiatric comorbidities, family history of ADHD or of any other psychiatric disorder). Differences in DUI among employment status subgroups were analysed with the Kruskal-Wallis test. The strength of the associations between DUI and other continuous/ordinal variables was studied performing a correlation matrix, reporting Kendall's rank correlation coefficients and their P values (ie, current age, age of onset, age at first proper treatment administration, education level, AISRS baseline score). Finally, continuous variables significantly correlated with DUI and the categorical variables defining subgroups with significant differences in DUI were included as independent variables in a multiple linear regression model through a forward method (P value < .05 to enter and P value > .01 to exit the predictor), in order to estimate their single predicting value for DUI.

A P value of .05 was used to designate statistical significance.

The analyses were performed using the IBM SPSS Statistics for MAC OS package (version 22.0, IBM Corporation, Armonk, NY).

3 | RESULTS

3.1 | Sample description

All socio-demographic and clinical features are reported in Table 1.

One hundred and fifty patients were eligible for the present study, and less than a third of these were female. Less than a half of the sample had a high school diploma (70, 46.7%) and about a quarter finished middle school (24, 16%), whereas only a smaller had obtained a Bachelor's (14, 9.3%) or a Master's (16, 10.7%) degree. A little less than a third of the sample was unemployed and another third was studying at time of the assessment.

The median age of our population was 25 years (interquartile range [IQR] = 13), whereas the median DUI was 17 years (IQR = 14, Min = 0, Max = 55), with a median age of onset of 6 years (IQR = 1) and a median age at first proper treatment administration of 24 years (IQR = 14). Notably, the age of first proper treatment administration coincided with the age of first diagnosis in all patents (n = 150, 100%). The majority of the sample (n = 107, 71.3%) underwent an ADHD assessment for the first time within the study period, the remainder

TABLE 1 Socio-demographical and clinical variables (N = 150)

	N (%)	Mdn (IQR)
Gender		
Men	106 (70.7)	
Women	44 (29.3)	
Employment status		
Unemployed	48 (32)	
Employed	59 (39.3)	
Students	43 (28.7)	
Education level		13 (3)
Age at onset		6 (1)
Age at first PTA		24 (14)
Current age		25 (13)
DUI		17 (14)
AISRS total score		35.2 (9)
ADHD type in childhood		
ADHD-C (Combined)	78 (52)	
ADHD-I (Predominantly inattentive)	72 (48)	
ADHD type in adulthood		
ADHD-C (Combined)	75 (50)	
ADHD-I (Predominantly inattentive)	75 (50)	
Family history of ADHD	29 (19.3)	
Family history of any psychiatric disorder	62 (41.3)	
Any psychiatric disorder	125 (83.3)	
Any specific learning disorder	48 (32)	
Dysgraphia	28 (18.7)	
Dyscalculia	21 (14)	
Dyslexia	22 (14.7)	
Oppositional-defiant disorder	24 (16)	
Autism spectrum disorder	4 (2.7)	
Major depression	35 (23.3)	
Bipolar disorder	35 (23.3)	
Any personality disorder	25 (16.7)	
Any anxiety disorder	26 (17.3)	
Alcohol use disorder	56 (37.3)	
Substance use disorder	73 (48.7)	
Any sleep disorder	73 (48.7)	

Abbreviations: AISRS, Adult ADHD investigator symptom scale; DUI, Duration of untreated illness; PTA, proper treatment administration.

had been already assessed and diagnosed with ADHD in the past and were on specific medication since then (ie, methylphenidate, atomoxetine).

About half the sample had a predominantly inattentive type in childhood and in adulthood. The remainder had a combined type since no patients showed a predominantly hyperactive/impulsive type both in childhood and in adulthood. Adult ADHD was confirmed to have high rates of psychiatric comorbidities as only around one-sixth of the sample did not have any comorbid disorders. A high prevalence of a positive family history of ADHD and of other psychiatric disorders could be also observed in the study sample.

Comparison of DUI between subgroups defined by dichotomous variables.

The DUI was longer in patients with a positive family history for ADHD, those with major depressive disorder and those with a predominantly inattentive type of ADHD in childhood (Table 2). Conversely, patients with a diagnosis of a specific learning disorder(s) had a shorter DUI. A significant difference was observed between the DUI observed in the different employment status groups and, according to the nonparametric post-hoc tests (Mann-Whitney's tests), employed patients had a higher DUI than students and unemployed patients (employed > unemployed, $U = 927.5$, $P = .002$; employed > students, $U = 427.5$, $P < .001$; unemployed = students, $U = 815.5$, $P = .085$).

3.2 | Correlations between DUI and other continuous variables

The correlation matrix with continuous variables confirmed the expected relationship of DUI with the age at first proper treatment administration (Tau $B = 0.940$, $P < .001$) but not with the age of onset (Tau $B = 0.111$, $P = .072$, Table 3). Both current age and education (as ordinals) showed a significant correlation with DUI (Tau $B = 0.735$, $P < .001$ and Tau $B = 0.168$, $P = .006$, respectively) and also with the age at first proper treatment administration (Tau $B = 0.783$, $P < .001$ and Tau $B = .162$, $P = .008$). The severity of ADHD symptoms on the AISRS scale had no significant relationship with other continuous variables ($P < .05$, Table 3).

3.3 | Evaluation of potential predictors for DUI

The multivariate linear regression, forward method, was built including the current age as a continuous variable and family history of ADHD, education (as an ordinal), employment status, prevalent inattentive ADHD type in childhood, any specific learning disorder and major depressive disorder as factors (Table 4). The age of onset and the age at first proper treatment administration were intentionally excluded as they were involved in the calculation of DUI. The current age was the most important predictor among the variables included in the model and was responsible of 63.3% of the total variance of the DUI (Table 4). As regards the included factors, the family history of ADHD and a predominantly inattentive type in childhood were also significant positive predictors, although together they explained only 2.6% of the variance of the DUI (R^2 change = 0.026, Table 4). All the other variables were excluded from the model because they did not contribute to the variance of DUI (in the last model: Education, $\beta = 0.080$, $P = .127$; employment status, $\beta = 0.061$, $P = .241$; major depressive disorder, $\beta = 0.043$ $P = .405$; any specific learning disorder, $\beta = -0.43$, $P = .375$).

TABLE 2 Comparisons of DUI among subgroups defined by categorical variables

	DUI Mdn (IQR)	U (dF)	*P*
Gender		1913.0 (1)	.084
Men	16.5 (13)		
Women	20.8 (19)		
Employment status		30.5 (2)[a]	<.001*
Employed	24.6 (16)		
Unemployed	15.5 (20)		
Student	13 (6)		
ADHD type in childhood		2251.5 (1)	.036*
ADHD-C (Combined)	15.8 (23)		
ADHD-I (Predominantly inattentive)	18.3 (11)		
ADHD type in adulthood		2581.5 (1)	.385
ADHD-C (Combined)	16.6 (14)		
ADHD-I (Predominantly inattentive)	18.0 (14)		
Family history of ADHD		827.5 (1)	<.001*
Yes	28.0 (21)		
No	16.0 (12)		
Family history of any psychiatric disorder		2615.5 (1)	.668
Yes	17.3 (15)		
No	17.0 (13)		
Any psychiatric disorder		1413.5 (1)	.452
Yes	17.6 (13)		
No	14.0 (16)		
Any specific learning disorder		1853.0 (1)	.016*
Yes	14.5 (10)		
No	19.0 (14)		
Autism spectrum disorder		184.5 (1)	.210
Yes	14 (12)		
No	17.6 (14)		
Oppositional-defiant disorder		1325.5 (1)	.339
Yes	15.0 (16)		
No	17.6 (14)		
Major depressive disorder		1423 (1)	.009*
Yes	22.0 (15)		
No	16 (14)		
Bipolar disorder		1893.5 (1)	.596
Yes	18.0 (18)		
No	17.0 (13)		
Any anxiety disorder		1521.5 (1)	.653
Yes	18.5 (12)		
No	17.0 (14)		
Any personality disorder		1511.5 (1)	.797
Yes	17.6 (17)		
No	17.0 (13)		
Alcohol use disorder		2541.5 (1)	.725
Yes	17.0 (11)		
No	18.0 (16)		

(Continues)

TABLE 2 (Continued)

	DUI Mdn (IQR)	U (dF)	*P*
Substance use disorder		2413.5 (1)	.135
Yes	16.0 (11)		
No	18.0 (20)		
Any sleep disorder		2668.5 (1)	.593
Yes	17.6 (12)		
No	17.0 (16)		

*Statistically significant, $P < .05$.
[a]χ^2(dF), nonparametric Kruskal-Wallis's test.

TABLE 3 Bivariate correlation matrix of continuous variables

	DUI	Age of onset	Age at first PTA	Current age	AISRS score	Education
DUI	1	—	—	—	—	—
Age at onset	−0.111	1	—	—	—	—
Age at first PTA	0.940**	−0.027	1	—	—	—
Current age	0.735**	0.040	0.783**	1	—	—
AISRS score	−0.012	−0.072	−0.010	−0.009	1	—
Education	0.168**	−0.043	0.162**	0.116	−0.078	1

Abbreviation: PTA, proper treatment administration.
**Kendall's tau-*b*, $P < .01$ (two-tailed).

TABLE 4 Linear regression model for the prediction of DUI

			Change statistic		Coefficients of predictors			
Models and predictors	R^2	Adjusted R^2	*F* (dF)	*P*	*β*	*B*	95%CI	*P*
Model 1	0.633	0.631	255.5 (1-148)	<.001				
Current age					0.796	0.892	0.781-1.002	<.001
Model 2	0.648	0.644	6.334 (1-147)	.013				
Current age					0.751	0.842	0.727-.957	<.001
Family history of ADHD					0.131	4.045	0.869-7.221	.013
Model 3	0.659	0.652	4.570 (1-146)	.034				
Current age					0.749	0.839	0.725–0.953	<.001
Family history of ADHD					0.128	3.956	0.816-7.096	.014
Childhood ADHD-I					0.103	2.527	0.191-4.864	.034

Abbreviation: ADHD-I, ADHD predominantly inattentive type.

4 | DISCUSSION

The current age was the main predictor for DUI in our sample of adult ADHD outpatients and it was also strongly associated with the age at first proper treatment administration. Most of the patients were indeed first diagnosed with ADHD at the end of the assessment at the adult ADHD centre (71.3%), though they had suffered at least from attention deficit, and in about half of the cases even from hyperactivity/impulsivity, since childhood without receiving any proper treatment.

Together, these findings suggest that, consistently with previous reports (Ginsberg, Quintero, Anand, Casillas, & Upadhyaya, 2014; Kooij et al., 2019), ADHD is underdiagnosed in adulthood and even in childhood, and this appears to be the main reason for its under treatment. This may be particularly true for Italy, where the few expertise centres have only recently established a national network for adult ADHD and psychiatrists are still poorly trained in diagnosing this condition.

Moreover, the DUI obtained in the present study sample was much longer than the DUI reported by previous studies concerning

other psychiatric disorders: schizophrenia, less than 6 years (Albert et al., 2017); bipolar disorder, under 14 years (Altamura, Dell'Osso, et al., 2010); major depressive disorder, less than 11 years (Altamura, Buoli, Albano, & Dell'Osso, 2010); any anxiety disorder, about 13 years (Dell'Osso, Camuri, Benatti, Buoli, & Altamura, 2013).

According to our findings, ADHD patients may deal with their symptoms from childhood (median age of 6) to adulthood (up to the median age of 25) for a median time-lag of 17 years without treatment. Meanwhile, the onset of some psychiatric comorbidities first in childhood and then in adulthood seemed to increase the burden of ADHD, as about 83.3% of patients had at least one additional comorbid psychiatric disorder. This high prevalence of comorbid psychiatric disorders is more consistent with a previous clinical study (Jacob et al., 2007) than that estimated by the most recent cross-national community epidemiological survey (51.7%; Fayyad et al., 2017). Such high rates could be partially explained, at least in the present study, by the referral to the ADHD centre from child neuropsychiatrists, psychiatrists and general practitioners who had probably assessed the patients for any other confounding symptoms or disorders. Hence, as previously noted (Fayyad et al., 2007; Ginsberg et al., 2014), ADHD patients are more likely to be treated for comorbid disorders than for ADHD in psychiatric services. However, no comorbid psychiatric disorder was observed to predict DUI; thus, contrary to expectations, in the present study, the co-occurrence of any other psychiatric condition did not seem to foster nor hinder the diagnosis of ADHD. Although non predictive for DUI, depression was significantly associated with longer diagnostic delays. It could suggest that health care professionals tend to consider ADHD diagnosis only belatedly during the assessment. Thus, ADHD symptoms might be, at first, misinterpreted as depression rather than a separate or even a differential diagnosis. This could be a possible and partial explanation for the lower detection rates and longer DUI found in ADHD compared to other psychiatric disorders. On the other hand, depression might be a consequence of persisting ADHD symptoms.

Furthermore, clinical ADHD type in adulthood did not affect DUI; thus, it could be suggested that the small proportion of patients without comorbidities came to the ADHD centre because of functional impairment and the burden of ADHD symptoms themselves, regardless of the current clinical type.

As far as the other predictors are concerned, although with a weak contribution, a predominantly inattentive clinical type in childhood and a family history of ADHD appeared to further lengthen DUI.

Inattentive symptoms are less overt during childhood and commonly underestimated by parents, relatives and teachers, often being misinterpreted as unwillingness or tiredness (Asherson et al., 2012; Gershon, 2002; Katzman et al., 2017; Milich, Balentine, & Lynam, 2001). Possibly healthcare professionals themselves often fail to recognize these symptoms. Nevertheless, studies focused on the accuracy of self-reports highlighted the tendency of adult ADHD patients to underestimate their past symptoms, especially inattentive symptoms (Barkley, 2002; Zucker, Morris, Ingram, Morris, & Bakeman, 2002).

Both these issues may concur to explain the significant effect of inattentive symptoms and a family history of ADHD on DUI. Since parents with ADHD are so unaware of their dysfunctional core symptoms, they can be extremely tolerant of children's ADHD symptoms, often considering them self-limiting and unworthy of referral to child or adult psychiatric services (Ghanizadeh, 2007; Yamauchi et al., 2015).

According to our findings, the severity of ADHD, measured on the validated scale, did not show any predictive value nor any significant correlation with DUI, supporting prior suggestions by some studies concerning the time-lag between the onset of ADHD symptoms and the referral to specific services for children (Ghanizadeh, 2007; Yamauchi et al., 2015).

The main limitation of the present study is the single-centre design. However, although our study included only one centre in the Northwest of Italy, it accurately depicts a real-world context where adult ADHD is commonly recognized and diagnosed for the first time during adulthood, alongside several comorbid disorders.

On the other hand, to our knowledge, this is the first report on the long DUI among adult ADHD patients, which also includes an appraisal of the predicting value of some socio-demographic and clinical variables. According to our findings, more attention should be paid to the covert inattentive symptoms in children, both by clinicians and teachers. Education and information programmes are needed to raise awareness, not only among clinicians and general practitioners, but also among other significant figures (ie, sport coaches and trainers, care-givers, baby-sitters). A lack of information regarding specific mental health services is indeed commonly reported by parents (Ghanizadeh, 2007; Yamauchi et al., 2015). This could reflect the lack of knowledge and training among health care professionals, who should refer patients for specific consultations.

An additional limitation of the present study is the absence of a comprehensive assessment of comorbid psychiatric disorders. Particularly, an in-depth evaluation of treatment history is worthy of further investigation as it could clarify patients' pathway through mental health services and help identify the missed opportunities for a proper diagnosis.

Moreover, further observational studies should be conducted to better investigate DUI predictors, not only in a clinical sample of patients attending child and adult psychiatric services but also in the general population.

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AUTHOR CONTRIBUTIONS

Francesco Oliva and Giulia di Girolamo conceived the study and drafted the manuscript. Santina Mirabella, Paolo Ferreri, and Francesca Malandrone collected the data. Francesco Oliva and Francesca Malandrone performed the statistical analysis. Giuseppe Maina participated in the design and coordination of the study. All authors read and approved the final manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Francesco Oliva https://orcid.org/0000-0002-1939-552X

Francesca Malandrone https://orcid.org/0000-0002-9438-8637

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4. Discussion

This dissertation presents the main findings of studies investigating the relationships between psychological treatments, psychological distress and organic pathology. The primary aim of this work was to critically examine the state of the art and effectiveness of psychological interventions in the domains of cancer, depression, and ADHD.

Psychological interventions demonstrate effectiveness not only clinically but also as promoters of neurobiological changes, as extensively discussed in the literature (Beauregard, 2014; Mancke et al., 2018; Scult et al., 2019). The scoping review presented in Rossini and colleagues (Rossini et al., 2022) investigated the neural correlates of psychological interventions in the oncological population. The scoping review outlined the neural effects of different interventions, in particular bottom-up psychological interventions, strengthening prefrontal cognitive control mechanisms and impacting areas of the prefrontal cortex and cingulate cortex. The review identified improvements in clinical psychological measures, indicating the effectiveness of interventions in reducing anxiety, depression, stress-induced pain, fatigue, and cognitive complaints in cancer patients. Psychological interventions play a pivotal role in addressing mental health challenges, especially in the context of trauma-related disorders. Among them, trauma-focused (TF) interventions like EMDR show promise in addressing conditions such as PTSD (Dimitrov et al., 2019; Portigliatti Pomeri et al., 2021) and depression (Carletto et al., 2021; Malandrone et al., 2019). In Carletto and colleagues (Carletto et al., 2021) a systematic review and meta-analysis assessing the efficacy of EMDR therapy for depression is presented. The meta-analysis, involving nine studies, revealed a substantial effect of EMDR on depression, with clinical significance observed in one-third of individuals undergoing EMDR therapy. As highlighted by Portigliatti Pomeri and colleagues (Portigliatti Pomeri et al., 2021), EMDR could be effective in the treatment of cancer-related PTSD. Malandrone and colleagues (Malandrone et al., 2024) conducted a study evaluating the functional Brain-Heart Interaction (BHI) in breast cancer patients with PTSD, examining improvements following TF intervention compared to Treatment as Usual (TAU). An enhanced heart-to-brain interplay was found, suggesting improved bottom-up and top-down regulation following successful PTSD treatment. The results could indicate that TF psychotherapy may decrease automatic and undifferentiated responses typical of PTSD leading to increased bottom-up information flow

and a restoration of the ability to discriminate danger levels of incoming stimuli. It could be speculated a reopening of the bottom-up communication flow which may have cascading effects on emotional regulation mechanisms, ultimately restoring the dysfunctional coupling between Autonomic Nervous System (ANS) and Central Autonomic Network (CAN) observed in PTSD patients. Approaches emphasizing bottom-up strategies demonstrate effectiveness in managing ADHD symptoms. Oliva and colleagues (Oliva et al., 2021) conducted a systematic review and meta-analysis to assess the efficacy of MBIs in addressing ADHD symptoms across diverse age groups. The results indicated that MBIs exhibited greater effectiveness compared to inactive controls, particularly demonstrating a medium effect size in improving attention symptoms in adults. Moreover, beyond mitigating ADHD symptoms, MBIs displayed a notable impact, with a medium effect size observed in enhancing mindfulness skills, reducing anxiety levels, and positively influencing global functioning. Notably, these effects were more pronounced when contrasted with inactive control groups. Furthermore, the findings suggested that MBIs were particularly effective in addressing inattention compared to hyperactivity-impulsivity in individuals with ADHD.

In addition to the primary aim, a secondary aim was to validate a psychological assessment tool tailored to facilitate the observation and measurement of changes resulting from psychological interventions and to deepen knowledge related to various mental health disorders. The validated tool is presented in the article published by Malandrone and colleagues (Malandrone et al., 2022), describing the Italian version of the Emotional Style Questionnaire (ESQ), a self-report instrument assessing emotional health across six dimensions: outlook, resilience, social intuition, self-awareness, sensitivity to context, and attention. The final version, ESQ-ITA, consists of 24 items grouped into six subscales, demonstrating reliability (Cronbach's alpha coefficients > 0.60) and stability through test-retest analysis. The ESQ-ITA overall score correlated positively with optimism, resilience, attention, self-awareness, and interoceptive awareness, while negatively correlating with autistic traits, depression, anxiety symptoms, and stress. A strong correlation between outlook and resilience dimensions was found, suggesting culture-related overlapping constructs. The cultural influence on resilience was acknowledged, emphasizing the need for further exploration at both psychometric and neural levels.

When addressing the bidirectional relationship between psychological distress and organic diseases, this dissertation emphasized their interconnected impact on both mental and physical well-being.

Specifically, it focused on various health conditions including cancer, Sars-Cov-2 infections, and early childhood infections as potential etiological factors for ADHD.

In Malandrone and colleagues (Malandrone et al., 2021) a narrative review on the impact of vulvar cancer on mental health, quality of life, sexuality, and relationships is presented. The study found that vulvar cancer negatively affects quality of life, emotional regulation, and the ability to self-care. Sexual functioning and activity were disrupted, contributing to lower quality of partner relationships and marital satisfaction. Women with vulvar neoplasia experienced prevalent depressive and anxiety symptoms throughout the diagnostic and therapeutic process, influenced by altered body image, social stigma, and sexual dysfunction.

Bovero and colleagues (Bovero et al., 2023) conducted the first systematic literature review on factors associated with Post-Traumatic Growth (PTG) induced by COVID-19. Their synthesis revealed associations between PTG and sociodemographic variables, such as young age and ethnic minority status, with younger individuals exhibiting higher levels of growth. Loneliness emerged as a factor associated with increased PTG, challenging traditional notions of the role of social support in growth. Individual factors like coping mechanisms and distress tolerance were linked to PTG, highlighting the multifaceted nature of trauma responses. Ostacoli and colleagues (Ostacoli et al., 2020) investigated postpartum depressive and post-traumatic stress symptoms (PTSS) in women who experienced childbirth during the COVID-19 pandemic. The study revealed a higher prevalence of these symptoms compared to pre-pandemic studies. Factors such as the health status of the unborn child, consequences of preventive measures, and fear of reduced support during childbirth contributed to increased psycho-emotional distress. Postpartum depressive symptoms were associated with high pain levels during childbirth and an insecure dismissive-avoidant attachment pattern, while postpartum PTSS were linked to a fearful avoidant attachment style. Perceived support from healthcare staff during childbirth was a protective factor against these symptoms. Additionally, the study identified the level of quiet on the ward (due to the absence of visitors) as a protective factor against PTSS. The study emphasized the need for early detection of distress, including evaluation of attachment style, to implement targeted interventions for women's psychosocial health and mother-infant bonding.

Oliva and colleagues (Oliva, di Girolamo, et al., 2020) conducted a preliminary study on adult patients with ADHD, investigating anti-GAS antibodies and ABGA titres. The study found a significant proportion of the sample was anti-DNase B positive (indicating prior GAS infections), and a quarter still showed ASO titre positivity (indicating recent GAS infection), with a similar amount presenting ABGA positivity (indicating acquired autoimmunity. The study identified a distinctive immune vulnerability in adult ADHD, supported by a history of recurrent infections in two-thirds of the sample. Moreover, the results highlighted the prevalence of basal ganglia autoimmunity in adult ADHD, suggesting a potential link between infections, autoimmunity, and ADHD pathogenesis. Another study from the same authors (Oliva et al., 2020) investigated Delayed Underdiagnosis Interval (DUI) in adult ADHD outpatients. Findings revealed underdiagnosis trends in adulthood. The study emphasized the impact of comorbid psychiatric disorders and highlighted depression's association with longer diagnostic delays. Notably, the clinical type of ADHD in adulthood did not affect DUI, suggesting patients sought diagnosis due to functional impairment. Factors contributing to a longer DUI included the predominantly inattentive clinical type in childhood and a family history of ADHD.

4.1. Limitations and Research and Clinical Implications.

The studies presented exhibit some limitations, including methodological heterogeneity across diverse designs, participant characteristics, and intervention protocols, posing challenges in synthesizing findings. Potential publication bias, a common concern in meta-analyses, emphasizes caution in generalizing conclusions, necessitating access to unpublished or non-significant results. Absence of control groups and small sample sizes in some investigations calls for more rigorous study designs, emphasizing the importance of larger-scale studies. Relying on retrospective data introduces potential recall bias, urging future studies to incorporate prospective designs for robust longitudinal insights. Recognizing these limitations is crucial for refining methodologies and ensuring the robustness and relevance of future research in psychological interventions and mental health.

Despite these limitations, significant research implications emerge. The results suggest a need for further investigations into the specific mechanisms underlying various psychological interventions. While

highlighting the efficacy of interventions like EMDR, mindfulness-based approaches, and trauma-focused psychotherapy, a deeper understanding of how these interventions induce neurobiological and psychological changes is essential. Future research should unravel the nuanced interplay between psychological and physiological factors, contributing to a more comprehensive knowledge base. Comparative studies could enhance understanding of the relative effectiveness of different therapeutic modalities, aiding clinicians in making informed decisions about tailored treatment plans. Longitudinal research is crucial to assess sustained effects over time, providing insights into the durability of therapeutic outcomes. Further exploration of cultural influences on emotional health, resilience, and treatment response can refine the applicability of psychological assessments and interventions across diverse populations. Large-scale studies investigating links between early childhood infections, autoimmunity, and adult ADHD pathogenesis are warranted, contributing to a more robust understanding of multifaceted factors influencing mental health.

These findings hold several implications for clinical practice. Clinicians across specialties can benefit from integrating evidence-based psychological interventions into treatment plans. For instance, EMDR shows promise in addressing depression, trauma-related disorders, and cancer-related PTSD. Mindfulness-based interventions demonstrate efficacy beyond core symptoms, suggesting potential as adjunctive treatments for conditions like ADHD. Trauma-focused psychotherapy emerges as a valuable approach for breast cancer patients with PTSD, emphasizing the interconnectedness of psychological and physiological well-being. The results underscore the importance of holistic care, considering psychosocial elements alongside traditional medical approaches, as well as the importance of timely diagnosis and identification of biomarkers of mental health disorders. Integrating these clinical implications into practice can enhance the quality of care provided to individuals facing diverse mental health challenges.

5. Conclusions

This dissertation contributes to advancing our understanding of the impact psychological interventions can have on mental and physical well-being and the bidirectional relationship between psychological distress and organic diseases. The main findings underscore the effectiveness of psychological interventions - such as TF interventions for PTSD and depression in cancer patients and MBIs for ADHD

- from a clinical and neurobiological point of view. Regarding adverse events, studies explore the impact of cancer, Sars-Cov-2 infections, and early childhood infections, revealing significant psychosocial consequences and emphasizing the need for early detection and targeted interventions. Despite methodological limitations, these findings prompt further investigations into the mechanisms underlying interventions and call for comparative studies, longitudinal research, and exploration of cultural influences. Clinical implications advocate for integrating evidence-based interventions into treatment plans, emphasizing holistic care and timely diagnosis to enhance the quality of care for diverse mental health challenges.

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