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TITOLO DELLA TESI:

A Neurocognitive Approach of Executive Control: From Normal Cognitive Aging to Neurocognitive Disorders

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Doctoral Thesis Abstract

Executive control is defined as a set of higher-order cognitive abilities that monitor thoughts and behaviors. Executive functions play an important role in maintaining independence in activities of daily living, the lack of which is suggestive of cognitive decline. Considering the cognitive-behavioral framework, prefrontally mediated attentional-executive functions have been associated with age-related psycho-physical changes that cause a reduced resistence to stressors (i.e., frailty), leading to a higher risk of disability and mortality, particularly in patients with neurodegenerative diseases. Furthermore, metacognitive-executive functions seem to mediate the degrees of self-awareness in neurocognitive disorders with different etiopathogenesis.

In light of this, my Thesis sought to analyze the role of executive dysfunction in the onset of frailty on the continuum from normal cognitive aging to neurocognitive disorders, and in reduced self-awareness in neurological disorders with different etiopathogenesis. In addition, another aim was to investigate how psychological distress may influence the occurence of the nocebo effect in older adults during the COVID-19 pandemic.

After a first introductive chapter, I will present the studies I worked on during my PhD program (i.e. five research articles, two systematic reviews, three mini-reviews, two perspective articles, and one case report). Specifically, Chapter 2 will describe two published articles concerning a follow-up study carried out on 81 subjects in healthy cognitive aging, to assess their cognitive status (with a particular focus on executive control), functional (in terms of frailty), and behavioral aspects, before and during the restrictive measures due to COVID-19. We found a relationship between frailty – in terms of handgrip strength and walking speed – and attentional-executive domain, assessed before the pandemic. In addition, specific cognitive dysfunction (i.e., attentional-executive), mood changes, and pre-frailty seem to affect the older adults' psychological well-being during the lockdown. In Chapter 3 I will present three published studies, in which we have examined the occurrence of frailty in different neurocognitive disorders. In particular: [A] we found a relationship between a (pre)frailty status and executive dysfunction, mood deflections, and reduced awareness of deficits in instrumental activities of daily living in patients on the continuum from Mild Cognitive Impairment (MCI) likely due to Alzheimer's Disease (AD) to mild AD; [B] we identified, through the combination of structural and functional neuroimaging, the anterior insular cortex as a possible anatomical correlate of (pre)frailty in patients with the behavioral variant of frontotemporal dementia (n = 18), also hypothesizing a relationship with executive dysfunction that characterize such disease; [C] in a mini-review, we highilighted the

association between frailty and executive dysfunction in different neurocognitive disorders, particularly due to AD and Parkinson's Disease. Chapter 4 will describe the three articles concerning the relationship between impaired awareness and executive dysfunction, also considering their impact on the level of independent living skills. Specifically: [I] we found a relationship between instrumental activities of daily living and executive dysfunction and reduced self-awareness, in 144 patients on the continuum from MCI to mild AD; [II] in a mini-review, we highlighted that reduced awareness of cognitive and/or functional deficits was associated with prefrontally mediated executive dysfunction in different neurological disorders; [III] a case study underlined how a bilateral thalamic infarction may lead to executive dysfunction and persisting reduced self-awareness, probably due to the fronto-thalamic pathway disruption. Such condition might also have affected the patient's ability to monitor her actions in daily living during the pandemic, as she resulted positive on serologic testing for SARS-CoV-2. Finally, Chapter 5 will address the nocebo effect related to the COVID-19 pandemic, highlighting how personal, relational, and situational factors, as well as misinformation communicated by the media, can lead to greater psychological distress, which can result in increased resistance to immunization, particularly in older adults. Finally, in our systematic review we showed that adverse events of SARS-CoV-2 vaccines may be partially attributed to a nocebo effect, also making a differentiation between younger and older participants.

Taking together, these findings highlight the importance of addressing executive dysfunction in aged subjects, in order to tailor specific interventions with important clinical implications, also considering the impact of the SARS-CoV-2 pandemic on neuropsychological functioning.

Abbreviations

AAT:	Aachner Aphasia Test
ABI:	Acquired Brain Injury
ACC:	Anterior Cingulate Cortex
ACE-R:	Addenbrooke's Cognitive Examination-Revised version
AD:	Alzheimer's Disease
ADL:	Activities of Daily Living
AEs:	Adverse Events
AEFI:	Adverse Events after Immunization
aMCI:	amnesic Mild Cognitive Impairment
AQ-D:	Anosognosia Questionnaire for Dementia
AR:	Adverse Reaction
ARDs:	Age-Related Diseases
BADS:	Behavioral Assessment of the Dysexecutive Syndrome
BDI:	Beck Depression Inventory
bvFTD:	behavioral variant Frontotemporal Dementia
CAM:	Cognitive (or Conscious) Awareness Model
CI:	Confidence Interval
CIRS:	Cumulative Illness Rating Scale
COVID-19:	Coronavirus disease - 2019
CPM-36:	Raven's Coloured Progressive Matrices - 36
CSF:	Cerebrospinal Fluid
CT:	Computed Tomography
Df:	Degrees of freedom
DIS-s:	Disinhibition Scale
dlPFC:	dorsolateral Prefrontal Cortex
DRSA:	Dyskinesias-Reduced-Self-Awareness
DSM-5:	Diagnostic and Statistical Manual of Mental Disorders – 5th edition
ECDC:	European Centre for Disease Prevention and Control
EFs:	Executive Functions
EMA:	European Medicines Agency
EU:	European Union
FDG-PET:	Fluorodeoxyglucose Positron Emission Tomography

FI:	Frailty Index
GM:	Gray Matter
HAROLD:	Hemispheric Asymmetry Reduction in Older Adults
HARS:	Hamilton Rating Scale for Anxiety
HDR-S:	Hamilton Depression Rating Scale
HI:	Hollingshead Index
IgG:	Immunoglobulin G
IADL:	Instrumental Activities of Daily Living
LAB:	Laboratory
LFS:	Lockdown Fatigue Scale
LLCI:	Lower level of confidence interval
m-WCST:	Wisconsin Card Sorting Test – metacognitive version
MAS:	Mania Scale
MCI:	Mild Cognitive Impairment
MedDRA:	Medical Dictionary for Regulatory Activities
mdMCI:	multiple domain Mild Cognitive Impairment
MoCA:	Montreal Cognitive Assessment
mPFC:	medial Prefrontal Cortex
MPI:	Multidimentional Prognostic Index
MRI:	Magnetic Resonance Imaging
Ms:	milliseconds
MSE:	Mean Squared Error
N:	Number
PANSS:	Positive and Negative Syndrome Scale
PASA:	Posterior-Anterior Shift in Aging
PCA:	Principal Component Analyses
PD:	Parkinson's Disease
PFC:	Prefrontal Cortex
PRISMA:	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT:	Randomized Controlled Trial
RT:	Reaction time
RR:	Relative Risk
SARS-CoV-2:	Severe Acute Respiratory Syndrome Coronavirus - 2
SAEs:	Serious Adverse Events

SCD:	Schizophrenia spectrum Disorders
SD:	Standard deviation
Se:	Standard error
SN:	Salience Network
SRSI:	Self-Regulation Skills Interview
TIB:	Brief Intelligence Test
TMT:	Trail Making Test
TT:	Token Test
UNITRE-TO:	University of the Third Age - Turin
ULCI:	Upper level of confidence interval
WAIS-III:	Wechsler Adult Intelligence Scale-III
WCST:	Wisconsin Card Sorting Test
WHO:	World Health Organization

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1. Introduction

1.1. Executive Control: A brief overview

Executive Control refers to a set of top-down cognitive processes required to manage goal-directed behaviors, particularly in novel situations or in the midst of competing choices (Diamond et al., 2013, 2020; Salehinejad et al., 2021).

An umbrella term that describes the mechanisms of executive control involved in self-regulation is “executive functions” (Chan et al., 2008; Karr et al., 2018).

Several high-level cognitive functions fall under the classification of executive functions (EFs), such as: sequencing behavior, inhibiting automatic responses, identifying the most relevant task for current purposes – providing resistance to distracting information – and using such relevant information to support decision making, goal-switching, categorizing or abstracting commonalities among items, and handling novel situations (Banich, 2009).

Although many cognitive functions could fit into this category – and, furthermore, there is still no consensus on which ones may or may not be considered as EFs (Poon, 2018) – there is a general agreement that shifting, updating/monitoring, and inhibition are the core EFs (Diamond, 2013; Karr et al., 2018). In fact, they play different and complementary roles in the performance of complex executive tasks (Friedman and Miyake, 2017; Miyake and Friedman, 2012). To understand the unity but also the heterogeneity of EFs, Miyake et al. (2000) proposed a structural model characterized by mental set-shifting, information monitoring and updating in the working memory, and inhibition of preponderant responses. From these, higher-order EFs – such as problem solving and planning – might arise (Collins and Koechlin, 2012; Lunt et al., 2012). In particular, although showing unique variants and separability (called "diversity"), core EFs, also show an overlap ("unity"), mostly characterized by goal-directed behavior, active maintenance of goals, and the use of them to influence ongoing processing (Friedman and Robbins, 2021).

It is well known that the frontal lobes – in particular the prefrontal cortex (PFC) –, and cortical and subcortical related areas, are strictly related to executive control (Badre and Nee, 2018; Friedman and Miyake, 2012; Fuster, 2001; Kamigaki et al., 2019; Stuss and Benson, 1984). However, to date, controversy persists regarding the functional organization of such brain area and associated networks and how these components interact to support executive control (Alexander and Brown, 2018; Banich, 2009; Badre and Nee, 2018).

In spite of this, over the time, a wide range of functional neuroimaging studies have showed that dorsolateral (dl) PFC and the anterior cingulate cortex (ACC) are specifically activated when

cognitive control and monitoring demands increase due to conflict in information processing and competing response plans (Cieslik et al., 2013; Cole and Schneider, 2007; MacDonald et al., 2000; Prutean et al., 2021; Sohn et al., 2007).

Miller and Cohen (2001) developed one of the first theoretical models highlighting that executive control was mediated by specific PFC circuits. In their review, the authors showed that the ACC seems to be responsible for detecting conflicts between two or more tasks, which are addressed by the control response elicited by the dlPFC (Miller and Cohen, 2001).

According to the *Error Likelihood Mode*l (Brown and Braver 2005), ACC activity predicts the probability of committing a response error in a given behavioral context and – depending on this probability – it recruits the dlPFC in order to jointly modulate activity in other brain structures depending on the task demands.

More recently, Alexander and Brown (2015, 2018) proposed the *Hierarchical Error Rappresentation Model*. This computational model involves a hierarchical organization of the prefrontal cortex, according to which higher levels compute and modulate expected errors in relation to predictions made by lower levels. In particular, prediction error and the maintenance of this representation are associated with the activity of medial regions of the PFC – in particular ACC – and the dlPFC, respectively.

In light of the above, it can be summarized that the dlPFC is heavily involved in working memory tasks, allowing for sustained representation and retention of information required to guide behavior (Alexander and Brown, 2015; Nee and Brown, 2012), while ACC is involved in conditions of information conflict, calculating the prediction errors in relation to the expected results and those obtained from the response, situations that require cognitive effort, and difficult choices (Friedman and Robbins, 2021; Vassena et al., 2017).

Executive control/EFs play an important role in the activities of daily living, allowing individuals to live independently (Ferguson et al., 2021) and interacting with others appropriately (Amodio and Frith, 2006). Furthermore, several studies have shown that many psychiatric and neurological disorders are related to executive dysfunction (Friedman and Robbins, 2021; Rabinovici et al., 2015), which refer to the inability to develop, organize, and plan goal-directed behaviors and novel cognitive tasks (Parker et al., 2013). However, EFs decline has been observed also in normal aging (Ferguson et al., 2021; Fisk and Sharp, 2004; Kirova et al., 2015), as well as other cognitive functions (Micera, 2008; Murman, 2015). Nevertheless, little is known about this phenomenon in the normal aging population (Oschwald et al., 2019).

In the next paragraphs, cognitive decline – with a particular focus on EFs – in aging will be analyzed in detail, highlighting how a continuum is present from normal cognitive aging to

neurocognitive disorders. Physical and cognitive factors that may influence the involution toward a major neurocognitive disorder, in relation to executive dysfunction, will also be explored.

1.2. Executive Functioning on the continuum from Normal Cognitive Aging to Neurocognitive Disorders

EFs show different developmental and aging patterns (Diamond, 2013).

Whereas, some cognitive abilities – such as vocabulary and semantic knowledge – show little or no changes until very late in life (Hedden and Gabrieli, 2004), executive control undergoes a decline in aging, which is associated with structural and functional changes in the PFC (Dickson et al., 2007; Ferguson et al., 2021; Fjell et al., 2017; Gogtay et al., 2004; Oschwald et al., 2019; Raz et al., 2005; West, 1996).

Decreases in gray and white matter and ventricular volumes are characteristic features of normal brain aging (Harada et al., 2013; Spreng and Turner, 2019), and the PFC seems particularly susceptible to such age-related structural changes (Raz et al., 2005). Furthermore, older adults frequently show multimorbidity (i.e., polypathology) and consequent intake of therapies (i.e., polypharmacy) (Masnoon et al., 2017). Such issues have been linked to both a higher incidence of deficits in cognitive functioning and a greater likelihood of developing a major neurocognitive disorder (Soysal et al., 2019).

Cognitive neuroscience has risen several theories on cognitive aging, focusing on structural and functional changes that could explain both the decline and the maintenance of cognitive performance found in older subjects (Reuter-Lorenz et al., 2010). One of the most commonly highlighted aspects of brain functioning in aging is the increased recruitment of prefrontal regions, likely related to the increased demands of executive control processes (Spreng and Turner, 2019). Regarding this pattern, functional neuroimaging studies have led to the conceptualization of two main theoretical models: the *Hemispheric Asymmetry Reduction in Older Adults* (HAROLD; Cabeza, 2002) and the *Posterior-Anterior Shift in Aging* (PASA; Davis et al., 2008). The *HAROLD* model suggests that PFC activation during the performance of cognitive tasks is less lateralized in older adults than in younger subjects; this could result from a functional reorganization of the brain in response to age-related structural and functional changes; such bilateral activation in older subjects (as opposed to selective, focused activation occurring in younger adults) is a strategy for coping with neurocognitive deficits associated with age (Cabeza, 2002; Cabeza et al., 1997).

The *PASA* model hypothesizes the occurrence of an age-related reduction in occipital neural activity, and a subsequent increase in the activation of frontal regions. Such neural pattern would act as a compensatory mechanism for a physiological decline in brain activity in the older adults, also to address more difficult cognitive tasks (Davis et al., 2008).

Although cognitive functioning decline in normal aging does not usually impair a person's capacity to perform activities of daily living, nevertheless, it may lead to subtle deficits in more complex functional abilities (Harada et al., 2013), such as driving and making financial and healthcare decision (Blazer et al., 2015). In fact, a decline in EFs had been related to deficit in activities of daily living – specifically the instrumental ones – from normal aging to Mild Cognitive Impairment (MCI) to major neurocognitive disorders (Cahn-Weiner et al., 2007; Marshall et al., 2011; Pereira et al., 2008). Furthermore, impairment of these functional abilities is an essential hallmark for the diagnosis of major neurocognitive disorder, along with a substantial decline in one or more cognitive domains (American Psychiatric Association, APA, 2013; Jefferson et al., 2006; Word Health Organization, 2018). On the other hand, MCI is characterized by mild but noticeable cognitive decline in one or more domains (Kirova et al., 2015; Petersen, 2016), which may lead to deficits in more complex instrumental activities of daily living (Jekel et al., 2015). Such functional deficits seem to be more pronounced in MCI patients than in cognitively preserved older adults (Hughes et al., 2012). Furthermore, they appear to be predictive of a greater risk of involution to a neurocognitive disorder, even in individuals with subjective cognitive decline (Roehr et al., 2018) – a very common condition in aging, characterized by the self-perception of a persistent decline in cognitive functioning from a previous cognitive status, which is not, however, supported by a objective data (i.e. neuropsychological assessment) (Jessen et al., 2020).

In light of the above, it is crucial to monitor the ability of older adults to independently perform activities of daily living, as it may be suggestive of the development of a neurocognitive disorder (Harada et al., 2013).

Several studies have highlighted how a *continuum* from normal cognitive aging to major neurocognitive disorders may exist (Franceschi et al., 2018; Kirova et al., 2015; Krivanek et al., 2021; Sperling et al., 2011). According to the *Cognitive Decline Model* (Krivanek et al., 2021), while the presence of a possible neurodegenerative disease and additional brain insult may accelerate cognitive impairment, conversely, cognitive reserve may slow such decline. The term "cognitive reserve" refers to the ability to engage alternative brain networks or cognitive strategies to address the effects of cognitive impairment. In addition, "brain reserve", the brain's ability to resist pathological insult – perhaps due to greater synaptic density or a greater number of healthy neurons – may allow sustaining normal cognitive functioning. Both types of reserve

seem to be influenced by several common factors, such as the engagement in cognitively stimulating activities and a high socioeconomic status (Sperling et al., 2011).

Sperling and colleagues (2011) postulated that Alzheimer's Disease (AD) begins with a long asymptomatic period (lasting years or even decades) during which the pathophysiological process is progressing. However, some subjects with the neuropathological features of the disease do not manifest clinical symptoms throughout their lifetime (Nelson et al., 2012). Epidemiological data suggest that there are several factors that may modulate the rate of clinical expression of the AD pathophysiological process. In particular, vascular risk factors (Arvanitakis et al., 2004; Craft, 2009; Lee et al., 2020) and depressive symptomatology (Almeida et al., 2017; Wilson et al., 2006) have been associated with an increased risk of mild and major neurocognitive disorder (Sperling et al., 2011). On the other hand, additional features, such as cognitive and brain reserve, may influence the ability to tolerate the neuropathological AD features (Stern, 2012; Stern and Barulli, 2019). Therefore, it is crucial to identify the factors that best predict progression to neurocognitive disorder, in order to intervene during the pre-clinical phase, before the onset of the symptoms [*Figure 1.1*].

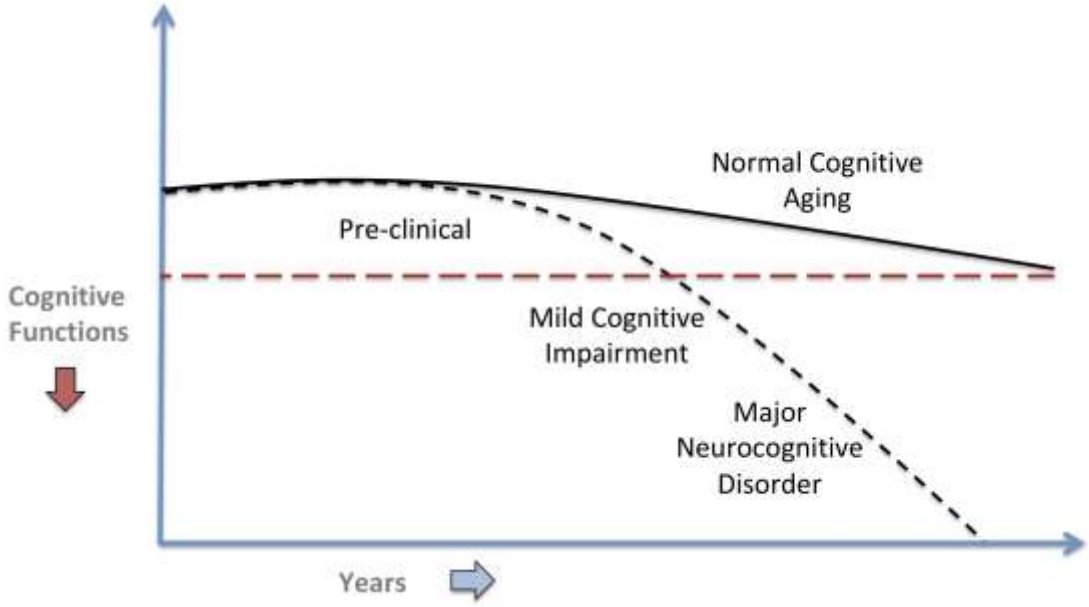

Figure 1.1. The hypotetical model of the continuum from Normal Cognitive Aging to Major Neurocognitive Disorder.
The solid black line represents the trajectory of normal cognitive aging. The descending dashed black line indicates the possible cognitive decline during years, while the dashed red line marks the threshold for clinical cognitive impairment (adapted from *Sperling et al., Alzheimers Dement.*, 2011).

1.2.1. The Characterization of Aging

Aging is a progressive natural multifactorial process ongoing with time, influenced by biological, genetic, environmental, psychological, and social factors (Dziechciaż et al., 2014; Rodrìguez-Rodero et al., 2011). It can be considered in different ways, according to the perspective adopted. In particular, the models most commonly employed to describe the aging process are (Smith and Bondi, 2013):

- The "senescence" model, according to which – from a biological perspective – aging is characterized by a loss in physiological integrity (López-Otín et al., 2013), with decreasing functionality and adaptability;
- The "life-span" model, which considers aging as one of the different stages of development, characterized by continuous changes. From this perspective comes the idea of "active" (Foster and Walker, 2015) and "healthy aging" (World Health Organization, 2002), according to which older adults – i.e., persons aged 60 years and older (World Health Organization, 2021) – are considered as an economic and social resource, in terms of their participation in community and political life and, above all, their right to remain healthy and live in environments suited to their capacities and abilities (Foster and Walker, 2015).

The aging process seems to show inter- and intra-individual differences, particularly concerning age-related diseases (Franceschi et al., 2018). Rowe and Khan (1987) were the first ones to highlight the heterogeneity of the older population, making a distinction between "normal" and "successful" aging. According to the authors, successful aging reflected an optimal physical and cognitive functioning, which did not significantly differ from that of younger adults – as it was shown by cross sectional studies (Depp and Jeste, 2006) –, and active engagement in social activities (Rowe and Khan, 1997). However, this model of aging is uncommon and has been criticized because it focuses on the simple passage of time alone, not analyzing the structural and social factors that influence aging (Martinson and Berridge, 2014; Riley, 1998). On the other hand, “normal” aging is characterized by the presence of typical age-related diseases (ARDs) and subsequent pharmacotherapies, which may negatively impact cognitive functioning (Smith and Bondi, 2013).

As the great inter- and intra-individual variability makes difficult to define a "normal" trajectory of aging, the term "cognitive aging" was introduced to better describe older individuals who, in the absence of neurocognitive and psychiatric disorders, present slight difficulties in both *day-to-day* functional aspects (such as driving or understanding instructions given by health care professionals) and the more complex cognitive tasks, such those involving prefrontal-mediated

functions (Blazer et al., 2015). Moreover, older adults seem to be more prone to exhibit mood deflections (Vink et al., 2008), particularly in terms of depression (Meeks et al., 2011) and anxiety (Balsamo et al., 2018). Since cognitive aging is not a disease, it was hypothesized that the best approach to study its neuropsychological, physical, and functional features is through longitudinal studies (Blazer et al., 2015).

Recently, it has been hypothesized that aging and ARDs may share common and interacting biological mechanisms (Franceschi et al., 2018; Kennedy et al., 2014; Lim et al., 2018). Furthermore, ARDs may accelerate aging process, affecting the homeostatic balance (Franceschi et al., 2018), also leading to cognitive complaints (Hill et al., 2021). Such aspects are also key features of a frailty status (Panza et al., 2018). Indeed, One of the most common age-related conditions analyzed in the literature is frailty (Franceschi et al., 2018; Fried and Ferrucci, 2016; Xue, 2011), which will be discussed in detail in the next paragraph.

1.3. Frailty in Aging

Frailty is a dynamic and complex age-related clinical status, characterized by reduced resistance to stressors due to cumulative decline in multiple neuropsychophysiological systems (Pilotto et al., 2020). This clinical condition is related on the one hand to a decrease in independence in daily activities and quality of life, and on the other hand to an increased risk of hospitalization, disability and mortality (Heuberger, 2011).

The estimated prevalence of frailty in the community-dwelling older population is 10% (Collard et al., 2012), but it is considerably higher in other settings; for example, in hospitalized older adults it ranges from 18% to 40% of patients (Cunha et al., 2019).

Despite the evidence of strong relationship between such issue and poor outcomes, currently there is no gold standard on how to define, assess, and diagnose frailty (Richards et al., 2018). In fact, in the last decades, several models have been proposed in order to evaluate frailty (Pilotto et al., 2020). There are mainly three models adopted to study frailty [*Figure 1.2*]: the phenotypical model (Fried et al., 2001), the deficit accumulation model (Rockwood et al., 2005; Rockwood and Mitnitski, 2007), and the bio-psycho-social model (Gobbens et al., 2010). The first two are based on the biomedical approach, while the last one considers frailty from a multidimensional perspective.

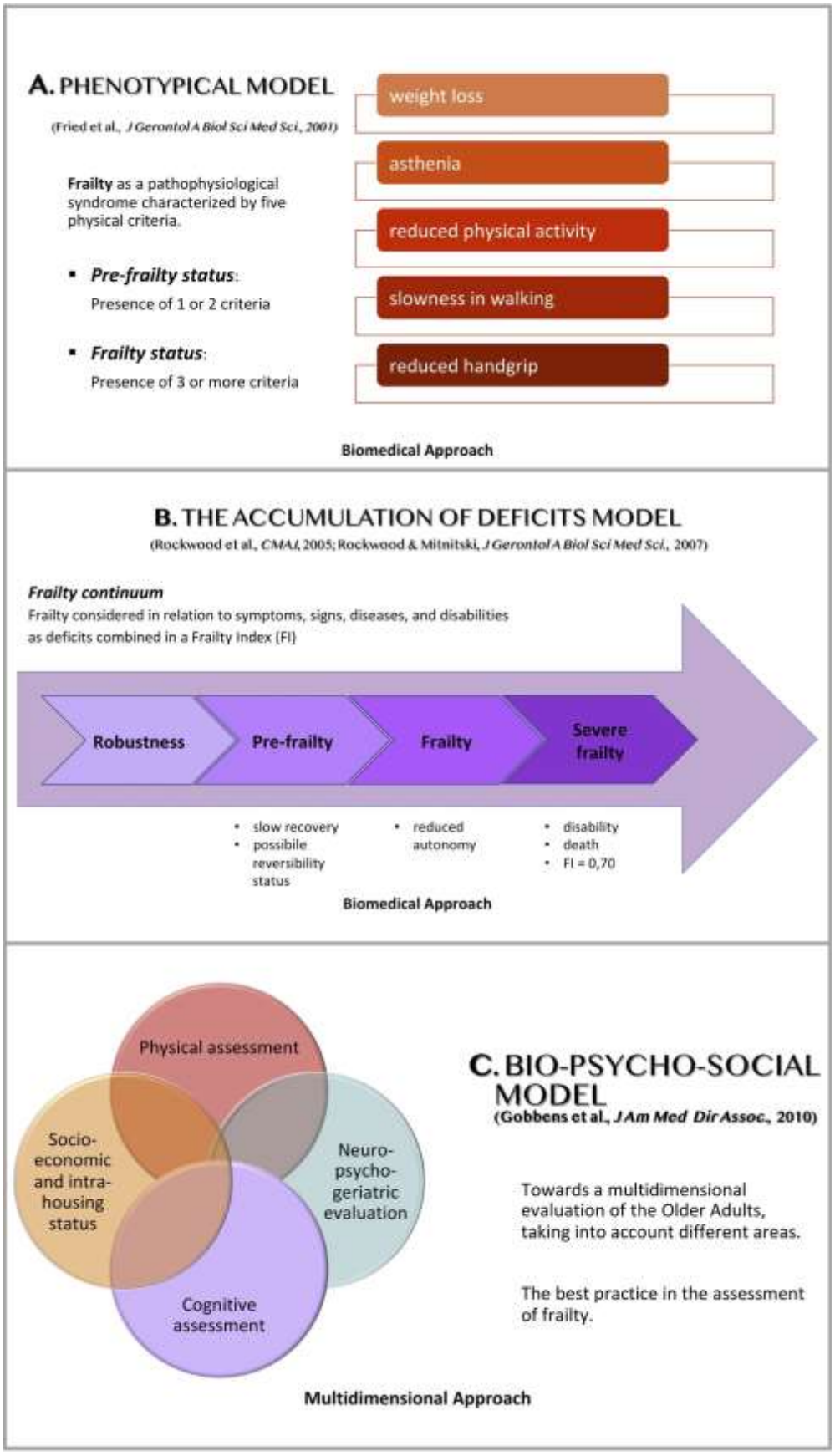

Figure 1.2. The three main Models to study Frailty.
The phenotypic model (Fried et al., 2001; **A**), the deficit accumulation model (Rockwood et al., 2005; Rockwood and Mitnitski, 2007; **B**), and the integral conceptual model, based on a bio-psycho-social approach (Gobbens et al., 2010; **C**) (adapted from Bartoli et al., Front Psychol., 2020).

The *phenotypical model* (Fried et al., 2001) considers frailty as a geriatric pathophysiological syndrome, taking into account five determinants [*Figure 1.2.* A]: 1) a consistent unintentional weight loss in the last year; 2) asthenia in the last week; 3) reduction in physical activity; 4) slow walking speed; 5) reduction in handgrip strength. The presence of three or more criteria defines frailty, while one or two criteria indicate a pre-frailty status: an intermediate, preclinical state, which is potentially reversible (Hanlon et al., 2018).

The *deficit accumulation model* (Rockwood et al., 2005; Rockwood and Mitnitski, 2007) considers frailty as a risk condition caused by the accumulation of age-related deficits – i.e., symptoms, signs, disorders or disabilities – related to the decline across various body organs and physiological systems [*Figure 1.2.* B]. The severity of the clinical condition is assessed using the so-called "Frailty Index" (FI), by calculating the proportion between the number of deficits that the older person suffers from, and the total number of common age-related deficits taken into consideration. The higher the FI, the frailer the individual.

Although the deficit accumulation model provides a more in-depth assessment than the phenotipic model – also better predicting negative outcomes (Rockwood et al., 2007) – it has not fully taken into account the psycho-social aspects that may influence the occurrence of frailty. In fact, the biomedical approach focuses primarily on the reduction in the ability to preserve homeostasis from a physiological perspective and the implications on the capacity to respond to environmental changes appropriately (Xue, 2011). Over time, the biomedical approach has been criticized (Canevelli et al., 2015) as it takes into account only the physical aspects of frailty. Furthermore, the majority of studies adopting this approach were limited to conducting a brief cognitive screening assessment (i.e., using the *Mini Mental Statement Examination*, Folstein et al., 1975), lacking a thorough neuropsychological assessment.

In light of this, a novel, general concept of frailty has emerged, based on its multidimensional nature, according to which the loss of harmonic interaction among several domains (i.e., biological, functional, neuropsychological, and social) determinates and characterizes a frailty status (Pilotto et al., 2020). The *bio-psycho-social* model (Gobbens et al., 2010) emerged from the multidimensional approach to frailty, which requires an assessessment not only from a biomedical perspective, but also taking into account socioeconomic, psychological, and cognitive factors [*Figure 1.2.* C].

1.3.1. The Relationship between Frailty and Executive Dysfunction

Although in its original definition frailty referred purely to a physical condition (Facal et al., 2019), recently, greater relevance has been attributed to the cognitive status, which is considered

a key aspect for understanding frailty and a new target to prevent older adults' dependency (Ruan et al., 2015). In fact, in 2013, a new concept of "cognitive frailty" has been suggested, characterized by specific features (Kelaiditi et al., 2013): (a) the co-occurrence of physical frailty and mild cognitive impairment, assessed by a score of 0.5 on the *Clinical Dementia Rating Scale* (Hughes et al., 1982); (b) no diagnosis of a neurocognitive disorder due to AD or other etiopathogenesis.

Physical frailty (i.e., biomedical models) is considered a risk factor for both MCI (Boyle et al., 2010) and major neurocognitive disorder (Petermann-Rocha et al., 2020) and, similarly, cognitive decline appears to predict the onset of frailty (Raji et al., 2010). Indeed, the interaction between cognitive impairment and physical frailty has been defined as a "feedback loop relationship" (Amanzio and Palermo, 2021) in which also psychological factors, such as mood changes, may play a role (Espinoza et al., 2013; Mezuk et al., 2012; Paulson and Lichtenberg, 2013). Nevertheless, a small number of studies has examined the relationship between physical frailty and different cognitive domains (Canevelli et al., 2015).

Robertson and colleagues (2014) analyzed the effect of each of the five frailty criteria, according to the phenotipical model (Fried et al., 2001), and different cognitive domains – i.e., global cognition, attention, memory, executive functions, processing speed, and self-rated memory – assessed with different neuropsychological tests, by multivariate linear regression. It was found that asthenia was associated with a decrease in global cognitive functioning, as well as handgrip strength. The latter was also associated with executive dysfunction. Furthermore, walking speed was also associated with processing speed, attention, and executive functioning.

As for the phenotipical model, several studies showed that handgrip strength and walking speed seem to be the two frailty determinants most related to cognitive decline, particularly to executive dysfunction (Delrieu et al., 2016; Hooghiemstra et al., 2017; Kang et al., 2009; Langlois et al., 2012; Sargent and Brown, 2017).

O'Halloran et al. (2014) found that frail and pre-frail subjects performed worse at the *Sustained Attention to Response Task* (Robertson et al., 1997) compared to robust older adults. Particularly, they made more omissions and commission errors, suggesting some deficits in the response monitoring. In this direction, other research pointed out a relationship between executive functioning and frailty. A 9-year longitudinal study found that greater decline in executive functioning was associated with a higher risk of frailty onset in a sample of 331 women (Gross et al., 2016). In addition, the *Toledo Study for Healthy Aging* showed that executive dysfunction is a strong predictor of frailty (Rosado-Artalejo et al., 2017).

In light of the above, the best neuropsychological model proposed to study frailty seems to be the paradigm of attentional and executive functions (Canevelli et al., 2015; Gross et al., 2016; Rosado-Artalejo et al., 2017; Sargen and Brown, 2017).

The relationship between executive dysfunction and frailty on the continuum from normal cognitive aging to mild and major neurocognitive disorders is one of the pivotal topics of my PhD project, which will be better discussed in Chapters 2 and 3 of my Thesis.

1.4. Reduced Self-Awareness in Neurocognitive Disorders

The awareness of illness is a multidimensional construct encompassing different aspects, such as the ability to recognize the symptoms of the disease, the capacity to understand its consequences, and to realize the need to be treated (Amanzio and Palermo, 2020).

Reduced self-awareness is known as a common feature in neurodegenerative disorders, such as AD (Amanzio et al., 2011, 2013; Hannesdottir and Morris, 2007; Morris and Mograbi, 2013), Frontotemporal dementia (Amanzio et al., 2016, 2017; Eslinger et al., 2005), and Parkinson's disease (Amanzio et al., 2014; Palermo et al., 2018), but also following acquired brain injuries (ABIs) in prefrontal areas (Bach and Devis, 2006; Ownsworth et al., 2007; Palermo et al., 2014). In fact, a reduction in self-awareness could be explained by considering anatomo-functional changes in the prefrontal cortex and, consequently, executive dysfunction (Amanzio et al., 2011, 2013, 2014, 2016; Palermo et al., 2014, 2018). In particular, O'Keffee and colleagues (2007) suggested that reduced self-awareness might be influenced by deficits in the core executive functions – also called "metacognitive-executive functions" (Palermo et al., 2017). In light of these, such phenomenon could be accurately explained by adopting a neurocognitive approach as a theoretical framework.

1.4.1. The Executive Dysfunction and Reduced Self-Awareness: a Neurocognitive Theoretical Framework

The neurocognitive approach emphasizes the association between impaired self-awareness – concerning cognitive, motivational, and emotional aspects – and brain pathology (McGlynn and Schacter, 1989; Palermo et al., 2014).

The neurocognitive model proposed by Stuss and colleagues (2001, 2004) provides the first an essential theoretical background for understanding how different brain networks are related to distinct awareness deficits [*Figure 1.3*]. The authors hypothesized a hierarchical organization referring to cortical and subcortical anatomical areas; the information follow a *bottom-up* pathway, whereby higher levels use the modeling capabilities of lower levels.

The dlPFC and the medial PFC (mPFC) – in which ACC may be included (Amodio and Frith, 2006) – represent the highest levels of this hierarchical model. Particularly, The dlPFC is implicated in the control and sequencing of behavior, as well as the generation of mental sets, whereas the mPFC is involved in metacognitive-executive functions, drive, and motivation.

In light of this, it is clear that EFs and anatomo-functional related brain areas are strongly implicated in self-awareness.

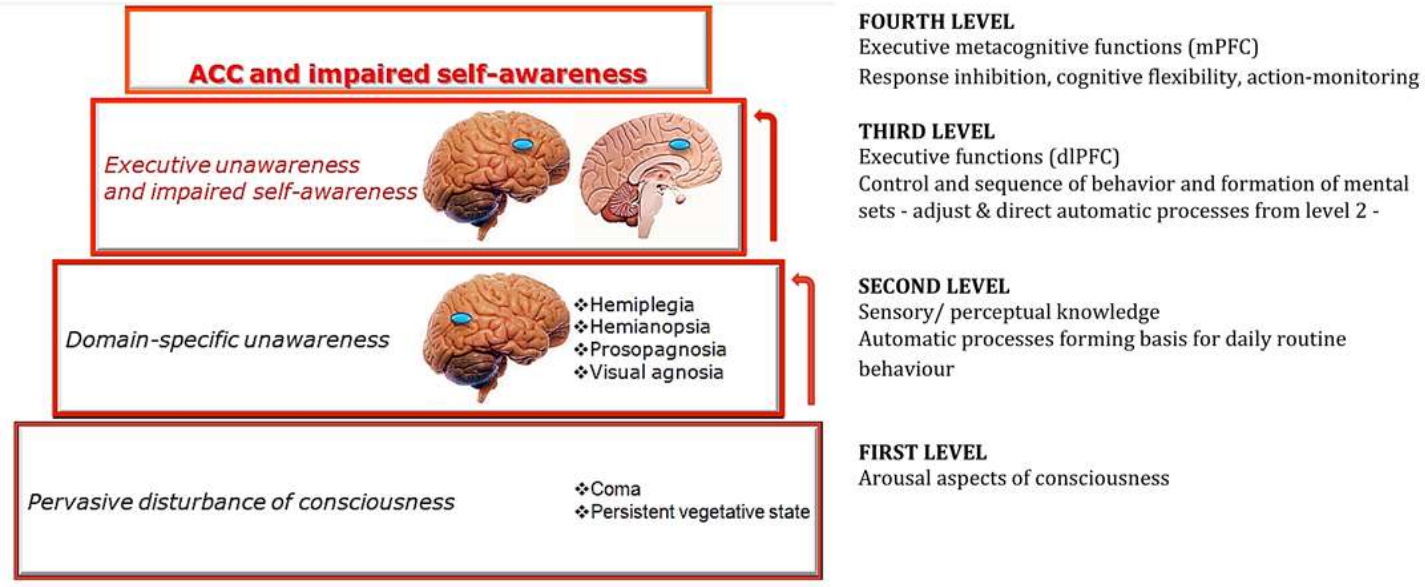

Figure 1.3. The graphical representation of the Awareness Model.
The figure depicts the processing of input information from the sensory/perceptual level of knowledge to the metacognitive-executive functions involving the mPFC (adapted from Amanzio et al., *Front Psychol.*, 2020).

Executive models of self-awareness have been developed focusing on the impairment of executive control processes, which seem to play a major role in self-monitoring-action-abilities (Schacter, 1990; Stuss and Levine, 2002).

Cieslik and colleagues (2013) identified two neural networks involving the dlPFC in relation to metacognition, defined as the ability to regulate and modulate cognitive processes and behavior in different contexts (Fernandez-Duque et al., 2000): a dlPFC-posterior parietal circuit and an anterior dlPFC-ACC. These networks seem to be hierarchically structured: the dlPFC-posterior parietal circuit may be implicated in working memory and stimuli processing, whereas the anterior DLPFC-ACC network seems to be involved in higher-order control processes of motor behavior, which are important in cognitive set-shifting and inhibition of responses to irrelevant stimuli.

The *Cognitive Awareness Model* or *Conscious Awareness Model* (CAM) (Agnew and Morris, 1998; Mograbi and Morris, 2014), originally developed to explain awareness deficits in AD, can be applied to other neurodegenerative disorders (O'Keeffe et al., 2007) and ABIs (Sherer et al., 1998; Prigatano, 2005; Ownsworth et al., 2002).

According to the CAM, a comparator system – which is part of the central executive system – is responsible for matching cognitive and behavioral performance to a personal database, in terms of success or failure (Agnew and Morris, 1998; Mograbi and Morris, 2014). When a mismatch is identified, a signal is sent to the *Metacognitive Awareness System*– which corresponds to the highest hierarchical level in the model proposed by Stuss et al. (2001, 2004) – leading to consciousness of failure. Conversely, if the executive system does not function properly, the comparator mechanism will not detect any mismatches. As a result, failures in the performance will not reach metacognitive awareness and the subject will not be able to modify her/his cognitive or behavioral performance accordingly.

As will be shown in Chapter 4, CAM has resulted to be a fruitful theoretical model to understand self-awareness deficits in patients with AD (Amanzio et al., 2011, 2013, 2018), Parkinson's Disease (Amanzio et al., 2014; Palermo et al., 2018), Frontotemporal Dementia (Amanzio et al., 2016, 2017), and also ABIs (Palermo et al., 2014; Bartoli et al., 2020).

1.5. Aging in the COVID-19 Pandemic Era and the influence of The Nocebo Effect

The Coronavirus disease-2019 (COVID-19) pandemic is a major health emergency that has affected the entire globe for the past two years. The older population seems to be particularly vulnerable to the virus, as frailty subjects and older adults with polypathologies have a higher risk of adverse outcomes (Onder et al., 2020; Zhang et al., 2021). Furthermore, the increased susceptibility to infection is probably also driven by reduced immunity due to the physiology of aging (Gavazzi and Krause, 2002).

Although lockdown measures played a key role in containing the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) infection, nevertheless, they led to an increased risk of developing mental and physical health problems (Sani et al., 2020; Talevi et al., 2020). In particular, due to social isolation, older adults may exeperience mood deflection and cognitive decline (Santini et al., 2020; Webb et al., 2021). Furthermore, sleep disturbances, related to this uncertain situation, may also arise (Parveen et al., 2021; Pires et al., 2021).

The pandemic situation may lead to negative emotions, such as fear, anxiety and depression (Lee, 2020; Liu et al., 2020). Stressors are mainly due to uncertainty and changes in the environment but also to negative news and information, which trigger pessimistic thoughts and expectations. In this direction, contextual factors, such as social networks and media, inundate people with dramatic, sometimes discordant, and mostly negative information (Gao et al., 2020). Such factors may result in the occurrence of the nocebo phenomenon, an unfavorable

expectation effects, resulting in psychological and/or somatic symptoms that may also lead to a reduction in treatment outcome (Daniali and Flaten, 2021).

Older adults may be more prone to exhibit the nocebo effect, as several late-life stage aspects have the potential to increase susceptibility to nocebo, such as mood changes in terms of depression and anxiety, neurocognitive disorders, adverse healthcare experiences (i.e., adeverse events to drugs), and patient-physician communication (Kravvariti et al., 2021).

As will be further explored in Chapter 5, it is highly likely that the COVID-19 pandemic may represent a "perfect storm" in which powerful nocebo effects may be enhanced in terms of psychological distress (Amanzio et al., 2020) and resistance to immunization (Amanzio et al., 2021) with a particular focus on older adults.

1.6. General Organization of the Research Project

The main goals of the research conducted during my Doctoral Degree are:

- Studying the role of executive functioning in relation to the occurence of frailty, on the continuum from Normal Cognitive Aging to Neurocognitive Disorders;
- Analyzing the association between prefrontal brain network disruptions, executive dysfunction, and reduced self-awareness in patients with Neurocognitive Disorders with different etiopathogenesis;
- Investigating how specific mood changes may influence the response to treatment in older adults, in terms of nocebo effect, and its consequences during the current pandemic.

In addition, the effects of the COVID-19 pandemic and the subsequent restrictive measures adopted to reduce its spread were taken into account, in relation to the purposes of my research.

Several studies were conducted during the 4-year doctoral training program (2017-2021), which will be described in my thesis.

The introductory chapter that just ended (Chapter 1) is followed by four chapters (Chapter 2, 3, 4, and 5), covering the different research area of my project. The last one (Chapter 6) summarises the primary findings across the studies, particularly focusing on their clinical implications and future directions.

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2. Neuropsychological impact of the COVID-19 Pandemic on Healthy Cognitive Aging

The SARS-CoV-2 has been first recorded in December 2019, in the city of Whuan, China (Chaimayo et al., 2020). Since then, the COVID-19 has spread all over the world.

Italy was one of the first countries to be affected by the virus (La Rosa et al., 2020) and to implement early containment measures to prevent the spread of COVID-19 (Italian Ministry of Health, 2020).

The pandemic and the resulting restrictive measures to contain the SARS-CoV-2 infection occurred in the middle of my doctoral activities. However, data collection has not ceased; instead, there has been an increase in scientific research, also through national and international collaborations by remote.

During the pre-pandemic period, I had collected data at the "University of the Third Age" (UNITRE-TO), in Turin, in order to investigate the neuropsychological characteristics of the so-called "Cognitive Healthy Aging" (Smith, 2016) and the possible relationship between subclinical cognitive impairment – particularly in terms of executive dysfunction – and a frailty (or pre-frailty) status. Specifically, the neuropsychological assessment was carried out thanks to the creation of an innovative laboratory (LAB) at UNITRE-TO on active and healthy aging for training, education, research, and development. Furthermore, the subjects who attended the LAB activities followed specific educational modules aimed at learning functional lifestyles in the perspective of active and healthy aging.

In order to continue this study during the lockdown, an integration of the research project was requested and obtained by the Bioethics Committee of the University of Turin (protocol number: 151786). In particular, our aim was to investigate the effects of COVID-19 and restrictive measures in relation to cognitive functioning – with a particular focus on EFs –, physical conditions (i.e. polypathology and frailty), and mood changes in cognitive aging, by adopting a longitudinal approach.

The subjects were neuropsychologically assessed before the pandemic (*T0;* April – October 2019), during the first Italian lockdown (*T1*; April – May 2020) and immediately after it (*T2*; May – July 2020). Furthermore, during another home confinement, they performed a psychological screening (*T3*; December 2020 – January 2021).

The results of this study have been presented in two articles published on Peer Reviewed international journals, which will be shown in the next paragraphs.

In the first study (Amanzio et al., 2021) – for which I served as corresponding author – we investigated the effects of the so-called *lockdown fatigue* on the healthy cognitive aging population, taking into account physical status, cognitive functions, and mood deflection.
The second study (Bartoli et al., 2021) analyzed the relationship between COVID-19 perceived threat and the neuropsychological characteristics (i.e. cognitive functioning, physical-health status, and mood changes) of cognitively preserved older adults.

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2.1. Lockdown Effects on Healthy Cognitive Aging During the COVID-19 Pandemic: A Longitudinal Study

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2.1.1. Abstract

The COVID-19 pandemic is a health issue leading older adults to an increased vulnerability to unfavorable outcomes. Indeed, the presence of physical frailty has recently led to higher mortality due to SARS-CoV-2 infection. However, no longitudinal studies have investigated the role of neuropsychogeriatric factors associated with lockdown fatigue in healthy cognitive aging. Eighty-one healthy older adults were evaluated for their neuropsychological characteristics, including physical frailty, before the pandemic (T0). Subsequently, 50 of them agreed to be interviewed and neuropsychologically re-assessed during the lockdown (T1) and immediately after it (T2). Moreover, during another home confinement, they performed a psychological screening (T3) to evaluate possible mood changes and fatigue. According to Fried's frailty criteria, at T0, 63% of the sample was robust, 34.5% pre-frail, and only 2.5% frail. Significantly, these subjects presented a decrease in handgrip strength and walking speed (29.6 and 6.1%, respectively). Results from Principal Component Analyses and multiple regression models highlighted the contribution of "cognitive" and "psychological" factors (i.e., attentive-executive performance and mood deflections) in explaining handgrip strength and gait speed. At T3, lockdown fatigue was explained by higher scores on the Beck Depression Inventory and lower scores on the Trail Making Test part A. Results from a moderated-mediation model showed that the effect of psychomotor speed on lockdown fatigue was mediated by depression, with a

moderating effect of gait speed. Our findings highlight the complex interrelationship between cognitive, psychological, and physical factors in the emergence of pandemic fatigue in a carefully selected older population.

2.1.2. Introduction

The presence of a state of frailty, characterized by a clinical history of polypathology, has recently led to higher mortality due to the SARS-CoV-2 pandemic among the older population (Onder et al., 2020). Polypathological subjects suffer from two or more chronic diseases, which could lead to disability and higher mortality rates (Gómez-Salgado et al., 2019).

The increased susceptibility to epidemic effects is likely to be determined not only by existing comorbidity conditions, but also by reduced immunity, partly due to the physiological aging process (Gavazzi and Krause, 2002).

Lockdown measures play a major role in the containment of SARS-CoV-2 infection. However, isolation and social distancing are associated with cognitive decline, depression, and anxiety in the older population (Santini et al., 2020). Faced with prolonged confinement, older people may experience loneliness, pessimism, health problems, negative stereotyping, and sleep disorders (Luchetti et al., 2020). Furthermore, social isolation is an important public health issue that can lead to higher probabilities of cognitive and mental problems (Gerst-Emerson and Jayawardhana, 2015).

Recently, a feeling of "lockdown fatigue" has been associated with home confinement due to the COVID-19 pandemic. Only a few authors have investigated this particular phenomenon, without specifically targeting the older population. For instance, Bartoszek et al. (2020) examined a sample of 471 subjects predominantly young (mean age = 25 years, SD = 2.1) and female (85.6%). The authors found that living alone and starting new therapies during the lockdown were associated with higher levels of fatigue. In a cross-sectional community-based survey, COVID-19 pandemic fatigue was experienced in about 64% of the sample; again, the over-60 population was underrepresented (Morgul et al., 2020). Labrague and Ballad (2021) analyzed the fatigue among Philippines college students during the COVID-19 lockdown in a remote cross-sectional study. Their results indicated moderate levels of fatigue, in terms of physical exhaustion, body pain, headaches, worries, and reduced motivation. Finally, in a survey of 260 subjects (mean age = 47 years), lockdown fatigue was related to worsened mood and lifestyle (Field et al., 2021).

Despite the problems highlighted in these studies, to date no longitudinal ones have analyzed the associations among lockdown fatigue, physical conditions, cognitive functions, and mood

deflections in cognitively normal older adults during home confinement. This is unfortunate, as targeted psychological interventions may have a role in primary prevention and psychological well-being, by enhancing resilience during periods of health emergency while also reducing the negative impact on physical and cognitive dysfunctions and mood deflections disorders.

To fill this gap, we investigated the relationships between pandemic lockdown fatigue, physical-cognitive functions, and mood changes in 50 older adults − 60 years and older (World Health Organization, *WHO*, 2021) – engaged as volunteers, suffering from two or more age-related diseases (polypathology) and receiving subsequent pharmacotherapy (Masnoon et al., 2017).

The availability of pre-COVID19 baseline data (T0) of this sample allowed us to investigate the contribution of cognitive functioning and psychological state in explaining the variability of grip strength and gait speed, two crucial components of the frailty phenotypic model (Fried et al., 2001).

A longitudinal approach (from April 2019 to January 2021) was used to analyze: (a) the neuropsychogeriatric profile of the participants before and after the lockdown; (b) whether these subjects had developed lockdown pandemic fatigue; (c) whether this fatigue could be predicted by variables measured at baseline using a moderate-mediation model.

In particular, as lockdown fatigue had been previously related to depressive symptoms (Bartoszek et al., 2020; Field et al., 2021; Seiter and Curran, 2021) and a slowdown in attentional abilities (Fiorenzato et al., 2021), we expected both to be useful in predicting exhaustion due to the restrictive measures in our sample. Furthermore, as mood deflection may be influenced by cognitive dysfunction (e.g., attention deficit; Keller et al., 2019), and physical frailty (Buigues et al., 2015) – particularly gait speed (Marino et al., 2019) – we hypothesized that attentional skills and gait speed would interact in modulating depression mood changes.

Our hypothesis is that decreased psychomotor and gait speed may interact to produce a depressive state that mediates their effect on lockdown fatigue.

2.1.3. Materials and Methods

The creation of an innovative laboratory (LAB) on active and healthy aging for training, education, research, and development allowed neuropsychological interventions on members of the University of the Third Age in Turin (UNITRE-TO). The subjects attending the LAB activities were numerous (N = 200) and, during the academic year 2018–19, they followed specific teaching modules aimed at learning functional lifestyles in view of active and healthy aging.

Eighty-one Italian volunteer subjects (64 females, age range 60–84) out of the 200 participants (40.5%) were selected if they: (a) suffered from at least two chronic pathologies and received pharmacotherapy treatments (Smith and Bondi, 2013); (b) were aged 60 years or older in order to be classified as "older adults" (World Health Organization, 2021); and (c) had a Mini Mental State Examination (*MMSE*, Folstein et al., 1975) raw score ≥ 27. The latter is the best cut-off for MCI detection in highly educated populations (O'Bryant et al., 2008), such as the one involved in our study. Moreover, the subjects did not report subjective cognitive decline (Jessen et al., 2020) and had not undergone any medical or neurological examination for suspected MCI (Petersen and Negash, 2008).

Participants were excluded from the study if they: (1) suffered from psychiatric or neurocognitive disorders based on DSM-5 criteria (American Psychiatric Association, 2013); (2) were taking any medications that could substantially affect cognitive functioning.

All subjects were functionally independent and socially active. We performed a screening in order to investigate their cognitive, functional, and behavioral domains, and to detect the mildest neuropsychogeriatric dysfunction considering their physical health status, their cognitive functioning, and possible mood deflections in terms of anxiety and depression (T0).

During the COVID-19 pandemic, 50 out of the 81 subjects agreed to participate in LAB activities remotely in compliance with restrictive lockdown measures. They underwent semi-structured interviews (T1), neuropsychological (T2), and psychological assessment (T3) to identify any possible under cut-off values in their individual profile.

All participants gave written informed consent prior to the study, which was performed in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the University of Turin (Prot. n. 10038 and Prot. n. 151786, before and after the pandemic, respectively).

Assessments Measures at the Baseline (T0)

From April to October 2019, the subjects underwent a multidimensional neuropsychogeriatric assessment, which consisted of cognitive tests, functional, and behavioral scales. Three different neuropsychologists evaluated the subjects in two experimental sessions, held 1 day apart and each lasting about 90 minutes, in order to prevent fatigue and lack of adherence to the tasks.

Information about clinical history, symptoms, and chronic pathologies was collected using the Cumulative Illness Rating Scale (*CIRS*: Linn et al., 1968).

Global cognitive functioning was assessed by using the Addenbrooke's Cognitive Examination-Revised version (*ACE-R*: Mioshi et al., 2006) and the Montreal Cognitive Assessment (*MoCA*: Conti et al., 2015). Then, a detailed evaluation was carried out considering several cognitive

domains: episodic long-term memory (*Rey Memory Test and Short Story Recall*: Spinnler and Tognoni, 1987), short-term memory (*Digit Span* and *Corsi Test*: Spinnler and Tognoni, 1987), attention (*attentional matrices*: Spinnler and Tognoni, 1987), language and fluencies (*Token Test—TT*: De Renzi and Vignolo, 1962; *Phonemic* and *Semantic Fluency*: Spinnler and Tognoni, 1987; Naming subtest of *Aachner Aphasia Test—AAT*: De Bleser et al., 1986), visuo-constructive abilities (*Copy Design*: Carlesimo et al., 1996), problem-solving (*Raven's Coloured Progressive Matrices—CPM-36*: Spinnler and Tognoni, 1987), and attentive-executive functions (*Trail Making Test—TMT*: Giovagnoli et al., 1996).

Psychiatric rating scales were used to assess: depression (*Beck Depression Inventory—BDI*: Beck et al., 1988), apathy (*Apathy Evaluation Scale—AES*: Marin, 1996), anxiety (*Hamilton Rating Scale for Anxiety—HARS*: Hamilton, 1959), disinhibition (*Disinhibition Scale—DIS-S*: Starkstein et al., 2004), and hypomania (*Mania Scale—MAS*: Bech et al., 1978).

The possible presence of a physical frailty status was assessed by adopting the phenotypic model (Fried et al., 2001). According to Fried's criteria, frailty is a pathophysiological syndrome characterized by 5 determinants: (1) unintentional weight loss; (2) limitation of physical activity; (3) asthenia; (4) handgrip strength reduction; and (5) slowing in walking speed. The presence of three out of five criteria indicates a state of frailty, while one or two criteria identify a pre-frailty status.

Semi-Structured Interviews at T1

From April to May 2020, during the lockdown period, all 81 subjects assessed at T0 were contacted by phone, text message, or email in order to ask for their availability to participate in the study. Fifty of them agreed. At first, a semi-structured interview was carried out to collect information about housing status, health conditions, measures to avoid contagion, and sources of information considered as reliable. In addition, they were asked for any changes in their habits in terms of diet, physical activity, sleep, smoking, use of drugs and alcohol, and cognitively stimulating activities.

At the end of the interview, the participants were asked to schedule a second appointment for a neuropsychological evaluation.

Neuropsychological Assessment at T2

This third phase was carried out remotely via video-call from May to July 2020, during the so-called "phase 2" of the Italian quarantine, when restrictive measures were eased.

The choice of neuropsychological tests was as close as possible to T0. Cognitive functioning was assessed by ACE-R, and MMSE. The test subsections involving visuo-spatial skills were presented in screen-sharing mode. We also used the *MoCA-Blind* test (Wittich et al., 2010). This

version was originally designed for people with visual impairment. In our research, we used such instrument in order to overcome the issues related to the performance of some of the visual tasks of the original test (e.g., TMT-B, short version) through the screen-sharing mode. The blind version is scored out of 22 but, as suggested on *www.mocatest.org* (Nasreddine, 2020), the official MoCA website, it needs to be converted back to 30 as the original test.

Mood changes were evaluated using BDI, AES, HARS, DIS-S, and MAS. The socioeconomic characteristics of the sample were analyzed using the Four Factor Index of Social Status (Hollingshead index, HI: Hollingshead, 1975, 2011). This index is based on the educational level and the type of employment of family members (for more details on scoring, please see Hollingshead, 1975, 2011). In this case, since our group consisted of retired people, their last job was taken into account.

Neuropsychological Assessment at T3

Remote phone calls were used to carry out this last phase, which occurred during another period of very restrictive measures in Italy (December 2020 - January 2021).

In order to achieve our aims, we chose to test the subjects only on BDI and HARS. These scales are very suitable for a remote assessment and, furthermore, depression and anxiety are two of the most frequently reported and studied psychological aspects in the literature concerning the COVID-19 pandemic (Salari et al., 2020) and subsequent home confinement (Bartoszek et al., 2020; Morgul et al., 2020; Field et al., 2021).

In addition, we investigated the subjects' fatigue related to restrictive measures using the *Lockdown Fatigue Scale* (LFS: Labrague and Ballad, 2020), which has been recently designed to assess exhaustion during quarantine due to the COVID- 19 pandemic. The LFS consists of 10 items concerning the psychological effects of lockdown, such as mood deflection, attentional deficits, and possible somatization (i.e., weakness, headache). Subjects are asked how often they experience those effects during home confinement. Each item is scored on a Likert scale that ranges from 1 (never) to 5 (always). This instrument allows the detection of four different levels of fatigue: low (1–12), mild (13–25), moderate (26–37), and severe (38–50).

DATA ANALYSES: Principal Component Analyses

T0 data were examined in order to investigate whether handgrip strength and walking speed could be predicted by a combination of variables concerning cognitive performance, psychological status, and physical comorbidity. In our analyses, only grip strength and walking speed were taken into consideration because: (a) their values presented more variance, not being dichotomous (presence/absence); and (b) they are more related to cognitive functioning – particularly concerning executive control (Hooghiemstra et al., 2017) – and mood changes

(Gordon et al., 2019; Brooks et al., 2020). To this purpose, in a preliminary data-reduction stage, two Principal Component Analyses (PCA) were used to unveil superordinate factors transcending: (a) the single scores of cognitive functioning; and (b) the single scales of psychological status. The first PCA was carried out on cognitive tasks, while the second included the scales used to assess possible mood changes in terms of depression (BDI), apathy (AES), anxiety (HARS), disinhibition (DIS-S), and hypomania (MAS). We retained the components with eigenvalue >0.70 (Jolliffe, 1972), using an orthogonal rotation (Varimax) to facilitate their interpretation. Subsequently, two multiple regression models were used to estimate the contribution of the resulting "cognitive" and "psychological" factors (independent variables), in explaining variability in grip strength and gait speed (adjusted for gender/Body Mass Index and for gender/height, respectively). Then, the "cognitive" and "psychological" factors associated with a significant effect were modeled in additional multiple regressions including grip strength and gait speed as dependent variables, and comorbidity, age, and education as predictors.

Based on the outcome of these analyses, we assessed a moderate-mediation model to investigate the direction of the relationship among the factors predicting lockdown pandemic fatigue. Specifically, a moderate mediation, also known as conditional indirect effects, occurs when the effect of the independent variable "TMT-A" on the outcome variable "LFS" via the mediating variable "BDI" differs according to the levels of the moderating variable "gait speed."

DATA ANALYSES: Moderate-Mediation Model

We tested a moderate-mediation model to assess the hypothesis that: (a) depression at T0 mediates the negative relationship between attentional/executive resources (as tracked by TMT-A performance) at T0 and lockdown-fatigue scale at T3; and (b) this indirect effect is conditional on a moderating variable represented by frailty (as tracked by walking speed). Age, gender, and educational level were modeled as nuisance variables. We used the PROCESS macro (v.3.5) for SPSS (IBM, v.23) to test Hayes's (2017) model 7 (moderated mediation), after checking for the assumptions concerning the lack of outliers (based on Mahalanobis distance), the normal distribution of the residuals (Lilliefors, $p > 0.05$), multicollinearity (maximum variance inflation factor = 1.31; minimum tolerance = 0.763), independence of residuals (Durbin-Watson = 2.184), homoscedasticity (Breusch-Pagan test, $p > 0.05$). Our hypothesis concerning the moderation of mediated effects was tested through conditional process analysis based on Ordinary Least Squares (OLS) regression, using bootstrapping resampling (50,000 samples) to generate confidence intervals for direct and mediated effects, as well as for an index of moderated-mediation. Interaction variables were centered (to a mean of 0) before entering the analyses, and the Johnson and Neyman's (1936) approach was used to compute the range of significance and

simple slopes for the interaction analyses, which were assessed 1 standard deviation below and above the mean. The statistical threshold was set at $p < 0.05$ (two-tailed).

2.1.4. Results

T0 Main Results

The mean scores obtained at T0 on global cognitive tests and behavioral scales are reported in *Table 2.1.1*.

Table 2.1.1. Demographic and neuropsychological characteristics (T0).

	N	M	SD	cut-off
Demographic characteristics				
Subjects	81			
Gender [Male/Female]	17/64			
Age [years]		70.15	6.37	
Education [years]		12.41	3.05	
Neuropsychological assessment				
Mini Mental State Examination		28.95	1.05	≥23.8
Addenbrooke's Cognitive Examination – Revised		91.68	4.89	≥79 (<75 years old); ≥60 (>75 years old)
Montreal Cognitive Assessment		24.21	2.87	≥17.363
Rey Memory Test - 15 instant words		42.16	9.11	≥ 28.53
Rey Memory Test - 15 delayed words		8.54	2.95	≥ 4.69
Babcock Short Story recall test		16.93	4.45	≥ 8
Digit span forward		6.07	1.12	≥ 4.25
Corsi Test		5.07	0.97	≥ 3.75
Phonemic verbal fluency		39.57	10.89	≥ 17.35
Semantic verbal fluency		25.00	5.27	≥ 7.25
Token Test		32.67	2.56	≤ 29
Aachener Aphasie Test		115.63	2.56	≥ 106
Coloured Progressive Matrices-36		30.81	4.69	≥ 18.96
Attentional Matrices		48.19	6.85	≥ 30
Coping design - without programming elements		10.32	1.25	≥ 7.18
Coping design - with programming elements		68.11	2.02	≥ 61.85
Trail Making Test-part A		42.36	12.73	≤ 94
Trail Making Test-part B		105.49	40.81	≤ 283
Trail Making Test B-A		63.14	34.90	≤ 187
Neuropsychiatric assessment				
Apathy Evaluation Scale		3.00	3.66	≤ 14
Beck Depression Inventory		8.53	5.63	≤ 9
Disinhibition Scale		2.91	2.83	≤ 16.9
Hamilton Rating Scale for anxiety		5.83	4.44	≤ 14
Mania Scale		2.40	2.65	≤ 15
Frailty and functional assessment				
CIRS - severity index		1.29	0.20	
CIRS - comorbidity index		0.93	0.91	

Note: N= number. M= mean. SD= standard deviation. CIRS= Cumulative Illness Rating Scale.

Even if the MMSE scores did not suggest the presence of MCI (i.e., O'Bryant et al., 2008) and the participants did not report subjective cognitive decline, their performance was below the reference cut-off value on some tests. In particular, on: MoCA (2.5%), Attentional matrices

(1%), Copy design with programming elements (1%), Rey memory test instant recall (1%), Delayed recall (4%); Short story recall (1%), Digit span (4%); Corsi test (1%), and the Phonetic fluency test (4%). Although some deficits were found on neuropsychological tests, the percentages of under cut-off scores are consistent with the margin of error on tests in the normative population. Moreover, considering the behavioral scales, the subjects presented mood changes in terms of depression (BDI = 39%) and states of anxiety (HARS = 4%).

According to Fried criteria, 63% of the sample was robust, 34.5% pre-frail, and only 2.5% frail. Significantly, these subjects presented a decrease in handgrip strength and walking speed (29.6 and 6.1%, respectively).

As detailed above, a PCA led to reduce the initial dataset of cognitive scores (10 cognitive tests) to 5 factors explaining 82.8% of their variance [*Table 2.1.2*]: (1) Attention/Executive, which refers to attention and executive functions, in term of cognitive set- shifting, assessed by the attentional matrices, and TMT-A, TMT- B; (2) Memory, represented by Short Story Recall (immediate and delayed recall); (3) Visual-Constructive, which refers to visuo-constructive abilities and abstract-non-verbal reasoning, assessed by Design Copying (with and without programming elements) and CPM-36; (4) Language, represented by AAT; (5) Fluency, represented by the Phonemic Verbal Fluency.

Table 2.1.2. Pattern matrix for the principal components analysis – cognitive factors (T0).

Cognitive factors	Factor				
	1	2	3	4	5
Attention					
Attentional Matrices	**.768**	.311	.231	.226	- .152
Trail Making Test-A	**.873**	.009	.085	- .067	.294
Trail Making Test-B	**.559**	.492	.104	.097	.443
Language					
Aachner Aphasia Test	.071	.133	.073	**.960**	.158
Memory					
Short story recall - instant recall	.030	**.915**	.196	.051	- .009
Short story recall - delayed recall	.239	**.880**	.126	.135	.126
Problem Solving					
Coloured Progressive Matrices-36	.376	.406	**.541**	.069	.372
Visuospatial abilities					
Copy design - without programming elements	.374	.026	**.716**	.138	.183
Copy design - with programming elements	- .031	.219	**.838**	- .006	.031
Verbal fluency					
Phonemic fluency	.124	.057	.162	.156	**.904**

Note: Factor loadings > 0.50 are expressed in bold type.

We used the same approach to reduce the 5 scales of psychological status to 2 factors explaining 74.3% of their variance [*Table 2.1.3*]: (1) Mania-disinhibition, measured with MAS, DIS-S; and (2) Depression-apathy-anxiety, assessed by BDI, HARS, AES.

Table 2.1.3. Pattern matrix for the principal components analysis – psychological factors (T0).

Psychological factors	Factor	
	1	2
Beck Depression Inventory	− .102	**.790**
Hamilton Rating Scale for anxiety	.418	.698
Mania Scale	**.946**	− .128
Apathy Evaluation Scale	.093	**.774**
Disinhibition Scale	**.890**	.319

Note: Factor loadings > 0.50 are expressed in bold type.

Subsequently, the contribution of these components was estimated in order to explain the variability of the crucial determinants of Fried's phenotypic model. When testing the predictors of grip strength, a significant model (p = 0.0051) showed that "cognitive" and "psychological" status explained 13% of the variance. In particular, increased grip strength reflected: (a) an increase of the Attention/Executive performance FACTOR 1-on PCA 1 (p = 0.0228); and (b) a decrease of "depression-apathy-anxiety," FACTOR 2-on PCA 2 (p = 0.01006). There was no multicollinearity among explanatory variables (maximum variance inflation factor: VIF = 1.004), and the residuals were normally distributed (Kolmogorov–Smirnov test: K-S = 0.7795, p > 0.2). Moreover, 15% of the variance in gait speed (p = 0.0015) was also explained by Attention/Executive performance FACTOR 1-on PCA 1 (p = 0.0046), and depression-apathy-anxiety FACTOR 2-on PCA 2 (p = 0.0100). There was no multicollinearity among explanatory variables (maximum VIF = 1.004), and the residuals were normally distributed (K-S = 0.05775, p > 0.2). None of the other cognitive or psychological factors was significantly associated with handgrip strength or walking speed. To refine this finding, the contribution of Attention/Executive and depression-apathy-anxiety factors to grip strength and gait speed was assessed while taking into account age, education, and comorbidity (in terms of CIRS). In line with the above results, a significant model showed that 10% of the variance in grip strength (r^2 = 0.10395, p = 0.0051) was explained by the Attention/Executive performance FACTOR 1- on PCA 1 (p = 0.0229), and depression-apathy-anxiety FACTOR 2-on PCA 2 (p = 0.0100). There was no multicollinearity among explanatory variables (maximum VIF = 1.37), and the residuals were normally distributed (K-S = 0.07795, p > 0.2). Moreover, a significant model showed that 13% of the variance in gait speed (r^2 = 0.1315, p = 0.0015) was explained by the same factors: Attention/Executive performance FACTOR 1-on PCA 1 (p = 0.0046) and depression-apathy-anxiety FACTOR 2-on PCA 2 (p = 0.0100). There was no multicollinearity among explanatory variables (maximum VIF = 1.37), and the residuals were normally distributed (K-S = 0.05774, p > 0.2).

T1 Main Results

The subjects' socio-demographic characteristics, most reliable sources of information, percentages on the use of protective devices, and changes in daily life habits are shown in *Table 2.1.4*.

Table 2.1.4. Socio-demographic characteristics, pandemic-related information, and changes in habits of the study population at T1.

	N	%	M	SD	improve-ment	simila-rity	worse-ning
Socio-demographic characteristics							
Subjects	50						
Gender [M/F]	10/40						
Age [years]			70.02	5.69			
Education [years]			12.84	2.76			
Housing status [single/cohabitant]	19/31						
Information pandemic-related							
Health conditions							
symptoms COVID-19 related		18%					
medical examination		8%					
nasal swap		2%					
positivity to COVID-19		0%					
Main preventive measures							
using face masks		96%					
wearing latex gloves		90%					
keeping social safety distance:1.5-2 metres		96%					
washing hands (rubbing with soap for at least 60 seconds)		96%					
avoiding crowded places		84%					
Sources of information							
newscast		90%					
newspaper		60%					
websites and social networks		6%					
television programs		38%					
other		12%					
Changes in habits							
cognitively stimulating activities					0%	90%	10%
physical activity					0%	30%	70%
diet					2%	84%	12%
social interactions					0%	6%	94%
sleep					12%	56%	32%
smoking, drugs, and alcohol					0%	100%	0%

Note: N= number. M= mean. SD= standard deviation. M= male. F= female.

T2 Main Results

Table 2.1.5. reports the subjects' mean scores on the global cognitive tasks and their socioeconomic status (SES). Specifically, they performed well on all cognitive tests, without any scores under the cut-off, on ACE-R, MMSE, and MoCA.

On mood assessment scales, they obtained normal scores on DIS-S and MAS; on the other hand, there were under cut-off values on BDI (28%), AES (20%), and HARS (10%).

With regard to their SES, according to the Hollingshead Index (HI) 8% of the subjects fell into the highest social stratum, 48% in the second, 34% in the third, 10% in the fourth, and none of them in the lowest one.

Table 2.1.5. Follow-up: socio-demographic characteristics and neuropsychological assessment (T2).

	N	M	SD	cut-off	
Socio-demographic characteristics					
Subjects	50				
Gender [Male/Female]	10/40				
Age [years]		70.04	5.70		
Education [years]		12.84	2.76		
SES (Hollingshead Index)		41.62	9.14		
social stratum 66-55		8%			
social stratum 54-40		48%			
social stratum 39-30		34%			
social stratum 29-20		10%			
social stratum 19-8		0%			
Neuropsychological assessment					
Mini-Mental State Examination		29.44	0.67	≥23.8	
Addenbrooke's Cognitive Examination – Revised version		95.04	3.37	≥79 (<75 years old);	≥60 (>75 years old)
Montreal Cognitive Assessment		27.02	2.61	≥17.363	
Neuropsychiatric assessment					
Apathy Evaluation Scale		8.84	6.25	≤ 14	
Beck Depression Inventory		7.70	6.10	≤ 9	
Disinhibition Scale		2.88	2.35	≤ 16.9	
Hamilton Rating Scale for anxiety		6.64	5.45	≤ 14	
Mania Scale		1.78	1.72	≤ 15	

Note: N, number; M, mean; SES, Socio-economic status; SD, standard deviation. Wherever there is a normative value, the cut-off scores are given in the statistical normal direction.

T3 Main Results

The scores obtained at T3 on LFS, BDI, and HARS are reported in *Table 2.1.6*.

Although results on psychological scales indicated mean scores in the normal range, 28% of subjects showed mood deflections in terms of depression (BDI) and 18% in terms of anxiety (HARS). Regarding LFS scores, 10% of the sample fell into low level of fatigue, 56% into mild level, 30% presented moderate fatigue, while 4% reported severe lockdown fatigue.

In order to test for possible differences concerning the degree of lockdown fatigue, the subjects were divided into two groups according to the median scores: low-mild level of fatigue (17 females and 8 males) and moderate-severe level of fatigue (23 females and 2 males). Interestingly, 62.5% of the pre-frail subjects fell into the moderate-severe fatigue group.

Considering these two groups, the t-test showed a significant difference in terms of mood changes. Specifically, subjects feeling more fatigued due to the lockdown presented higher levels of anxiety, in terms of HARS scores (t-value = 5.27110; p = 0.000003), and depression as assessed by BDI (t-value = 5.46071; p = 0.000002).

Table 2.1.6. Follow-up: psychological assessment (T3).

	M ± SD (N=50)	**Low-Mild fatigue (N=25)**	**Moderate-Severe fatigue (N=25)**	***t*- scores**	***P*-values**
LFS	23.18 ± 8.40	16.68 ± 3.40	29.68 ± 6.72		
BDI	8.32 ± 7.24	3.84 ± 2.82	12.80 ± 7.70	5.46071	0.000002
HARS	7.86 ± 6.71	3.80 ± 3.30	11.92 ± 6.96	5.27110	0.000003

Note. M= mean. SD= standard deviation. N= number. LFS= Lockdown Fatigue Scale. BDI= Beck Depression Inventory. HARS= Hamilton Rating Scale for anxiety.
The subjects were divided into two groups with reference to LFS scores (low-mild and moderate-severe level of fatigue) and a comparison was made on mood changes between the two groups. Significant results are expressed in *t*-scores and *P*-values.

On the basis of these findings, we assessed our hypotheses regarding the role of specific cognitive, physical, and psychological aspects in the emergence of lockdown fatigue.

A significant moderated-mediation model highlighted the interacting effects of psychomotor speed, gait speed, and depression at T0 on lockdown fatigue scale at T3 (see *Table 2.1.7*). Indeed, a conditional process analysis showed that the effect of TMT-A performance on lockdown fatigue at T3 was mediated by depression, but this mediation was moderated by gait speed. Namely, a significant interaction between low psychomotor speed (TMT-A) and low gait speed (i.e., moderation) was associated with stronger mood deflection. Therefore, only at low gait speed the strength of depressive state mediated the enhancing effect of low psychomotor speed on lockdown fatigue.

Table 2.1.7. Moderated-mediation analysis for predicting lockdown fatigue scale at T3 based on TMT-A, BDI, and gait speed at T0.

Model Summary						
Outcome variable: Lockdown Fatigue Scale at T3						
R	R^2	MSE	F	df1	df2	p
0.6297	0.3965	48.4091	7.0476	5	44	0.0001
Model						
	coeff	se	t	p	LLCI	ULCI
TMT-A at T0	-0.1549	0.1099	-1.4097	0.1656	-0.3394	0.0297
BDI at T0	0.5074	0.1884	2.6924	0.01	0.1907	0.824
Age	-0.3582	0.2456	-1.4584	0.1518	-0.7708	0.0545
Gender	4.4119	1.9601	2.2508	0.0294	1.1184	7.7054
Educational level	-0.2855	0.34	-0.8396	0.4057	-0.8567	0.2858
Direct effect of TMT-A at T0 on Lockdown Fatigue Scale at T3						
	Effect	se	t	p	LLCI	ULCI
TMT-A at T0	-0.1549	0.1099	-1.4097	0.1656	-0.3394	0.0297
Conditional indirect effects of TMT-A at T0 on Lockdown Fatigue Scale at T3						
Indirect effect: TMTa-T0 → BDI-TO → Lockdown fatigue-T3						
	Effect	BootSE	BootLLCI	BootULCI		
Gait speed at T0						
-1 SD	0.0612	0.0603	-0.0441	0.1483		
0	-0.0249	0.0419	-0.1099	0.0232		
+ 1 SD	-0.111	0.0739	-0.2491	-0.0142		
Index of moderated mediation						
	Index	BootSE	BootLLCI	BootULCI		
Gait speed at T0						
	-0.0861	0.0529	-0.1755	-0.0076		

Note: MSE=Mean Squared Error; df=degrees of freedom; LLCI=lower level of confidence interval; ULCI=upper level of confidence interval; coeff=coefficient; se= standard error. SD=standard deviation. Data are reported with coefficients and a 95% confidence intervals.

2.1.5. Discussion

To the best of our knowledge, this is the first study in the literature monitoring healthy cognitive aging subjects before and after very restrictive COVID-19 containment measures. We analyzed the impact of the lockdown fatigue in relation to pre-existing aspects of physical frailty, cognitive functioning, and mood deflections. Indeed, T0 data allowed us to better study the associations between neuropsychological variables assessed before the pandemic and the subsequent home confinement.

Although most of the participants were robust at T0, some of them were pre-frail or frail. Only a few minor neuropsychological deficits were observed in cognitive functioning. However, mood changes, particularly in terms of depression, were present in about 40% of the population.

We considered the association among the main characteristics of frailty and cognitive and behavioral aspects in a socially active population with a medium-high SES.

In the first place, the contribution of "cognitive" and "psychological" factors was estimated, resulting from PCAs, in order to explain variability in grip strength and gait speed. The choice of these frailty determinants, associated with cognitive changes, was also supported by studies on community-dwelling people. In particular, Robertson et al. (2014) showed that individuals with slow gait and weak grip had lower scores on executive functions tests. Slow gait speed also showed an important effect on attention and psychomotor speed. Asthenia was associated with global cognition, while low physical activity and unintentional weight loss were not independently associated with cognitive domains. Moreover, a small number of studies on patients with functional and/or cognitive impairment, due to major neurocognitive disorder, highlighted a relationship between a reduction in gait speed or grip strength and impaired attention and executive dysfunction (i.e., Hooghiemstra et al., 2017). Nevertheless, executive-attentional functions mediated by the prefrontal cortex were also related to gait speed in physical frailty (Amboni et al., 2013).

Mood changes – particularly depression and anxiety – are not only common in older people but they are also significant risk factors for frailty. For instance, in a cross-sectional study on community-dwelling older people, Ní Mhaoláin et al. (2012) found that higher levels of depression and anxiety were more prevalent in pre-frail and frail subjects than in robust ones. In addition, they showed a significantly higher probability of anxiety and depressive symptoms. Some authors reported how depression could be considered not only a consequence but also a risk factor for frailty (i.e., Robertson et al., 2013). Particularly, a decrease in handgrip strength was associated with an increased depressive symptomatology (Brooks et al., 2020), which seemed also to be a predictor of slow walking speed (Staples et al., 2020). Another study showed that higher levels of depression and anxiety were associated with a slowdown in gait speed in subjects aged 65 and older with atrial fibrillation (Marino et al., 2019). On the other hand, anxiety seemed to be inversely related to grip strength in the older population (Gordon et al., 2019).

Our results showed how increased grip strength reflects better Attention/Executive performances and lower mood changes, in terms of depression, apathy, and anxiety. In the same direction, a variance in gait speed was also explained by Attention/Executive performance and depression-apathy-anxiety mood changes. Significantly, the contribution of these factors was not explained by age, comorbidity, or educational level.

T1 results showed that almost all subjects took the precautions recommended by the Italian Ministry of Health (Ministero della Salute, 2020) to prevent SARS-CoV-2 infection. It is noteworthy that the majority of our sample (90%) belongs to the middle-high social class, according to HI. Combined with a high level of education, such aspect highlights the peculiarity

of this population, characterized by social resources, which allowed them to take the necessary precautions to avoid the risk of contagion.

Our T2 results showed no cognitive decline nor mood deflection. However, some under cut-off scores were found in terms of depression, apathy, and anxiety. These aspects align with previous studies on the general population during the COVID-19 pandemic (Prati and Mancini, 2021).

With regard to the subsequent lockdown (T3), which occurred from December 2020 to January 2021, subjects complaining of higher lockdown fatigue exhibited increased levels of depression and anxiety than those with lower fatigue.

These results are consistent with another study on COVID- 19 lockdown fatigue (Field et al., 2021), in which the fatigue was related to depression and anxiety but also to sleep disturbance, increased posttraumatic stress symptoms, and a worsened lifestyle (e.g., decreased physical activity, fewer experiences of recreational activities, fewer interactions with others, and more time spent gaming and chatting about the virus). In particular, psychological factors, such as depression, sleep disturbance, and anxiety, explained 51% of the variance of lockdown fatigue (Field et al., 2021).

The mechanism related to physical, behavioral and cognitive factors, and LFS is still unknown. Therefore, we used a moderate-mediation model to explore the complex pathways leading to the onset of lockdown pandemic fatigue. Specifically, we examined the potential mediating effect of depression and attention, and the moderated effect of gait speed in this well-established association. We found a two-way interaction (moderation) between TMT-A and gait speed in influencing the mediator BDI; thus, when walking speed is below the mean, limited psychomotor speed resources are associated with greater depression. Consequently, for above-average slow walk values, the depressive state mediates the effect of limited psychomotor speed resources on subsequent fatigue. Some studies have highlighted how not only attention performances are impaired in normal aging (e.g., Periáñez et al., 2007), but also how usual walking speed is associated with slower test performance on TMT-A in MCI patients (Knapstad et al., 2019). The association between depression and psychomotor speed is already well-known. Patients with major depressive disorders aged 60 years and older showed worse attention abilities, especially when frail (Potter et al., 2016).

Concerning the lockdown pandemic fatigue, higher scores of depression and everyday fatigue were found in the Polish population during COVID-19 home confinement (Bartoszek et al., 2020). Moreover, a previous study on social distancing issues related to the COVID-19 pandemic in the general population (aged 18 years and older) showed an association between exhaustion and depressive symptoms (Seiter and Curran, 2021). Indeed, increased stress levels

due to pandemic uncertainty and restrictions could trigger depressive symptoms and greater fatigue burden (Schrack et al., 2020).

A recent study investigated the psychological effects of lockdown on cognitive functions showing general deterioration, in particular regarding concentration and attention (Fiorenzato et al., 2021). Difficulties in keeping focused and concentrated could lead to mental fatigue and, consequently, to greater feelings of lockdown pandemic fatigue in older adults.

2.1.6. Conclusion

To our knowledge, this is the first study examining the association among specific cognitive, physical, behavioral, and functional characteristics before, during, and after restrictive lockdown measures in cognitively normal aging subjects. It is important to underline how UNITRE participants, with mild neuropsychological and physical alterations, represent an optimal reference sample to implement possible primary prevention pathways on older adults.

Our results highlight that: (a) physical functions, executive attention, and mood changes can play an important role in the current COVID-19 pandemic; (b) the subjects showing moderate-severe fatigue reported more depressive and anxiety issues than subjects with low-mild fatigue; (c) cognitive functioning, in terms of psychomotor speed, seems also to play an important role in the perception of fatigue due to COVID-19 restrictive measures.

Since lockdown fatigue is related to mood deflections, such as depression and anxiety, it would be useful to study this aspect more in depth, as well as other COVID-19 related psychological issues (Field et al., 2021).

Limitation Section

Although this novel study was carefully designed and achieved its aims, the sample size, set at 50 participants, may be considered a critical aspect.

Furthermore, because of the COVID-19 containment measures in place, it was not possible to perform a proper face-to-face neuropsychogeriatric assessment, as in T0. The restrictions led us to select the most suitable neuropsychological tests for remote administration in line with our aims. To address any potential critical issue related to the remote administration of neuropsychological tests, we adopted ad hoc tools for screen sharing in video calls (e.g., MOCA-Blind test).

2.1.7. References

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2.2. The Role of Neuropsychological Factors in Percieved Threat of SARS-CoV-2 in Healthy Aging

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2.2.1. Abstract

The COVID-19 pandemic is known to increase older adults' vulnerability to adverse outcomes. Alongside increased physical frailty, anxiety symptoms associated with the risk of SARS- CoV-2 contagion appear to represent its most prominent 'sequelae'. The attentional and linguistic resources required for decoding virus-related information may also influence the perceived threat of contagion. However, the possible role of neuropsychogeriatric factors on the latter dimension has never been assessed in a longitudinal study on the older population. To fill this gap, 50 healthy cognitively preserved older adults underwent a neuropsychological and physical frailty assessment before the pandemic (T0). Subsequently, they agreed to be interviewed and re-assessed during the lockdown (T1) and immediately after it (T2) through a longitudinal one-year study. Perceived threat of SARS-CoV-2 at T2 was predicted both by baseline anxiety and frailty scores, and by decreased performance in information processing speed and language comprehension tests. While confirming the joint role of frailty and anxiety, a moderation/interaction model showed that each of them was sufficient, at its highest level, to support the maximum degree of perceived threat of contagion. The contribution of neuropsychological factors to perceived threat of SARS-CoV-2 highlights their importance of tailoring information campaigns addressed to older people.

2.2.2. Introduction

The SARS-CoV-2 is an emerging infectious disease that causes serious threats to the physical and mental health of the population.

The behavior of the general population, or of specific at-risk groups, such as aging subjects, can play an important role in both the spread and control of infectious diseases. The older population with a frailty status, which is characterized by a clinical history of polypathology, had higher mortality due to SARS-CoV-2 (Onder et al., 2020; Zhang et al., 2021). This increased susceptibility to infection is probably driven not only by comorbidity but also by reduced immunity due to the physiology of ageing (Gavazzi and Krause, 2002).

Lockdown measures play a key role in containing SARS-CoV-2 infection. However, in the older population, aspects associated with isolation and social distancing are related to increased cognitive decline (Santini et al., 2020). As a result of COVID-19 containment measures, older adults may experience physical and other mental health problems (Luchetti et al., 2020), such as depressive mood and anxiety-related fear of contagion (Gokseven et al., 2021). In line with these aspects, a recent study (Amanzio et al., 2021a) highlighted how both cognitive and physical issues related to the COVID-19 pandemic may play a key role in the novel "lockdown fatigue". In particular, the authors found that pandemic fatigue was associated with decreased processing and walking speed and with mood changes in terms of depression.

While all these conditions represent the likely consequences of a pandemic, the variables driving modifications of behavior patterns – particularly concerning contagion prevention – also need to be considered and analyzed. One of the factors that can influence the willingness and motivation to adopt precautionary behavior is the perception of risk (Brewer et al., 2007; de Zwart et al., 2009), i.e., the perceived personal vulnerability or likelihood of contracting a disease. Feeling vulnerable, together with realizing disease severity, can be jointly considered as "perceived threat". People are expected to experience the highest perceived SARS-CoV-2 threat if they think that a likely infection will have serious health consequences. Indeed, people who are more vulnerable – such as older adults – present a higher level of fear (Han et al., 2021) and anxiety (Bergman et al., 2020) related to COVID-19.

On the other hand, some studies concerning outbreaks, such as the H5N1 and the current COVID-19 pandemic, found a lower risk perception in older adults than in younger people (Fielding et al., 2005; Pasion et al., 2020). A recent study reported a lower perceived risk of being infected by COVID-19 in the oldest-old (75 years and older) than in the youngest-old (60–69 years) and middle-old (70–75 years) groups (Guastafierro et al., 2021). According to the authors, this result might reflect an age-related cognitive decline, particularly concerning

executive control functioning, as risk-taking and risk perception are associated with monitoring abilities (Capone et al., 2016). In light of this evidence, a reduction in perceived risk may lead older adults – who are more prone to unfavorable outcomes – to underestimate the importance of proper precautions to avoid COVID-19 infection.

To date, however, no longitudinal studies have analyzed the association among risk threat perception of SARS-CoV-2 contagion, physical-health status, cognitive functions, and mood deflections in cognitively preserved older adults during home confinement. These aspects should be further emphasized as personalized psychological interventions are found to play an important role in primary prevention and psychological well-being by reducing the negative impact on physical status, cognitive function, and mood disorders.

To fill this gap, we investigated the relationships among perceived risk of SARS-CoV-2 contagion, physical-cognitive functioning, and mood changes in cognitively preserved older adults, engaged as volunteers, and characterized by the presence of two or more age-related diseases (polypathology) and subsequent pharmacotherapy (Masnoon et al., 2017). The availability of pre-pandemic data (T0) of 50 subjects allowed us to investigate the extent to which perceived threat of SARS-CoV-2 was predicted by cognitive functioning, psychological state, and frailty determinants assessed with the phenotypic model (Fried et al., 2001), and by their interaction.

To the best of our knowledge, this is the first longitudinal study investigating: (a) the neuropsychological profile and frailty determinants of healthy older adults before the pandemic; (b) the perceived threat of SARS-CoV-2 contagion during the lockdown; and (c) whether the latter reflects the interacting effects of baseline variables concerning cognitive, psychological, and/or physical status.

Since perceived threat has been previously related to psychological issues, such as anxiety (Shahzad et al., 2020), and the latter may influence the occurrence of attentional and interpretation threat biases (Beard, 2011; Wieser and Keil, 2020), also related to information about contagion, we expect that both psychological and cognitive factors might be useful in predicting perceived risk of contagion in our sample.

2.2.3. Materials and Methods

During the academic year 2018–2019, the creation of an active and healthy aging laboratory allowed us to carry out an in-depth neuropsychological assessment on members of the UNITRE-TO. Before the pandemic onset, these subjects attended specific teaching modules on cognition, physical exercise, nutrition, and social inclusion to achieve active and healthy aging. Among

them, 81 agreed to participate in a longitudinal study with an expected duration of about one year. The subjects were aged 60 years or older in order to be classified as "older adults" (WHO, 2021), and fifty of them (40 females, age range 60–80) were selected due to the presence of polypathology and related pharmacotherapy (Masnoon et al., 2017). However, the subjects were not taking psychotropic medications that could affect their cognitive functioning. Moreover, they did not complain of a subjective cognitive decline (Jessen et al., 2020) and had not gone through any medical or neurological examination for suspected MCI (Petersen and Negash, 2008). All participants were involved in social activities and characterized by functional autonomy. They performed an initial neuropsychogeriatric assessment (T0) aimed to detect any possible dysfunctions. We analyzed their cognitive functioning, physical health, and mood changes in terms of depression and anxiety.

During the pandemic, due to preventive measures, the subjects agreed to participate in the study remotely. They went through a semi-structured interview (T1) and a neuropsychological evaluation (T2) to identify any possible below cut-off scores.

The study was performed in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the University of Turin before the pandemic (Prot. n. 10038) and after it (Prot. n. 151786). All participants gave written informed consent prior to the study.

Neuropsychogeriatric Assessment at the Baseline (T0)

From April to October 2019, all participants went through an extensive neuropsychi- atric evaluation characterized by cognitive, functional, and behavioral tests. To prevent fatigue and lack of adherence to the tasks, three experienced neuropsychologists assessed the subjects in two different sessions, lasting about 90 minutes, held one day apart.

The Cumulative Illness Rating Scale (*CIRS*: Linn et al., 1968) was used to collect information on clinical history, symptoms, signs, and chronic diseases.

We assessed global cognitive functioning adopting Addenbrooke's Cognitive Examination—Revised version (*ACE-R*: Mioshi et al., 2006) and the Montreal Cognitive Assessment (*MoCA*: Conti et al., 2015). Subsequently, we analyzed different cognitive domains: attention (*attentional matrices*: Spinnler and Tognoni, 1987), language and fluencies (*Token Test—TT*: De Renzi and Vignolo, 1962; *Phonemic and Semantic Fluency*: Spinnler and Tognoni; *Naming subtest of Aachener Aphasie Test Aphasia Test—AAT*: De Bleser et al., 1987), short-term memory (*Digit Span* and *Corsi Test*: Spinnler and Tognoni, 1987), episodic long-term memory (*Rey Memory Test* and *Short Story Recall*: Spinnler and Tognoni, 1987), problem-solving (*Raven's Colored Progressive Matrices*— CPM-36: Spinnler and Tognoni, 1987), visuo-constructive abilities

(*Copy Design*: Carlesimo et al., 1996), and executive functions (*Trail Making Test—TMT*, Giovagnoli et al., 1996).

The Hamilton Rating Scale for Anxiety (*HARS*: Hamilton, 1969) and the Beck Depression Inventory (*BDI*: Beck et al., 1988) were used to assess anxiety and depression, respectively.

To estimate a physical frailty status, we adopted Fried's phenotypic model (Fried et al., 2001). This approach defines frailty as a pathophysiological syndrome characterized by five criteria: (a) unintentional weight loss; (b) poor grip strength; (c) self-reported exhaustion; (d) slow walking speed; and (e) low level of physical activity. If one or two determinants are present, we can identify a pre-frail person; if three or more, a frail one.

Semi-Structured Interviews at T1

During the first Italian lockdown, from April to May 2020, all subjects previously recruited for the neuropsychological assessment at T0 were asked for their availability to participate in this study. After agreeing, the participants went through a semi-structured interview to get information on their health conditions (i.e., symptoms related to SARS-CoV-2 infection and possible results of medical consultations, nasal swabs, or serological examinations), housing status, and the acceptance of the preventive measures to avoid contagion on the recommendations of the Italian Ministry of Health. Before ending the interview, the subjects gave their availability for a new neuropsychological assessment.

Neuropsychological Assessment at T2

This third phase was carried out from May to July 2020, during the Italian "phase 2" of quarantine, when restrictive measures introduced during the first lockdown were progressively relaxing. The neuropsychological assessment was as close as possible to T0 but characterized by limitations posed by a remote evaluation via video call.

We assessed cognitive functioning using ACE-R and Mini Mental State Examination (*MMSE*: Folstein et al., 1975). To overcome visual issues, we presented visuo-spatial subsections in screen-sharing mode. In addition, we adopted the *MoCA-Blind* (Wittich et al., 2010). This blind version of the test was originally created for patients with visual disorders. As indicated on the official MoCA website (Nasreddine, 2020), it is scored out of 22 and converted back to 30 as the original version.

BDI and HARS were used to assess possible mood changes. Finally, to analyze the socioeconomic status of the participants, we adopted the Four Factor Index of Social Status. Based on the educational level and the type of job of family members, this index (*Hollingshead index*, HI) was calculated considering the last employment of these retired people. The HI score ranges from 8 to 66 points and identifies 5 different social strata (Hollingshead, 1975, 2011).

To detect participants' perceived risk of contracting SARS-CoV-2, we used a modified version of the *Risk Perception of Infectious Diseases Questionnaire* (Brug et al., 2004; Commodari, 2017; de Zwart et al., 2009). This tool was based on a previously developed SARS risk perception questionnaire (Brug et al., 2004) and focused on risk perception and perceived severity of SARS, and other (infectious) diseases (i.e., flu; Commodari, 2017). The questionnaire is divided into 5 sections, requiring participants to report the perceived: (1) severity (i.e., how serious it would be for them to get the disease); (2) vulnerability or personal risk (i.e., how likely they were to contract the disease); (3) comparative risk (i.e., whether they were more or less likely to contract the disease than individuals of their own sex and age); (4) response efficacy (i.e., to what extent they thought people could take effective actions to prevent the onset or contagion of the disease); (5) self-efficacy (i.e., to what extent they considered themselves capable of taking effective actions to prevent the disease onset or contagion). In the original version, some sections (e.g., personal and comparative risk) were assessed on a 5-point Likert scale, while others (e.g., severity) were evaluated on a 10-point scale (de Zwart et al., 2009). In our study, participants were asked to answer on a 10-point Likert-type scale in all sections to uniform the attribution of scores. In line with a previous study (de Zwart et al., 2009), we obtained the "perceived threat" value by multiplying the measures of perceived severity and vulnerability. In the original version, these two categories were measured respectively on 1–10 and 1–5 point scales, with the former being halved to make their values comparable. In the present version, this operation was not performed because the scores of all 5 questionnaire sections were assessed on a 1–10 scale. To normalize the distribution of this new variable, a square root transformation was performed giving a measure of perceived threat on a scale of 1 (low) to 10 (high). In the present study, we have considered only the "perceived threat" section of the Risk Perception of Infectious Diseases Questionnaire. Particularly, we focused our attention on the data concerning the COVID-19 pandemic and a possible emerging new virus. In fact, our aim was to understand the extent to which older adults perceived COVID-19 as threatening in relation to their physical, cognitive, and mental health status. In addition, given the sudden onset of the current pandemic, we wanted to verify whether these aspects, assessed at T0, could affect the perceived threat of the risk of a possible emerging virus.

Data Analyses

At first, we have taken into account baseline physical, cognitive, and mental health status variables (collected at T0), trying to identify those associated with the perceived threat of SARS-CoV-2 infection (assessed at T2). Specifically, we hypothesized that a higher perceived threat of contagion might be related to an increased physical pre-frailty status and anxiety symptoms.

Moreover, from a cognitive perspective, attentional and linguistic resources required for decoding virus-related information may also influence the perceived threat of contagion.

To this end, we first assessed variables that showed a significant linear relationship with the 'Perceived Threat'. The results of the correlation analyses confirmed our initial hypothesis: perceived threat of contagion was associated with higher anxiety (HARS) and higher pre-frailty status. In addition, greater susceptibility to threat perception was associated with lower performance in information processing speed (TMT-A score) and language resources (TT score).

On this basis, we performed two multiple regressions to estimate the extent to which the perceived risk of contracting SARS-CoV-2, or a new virus, was explained by socio-demographic variables (age, gender, education), anxiety (HARS) and frailty status, attentional (TMT-A score) and linguistic comprehension (TT) performance.

A preliminary check of assumptions confirmed the lack of multicollinearity among explanatory variables (maximum variance inflation factors – VIFs = 2.54 and 2.08, respectively), as well as the normal distribution (Kolmogorov–Smirnov tests, $p > 0.2$ in both cases) and independence (Durbin-Watson = 1.851 and 1.891, respectively) of residuals.

Based on the results of multiple regressions, we assessed a moderation model to test interaction between anxiety and frailty on the perceived risk of contracting SARS-CoV-2 (while modeling age, gender, and educational level as nuisance variables). We used the PROCESS macro (v.3.5) for SPSS (v.23, IBM) to test Hayes' (2017) model 1 (moderation), through conditional process analysis based on Ordinary Least Squares (OLS) regression, using bootstrapping resampling (50,000 samples) to generate confidence intervals for direct and moderated effects. Interaction variables were centered (to a mean of 0) before entering the analyses and Johnson and Neyman's (1936) approach was used to compute the range of significance and simple slopes for the interaction analyses, which were assessed 1 standard deviation below and above the mean. The statistical threshold was set at $p < 0.05$ (two-tailed).

2.2.4. Results

T0 Main Results

The mean scores obtained at T0 on cognitive tests and behavioral scales are shown in *Table 2.2.1*. Subjects had a MMSE raw score ≥ 27. Participants performed below the reference cut-off value on some tests: Digit span (4%); Attentional matrices (2%); Phonetic fluency test (2%); Corsi test (2%); Rey memory test instant recall (2%), and delayed recall (2%). However, the percentage of under cut-off scores is consistent with the margin of error in tests administered to

the normative population. Moreover, they displayed mood changes concerning depression (BDI = 28%) and anxiety (HARS = 4%).

According to Fried criteria, 68% and 32% of participants could be classified as robust and pre-frail, respectively. Particularly, the latter presented a decrease in handgrip strength and walking speed (26% and 2%, respectively).

Table 2.2.1. Demographic and neuropsychological characteristics (T0).

	N	M	SD	cut-off
Demographic characteristics				
Subjects	50			
Gender [Male/Female]	10/40			
Age [years]		68.32	5.75	
Education [years]		12.84	2.79	
Neuropsychological assessment				
Mini Mental State Examination		29.12	0.98	≥23.8
Addenbrooke's Cognitive Examination – Revised version		92.80	4.27	≥79 (<75 years old); ≥60 (>75 years old)
Montreal Cognitive Assessment		25.18	2.29	≥17.363
Rey Memory Test - 15 instant words		44.20	8.39	≥ 28.53
Rey Memory Test - 15 delayed words		9.36	2.44	≥ 4.69
Babcock Short Story recall test		18.05	4.15	≥ 8
Digit span forward		6.20	1.05	≥ 4.25
Corsi Test		5.32	0.96	≥ 3.75
Phonemic verbal fluency		41.44	10.99	≥ 17.35
Semantic verbal fluency		26.15	5.21	≥ 7.25
Token Test		33.34	2.07	≤ 29
Aachener Aphasie Test		116.02	2.55	≥ 106
Coloured Progressive Matrices-36		32.26	3.11	≥ 18.96
Attentional Matrices		49.62	6.96	≥ 30
Coping design - without programming elements		10.32	1.22	≥ 7.18
Coping design - with programming elements		68.42	1.59	≥ 61.85
Trail Making Test-part A		39.58	12.01	≤ 94
Trail Making Test-part B		93.04	29.24	≤ 283
Trail Making Test B-A		53.47	25.75	≤ 187
Neuropsychiatric assessment				
Beck Depression Inventory		7.62	5.82	≤ 9
Hamilton Rating Scale for anxiety		5.34	3.94	≤ 14
Functional assessment				
CIRS - severity index		1.25	0.15	
CIRS - comorbidity index		0.80	0.66	

Note: N = number. M = mean. SD = standard deviation. CIRS = Cumulative Illness Rating Scale.

T1 Main Results

The socio-demographic characteristics of the subjects and the percentages on the use of protective devices are reported in *Table 2.2.2*. According to the outcome of semi-structured interviews, 62% of the subjects lived with at least one person (in most cases the spouse), while the remaining 38% lived alone.

Table 2.2.2. Socio-demographic characteristics, pandemic-related information, and changes in habits of the study population at T1.

	N	%	M	SD
Socio-demographic characteristics				
Subjects	50			
Gender [M/F]	10/40			
Age [years]			70.02	5.69
Education [years]			12.84	2.76
Housing status [single/cohabitant]	19/31			
Information pandemic-related				
Health conditions				
symptoms COVID-19 related		18%		
medical examination		8%		
nasal swap		2%		
positivity to COVID-19		0%		
Main preventive measures				
using face masks		96%		
wearing latex gloves		90%		
keeping safety distance		96%		
washing hands		96%		
avoiding crowded places		84%		

Note: N = number. M = mean. SD = standard deviation. M = male. F = female.

Subjects' high awareness of the risk of contagion was confirmed by their compliance with most of the prevention behaviors indicated by the Italian Ministry of Health (Ministero della Salute, 2020) [see *Table 2.2.3*]. In particular, 96% of the participants stated they had used masks, had respected the minimum safety distances, and had often sanitized their hands (with soap and water or disinfectant solutions). Moreover, 90% used latex gloves outside, while 84% avoided crowded places. Furthermore, none of the participants declared to have developed symptoms associated with COVID-19 and none of them was diagnosed with COVID-19 infection or was hospitalized.

Table 2.2.3. Recommendations of the Italian Ministry of Health to contain the spread of coronavirus.

- Wash your hands frequently with soap, and clean surfaces with chlorine or alcohol-based disinfectants.
- Avoid crowded places and keep a distance of at least one metre from others.
- Avoid touching your eyes, nose and mouth.
- Stay at home if you are elderly or have a weakened immune system.
- Avoid handshakes, hugs and sharing bottles and glasses with others.
- Cover mouth and nose with a disposable tissue when you sneeze or cough. If you do not have a tissue, use your bent elbow.
- If you have flu-like symptoms stay at home, do not go to the emergency room or doctor's office, but call your general practitioner, paediatrician, primary care out-of-hours service ("guardia medica") or regional information hotline.

T2 Main Results

Table 2.2.4 reports the socio-economic status (SES) of our sample and the mean scores obtained by the subjects on the cognitive screening test. Specifically, they performed well on all cognitive tests (MMSE, ACE-R, and MoCA Blind). As to mood assessment, there were below cut-off scores on BDI (28%), and HARS (10%). It should be noted that the percentage of subjects with anxiety-related issues had increased from T0 to T2 (from 4% to 10% of the sample) but no differences were found in the percentage of subjects with mood deflection compatible with depression. According to the Hollingshead Index (HI), most of the sample belonged to the medium-high SES (90%). Particularly, 8% of the subjects fell into the highest social stratum, 48% in the second, 34% in the third, 10% in the fourth, and none of them in the lowest one.

Table 2.2.4. Socio-demographic characteristics and neuropsychological assessment (T2).

	N	M	SD	cut-off
Socio-demographic characteristics				
Subjects	50			
Gender [Male/Female]	10/40			
Age [years]		70.04	5.70	
Education [years]		12.84	2.76	
SES (Hollingshead Index)		41.62	9.14	
social stratum 66-55		8%		
social stratum 54-40		48%		
social stratum 39-30		34%		
social stratum 29-20		10%		
social stratum 19-8		0%		
Neuropsychological assessment				
Mini-Mental State Examination		29.44	0.67	≥23.8
Addenbrooke's Cognitive Examination – Revised version		95.04	3.37	≥79 (<75 years old); ≥60 (>75 years old)
Montreal Cognitive Assessment		27.02	2.61	≥17.363
Neuropsychiatric assessment				
Beck Depression Inventory		7.70	6.10	≤ 9
Hamilton Rating Scale for anxiety		6.64	5.45	≤ 14
Perceived Threat assessment				
COVID-19		5.65	1.88	
New Virus		5.01	2.55	

Note: N= number. M= mean. SD= standard deviation. SES= Socioeconomic status.

Analyzing COVID-19 perceived threat as a dependent variable, fifty percent of variability in the perceived risk of contracting SARS-CoV-2 was associated with a combination of measures related to cognitive, psychological, and physical status. Namely, higher risk perception was predicted by: (a) decreased information processing speed (TMT-A score) and linguistic comprehension (TT) performance; (b) increased anxiety on HARS, and frailty status in terms of the phenotypic model (p = 0.000002) [see *Table 2.2.5*].

Table 2.2.5. Multiple linear regression analysis for predicting the perceived threat of SARS-CoV-2 contagion.

Predictors	**B**	**SE**	***t***	***p***	**R-square**	**F (4,45)**	**p**
TMT-A	-0.344	0.106	-3.231	0.002	0.506	11.536	<0.0001
Token Test	-0.330	0.105	-3.145	0.002			
HARS	0.405	0.105	3.839	<0.001			
Frailty	0.269	0.106	2.528	0.015			

Note: B= Regression coefficient. SE= Standard Error. TMT-A= Trail Making Test - part A. HARS= Hamilton Rating Scale for anxiety. The table reports the significant predictors of the perceived threat of SARS-COV-2 based on linear multiple regressions. The statistical values of both the whole model and the single predictors are reported.

Furthermore, analyzing the risk of infection by a 'new virus' as a dependent variable, 40% of the variance in the perceived risk of contracting other (emerging) infectious diseases was also explained by decreased information processing speed (TMT-A score) and linguistic comprehension (TT) performance, and by increased anxiety on HARS (p = 0.00003) [*Table 2.2.6*]. This dependent variable was not significantly predicted by frailty. Therefore, it seems to be more strongly associated with perceived risk of COVID-19 contagion.

Table 2.2.6. Multiple linear regression analysis for predicting the perceived threat of a new, emerging virus contagion.

Predictors	**B**	**SE**	***t***	***p***	**R-square**	**F (3,46)**	**p**
TMT-A	-0.306	0.115	-2.672	0.010	0.400	10.251	<0.0001
Token Test	-0.355	0.114	-3.114	0.003			
HARS	0.441	0.114	3.849	<0.001			

Note: B= Regression coefficient. SE= Standard Error. TMT-A= Trail Making Test - part A. HARS= Hamilton Rating Scale for anxiety.
The table reports the significant predictors of the perceived threat of a new emerging virus based on linear multiple regressions. The statistical values of both the whole model and the single predictors are reported.

Based on the latter finding, and on the role of anxiety in risk perception (Cori et al., 2020; Shahzad et al., 2020; Wieser and Keil, 2020), we selected these variables as predictors of a moderation model assessing the effect of baseline frailty and anxiety levels, and their interaction, on risk perception of SARS-CoV-2 at T2 [see *Table 2.2.7*]. Indeed, we found that the perceived threat of contracting SARS-CoV-2 was predicted by higher frailty ($p = 0.0034$) and anxiety ($p = 0.0075$), while additionally showing an interaction between these two predictors ($p = 0.0338$).

Table 2.2.7. Moderation analysis for predicting the perceived threat of SARS-CoV-2 at T2 based on frailty and anxiety, and their interaction, at T0

Model Summary						
R	R^2	MSE	F	df1	df2	p
0.6009	0.3611	2.5642	4.0512	6	43	0.0026
Model						
	coeff	se	t	p	LLCI	ULCI
constant	8.583	3.6846	2.3294	0.0246	1.1522	16.0138
Frailty	1.3324	0.4302	3.0971	0.0034	0.4648	2.2
Anxiety	0.1677	0.0597	2.8085	0.0075	0.0473	0.2881
Frailty x Anxiety	-0.2476	0.1129	-2.1927	0.0338	-0.4754	-0.0199
gender	-0.3951	0.6112	-0.6464	0.5214	-1.6276	0.8375
age	-0.0098	0.0421	-0.2334	0.8165	-0.0948	0.0751
education	-0.1175	0.0889	-1.3216	0.1933	-0.2969	0.0618
Test(s) of highest order unconditional interaction(s):						
	R2-chng	F	df1	df2	p	
Frailty x Anxiety	0.0714	4.8077	1	43	0.0338	
Conditional effects of frailty at values of anxiety						
HARS_T0	Effect	se	t	p	LLCI	ULCI
-3.9363	2.3071	0.6833	3.3767	0.0016	0.9292	3.6851
0	1.3324	0.4302	3.0971	0.0034	0.4648	2.2
3.9363	0.3576	0.5464	0.6545	0.5163	-0.7443	1.4596

Note: MSE=Mean Squared Error; df=degrees of freedom; LLCI=lower level of confidence interval; ULCI=upper level of confidence interval; coeff=coefficient; HARS_T0= Hamilton Rating Scale for anxiety, assessed at T0; se= standard error.
The table reports the results of a moderation model testing the effect of frailty and anxiety at T0, and their interaction, on the perceived threat of SARS-COV-2 at T2. The statistical values of both the whole model and the single predictors, alongside their interaction, are reported.

As shown in *Figure 2.2.1*, the perceived threat of SARS-CoV-2 contagion is maximal at the highest anxiety level regardless of frailty, and at the highest frailty level regardless of anxiety. Therefore, each of these predictors is sufficient, at its highest level, to support the maximum degree of perceived threat. Instead, when their values are average or under-the-mean, both predictors are required to promote perceived threat, which indeed is minimum at the lowest frailty and anxiety levels.

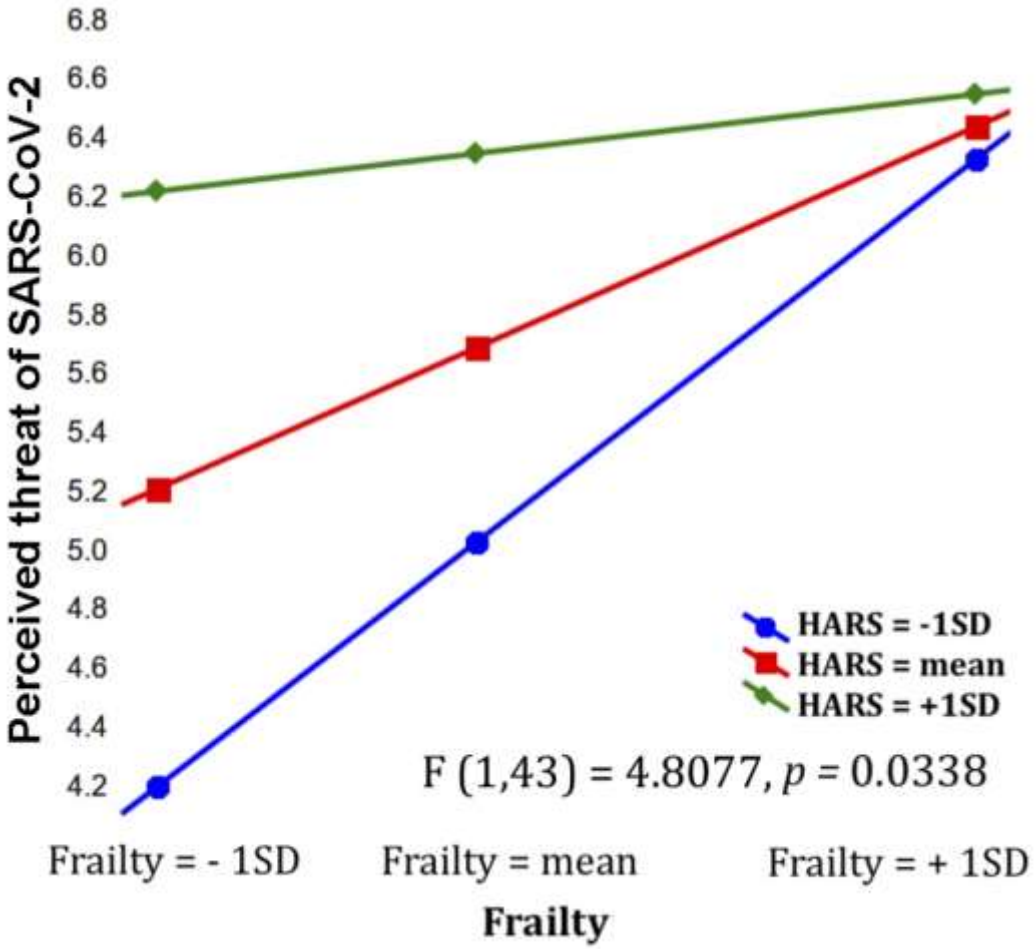

Figure 2.2.1. Longitudinal Study on Healthy Cognitive Aging: the interacting effects of physical frailty (based on Fried's phenotypic model) and anxiety (HARS) at T0 on perceived threat of SARS-CoV-2.

2.2.5. Discussion

To the best of our knowledge, this is the first published study that has monitored subjects in healthy cognitive aging for more than one year, before and after extremely restrictive measures due to the COVID-19 pandemic (i.e., from April 2019 to July 2020). This longitudinal design has provided a unique opportunity to investigate whether, and to what extent, the perceived threat of contracting SARS-CoV-2 is explained by pre-existing individual differences concerning physical pre-frailty, cognitive performance and mood deflections. Indeed, unlike related studies on the effect of the pandemic, T0 data allowed us to unveil novel associations between pre-COVID-19 neuropsychological variables and perceived risk of contagion in the last stage of the lockdown. Although most of the participants were robust at T0, some of them were pre-frail. Only a few minor neuropsychological deficits were observed in cognitive functioning and in line with the margin of error in tests administered to the normative population. Moreover, some participants showed mood changes in terms of depression and anxiety but these deflections were not significant from a mental health perspective.

Concerning the T1 results, almost all subjects complied with the precautions recommended by the Italian Ministry of Health (2020) to prevent infection with SARS-CoV-2 and showed correct behaviors regarding the prevention of infection. It is noteworthy that almost the whole sample (90%) belonged to an upper-middle social class, according to HI. Combined with the high level of education, such aspects make clear the peculiarity of this population, characterized by social resources, which have enabled them to take the necessary precautions to avoid the risk of contagion. In fact, risk perception can be influenced by several aspects, including knowledge of the virus (Cori et al., 2020) and the socio-economic status. Previous studies (Traves et al., 2020; Wolf et al., 2020) have shown that older, socio-economically disadvantaged, and poorly-educated individuals are less informed about COVID-19 spreading and, therefore, do not take adequate precautions.

The T2 data collected immediately after the isolation period showed neither a significant worsening of cognitive functions nor mood deflections in terms of depression. However, the level of anxiety increased during the COVID-19 pandemic, from 4% to 10%.

Multiple linear regression analyses showed that perceived risk of SARS-CoV-2 at T2 was predicted by worse performance on the information processing speed component and on language comprehension, as well as higher levels of pre-frailty and anxiety, at T0. These cognitive difficulties may hamper the correct interpretation of the information provided on the risk of infection, leading to attentional threat bias, further increasing anxiety (Beard, 2011). Moreover, conflicting and confusing sources of information about the ongoing pandemic, in terms of 'infodemia', could exacerbate psychological distress in terms of anxiety and fear of contagion (Amanzio et al., 2020, 2021b). This would be even more pronounced in language processing in normal aging. Older subjects' comprehension, even in the normative group, may also be less accurate due to an age-related slowdown in processing time, which increases in syntactically complex sentences. This pattern suggests an age-related decrease in parsing and interpretation efficiency suggesting how task-related operations are related to overall processing speed and working memory (Caplan et al., 2011).

In addition, the presence of a frailty state may reasonably lead to a greater perceived threat, as mortality rates from Covid-19 are higher in older adults suffering from this condition (Bonanad et al., 2020).

In line with these considerations, the perceived threat caused by a new emerging virus, assessed at T2, was explained by reduced baseline performance in tasks of information processing speed and in linguistic comprehension (TMT-A and TT, respectively), and an increased level of anxiety (HARS), but not by frailty status. An unknown risk is usually perceived as more frightening (Cori et al., 2020); thus, a high level of anxiety at baseline may intensify the sense of

danger. Furthermore, anxiety may influence attentional abilities (Wieser et al., 2020) but also the comprehension and the interpretation of stimuli (Beard et al., 2011).

Since multiple regression models showed that frailty was related only to the perceived threat of SARS-CoV-2, we hypothesized that this factor, along with the anxiety status assessed at baseline, might play an important role in explaining perceived risk. Indeed, a moderation model showed an interaction between these two independent variables in predicting SARS-CoV-2 perceived threat. Particularly, at their highest level, both frailty and anxiety are sufficient to support the maximum degree of risk perception, on the other hand, when their values decrease, both are required to promote SARS-CoV-2 threat perception.

2.2.6. Conclusion

To the best of our knowledge, this is the first study examining the association between perceived threat of SARS-CoV-2 during the lockdown and a set of cognitive, psychological, and physical variables measured before and during restrictive lockdown measures, in cognitively normal aging subjects. Therefore, it is important to underline how UNITRE-TO healthy participants represent a very distinctive reference sample to implement possible primary prevention pathways on older adults, with a particular focus on early determinants that may affect well-being in the current pandemic.

Our results showed, on the one hand, how physical frailty and mood deflection in terms of anxiety and, on the other hand, how cognition involved in information processing speed tasks and language comprehension, could influence the perceived threat of SARS- CoV-2 infection risk. The evidence that neuropsychogeriatric factors contribute to the perception of risk of an infectious disease shows the need to consider these variables.

Particular attention should be paid to frailty, as the pandemic lifestyle, characterized by reduced social interaction and a decrease in physical activities, may lead to the so-called “Corona-Frailty” (Shinohara et al., 2020). Moreover, the level of anxiety should be considered as it seems to modulate the perception of fear concerning COVID-19 infection.

The evidence that neuropsychological factors contribute to the perceived threat of an infectious disease (i.e., new virus) shows the need to consider these variables when planning information campaigns in older people, with the aim of achieving favorable changes in public behavior.

The present study emphasizes the contribution of neuropsychological factors to perceived threat of SARS-CoV-2 highlighting the importance of tailoring information campaigns addressed to older people.

The presence of pre-pandemic neurocognitive measures has provided a unique opportunity to investigate which facets of psychological, physical, and cognitive status predict a crucial variable such as perceived threat of SARS-CoV-2 in the aftermath of the lockdown. Furthermore, the COVID-19 containment measures, constrained to perform T2 neuropsychogeriatric assessment via selected neuropsychological, tests as suitable for remote administration.

Limitation Section

Although the present study was carefully designed and achieved its purposes, some limitations should be addressed.

Firstly, an important aspect to be clarified concerns the scale used to assess threat perception. Even though the evaluation of "Perceived Threat" was performed indirectly, multiplying the measures of perceived "severity" and "vulnerability" of the Risk Perception of Infectious Diseases Questionnaire, it should be noted that this methodology has been validated and used in previous studies (i.e. de Zwart et al., 2009). In particular, the "Perceived Threat" scale was considered a reliable tool for assessing risk perception of infection due to a very contagious and dangerous virus.

Secondly, our subjects were enrolled at the University of the Third Age, which promotes learning during aging. For this reason, they represent a very distinctive sample of older adults, characterized by a medium-high socioeconomic status and a medium-high level of education.

Finally, a sample size of 50 participants represents a limitation to this study; however, this population was studied in-depth through a neuropsychogeriatric assessment before the COVID-19 pandemic (T0) and during the first lockdown, both with strong restrictive measures (T1) and when they were eased (T2).

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3. Frailty in Mild and Major Neurocognitive Disorders

The considerable increase in life expectancy, particularly in the Western world, has led public health to address the management of growing numbers of older persons with age-related pathologies (Robertson et al., 2013). These conditions have a significant impact on health status, increasing disability and reducing independence and quality of life, leading to a greater risk of poor outcomes (Kojima et al., 2017). Among those, the two most common issues are cognitive decline and frailty (Panza et al., 2015).

As stated above (see Chapter 1, paragraph 1.3.1.), frailty and cognitive decline, in terms of MCI and major neurocognitive disorders, affect each other (Robertson et al., 2013) and, to date, the direction of their relationship has not been identified yet (Amanzio and Palermo, 2021; Canevelli et al., 2015). Nevertheless, understanding the association between these two age-related issues would help the development of preventive and treatment strategies in order to improve the quality of life in older individuals and increase their independence in the activities of daily living (Fabrício et al., 2020).

During my doctoral program, I was involved in two studies that investigated frailty in neurocognitive disorders with different etiopathogenesis. Specifically, I collaborated in the research carried out at the Neuroradiology and Nuclear Medicine Unit of the "Città della Salute e della Scienza" (Neurology I) in Turin, at the Neurology division of the Martini Hospital (Turin), and at the "Aging Brain and Memory Clinic" of the Department of Neuroscience, University of Turin.

The first study analyzed the influence of cognitive-behavioral aspects on the (pre)frailty status in patients with mild and major neurocognitive disorder due to AD (see Amanzio et al., 2017); the second one investigated the neuroanatomical and neurofunctional correlates of (pre)frailty in patients with behavioral variant frontotemporal dementia (bvFTD) (see Amanzio et al., 2021).

Furthermore, I carried out a mini-review with the aim of analyzing the possible relationship between executive dysfunction and frailty in patients with neurocognitive disorders (Bartoli et al., 2020).

Studies involving patients with MCI likely due to AD and mild AD, and subjects with bvFTD will be briefly described in the following paragraphs (3.1. and 3.2., respectively), while the mini-review, of which I am the first author, will be discussed in more detail (see paragraph 3.3.).

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3.1. Neuropsychological Correlates of Pre-Frailty in Neurocognitive Disorders: A Possible Role for Metacognitive Dysfunction and Mood Changes

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3.1.1. Abstract

Recent studies have suggested that cognitive functions in patients with neurocognitive disorders have a significant role in the pathogenic mechanisms of frailty. Although pre-frailty is considered an intermediate, preclinical state, epidemiological research has begun to dislodge cognition and frailty into their specific subcomponents to understand the relationship among them. We aim to analyze the possible association between pre-frailty and neuropsychological variables to outline which factors can contribute to mild and major neurocognitive disorders.

60 subjects complaining of different cognitive deficits underwent a deep-in-wide frailty and neuropsychological assessment. We conducted three multiple linear regression analyses adjusted for a combination of demographic measures and involving several neuropsychological–behavioral parameters selected by the literature on physical frailty.

We found a significant association between frailty – as measured by the multidimensional prognostic index (MPI) – and action monitoring and monetary gain (cognitive domain), depression and disinhibition (behavioral domain). Moreover, an association between MPI and impaired awareness for instrumental activities disabilities exists. We propose a novel framework for understanding frailty associated with metacognitive–executive dysfunction.

3.1.2. Summary

Frailty is an age-related condition characterized by functional decline in various physiological

systems, leading to high vulnerability to stressors (Hoogendijk et al., 2019). Frailty and neurocognitive disorder, especially due to AD, seem to be closely linked. In particular, it has been hypothesized that these clinical issues share the underlying pathophysiology, in terms of inflammatory or stress responses, or as a consequence of aberrant repair mechanisms (Wallace et al., 2018). Furthermore, the presence of cognitive decline and neurocognitive disorders has been related to frailty and pre-frailty conditions (Robertson et al., 2014; Wallace et al., 2018).

The aim of this study was to investigate whether pre-frailty might be influenced by cognitive–behavioral measures in individuals with mild and major neurocognitive disorders (DSM-5; APA, 2013), on the continuum from MCI likely due to AD, to mild AD patients (Albert et al., 2011).

60 subjects (male/female = 22/38; mean age ± SD = 69.6 ± 6.8 years) were enrolled in the study: 24 MCI due to AD patients according to the cerebrospinal fluid (CSF) analysis, and 36 patients with major neurocognitive disorders, for whom the CSF diagnosis provided *in vivo* evidence of Alzheimer's pathology. The decision to include subjects with different degrees of cognitive impairment in the same sample was made in accordance with international guidelines on aging, which consider patients with cognitive impairment on a continuum between MCI and mild AD (Albert et al., 2011; Dubois et al., 2014; Petersen and Negash, 2008).

All subjects underwent an in-depth neuropsychological evaluation. In particular, we focused on global cognitive functioning and specific cognitive varables (i.e., selective attention, episodic memory, language comprehension, and reasoning in the visual modality), behavioral aspects (i.e., mood changes, quality of life and awareness of the autonomy in instrumental activities of daily living), and metacognitive-executive functions. Specifically, the latter were analysed by the metacognitive version of the Wisconsin Card Sorting Test (m-WCST; Koren et al., 2006). During the test, for each card patients were asked to answer two questions, which evaluated "on-line" metacognitive monitoring ("What is your degree of confidence in this answer?") and control ("Do you want to take this response into account in your total score?") (Koren et al., 2006; Quiles et al., 2014). Furthermore, the patients received a monetary gain of 10 cents for each correct answer and they were deprived of the same amount for every wrong answer (Amanzio et al., 2014). Then, a set of metacognitive indices were evaluated, including: *monitoring resolution* – the gamma correlation calculated between the confidence and correctness of the sorts in the entire test – and *monetary gains*, given by the number of correct voluntary responses—incorrect number of voluntary responses (Amanzio et al., 2014).

Frailty was assessed by adopting a multidimensional approach. In particular, we use the Multidimentional Prognostic Index (MPI), which includes information on clinical, functional, nutritional, and neuropsychological aspects, as well as polypathology, pharmacological treatment, and the social support network (Pilotto et al., 2009, 2013). The MPI was originally

conceived as a prognostic index of mortality in the short- and long-term period (Pilotto et al., 2009, Gallucci et al., 2014), but it is also considered suitable for assessing frailty in the older population (Pilotto et al., 2008).

According to the MPI score, all patients presented a low risk of severe prognosis. Furthermore, 97% of the sample was classified as pre-frail, while 3% with a medium level of frailty.

In order to understand whether the level of the MPI index could be associated with cognitive and behavioral measurements, we conducted three multiple linear regression analyses, adjusted for age, gender, and education (model 1: global cognitive functioning and specific cognitive variables; model 2: metacognitive-executive functions; model 3: behavioral aspects).

We found a significant association between pre-frailty and executive functions – in terms of action monitoring (p = 0.01) and monetary gain (p = 0.04) –, apathy-depression (*Hamilton depression rating scale*, Hamilton, 1960*;* p <0.001), and disinhibition (*Disinhibition Scale*, Starkstein et al., 2004*;* p <0.001). Moreover, an association between MPI and impaired awareness for instrumental activities disabilities were shown (*Anosognosia Questionnaire-Dementia – instrumental activity domain*, Migliorelli et al., 1995; p = 0.02 – for a detailed description of the questionnaire, please see Chapter 4).

Since apathy, disinhibition, and executive dysfunction seem to be attributable to the malfunction of the same brain network (Bonelli and Cummings, 2007; Masterman and Cummings, 1997), we hypothesized that pre-frailty in patients with AD might also be due to a dysfunction of the medial prefrontal-ventral striatal network, observed throughout action-monitoring disability, mood changes, and reduced awareness of iADL.

This study (Amanzio et al., 2017) has been analyzed also in the mini-review, of which I am the first author (see paragraph 3.3.).

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3.2. Investigating Neuroimaging Correlates of Early Frailty in Patients With Behavioral Variant Frontotemporal Dementia: A MRI and FDG-PET Study

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3.2.1. Abstract

Frailty is a dynamic clinical condition characterized by the reduction of interconnections among different psychobiological domains, which leads to a homeostatic vulnerability. The association between physical frailty and cognitive dysfunctions is a possible predictor of poor prognosis in patients with neurodegenerative disorders. However, this construct has not been fully analyzed by a multidimensional neuropsychogeriatric assessment matched with multimodal neuroimaging methods in patients with behavioral variant frontotemporal dementia (bvFTD). We have investigated cognitive dysfunctions and frailty status, assessed by both a neuropsychological evaluation and the Multidimensional Prognostic Index (MPI), in a sample of 18 bvFTD patients and compared to matched healthy controls. Gray matter (GM) volume (as assessed by voxel-based morphometry) and metabolism (on ^{18}fluorodeoxyglucose positron emission tomography) were first separately compared between groups, then voxelwise compared and correlated to each other within patients. Linear regression of the MPI was performed on those voxels presenting a significant correlation between altered GM volume and metabolism. The neuropsychological assessment reflected the diagnoses and the functional-anatomical alterations documented by

neuroimaging analyses. In particular, the majority of patients presented significant executive dysfunction and mood changes in terms of apathy, depression, and anxiety. In the overall MPI score, the patients fell in the lower range (indicating an early frailty status). On imaging, they exhibited a bilateral decrease of GM density and hypometabolism involving the frontal pole, the anterior opercular region, and the anterior cingulate cortex. Greater atrophy than hypometabolism was observed in the bilateral orbitofrontal cortex, the triangular part of the inferior frontal gyrus, and the ventral striatum, whereas the contrary was detected in the bilateral dorsal anterior cingulate cortex and pre-supplementary motor area. MPI scores significantly correlated only with the co-occurrence of a decrease of GM density and hypometabolism in the right anterior insular cortex, but not with the separate pathological phenomena. Our results show a correlation between a specific pattern of co-occurring GM atrophy and hypometabolism with early frailty in bvFTD patients. These aspects, combined with executive dysfunction and mood changes, may lead to an increased risk of poor prognosis, highlighting a potentially critical and precocious role of the insula in the pathogenesis of frailty.

3.2.2. Summary

This study takes into account the need to define frailty as a biomarker associated with a decrease in the body's physical and cognitive reserves (Canevelli et al., 2019). This condition increases the risk of a rapid decline in physical and cognitive well-being in the older population, leading to a worse prognosis, especially among patients with neurodegenerative diseases (Jack Jr et al., 2011).

Previous researches have analyzed biomarkers associated with frailty status in patients with AD (Canevelli et al., 2020; Wallace et al., 2018, 2019). For example, Canevelli et al. (2020), found that subjects with more severe frailty status had lower cerebrospinal fluid (CSF) levels of amyloid beta 1–42 (Aβ1–42), lower hippocampal volumes on MRI and glucose metabolism on fluorodeoxyglucose positron emission tomography (FDG-PET), and greater amyloid deposition on 18F- AV-45 (Florbetapir F-18) PET. In addition, the authors showed that worsening frailty status was associated with a stronger relationship between dementia and FDG-PET, and a weakened relationship between dementia and 18F-AV- 45 uptake, and hippocampal volume.

However, no previous studies have investigated the correlates of frailty in patients with behavioral variant frontotemporal dementia (bvFTD), i.e., by means of a comprehensive *multidimensional* neuropsychogeriatric assessment and *multimodal* neuroimaging techniques.

In light of the above, we hypothesized and sought to investigate a potential relationship between a frailty status in patients with bvFTD and the presence of possible early disease-specific

structure functional cerebral changes. To address this issue, we directly correlated brain *structural* (MRI) and *metabolic* (18 fluorodeoxyglucose PET, 18 FDG-PET) imaging modalities with each other and with the MPI in a dataset of bvFTD patients. The aims of the study were (1) to investigate gray matter volumetric and metabolic modifications together with the regional variations of their reciprocal hierarchy and (2) to correlate the imaging results with a well-validated clinical prognostic score of frailty (Pilotto et al., 2008, 2009), also associated with possible metacognitive dysfunctions and mood changes, in line with the results obtained in subjects with MCI likely due to AD and with AD (Amanzio et al., 2017).

18 patients with bvFTD diagnosis (Rascovsky et al., 2011) were enrolled in the study and underwent extensive clinical, genetic (in order to esclude other kinds of neurodegenerative pathologies), neuropsychological, and neuroradiological investigations, the latter including both brain ^{18}FDG-PET and high-resolution structural MRI. A voxelwise regression of the MPI (adjusted for total intracranial volume, age, and time since diagnosis) was performed on those voxels presenting a linear correlation between density of tissue and hypometabolism or any predominance of density of tissue over hypometabolism (and *vice versa*).

The neuropsychological assessment reflected the diagnoses and functional-anatomical alterations documented by neuroimaging. In particular, the patients presented executive dysfunction – for example, all of the subjects fell below the cutoff scores on the Behavioral Assessment in Dysexecutive Syndrome (*BADS*; Wilson, 1996), and some of them presented deficit on the m-WCST (Koren et al., 2006). Moreover, the patients showed mood changes, particularly in terms of depression (*Hamilton depression rating scale*, Hamilton, 1960; 67%), anxiety (*Hamilton Anxiety Rating Scale*, Hamilton, 1959; 47%) and disinhibition (*Disnhibition Scale*, Starkstein et al., 2004; 22%).

Considering the frailty evaluation, the MPI score attested a low risk of severe prognosis. On imaging, the patients exhibited a bilateral decrease of GM density, and hypometabolism involving the frontal pole, the anterior opercular region, and the anterior cingulate cortex. Greater atrophy than hypometabolism was observed in the bilateral orbitofrontal cortex, the triangular part of the inferior frontal gyrus, and the ventral striatum, whereas the contrary was detected in the bilateral dorsal anterior cingulate cortex and pre-supplementary motor area.

In line with the neuropsychological assessment, these early pathological changes in bvFTD converge to the brain circuits of "top-down" cognitive control mechanisms. Furthermore, since executive dysfunction, depression–apathy, and disinhibition seem to be attributable to the malfunction of a common brain network (Masterman and Cummings, 1997; Bonelli and Cummings, 2007), an early frailty status in bvFTD patients might also be due to a disruption of the same “top-down” circuits.

The correlation between the MPI values and those voxels where GM density loss and hypometabolism "co-occurred", was found to be significant (peak $r = 0.86$ at pFWEC < 0.05) only in the right anterior insular cortex (cluster size in voxels = 8,943; MNI peak coordinates: $x = 39$, $y = 19$, $z = -4$). No significant results were obtained for MPI correlation with those voxels showing any predominance of GM density loss vs. hypometabolism or *vice versa*.

These findings, showing that the metabolic and structural damages were of equal severity in the insula, suggest that frailty (in its early stage) might be associated both with regional hypometabolism and atrophy, without the prevalence of either.

The anterior insular cortex play also a key role in emotional awareness social conduct and behavioral guidance (Craig, 2009). In particular, this area and the anterior cingulate cortex may be involved in a cerebral circuit related to executive control: the former may be a probable site for awareness on the basis of its afferent representation of the "feelings" from the body, and the latter may be a probable site for the initiation of behaviors (Craig, 2009). The simultaneous presence of structural and functional alterations in the anterior insular cortex may leave the patients unable to model the emotional impact of their own physical and cognitive difficulties, such as those seen in the progressive salience network (SN) breakdown (Seeley, 2010). The SN works to adjust arousal and attention on the basis of perceived relevance of stimuli (Seeley et al., 2008), processing information salient for survival. The worsening of the SN connectivity in the right frontoinsular cortex is associated with increased disease severity in bvFTD (Zhou et al., 2010) and the presence of frailty may, in turn, cause an increased risk of negative health outcomes and mortality.

Although these results suggest that the insula might be an early biomarker of frailty, they must be viewed cautiously and are intended as explorative. Nevertheless, our study sheds light on the possible neural correlates of frailty in its prodromal stages in patients with bvFTD.

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3.3. A possible Association Between Executive Dysfunction and Frailty in Patients with Neurocognitive Disorders

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3.3.1. Abstract

Frailty is an age-related dynamic status, characterized by a reduced resistance to stressors due to the cumulative decline of multiple physiological systems. Several researches have highlighted a relationship between physical frailty and cognitive decline; however, the role of specific cognitive domains has not been deeply clarified yet. Current studies have hypothesized that physical frailty and neuropsychological deficits may share systemic inflammation and increased oxidative stress in different neurodegenerative disorders, such as Alzheimer's and Parkinson's disease. However, the role of the executive dysfunction should be investigated in a more detailed way using a multidimensional approach. With this aim, we conducted a review of the literature on the few experimental articles published to discuss the existence of a relationship between frailty and cognitive impairment in neurocognitive disorders, particularly focusing on the domain of executive dysfunction. The data suggest that physical frailty and cognitive decline, especially executive dysfunction, are two aspects strongly linked in mild and major neurocognitive disorders due to Alzheimer's and Parkinson's disease. In light of this, a new framework linking aging, cognitive decline, and neurodegenerative diseases is needed. In order to analyze the effects that aging processes have on neural decline and neurocognitive disease, and to identify relevant groups of users and patients, future longitudinal studies should adopt a multidimensional approach, in the field of primary prevention and in the continuum from mild to major neurocognitive disorder.

3.3.2. Introduction

Frailty is a complex and heterogeneous clinical status described as the loss of harmonic interactions among various dimensions, such as biological, genetic, functional, psychological, cognitive, and social domains (Pilotto et al., 2020), that lead to homeostatic instability. Although the relationship between this issue and poor outcomes has been highlighted, currently there is no

gold standard on how to define measure and diagnose frailty (Richards et al., 2018). Nowadays, there are at least three main models to study frailty in aging subjects: the phenotypic model (Fried et al., 2001), the deficit accumulation model (Rockwood et al., 2005; Rockwood and Mitnitski, 2007), and the bio-psycho-social model (Gobbens et al., 2010); the first two characterize the biomedical approach. Although the latter approach is the most represented in the literature (Lacas and Rockwood, 2012), lately, the importance of a multidimensional approach (i.e. bio-psycho-social model) has been emphasized to better comprehend frailty, not only as a physiopathological syndrome (Amanzio et al., 2017). According to this approach, the multidimensional prognostic index (MPI) could be considered a more comprehensive evaluation tool (Pilotto et al., 2020; Angleman et al., 2015), useful for the assessment of subjects with neurodegenerative disorders, from minor to major neurocognitive decline, with different frailty status (Amanzio et al., 2017).

Originally, the concept of frailty referred only to a physical condition; recently, it includes also a cognitive status, which could be related to a reduction of neurophysiological reserves (Ruan et al., 2015). The first studies on frailty analyzed the association with cognitive impairment through the biomedical model. In particular, one of the first research analyzed the association between physical frailty and a progressive cognitive decline (Samper-Ternent et al., 2008). 1370 subjects were studied and baseline values for physical frailty (according to Fried's paradigm) and *MMSE* (Folstein et al., 1975) were observed after 3, 5, and 10 years. The results showed a substantial reduction of the mean of MMSE among frail individuals compared to pre-frail and robust ones.

Subsequent studies, while analyzing the presence of frailty with Fried's paradigm, began to investigate different cognitive sub-domains, widening the focus of observation. Interestingly, attention domain and executive functions seemed to be associated with frailty (O'Halloran et al., 2014; Robertson et al., 2014; Sargent and Brown, 2017); on physical side, gait speed and grip strength were mainly related to cognitive impairment, with a particular role played by executive dysfunction (Delrieu et al., 2016; Hooghiemstra et al., 2017; Langlois et al., 2012).

Even if these studies represent a first important attempt to describe the association between cognitive functions and physical frailty, there is still a need to assess frailty with a multidimensional approach (Avelino-Silva et al., 2014; Sternberg and Bentur, 2014). Future studies should clarify the type of association between cognitive impairment and frailty, in order to implement effective treatments. It also remains to be determined whether this association is causal or shares aging-related mechanisms, such as neurodegeneration. To understand which one is predominant on the other, longitudinal studies should be set up in the field of primary prevention and on the continuum from MCI to major neurocognitive disorder.

The progression of cognitive frailty towards neurodegenerative disorders is not currently clear. However, several longitudinal studies have investigated the possible association (Gómez-Gómez and Zapico, 2019). It has been suggested that classic aging mechanisms, such as oxidative stress, mitochondrial malfunction, and systemic inflammation could play a role in the pathogenesis of cognitive frailty and other associated neurodegenerative diseases (such as AD and Parkinson' diseases, PD) (Ahmed et al., 2008; Buchman et al., 2007; Gómez-Gómez and Zapico, 2019; Robertson et al., 2013). Despite this, very few studies investigated the impact of cognitive functions (more specifically on executive functions) as a precipitating and perpetuating factor of frailty in subjects suffering from neurodegenerative disorders.

The proposed mini-review focuses on common points characterizing executive dysfunction, neurocognitive and neurobiological factors potentially involved in frailty in such patients. In particular, the present study aims to investigate and address the following issues: (1) since physical frailty and cognitive decline (in particular executive dysfunction) are two aspects strongly connected within neurodegenerative disorders (i.e., Alzheimer's disease and Parkinson's disease), are the latter duly taken into consideration in the literature?; (2) Which of the frailty models are referred to in these studies (biomedical, bio-psycho-social)?; (3) What kind of executive dysfunction are considered and with what neuropsychological tools are they detected?

3.3.3. Selection of the Studies

A systematic search strategy was implemented to identify studies on frailty, published until 31st March 2020, across the online database most frequently used in the international literature (Medline database with PubMed literature search: http://www.ncbi.nlm.nih.gov/pubmed). We used a single set of query terms: *Frailty* AND *Executive Functions* [ALL]. We adopted the "PRISMA Statement" in order to make the selection and data collection process clear (Liberati et al., 2009). With this aim, we reviewed the relevant literature in order to ensure to select only papers regarding patients with mild or major neurocognitive disorders (DSM 5; APA, 2013) due to neurodegenerative disorders. We only selected original studies. Moreover, descriptive reviews, systematic reviews or meta-analyses were excluded. During the selection phase, we found 69 studies analyzing frailty in the above-mentioned pathologies. 64 studies were excluded because not consistent with the purpose of the review, while 5 were selected (see the flow chart in *Figure 3.3.1*).

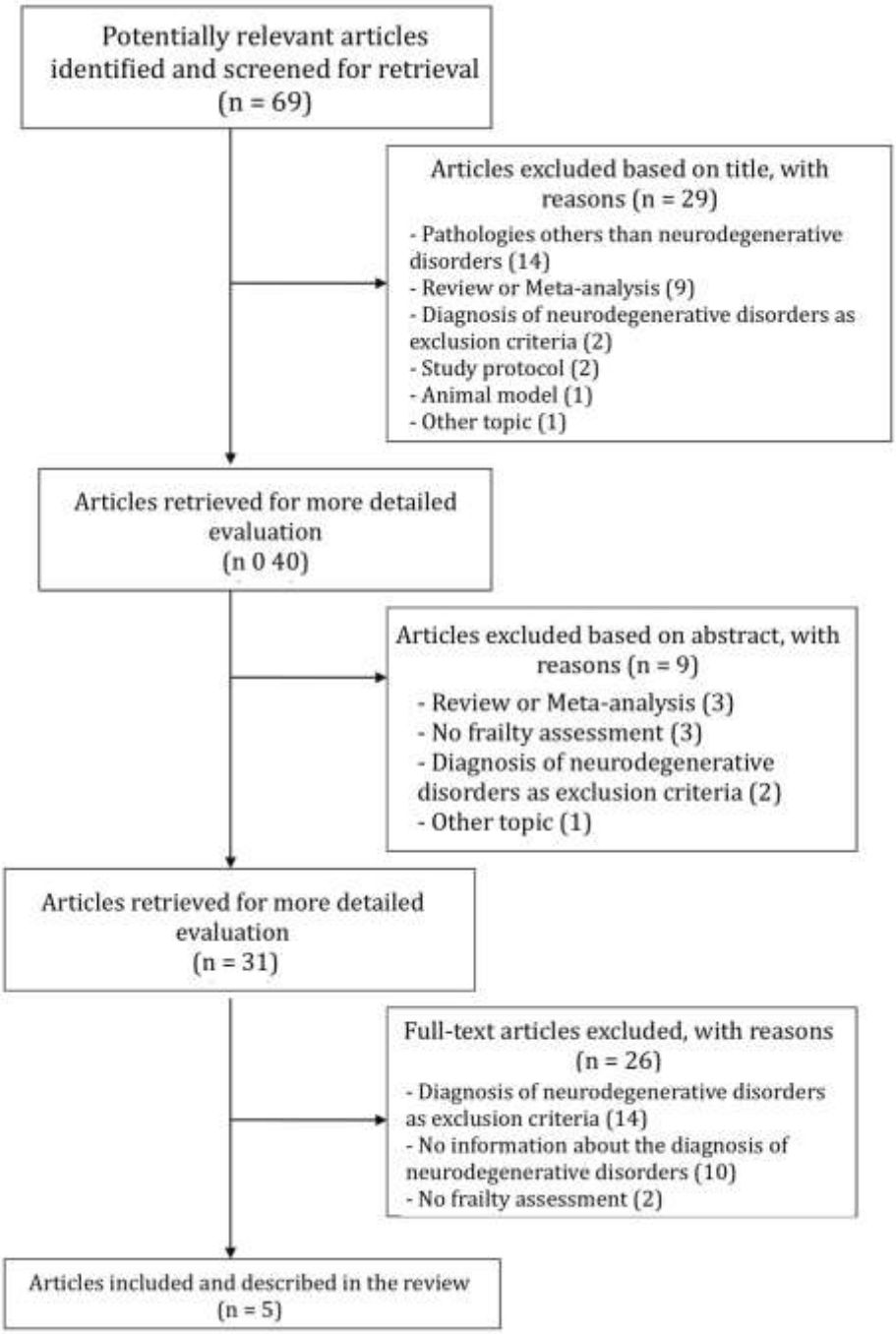

Figure 3.3.1. Mini-Review Frailty: Article selection flow chart according to the PRISMA statement (Liberati et al., *PloS medicine*, 2009).

3.3.4. Description of the Selected Studies

The selected studies mainly concerned subjects with AD and PD, focusing in particular on the two most common neurodegenerative disorders (Xie et al., 2014). Four out of the five selected studies assessed frailty through the biomedical paradigm. In particular, three of those (Shimada et al., 2013; Chen et al., 2019; Lin et al., 2019) adopted Fried's criteria, while one (Dutzi et al., 2017) used the model proposed by Rockwood et al. (2005) and Rockwood and Mitnitski (2007).

Shimada et al. (2013) analyzed the relationship between physical frailty and Mild Cognitive Impairment (MCI) in 5104 community-dwelling persons aged 65 years and older (mean age 71 years). The criteria used to define mild cognitive impairment are those reported by Petersen et al. (1999, 2001) for the "MCI- amnestic" type, which presents a high risk of conversion into a major neurocognitive disorder due to Alzheimer's disease (Petersen et al., 1999; Grundman et al., 2004; Petersen and Negash, 2008). By adopting the phenotype model, Shimada and colleagues subdivided participants in respect of frailty status and level of cognitive impairment using the MMSE and 8 cognitive tests on memory, attention and executive functions, processing speed, and visuospatial skills. Particularly, the executive functioning – in terms of cognitive flexibility – was assessed through the trail making test (part A and B; Reitan and Wolfson, 1994). The authors reported the presence of a frailty status in about 11% of the subjects and a MCI in about 19% of the participants. Considering the two aspects together, about 3% of subjects had both, frailty status and MCI, i.e., a cognitive frailty status (Kelaiditi et al., 2013). Moreover, authors found that the subjects at higher risk for frailty were 80 years and older, with 9 years or less of education. As for cognitive impairment, the subjects with a higher probability of developing MCI were men, with 9 years or less of education. Finally, the co-occurrence of frailty and MCI (cognitive frailty) increased in relation with age and lower level of education.

The other two selected studies adopting the phenotypic model analyzed the relationship between physical frailty and cognitive impairment in patients with PD (Chen et al., 2019; Lin et al., 2019).

Chen et al. (2019) investigated structural brain changes in relation to physical frailty and cognitive decline in sixty-one PD patients (mean age 62.61 ± 8.59 years), by using MRI. Voxel-wise multiple linear regression analyses were carried out in order to identify the overlapping areas of gray matter volume decrease concerning such aspects.

Frailty was assessed by adopting Fried's criteria. Several cognitive domains, such as attention, memory, language, visuospatial skills, and executive functions, were neuropsychologically evaluated. In particular, EFs were investigated, as indicated by the authors, by using some Wechsler Adult Intelligence Scale-III subtests (picture arrangement, arithmetic, digit symbol coding, and matrix reasoning) (Wechsler et al., 2002), and by the abstract thinking scores from the Cognitive Ability Screening Instrument (Lin et al., 2012). The authors identified the lateral occipital cortex as an overlapping region of physical frailty and cognitive impairment. Specifically, an overlapping region was observed in the left lateral occipital cortex for every cognitive domain in relation to frailty. This cerebral region is part of the ventral object-based visual pathway (Mishkin et al., 1983), whose decrease in thickness had previously been

identified in PD patients in relation to impaired cognitive functioning, in particular visuospatial skills, memory, and executive functions (Pereira et al., 2014). Moreover, an additional overlapping region relating to the superior frontal gyrus had been identified in connection with executive functioning and frailty. These findings highlighted how frailty and cognitive decline are connected in the brain (Chen et al., 2019).

As a precaution, considering the elements of difficult disambiguation between frailty and PD, it is appropriate to consider the correlations between frailty and cognitive impairments observed in the study by Chen and collaborators related to the pathophysiology (e.g., alpha synuclein in the brain) rather than a sign of frailty.

Finally, by adopting Fried's criteria, Lin et al. (2019) divided their sample of 76 PD patients (mean age 62.64 ± 9.23 years) into two groups: "with physical frailty" (38.2%) and "without physical frailty" (61.8%). PD patients with frailty were significantly older, showed worse disease severity, and poorer cognitive functions compared to robust ones. The neuropsychological assessment was the same carried out in Chen et al.'s study (2019). A stepwise logistic regression analysis indicated how impaired executive functions increased considerably the risk of physical frailty. In light of these results, the authors suggested that assessing cognitive functions in PD patients might be a useful approach to identify the subjects at greatest risk of developing frailty and to prevent negative outcomes through targeted strategies of intervention (Lin et al., 2019).

Dutzi et al. (2017) assessed frailty by using the model proposed by Rockwood et al. (2005). The authors investigated cognitive changes following hospital rehabilitation in 154 patients (mean age 83.7 ± 5.9) with mild and major neurocognitive disorder, with different etiopathogenesis (AD prevalently). They considered several aspects that could affect rehabilitation, including cognitive functioning, independence in basic activities of daily living (bADL), and frailty status. Particularly, frailty was evaluated using the *Clinical Frailty Sc*ale (Rockwood et al., 2005), which allows the clinician to assess the patient's degree of frailty through clinical data. This tool correlates strongly with FI but is faster and easier to administer (Rockwood et al., 2005). The executive functioning was evaluated by the verbal fluency and the modified version of the trail making test, from Nuremberg Gerontopsychological Inventory (Oswald and Fleischmann, 1985). The verbal fluency test is considered a task for the assessment of cognitive flexibility (Diamond, 2013), as well as the trail making test (Lezak et al., 2004). The authors found that patients presenting a worse frailty status and lower functional independence during the admission were those who did not benefit from cognitive rehabilitation. They suggested that frailty and deficit in the bADL may have played an important role in the worsening of cognitive decline and in the ineffectiveness of the rehabilitation intervention (Dutzi et al., 2017).

As previously mentioned, 4 out of the 5 selected studies analyzed frailty by adopting the biomedical models. Only one study (Amanzio et al., 2017) provided for the assessment of frailty through the bio-psycho-social model, highlighting its multidimensionality (Pilotto et al., 2020). Amanzio et al. (2017) investigated the association among a multidimensional assessment of frailty, executive dysfunction, and specific cognitive and behavioral changes, using an overall neuropsychological battery in sixty patients with mild and major neurocognitive disorders due to AD (mean age 66.62 ± 6.80). The authors used the MPI for a comprehensive assessment of frailty (Angleman et al., 2015; Pilotto et al., 2020). This tool not only takes into consideration the clinical, functional, neuropsychological, and nutritional status, but also gives information on the associated pathologies and pharmacological therapies, and on the social support network (Pilotto et al., 2020). Executive functions, in terms of self-monitoring, were assessed through the metacognitive version of the Wisconsin Card Sorting test (m-WCST: Koren et al., 2006). This version differs from the original one as the subject is asked to answer two questions: to assess his or her online self-monitoring ("What is your degree of confidence in this answer?") and to control abilities ("Do you want to take this response into account in your total score?") (see Amanzio et al., 2017). These findings suggested that also a pre-frailty status was associated with metacognitive-executive dysfunction, in terms of action monitoring in MCI-likely due to AD and AD patients. Specifically, it was observed a significant association between the MPI and monitoring resolution at the m-WCST, where patients failed to distinguish between correct and incorrect sorts. These results were specific and not influenced by other cognitive functions such as global cognition, memory, language comprehension, and non-verbal reasoning, with the exception of the selective attention task that reached a near significance level. Moreover, taking into account the MPI scores, this study demonstrated an involvement of mood depression changes, apathy, disinhibition, and a reduced awareness of IADL, associated with a higher frailty status (Amanzio et al., 2017). Since apathy, disinhibition, and executive dysfunction seemed to be attributable to the malfunction of the same brain network (Masterman and Cummings, 1997; Bonelli and Cummings, 2007), the authors hypothesized that pre-frailty might also be due to a dysfunction of the medial prefrontal-ventral striatal network (Amanzio et al., 2017).

3.3.5. Conclusion

The studies analyzed in this mini-review highlighted how physical frailty and cognitive decline, particularly executive dysfunction, are two aspects heavily connected within neurodegenerative disorders (i.e., AD and PD).

Several cognitive domains have been taken into account in the selected studies due to the lack of a univocal definition of EFs, assessed by different neuropsychological instruments.

The analyzed studies showed that frailty is related to executive dysfunction, in terms of cognitive flexibility (Shimada et al., 2013; Dutzi et al., 2017) and self-monitoring (Amanzio et al., 2017) in neurocognitive disorders.

In our opinion, the Wechsler Adult Intelligence Scale-III (WAIS-III) subtests, used by Chen et al. (2019) and Lin et al. (2019), are not the gold-standard instruments to assess EFs, as WAIS-III was created for the evaluation of reasoning and intellectual abilities (Wechsler, 1997). However, as reported by Robertson et al. (2014), several cognitive functions such as global cognition, attention, executive functions – including reasoning – and memory are associated with frailty status. These results confirm the hypothesis that there is a relation between frailty and cognitive decline in different domains, even within neurodegenerative disorders (such as PD).

Previous researches had shown a strong association between physical frailty and the incident of neurocognitive disorders, such as AD, MCI (Panza et al., 2015; Xu et al., 2015; Kojima et al., 2016), and cerebral vascular diseases (Avila-Funes et al., 2012). Frailty and cognitive impairment share several risk factors such as age-related chronic diseases, inflammation or cardiovascular problems (Robertson et al., 2013).

In a recent work of systematic review and meta-analysis, Borges et al. (2019) investigated the relationship between physical frailty and cognitive impairment, highlighting how frailty seemed to be one of the greatest risk factors for the development of major neurocognitive disorders.

However, it is important to underline how, to date, the studies have not clarified the direction of the association between frailty and the presence of a cognitive impairment yet. In particular, it is the presence of frailty that determines cognitive impairment or vice versa? In our opinion, given the multidimensional nature of frailty, the bio-psycho-social model is the most appropriate paradigm for the evaluation and management of frail older people with cognitive decline.

Longitudinal studies may be the most correct approach to assess the presence of cognitive disorders many years before the development of frailty itself. Further studies will be important to better characterized this association over time and replicate these findings in a larger group of patients. Analyzing the association between frailty and cognitive dysfunction in this at- risk population, would allow to develop specific physical and/or cognitive empowerment and rehabilitation measures.

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4. The Role of Reduced Self-Awareness in Neurodegenerative Disorders and Acquired Brain Injury

The awareness of illness is a theoretical term adopted to describe the ability to detect, discriminate, and diagnose the occurrence of different deficits in affective and cognitive domains (Amanzio et al., 2011), and also to recognize the consequences of such issues on both basic and instrumental activities of daily living (Amanzio et al., 2013).

As previously mentioned (see Chapter 1, paragraph 1.4.), the neurocognitive approach allows investigating a reduction in awareness by integrating neurobiological and neuropsychological factors, representing them in terms of concomitant brain dysfunction and cognitive-behavioral disorder (Amanzio and Palermo, 2020).

In fact, several studies (previously conducted by the research group of which I am part of) have shown that the reduction in self-awareness may be explained by considering both anatomical-functional disruptions in the prefontal cortex and deficits in executive functions (Amanzio et al., 2011, 2013, 2014, 2016, 2017; Palermo et al., 2014, 2018).

During my doctoral program I have deepened this issue, participating in some research published in Peer Reviewed international journals.

In the next section, I will briefly summarize a study in which the relationship between reduced awareness in IADL deficits and executive dysfunction in patients with MCI likely due to AD and mild AD was investigated (Amanzio et al., 2018). In the one following, I will deeply describe a mini-review on the relationship between executive dysfunction and reduced self-awareness in neurological disorders (Amanzio et al., 2020), for which I served as corresponding author. Finally, I will present a case report, of which I am the first author, of a selective vascular lesion that led the patient to a reduced awareness of her cognitive-behavioral deficits (Bartoli et al., 2020). Since the patient resulted positive on serologic testing for SARS-CoV-2 (IgG antibodies present/IgM absent), we hypothesized that metacognitive-executive dysfunction, which affects activities of daily living, may have played a role in her ability to take appropriate precautions to avoid infection.

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4.1. Neuropsychological correlates of instrumental activities of daily living in neurocognitive disorders: a possible role for executive dysfunction and mood changes

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4.1.1. Abstract

Since baseline executive dysfunction predicts worsening Instrumental Activities of Daily Living (i-ADL) over time and progression to Alzheimer's Disease (AD), we aimed to analyze the role of neuropsychological variables to outline which factors can contribute to functional impairment. Specific attention to executive functions (EFs) has been given.

A total of 144 subjects complaining of different cognitive deficits – ranging from "MCI likely due to AD" to "mild AD patients" – underwent an overall neuropsychological assessment. The Behavioral Assessment of the Dysexecutive Syndrome was used to analyze EFs. We conducted multiple linear regression analyses to study whether the level of independent living skills – assessed with the Lawton-scale – could be associated with cognitive and behavioral measurements.

We found a significant association between i-ADL and specific EFs measured by Rule Shift Cards ($p = 0.04$) and Modified Six Elements ($p = 0.02$). Moreover, considering i-ADL scores, we observed an involvement of mood changes and a reduced awareness of deficits in terms of Hamilton Depression Rating Scale ($p = 0.02$) and Awareness of Deficit Questionnaire – Dementia scale ($p < 0.0001$), respectively.

Our results suggest the importance of considering the association between a reduction in i-ADL and executive dysfunction in patients who have AD etiopathology, for which the ability to inhibit a response, self-monitoring, set-shifting and mood deflection play a key role. Besides, no straightforward associations between i-ADL scores and global cognition, memory, language comprehension, attention, and perspective taking abilities were found.

4.1.2. Summary

Alzheimer's disease is one of the most common age-related neurodegenerative diseases in the world (DeTure and Dickson, 2019; Ruffini et al., 2020; Santiago et al., 2021). It lies on a continuum that, in relation to clinical symptoms, progresses from MCI to major neurocognitive disorder (APA, 2013; Sperling et al., 2011).

Research concerning the biomarkers of AD has suggested that functional impairment appeared before cognitive decline (Jack et al., 2010).

IADL seem to be impaired even in the early stages of AD (Marshall et al., 2014). Furthermore, even subjects with MCI may present slight difficulties in IADL (Petersen et al., 2014).

Marshall and colleagues (2011) have shown that executive dysfunction and IADL impairment seem to be associated in normal cognitive aging and in mild and major neurocognitive disorder due to AD. In addition, it was found that both predict the involution from MCI to mild AD, leading to the hypothesis that they are both associated with deficits in the prefrontal cortex (Tabert et al., 2002). Moreover, previous studies have shown that reduced awareness of deficits in IADLs, related to executive dysfunction, leads patients with mild AD to overestimate their functional abilities (Amanzio et al., 2011, 2013).

In light of the above, we aimed to further analyze the role of neuropsychological variables – with a particular focus on EFs – in relation to functional impairment in patients on the continuum from MCI to mild AD.

144 hospitalized patients (male/female = 55/89; mean age ± SD = 74.60 ± 6.42 years) were enrolled in the study: 32 subjects with MCI likely due to AD, and 112 patients with AD, according to the CSF analysis. All subjects underwent an in-depth neuropsychological evaluation. In particular, we focusing on: (1) global cognitive functioning and specific cognitive variables (global cognition, selective attention, episodic memory, and language comprehension); (2) executive functioning, taking into account the subtests of the BADS (Wilson et al., 1996); (3) theory of mind (ToM), mood changes – in terms of depression and mania – and unawareness of deficit. For the latter aspect, we used the Anosognosia Questionnaire-Dementia (AQ-D; Migliorelli et al., 1995), composed of 30 items (i.e. questions) concerning cognitive and behavioral aspects in everyday activities. All the questions were asked to both patient and his/her caregiver blinded to the patient's responses. The total AQ-D score is given by the difference between the caregiver and the patient's forms. Higher scores indicate greater unawareness of the disease and a reduced awareness of deficits, as the caregiver rated the patient as more impaired than did the patient him/herself.

Instrumental activities of daily living were assessed by the Lawton i-ADL Scale (Lawton and Brody, 1969), which evaluates functional autonomy in the performance of different functions (i.e., using the telephone; shopping; preparing food; housekeeping; doing laundry; using transportation; handling medications; and ability to handle finances). Each item is rated dichotomously (0 = less able, 1 = more able). The higher the score the lower the level of dependence. Our sample showed a low level of impairment.

We conducted multiple linear regression analyses – adjusted for gender – to study whether the level of independent living skills (iADL Scale) could be associated with cognitive and behavioral measurement (Model 1: global cognitive functioning and specific cognitive variables; Model 2: EFs; Model 3: ToM, mood changes, and unawareness of deficits). We found a significant association between i-ADL and specific EFs measured by *Rule Shift Cards* (RSC, $p = 0.04$) and *Modified Six Elements* (MSE, $p = 0.02$) subtest of the BADS. The RSC evaluates the ability to respond correctly to a rule and to shift from the use of one simple rule to another more complex, while the MSE evaluates the ability to divide attention, task scheduling, performance monitoring, and prospective memory: subjects should complete 6 trials within 10 minutes, following certain rules. This means that the ability to set-monitoring, inhibiting responses, and set-shifting may play a key role in IADL.

Moreover, considering i-ADL score, we observed an involvement of mood changes, i.e., depression (*Hamilton Depression Rating Scale*, Hamilton, 1960; $p = 0.02$) and a reduced awareness of deficits in terms of AQ-D score ($p < 0.0001$), respectively. These results are in line with the previous literature on AD (Amanzio et al., 2013; Boyle et al., 2003; Marshall et al, 2011). In particular, concerning the reduced awareness of deficits, the CAM (Agnew and Morris, 1998; Mograbi and Morris, 2014) may provide an explanation of such relationship. In fact, executive dysfunction leads to a disruption in the self-monitoring comparator mechanisms within the central executive system; therefore, discrepancies between current and previous performance states (stored within a personal database) are not detected. Such issue leads to reduced awareness of deficits in the instrumental domain (Amanzio et al., 2013).

These findings support the hypothesis that patients on the AD continuum present i-ADL deficits in the context of overlapping executive dysfunction, reduced awareness, and mood changes.

This study (Amanzio et al., 2018) has been analyzed also in the mini-review, of which I served as correspoding author (see paragraph 4.2.).

4.1.3. References

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4.2. Executive Dysfunction and Reduced Self-Awareness in Patients with Neurological Disorders: A Mini-Review

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4.2.1. Abstract

Awareness of deficits in patients with neurological disorders may be described as a theoretical unitary phenomenon, which has been analysed reaching interesting results in the last decades. Awareness of deficits manifests itself on a continuum ranging from full awareness to total absence. In line with a neurocognitive approach, a reduction in self-awareness could be explained considering executive dysfunction associated with prefrontal cortex anatomo-functional changes. Our mini-review will focus on reduced self-awareness in neurological disorders, such as Alzheimer's disease, behavioral Frontotemporal Dementia and Acquired Brain Injuries. Results achieved thanks to an explanatory investigative approach combined with a theoretical reference model will be presented. Data suggest the key role of executive functions in supporting adequate self-awareness towards patients' cognitive-behavioral profile and instrumental activity autonomy. The Cognitive Awareness Model seems to be one of the best theoretical model to better approach this phenomenon.

4.2.2. Introduction

Awareness of deficits appears on a continuum ranging from full awareness to total absence. In patients with neurological disorders, it may be described as a theoretical unitary phenomenon, which has been analyzed reaching interesting results in the last two decades. A reduction in self-awareness could be explained considering both prefrontal cortex anatomo-functional changes and executive dysfunction in patients with Alzheimer's disease (AD), behavioral Frontotemporal Dementia (bvFTD) and Acquired Brain Injury (ABI) (Amanzio et al., 2011, 2013, 2016, 2017; Palermo et al., 2014). Indeed, executive functions are important in supporting adequate self-awareness with respect to the cognitive-behavioral framework and instrumental activities of daily living (IADL) autonomy (Amanzio et al., 2016, 2018). O'Keeffe et al. (2007) suggested

that deficits in some executive functions–monitoring, response inhibition and cognitive flexibility–might affect patients' judgment in terms of reduced self-awareness.

In our opinion, this phenomenon could be accurately described only by adopting a neurocognitive approach as a theoretical framework. In particular, this perspective allows to estimate neuroimaging anatomical-functional data and neuropsychological evidence in an unicum, considering the role of executive dysfunction in reducing self-awareness.

Our mini-review we will focus on reduced self-awareness in neurological disorders, such as AD, bvFTD, and ABI.

4.2.3. Selection of the Studies

Studies on self-awareness, published from 30th April 2000 until 30th April 2020, were identified by a selection strategy across the online international database (Medline database with PubMed literature search). We used a single set of query terms: "reduced awareness" combined with pathology. Only relevant literature on neurological patients on AD, bvFTD and ABI was considered. Inclusion criteria contemplate original studies using structural or functional MRI and/or neuropsychological assessment. The complete list of articles identified through research and the selection process are presented in *Table 4.2.1*.

Only eleven articles suited criteria for this mini-review. They will be described according to the theoretical framework previously introduced (see Chapter 1, Paragraph 1.4.1.).

Table 4.2.1. Synopsis of the studies selection. The characteristics of the original articles (considering etiopathogenesis, methods and awareness assessment scales) are presented.

	Pubmed ID	First autor (year of pubblication)	Inclusion/exclusion (with reasons)	Methods (neurpsychological/ neuroimaging)	Awareness assessment
Alzheimer's Disease	10733015	Robinson (2000)	Excluded (No neuropsychological or neuroimaging evaluation)		
	18161073	Bonney et al. (2007)	Included	Neuropsychological assessment	Dysexecutive Questionnaire (DEX, Wilson et al., 1996)
	20808100	Orfei et al. (2010)	Included	Neuropsychological assessment	Anosognosia Questionnaire for Dementia (AQ-D, Migliorelli et al., 1995) Clinical Insight Rating Scale (CIRS, Ott et al., 1996)
	20921874	Greenop et al. (2011)	Excluded (No diagnosis of AD or MCI likely due to		

			AD)		
	21385751	Amanzio et al. (2011)	Included	Functional MRI and neuropsychological assessment	Anosognosia Questionnaire for Dementia (AQ-D, Migliorelli et al., 1995)
	21495076	Galeone et al. (2011)	Included	Neuropsychological assessment	Questionnaire based on patients and caregivers discrepancy score (adapted from Ansell and Bucks, 2006).
	22697174	Brookes et al. (2013)	Excluded (No diagnosis of AD or MCI likely due to AD)		
	22995647	Amanzio et al. (2013)	Included	Neuropsychological assessment	Anosognosia Questionnaire for Dementia (AQ-D, Migliorelli et al., 1995)
	25481475	Spalletta et al. (2014)	Included	structural MRI and neuropsychological assessment	Memory Insight Questionnaire (MIQ, Markova et al., 2004)
	26385947	Tonga et al. (2016)	Excluded (No neuropsychological or neuroimaging evaluation)		
	27534380	Amanzio et al. (2016)	Excluded (No diagnosis of AD or MCI likely due to AD)		
	28633865	Amanzio et al. (2017) *corrigendum*			
	29789032	Amanzio et al. (2018)	Included	Neuropsychological assessment	Anosognosia Questionnaire for Dementia (AQ-D, Migliorelli et al., 1995)
	30531365	Defeis et al. (2019)	Included	Neuropsychological assessment	Patients and caregivers report of symptoms
Frontotemporal Dementia	27534380	Amanzio et al. (2016)	Included	Structural MRI and neuropsychological assessment	Anosognosia Questionnaire for Dementia (AQ-D, Migliorelli et al., 1995)
	28633865	Amanzio et al. (2017) *corrigendum*			
Acquired Brain Injury	23962086	Palermo (2014)	Included	Functional MRI and neuropsychological assessment	Anosognosia Questionnaire for Dementia (AQ-D, Migliorelli et al., 1995)

Note: AD = Alzheimer's disease; MCI = mild cognitive impairment; MRI = magnetic resonance imaging.

4.2.4. Description of the Selected Studies

"REDUCED AWARENESS" [AND] "ALZHEIMER"

Among the articles selected on the AD, from the first published to the most recent, there are those of Bonney et al. (2007), Orfei et al. (2010), Amanzio et al. (2011, 2013), Galeone et al. (2011), Spalletta et al. (2014), another one by Amanzio et al. (2018) and De Feis et al. (2019).

Bonney et al. (2007) analysed how a reduced awareness of executive dysfunction, characterizing a "dysexecutive syndrome" in 24 participants with mild AD, may be related with their caregivers' burden. In line with their hypotheses, the authors observed an association between caregiver's burden and reduced awareness of deficits related to executive dysfunction, suggesting that early detection of executive dysfunctions may help develop effective strategies to reduce the care burden.

In order to analyze awareness of illness, Orfei et al. (2010) recruited 38 mild AD patients, 35 amnesic mild cognitive impairment (aMCI) and 38 multiple domain MCI (md-MCI) subjects. Results showed that patients with mild AD were more anosognosic than both MCI groups, and md-MCI subjects presented a reduced awareness of their illness. The authors pointed out that a reduced awareness of illness should be studied along with anosognosia in AD. Moreover, anosognosia in mild AD was associated to increased age and reduced basic ADL autonomy, while verbal episodic memory deficits were correlated with decreased awareness of cognitive impairment only in a-MCI patients.

Galeone et al. (2011) investigated a reduced awareness of memory deficits in 25 aMCI and 15 mild AD patients, pointing out that both groups overestimated their memory performances. In particular, subjects presented decreased awareness for memory deficit and memory-monitoring difficulties, associated with executive functioning. The authors demonstrated that a reduced awareness could characterise even early stages of AD, such as a-MCI subjects.

Spalletta et al. (2014) analyzed the neuroanatomical correlates of awareness of illness in 36 a-MCI patients, followed for five years, in order to understand whether they could be considered risk factors for conversion to AD. The authors reported that converter subjects showed a greater reduction of self-awareness of memory deficits, which correlated with reduced gray matter volume of the ACC and of the inferior frontal cortex. Their results highlight how the awareness of deficit in converter and non-converter aMCI patients is characterized by different pathogenic mechanisms. In particular, converter subjects showed a dysregulation of the cognitive control, such as selection, manipulation and inhibition of self-information. The authors concluded that

these pathogenic mechanisms, related with augmented risk of AD conversion, could also support reduced self-awareness in other neurological conditions.

More recently, De Feis et al. (2019) investigated the relationship between a reduced awareness of memory deficits and the need for in-home assistance in 192 patients with probable AD and Lewy Bodies Dementia. The authors reported that a reduced self-awareness of memory deficits could be associated with a more frequent use of home health care services. These results are important as they might have clinical, caregivers, and health care implications.

Finally, Amanzio et al. (2018) analyzed the association between reduced awareness and executive dysfunction in 144 patients with different cognitive deficits – from "Mild Cognitive Impairment (MCI) likely due to AD" to "mild AD patients." As baseline executive dysfunction predicts worsening of IADL over time and progression to AD, results showed that executive dysfunction, associated with reduced IADL awareness, were selectively characterized by a worst performance on response inhibition, self-monitoring and set-shifting tasks (Amanzio et al., 2018).

In their other studies, considered in this mini-review, Amanzio et al. (2011, 2013) underlined the importance of executive dysfunction related with mPFC and impaired self- awareness in AD. In particular, the authors (Amanzio et al., 2013) estimated the role of different cognitive and mood changes variables taking into consideration 117 AD patients. Results showed that inhibition, self-monitoring and set-shifting were associated with awareness of iADL. Moreover, a tendency to hypomania and apathy seemed related to reduced behavioral awareness. Amanzio et al. (2011) also evaluated the neural underpinnings of reduced self-awareness in 29 AD patients, focusing on mPFC and anterior cingulate cortex functionality. Unaware patients showed a more evident reduction of activity of the right anterior cingulate area and of the rostral prefrontal cortex, a higher dysfunction of the mPFC, in particular in the dorsal division of the ACC, and in heteromodal association areas. In addition, they showed an hypofunctionality of the right post-central gyrus, of the associative cortical areas, such as the right parieto-temporal-occipital junction and the left temporal gyrus, of the striatum, and of the cerebellum.

These results show that reduced awareness of deficits during the first phases of AD is related to an hypoactivity of the cingulo-frontal and parieto-temporal regions and, on the behavioral side, to apathy and disinhibition (Amanzio et al., 2011).

"REDUCED AWARENESS" [AND] "FRONTOTEMPORAL DEMENTIA"

The only work concerning the reduction of awareness in FTD patients, identified through the research strategy, is the original article by Amanzio et al. (2016, 2017). The authors explored primarily the anatomo-functional brain changes related to IADL in 67 bvFTD patients and, secondly, the neural correlates of reduced awareness in the IADL domain.

The Anosognosia Questionnaire for Dementia (AQ-D: Migliorelli et al., 1995) was used to assess the precence of reduced awareness for the instrumental domain (AQD_iADL).

The authors found disabilities in IADL and a reduced AQD_iADL to be associated with atrophy of the medial prefrontal cortex, in which the mid-cingulate cortex, the anterior dorsal cortex, cuneus and insula played an important role (Amanzio et al., 2016, 2017). The neurocognitive approach applied to bvFTD proves effectiveness in illustrating the association between brain pathology and cognitive and behavioral deficits (McGlynn and Schacter, 1989; Lezak et al., 2004).

"REDUCED AWARENESS" [AND] "ACQUIRED BRAIN INJURY"

Palermo et al. (2014) reported a clinical description of a self-unaware patient with an ischemic injury in the right ACC. In their study, the only one present in literature on this topic, the authors suggested that the damage in the cingulo-frontal region could be considered as one of the neurobiological substrates of the persistent reduced self-awareness of the patient. In patients with ABI, the association between executive functions and self-awareness is characterized by deficits in: response inhibition abilities, mental flexibility (Burgess et al., 1998; Trudel et al., 1998), self-regulation of errors (Burgess et al., 1998; Ownsworth and Fleming, 2005), self-monitoring of action performance with the impact of error (in terms of online awareness), and updating self-information about errors (Vuilleumier, 2004; Ownsworth et al., 2008). Thus, measures for self-regulating errors provide a method that can be useful to examine the contribution of neuropsychological factors in awareness deficits, mainly focusing on the role of mPFC in ABI patients (Amodio and Frith, 2006; Ownsworth et al., 2007). Indeed, mPFC and the cingulate cortex are considered primary areas for self-awareness (Johnson et al., 2002).

REDUCED AWARENESS AND OTHER NEURODEGENERATIVE DISORDERS: PARKINSON'S DISEASE (PD)

Considering PD, the presence of dyskinesias-reduced-self-awareness (DRSA) had been related to executive and metacognitive impairments and, apparently, it arose because of the dopaminergic overstimulation of the mesocorticolimbic areas (Amanzio et al., 2010, 2014; Palermo et al., 2017). In addition, a relationship between DRSA and an hypoactivity of the bilateral ACC, bilateral anterior insular cortex and right dorsolateral prefrontal cortex had been

showed (Palermo et al., 2018). These results indicate how the executive deficits impact on reduced self-awareness in neurodegenerative disorders, and how the ACC is the main hub of the damaged response-inhibition circuit.

4.2.5. Clinical Implications and Recommended Good Practices

A detailed neuropsychological assessment that includes investigation of possible self-awareness disturbances – and its behavioral sequel – across a wide range of domains, should be set in AD, bvFTD, and ABI.

Specific executive-metacognitive functions, often associated with the presence of self-awareness reduction, should be accurately studied. When cognitive and functional changes occur, it seems that metacognitive functioning plays an important role in modifying the approach to everyday activities. Indeed, a reduction in IADL self-awareness should also be taken in great consideration. Moreover, neuroimaging assessment should be implemented both from a functional and structural point of view to better outline dlPFC-ACC system dysfunction, tapping cognitive-action-control, that may cause reduced self-awareness disorders (Amanzio et al., 2011; Palermo et al., 2015, 2018).

Self-awareness disorders can lead to poor adherence to pharmacological treatment and prognosis in patients with neurological diseases (Acharya and Sánchez-Manso, 2021). Therefore, frailty determinants and psychosocial factors should also be assessed in the context of a neurocognitive perspective, being essential variables to identify vulnerable subjects needing further support (Amanzio et al., 2016).

4.2.6. Limitation and Future Research Perspective

The studies described in this mini-review present some limitations. Additional studies are needed to better evaluate the appearance of self-awareness reductions throughout the duration of the disease, to better understand associations with executive and meta-cognitive domains, also in subjects with MCI. Particularly, longitudinal studies are required to better monitor neurological patients with a reduced self-awareness at different transition points, defining specific primary and secondary prevention assessments. The proposed evaluation approach should lead to a careful development of tailored longitudinal interventions for patients, and guidance for health professionals to maximise prognosis and quality of life.

Programs enhancing executive-metacognitive functions should be implemented to promote self-awareness in individuals with neurological disorders and cognitive impairment. Toglia et al. (2010) had previously showed how metacognitive strategy training could be useful for

ameliorate self-awareness. In fact, it seems that a punctual self-awareness assessment and intervention can assist in enabling better and earlier patients at risk of poor treatment response. Moreover, clinicians may improve adherence to treatments using the proper strategies of engagement.

4.2.7. Conclusion

Metacognitive-executive dysfunction and mPFC impairment, delineated through the neurocognitive model, may help to understand how the central executive system could contribute to self-awareness disorders related to AD, bvFTD and ABI (Starkstein et al., 1995; Litvan et al., 1996, 1997; Agnew and Morris, 1998; Amanzio et al., 2011, 2013, 2016; Palermo et al., 2014). The similarity of the neuropsychological profile, in terms of overlapping the symptoms associated with the onset of self-awareness, seems to authorize a transposition of the interpretative model in different neurological disorders (Palermo et al., 2014).

Conscious experience of post-injury/neurodegenerative disease changes requires an interaction among relevant functional domains, comparator mechanisms within the central executive system to detect deficits, and the CAM. The studies presented highlight an association between reduced self-awareness and executive dysfunction related with mPFC anatomo-functional impairment, causing difficulties in response-inhibition, cognitive set-shifting and action- monitoring performances. Results suggested that a selective mid cingulate cortex lesion might be associated with reduced self-awareness, which could remain over time even in a context of partial recovery of cognitive functions different from the executive ones.

This mini-review results support the explanatory effectiveness of the CAM theoretical model (Agnew and Morris, 1998; Amanzio et al., 2013; Mograbi and Morris, 2014), for which damage to the “comparator mechanisms” in the executive system compromises the capacity to update the “personal database” with current information about themselves, sometimes referred to as «developing a “petrified-self”» (Mograbi et al., 2009; Steward et al., 2019).

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4.3. Reduced Self-Awareness Following a Combined Polar and Paramedian Bilateral Thalamic Infarction. A Possible Relationship With SARS-CoV-2 Risk of Contagion?

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4.3.1. Abstract

Reduced self-awareness is a well-known phenomenon investigated in patients with vascular disease; however, its impact on neuropsychological functions remains to be clarified. Importantly, selective vascular lesions provide an opportunity to investigate the key neuropsychological features of reduced self-awareness in neurocognitive disorders. Because of its rarity, we present an unusual case of a woman affected by a combined polar and paramedian bilateral thalamic infarction. The patient underwent an extensive neuropsychological evaluation to assess cognitive, behavioral, and functional domains, with a focus on executive functions. She was assessed clinically in the acute phase and after 6 months from the stroke, both clinically and by magnetic resonance imaging. The patient developed a cognitive impairment, characterized by prevalent executive dysfunction associated with reduced self-awareness and mood changes, in terms of apathy and depression. Such condition persisted after 6 months. In May 2020, the patient underwent the serology test in chemiluminescence to detect IgG antibodies against SARS-CoV-2. The result of the quantitative test highlighted a high probability of previous contact with the virus. We suggest that reduced self-awareness related to executive dysfunction and behavioral changes may be due to combined polar and paramedian bilateral thalamic lesion. Metacognitive–executive dysfunction affecting the instrumental abilities of everyday life might make people less able to take appropriate precautions, facilitating the risk of SARS-CoV-2 contagion.

4.3.2. Introduction

Awareness of illness is the more general theoretical term used to describe the ability to detect, distinguish, and diagnose the occurrence of different deficits in cognitive and affective domains (Amanzio et al., 2011).

Considering acquired brain injury (ABI), reduced self-awareness is a phenomenon characterized by impairments in recognising deficits together with their impact on the patient's functioning and, consequently, in making realistic plans (Palermo et al., 2014).

Studies on reduced self-awareness in brain injury patients showed the key role played by the frontal lobes (Bach and David, 2006; Ownsworth et al., 2007) and subcortical regions (Starkstein et al., 1992). In particular, specific cingulofrontal areas dysfunctions (Palermo et al., 2014), damages involving primarily the temporoparietal junction (Devinsky, 2008), the lateral ventricles, the frontal horns, and diencephalic regions (Starkstein et al., 1992) – such as the thalamus and the basal ganglia (Starkstein et al., 2010) – might contribute to a reduced self-awareness (Devinsky, 2008; Starkstein et al., 2010; Palermo et al., 2014; Bourlon et al., 2017), also in terms of interoceptive awareness (i.e., the perception of heartbeat, breathing, hunger, thirst, and visceral sensations) (Raimo et al., 2019). De Witte et al. (2011) confirmed that the thalamus might be considered an attractive "hub" for the study of reduced self-awareness of cognitive deficits in ABI. Those authors reviewed 465 patients with vascular thalamic lesions, finding that two thirds of those with bilateral thalamic damage presented specific cognitive and behavioral deficits, such as reduced self-awareness and executive dysfunction, disrupted memory, constructional apraxia, disorientation, and global cognitive deficits associated with behavioral abnormalities (De Witte et al., 2011). Stroke in the left dorsomedian thalamus (Lanna et al., 2012) and bilateral paramedian thalamus (Rusconi et al., 2014) had been previously associated with anosognosia.

Regarding the association between executive dysfunction and reduced self-awareness, frontal areas seem to be implicated in self-awareness and in the control of cognitive functioning. Thus, in ABI patients, a reduction of awareness might be considered as a damage in self-monitoring (Stuss and Benson, 1984). This mechanism also occurs in patients with neurodegenerative disorders, such as frontotemporal dementia (FTD) (O'Keeffe et al., 2007; Amanzio et al., 2016; Levy et al., 2018), Alzheimer (Amanzio et al., 2010, 2011, 2013) and Parkinson (Amanzio et al., 2014; Palermo et al., 2017) diseases. Moreover, deficits in basic executive functions, i.e., cognitive set-shifting, response inhibition, and self-monitoring, have been previously proposed as possible mechanisms of reduced self- awareness in patients with a selective anterior cingulate cortex ABI (Palermo et al., 2014).

The present report illustrates the unusual case of a patient with self-awareness reduction due to combined polar and paramedian bilateral thalamic infarction. The aim of this study is to outline the association among bilateral thalamic stroke, reduced self-awareness, and executive dysfunction. Such aspects have not been evaluated in the literature on patients with thalamic lesions yet. We would also suggest that reduced awareness related to executive dysfunction and consequent deficits in the instrumental activities of daily living (iADL) may be considered in assessing the possibility of SARS-CoV-2 contagion risk, as they would affect the subject's ability to take appropriate precautions.

4.3.3. Case Presentation

At the time of this study, G.A. was a 63-year-old married woman, with 5 years' education. She had normal developmental milestones and no medical history of note. She had been a factory worker all her life, but at the time of evaluation, she retired. Her father died at an early age due to unspecified causes, her mother died at 62 for complications of surgery. She had five brothers and two sisters, all deceased (two of which at a young age, one for stroke and one for cancer).

Her presenting symptoms were drowsiness, loss of balance, and strength, which have suddenly developed within few hours. Then, G.A. lost consciousness for a short while. She was transferred to the Emergency Department at the "Martini" Hospital in Turin, where she received adequate assistance.

At admission, her level of consciousness was fluctuating; no sensory-motor deficits were observed, pupils were normal and cranial nerves examination was unremarkable. The score on the National Institute of Health Stroke Scale (Brott et al., 1989) was 3 (minor stroke).

Brain computed tomography (CT) showed bilateral thalamic hypodensity suggestive of bilateral infarction; angio-CT showed no occlusion of large vessels. Electrocardiogram disclosed atrial fibrillation, which highlighted the cardioembolic nature of stroke. Thrombolysis was not considered because the onset of symptoms was > 4.5 h. Laboratory analyses were unremarkable, and vital signs were normal, except for mild hypertension.

Subsequently, G.A. was admitted to the neurological unit and subjected to more in-depth neurological investigations. The patient showed a slowly progressive and spontaneous amelioration of vigilance and consciousness. Five days after the admission, she could walk independently and appeared quite alert with reduced time and space orientation. Her speech was hypophonic and slowed down, although she spoke correctly. She presented quite apathetic and depressed.

Specifically, the neurologist conducted an interview with the patient and her primary caregiver (the cohabitant husband) before the neuropsychological assessment, carried out five days after admission to the neurological department (T0). The interview allowed collecting patient's information, double checked with the primary caregiver, through the following topics: demographic data and marital status, daily living habits, and remote anamnesis that excluded family history of neurodegenerative diseases. Finally, functional anamnesis was carried out in order to investigate aspects useful to set up an accurate neuropsychological assessment.

After spending 2 weeks in hospital, G.A. left the neurology unit and went home with a therapy consisting of oral anticoagulation therapy and folic acid. Neurologists recommended a neuropsychological rehabilitation focused on cognitive affected domains. Finally, the patient was asked to perform a follow-up examination after 6 months.

At the follow-up examination, 6 months later (T1), during the neurological evaluation, G.A. appeared alert and collaborative, adequate on relationship. Her speech was fluent and correct. Her ideation was sometimes slowed down, but always consistent with the themes proposed by the examiner. The neurological exam disclosed neither nystagmus nor other cranial nerve alterations. G.A. maintained Mingazzini I and II for more than 60 s. All tests on segmental cerebellar were accurate. She showed symmetrical tendon reflexes. G.A. ambulated independently and presented a good motor and functional recovery. At T1, G.A. also underwent a magnetic resonance imaging (MRI), which showed combined polar and paramedian bilateral thalamic infarction [*Figure 4.3.1*].

Subsequently some of the patients were contacted, through their caregivers, during and after the lockdown period, to make sure of their state of health and of SARS-CoV-2 risk of contagion. In particular, in May 2020, G.A. underwent the serology test in chemiluminescence to detect IgG antibodies against SARS-CoV- 2, recommended by the Italian Ministry of Health (Ministero della Salute, 2020).

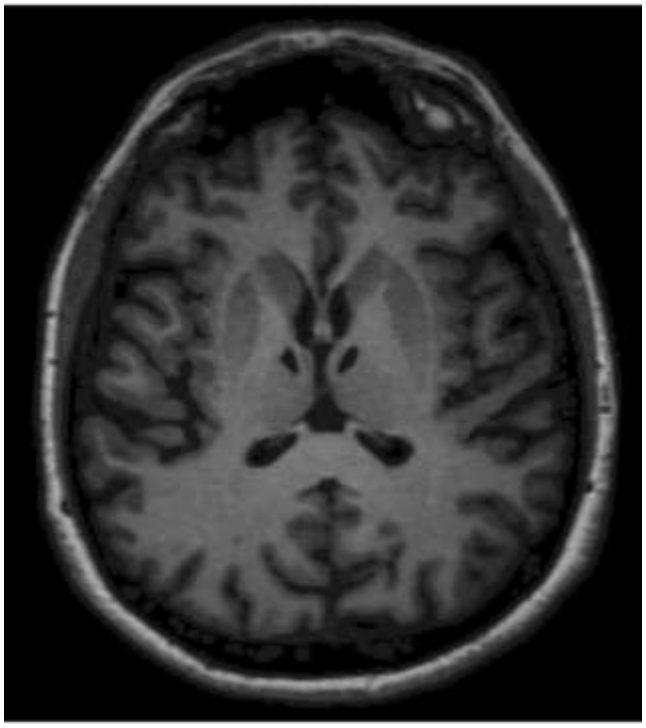

Figure 4.3.1. Reduced Self-awareness Case Report: Magnetic resonance imaging (MRI).
G.A.'s MRI shows lacunar thalamic infarcts symmetrically located within the polar and paramedian vascular territories of both thalami. Lesions are well-demarcated and isointense to cerebrospinal fluid as observed in chronic settings. The anatomical symmetry was the distinctive feature in this patient.

Neuropsychological Evaluation

G.A. was assessed during the acute phase (T0) and after 6 months (T1), undergoing the same neuropsychological evaluation, to estimate possible changes in response to the administrated therapy.

Her premorbid intellectual efficiency was assessed with the Brief Intelligence Test (*TIB*: Colombo et al., 2002), which is the Italian version of the *National Adult Reading Test* (Nelson, 1982). Her global cognition was measured with the Addenbrooke's Cognitive Examination–Revised (*ACE-R*: Mioshi et al., 2006), which includes the Mini-Mental State Examination (*MMSE*) score (Folstein et al., 1975). A detailed neuropsychological evaluation of specific cognitive domains were performed, considering: memory (*Corsi Test*; *Digit Span*; *Incidental Semantic Memory*; *Rey Memory Test*; *Short Story Recall*; Spinnler and Tognoni, 1987); language (*Token Test*: De Renzi and Vignolo, 1962; *semantic verbal fluency*: Spinnler and Tognoni, 1987); visuoconstructive abilities and praxia (*Coping Design*: Gainotti et al., 1977; *buccofacial and ideomotor Apraxia Test*: Spinnler and Tognoni, 1987); and deductive ability (*Coloured Progressive Matrices-36*: Spinnler and Tognoni, 1987). In order to exclude unilateral visual–attentional neglect, space, and percepts exploration deficits, the following tests were performed: the *Bells Test* (Gauthier et al., 1989), *lines bisection and cancellations test* (Spinnler and Tognoni, 1987), and the *entangled figures test* (Mondini et al., 2011). Executive functions and

attention were measured using: the Montreal Cognitive Assessment (*MoCA*: Conti et al., 2015), the *Attentional Matrices test* (Spinnler and Tognoni, 1987), the Trial Making Test part A, B (*TMT*: Reitan and Wolfson, 1994), *Phonemic Fluency Test* (Spinnler and Tognoni, 1987), the *Stroop Test*–Short version (Caffarra et al., 2002), and the *Wisconsin Card Sorting Test* (WCST: Kongs et al., 2000). Last, her perspective-taking capacities abilities were evaluated with Theory of Mind visual stories (ToM1 and ToM2: Amanzio et al., 2008). Executive functions were also assessed using the Behavioral Assessment of the Dysexecutive Syndrome battery (*BADS*: Wilson et al., 1996), which is composed of six subtests; each of them evaluates different abilities involved in everyday life, affected by frontal lobe impairment. Finally, in order to fully assess her executive functions, G.A. performed a *Go–NoGo task* (Amanzio et al., 2011), which is a response inhibition paradigm, estimating her errors before and after the test.

In line with previous studies (Amanzio et al., 2011, 2016, 2017, 2018; Palermo et al., 2014), we used the Anosognosia Questionnaire for Dementia (AQ-D: Migliorelli et al., 1995), in order to quantify the severity of reduced self-awareness for cognitive and behavioral deficits. Moreover, a clinician-rated semistructured interview, which is focused on difficulties typically involved in ABI, was applied: the Self-Regulation Skills Interview (*SRSI*: Ownsworth et al., 2000). The evaluation of behavioral mood changes was carried out using: the Apathy Evaluation Scale–Clinician version (*AES-C*: Marin et al., 1991); the Hamilton Anxiety Rating Scale (*HARS*: Hamilton, 1959); the Hamilton Depression Rating Scale (*HDR-S*: Hamilton, 1960); the Mania Scale (*MAS*: Bech et al., 1978); and the *Disinhibition Scale* (Starkstein et al., 2004). Finally, the functional independence in everyday life was assessed using the Autonomy in Daily Living (*ADL*: Katz et al., 1963) and the Instrumental Activity of Daily Living (*iADL*: Lawton and Brody, 1969).

Results of the Neuropsychological Assessment at T0

Data from the neuropsychological evaluation, concerning the neuropsychological tests and the Go–NoGo task, are listed in *Table 4.3.1*, and *Table 4.3.2*. The cutoff scores reported in *Table 4.3.1* (cognitive functions evaluation) are given in the statistical normal direction; the values refer to the normative data for healthy controls matched for age and education.

The neuropsychological screening assessment revealed a global cognitive impairment (MMSE, ACE-R) starting from a premorbid intellectual level slightly below the lower limits of the standard statistical norm (TIB). Moreover, the management of basic and instrumental activities of daily living was compromised. The second assessment phase (cognitive profile completion) revealed difficulties in the following functions (values below the cutoff): visual perception (Bells Test) and visual recognition of complex percepts (test of the entangled figures), buccofacial

praxia, memory (Babcock, Rey Memory Test), learning (Incidental Semantic Memory Test), access to the internal vocabulary (semantic fluencies), and first and second type of Theory of Mind. A loss of attentional capabilities was also found (Attentional Matrices, TMT-A). The MoCA score revealed the presence of executive dysfunctions, confirmed by BADS, TMT-B, phonemic fluency, Stroop test, and WCST in terms of cognitive set-shifting, inhibition of dominant responses, flexible thinking, and monitoring.

Table 4.3.1. Neuropsychological assessment: cognitive function evaluation

	T0 (post-acute phase)		T1 (stabilisation phase)		
	GA		GA		Cut-off
Cognitive and Intellective Assessment					
MMSE	**18**		**19.3**		≥ 24
ACE-R	**35**		**41**		≥ 82
TIB:					
Estimeted IQ total	**85.306**				90-110
Estimated IQ V	**80.115**				90-110
Estimated IQ P	91.144				90-110
CPM-36	26.2	ES = 3	28.2	ES = 3	≥ 18.96
Memory Assessment					
Corsi Block task	4.75	ES = 3	4.75	ES = 3	≥ 3.5
Digit Span forward	4.25	ES = 2	4.5	ES = 2	≥ 3.75
Incidental semantic memory	**2**	**ES = 0**	7.01	ES = 1	≥ 6.67
Rey Memory Test					
Immediate Recall	**18.3**	**ES = 0**	**23.1**	**ES = 0**	≥ 28.53
Delayed recall	**0.7**	**ES = 0**	**2.6**	**ES = 0**	≥ 4.69
Babcock	**3.75**	**ES = 0**	**0.75**	**ES = 0**	≥ 7.5
Language Assessment					
Token Test	33.25	ES = 4	33.75	ES = 4	≥ 26,50
Semantic Verbal Fluency	**5.5**	**ES = 0**	10.5	ES = 1	≥ 7.25
Visuospatial and visuomotor Assessment					
Bells test total score	**24**		**26**		≥ 32
Bell test (right minus left)	0		0		≤ 3
Lines bisection	17		17		17
Lines cancellation	40		40		40
Entangled figures test	**6**		**12**		50
Praxia Assessment					
Coping design:					
without programming elements	8.6	ES = 3	9.1	ES = 3	≥ 7.18
with programming elements	63.3	ES = 1	65.5	ES = 2	≥ 61.85
Constructive praxia	10.75		12.75		≥ 10.25
Ideomotor praxia	19.25		20.25		≥ 18.42
Buccofacial praxia	**12.25**		20.25		≥ 18.78
Perspective Taking Assessment					
ToM-1st type	**2**		3		≥ 3
comprehension	2		3		
memory	2		3		
ToM-2nd type	**0**		**2**		≥ 3
comprehension	2		2		
memory	2		2		

Attentional Assessment						
Attentional Matrices		**14.75**	**ES = 0**	**14.75**	**ES = 0**	≥31
TMT A		**689**	**ES = 0**	**650**	**ES = 0**	≤ 94
TMT B		**NE**	**ES = 0**	**NE**	**ES = 0**	≤ 283
TMT B-A		**NE**	**ES = 0**	**NE**	**ES = 0**	≤ 187
Executive Functions Assessment						
MoCA		**16**		18		≥ 17.36
Phonemic Verbal Fluency		**11.4**	**ES = 0**	**14.4**	**ES = 0**	≥ 17.35
Stroop Test - Short version:						
Time interference effect		**92.25**	**ES = 0**	**81.25**	**ES = 0**	≤ 36.91
Error interference effect		**11.5**	**ES = 0**	**14**	**ES = 0**	≤ 4.24
BADS		**3**		**6**		**≥ 13**
	RSC	0		0		
	KS	0		1		
	AP	1		2		
	TJ	1		2		
	ZM	1		1		
	MSE	0		0		
WCST						
	Completed categories	**0**		**2**		≥ 3
	% errors	**86**		**73**		≤ 29.90
	% perseverative errors	40		42.478		≤ 42.70

Wherever possible Equivalent Scores (ESs) are shown: ES equal to 0 corresponds to a performance of less than 5% of the normal population, thus having pathological meaning. ES equal to 1 indicates a performance to the lower limit of the norm, ES equal to 2 indicates a performance in the standard, ES equal to 3 indicates a performance higher than normal and, finally, ES equal to 4 provides a considerably higher than normal performance. Wherever there is a normative value, the cutoff scores are given in the statistical normal direction; the values refer to the normative data for healthy controls matched for age and education. Abnormal scores are reported in bold. NE, not executable.

As to the performance obtained on the response inhibition test [*Table 4.3.2*], G.A. made four times the number of errors made by healthy controls in the NoGo condition. Nevertheless, she was not able to predict the number of her errors or to monitor her own performance.

Table 4.3.2. Neuropsychological assessment: Braver's Go–NoGo response–inhibition test.

	GA		
	T0 (post-acute phase)	T1 (stabilisation phase)	Normal Control subjects
Response inhibition task Go			
% TARGET	**70**	**78.8**	98.9
RT (ms)	**467.53**	**396.25**	367
% ERRORS	**30**	**21.2**	1.1
Response inhibition task NoGO			
% TARGET	**36.4**	**39.6**	85.3
% ERRORS	**63.6**	**60.4**	14.7
Pre-performance judgement	4/40 X	5/40 X	
Post- performance judgement	5/40 X	4/40 X	

Comparison with normative data for normal control subjects (Braver et al., 2001). RT, reaction time. Pre-performance and post-performance judgments refer to the number of errors G.A. thought she would do and she did in her opinion. Abnormal scores are reported in bold.

Data from the neuropsychiatric, functional, and self- awareness evaluation are listed in *Table 4.3.3*. At T0, the evaluation detected a mood deflection under cutoff in terms of depression and apathy. It is noteworthy that AQ-D scores indicated a great impairment in self-awareness, AQ-D iADL, and AQ-D depression domains. G.A. judged the implications of the pathological event as less severe than its real nature, especially when compared with the perception of the primary caregiver.

Table 4.3.3. Neuropsychological assessment: awareness of deficits, neuropsychiatric, and functional assessment

	T0 (post-acute phase)			T1 (stabilization phase)			
	Caregiver	GA	Total Score	Caregiver	GA	Total Score	Cut-off
Awareness Assessment							
AQ-D overall	62	19	**43**	47	11	**36**	≤ 14
AQ-D cognitive part	46	15	31	38	7	31	
AQ-D behavioral part	16	4	12	8	3	5	
AQ-D ADL	4	2	2	2	2	0	≤ 4
AQ-D iADL	28	11	**17**	24	5	**19**	≤ 4
AQ-D depression	14	6	**8**	12	6	**6**	≤ 4
AQ-D disinhibition	0	0	0	0	0	0	≤ 4
SRSI						28	
Neuropsychiatric Assessment							
AES-C			**27**			**29**	≥ 37.5
HDR-S			**11**			**9**	≤ 7
HAR-S			9			8	≤ 17
Disinhibition scale overall			15			14	≤ 16.9
Apathy			9			8	
Abnormal motor behavior			1			1	
Stereotypy			1			1	
Hypomania			1			1	
Psychosis			1			1	
Poor self-care			2			2	
MAS			4			3	≤ 15
Functional Assessment							
ADL			**1**			6	6
IADL			**2**			**3**	5

Note: abnormal scores are reported in bold.

Results of the Neuropsychological Assessment at T0 after 6 Mounths follow-up

G.A. underwent a new neuropsychological assessment, using the same batteries performed at T0 [see Tables *4.3.1*, *4.3.2*, and *4.3.3*]. The patient seemed to show some improvements in her cognitive functioning but, unfortunately, she still exhibited several cognitive deficits. A specific and persistent reduced self-awareness associated with executive dysfunction and mood changes

in terms of apathy and depression were also still present.

Although G.A. showed improvements in terms of overall evaluation, she still exhibited several cognitive deficits considering: visual perception (Bells Test) and visual recognition of complex percepts (test of the entangled figures), and memory (Babcock, Rey Memory Test). Attentional deficits (Attentional Matrices, TMT-A) and executive dysfunction (BADS, TMT-B, Stroop test, WCST and Go–NoGo task) were still present. Moreover, she exhibited a persistent apathetic mood orientation (AES-C).

Indeed, G.A. was still unaware of her cognitive and behavioral deficits (in terms of global AQ-D, AQ-D iADL, and AQ-D depression). Moreover, SRSI revealed that G.A. was unable to self-monitor everyday activities, to anticipate outcomes and consequences, or to adopt new strategies in order to better face events. Awareness of functional implications, expectations of recovery, and need for treatment were not sufficient at the time of evaluation.

Results of the Serology Test in Chemiluminescence (CLIA) to Detect IgG Antibodies Against SARS-CoV-2

The serology test, carried out on May 18th, 2020, highlighted IgG antibodies present/IgM absent: high probability of previous contact with the virus (at least prior to 20–25 days). This is an indirect, quantitative test, approved by the Italian Ministry of Health (Ministero della Salute, 2020), which highlights the immune system's response to infection following contact with the coronavirus.

4.3.4. Discussion

This case report can contribute to novel insights about the neuropsychological consequences of ABI (Rusconi et al., 2014). Importantly, G.A. was affected by one of the rare cases of bilateral thalamic infarction. In fact, as documented by Kumral et al. (2001), over 2,750 patients with ischemic stroke, only 0.6% of them present this kind of infarction.

From an etiopathogenetic point of view, G.A.'s bilateral thalamic lesion was conceivably produced by an unfortunate combination of paramedian and polar artery territories infarction (Perren et al., 2005).

At T0, the neuropsychological evaluation underlined a cognitive impairment due to ABI. She showed deficits in visual perception and visual recognition of complex percepts, buccofacial praxia, attention, memory, access to the internal vocabulary, and first and second type of Theory of Mind. Executive dysfunction, in terms of cognitive set-shifting, flexible thinking, inhibition of dominant responses, and monitoring, were also present. She also showed functional disorders

and mood changes, in terms of depression and apathy. Finally, she presented a clear-cut reduction in self-awareness.

Six months later, during the follow-up phase (T1), cognitive, behavioral, and functional disorders persisted. Cognitive deficits, in terms of visual perception and visual recognition, attention, and memory, were still present.

It is noteworthy that impaired self-awareness and executive dysfunctions, concerning response-inhibition, cognitive set- shifting, and monitoring abilities, were present as residual deficits after the bilateral thalamic infarction in the post- acute phase. Importantly, the secondary disruption of self-awareness related to executive dysfunction might arise from frontal impairment or from frontal-subcortical damages (O'Keeffe et al., 2007). Considering that frontal-subcortical or diencephalic structures injuries could be predisposing factors to produce reduced self-awareness, reduction of self-awareness may be a direct consequence of frontal and diencephalic damages after lesions. This mechanism could clarify the reason why patients with a right temporoparietal or thalamic damage do not always present these clinical deficits (Starkstein et al., 1992). It is important to point out that ABI was bilateral in G.A.: in this case, it should be hypothesised a more severe clinical picture related to reduced self-awareness. Moreover, the findings by Starkstein et al. (1992) supported Nielsen's (1938) suggestion that unawareness of deficits "*may be caused by thalamic lesions or isolation of the thalamus from the parietal cortex*" (Starkstein et al., 1992, p. 1,452).

Consistent with the findings in G.A., O'Keeffe et al. (2007) suggested that any deficits in monitoring, response inhibition or cognitive flexibility, can affect patients' foresight (i.e., self-awareness).

Thus, probably G.A.'s impairment in the maintenance of cognitive representation of her experimental tasks through self-monitoring – determined by control executive processes sustained by the connection between dorsolateral and medial prefrontal cortices – may have a function in her reduced self- awareness (Palermo et al., 2014).

While considering the different etiopathogenesis between ABI and neurodegenerative disorders, the similarity of the neuropsychological profile associated with the onset of reduced self-awareness seems to authorise a transposition of the interpretative models. Therefore, we can affirm that overlapping symptoms appear consequently to specific dysfunction of the frontal networks and of the diencephalic structures. In fact, deficits in response inhibition, set-shifting, and self-monitoring contribute to reduced self-awareness (Amanzio et al., 2011, 2013, 2014, 2016; Palermo et al., 2014, 2015, 2017).

Considering the relationship between subcortical area and awareness, Ownsworth et al. (2008) reported how thalamic damages seemed to generate various deficits in functional domains, such

as cognitive, motor, sensory, and perceptual processes (Kumral et al., 1995). Instead, mood changes and reduced self-awareness can be observed with right thalamic injuries (Leibson, 2000). Finally, direct lesion of the thalamus and disconnection of different cortical networks (for example, frontal-thalamic pathways) were related to impaired awareness and emotional dysregulation (Bogousslavsky, 1994). However, these studies have the limitation of considering heterogeneous lesion sites and, consequently, patients with dissimilar cognitive disorders as unicum.

As stated above, mood changes observed in G.A. are not surprising. She obtained abnormal, but near the cutoff, scores on HDR-S and AES, in both T0 and T1. These results suggest that G.A. had a slight change in behavior, even if not so psychopathologically relevant.

G.A.'s executive dysfunction – together with the Cognitive Awareness Model (CAM), a neurocognitive model proposed by Agnew and Morris (1998) – help to comprehend the impact of executive system on self-awareness in ABI patients (Agnew and Morris, 1998). Consciousness of changes following injuries needs an interaction among comparator mechanisms of the executive system (in order to perceive modifications), different functional domains (such as cognitive, motor, sensory, and perceptual ones), and the metacognitive awareness system. Being characterized by a feedback mechanism, the CAM depends on updated information about experiences of success or failure. Consequently, it is important for self-knowledge on personal capacities and deficits (Morris and Hannesdottir, 2004). Nevertheless, G.A.'s comparator mechanisms become unable to detect discrepancies between actual and past performances, failing in cognitive tasks both of everyday activities and during test sessions.

These neuropsychological changes can make the patient less able to understand risky situations and affect the iADL. Such aspects may promote exposure to infection, as the patient may not be able to take preventive measures (e.g., social distancing, hand washing, and face mask use). The latter could represent only a suggested hypothesis, which needs to be verified through in-depth multidisciplinary investigations (neuropsychological, virological, and epidemiological).

Finally, it is important to underline that a recent article (Kummer et al., 2020) showed how a history of stroke was significantly related to poor prognosis among SARS-CoV-2 patients, admitted in the hospital from March to May 2020. Considering these results, which further studies should confirm, the authors suggested how patients with COVID-19 have higher probabilities of poor illness outcomes (Kummer et al., 2020).

The present study seems to suggest that G.A.'s comparator mechanisms, responsible for monitoring attentive performance, were compromised; however, the unfortunate co-occurrence of thalamic bilateral injury cannot be considered as the only explanatory mechanism.

4.3.5. Limitations and Conclusion

Although our results were collected from a single case study, and therefore cannot be generalized to the entire population, our work is based on strong neuropsychological methodologies that allow us to substantiate our inferences. However, future studies are needed in order to understand how metacognitive–executive dysfunction and reduced awareness can influence the possible risk of SARS-CoV-2 contagion in the elderly population.

In spite of this, this case study contributes to the poor literature on the impact of a bilateral thalamic lesion on self-awareness. Future studies will help to better analyse the possible impact of bilateral frontothalamic lesions in subjects with a reduction of self- awareness and executive dysfunction, through the combined results of MRI and positron emission tomography, in order to document a possible framework of atrophy and hypometabolism at the level of the medial prefrontal cortex.

We believe that studying reduced self-awareness more closely may be useful for developing compliance to the treatment of COVID-19 patients. Currently, older people in Italy represent the category at greatest risk, as reported by the epidemiological analysis of infected and deceased subjects due to COVID-19 (Ministero della Salute, 2020). Executive dysfunction, which makes the supervision of the iADL inadequate (Amanzio et al., 2016, 2017, 2018), could lead to a greater risk of contagion in elderly patients with neurological disorders.

Considering the above, a supervision of the iADL and rehabilitation programs of executive dysfunction might be somehow helpful in reducing the impact of COVID-19, making elderly less susceptible to the contagion.

4.3.6. References

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5. The Nocebo effect due to the COVID-19 Pandemic

The COVID-19 pandemic represents a perfect storm in which powerful nocebo effects may arise. In fact, the pandemic and subsequent restrictive measures to contain it, as well as the fear of contagion – in part exacerbated by media reports – can amplify psychological distress, worsening pre-existing clinical symptoms (Chatterjee et al., 2020). Older adults, who often present polypathologies and polypharmacies, seem to be more prone to this effect (Wong et al., 2020).

Recently, we have conducted a review on the relationship between psychological distress and sleep problems in older adults during the SARS-CoV-2 pandemic (see Cipriani et al., 2021). The purpose of this research, for which I served as corresponding author, was: (a) to review the existing literature on sleep disturbances during the current pandemic in healthy aging subjects, and (b) to highlight possible relationships between sleep problems and psychological distress, defined as a set of non-specific symptoms concerning depressive mood and anxiety manifestation (McLachlan and Gale, 2018). A systematic search strategy was implemented according to PRISMA guidelines in the international literature online databases, up to 1st July 2021. After identification and screening phases, 11 articles were included in this review. Despite the heterogeneity of the methodology adopted by the authors of the reviewed articles – which does not allow a full generalization of the results – we pointed out possible associations between sleep problems and mood changes (i.e., depression and anxiety). Furthermore, altered sleep patterns seemed to be related to changes in individual aspects, lifestyle, and attitudes adopted by older adults during the COVID-19 lockdown. Thus, the pandemic could affect both quality and quantity of sleep and psychological wellbeing of the older population, even in healthy aging.

In our perspective review, concerning the nocebo phenomena during the SARS-CoV-2 pandemic (see Amanzio et al., 2020), we highlighted that subjects with anxiety, depression, and tendency to somatization may be more susceptible to pessimistic contextual factors (i.e., negative information about the pandemic and conspiracy theories) leading to psychological stress. Furthermore, considering Randomized Controlled Trials (RCTs), the level of psychopathology (i.e., the severity of positive symptoms and signs of depression and anxiety) may largely affect patients' perceptions and attribution of bodily sensations to medication (Hwang et al., 2010). Indeed, a higher level of psychiatric symptomatology makes patients more likely to express adverse events (AEs) that manifest as nocebo-like effects (Amanzio and Palermo, 2020).
Since the evaluation of AEs in the placebo group of RCTs – combined with a specific psychotropic drug – provides an important perspective for understanding the nocebo effect

(Amanzio, 2015), we previously conducted a meta-analysis on patients with schizophrenia spectrum disorders (SCD). In particular, we analyzed the relationship between the level of psychiatric symptomatology – expressed as *Positive and Negative Syndrome Scale* (PANSS) scores (Kay et al., 1987) – and AEs rates reported in the placebo arms of double-blind clinical trials for atypical antipsychotic drugs (see Palermo et al., 2019). We selected 58 RCTs describing AEs in the placebo SCD groups, with a total of 6,301 patients. AE profiles were clusterized using the Medical Dictionary for Regulatory Activities (MedDRA) classification (Brown et al., 1999) and analyzed using a meta-regression approach. We found an association between the level of psychiatric symptomatology (i.e., PANSS score) and the highest AEs reported as nervous system disorders (p = 0.020) and gastrintestinal disorders (p = 0.004). In addition, the level of higher psychiatric symptomatology expressed with PANSS scores was also correlated with higher AEs associated with psychiatric symptoms (p = 0.017). These results showed how a higher level of psychiatric symptomatology makes patients with SCD more prone to express AEs, thus contributing to possible drop-outs and to a lower adherence to treatments.

RCTs are also useful to study the role of individual and contextual factors in which therapies vs placebos are administered, providing an important perspective for understanding the phenomenon of nocebo-related risks (Amanzio et al., 2009). In light of this, in our recent perspective article (Amanzio et al., 2021a), which will be better described in the next paragraph, we have presented the results of nocebo effects in RCT placebo groups, measured in terms of AEs and dropouts, as an explicative framework for the COVID-19 pandemic. In particular, we focused our attention on the older population, as they are more prone to exhibit the nocebo effect (Kravvariti et al., 2021), especially during the current pandemic.

Since SARS-CoV-2 vaccines were the only RCTs routinely conducted in the early stages of the pandemic, information about efficacy and safety of different vaccines provided a fertile ground for nocebo phenomena. However, little was known about the nature of the AEs associated with clinical trials of COVID-19 vaccines and the extent to which these could be traced to nocebo effects, where negative treatment-related expectations favor their occurrence.

In light of the above, we conducted a systematic review in order to compare the rates of solicited AEs in the active and placebo groups of SARS- CoV-2 vaccines approved by the Western pharmaceutical regulatory agencies (i.e. BNT162b2, mRNA-1273, and AD26.COV2.S). We also analyzed the safety data taking into account the age ranges, as reported in the original trials. Our results have been published in the prestigious journal "*The Lancet Regional Health – Europe*" (Amanzio et al., 2021b). This study will be discussed in section *5.2.*

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5.1. How do nocebo effects in placebo groups of randomized controlled trials provide a possible explicative framework for the COVID-19 pandemic?

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5.1.1. Abstract

Randomized clinical trials (RCTs) are useful to study the role of individual and contextual factors in which therapies vs placebos are administered and to provide an important perspective for understanding the phenomenon of nocebo-related risks.

The results of nocebo effects in RCT placebo groups, measured in terms of adverse events (AEs) and dropouts, will be presented as an explicative framework for the COVID-19 pandemic. Currently, SARS-CoV-2 vaccines are the only RCTs routinely conducted during the pandemic. Information about efficacy and safety of different vaccines represents a fertile ground for nocebo phenomena. Individual and contextual factors will be emphasized in order to understand the presence of a refusal of immunization associated with a specific vaccine considered less effective and safe. Critical aspects and some guidelines will be presented in order to counteract the nocebo effects and to improve adherence to drug treatments and the vaccination campaign.

The nocebo effect could explain the presence of strong resistance in European countries to immunization with a vaccine perceived as less effective, compared to others. Increased awareness of the nocebo effect would be relevant as it could lead to a greater participation in the vaccination campaign and in protecting individuals against SARS-CoV-2 infection.

5.1.2. Introduction

The COVID-19 pandemic is a major health emergency issue, which can be seen as a fertile ground for the amplification of psychological and emotional distress leading to an exacerbation of preexisting clinical symptoms (Chatterjee et al., 2020). An increased susceptibility to the effects of the pandemic is a major stress factor, especially for patients suffering from psychiatric and neurological diseases, often older people, frequently with polypathology and associated pharmacotherapy (Wong et al., 2020). It can also lead to reduced immunity, partly due to the

physiological aging process (Gavazzi and Krause, 2002). In addition, the psychological impact of quarantine measures has caused, especially in older people, significant isolation and social disconnection, which are often associated with cognitive decline, depression, and anxiety (Sepúlveda-Loyola et al., 2020). Pandemic-related stress can also have far-reaching and unforeseen effects on data collected in experimental settings (Goldfarb, 2020). Therefore, it is very likely that COVID-19 pandemic may represent a 'perfect storm' in which powerful nocebo effects may be amplified (Amanzio et al., 2020).

Nocebo effects may be observed in placebo groups of randomized clinical trials (RCTs) and measured in terms of adverse events (AEs) and dropout due to AEs, partly due to negative expectations of treatment outcomes. Patients' negative expectations for specific therapies, rather than the drugs' pharmacological action, are frequently responsible for AEs (Slomski, 2021). For example, drugs that have been claimed to produce high rates of adverse events and consequently dropouts, such as statins, actually cause no more symptomatic effects than those elicited by placebo in RCTs (Wood et al., 2020).

Currently, due to the pandemic and the associated challenges in arranging face-to-face medical review appointments, SARS-CoV-2 vaccines are the only RCTs routinely conducted. The Emergency Use Authorization for vaccines has generated negative expectations or misconceptions based on data from interim safety and efficacy analyses. In addition, the role of information presented on social media and the Internet provides a background for the presence of the nocebo effect, which may lead to refusal of immunization if some individuals believe they are receiving the less effective vaccine.

Critical aspects and some guidelines will be presented in order to counteract nocebo effects and to improve adherence to drug treatments.

5.1.3. Body

RCTs are useful to study the role of individual characteristics and contextual factors in which therapies vs placebos are administered. The evaluation of AEs and the presence of dropouts in the placebo group provide an important perspective for understanding the phenomenon of nocebo-related risks (Amanzio et al., 2009). The nocebo effect can lead to perceive a treatment as less safe or effective, eventually causing discontinuation of therapy or withdrawal from an RCT. These may be especially pertinent for patients suffering from psychiatric and chronic pain states that can augment nocebo susceptibility (Amanzio et al., 2016). Indeed, hyperalgesic nocebo effects seem to be related to biochemical and neuroendocrine mechanisms which involved both nociception and mood deflections in terms of anxiety and activating the

cholecystokininergic system (Benedetti et al., 2006). Specifically, it is associated with the activation of the hypothalamic-pituitary-adrenal axis, which controls stress reactions, and with increased blood cortisol concentrations (Benedetti et al., 2006).

Nocebo effects and responses seem to be more common in patients with mood disorders, such as depression and anxiety, and with a tendency toward somatization (Planès et al., 2016).

Importantly, not all nocebo-related negative effect events are 'nonspecific' (Amanzio et al., 2009). Some complaints may be disease-specific, as patients may confuse symptoms of an underlying disease with adverse effects of treatment (Fine et al., 1993), as reported for immunization with nonlive vaccines, where patients/people and health-care professionals tend to report symptoms of the disease against which the vaccine was administered (Okaïs et al., 2014). Moreover, the efficacy of pharmacologically active substances was greatly reduced when they were given with contradictory information (Aslaksen et al., 2015) or when negative verbal suggestions come from other patients (Colloca et al., 2004), friends and family, or the media and the Internet (Crichton and Petrie, 2015).

The current COVID-19 pandemic may represent a fertile ground for the occurrence of the nocebo phenomenon, amplified by emotional distress, with reference to the vaccination campaign in the general population. In particular, the negative expectation, amplified by information on specific vaccines with lower efficacy, may foster the presence of more spontaneous reports of adverse events after immunization (AEFI). In this phase of the vaccination campaign characterized by a lack of blindness, the knowledge of receiving a vaccine considered less effective than others may introduce distortions due to the nocebo effect. Negative information from the media, or on the Internet, about a vaccine considered less effective, on the one hand, may lead to a refusal to inoculate and, on the other hand, may increase the side effects, thus amplifying the discomfort due to AEFI.

The nocebo effects associated with the current vaccination campaign cannot be studied since the placebo groups have already received, or are about to receive, the vaccine. However, highlighting the different safety profiles and the propensity to refuse immunization with a vaccine perceived to be less effective than others, among those approved by the European Medicines Agency (EMA) (Baden et al., 2021; Polack et al., 2020; Voysey et al., 2021), is an interesting approach to study the nocebo phenomenon.

The phenomena that favor the appearance of the nocebo effect will be presented, in order to outline possible analogies with the distress generated by the current vaccination campaign, together with possible guidelines to mitigate the criticalities on treatment adherence and outcomes, also considering the factors related to the current pandemic.

5.1.4. Nocebo risk factors: negative contextual and therapeutic factors

Several aspects can influence the outcome of the nocebo phenomena. In particular, risk factors for the nocebo effect concern specific individual, contextual, and drug-related characteristics, which should be emphasized [see *Table 5.1.1*].

Patient's psychological characteristics may increase the likelihood of occurrence of nocebo-related AEs in RCTs. In particular, depression and anxieties and its somatic symptoms, such as tachycardia, dyspnea, and sweating, are considered some of the psychological factors involved in nocebo related side effects in RCTs (Amanzio, 2015; Amanzio and Palermo, 2020). This symptomatology could be wrongly ascribed to the treatment (Barsky et al., 2002).

Furthermore, psychiatric patients also represent an interesting population, as they are prone to nocebo adverse reactions. Indeed, AEs affect adherence and dropout rates among patients with psychiatric disorders in RCTs (Palermo et al., 2019). In particular, a meta-analysis study of AEs in placebo groups of patients with schizophrenia spectrum disorder (SCD) showed that their symptoms were related with the rates of adverse reactions reported, demonstrating how the level of psychiatric symptomatology makes patients with SCD prone to a negative outcome associated with treatment (Palermo et al., 2019).

Characteristics associated with the patients' age and physical status may affect the occurrence of the nocebo effect (Kravvariti et al., 2021). Indeed, lack of evidence of a treatment's efficacy on a specific cohort, such as older adults, or the safety concerning frail subjects with polypathology, may lead to AEs related to the nocebo effect being more likely to be experienced (Kravvariti et al., 2021). Nevertheless, there is underrepresentation of older adults in RCTs, partially due to the medical complexity of geriatric patients (Kravvariti et al., 2021).

In RCT studies, nocebo-related AEs may also vary significantly in relation to the *physician-related factors* and the verbal cues provided (Palermo et al., 2019). The communication issues concerning efficacy, reactogenicity and safety profile may induce increased AEs in patients. In relation to these aspects, studies on the nocebo effect related to biosimilar drug therapy highlighted how a style of communication focused on negative aspects of the new drug, compared to the original therapy, may increase the risk of nocebo response (Kravvariti et al., 2018). In this direction, some physicians perceive generic drugs as lower quality and such aspect, if recognized by the patient, may enhance the nocebo effect and the anchoring of negative expectations regarding the treatment, which will persist over time (Häuser et al., 2012; Heikkilä et al., 2007).

The nocebo effect may also be elicited by physicians' body language rather than verbal language (Häuser et al., 2012). In particular, negative non-verbal behaviors, such as not smiling and avoiding eye contact with the patient, contribute to the nocebo effects (Daniali and Flaten, 2019). Other factors that may increase the risk of the nocebo effect in relation to physician-related factors are a paternalistic attitude or a disease-centered approach, where very little attention is given to the patient's narrative or emotional experiences (Kravvariti et al., 2021).

With regard to the *drug-related factors*, frailty patients frequently present polypathology combined with polypharmacy. Such condition is likely to be associated with adverse drug reactions during the lifespan, which have potential toxic effects (amanzio et al., 2016) and may facilitate the occurrence of nocebo (Kravvariti et al., 2021). Particularly, previous adverse experiences with drug treatments, especially of long duration, may increase the likelihood of adverse effects and reduce the likelihood of therapeutic benefit in the future (Planès et al., 2016). Furthermore, package leaflet information – which aims to enhance safety by providing detailed information about the drug – the interactions with other therapies, and possible side effects, can trigger nocebo responses in more susceptible patients, particularly the older ones (Kravvariti et al., 2021).

Other issues, such as periodic medical examinations to monitor the therapy, may highlight the possible AEs and let the patient believe that follow-up visits may be due to the unsafety of the drug (Kravvariti et al., 2021).

In addition to the above, the current COVID-19 pandemic can negatively affect the mental health of subjects, due to the risk of SARS-CoV-2 contagion, possibly facilitating the onset of the nocebo effect (Fragoulis et al., 2020). Moreover, the situational and contextual factors, such as isolation and lack of social contact, can lead to depression and anxiety (Sepúlveda-Loyola et al., 2020), which can also be exacerbated by infodemia (WHO, 2021) represented by media negative information (Amanzio et al., 2020). In addition, because of the COVID-19 pandemic, outpatient clinics took restrictive measures in order to contain the spread of the contagion; such aspect negatively affected the patient–physician relationship and, consequently, led to the inability of the patient to be reassured with respect to his or her health condition, resulting in increased nocebo phenomena (Fragoulis et al., 2020). As mentioned above, in the current health emergency, the only RCTs that are regularly conducted are those concerning SARS-CoV-2 vaccination. Once again, the older adults are poorly represented within these trials (Soiza et al., 2021).

Table 5.1.1. Nocebo risk factors in COVID-19 pandemic

Patients-related Factors	• Age (lack of evidence on specific cohort of subjects) • Disease process (lack of evidence on subjects with polipathologies) • Psychological and psychiatric factors
Physician-related Factors	• Communication issues concerning: efficacy, reactogenicity and safety profile • Paternalistic attitude or a disease-centered approach • Non-verbally negative issues
Drug-related Factors	• Package leaflet information • Possible drug interactions • Long term prescribing history • Prior adverse drug reactions
COVID-19 related Factors	• Negative media information (infodemia) • Misinformation (such as fake news) • Psychological distress due to the pandemic • Pejorative perceptual distortion •
Vaccine-related Factors	• Information about efficacy and safety of different vaccines • Cost of different vaccines • Difficulty in scheduling inoculation due to reduced delivery of vaccines • Lack of blinding for vaccines emergency use authorized by EMA

Note: EMA = European Medicines Agency.

Conflicting information on the efficacy of different vaccines, as well as the spread of data from vaccine approval studies, that may be misinterpreted, could lead the general population to draw inaccurate conclusion (Olliaro, 2021), favoring the possible occurrence of nocebo effects. Such aspects, communicated mainly by the media, may induce people to believe that there are 'second-order' vaccines, and this biased perception could lead more easily to experience a nocebo effect after vaccine inoculation, which could occur through the symptomatology induced by the virus itself. Indeed, several types of vaccines, even nonlive ones, can cause adverse reactions indistinguishable from the symptoms of the disease against which the vaccine is administered, due to the nocebo effect (Okaïs et al., 2011). On the other hand, difficulty in scheduling inoculation due to reduced vaccine delivery may exacerbate pandemic-related stress, which negatively affects preexisting clinical symptoms (Chatterjee et al., 2020).

Although there are critical aspects that affect all new vaccines for SARS-CoV-2 contagion, such as:

- the speed of the synthesis and the production;
- the acceleration of testing phases to assess their safety and efficacy;
- the lack of blinding for vaccine emergency use authorized by the regulatory agencies, such as European Medicines Agency (EMA), in one or in all study arms, which may distort trial results in terms of reported AEs;
- the emergency approval by the regulatory agencies based on data of interim analyses;
- the phase III not yet completed to know better the safety profile of the vaccines;
- the recommendations for their use in limited categories of subjects and not in the general population.

However, these aspects were primarily emphasized for the AZD1222 vaccine (Voysey et al., 2021). Several factors triggered the nocebo phenomenon with respect to the AZD1222 vaccine, to the point of leading to refusal to be immunized by it.

For example, the age for which the AZD1222 against SARS-CoV-2 vaccine is recommended ranges from 18 to 55 years (Voysey et al., 2021). As the European Medicines Agency reported, most of the participants in these studies were between 18 and 55 years old. Results in older adults – 55 years and older – are not sufficient to comprehend whether the vaccine will be safe and effective among these subjects. For this reason, even if EMA approved the AZD1222 vaccine for any age, some European countries have advised of avoiding the administration of this vaccine in the older population. Another factor could be the reluctance of some citizens to be given the AZD1222 vaccine, after the press campaign questioning its safety and efficacy. In this direction, some people rejected the vaccine after a series of bad publicity, in terms of the number of doses delivered in some European countries (European Centre for Disease Prevention and Control, 2021). In particular, four out of five doses of the vaccine delivered to EU countries have not been used yet. Data from the European Centre for Disease Prevention and Control estimate that 4,849,752 doses of the 6,134,707 distributed among the 27 EU countries have to be administered yet [see *Table 5.1.2*].

The refusal to undergo immunization with AZD1222 vaccine may also be due to media reports such as the temporary suspension from the market, for different reasons, in some EU countries (for example, some regions of Sweden and Germany) together with South Africa may have added further skepticism. Moreover, the lower cost of this vaccine compared to mRNA ones (i.e. BNT162b2 and mRNA-1273) may be another factor explaining the skepticism toward it (Dyer, 2021).

Table 5.1.2. ECDC analysis of AZD1222 doses distributed and administered

	Doses distributed	**Doses administered**	**Doses administered (%)**
Austria	156,000	39,218	3.9%
Belgium	201,600	9,832	20.5%
Bulgaria	117,600	2,035	1.73%
Germany	1,452	189,206	13%
Italy	499,200	96,621	19%
Sweden	100,200	26,595	3.8%
France*	1,137.600	125,859	11%

European Centre for Disease Prevention and Control (ECDC): data corrected to 24 February 2021.
* France did not provide ECDC with data on AZD1222 doses (Source Covidtracker.fr site).

5.1.5. Expert Opinion

This commentary examines the nocebo phenomena observed in RCTs, and it is important to outline possible guidelines to improve not only adherence to treatment but also the health status of subjects at risk of a poorer treatment outcome. These guidelines could help to assess the impact of the current pandemic on the vaccination campaign in the general population, which may amplify nocebo-prone behaviors.

In order to a better identification of patients at risk, important aspects of individual characteristics should be more considered, together with context-related factors.

Further studies are needed on the older population, which is currently underrepresented in RCTs (Shenoy and Harugeri, 2015), and in phase III studies of SARS-CoV-2 infection vaccines (i.e. Voysey et al., 2021). The characteristics of these subjects, such as the presence of physical frailty, polypathology and in polypharmacotherapy, could represent an important distorting factor in the observed results in terms of efficacy and AEFI, and the outcomes of these trials may not be fully generalizable to persons 65 years and older (Lockett et al., 2019).

Phase III study of COVID-19 vaccines could cause the nocebo effect and alter results. At this stage, subjects are aware of which vaccine will be associated with them; therefore, they are not blind. This condition has been reported in RCTs to increase nocebo effects (Bartley et al., 2016). If the received treatment is known, the incidence of AEs and the trial results could be affected (Silvestri et al., 2003). These aspects may be more frequently observed in the group associated with the vaccine considered less effective. Adverse events following immunization and interpretation bias were also associated with nocebo effects for nonlive vaccine inoculation (Okaïs et al., 2011).

Strategies to minimize the nocebo-related risks and to improve adherence to drug treatment should also be considered.

It would be important to analyze the emotional and psychological impact of patients participating in RCTs, as these aspects may be more present due to the COVID-19 pandemic (Goldfarb, 2020).

Since nocebo effects involve a psychological stress response characterized by increased anticipatory anxiety (Elsenbruch et al., 2012), negative expectations should be measured with scales to assess their intensity to the propensity to develop a nocebo prone behavior (Kravvariti et al., 2018). If patients have negative expectation on a prescribed drug, they have a higher probability to report AEs at follow-up (Barsky et al., 2002), above all in case of a new therapy (Nestoriuc et al., 2010).

Moreover, as individual factors such as personality traits may promote the occurrence of the nocebo response, it would be appropriate to identify individuals with anxious and pessimistic dispositions and to carry out cognitive-behavioral side-effect prevention training interventions (Kern et al., 2020). Psychotherapy may also reduce or remove the nocebo effect, particularly by discussing and possibly modifying negative expectations related to treatment, referring to the patient's background and prior experiences (Locher et al., 2019). Positive framing has also proved to be an effective strategy for preventing AEs in the influenza vaccination campaign (O'Connor et al., 1996). In this direction, it would be helpful to focus on benefits rather than negative effects, for example by highlighting the proportion of patients who usually tolerate the treatment well without experiencing any particular AEs (Slomski, 2021). In particular, a proactive attitude and language of the health-care provider evokes positive expectations in the patient, promoting the placebo effect and discouraging the nocebo effect, as well as moving from a problem-oriented to a solution-oriented approach (Hansen and Zech, 2019). Moreover, using the so-called 'contextualized informed consent' approach could reduce the occurrence of benign nontreatment-specific adverse effects. Indeed, after advising subjects of the nocebo effect that might occur in association with disclosure of its discosure, they could be asked whether they want to be informed (Colloca and Barsky, 2020).

Another appropriate strategy to minimize the nocebo effect would be to introduce an additional natural history group in RCTs. The introduction of this third group would allow, on the one hand, to distinguish drug-related AEs from base rates of preexisting general symptoms and, on the other hand, to identify AEs caused by the nocebo effect as the difference between the symptoms collected in the natural history group and the side effects presented in the placebo group (Amanzio, 2015). This research design was first applied to a clinical trial of a statin by Wood and colleagues (Wood et al., 2020). The authors showed that 90% of the side effects of

statins were explained by the nocebo effect. Taking into account the natural course in RCTs, such as Zelen Design (Zelen, 1979), would provide better monitoring of the natural history of the disease and avoid the need to randomize patients into control groups without treatment, so as not to incur ethical issues (Enck et al., 2013).

Awareness of nocebo effects is relevant as it could lead to a wrong consideration of treatment as unfavorable. The nocebo effect is also responsible for non-adherence to treatment and for discontinuation. When patients expect no improvements, they blame the treatment and, subsequently, reduce or interrupt the therapy. In this regard, the nocebo effect could explain the presence of a strong resistance within European countries to immunization with the vaccine perceived as less effective, compared to others, in protecting against SARS-CoV-2 infection.

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5.2. Adverse events of active and placebo groups in SARS-CoV-2 vaccine randomized trials: A systematic review

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5.2.1. Abstract

For safety assessment in clinical trials, adverse events (AEs) are reported for the drug under evaluation and compared with AEs in the placebo group. Little is known about the nature of the AEs associated with clinical trials of SARS-CoV-2 vaccines and the extent to which these can be traced to nocebo effects, where negative treatment-related expectations favor their occurrence.

In our systematic review, we compared the rates of solicited AEs in the active and placebo groups of SARS-CoV-2 vaccines approved by the Western pharmaceutical regulatory agencies. We implemented a search strategy to identify trial-III studies of SARS-CoV-2 vaccines through the PubMed database. We adopted the PRISMA Statement to perform the study selection and the data collection and identified three trial: two mRNA-based (38403 participants) and one adenovirus type (6736 participants).

Relative risks showed that the occurrence of AEs reported in the vaccine groups was higher compared with the placebo groups. The most frequently AEs in both groups were fatigue, headache, local pain, as injection site reactions, and myalgia. In particular, for first doses in placebo recipients, fatigue was reported in 29% and 27% in BNT162b2 and mRNA-1273 groups, respectively, and in 21% of Ad26.COV2.S participants. Headache was reported in 27% in both mRNA groups and in 24% of Ad26.COV2.S recipients. Myalgia was reported in 10% and 14% in mRNA groups (BNT162b2 and mRNA-1273, respectively) and in 13% of Ad26.COV2.S participants. Local pain was reported in 12% and 17% in mRNA groups (BNT162b2 and mRNA-1273, respectively), and in 17% of Ad26.COV2.S recipients. These AEs

are more common in the younger population and in the first dose of placebo recipients of the mRNA vaccines.

Our results are in agreement with the expectancy theory of nocebo effects and suggest that the AEs associated with COVID-19 vaccines may be related to the nocebo effect.

5.2.2. Summary

Adverse events of drugs are a central feature of safety assessment information. It is known that randomized clinical trials provide a perspective for understanding the role of negative expectations in treatment outcomes – the nocebo effect, originally introduced to describe the negative effects of a placebo treatment (Kennedy, 1961).

In a RCT, subjects know that they can receive either the active drug or the placebo and, accordingly, they are informed about the AEs they may experience. This can have a significant impact on the experience of associated discomfort. Indeed, drugs that produce more AEs cause highest symptomatic effects, even in the placebo groups (Amanzio et al., 2009; Smolen et al., 2021), and consequently higher dropout rates due to a negative treatment outcome. Significantly, Benedetti et al. (2021) have recently demonstrated an involvement of hypothalamic-pituitary-adrenal activity and state anxiety in AEs reporting after placebo administration. AEs may also be related to disease symptoms as reported for immunization with non-live vaccines. This highlights that symptoms are not always caused by the vaccine, but may be due to negative expectations and linked to nocebo risks (Okaïs et al., 2011). The reason why these AEs occur is unclear, and understanding the underlying mechanisms is an ongoing challenge.

Little was known about the nature of the AEs associated with clinical trials of SARS-CoV-2 vaccines and the extent to which these are nocebo effects, where negative treatment-related expectations favor their occurrence. With this aim, we conducted an analysis of the solicited AEs in clinical trials for SARS-CoV-2 vaccines. We analyzed both active recipients and placebo groups, in order to test whether any of these AEs might be associated with nocebo effects.

We implemented a search strategy to identify through the PubMed database (https://pubmed.ncbi.nlm.nih. gov), trial-III studies of SARS-CoV-2 vaccines published until 1st July 2021. No filter or limits were used. We adopted the "PRISMA Statement" (Page et al., 2021) to perform the study selection and the data collection. We only considered trials approved by Western pharmaceutical regulatory agencies – i.e. the EMA or the Food and Drug Administration – as safety data could cross-checked with results included in trial publications. As inclusion criteria, we considered studies in which the placebo control group was treated with a saline solution and data collected considering the adult population (> 18 years). Particularly,

we analyzed studies concerning three different vaccines: BNT162b2 (Polack et al., 2020), mRNA-1273 (Baden et al., 2021), and Ad26.COV2.S (Sadof et al., 2021). For all studies, the AEs were collected in both vaccine and placebo group arms. We only considered and included in the database AEs that were present in at least two out of three trials of each vaccine. the AEs were coded according to the Medical Dictionary for Regulatory Activities (MedDRA).

The total number of subjects included in the safety population set for BNT162b2 was 8080 (4040 in both the vaccine and placebo groups), for mRNA-1273 was 30323 (15168 in the vaccine group and 15155 in the placebo) and for Ad26.COV2.S was 6736 (3356 in the vaccine group and 3380 in the placebo group).

The Relative Risks (RR) showed that, in each study, the probability of occurrence of almost all AEs reported in the vaccine groups was higher compared to the placebo groups [see *Table 5.2.1*].

The most frequently solicited AEs in both the active and placebo groups were fatigue, headache, local pain (as injection site reactions), and myalgia/muscle pain. The most frequently reported adverse reaction in the active groups was local pain, with a higher percentage frequency observed for the mRNA vaccines (BNT162b2: 79%; mRNA-1273: 84%; Ad26.COV2.S: 49%); whereas fatigue (BNT162b2: 29%; mRNA-1273: 27%; Ad26. COV2.S: 21%) and headache (BNT162b2: 27%; mRNA-1273: 27%; Ad26.COV2.S: 24%) were the most common AEs among placebo recipients.

After the first dose, a significant increase of fatigue and headache was observed in younger subjects in the placebo groups of the mRNA vaccines (CI: 0.3 to 0.4) in comparison to the older groups. In contrast, the percentage of these adverse events (fatigue and headache) in the younger and older recipients was similar for placebo group of the viral vector type vaccine.

Considering participants aged 18-54 years, fatigue and headache were reported more in the placebo groups combined with BNT162b2. Interestingly, in the vaccine recipients local pain was the most reported symptom, as injection site reaction, with a higher representation in the younger subjects (for the mRNA vaccines with a C.I. between 0.7-0.9, and for the viral vector type vaccine between 0.3-0.6). However, in the placebo recipients, this specific AE was reported in the same C.I., between 0.1-0.2, in the two age groups and for all three vaccines. The systemic side effect of myalgia/muscle pain was reported in vaccine recipients in a C.I. between 0.1 and 0.4, with a higher representation for younger subjects in the three groups, and considering placebo recipients between 0.1-0.2 for the two age groups [see *Figure 5.2.1*].

Table 5.2.1. Relative risk (95 % CI) of solicited adverse events – any grade - for BNT162b2, mRNA-1273, and Ad26.COV2.S (safety set)

		Active group		Placebo group		RR	lower CI	upper CI
AEs	Vaccine	N	n_AEs (%)	N	n_AEs (%)			
	BNT162b2	4040	406 (10.05)	4040	247 (6.11)	1.644	1.412	1.914
Arthralgia/joint pain	mRNA-1273	15168	2511 (16.55)	15155	1783 (11.76)	1.407	1.330	1.489
	Ad26.COV2.S					–	–	–
	BNT162b2	4040	996 (24.65)	4040	545 (13.49)	1.828	1.662	2.009
Antipyretic/analgesic use	mRNA-1273					–	–	–
	Ad26.COV2.S	3356	668 (19.90)	3380	191 (5.65)	3.522	3.021	4.107
	BNT162b2					–	–	–
Any local AR	mRNA-1273	15168	12765 (84.15)	15155	2997 (19.77)	4.256	4.118	4.398
	Ad26.COV2.S	3356	1685 (50.20)	3380	657 (19.43)	2.583	2.393	2.788
	BNT162b2					–	–	–
Any systemic AEs	mRNA-1273	15168	8320 (54.85)	15155	6399 (42.22)	1.299	1.269	1.330
	Ad26.COV2.S	3356	1850 (55.12)	3380	1185 (35.06)	1.572	1.488	1.661
	BNT162b2	4040	434 (10.74)	4040	203 (5.02)	2.138	1.820	2.511
Chills	mRNA-1273	15168	1253 (8.26)	15155	878 (5.79)	1.426	1.312	1.550
	Ad26.COV2.S					–	–	–
	BNT162b2	**4040**	**1700 (42.08)**	**4040**	**1172 (29.01)**	**1.451**	**1.366**	**1.541**
Fatigue	**mRNA-1273**	**15168**	**5635 (37.15)**	**15155**	**4133 (27.27)**	**1.362**	**1.318**	**1.408**
	Ad26.COV2.S	**3356**	**1283 (38.23)**	**3380**	**728 (21.54)**	**1.775**	**1.643**	**1.918**
	BNT162b2	4040	111 (2.74)	4040	27 (0.67)	4.111	2.706	6.246
Fever	mRNA-1273	15168	115 (0.75)	15155	44 (0.29)	2.611	1.846	3.694
	Ad26.COV2.S	3356	302 (8.99)	3380	20 (0.59)	15.208	9.697	23.851
	BNT162b2	**4040**	**1413 (34.97)**	**4040**	**1100 (27.23)**	**1.285**	**1.203**	**1.372**
Headache	**mRNA-1273**	**15168**	**4951 (32.64)**	**15155**	**4027 (26.57)**	**1.228**	**1.186**	**1.272**
	Ad26.COV2.S	**3356**	**1306 (38.91)**	**3380**	**802 (23.73)**	**1.640**	**1.523**	**1.766**
	BNT162b2	4040	189 (4.67)	4040	45 (1.11)	4.200	3.043	5.796
Local erythema/redness	mRNA-1273	15168	430 (2.83)	15155	67 (0.44)	6.412	4.962	8.287
	Ad26.COV2.S	3356	245 (7.30)	3380	131 (3.87)	1.884	1.532	2.316
	BNT162b2	**4040**	**3186 (78.86)**	**4040**	**488 (12.08)**	**6.529**	**5.998**	**7.106**
Local pain	**mRNA-1273**	**15168**	**12690 (83.66)**	**15155**	**2658 (17.54)**	**4.770**	**4.605**	**4.941**
	Ad26.COV2.S	**3356**	**1632 (48.63)**	**3380**	**564 (16.68)**	**2.914**	**2.682**	**3.166**
	BNT162b2	4040	250 (6.19)	4040	32 (0.79)	7.812	5.421	11.258
Local swelling	mRNA-1273	15168	932 (6.14)	15155	52 (0.34)	17.908	13.556	23.656
	Ad26.COV2.S	3356	178 (5.30)	3380	53 (1.56)	3.383	2.498	4.579
	BNT162b2	**4040**	**738 (18.26)**	**4040**	**398 (9.85)**	**1.854**	**1.655**	**2.078**
Myalgia/muscle pain	**mRNA-1273**	**15168**	**3441 (22.68)**	**15155**	**2071 (13.66)**	**1.660**	**1.580**	**1.745**
	Ad26.COV2.S	**3356**	**1113 (33.16)**	**3380**	**430 (12.72)**	**2.607**	**2.358**	**2.883**
	BNT162b2	4040	37 (0.91)	4040	37 (0.91)	1.000	0.635	1.574
Nausea/vomiting	mRNA-1273	15168	1262 (8.32)	15155	1074 (7.08)	1.174	1.086	1.270
	Ad26.COV2.S	3356	477 (14.21)	3380	327 (9.67)	1.469	1.287	1.677

Abbreviations: AEs= Adverse Events. N= sample size. n AEs= number of Adverse Events. RR=Relative Risk. CI= Confidence Interval. AR= Adverse Reaction.

[a] The bold lines represent the most frequently reported symptoms.

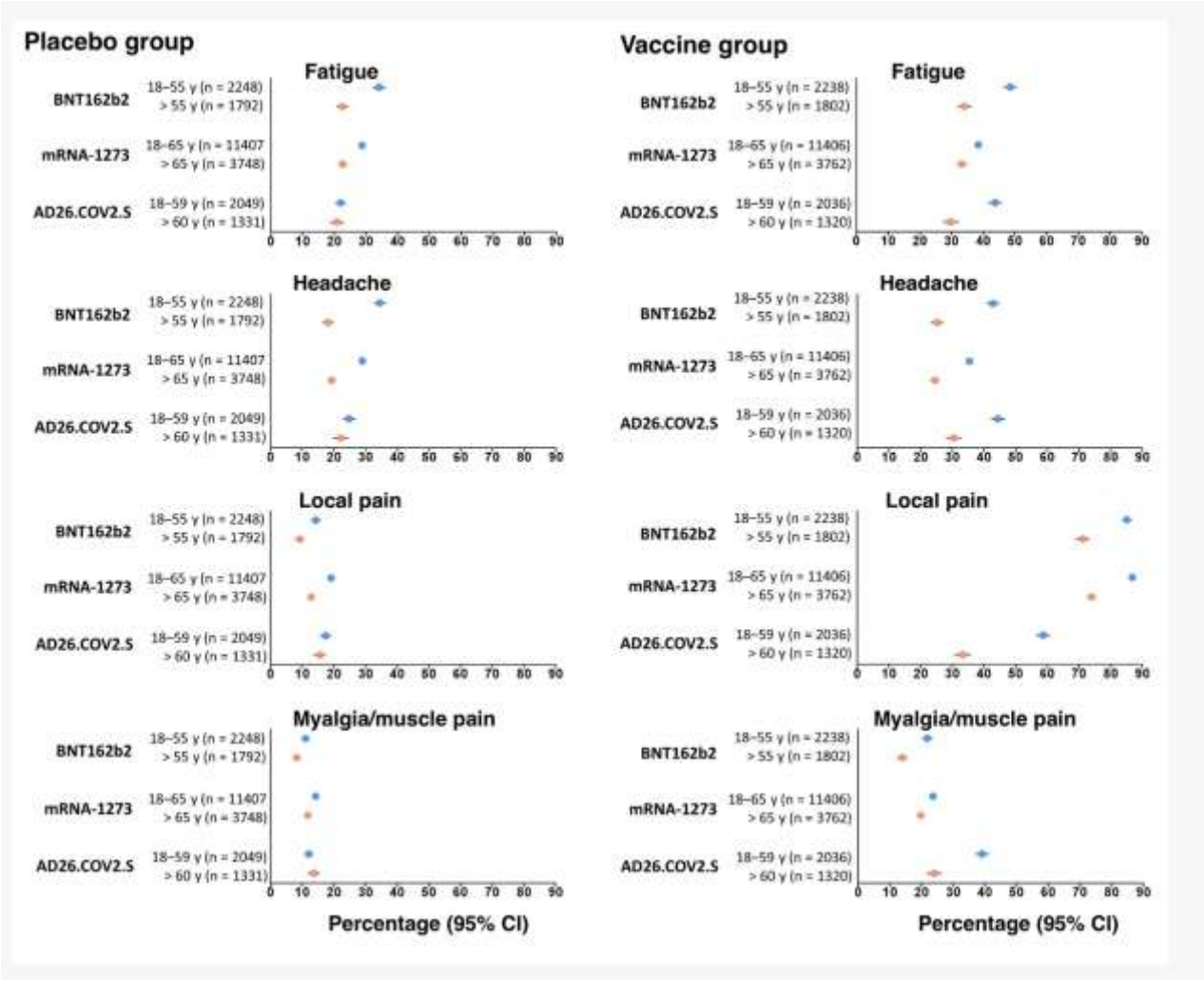

Figure 5.2.1. AEs elicited in the placebo and active groups of RCTs for SARS-CoV-2 vaccines by younger and older subjects.
Percentage (95% CI) of solicited AEs in younger (blue spots) and older (orange spots) placebo recipients, compared to the vaccine arms, of mRNA based vaccines (first doses) and viral vector vaccine considering fatigue, headache, local pain, and myalgia/muscle pain.

The percentage (95% CI) with AEs was less after the second dose of placebo. Specifically, among the systemic reactions, fatigue, headache, and myalgia/muscle pain were observed to a lesser extent after the second doses of placebo in comparison to the first doses. Particularly, fatigue decreased from 29% to 20% in the BNT162b2-associated group, and from 27% to 23% in mRNA-1273-associated group. Headache decreased from 27% to 20% in the BNT162b2-associated group and from 27% to 23% in mRNA-1273-associated group. Finally, myalgia/muscle pain decreased from 10% to 7% in the BNT162b2-associated group and from 14% to 12% in mRNA-1273-associated group. On the contrary, considering local pain as a specific adverse reaction, we observed a decrease following the second dose of placebo for the BNT162b2-associated group (from 12% to 10%) and not for the mRNA-1273- associated group. On the other hand, in the vaccine groups, we observed an increase of almost all AEs following the second dose, with the exception of local pain.

As for Unsolicited AEs, they were more common in the vaccine groups than in the placebo groups (BNT162b2: 27% vs 12%; mRNA-1273: 22% vs 19%; Ad26.COV2.S: 13% vs 12%). Serious AEs (SAEs) observed in the active and placebo groups of the three different vaccines occurred at a similar rate. Particularly, any type of SAEs was reported in less than 1% of both vaccine and placebo groups for all the trials (BNT162b2: 0.6% vs 0.5%; mRNA-1273: 0.5% vs 0.6%; Ad26.COV2.S: 0.4% in both vaccine and placebo groups). Interestingly, SAEs considered related by the investigators to the administration of the drug or placebo were < 0.1% for all the studies analyzed. Furthermore, deaths only occurred in < 0.1% in both vaccine and placebo groups.

Taking together, these findings seem to suggest a role for nocebo in systemic adverse reactions, as mild symptoms, most of which are not vaccine related.

The recording of solicited AEs, assessed in the placebo recipients after the first doses, allowed us to analyze the role of negative expectations in treatment outcomes. In addition, the results of the second doses of vaccines and placebos allowed us to investigate aspects not only related to the negative expectations associated with a new treatment, but also in terms of learning from previous experience, as a conditioning phenomenon. Non-pharmacodynamic factors, such as expectation alone, analyzed in the placebo groups of the considered trials after the first treatment dose, may have triggered distressing symptoms – as an effect of the nocebo phenomenon (Kennedy, 1961; Hahn and Chater, 1997). Self-fulfilling prophecy is a phenomenon whereby the belief that a future event will occur contributes to the actual occurrence of that adverse reaction. It plays a crucial role in modelling experiences and can be considered causal, rather than simply predictive (Eden and Zuk, 1995). Such beliefs, as response expectations, can influence health outcomes (Shelke et al., 2008). This phenomenon may be particularly relevant during the current state of pandemic emergency and when testing new vaccines (Amanzio et al., 2020; 2021). The fairly high proportions of placebo and vaccine recipients who have experienced AEs, and the adverse reactions observed, may suggest prevention strategies to promote a possible greater adherence to the vaccination campaign. The media and health professionals could potentially reduce these side effects through positive framing and by raising awareness of the nocebo effect, which may lead to a greater participation in the COVID-19 immunization and to a greater protection from infection (Myers et al., 1987). Significantly, it would be also crucial to emphasize how the levels of occurrence of SAEs in the analyzed trials were similar in vaccine and placebo recipients, and how they were defined by the authors as unrelated to vaccination and in line with the expected background rate in the general population (Baden et al., 2021; Polack et al., 2020; Sadof et al., 2021).

5.2.3. References

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6. Conclusions

The first chapter of this PhD Thesis is an introduction to the executive control in aging, outlining the rationale behind the studies conducted during my doctoral program. Specifically, three main topics were presented, each of which has been discussed in the subsequent chapters of this Thesis (Chapter 2, 3, 4, and 5). In particular, the presented studies investigated the role of executive dysfunction in frailty and self-awareness on the continuum from normal cognitive aging to neurocognitive disorders, also considering the psychological implications of the COVID-19 pandemic and the resulting restrictive measures adopted to contain the spread of the virus.

In this last Chapter, the primary findings of this research are summarised and discussed in relation to their clinical implications. Furthermore, their strengths and limitations are outlined, along with suggestions for future directions.

6.1. Executive Dysfunction and Frailty in Normal Cognitive Aging

The studies described in the second Chapter highlighted how executive dysfunction and frailty are two aspects strictly connected in older subjects. Furthermore, both may have powerful implications on the psychological well-being of individuals in healthy cognitive aging, during the COVID-19 pandemic.

In our longitudinal study (Amanzio et al., 2021a), we first analyzed the relationship between neuropsychological factors and physical frailty before the pandemic (T0). We found that two determinants of the phenotypical model (Fried et al., 2001) – i.e., handgrip strength and gait speed – were explained, from a cognitive point of view, by attentive-executive performances (p = 0.0229 and p = 0.0046, respectively). These results are in line with what has been previously found in the literature (Chou et al., 2019; Hooghiemstra et al., 2017; Robertson et al., 2014), according to which attentional-executive functioning, mediated by prefrontal cortex, is related to walking speed (Amboni et al., 2013) and handgrip strength (MacDonald et al., 2011). In addition, in our study, these two components of frailty were predicted by mood changes (p = 0.0100 both, handgrip and walking speed), in terms of depression, apathy, and anxiety.

In the COVID-19 pandemic, (T3) we investigated whether lockdown fatigue could be influenced by such attentional-executive and psychological factors, assessed during the pre-pandemic period (T0). A significant moderate-mediation model revealed the interacting effects of psychomotor speed, gait speed, and depression (assessed at T0) on lockdown fatigue (T3). Specifically, a significant interaction between low psychomotor speed (attentional-executive

functioning) and low gait speed (frailty determinant) was associated with stronger mood deflection (in terms of depression). Thus, only at the lowest levels of gait speed the strength of the depressive mood mediate the effect that low psychomotor speed had on lockdown fatigue.

Furthermore, we found that physical frailty and attentional-executive functions seem to have a major role also in the perceived threat of SARS-CoV-2 infection in healthy cognitive aging (Bartoli et al., 2021). Specifically, multiple linear regression analysis showed that the perceived threat of SARS-CoV-2 infection was predicted not only by lower levels of language performance and increased levels of anxiety, but also by decreased attentional-executive performance, in terms of information processing speed ($p = 0.002$) and more severe frailty status ($p = 0.015$). In addition, a mediation/interaction model showed that the perceived threat of contracting SARS-CoV-2 was predicted by increased frailty ($p = 0.0034$) and enhanced anxiety ($p = 0.0075$), further showing an interaction between these two predictors ($p = 0.0338$).

Taking together, the results of both studies (Amanzio et al., 2021; Bartoli et al., 2021) showed that physical health, in terms of frailty, and executive functioning may play an important role during the COVID-19 pandemic, even in cognitively healthy aging subjects. Furthermore, in line with others studies, psychological distress – in terms of depression and anxiety – may be involved in the lockdown fatigue (Field et al., 2021) and perceived risk of infection (Terraneo et al., 2021), in older adults too (Hansen et al., 2021; Pasion et al., 2020). Interestingly, the PFC is implicated in mood changes, both in terms of depression and anxiety (Hare and Duman, 2020).
Although these longitudinal studies were carefully designed and achieved their purposes, some limitations should be addressed. Firstly, the small sample size; however, the subjects were studied in-depth through a neuropsychogeriatric assessment before the COVID-19 pandemic (T0), and both during the first lockdown – either with strong restrictive measures (T1) and when they were eased (T2) – and during the second one (T3). Secondly, the subjects of our studies were enrolled at the UNITRE-TO, which promotes learning about active and healthy aging life-style. As such, they represent a very distinctive sample of older adults, characterized by medium-high level of education and socioeconomic status – which are characteristics of cognitive reserve (Sperling et al., 2011). Future research should investigate the impact of the neuropsychological variables involved in the psychological issue related to the COVID-19 pandemic in older adults with different socioeconomic characteristics. Finally, due to the *stay-at-home* policy, we could not conducted a frailty evaluation and a more in-depth assessment of executive functions during the lockdown period. This would have allowed to better understand whether frailty status and/or executive functioning had declined during the pandemic period (T3) compared to the baseline (T0). Indeed, later studies have shown that social isolation during the COVID-19 lockdown may

lead to cognitive decline – also in terms of deficit in EFs (Ingram et al., 2021) –, particularly in the older population (Noguchi et al., 2021). In addition, it has been hypothesized that lifestyle changes due to the pandemic, characterized by increased sedentariness, may lead older subjects to the so-called "Corona-Frailty" (Shinohara et al., 2020).

Despite these limitations, our findings highlight the importance of tailoring information campaigns addressed to the older population, focused on the implementation of these factors that may impact psychological and physical well-being during the COVID-19 pandemic period. In addition, evidence that attentional-executive functions and anxiety may contribute to the perceived threat of a possible new infectious disease (Bartoli et al., 2021) shows the need to consider these neuropsychological variables when planning education campaigns with the goal of achieving favorable changes in public behavior.

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6.2. Executive Dysfunction and Frailty in Neurocognitive Disorders

The studies described in the third Chapter confirm the relationship between executive dysfunction and frailty, even in patients with mild and major neurocognitive disorders with different etiopathogenesis.

In the first study (Amanzio et al., 2017), we analyzed the association between (pre)frailty, assessed by adopting a multidimentional approach (i.e., MPI; Pilotto et al., 2008), and specific cognitive and behavioral aspects in 60 patients with mild and major neurocognitive disorder due to AD. Firstly, we found that pre-frailty was associated with metacognitive-executive functions, in terms of action monitoring (p = 0.01). In particular, the patients showed an inability to monitor their own performance considering the errors made during the m-WCST (Koren et al., 2006), which is indicative of low metacognitive self-awareness. Furthermore, MPI was associated with monetary gain (p = 0.04), i.e., the ability of the subjects to benefit from environmental feedback, anticipate the consequences of their future actions, and make decisions accordingly. With regard to behavioral aspects, MPI scores were related to mood changes in terms of depression-apathy and disinhibition ($p < 0.01$ in both cases). In addition, an association between pre-frailty and reduced awareness of deficits in the IADL (i.e., AQ-D – IADL domain; Migliorelli et al., 1995) was found (p = 0.02). In other studies on AD patients, our research group showed that reduced self-awareness was related executive dysfunction and mood orientation changes (Amanzio et al., 2011, 2013, 2018, 2020), allowing us to hypothesize – by adopting the CAM (Agnew and Morris, 1998; Mograbi and Morris, 2014) – that the reduced awareness was related to a disruption in the comparator mechanisms of the central executive system, neurally inscribed in the prefrontal cortical areas (see Chapter 1, paragraph 1.4.). Since depressive-apathetic mood, disinhibition, and metacognitive-executive dysfunction, as well as reduced self-awareness, seem to be imputable to the same brain network (Bonelli and Cummings, 2007; Masterman and Cummings, 1997; Tekin and Cummings, 2002), we proposed the suggestive hypothesis that pre-frailty may also be due to possible dysfunction of the medial prefrontal-ventral striatal network, observed through deficits in action monitoring, mood changes, and reduced awareness of iADLs.

The results of this cross-sectional study are not generalizable to patients with etiopathogenesis other than AD and require new neuroimaging investigations. However, they represent a first attempt to investigate the association between pre-frailty and neuropsychological variables in a selected patient population, in order to identify the pathogenetic mechanisms of frailty. Future longitudinal studies on a larger sample and using neuroimaging tools will be important to better characterize this association over time and replicate these findings.

The evaluation of pre-frailty conditions and their neuropsychological correlates is clinically relevant. Indeed, this multifaceted phenomenon has diagnostic, nosological, and prognostic implications that may affect patients' wellbeing on the continuum from MCI to AD.

In the second study (Amanzio et al., 2021) – conducted on 18 patients with bvFTD – we aimed at describing GM density and metabolic modifications together with the regional variations of their reciprocal hierarchy and neuropsychological deficits and to correlate individual MPI (Pilotto et al., 2008) scores with the location, degree, and reciprocal hierarchy of GM atrophy and hypometabolism. As a result, we found a unique correlation of the individual MPI scores with the right anterior insula (peak $r = 0.86$ at pFWEC < 0.05). Furthermore, the fact that metabolic and structural damage in the insula were of equal severity means that the neural correlate of frailty, in its early phase, may be associated with both hypometabolism and atrophy.
It should be noted that atrophy of such cerebral area has been previously identified in community-dwelling subjects (Chen et al., 2015) and in AD patients (Gallucci et al., 2018), in relation to frailty.
Patients with bvFTD presented metacognitive-executive dysfunction and mood deflections in term of depression, anxiety, and dishinibition. In our previous study on patients on the continuum from MCI to mild AD (see Amanzio et al., 2017), we found an association between (pre)frailty, executive dysfunction, and mood changes (i.e. depression-apathy and dishinibition). Since such cognitive and behavioral aspects seem to be attributable to the malfunction of the same brain network (Bonelli and Cummings, 2007; Masterman and Cummings, 1997), an early frailty status might also be due to a dysfunction of the brain circuits of "top-down" cognitive control mechanisms, characterized as early pathological changes in bvFTD.
Not surprisingly, the anterior insular cortex seems to be involved in executive control processes and awareness of emotional stimuli (Craig, 2009). Furthermore, it is involved in the Silience Network, in order to integrate and interpretate the homeostatic, affective, motivational, and hedonic signals (Craig, 2009) that are required for survival. Deficits in these aspects, combined with executive dysfunction and mood changes, may lead to an increased risk of poor prognosis, highlighting a potentially critical and precocious role of the insula in the pathogenesis of frailty.
However, our results, obtained from a small sample, should be considered with caution and from an exploratory perspective. Further researches will be necessary to better clarify the role of the insula, associated with other regions belonging to the SN, which might represent additional biomarkers to frailty. These biomarkers should help in tailoring early specific interventions ameliorating patients' prognosis.

Finally, in our mini-review (Bartoli et al., 2020), we have analyzed the relationship between frailty and executive dysfunction in neurocognitive disorders with different etiopathogenesis.
Initially, we found 69 articles during the selection phase, but only five met the inclusion criteria. Of these, two were conducted on patients with PD (Chen et al., 2019; Lin et al., 2019), and three on patients on the continuum from MCI to AD (Amanzio et al., 2017; Dutzi et al., 2017; Shimada et al., 2013). In the majority of cases (4 out of 5 articles), frailty was evaluated by adopting the biomedical approach, whereas only in one study a multidimensional evaluation was performed (Amanzio et al., 2017).
Although the selected studies adopted different EFs definitions and, consequently, different neuropsychological tests for their assessment, all the authors found an association between frailty and executive dysfunction, particularly in terms of set-shifting (Dutzi et al., 2017; Shimada et al., 2013) and monitoring (Amanzio et al., 2021). The studies analyzed in this mini-review are few in number. In addition, the variety of approaches adopted to define frailty and the multiplicity of neuropsychological tests used to assess executive functions did not allow more in-depth data analyses (i.e., quantitative analyses). However, this review study brings more evidence regarding the relationship between EFs deficits and the onset of frailty in different neurocognitive disorders.

Taking together, the results of these three studies highilight that cognitive decline, particularly in terms of executive dysfunction, and frailty are strongly linked in neurodegenerative disorders. In light of this, it is important to jointly analyze these aspects in the older population (Canevelli et al., 2019). To this end, the bio-psycho-social model seems to be the most appropriate paradigm for the assessment and management of frail older adults with cognitive decline (Pilotto et al., 2020).
Longitudinal studies are needed in order to assess the occurrence of cognitive impairment many years before the onset of frailty itself. Moreover, further studies will be important to better characterize the association between executive dysfunction and frailty over time and replicate these findings in a larger group of patients. In addition, neuroimaging studies will help to understand the possible existence of brain networks that are common to these aspects, also leading to the identification of specific biomarkers.
Analyzing the association between frailty and executive dysfunction in this at risk population would allow developing specific measures of physical and/or cognitive empowerment and rehabilitation, even in a preventive perspective.

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6.3. Executive Dysfunction and Reduced Self-awareness in Neurocognitive Disorders

In Chapter 4, it was shown that the reduced awareness of functional and cognitive deficits in patients with neurocognitive disorder could be explained by considering executive dysfunction associated with functional and structural changes in prefrontal cortical and subcortical networks.

In the first study analyzed (Amanzio et al., 2018), we aimed to investigate the role of executive dysfunction, mood changes, and reduced self-awareness in performing IADL in 144 patients on the continuum from MCI to mild AD. Although the assessment of the activities of daily living using the Lawton scale may seem fairly straightforward, this tool is part of the multidimensional geriatric assessment and it is considered appropriate for the functional assessment of older adults (Pilotto et al., 2020).

We conducted multiple linear regression analyses and found that worse performance on tests concerning metacognitive-executive functions (i.e., the RSC and MSE subtests of the BADS; Wilson et al., 1996) predicted a greater likelihood of IADL impairment. Similarly, problems found through the iADL scale (Lawton and Brody, 1969) were related to mood changes – in terms of depression (Hamilton depression rating scale; Hamilton, 1960) – and, importantly, to poor awareness (AQ-D; Migliorelli et al., 1995). Interestingly, executive dysfunction – in terms of inhibition, self-control, and set-shifting – was found to be associated with reduced awareness of functional impairments in a previous study by Amanzio and colleagues (2013) in patients with mild AD. Not surprisingly, deficit of executive functions and both problems in activities of daily living (Tabert et al., 2002) and reduced self-awareness (Amanzio et al., 2011, 2013, 2020) are thought to be all associated with prefrontal dysfunction.

Our findings are consistent with previous studies in the literature (Amanzio et al., 2013; Boyle et al., 2003; Marshall et al., 2011), highlighting the role of executive dysfunction, mood changes, and reduced self-awareness of IADL in patients on the continuum from MCI to mild AD. In light of these, a complete neuropsychological evaluation might be appropriate to identify patients with reduced i-ADL functionality at greater risk of developing a major neurocognitive disorder, on the AD continuum. Furthermore, patients with reduced self-awareness and functional limitation in their daily living may represent an important target for tailoring specific interventions with important clinical implications, in terms of adherence to treatments and prognosis.

In our mini-review (Amanzio et al., 2020) we analyzed studies published in the last 20 years that had investigated impaired awareness in patients with different neurodegenerative diseases. 11 studies were selected according to the inclusion criteria: eight on subjects with AD (Amanzio et

al., 2011, 2013, 2018; Bonney et al., 2007; DeFeis et al., 2019; Galeone et al., 2011; Orfei et al., 2010; Spalletta et al., 2014), two on patients with FTD (Amanzio et al., 2016, 2017), and a case report on acquired brain injury (Palermo et al., 2014). Despite the neuropsychological assessment was conducted using different instruments and the patients presented distinct types of brain pathologies, all studies converged on the relationship between reduced awareness of cognitive and/or functional deficits and executive dysfunction related to cortical prefrontal networks disruption. These results can be interpreted in light of the CAM (Agnew and Morris, 1998; Mograbi and Morris, 2014), according to which damage to the comparator mechanisms in the central executive system compromises the ability to update the "personal database" with current information about themselves, leading to awareness deficits with regard to their own cognitive and/or functional status.

Further longitudinal studies are needed to better assess the occurrence of self-awareness reduction throughout the duration of the illness, in order to better understand its associations with metacognitive-executive domains. This would allow identifying specific primary and secondary prevention assessments.

Finally, we reported an unusual case of a patient that presented reduced self-awareness following a combined polar and paramedian bilateral thalamic infarction (Bartoli et al., 2020). In the post-acute phase (T0) she showed cognitive impairment in several domains – particularly concerning executive functioning –, apathethic-depressive mood and, importantly, reduced awareness of her cognitive and functional deficits. Although a slight improvement in her cognitive functioning had been observed after six months (follow-up phase, T1), mood deflections, executive dysfunction, and reduced awareness of her deficits persisted.

Metacognitive-executive dysfunction would itself seem to influence self-awareness (O'Keeffe et al. 2007). Since frontal-subcortical and/or diencephalic lesions may be predisposing factors to a reduction in self-awareness, we hypothesized – consistent with previous studies (Bogousslavsky, 1994; Leibson, 2000; Starkstein et al., 1992) – that reduced self-awareness might be caused by bilateral thalamic lesions and the subsequent disconnection with the prefrontal networks (i.e., fronto-thalamic pathways), responsible for awareness. Once again, the CAM (Agnew and Morris, 1998; Mograbi and Morris, 2014) may be adopted as an explicative model to understand the presence of reduced self-awareness in this patient.

Furthermore, it is noteworthy that the serology test performed by the patient in May 2020, to detect IgG antibodies against SARS-CoV-2, highlighted a high probability of previous contact with the virus. It might be possible that executive dysfunction and reduced self-awareness affected the patient's indipendent living skills, making her less able to understand infectious risk

situations. However, future studies are needed in order to understand how metacognitive–executive dysfunction may influence the potential risk of SARS-CoV-2 contagion in older adults with neurocognitive disorders.

The results of these studies support the explanatory effectiviness of the Cognitive Awareness Model (Agnew and Morris, 1998; Amanzio et al., 2013; Mograbi and Morris, 2014). In particular, the conscious experience of changes consequent to acquired brain injury or neurodegenerative disease requires an interplay between relevant functional domains and comparator mechanisms within the central executive system to detect deficits. These findings showed an association between impaired self-awareness and executive dysfunction related to anatomo-functional impairment of cortical and subcortical frontal networks. The studies suggest that such issues may persist over time, even in the context of partial recovery of other cognitive functions.

In order to address self-awareness in patients with neurocognitive disorders, it would be appropriate to implement programs that improve executive control. In particular, metacognitive strategy training may be useful for this purpose. In fact, it seems that early assessment of self-awareness and timely intervention on it can help limit the risk of poor patient response to treatment (Toglia et al., 2010).

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6.4. Nocebo Effects during the COVID-19 pandemic: a possible role of Aging?

Chapter 5 discussed the nocebo effect related to the COVID-19 pandemic. In particular, it was highlighted how several factors may influence the occurrence of this phenomenon related to negative expectations, such as stressful and discordant information regarding the pandemic (i.e., number of infections and deaths, social isolation due to infection or risk of infection, images of patients in intensive care spread by the media) (Amanzio et al., 2020). Furthermore, misinformation and conflicting opinions presented by the media may act as major stressors making people more likely to believe in conspiracy theories (Grzesiak-Feldman, 2013; Swami et al., 2016).

Anxiety regarding the pandemic, fear of contagion, and depression related to social isolation to reduce the spread of the virus, may affect the psycho-physical health of frail people, especially older adults (Sepúlveda-Loyola et al., 2020; Wong et al., 2020), who seem to be more prone to experience the nocebo effect (Kravvariti et al., 2021). For example, in our mini-review (see Cipriani et al., 2021) we highlighted that psychological distress seems to influence the quality and quantity of sleep in older adults during the COVID-19 pandemic, which may lead to worse outcome and lower well-being perception.

As stated above, the nocebo effect, arising from contextual and individual factors, can be studied thanks to RCTs, in terms of AEs and dropouts in the placebo groups matched with the active drugs (Amanzio, 2015). In fact, in our previous meta-analysis study (Palermo et al., 2019) we found that higher level of psychiatric symptoms in patients with SCD seem to influence the occurrence of AEs in the placebo groups of RCTs for atypical antipsychotic medication.

In our perspective article (Amanzio et al., 2021a), we have taken into consideration the characteristics that may elicitate the nocebo effect in the placebo group of RCTs, in order to provide a possible explanatory framework for the negative effects of the COVID-19 pandemic. Along with factors related to the subject (such as anxiety, depression, and somatic the symptoms), the physician (i.e., verbal and nonverbal communication style), and the medication (e.g., possible AEs to different therapies in the past), we showed that information provided with regard to SARS-CoV-2 vaccines may explain immunization resistance and the occurrence of AEs. In particular, the nocebo effect could be triggered by misinterpretation of the emergency use authorization of the vaccines and concomitant discordant information related to the vaccines efficacy and safety. Furthermore, in older adults, the fear of inoculation may also stem from the poor representation of the over-60 population in clinical trials of SARS-CoV-2 vaccines (Soiza et al., 2021). In addition, the characteristics of these subjects (i.e., frailty, polypathology, and

polypharmacy) could represent an important bias in the observed results in terms of efficacy and AEs after immunization. It is therefore important to increase the representation of older adults in RCTs, also analyzing the psychological and emotional aspects of subjects participating in these trials – particularly in the pandemic era –, as they could influence the results in terms of AEs and dropouts.

In our recent systematic review (Amanzio et al., 2021b) we have analyzed the occurrence of AEs in both placebo and active groups of RCTs for the SARS-CoV-2 vaccine, in order to investigate how much the adverse events might be due to a negative expectation (i.e., nocebo effect). We took into consideration trial-III studies of SARS-CoV-2 vaccines approved by the Western Regulatory Agencies: two mRNA-based (BNT162b2 and mRNA-1273; 38403 participants) and one adenovirus type (Ad26.COV2.S; 6736 participants). We found that the solicited AEs profile in the placebo arms of the studies is comparable to those of the vaccine with which placebo was compared, although the percentage was higher with vaccine. The most frequently AEs in both groups were fatigue, headache, local pain – as injection site reactions – and myalgia. Specifically, for the first doses, fatigue was reported by (percentage range of participants who experienced AEs, considering the three vaccine studies) 21-29% in the placebo and 37-42% in the active drug groups; headache by 24-27% and 33-39% in the placebo and active drug groups, respectively; and muscle pain by 10-14% in the placebo and 18-33% in the active drug groups. Injection site reactions were also common: 12-17% in the placebo and 48-84% after active vaccination. These AEs decreased with the second dose in the placebo group, whereas they increased – with the exception of local pain – in the active groups. Furthermore, serious AEs were consistent with the expected rate of occurrence in the general population and unrelated to vaccination. Although there was a higher incidence of AEs in the vaccine groups than in the placebo-treated groups, our findings showed that these side effects are not fully due to the vaccine per se but may be attributed to the nocebo effect.

As for the effect of age, younger adults experienced headache, fatigue, and pain more frequently than older participants, in both active and placebo groups of the mRNA vaccines, after the first dose. This result is not in consistent with what we expected (Amanzio et al., 2021a) and what has been reported in the literature (Kravvariti et al., 2021; Zazzara et al., 2021). However, the short duration of phase III safety follow-up of the RCTs analyzed may have influenced these findings, as well as the the small number of older subjects involved in the study compared to younger subjects. Furthermore, not all three studies of SARS-CoV-2 vaccines categorized the older groups according to the WHO (2021) classification (i.e., 60 years and older). In fact, the subjects who were allocated in the older groups in the BNT162b2 vaccine trials were 55 years and older.

Nevertheless, these findings show that AEs from SARS-CoV-2 vaccines may be due to the nocebo effect rather than the effect of the vaccine itself. This could lead to a reduction in immunization resistance by those parts of the population most afraid of AEs, including older adults.

The articles published on this topic and discussed within my Thesis highlight the importance of sheding awareness about the nocebo effect. The nocebo effect may be responsible for treatment misperception as unfavorable, non-adherence to therapy, and its discontinuation. Since specific individual and contextual factors may play a role in the occurrence of negative expectations to a tratment, it is therefore crucial to develop strategies to minimize nocebo-related risk. For example, in the context of RCTs, it would be important to analyze the emotional and psychological impact of patients participating in RCTs, as these aspects may occur more often due to the COVID-19 pandemic (Goldfarb, 2020). In this direction, cognitive-behavioral interventions allow side-effects prevention training (Kern et al., 2019) as well as reducing psychological distress (Amanzio et al., 2020). In addition, more emphasis should be given to positive information (i.e., efficacy of vaccines and therapies, number of immunized subjects) rather than on negative aspects (e.g., number of deaths, number of infections). This would give more chance for positive expectations to rise, especially in older adults, who are at greater risk for adverse outcomes due to SARS-CoV-2 infection. To better study the nocebo effect in older adults, it would be appropriate to conduct more RCTs – including those for SARS-CoV-2 vaccines – addressing this population.

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6.5. General Conclusions

The studies presented within this Doctoral Thesis have shown that executive control plays a key role in self-awareness in neurological disorders and in the occurrence of frailty on the continuum from normal cognitive aging to major neurocognitive disorders with different etiopathogenesis. Also mood deflections seem to affect such aspects.

These findings are consistent with a neurocognitive approach, according to which executive dysfunctions and mood changes may be ascribed to the same prefrontal brain networks. Indeed, adopting the neurocognitive approach as a theoretical framework has allowed to further highilight how anatomical-functional changes in specific brain areas may lead to metacognitive-executive, psychological and functional impairment at different levels in older adults, starting form healthy cognitive aging to mild and major neurocognitive disorders (i.e., AD, bvFTD, and PD), passing also through ABI.

Furthermore, cognitive functioning – especially executive functions –, physical frailty, and psychological distress, in terms of anxiety and depression, may influence the impact of COVID-19 pandemic on older adults, making them more likely to exhibit the nocebo effect.

These results are particularly relevant for clinical settings and underline the need to conduct information campaigns aimed at the older population, focusing on the importance of neuropsychological rehabilitation and empowerment, in order to promote the maintenance of autonomy in daily activities and psychophysical well-being, especially during the COVID-19 pandemic.

Future research – particularly by adopting neuroimaging techniques – is needed to better analyze the relationship between cognitive, functional, physical (i.e., frailty) decline, and mood deflection in the older population, to identify possible specific biomarkers on which action should be taken in a primary prevention perspective.