Investigating the link between drug-naive first episode psychoses (FEPs), weight gain abnormalities and brain structural damages: Relevance and implications for therapy

Title

Investigating the link between drug-naive First Episode Psychoses (FEPs), weight gain abnormalities and brain structural damages: relevance and implications for therapy.

Aim

To shed light on the effect that weight gain abnormalities may have on brain structural abnormalities in untreated FEPs individuals.

Hypotheses

1) Obesity and overweight may increase the severity of those brain structural abnormalities typically associated with FEPs, thus potentially leading to a more severe course of illness and to worst prognostic outcomes.
2) Shared vulnerability factors may explain findings on the high rates of obesity and overweight in drug naive FEPs.
3) In FEPs, early interventions aimed at limiting the development of weight gain abnormalities may result not only in a reduction of risk of future onset of cardiovascular diseases, type 2 diabetes and overall mortality, but also in a limitation of neural network dysfunctions with potential positive effects on clinical, cognitive and functional outcomes.

Relevance

Despite the high prevalence of being overweight or obese in patients with psychosis spectrum disorders (PSDs) and the relationship of obesity to reduced brain volume and poor cognitive and functional outcomes in the general population, there are no neuroimaging studies comparing brain volumes in overweight or obese patients versus normal weight individuals in the earliest stages of the disorders.

Shedding light on the association between obesity, PSDs and brain structural abnormalities may have relevant implications in terms of prognostic outcomes, especially if the target of the investigation is the earliest phase of the disorder, when individuals are less impaired and more amenable to therapeutic intervention.

Abstract

Evidence suggests that obesity and overweight may be associated with severe brain structural abnormalities and poor cognitive and functional outcomes in the general population. Despite these observations and the high prevalence of weight gain abnormalities in patients with psychosis spectrum disorders (PSDs), no studies has investigated the impact that these metabolic disturbances may have on brain structures and development in the earliest stages of PSDs. In the present review we shed light on the association between weight gain and brain structural abnormalities that may affect the course of illness in drug-naïve FEPs. Given the lack of studies directly investigating this issue, we firstly identified and critically evaluated the literature assessing weight gain abnormalities and gray or white matter (GM, WM) volumes (either globally or in specific regions of interest) in otherwise healthy obese/overweight adolescents and young adults. We then compared the results of this systematic review with those of two recent meta-analysis investigating GM and WM abnormalities in drug-naïve FEPs. Weight gain in otherwise healthy subjects was consistently associated with frontal and temporal GM atrophy and with reduced integrity of WM in the corpus callosum. Of relevance, all these brain regions are affected in drug-naïve FEPs, and their integrity is associated with clinical, cognitive and functional outcomes. The underlying mechanisms that may explain the association between weight gain, adiposity, and brain damage in both healthy subjects and drug-naïve FEPs are widely discussed. On the basis of this knowledge, we tried: a) to deduce an integrative model for the development of obesity in psychosis spectrum disorders; b) to identify the key vulnerability factors underlying the association between weight gain and psychosis; c) to provide information on new potential targets of intervention.

1. Introduction

Obesity and excessive weight are pervasive problems in patients with psychotic spectrum disorders (PSDs), with rates of comorbidity ranging from 40 to 60% in recent studies[1,2]. Even if multi-episode patients are at increased risk compared to first episode patients[2], weight gain abnormalities have also been often described in the earliest stages of illness with higher prevalence rates compared to those of same-age general population[3–5].

Reasons for this high prevalence are not fully understood. A complex interplay between unhealthy life-style, side-effects of medications, and pathophysiological mechanisms innate to the psychiatric illness, has been so far the most cited explanation[1].

It is well established that obesity increases the risk for cardiovascular diseases (CVD), type 2 diabetes, various cancers, and overall mortality[6]. This is of particular concern because recent meta-analyses demonstrate that these metabolic disturbances contribute to a larger extent to the dramatic increase in premature mortality among people with PSDs[2,4].

In addition to their well-known role in increasing risk for various cardio-metabolic conditions, weight gain abnormalities have been shown to be associated with brain structural abnormalities in otherwise healthy individuals[7,8]. Obesity/overweight-related brain volume reductions have been detected in a range of regions implicated in reward (e.g. striatum, orbitofrontal cortex, insula), emotion and memory (e.g. amygdala, hippocampus), homeostatic regulation of intake (e.g. hypothalamus), sensory and motor processing (e.g. insula, precentral gyrus), and cognitive control and attention (e.g. prefrontal cortex, cingulate)[7–10] in obese and overweight individuals.

Of note, all these brain areas, the associated neural networks, and their physiological functions are often disrupted in PSDs[11–15].

Furthermore, a growing body of literature pointed out that: (i) weight gain-related brain abnormalities are responsible for poor cognitive and functional outcomes in the general population[16,17]; and (ii) obese/overweight patients with PSDs usually have worse prognostic outcomes compared with their lean counterparts[18]. Taken together, this evidence suggests that obesity and overweight, when expressed in comorbidity with PSDs, may increase the severity of those brain structural abnormalities associated with core features of the psychiatric disorder, thus leading to a more severe course of illness. In line with this hypothesis, a recent series of papers on patients with a first episode mania and a study on subjects at familiar risk for psychosis showed that obese vs lean patients have more severe brain structural abnormalities and worse prognostic outcomes[19,20].

Shedding light on the association between obesity, PSDs and brain structural abnormalities may thus have relevant implications in terms of future clinical outcomes, especially if the target of the investigation is the earliest phase of the disorder, when individuals are less impaired and more amenable to therapeutic interventions[21]. Of relevance, longitudinal studies in otherwise healthy individuals show that obesity/overweight-related brain structural abnormalities might be reversible with weight loss and dietetic interventions, in particular when adolescents and young adults are targeted[22–24]. In line with this evidence, lifestyle interventions for enhancing psychological well-being and weight management have been proved to be effective in terms of clinical, cognitive, and functional outcomes in a wide range of psychiatric syndromes[25,26].

These observations suggest that early interventions aimed at reducing the negative influence that weight gain abnormalities may have on brain structures during the early stages of PSDs may result not only in a reduction of cardiovascular risk and future overall mortality, but also in a limitation of brain volume loss

in neural networks often associated with clinical, cognitive and functional outcomes of the psychiatry illness[27].
Surprisingly, so far no neuroimaging studies have compared brain volumes in patients during the early stages of PSDs with or without obesity and overweight.

1.1 Aims

The aim of the present paper is to shed light on the effect that obesity and excessive weight may have on those brain structural abnormalities most commonly found in drug naïve patients with a first psychotic episode (FEP). We focused on antipsychotic-naïve individuals because, given the well-known pro-adipogenic effect of antipsychotic medications[28], this population provides a unique opportunity to clearly understand the nature of the association between the psychiatric illness and the weight gain disturbances.

1.2 Hypotheses

We specifically hypothesize that: (i) obesity and overweight may increase the severity of those brain structural abnormalities typically associated with FEPs, thus potentially leading to a more severe course of illness and to worst prognostic outcomes; (ii) shared vulnerability factors may explain findings of high rates of obesity and overweight in drug naive FEPs; and (iii) in these patients, early interventions aimed at limiting the development of obesity/overweight may result not only in a reduction of the risk of future onset of cardiovascular diseases, type 2 diabetes and overall mortality, but also in a reduction of brain structural damages with potential positive effects on clinical, cognitive and functional outcomes.

We thus conducted a systematic review of the literature on brain structural abnormalities in obese/overweight otherwise healthy adolescent and young adults. We then compared our findings with those reported in the most recent meta-analyses and systematic reviews investigating gray and white matter abnormalities in drug-naive individuals with FEP and discuss potential underlying mechanisms of obesity-induced brain damages.
Finally, based on this knowledge, we tried to deduce an integrative model for the development of obesity in drug naive-FEP followed by a discussion of potential therapeutic interventions.

2. Methods

2.1 Systematic review

The systematic review was conducted in accordance with the MOOSE guidelines[29] and in line with the PRISMA statement[30], following a predetermined, but unpublished protocol.

2.2 Data sources

Titles, abstracts and topics were searched using the following terms: "*Body Mass Index" OR "Adiposity" OR "Waist Circumference" OR "Waist to hip ratio" OR "Body Weight" OR "Obesity" OR*

"Overweight" AND *"Neuroimaging" OR "Gray Matter" OR "White Matter" OR "Brain Volume" OR "Magnetic Resonance Imaging"*
The electronic research literature databases included the PubMed and Web-of-Science from inception to May 2016. Limits were set to humans and English language. In addition, reference lists and citations of initially identified reports were examined. Additional studies were searched manually.

2.3. Study selection

Search was carried out independently by three investigators (A.M., A.A., M.F.); disagreements were resolved by consensus among these primary raters and the other investigators.

Articles were considered to be eligible if 1) published in peer-review journals; 2) included at least one brain scan; 3) examined global, lobar and regional brain volumes; 4) included at least one anthropometric or quantitative assessment of central or global adiposity, such as body weight, BMI, WC, or abdominal girth, WHR, visceral adipose tissue (VAT) and/or subcutaneous adipose tissue (SAT), percentage body fat and similar indices; 5) focused on the weight spectrum from normal to class III obesity, which did not include studies on being underweight; 6) included studies with subjects having a mean age of 17 to 32 years (adolescents and young adults); 7) included at least 10 participants**.**

The age criterion was set in order to obtain comparable data with those from brain imaging meta-analyses on drug-naïve patients with FEP.

Studies were excluded if participants had additional co-occurring metabolic or main neurological/psychiatric disorders (including binge eating, anorexia and bulimia nervosa) other than overweight/obesity and if they were focused on sample other than the general population (e.g. Prader-Willis or other genetic causes of obesity; twins' studies; etc.).

2.4. Data Extraction

Data were independently extracted by the three reviewers with a use of a precoded form. The following data were extracted from studies meeting the criteria for inclusion in the systematic review: age, gender distribution, study design, measure of adiposity, number of subjects (obese-overweight and lean), neuroimaging methods, covariates adjustment, and main findings.

3. Results

3.1 Systematic review of brain structural abnormalities in obese/overweight otherwise healthy adolescent and young adults

The literature search is summarized in **Figure 1**. Eleven studies[10,24,31–39] met our inclusion criteria and were included in the present systematic review (more details are given in Supplementary Material, Results).

The most consistent findings were that obese/overweight otherwise healthy individuals have: (i) lower GM volumes of the temporal and prefrontal regions; and (ii) reduced WM integrity in the corpus callosum compared to their lean counterparts. Weaker evidence suggests that reduced WM and GM volumes of the insula may also be expressed in obese/overweight individuals.

A detailed description of findings can be found in Supplementary material, Results and in **eTable1**

3.2 Brain structural abnormalities in drug-naïve FEPs

We searched for the most recent systematic review and meta-analysis on brain structural abnormalities in drug-naïve patients with FEP in PubMed using the following key words: "white matter" OR "gray matter AND "schizophrenia" OR "psychosis" AND "first episode psychosis" OR "first episode schizophrenia" AND "diffusion tensor MRI" OR "structural connectivity" OR "structural MRI" OR "neuroimaging".

The most consistent findings were that drug-naïve individuals with FEP have: (i) lower GM volumes of the right temporal lobe, the left and right insula, and the left cerebellum[40]; (ii) reduced WM integrity in the corpus callosum, the cingulum bundle, the left inferior longitudinal fasciculus, and the left inferior fronto-occipital fasciculus[41,4243].

Results are summarized in **Table 1** and **Table 2**. Detailed information is given in Supplementary Material, Results.

3.3 Weight gain- and drug-naïve FEPs-related brain structural abnormalities: overlaps

The most consistent findings suggesting the existence of brain structural abnormalities overlap in FEP and obese/overweight individuals include: 1) temporal lobe GM volume; and 2) the interhemispheric WM fibers running though the corpus callosum. Sparse and less consistent evidence suggests that the left insula may represent another area of overlap (See also **Table 1** and **Table 2)**.

4. Discussion

4.1 Overall findings

The first hypothesis of the review was that obese/overweight FEPs might have more severe brain structural abnormalities compared to their lean counterparts. In line with this hypothesis, we found that weight-gain related brain structural abnormalities in otherwise healthy adolescents and young adults frequently overlap with those reported for drug-naïve FEPs by two recent meta-analyses (**Table 1** and **2**).

Of relevance and in line with our results, a recent study demonstrated that obese/overweight young adults with a familiar risk for PSDs have more severe brain structural abnormalities (i.e., reduced white matter integrity) compared to their lean counterpart[44]s. A detailed discussion of these findings and their clinical implications can be found in Supplementary Material, Discussion.

4.2 Weight gain-induced brain damages: potential underlying mechanisms. Implications for drug-naive FEPs

In this section we will review all the potential biological mechanisms that may explain the association between obesity/overweight and brain structural abnormalities in healthy individuals. Furthermore, we will provide evidence to support the hypothesis that obesity and overweight may contribute to worsening

brain structural abnormalities in FEPs by increasing the severity of disease-inherent pathophysiological mechanisms typically associated with the psychiatric disorder.

4.2.1 Cytokines and inflammation

It is now clearly established that adipose tissue, especially in its visceral/abdominal form, is highly metabolically active, producing and releasing hundreds of different compounds, such as adipokines and cytokines[45], which are directly involved in the pathogenesis of some of the cardiovascular complications commonly seen in association with obesity[6]. Other than their role in increasing cardiovascular risk, some of these compounds seem to have a relevant effect on brain structure and development[46,47], thus potentially playing a role in contributing to brain volume loss in both obese/overweight otherwise healthy subjects and FEPs.

Obesity is characterized by a chronic low inflammation state partly mediated via production of pro-inflammatory cytokines[48]. Some pro-inflammatory cytokines may cross the blood brain barrier (BBB) and affect brain plasticity and signaling processes[47]. Among them, the most commonly investigated is interleukin IL-6[49]. This cytokine crosses the BBB by a saturable transport mechanism, entering both the cerebrospinal fluid (CSF) and brain parenchyma[50]. The hippocampus is particularly vulnerable to adverse effects of IL-6, affecting brain functions like synaptic plasticity and neurogenesis, with a similar effect being also described for IL-1β[51].

An early onset of IL-6 elevation due to childhood and adolescent obesity[52], and its persistence in aging obese adults[47], has been proposed to negatively affect brain functioning by inhibiting neurogenesis, decreasing synaptic plasticity and subsequently disrupting learning and memory processes, particularly in the hippocampus, which may increases the risk of cognitive deficits[47,51].

Meta-analytic evidence shows that drug-naïve FEPs have higher serum or plasma levels of pro-inflammatory cytokines[53], such as IL-1β and IL-6[54]. Some authors have suggested that high levels of pro-inflammatory cytokines in psychosis could be related to an over-activation of the lymphocytes T-helper (Th) type 1[55], resulting in an imbalance in the Th1/Th2 cytokines ratio, with a shift towards the Th2 system[56]. However, other sources may play a relevant role in determining the low-chronic inflammatory state often associated with FEPs, with abdominal visceral obesity being one of the most plausible candidates[45]. Furthermore, it has been demonstrated that obesity can induce microgliosis[57], a mechanism that seems to be tightly related to PSDs since the earliest stages of the disorders[58].

It is possible to hypothesize that obesity and overweight in FEPs may contribute to worsening the low-grade chronic inflammatory status typically associated with these disorders, with relevant consequences on brain structures and development.

4.2.2 Adipokines

Adipokines, with leptin being the most widely investigated in the field of PSDs[59], are compounds released by the adipose tissue having pleiotropic effects on the body and largely interacting with the central nervous system[46]. Thus, they represent one of the most plausible factors mediating the association between obesity/overweight and brain structural abnormalities. Leptin is a pleiotropic hormone circulating at levels that are proportional to body adipose stores[60], such that to increase in body fat mass correspond increased leptin levels. In addition, leptin, that may cross the BBB through a specific receptor[61], appears to facilitate pre- and postsynaptic transmitter release and sensitivity in hippocampal CA1 neurons[47] and to modulate mesolimbic dopamine system activity[59,62]. This may explain findings of a

positive association between circulating leptin levels, spatial learning and memory function in healthy individuals[47], and with response to treatment in FEP[63]. Of note, there is evidence showing that childhood and adolescent obesity may facilitate the development of leptin resistance[64], which has been associated with brain atrophy, poor cognitive performances, and with increased risk of Alzheimer disease when expressed in middle-aged adults[47].
This suggests that obese/overweight vs lean FEPs may be at greater risk to develop leptin-resistance, which might have relevant implications on brain structure and development, cognitive functions and response to treatment[65,66].

4.2.2 Glucocorticoid-induced brain atrophy

Obesity and overweight are associated with higher circulating cortisol levels[67]. Many studies have shown that higher cortisol levels may induce brain atrophy and worse cognitive performance, with recent evidence suggesting that obesity per se, at least in adolescents, mediates the relationship between HPA axis abnormalities and atrophy in the hippocampus and frontal lobe[68,69].
Dysregulations of the HPA axis and consequent glucocorticoid signaling abnormalities have been widely described in drug-naive FEP and in youths considered "at risk" for future psychosis conversion[70,7172]. These abnormalities may lead to reduced brain volumes in area such PFC, amygdala and hippocampus[68], by reducing brain derived neurotrophic factor (BNDF) release and increasing glutamate neuro-toxic effects[73]. Based on this knowledge, it is possible to hypothesize that weight gain can worsen HPA dysfunctions in FEP leading to more severe brain structural abnormalities.

4.2.3 Insulin resistance

Physiologically, insulin facilitates cellular glucose uptake into brain tissue, while systemically it regulates body weight, energy disposal, food intake and locomotion[74]. Insulin resistance is one of the most common complications of obesity, especially in its abdominal visceral form[75,76].
Impaired cerebral insulin receptor signaling, resulting from the development of obesity-induced insulin resistance, may cause disturbances in the uptake of glucose into brain tissue, resulting in cellular glucose deprivation, eventually leading to tissue atrophy[75,76].
Of relevance, consistent evidence suggests that impaired glucose abnormalities are expressed in drug-naïve patients with FEP and are related to higher WHR and WC[77]. These observations suggest that obesity and overweight may contribute to worsening of insulin-resistance phenomena in FEP, with potential negative consequences on brain volumes.

4.2.4 Vascular risk factors

Cardiovascular risk factors other than insulin resistance and abdominal/visceral obesity, such as dyslipidemia[78], hypertension[79], and other components of the metabolic syndrome[80] can affect the brain vasculature and may contribute to brain volume loss in obese/overweight individuals. In patients with FEP, cardiovascular risk factors are present early in the illness and likely related to the underlying illness, unhealthy lifestyle, and antipsychotic medications, which interact with each other[3]. However, evidence for a role of hypertension and dyslipidemia as mediators of brain damage during this early stage of illness are lacking and it is reasonable to hypothesize that these obesity-related cardiovascular risk factors may play a significant role in inducing brain atrophy during later stages of PSDs.

4.2.5 The gut microbiome

The gut microbiome has received greater attention during the last few years as a potential mediator of gut-brain interactions[81,82]. Despite a significant interpersonal variation in the enteric microbiota, there seems to be a balance that confers health benefits, and alteration in beneficial bacteria can negatively influence both mental and physical well being[82,83].
Obesity is closely tied to changes in the composition of the intestinal microbiota. In animal models of obesity, the interplay between the dominant gut phyla, Bacteroidetes and Firmicutes, is shifted with a significant reduction of the former and a corresponding increase in the latter[81]. The shift in the relative abundances of these phyla has been associated, among several factors, with a diet rich in high saturated fats and calories, high fructose consumption, and an increased sensitivity to stress (through the HPA axis), all factors that are closely related to PSDs since the earliest stages of the disorders[81,84].

The influence of the microbiota extends beyond the gastrointestinal tract, playing a major role in the development and functioning of the central nervous system[83]. Obesity-induced modifications on the microbiome may have a significant impact on brain functions[82,85]. It is now clear that a broad range of bacteria manufacture and secrete neurochemicals that are essential for brain structure and development. A growing body of literature shows that γ-Aminobutyric acid (GABA), dopamine, serotonin, norepinephrine and acetylcholine are produced by different strains of gut bacteria, such as Lactobacillus, Bifidobacterium, Saccaromyces, Bacillus, and Serratia (see Dinan and colleagues for an extensive review[85]). Furthermore, evidence suggests the existence of an interplay between alterations in the microbiome, HPA axis dysregulation, and increased pro-inflammatory cytokines release[81]. Stress and glucocorticoids alter the permeability of the gut barrier, allowing lipopolysaccharide, an essential component of gut gram-negative bacteria, and other molecules to gain access in the blood stream stimulating immune activation through Toll-like receptors and release of pro-inflammatory cytokines (e.g. IL-6 and IL-1β)[83], which circulating levels may contribute to brain volume loss in both FEPs and otherwise healthy obese individuals.

Even if the evidence is mostly preclinical, it is reasonable to hypothesize that weight gain-induced variation in the gut microbiota may represent an additional factor contributing to the development of brain structural abnormalities in obese/overweight adolescents and young adults and to more severe brain volume loss in obese/overweight vs lean FEPs.

4.3 The path to weight gain abnormalities in psychotic disorders before antipsychotic exposure: evidence from drug-naive FEP.

It is undeniable that exposure to APDs, especially atypical APDs such as clozapine and olanzapine, constitute one of the major contributing factors to the development of obesity and overweight in patients with psychotic-spectrum disorders[86]. However, accumulating evidence indicates that such abnormalities cannot solely be accounted for by APDs exposure because they occur (albeit in a somewhat less severe form) already in drug naïve or minimally medicated first episode patients[87–89]. This suggests that at least a part of the vulnerability to develop weight gain disturbances in psychotic-spectrum disorders might be related to mechanisms innate to the psychiatric illness[89].
In this section, firstly, we will briefly summarize evidence for weight gain abnormalities in drug-naive patients with FEP, and provide a definition for heterogeneous conditions such as obesity and overweight.

This clarification is of particular relevance given the influence that different measurements of weight gain abnormalities may have on findings on FEPs individuals, and their importance in terms of both general and mental health.
Secondly, we will show that most of the vulnerability factors underlying obesity and overweight (especially in their abdominal form) in otherwise healthy individuals are tightly related to psycho-physio-pathological mechanisms of psychosis spectrum disorders expressed prior of APDs exposure. This observation suggests that innate mechanisms of psychiatric illness may represent key vulnerability factors for the development of weight gain abnormalities in FEPs.
Thirdly, we will discuss how some specific neural network dysfunctions, typically associated with psychotic spectrum disorders since their earliest stages, may facilitate the onset of weight gain abnormalities triggering this pre-existent vulnerability.
Finally, implications for treatment will be discussed.

4.3.1 Defining weight gain abnormalities in drug-naive FEPs: the importance of body fat distribution, beyond the body mass index.

Obesity and overweight are generally defined by an excess of body fat and are most often estimated by the ratio of weight over height, the most commonly used anthropometric index being the Body Mass Index (BMI)[90].
However, weight gain abnormalities are heterogeneous conditions, with measurement methods varying accordingly across different studies. Such heterogeneity appears to be explained, to a very significant extent, by individual differences in regional body fat distribution, particularly in abdominal/visceral adipose tissue[91,92]. Abdominal visceral obesity, as measured by proxy indicators such as waist to hip ratio (WHR), Waist Circumference (WC) and hyper-triglyceridemic waist[93] (HTW, a measure resulting from a combination of WC size and triglyceride blood levels), is more strongly related to metabolic complications, brain structural abnormalities and to cardiovascular outcomes than BMI[6].
For these reasons, distinguishing between different types of weight gain abnormalities is of particular relevance for future studies investigating the underlying mechanisms of the association between obesity, overweight and brain structures in drug-naive FEPs. Furthermore, this differentiation allows identifying more relevant targets in terms of novel diagnostic and interventional strategies.
In line with these considerations, recent studies demonstrate that more than a higher BMI, drug-naive patients with FEP are more likely to have a metabolically unfavorable body composition, comprising greater WC and WHR, high fat percentage and low muscle mass when compared to same-age general population[4,94]. These findings were confirmed in a recent meta-analysis on drug naïve individuals with FEP suggesting that these patients "may have a higher waist to hip ratio and more intra-abdominal fat relative to BMI than healthy controls"[4]. Even if higher BMI in drug-naive FEP is a replicated (but not always consistent) finding, meta-analytic evidence failed to find enough statistical power to demonstrate significant differences with the general population[2], highlighting the need of more studies investigating the link between psychosis-spectrum disorders and weight gain abnormalities in the pre-antipsychotic stages of the psychiatric illness.

4.3.2 Abdominal obesity in drug-naive FEP: vulnerability factors

Abdominal obesity and psychosis-spectrum disorders shared a surprising number of vulnerability factors.

Most of these factors are tightly linked with PSDs and expressed at illness onset, even in never medicated patients. This suggests that patients with PSDs may have an innate vulnerability to develop abdominal obesity that is, at least partially, independent of APDs exposure.
Starting from a really comprehensive list of etiopathogenetic factors of abdominal obesity in the general population (widely reviewed by Tchernof and Després[93]), we highlight differences and commonalities with findings on psycho-physio-pathological mechanisms often expressed in drug-naive FEP.
Of note, some of the identified vulnerability factors might be easily targeted with both pharmacological and non-pharmacological interventions (see section **4.5**). These interventions might significantly reduce the risk of developing weight gain abnormalities and their negative consequences on both mental and general health during a critical, early stage of the psychiatric illness[95].

Gender

Human males and females greatly differ in terms of body fat distribution. Evidence indicates that the amount of visceral adipose tissue is up twofold higher in men than in premenopausal women, even after correcting for total body fat mass[96]. Indeed, even if for a given body mass index men usually have more lean mass and women higher adiposity, adipose tissue in men is usually located around viscera while in women in peripheral or subcutaneous storages[97].
Gender differences have been reported in various aspect of PSDs, including epidemiology, clinical course, and response to antipsychotic medications (see Markham for an extensive review[98]). In particular, men are approximately 40% more likely to develop a FEP compared to women, have a earlier age of onset, more severe illness course, more negative symptoms, poorer response to antipsychotic treatment, and possibly greater brain structural abnormalities[98].

Sex Hormones

Gender differences observed in psychosis-spectrum disorders[98] and abdominal obesity[99] can be partly accounted for by altered levels of sex steroid hormones. In otherwise healthy men, low plasma levels of total testosterone[100], sex hormone-binding globulin (SHBG, a determinant of testosterone bioavailability)[101], are generally associated with visceral obesity and a greater number of metabolic syndrome features[102]. Similarly, drug-naive men with FEP have lower levels of testosterone, and there is an inverse relationship between testosterone levels and severity of negative symptoms[98]. Association studies that address circulating androgens and body fat distribution in otherwise healthy women are equivocal[103,104]. In some studies, high total or free plasma testosterone levels are positively associated with visceral fat accumulation[103]. However, others have reported negative associations[104], and some failed to observe any correlation[105]. Limitations in the measurement of androgens levels in women may possibly explain these discrepancies[6].
Blood levels of estrogen seem to play a role in both FEPs and visceral obesity as well. In both otherwise healthy men and women low levels of estrogens seem to be related to increased body weight and visceral fat accumulation[6]. This observation is of particular relevance because of the well-known protective effect of estrogens against psychoses[98,106]. Indeed, several authors showed an inverse relationship between circulating estradiol levels and severity of psychotic symptoms, cognitive impairments, and antipsychotic-resistance in patients with psychotic spectrum disorders[106].

Genetics

A recent systematic review by Malan-Muller and colleagues[107] aimed at identifying genetic variants potentially contributing to the high comorbidity between metabolic syndrome (MetS) and schizophrenia. Among those genes that showed strong evidence for an association with MetS, some were specifically associated with weight gain abnormalities in schizophrenia. Specifically: α2A adrenergic receptor gene (ADRA2A); insulin-induced gene 2 (INSIG2); leptin-receptor gene (LEPR); and fat mass and obesity associated gene (FTO). Minor evidence coming from single study analyses were also available for endocannabinoid receptor type 1 gene (CNR1) and BDNF gene polymorphisms that, of note, have been implicated in the pathophysiology of schizophrenia[107].

Ethnicity

Ethnic differences may influence both body fat distribution and severity of illness in psychotic spectrum disorders.

A review of 8349 published studies on abdominal obesity showed that, for a similar level of total adiposity, Asians have the highest propensity to develop visceral abdominal obesity, with Caucasians intermediate between Asians and Black-Africans, which have the lowest risk[6].

A similar stratification of risk has been reported by one of the earliest studies investigating the association between ethnicity and severity of illness in psychotic-spectrum disorders[108]. However, subsequent cross-ethnic empirical studies of individuals with schizophrenia and related-psychosis have produced inconsistent findings[109].

The Endocannabinoid system

Recent evidence suggests that the endocannabinoid system is chronically activated in otherwise healthy obese individuals[110,111]. Of interest, dysregulation of the endocannabinoid system to be preferentially associated with visceral obesity rather than with overall adiposity[112,113]. Type-1 cannabinoid receptors (CB_1) are highly expressed in visceral adipose tissue[114]. Furthermore, CB_1 agonists, such as anandamide and 2-arachidonoylglycerol, activate adipogenesis and prolipogenesis[110], thus contributing to visceral fat accumulation.

A growing body of literature suggests that the endocannabinoid system is altered in PSDs[115].

Clinical studies in patients with PSDs demonstrated: (i) elevated levels of the endocannabinoid anandamide in the cerebrospinal fluid and serum of untreated patients with schizophrenia and antipsychotic naive FEP[116,117]; and (ii) increased density of CB_1 receptors in the dorsolateral prefrontal, anterior cingulate, and posterior cingulate cortices, brain regions involved in core dysfunctional psychopathological processes of PSDs[115,118].

Dysfunctions of this system, which has been shown to interact and promote dysregulations of core neurotransmitter systems (i.e., dopamine and glutamate), seem to play a key role in triggering psychotic onset and relapses[115,118].

Hypothalamo-Pituitary-Adrenal Axis (HPA), Stress, and Glucocorticoids

Excessive circulating glucocorticoids concentrations, as observed in Cushing's syndrome, create a pathological phenotype of abdominal obesity, dyslipidemia, insulin resistance, and hypertension[119,120]. These observations led several authors to hypothesize a central role for HPA dysfunction in the development of abdominal obesity in otherwise healthy individuals. A number of studies and review articles[93,102] suggest that chronic stress or poor coping in stressful situations is associated with mild

hypercortisolemia, and prolonged sympathetic nervous system activation, which in turn could favor accumulation of visceral fat.

Of note, HPA dysfunction have been proposed as a trait-marker of PSDs, being expressed since the earliest stages of the disorders and being not modifiable with psychotropic treatment[70,121,122]. A specific pattern of HPA abnormalities has been described in FEP, as characterized by: a) blunted Cortisol Awakening Response (CAR)[70]; b) reduced HPA response to stress[123]; and c) increased blood cortisol levels throughout the day[70]. Some of these abnormalities, in particular a blunted CAR and a reduced HPA response to stress, are expressed in drug naive patients and have been associated with core features of PSDs, such as severity of positive symptoms and cognitive decline[124].

Another recognized etiologic factor for abdominal obesity in otherwise healthy individuals is the increased local cortisol synthesis in adipose tissue. Local production of glucocorticoids by adipose tissue 11β-hydroxysteroid dehydrogenase (11β-HSD) has been clearly linked to the development of abdominal obesity in animal models and associated to increased visceral fat accumulation as well as with concomitant metabolic alterations in humans[125,126]. Of relevance, an increased activity of 11β-HSD, which converts local inactive cortisone to active cortisol, has been found in large samples of patients with PSDs[127,128], further highlighting the existence of a tight link between the glucocorticoids axis and body fat disposition in these patients.

Dietary habits

Apart from the obvious association between high caloric intake and obesity, few studies have investigated which specific nutritional factors might predispose to visceral fat accumulation in the general population. Animal studies have shown that saturated fat intake is associated with preferential accumulation of visceral fat and development of insulin resistance compared to other fatty acids[129]. In humans, fructose appears as one of the only nutrients that has been demonstrated to potentially affect body fat distribution independent of its impact on overall adipose tissue accretion, with mechanisms that have been widely reviewed elsewhere[130,131].

Of note, patients with PSDs often follow a dietary pattern rich in saturated fat, calories and fructose[132]. Despite this unhealthy dietary pattern can be a consequence of lifestyle related factors (i.e., low socio-economical status, smoking habits, and antipsychotic side effects), studies on drug naive and "at risk mental state" individuals suggest that disease-inherent neurobiological mechanisms may also play a key role[133,134] (see **4.3.3**).

Sedentary Life Factors/Physical Inactivity

A sedentary lifestyle could obviously contribute to the onset of weight gain abnormalities. What is interesting is that physical activity/exercise can selectively or at least preferentially reduce abdominal visceral adiposity, as shown by a review work by Ross and Janiszewski[135]. The authors suggest that regular physical exercise can induce a substantial reduction of visceral fat accumulation even in the absence of weight loss.

Several studies[136] and recent meta-analytic evidence[137] suggest that patients with PSDs have a more sedentary life and exercise less than the general population. Of relevance, a recent review suggests that also prodromal individuals have consistently lower levels of physical activity and exercise at a lower

intensity than controls[133], with a birth cohort study showing that those who later developed psychosis were more likely to be inactive during adolescence than those who did not[138].

The microbiome

As briefly reviewed in section **4.2.5** weight gain abnormalities are often linked to significant shifts in microbiome balance. Of interest, a shift in the relative abundances of the two dominant phyla (i.e., Bacteroides and Firmicutes) has been also associated with schizophrenia-like behavior in preclinical studies[84]. The shift in the relative abundances of these phyla can be caused, among several factors, by a diet rich in high saturated fats and calories, high fructose consumption, and an increased sensitivity to stress (HPA axis dysregulations)[81], which are all related with disease-inherent processes of psychotic-spectrum disorders[83] and expressed at illness onset even in never medicated patients.

Despite evidence suggesting a link between the gut microbiota composition and mental health is mostly preclinical, some clinical studies already demonstrated that administration of probiotics to babies significantly reduced the development of severe mental illnesses, such autism and ADHD, up to 13 years later[85]. For this reason, it is likely that findings suggesting that microbiome shifts may play a significant role in both PSDs and weight gain abnormalities will be replicated also in future clinical studies.

In summary: (i) male sex; (ii) low levels of androgens in men ad lower levels of estrogens in both men and woman; (iii) specific genetic polymorphisms; (iv) higher circulating levels of endocannabinoids and increased CB_1 expression; (v) hypercortisolemia and increased activity of 11β-HSD-1; (vi) lack of physical activity; (vii) poor dietary-habits; and (viii) shifts in the microbiome composition, represent key vulnerability factors for the development of abdominal obesity in psychotic spectrum disorders. Of relevance, all the mentioned factors are expressed at illness onset and in drug-naïve individuals. This observation further suggests that patients with FEPs might have an innate vulnerability to develop abdominal obesity, with its relevant consequences on both general and mental health.

4.3.3 Abdominal obesity in drug-naïve FEPs, triggering factors: unmasking the vulnerability

APDs play a relevant and undeniable role in unmasking the vulnerability to develop weight gain abnormalities in psychotic spectrum disorders. However, some of the triggering factors that might start the path to visceral fat accumulation in FEPs are independent of APDs medications. Based on a consistent body of literature, it is possible to hypothesize that the unhealthy lifestyle choices (i.e., dietary patterns and reduced physical activity) that trigger those mechanisms leading to the development of obesity and overweight in FEPs are consequent to specific neural network dysfunctions associated with disease-inherent mechanisms of psychosis.
As for most of the vulnerability factors, these triggers are present at illness onset and even in never medicated patients.

A "sluggish" reward system and a reduced inhibitory control

As previously highlighted, consistent evidence suggests that patients with PSDs are more likely to consume highly palatable food, which is often rich in saturated fat, fructose and calories. This unhealthy

life-style choice can be surely explained by the well know appetite-stimulating effect of APDs. However, the preference for highly palatable food in patients with PSDs seems also to characterize drug-naïve individuals. This observation suggests that mechanisms other than APDs may play a role in this unhealthy life style choice. A fascinating hypothesis stem from a comprehensive review by Elman et al.[12] in which the authors suggest that psychosis-spectrum disorders and unhealthy food preferences may be potentially explained by recursive partly shared neural systems. The mesolimbic hyper-dopaminergic state, a key neuro-pathological feature of the psychotic-spectrum, presumably renders the incentive reward system insensitive to less salient and palatable nutrition (e.g. vegetables). Furthermore, according to the authors, palatable food may produce dysregulated dopamine release in the ventral striatum, creating a rigid motivation state fixated on procurement of this type of food. These mechanisms, together with poor cognitive control from a hypofunctional PFC (involved in the inhibitory control of overeating behavior), may provide an explanation for the increased intake of palatable food in patients even before APDs exposure[12], being expressed in the earliest stages of PSDs and independent of medications[139–141].

Central insulin resistance

Post-mortem studies show a decreased expression of cerebral insulin receptors (β-subunit), a reduced activity of the signal transduction protein Akt1, and a diminished neuronal expression of insulin-degrading enzyme in the dorsolateral prefrontal cortex of PSDs individuals[142–145]. These changes may cause disturbances in neural glucose uptake and utilization, as suggested by measurements of elevated CSF glucose levels[146]. In vivo fluorodeoxyglucose positron emission tomography (FDG-PET) and functional magnetic resonance imaging (fMRI) studies also demonstrate impaired cerebral glucose utilization in brain areas that are important in the pathogenesis of schizophrenia, resulting in the "metabolic disconnection" of the dorsolateral prefrontal cortex and mediodorsal thalamus with the limbic system[147]. These findings have been interpreted by some authors in light of the "selfish brain" theory[75]. This theory describes the tendency of the human brain to cover its own, comparably high-energy requirements with the utmost priority when regulating energy fluxes within an organism. In this respect, the brain is thought to behave selfishly[148,149]. Given the assumption of disrupted cerebral energy supply in PSDs due to cerebral insulin resistance, the "selfish brain" theory may provide another, complementary, explanation for the preferred intake of high carbohydrate, high fat foods and diminished physical activity and exercise in psychotic patients as a way to improve the brain's energy supply.

4.4 A complex interplay generating a vicious cycle

All the listed vulnerability and triggering factors are mutual influencing. The mentioned weight-gain related dysregulations of bio-behavioral systems and their bio-mediators (insulin, cortisol, cytokines, metabolic and sex hormones) dynamically interact and worsen each other[150,151]. Of relevance, this chronic dysregulated state may in turn negatively impact neurogenesis and brain plasticity through both direct and indirect processes[151,152].

These mechanisms can be considered nodes of a vicious circle (**Figure 2**) that can be triggered and fed since the earliest stages of PSDs, being at least partially (or originally) independent of APDs exposure and likely related to a disease-inherent vulnerability.

4.5 Breaking the cycle: potential strategies for early intervention

Most of the nodes of this vicious cycle are modifiable and thus amendable to therapeutic interventions (see **Figure 2**). Antipsychotic medications remain the cornerstone of treatment in PSDs and FEP. For this reason, the well-know proadipogenic effect of APDs needs to be taken into consideration when discussing available therapeutic options to reduce the risk of developing obesity in FEPs. Thus, the list of potential interventions provided below should not be considered as mono-therapeutic options, but as a list of complementary interventions to APDs. These add-on therapies should aim at limiting the risk of developing weight gain abnormalities and visceral fat accumulation often unmasked by APDs, thus reducing the weight gain-related negative consequences on both mental and general health.

Antipsychotic medications: timing and choice

As extensively reviewed elsewhere[153], antipsychotic medications greatly differ in terms of ability to induce weight gain abnormalities. Thus, the choice of the antipsychotic represents the first-line strategy to reduce the risk of visceral fat accumulation in FEP. Among APDs, haloperidol, ziprasidone, lurasidone and aripripazole seem to be the better options in terms of metabolic tolerability compared to other drugs such as olanzapine, risperidone, clozapine, and paliperidone[153]. It has to be noted that the development of significant weight gain abnormalities in FEP may occur since the earliest weeks after APDs exposure[3], and recent evidence suggests that the critical period for intervention is the first year of treatment[95].

Sex hormones therapies

The protective effect of estrogen in schizophrenia is well researched and is hypothesized to be the result of its neuroleptic-like effect on the dopamine system[154]. Adjunctive estrogen therapy has been shown to be effective in enhancing the treatment of schizophrenia in women[155]. In men, consideration of estrogen therapy has been impacted by concerns of feminization. The development of new estrogen compounds - Selective Estrogen Receptor Modulators (SERMs), such as bazodoxifene and lasofoxifene - which do not cause feminization, opens up a potentially new and safe treatment strategy for men suffering from PSDs[154,156]. Furthermore, and relevant for the aims of this review, these compounds may also limit the development of weight gain abnormalities in FEP, given that low circulating blood levels of estrogens in both men and women are associated with increased risk of weight gain and visceral fat accumulation[6] (see **4.3.2**)

Cannabidiol

As mentioned in section 4.3.2 drug-naive individuals with FEP often have increased serum and CSF levels of CB_1 receptors agonist[115] (e.g., anandamide) and increased CB_1 density in the prefrontal brain areas[118]; the magnitude of these abnormalities is positively associated with symptoms severity[117,157], and evidence from healthy subjects[6] suggests that they can also increase the risk of developing weight gain abnormalities in these patients (see **4.3.2**). Findings from a recent study by McGuire and colleagues show that APDs augmented with cannabidiol, a CB_1 antagonist, may have relevant beneficial effects on clinical, cognitive and functional outcomes of patients with schizophrenia[158]. Given its action on CB_1 receptors, cannabidiol augmentation strategies may also have a relevant benefit in reducing the risk of development of weight gain abnormalities and visceral fat accumulation in FEP.

Anti-glucocorticoid treatment

HPA abnormalities are associated with both PSDs[123,134] and risk of developing visceral obesity[6] (see also **4.3.2**). Of note, a recent study investigated the effects of antiglucocorticoid treatment (mifepristone, RU486) on cognitive outcomes in patients with bipolar depression[159]. The authors showed that treatment with mifepristone reduce CAR abnormalities and improve spatial working memory performance in these patients. Therefore, APDs augmented with antiglucocorticoid may represent a new interesting therapeutic strategy to ameliorate psychotic symptoms and improve cognitive function in FEP, having also potential implications in reducing the risk of developing weight gain abnormalities and visceral fat accumulation.

Physical exercise

Meta-analytic evidence suggests that aerobic physical exercise can reduce severity of symptoms (negative, positive, and general), improve cognitive performances (in particular, processing speed), and lead to better functional outcomes in patients with schizophrenia[160]. A growing body of literature has shown that physical exercise results in increases in several growth factors in the brain, including BDNF, which in turn has a positive effect on neurogenesis, synaptic plasticity, and regional brain volume and integrity[161–163]. This effect, as shown by Mueller et al.[24] (see **Table 1**), appears to be associated with a reduction of BMI and leptin blood levels. These findings suggest that aerobic physical exercise intervention may ameliorate outcomes of PSDs and FEPs by having a positive influence on brain health and cognition, as recently demonstrated by several recent studies[161–163].

Diet and probiotics

It is already well known that specific dietetic interventions may significantly help in reducing the risk of cardiovascular accidents in patients with PSDs[132,164]. Of note, recent evidence suggests that dietary habits may also have a relevant impact on brain structural and cognitive outcomes in these patients[22]. Several studies have shown that particular types of food (omega 3 fatty acid, dietary polyphenols, and curcumin) and a low caloric and fructose intake may have beneficial effects on brain structures and cognitive functions by reducing oxidative stress levels and increasing neural plasticity[130,131,165]. Furthermore, it is known that high doses of omega-3 in prodromal individuals may play a role in delaying or preventing psychotic-onset through their positive effects on brain plasticity and inflammation[166]. Finally, a growing body of literature is now investigating the effect of probiotics on gut-microbiome composition and mental health, with encouraging preliminary evidence. In particular, positive effects on cognitive and clinical outcomes in severe mental illnesses have been demonstrated for B.infantis, L.Helveticus, B. Longus, and L.casei; these results led some authors to coin the term "psychobiotics"[85]. A diet characterized by consumption of probiotics, high doses of omega 3 fatty acid, polyphenols, curcumin, and low intake of calories and fructose may thus represent a novel and intriguing add-on therapy to prevent or reduce visceral fat accumulation in FEPs, limiting its negative consequences on brain structure, clinical, cognitive, and functional outcomes.

Psychotherapy

Evidence suggests that Cognitive Behavioral Therapy (CBT), and psycho-educational interventions may play a role in limiting dysfunctional behaviors (i.e. sedentary life style, dietary habits)[25,167] leading to weight gain abnormalities in FEPs. Furthermore, a growing body of literature pointed out that the bio-behavioral system dysregulation associated with obesity and overweight may be targeted indirectly with specific therapeutic interventions aimed at increasing resilience and reducing allostatic load[26,168]. In

particular, Well-Being Therapy (WBT) has been shown to be effective in normalizing HPA dysfunctions and proinflammatory status in a range of both mental and physical disorders[169–171]. This may in turn affect neurogenesis and improve neuroprotection (reviewed by Charney[172]).

4.6 Future directions

First, future studies should directly investigate if weight-gain abnormalities and in particular visceral fat accumulation, as measured by proxy (WC, WTC, or HTW) or direct (CT, MR) indices, might be associated with more severe brain damages when expressed in comorbidity with FEP; their relevance in terms of cognitive and functional outcome should also be addressed.

Second, predictive factors of visceral fat accumulation in FEPs after the first exposure to APDs should be identified. Sex hormones, gender, ethnicity, HPA and endocannabinoid system abnormalities, gut-microbiome composition, genetics, dietary habits and sedentary life style should be all taken into account (see section **4.3**).

The identification of the key predictive factors of visceral fat accumulation in FEP is of particular relevance given that the first line therapy of these disorders is represented by APDs, which have a well-known proadipogenic effect. Once identified, these factors may be specifically targeted since the first weeks of APDs exposure (see section **4.6**). Again, limiting the development of weight gain and visceral fat accumulation in FEPs might have relevant implications in terms of both general and mental health.

5. Conclusion

In the present review we tried to shed light on those weight gain-induced brain structural abnormalities that may affect the course of illness in individuals with FEP. Given the lack of studies directly investigating this issue, we started our review with a systematic review of the literature on brain structural abnormalities in obese/overweight otherwise healthy adolescents and young adults. We then compared the results of this systematic review with meta-analytic evidence on brain structural abnormalities in drug-naïve FEPs.

We showed that it is possible to hypothesize that obese/overweight vs lean FEPs may develop more severe brain structural abnormalities in areas such as temporal lobes, prefrontal regions, insula, and corpus callosum, which are tightly related to clinical, cognitive and functional outcomes of the psychiatric disorder. Weight gain and visceral fat accumulation may trigger a cascade of events, including central insulin and leptin resistance, HPA dysfunctions, gut-microbiome alterations, and low-grade inflammation that are potentially responsible for brain structural damages in obese and overweight individuals. Of relevance, all these factors are expressed in FEPs before the exposure to APDs. Development of obesity and overweight in FEP may thus contribute to worsening these pathophysiological mechanisms, resulting in more severe brain structural abnormalities and poorer prognostic outcomes.

Furthermore, most of the vulnerability factors associated the with risk of developing weight gain abnormalities and visceral fat accumulation in the general population also represent key psychopathological dimensions typically associated with disease-inherent mechanisms of psychotic-spectrum disorders, independent of APDs. These compounds surely play a key role in unmasking this pre-existent vulnerability, but others innate neurobiological mechanisms, expressed since the earliest stages of PSDs and in individuals never exposed to medications, may also explain why obesity and overweight are

often associated with FEP. Of relevance, these mechanisms may be specifically targeted with both pharmacological (sex hormones, anti-glucocorticoids, cannabidiol) and non-pharmacological (diet, probiotics, physical exercise, CBT) interventions.
Weight gain and visceral fat accumulation may significantly influence prognosis in FEP not only in terms of future-onset CVD and overall mortality, but also in terms of poor cognitive, symptomatic and functional outcomes through specific effects on brain structures and development.

Limitations

This review has several limitations. First of all, it was not possible to perform a quantitative synthesis of the results from different studies. Meta-analysis provides a pooled estimate based on statistical analysis of results from primary studies and meta-analysis of well-conducted studies is considered to be a superior level of evidence. Second, the age range of the studies investigating brain structural abnormalities was chosen arbitrarily, with the aim of achieving results that were comparable with those on drug-naïve FEPs.

Figure Legend

Figure 1. PRISMA Flow chart

Figure 2. The picture represents the complex interplay between modifiable vulnerability factors (in green) and triggering mechanisms (in red) that might explain why patients with FEPs often develop weight gain abnormalities. Obesity and overweight, especially in their abdominal/visceral form, may contribute to worsening a series of pathophysiological mechanisms typically associated with psychosis spectrum disorders and potentially responsible for more severe brain structural abnormalities in obese/overweight vs lean FEPs (more details are given in the main text). It could be possible to reduce the risk of developing weight gain abnormalities in FEPs through specific interventions (red crosses)

Figure 2-Legend. Green: modifiable vulnerability factors; Red: triggers; CSF: Cerebrospinal fluid; CAR: Cortisol Awakening Response; HPA: Hypothalamo-Pituitary-Adrenal Axis; SERMs: Selective Estrogen Receptor Modulators; CBT: Cognitive Behavioral Therapy; WBT: Well-Being Therapy; PFC: Prefrontal cortex

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