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Obesity, dyslipidemia and brain age in first-episode psychosis

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ABSTRACT

Introduction: Obesity and dyslipidemia may negatively affect brain health and are frequent medical comorbidities of schizophrenia and related disorders. Despite the high burden of metabolic disorders, little is known about their effects on brain structure in psychosis. We investigated, whether obesity or dyslipidemia contributed to brain alterations in first-episode psychosis (FEP).

Methods: 120 participants with FEP, who were undergoing their first psychiatric hospitalization, had < 24 months of untreated psychosis and were 18–35 years old and 114 controls within the same age range participated in the study. We acquired 3T brain structural MRI, fasting lipids and body mass index. We used machine learning trained on an independent sample of 504 controls to estimate the individual brain age of study participants and calculated the *BrainAGE* score by subtracting the chronological from the estimated brain age.

Results: In a multiple regression model, the diagnosis of FEP (B = 1.15, SE B = 0.31, $p < 0.001$) and obesity/overweight (B = 0.92, SE B = 0.35, $p = 0.008$) were each additively associated with *BrainAGE* scores ($R^2 = 0.22$, $F(3, 230) = 21.92$, $p < 0.001$). *BrainAGE* scores were highest in participants with FEP and obesity/overweight (3.83 years, 95%CI = 2.35-5.31) and lowest in normal weight controls (−0.27 years, 95%CI = −1.22-0.69). LDL-cholesterol, HDL-cholesterol or triglycerides were not associated with *BrainAGE* scores.

Conclusions: Overweight/obesity may be an independent risk factor for diffuse brain alterations manifesting as advanced brain age already early in the course of psychosis. These findings raise the possibility that targeting metabolic health and intervening already at the level of overweight/obesity could slow brain ageing in FEP.

1. Introduction

Schizophrenia is among the most disabling psychiatric disorders (Whiteford et al., 2013). It is frequently associated with neuroanatomical alterations (Vita et al., 2006; Fornito et al., 2009), which may contribute to impaired functioning (Dazzan et al., 2015). Yet, the origins of brain changes in schizophrenia remain poorly understood and there is no treatment for them. One potential source of neuroimaging abnormalities in psychotic disorders is the comorbidity with medical conditions known to affect the brain.

Almost 1 in 2 participants with schizophrenia are overweight, and at least 2 in 5 suffer from dyslipidemia (Mitchell et al., 2013b). Increased rates of metabolic alterations are found already early in the course of illness. Overweight/obesity, low HDL-cholesterol and hypertryglyceridaemia each affect about 20% of participants with first-episode psychosis (FEP) (Mitchell et al., 2013a). The early onset and lifelong presence of metabolic alterations contribute to poor medical and psychiatric outcomes in schizophrenia (Saha et al., 2007; Brown et al., 2010; Bora et al., 2017) and other psychotic disorders (Bora et al., 2017; Hajek et al., 2016). Among metabolic alterations, obesity and dyslipidemia are the strongest contributors to cognitive impairment and functional decline in psychotic disorders (Bora et al., 2017), which may

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be related to the negative effects of these comorbidites on the brain.

Neurostructural alterations are frequently reported in participants with obesity (Debette et al., 2010; Tiehuis et al., 2014; Sala et al., 2014; Cherbuin et al., 2015; Masouleh et al., 2016), even in absence of other pathology (Yau et al., 2014; Alosco et al., 2014; Ou et al., 2015). These changes manifest already in adolescence (Mueller et al., 2012; Alosco et al., 2014; Ross et al., 2015; Yokum and Stice, 2017) and tend to be most pronounced in frontal lobes and limbic regions, including insula and hippocampus (Willette and Kapogiannis, 2015). Dyslipidemia may contribute to neurostructural alterations in obesity, with which it often clusters (Friedman et al., 2014; Schwarz et al., 2018). Furthermore, obesity enhances the negative effects of psychiatric morbidity on the brain (Bond et al., 2011, 2014), which may in turn yield adverse psychiatric outcomes (Opel et al., 2015). Interestingly, brain alterations in obesity or dyslipidemia may be preventable or treatable (Mueller et al., 2015; Tuulari et al., 2016; Mansur et al., 2017b) and resemble some of the most replicated neurostructural findings in schizophrenia and related disorders.

Longitudinal studies have shown accelerated age related loss of fronto-limbic volumes, already early in the course of schizophrenia (Paus et al., 2008; Gogtay, 2008; Shaw et al., 2010; Gogtay and Thompson, 2010). Consequently, participants with FEP typically demonstrate smaller volumes of frontal lobes, hippocampus and insula (Ganzola et al., 2014; Torres et al., 2016; Lee et al., 2016; Dietsche et al., 2017). Many of these changes progressively worsen, especially in the first years of illness (van Haren et al., 2007; Andreasen et al., 2011; Vita et al., 2012; Lee et al., 2016). This is likely related to accumulation of certain clinical variables (Zipursky et al., 2013; Zipursky, 2014). Thus, studying the interplay between obesity, dyslipidemia and brain health could help identify preventable risk factors for neuroimaging abnormalities in schizophrenia and related disorders and could provide insight into their pathophysiology and treatment.

Access to large databases of brain scans and advances in neuroimaging analyses involving machine learning, allow us to estimate the biological age of the brain from MRI (Franke et al., 2013; Koutsouleris et al., 2014). The difference between brain age and chronological age captures diffuse, multivariate neurostructural alterations into a single number. This mitigates the problem of multiple comparisons and yields relatively unbiased estimates of effect size (Reddan et al., 2017). Aside from age related changes, this measure is sensitive to brain alterations in schizophrenia (Koutsouleris et al., 2014; Schnack et al., 2016; Nenadic et al., 2017) or obesity (Ronan et al., 2016), which typically show greater brain than chronological age.

Here, we used this novel technology to study the effects of metabolic markers on brain structure in FEP. We expected, that participants with FEP, obesity and possibly dyslipidemia would demonstrate neurostructural alterations, which would make their brains appear older than their chronological age and that the effects of these factors on brain structure would be additive.

2. Materials and methods

This was a part of the Early Stages of Schizophrenia study (Spaniel et al., 2016). To ensure generalizability, we recruited participants during their first hospitalization in a large general psychiatry hospital (1200 beds), which serves the Prague and part of Central Bohemia regions - catchment area of over 1.5 million subjects. We focused on individuals with FEP, who met the following inclusion criteria: 1) were undergoing their first psychiatric hospitalization, 2) had the ICD-10 diagnosis of schizophrenia (F20), or acute and transient psychotic disorders (F23) made by psychiatrist according to Mini-International Neuropsychiatric Interview (Sheehan et al., 1998), 3) had < 24 months of untreated psychosis, 4) were 18–35 years old. Patients with psychotic mood disorders were excluded from the study.

As the diagnosis of schizophrenia requires a minimal duration of symptoms, the retrospective diagnostic stability of schizophrenia is low (0.6; Fusar-Poli et al., 2016). A significant number of patients who are later diagnosed with schizophrenia receive a different initial diagnosis. We wanted to recruit participants at the early stages of illness, to minimize the effects of illness and medications on brain structure. Thus, participants who were hospitalized before meeting the duration criteria for schizophrenia are a particularly interesting group. These participants were included in the study and received the working diagnosis of acute and transient psychotic disorders, which is congruent with DSM-IV brief psychotic disorder. This approach is in keeping with other studies of FEP (Mitchell et al., 2013a; Fusar-Poli et al., 2016).

Healthy controls, 18–35 years old, were recruited via advertisement, using the following exclusion criteria: 1) lifetime history of any psychiatric disorders, 2) psychotic disorders in first or second-degree relatives.

Additional exclusion criteria for both groups included history of neurological or cerebrovascular disorders and any MRI contraindications.

Within one week before scanning, we acquired information about personal history of hypertension, diabetes, weight, height, duration of untreated/treated psychiatric illness, current medications. We extracted the following variables from the chart - blood pressure, weight at admission, history of substance use/abuse. The duration of illness was obtained from documentation and by direct assessment by board certified psychiatrists. On the day of scanning, we obtained symptom ratings and fasting blood samples. In medication naive participants, we also acquired fasting blood samples within 3 days following admission and calculated the cumulative medication exposure until MRI.

The assessment of lipids was performed in a single clinical laboratory using standard methods, see Supplemental material. We measured LDL-cholesterol, HDL-cholesterol and triglycerides (TG), as diabetes (2.1%) or hyperglycemia (6.4%) are uncommon in FEP and much less frequent then low HDL (20.6%) or hypertriglyceridemia (16.9%) (Mitchell et al., 2013a). The absence of diabetes was verified by fasting glucose from the chart. We measured body mass index (BMI) using the formula: BMI = weight (kg)/height (meters)^2. All diagnostic assessments and symptom ratings were performed by a psychiatrist using the Mini-International Neuropsychiatric Interview (Sheehan et al., 1998) and the Positive and Negative Syndrome Scale.

The study was carried out in accordance with the latest version of the Declaration of Helsinki. The study design was reviewed and approved by the Research Ethics Board. Each participant received a complete description of the study and provided written informed consent.

2.1. MRI acquisition

We acquired T1-weighted 3D MPRAGE scans (TE = 4.63 ms, TR = 2300 ms, bandwidth 130 Hz/pixel, FOV = 256 x 256 mm, matrix 256 x 256, voxel size 1 x 1 x 1mm3) on 3T Siemens Trio MRI scanner equipped with standard head coil.

2.2. Brain age estimation

We applied a machine learning method, which accurately and reliably estimates the age of individual brains across wide age range (Franke et al., 2010, 2012), is sensitive to effects of metabolic alterations or psychiatric disorders (Franke et al., 2013; Gaser et al., 2013), has been excessively validated (Franke and Gaser, 2012) and is robust to differences between scanners (Franke et al., 2010, 2012). The analyses included: 1) Preprocessing of MRI data using standard voxel-based morphometry, 2) Feature reduction using smoothing and principal component analysis, 3) Estimation of brain age using relevance vector regression (RVR). We trained the RVR model using an independent sample of 504 healthy individuals from the IXI database (http://www.brain-development.org). For detailed description of the method, see (Franke et al., 2010, 2013; Franke and Gaser, 2012) and Supplemental

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