Univerzita Karlova

3. lékařská fakulta

Disertační práce

Praha, 2020 MUDr. Marián Kolenič

Univerzita Karlova

3. lékařská fakulta

Studijní program: Neurovědy

Disertační práce

Asociace metabolických faktorů a strukturálních změn mozku u psychotických poruch.

Association between metabolic factors and structural brain changes in psychoses

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Podpis

Identifikační záznam:

KOLENIČ, Marián. Asociace metabolických faktorů a strukturálních změn mozku u psychotických poruch. *[Association between metabolic factors and structural brain changes in psychoses]*. Praha, 2020. 104s, 5 příloh. Disertační práce. Univerzita Karlova, 3. lékařská fakulta, Klinika / Ústav 3. LF UK 2020. MUDr. Tomáš Hájek, PhD.

Klíčová slova: *(v ČJ a AJ)*

Obezita; Psychóza; Dyslipidémie; První epizoda schizofrenie; Bipolární afektivní porucha; BrainAGE skór; Zánět; Voxel-based morfometrie

Keywords:

Obesity; Psychosis; Dyslipidemia; First-episode schizophrenia; Bipolar disorder; BrainAGE score; Low-grade inflammation; Voxel-based morphometry

Acknowledgements

I would like to thank my supervisor Tomas Hajek for his dedicated support and guidance. Tomas continuously provided encouragement and was always willing and enthusiastic to assist in any way he could throughout the research project. I would also like to thank co-supervisors Filip Španiel and Jaroslav Hlinka, and many thanks to all participants that took part in the study and enabled this research to be possible. Finally, I am especially grateful to my wife Miriama for her patience and support.

CONTENT

Abstract

Background: Schizophrenia (SZ) and bipolar disorders (BD) are often correctly diagnosed only years after the initial manifestations. Brain imaging may provide support for early differential diagnosis, but is complicated by marked heterogeneity of results between studies. Obesity, dyslipidemia and insulin resistance (IR) are frequent in psychiatric disorders and may contribute to brain alterations/heterogeneity. We studied BD and SZ in different stages of illness and specifically investigated the effects of metabolic parameters on brain structure and function. **Methods:** In Study 1 we used machine learning algorithm to estimate the individual brain age from MRI scans of 120 participants with first episode schizophrenia (FES) and 114 controls. We calculated the brain age gap (BrainAGE) score by subtracting the chronological age from the brain age. We also performed voxel-based morphometry (VBM) study to localize obesity or psychosis related pathology. In Study 2, we acquired biochemical and cognitive measures from 100 euthymic BD patients and explored the association between IR and memory. In Study 3, we explored differences in BrainAGE in early stages of SZ (43 participants) or BD (96 offspring of BD parents) and healthy controls (HC). In Study 4, we performed MRI cerebellar volume analyses on 648 participants with SZ, BD and HC. **Results:** In Study 1, the diagnosis of FES and obesity/overweight were each additively associated with higher BrainAGE scores. VBM confirmed association between FES, higher BMI and lower GM volume. In Study 2, BD participants with IR displayed worse composite verbal memory score, while composite working memory scores were comparable in patients with or without IR. In Study 3, brain age of FES was on average 2.64 years greater than their chronological age. In contrast, participants at risk or in the early stages of BD showed comparable BrainAGE scores to HC and to their chronological age. In Study 4 patients with SZ had smaller global cerebellar GM volume compared to HC, while patients with BD did not differ from HC. **Conclusions**: Overweight/obesity may be an independent risk factor for diffuse brain alterations manifesting as advanced brain age as well as for local lower GM volumes already early in the course of psychosis. IR may contribute to worse cognitive functions in BD. These findings raise the possibility that targeting metabolic health and intervening already at the level of overweight/obesity or IR could slow neurostructural alteration and preserve brain function in SZ or BD. BrainAGE method and cerebellar volume measurements could aid in early differential diagnosis between BD and SZ.

Abstrakt

Úvod: Schizofrenie (SZ) a bipolární afektivní porucha (BD) jsou často správně diagnostikovány až několik let po prvních projevech psychické poruchy. Neurozobrazovací techniky by mohly poskytnout podporu při časné diferenciální diagnostice, nicméně širší využití v klinické praxi je komplikováno výraznou heterogenitou výsledků mezi jednotlivými studiemi. Obezita, dyslipidémie a inzulinová rezistence (IR) jsou časté komorbidity psychických poruch, které mohou přispívat k heterogenitě nálezů/mozkovým změnám. Studovali jsme BD a SZ v různých stádiích onemocnění a zkoumali jsme účinky metabolických parametrů na struktury a funkce mozku. **Metody**: Ve Studii 1 jsme pomocí algoritmu strojového učení odhadovali individuální věk mozku ze snímků magnetické rezonance u 120 pacientů s první epizodou schizofrenie (FES) a u 114 kontrol. Počítali jsme BrainAGE skóre, jež tvoří rozdíl mezi odhadovaným věkem mozku a chronologickým věkem. Za účelem lokalizace mozkových abnormit asociovaných s obezitou nebo psychózou jsme provedli voxel-based morfometrii (VBM). Ve Studii 2 jsme za pomoci biochemických a kognitivní dat od 100 euthymních pacientů s BD zkoumali souvislost mezi inzulínovou rezistenci (IR) a pamětí. Ve Studii 3 jsme se zaměřili na neurostrukturální rozdíly mezi časnými stádii SZ (43 pacientů), BD (96 potomků rodičů s BD) a zdravými kontrolami (HC). Ve Studii 4 jsme provedli objemové analýzy mozečku z MRI dat u 648 účastníků s SZ, BD a HC. **Výsledky**: Ve Studii 1 byly diagnóza FES a stejně tak obezita/nadváha nezávisle a aditivně asociovány s vyšším BrainAGE skórem. VBM potvrdila asociaci mezi FES a vyšším BMI na jedné straně a nižším objemem GM na straně druhé. Ve Studii 2 vykazovali BD pacienti s IR horší skóre verbální paměti. Studie 3 ukázala, že mozek pacientů s FES vypadal dle MRI snímků v průměru o 2,64 roku starší, než ve skutečnosti byl. Naproti tomu účastníci v riziku nebo v raných stádiích BD vykazovali BrainAGE skóre srovnatelné s jejich chronologickým věkem a taky s HC. Ve Studii 4 měli pacienti se SZ menší globální objem mozečku ve srovnání s HC, zatímco pacienti s BD se od HC nelišili. **Závěry**: Nadváha/obezita může být již v úvodních stádiích psychóz nezávislým rizikovým faktorem pro difúzní změny mozku projevující se v MR obrazu jako předčasné stárnutí mozku. IR může přispívat k horším kognitivním funkcím u BD. Naše výsledky naznačují, že prevence nebo včasná léčba metabolických komorbidit u psychóz by mohla zpomalit neurostrukturální změny a snížit dopad na kognitivní funkce. Metoda BrainAGE a měření objemu mozečku by mohly pomoci při včasné diferenciální diagnostice mezi BD a SZ.

1. LIST OF ABBREVIATIONS

BD - bipolar disorder

BMI – body-mass index

CI - confidence interval

CRP - C-reactive protein

CVLT - California Verbal Learning Test

DS - Digit Span

FWE - family-wise error

FES - first episode schizophrenia

FEP- first episode psychosis

GM – gray matter

HC - healthy controls

HDL - high-density lipoprotein cholesterol

HOMA-IR - Homeostatic Model Assessment of Insulin Resistance

HR- high-risk

IR- insulin resistance

LDL - low-density lipoprotein cholesterol

MDD - major depressive disorder

MRI –magnetic resonance imaging

RVR - relevance vector regression

TFCE - Threshold-Free Cluster Enhancement

TG -triglycerides

T2DM –type 2 diabetes mellitus

SZ – schizophrenia

VBM - voxel-based morphometry

WM – white matter

2. INTRODUCTION

2.1. Studied disorders

Bipolar disorders (BD) and schizophrenia (SZ) are among the leading causes of morbidity and mortality worldwide (Gustavsson et al., 2011; Whiteford et al., 2013) due in part to their early onset and lifelong nature (Ortiz et al., 2011; Immonen et al., 2017). SZ is a chronic disorder characterized by an array of symptoms, including hallucinations, delusions, disorganized speech or behavior, and impaired cognitive ability (Patel et al., 2014). Characteristic feature of SZ is an ongoing presence of severe reality distortion (Krishnan et al., 2011). BD is classified as an affective disorder in which patients experience episodes of depression and either mania or hypomania (Phillips and Kupfer, 2013). Depression is characterized by low mood and related symptoms (e.g. loss of pleasure and reduced energy), episodes of mania are characterized by elated or irritable mood or both, and related symptoms such as increased energy and potential mood-congruent as well as incongruent delusions (Phillips and Kupfer, 2013; Yatham et al., 2018). In hypomania symptoms are less severe or less protracted than are those of mania (Yatham et al., 2018; Phillips and Kupfer, 2013). Schizophrenia is often accompanied by affective symptomatology and BD may often present with psychotic symptoms. In fact, more than half of all individuals diagnosed with BD experience psychotic mood episodes in their lifetime (Dunayevich and Keck, 2000). Differentiating between these disorders, especially early in the course of illness is often difficult. Both SZ and BD are often correctly diagnosed only years after the initial manifestations (Hirschfeld et al., 2003; Penttila et al., 2014), which leads to delayed treatment and contributes to poor prognosis (Penttila et al., 2014; Berk et al., 2009; Berk et al., 2011; Diaz-Caneja et al., 2015). Consequently, early differential diagnosis between BD and SZ is highly important, but it may require going beyond the traditional symptoms. This is where detailed studies of neurobiology/neuroanatomy may play a prominent role.

2.2. Brain imaging in schizophrenia and bipolar disorder

Schizophrenia is frequently conceptualized as a neurodevelopmental disorder (Shaw et al., 2010; Rapoport et al., 2005; Rapoport et al., 2012), where brain maturation is characterized by exaggerated developmental trajectories and accelerated age-related gray matter (GM) loss (Shaw et al., 2010; Paus et al., 2008; Gogtay et al., 2008; Gogtay et al., 2010). Lower GM volumes were reported already in medication-naive early stages of schizophrenia, especially in

superior temporal, insular and hippocampal regions (Shah et al., 2017). On the other hand, neurodevelopmental antecedents are mostly absent in individuals with BD (Walker et al., 2002; Sanches et al., 2008) who typically show preserved brain structure (Hajek et al., 2005) and even evidence for larger regional GM volumes in the early stages of the illness (Hajek et al., 2009; Ladouceur et al., 2008; Hajek et al., 2013; Roberts et al., 2016; Sarıcicek et al., 2015). Many of the brain changes progressively worsen in both SZ and BD (van Haren et al., 2007; Andreasen et al., 2011; Vita et al., 2012; Lee et al., 2016; Abé et al., 2020) and this is likely related to accumulation of certain clinical variables (Zipursky et al., 2013; Zipursky, 2014). In later stages of both disorders, abnormalities in grey matter become more widespread and start to show a greater overlap between both diagnoses. Specifically, SZ is characterized by thinner cortical gray matter, especially in frontal and temporal lobe, smaller volumes of hippocampus, amygdala, thalamus, accumbens, and larger ventricle volumes (van Erp et al., 2018). Participants with BD show similar alterations, with thinner cortical gray matter in bilateral frontal, temporal and parietal regions, with reduced hippocampal and thalamic volumes and enlarged lateral ventricles (Hibar et al., 2018).

Another key characteristic of neuroimaging literature in BD or SZ is heterogeneity of findings. Individual studies often differ in the direction and location of neurostructural findings (Wang et al., 2019, Leung et al., 2011; Radua et al., 2012; Shah et al., 2017) and certain brain alterations are more pronounced or found only in some individuals with BD or SZ. Since there are differences in brain imaging findings within BD or SZ, it is clear that brain changes in these conditions need to be related to additional factors, rather than just the diagnosis. Better understanding of the clinical factors which contribute to brain alterations is important for interpretation of findings. It is also the first step towards prevention or treatment of neurobiological changes, which may contribute to functional impairment in BD (Oertel-Knöchel et al., 2015) as well as SZ (Dazzan et al., 2015; Lieberman et al., 2001). Since there are differences in brain imaging findings within BD or SZ, it is clear that brain changes in these conditions need to be related to additional factors, rather than just the diagnosis. One of the potential sources of neuroimaging abnormalities in major psychiatric disorders could be the comorbidity with medical conditions known to affect the brain. Overlapping comorbidities could also explain the overlap between BD and SZ in brain imaging findings. One such comorbidity, which is associated with both BD, SZ and which clearly affects the brain is obesity.

2.3. Metabolic abnormalities in schizophrenia and bipolar disorder

Almost 1 in 2 participants with SZ are obese or overweight (40-60%), which is significantly more than in the general population (Mitchell et al., 2013a; Vancampfort et al., 2015). At least 2 in 5 people with SZ suffer from dyslipidemia (Mitchell et al., 2013b). Overweight or obesity are disproportionately frequent already in the earliest stages of illness (Correll et al., 2014; Foley and Morley, 2011; Galletly et al., 2012) and affect about 20% of participants with first episode psychosis (FEP) (Mitchell et al., 2013b). Hyperglycemia (6.4%) or diabetes (2.1%) are less frequent in FEP (Mitchell et al., 2013a), although higher rates of insulin resistance (IR) were described already in medication naive participants with FEP (Pillinger et al., 2017). Obesity and obesity-related metabolic abnormalities are also disproportionately more frequent in later stages of BD (Vancampfort et al., 2015; Fiedorowicz et al., 2008; Wang et al., 2006; Fagiolini et al, 2005). Interestingly, the overweight/obesity prevalence studies in the early stages of BD are inconsistent, with some reports finding higher prevalence (Mohite et al., 2020) while others not (Goldstein et al., 2016). Weight in BD increases over time, probably secondary to illness or treatment variables (Shah et al., 2006; Keck and McElroy, 2003).

The effects of metabolic comorbidities on life expectancy and medical outcomes in SZ and BD are well recognized (Correll et al., 2017; Firth et al., 2019; Saha et al., 2007; Carney et al., 2006; Regenold et al, 2002; Angst et al., 2002). What is much less appreciated, but equally as important, are the negative neuropsychiatric sequelae of these comorbidities. Long before the metabolic disorders result in premature mortality, they may contribute to poor neuropsychiatric outcomes in psychoses, possibly through their effects on brain structure (Bora et al., 2017; Calkin et al., 2015, 2009; Farruggia and Small, 2019; Godin et al., 2018; Kolenic et al., 2016; Manu et al., 2014; Rashid et al., 2013; Ruzickova et al., 2003; Fagiolini et al., 2003; Fagiolini et al., 2004).

2.4. Metabolic abnormalities and brain structure

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, temporal and cerebellar regions, brain areas which are also implicated in SZ and BD (Caunca et al., 2019; Dekkers et al., 2019; García-García et al., 2019; Moberget et al., 2018; Raschpichler et al., 2013; Shah et al., 2017; Willette and Kapogiannis, 2015; Wang et al., 2019). Opel and colleagues (Opel at al., 2020) recently reported that obesity-related cortical thickness reductions, which were most pronounced in fronto-temporal regions, revealed considerable similarities with patterns of changes in previously published studies of SZ (van Erp et al., 2018) and BD (Hibar et al., 2018). Obesity-related neurostructural alterations are not simply an artefact of atherosclerosis. They occur even in participants free of vascular complications or other obesity-related pathology (Alosco et al., 2014; Yau et al., 2014, Yau et al., 2010), possibly as a result of systemic low-grade inflammation, which is frequently associated with obesity (Wisse, 2004), as well as brain changes (Bettcher et al., 2012; Guillemot-Legris and Muccioli, 2017; Wersching et al., 2010). Among obesity-related metabolic changes, dyslipidemia or insulin resistance/type 2 diabetes mellitus (T2DM) may contribute to neurostructural alterations (Friedman et al., 2014; Schwarz et al., 2018). Participants with T2DM display smaller hippocampal volumes than nondiabetic controls (Hayashi et al., 2011; Wrighten et al., 2009). The hippocampal volume alterations may occur already in participants with impaired glucose tolerance (Convit et al., 2003) or insulin resistance (IR; Rasgon et al., 2011; Willette et al., 2013; Hajek et al., 2014; Ursache et al., 2012). The brain alterations in IR or T2DM may extend into cortical regions (Benedict et al., 2012; Moran et al., 2013; Willette et al., 2013; Garcia-Casares et al., 2014). Interestingly, brain alterations in obesity, dyslipidemia or IR may be preventable or treatable (Mueller et al., 2015; Tuulari et al., 2016; Mansur et al., 2017b).

2.5. Metabolic abnormalities and brain structure in SZ or BD

Previous neuroimaging studies addressing obesity-related brain changes focused primary at healthy participants (García-García et al., 2019; Hamer and Batty, 2019). Although metabolic comorbidities are disproportionally frequent in psychoses (Mitchell et al., 2013a; Vancampfort et al., 2015), their effects on brain structure are markedly understudied. There are few studies focusing on obesity and brain abnormalities in BD. Bond and colleagues described relationship between elevated BMI and reduced brain volumes in BD (Bond et al., 2011; Bond et al., 2014), similar finding were described by Islam (Islam et al., 2018). Hajek and colleagues provided the

first study demonstrating that type 2 diabetes mellitus or even prediabetes may be risk factors for smaller hippocampal and cortical volumes in BD (Hajek et al., 2014). Mansur et al. reported that alterations in brain structures in individuals at risk for BD may be moderated by BMI (Mansur et al., 2017b).

But studies addressing effect of obesity on SZ are still lacking. There is a single study showing that elevated BMI might contribute to WM disruption of schizophrenia (Spangaro et al., 2018), but no studies focused on obesity-related GM alterations in SZ, Importantly, metabolic disturbances enhance the negative effects of psychiatric morbidity on the brain (Bond et al., 2011; Bond et al., 2014), which may in turn yield adverse psychiatric outcomes (Opel et al., 2015).

2.6. Metabolic abnormalities and cognition

There is a highly replicated evidence showing that obesity is negatively associated with cognitive functions in non-psychiatric subjects (Prickett et al., 2015; Gunstad et al., 2010; Sabia et al., 2009). Similarly, obesity-related abnormalities, such as IR, have been associated with impaired verbal memory and fluency, processing speed and executive functions (Kullmann et al., 2016), reduced hippocampal volume (Ursache et al., 2012), and with a higher risk for developing dementia in old age (Gudala et al., 2013; Norton et al., 2014). This is not surprising, as insulin receptors are abundantly distributed throughout the brain, and insulin binding to its receptors not only produces numerous metabolic effects but also plays a promoting role in synaptic transmission and neuronal survival/growth (Ott et al., 2012). Participants with IR display cognitive impairments similar to those found in major psychiatric disorders.

Considering the high prevalence of IR in SZ and BD (Pillinger et al., 2017; De Hert et al., 2011; Vancampfort et al., 2013) and the similarity between cognitive impairments in both conditions, it is possible that some of the cognitive changes in both diseases may be related to the presence of comorbid metabolic alterations (Kolenic et al.,2016). In 2017, Bora and colleagues published review and meta-analysis investigating the association between metabolic factors and cognitive impairment in SZ. They found that metabolic syndrome, hypertension, dyslipidemia, abdominal obesity and diabetes were significantly associated with cognitive impairment (Bora et al., 2017). In the 2019, the same research group published similar results also in BD (Bora et al.,

2019). Perhaps the fact that only some patients with SZ or BD suffer from these comorbidities could also help explain why only some patients show cognitive impairments.

2.7. Aims, objectives, hypotheses

Brain imaging may provide potential support for early differential diagnosis between SZ and BD, with obvious consequences for treatment and future prognosis. To achieve this, we need to better understand which brain imaging alterations are related to the disorder itself and which may reflect the effects of additional clinical factors. Thus, studying SZ and BD in different stages of diseases and focusing on potential additional clinical contributors to brain changes could help translate brain imaging from bench to the bedside. Studies of medical comorbidities are particularly relevant to advance these objectives.

Despite the replicated obesity-related brain pathology and the high prevalence of obesity and IR in SZ and BD, the effects of metabolic disturbances on the brain health/structure and function in both diseases remain under-researched. Higher rates of obesity and metabolic alterations in SZ and BD may be related to the lifestyle, shared pathophysiology, or effects of medications. Regardless of the reasons for the comorbidity between metabolic and psychiatric disorders, it is imperative to know whether brain abnormalities found in participants with SZ or BD are associated with, or aggravated by metabolic alterations. Such knowledge could impact the clinical care of psychiatric patients vis-à-vis the currently suboptimal prevention and management of obesity and related metabolic alterations in both psychiatric diseases.

To address these knowledge gaps, we studied brain structure in BD and SZ in different stages of disease and also specifically investigated the effects of metabolic parameters on brain structure and function. We generated four hypotheses:

a) Metabolic abnormalities are associated with smaller volume of gray matter, independent of the effect of SZ

b) Individuals with SZ show smaller volume of gray matter compared to controls, independent of metabolic abnormalities.

c) Metabolic abnormalities are associated with cognitive functioning, independent of the effect of psychiatric disorders.

d) Neurostructural alterations in the brain are more pronounced in SZ compared to BD.

3. SECTION 1. ASSOCIATION BETWEEN METABOLIC FACTORS AND BRAIN STRUCTURAL OR FUNCTIONAL ABNORMALITIES

We performed 2 studies focusing on associations between metabolic factors and brain structures/function. In Study 1, we analyzed a large sample of 120 participants with FES and 112 healthy controls and used 2 types of analyses. Firstly, we focused on the effects of psychosis and obesity on a composite index of brain structure (BrainAGE). This study was published in Journal of Psychiatric Research, in 2018 (Kolenic et al., 2018). Secondly, using VBM, we investigated the localization of obesity-related neurostructural alterations and whether these directly overlap with regions associated with psychosis. This work was submitted to Frontiers in Psychiatry and is currently under review (preliminary analysis was presented at ECNP Workshop 2019 and the abstract was published in European Psychopharmacology). In Study 2, we studied association between insulin resistance and cognition in subject with BD. The study was published in Journal of Affective Disorders 2020 (Salvi et al., 2020).

3.1. Study 1: Effect of obesity and psychosis on brain structures.

3.1.1. Methods

3.1.1.1. Sample description

We analyzed a sample of 120 participants with FES and 114 controls (see table 1). These analyses are a part of the Early Stages of Schizophrenia study (Spaniel et al., 2016). To ensure generalizability, we recruited participants during their first hospitalization. We focused on individuals with first episode schizophrenia (FES), who met the following inclusion criteria: 1) were undergoing their first psychiatric hospitalization, 2) had the ICD-10 diagnosis of SZ (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 (including schizoaffective disorder, BD, and unipolar depression with psychotic symptoms), were excluded from the study. As the diagnosis of SZ requires a minimal duration of symptoms, the retrospective diagnostic stability of SZ is low (0.6) (Fusar-Poli et al., 2016). A significant number of patients who are later diagnosed with SZ receive a different initial diagnosis. We wanted to recruit participants at the early stages of disease, to minimize the effects of disease and medications on brain structure. Thus, participants who were hospitalized before meeting the duration criteria for SZ 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 DSMIV brief psychotic disorder. These criteria are in keeping with stringent definitions of first episode psychosis (Breitborde et al., 2009). 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 from scanning, we collected information about, weight, height, blood pressure, duration of untreated/treated psychiatric disease, current medications and personal history of hypertension or diabetes by direct assessment verified by chart review. On the day of scanning, we obtained symptom ratings and fasting blood samples. In participants who where medication naive prior to hospitalization we also calculated cumulative medication exposure until MRI, based on their prospective inpatient charts. Biochemical analyses were performed in a single clinical laboratory using Siemens ADVIA 1800 Clinical Chemistry systems and standard clinical method. We primarily focused on levels of HDL-cholesterol, LDL-cholesterol and triglycerides (TG) in this study, as hyperglycemia (6.4%) or diabetes (2.1%) are uncommon in FES 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 board certified psychiatrist using the Mini-International Neuropsychiatric Interview (Sheehan et al., 1998) and the Positive and Negative Syndrome Scale (Kay et al., 1987).

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.

3.1.1.2. Image processing

All data were acquired on the same scanner using the same imaging sequences.

MRI acquisition:

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

3.1.1.3. Brain imaging analyses

We used 2 methods of data analysis, so called BrainAGE and voxel based morphometry (VBM). VBM is a neuroimaging technique that estimates the distribution of grey matter tissue volume across the whole brain (Good et al., 2001). This neuroimaging method is sensitive to the effects of psychosis (Shah et al., 2017) or metabolic alterations (García-García et al., 2019). However, VBM uses mass univariate testing so that one has to correct for multiple comparison. Also, VBM fails to account for multivariate group differences, such as interactions between several voxels (Gaonkar et al., 2015).

On the other hand, multivariate analysis techniques have recently received increasing attention as they can achieve sparse representations of complex data to capture the complex and distributed nature of brain alterations in psychosis (Habeck et al., 2010). Access to large databases of brain scans and advances in neuroimaging analyses involving machine learning, allowed us to train a model 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.

3.1.1.3.1. Analysis 1: 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; Franke et al., 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; Franke et al., 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). In keeping with other studies (Franke et al., 2013; Nenadić et al., 2017) the brain-age gap estimate (BrainAGE) model was trained on a sample containing both males and females. As the number of training samples has been shown to be the most important factor for model performance (Franke et al, 2010), training separate BrainAGE models for males and females would have reduced prediction accuracy. We used the resulting age prediction model to individually estimate brain age in our study participants, thus aggregating the complex, multidimensional age related structural alterations across the whole brain into one single value (ie, estimated brain age). Our outcome measure was the BrainAGE score, which is the difference between estimated brain age and chronological age (Franke et al., 2010). Of note, the BrainAGE scores do not reflect a unitary molecular process. Depending on developmental period or particular disease, very different mechanisms may underlie changes in BrainAGE scores. The mean absolute percentage error for assessment of brain age in controls in this study was 16.29%, which is comparable to our previous validation of this method (Franke et al., 2010). For detailed description of the method, see (Franke et al., 2010, Franke et al., 2013; Franke and Gaser, 2012).

3.1.1.3.2. Analysis 2: Voxel-based morphometry analyses

We conducted FSL-VBM (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSLVBM, (Douaud et al., 2007), optimised VBM protocol (Good et al., 2001) carried out with FSL tools (Smith et al., 2004). First, structural images were brain-extracted and grey matter-segmented before being

registered to the MNI 152 standard space using non-linear registration (Andersson et al., 2007). The resulting images (GM volume probability maps) were averaged and flipped along the x-axis to create a left-right symmetric, study-specific GM template. Second, all native GM images were non-linearly registered to this study-specific template and "modulated" to correct for local expansion (or contraction) due to the non-linear component of the spatial transformation. The modulated GM images were then smoothed with an isotropic Gaussian kernel with a sigma of 3 mm. Finally, voxel-wise general linear model (GLM) was used to compute associations between local GM volume and studied variables (status - FES/controls, BMI, age, sex; see section Statistical analyses for details). Permutation-based non-parametric testing, correcting for multiple comparisons across space, was applied. The threshold for primary analyses was set to $p<0.05$ using threshold-free cluster enhancement (TFCE) and 5000 permutations, as the cluster-based thresholding was developed to be more sensitive to finding true signal than voxelwise thresholding (Smith and Nichols, 2009).

3.1.1.4. Statistical analyses

3.1.1.4.1. Analysis 1, BrainAGE

Our analytical plan of BrainAGE analyses included the following steps: 1) we investigated associations between individual metabolic variables and BrainAGE scores, using correlation coefficients for continuous and two-sample t-tests for categorical variables; 2) we explored the effects of age and sex on BrainAGE scores, to select, which nuisance variables to control for in multivariate analyses; 3) the variables significantly associated with BrainAGE scores in step 1, were entered into multiple linear regression analyses together with potential confounders from step 2 (primary analysis #1). We tested for interactions and included them where relevant. In line with our a-priori hypotheses, this approach allowed us to identify variables significantly associated with BrainAGE scores and to test whether their effects were additive.

We performed the following sensitivity analyses. To test the robustness of findings and eliminate any between group differences in potential confounders, we repeated the primary analyses only in participants with FES. Also, we repeated the primary analyses separately in each diagnostic subgroup (schizophrenia or acute and transient psychotic disorders).

In clinical practice, lipid levels and BMI are typically used to define groups with increased risk of adverse outcomes, based on well-validated cut-offs (De Backer et al., 2003). Thus, we used metabolic markers as continuous variables (referred to as lipid levels), but also as categorical predictors (referred to as lipid categories). This allowed us to focus on clinical endpoints and make the best use of these difficult to acquire data. When a specific marker was associated with BrainAGE scores both as a continuous and categorical predictor, we only used the more sensitive version in the multivariate analysis, so no factor was duplicated. In exploratory analyses evaluating the effects of medications, we compared participants who were medication naive prior to hospitalization with those previously medicated or controls, investigated the association between BrainAGE scores and medication dose at the time of scanning, or cumulative medication exposure during hospitalization, and studied the development of metabolic alterations during hospitalization. We also explored the association between BrainAGE scores and relevant clinical variables. We used correlation coefficients, paired t-tests, ANCOVA or Chi-square tests, as appropriate.

To control for multiple comparisons, we tested our a-priori hypothesis in a single multivariate model. We reported nominal p-values for the sensitivity and exploratory analyses.

3.1.1.4.2. Analysis 2, VBM

Primary VBM analyses:

These analyses were carried out on a combined sample of FES (N=120) and control (N=114) participants. In order to maximize the sensitivity to our studied conditions, we performed VBM analysis with small volume corrections to regions which have been previously associated with FES or obesity. To do this, we created a mask, which combined the results of a spatial meta-analysis of voxel based morphometry studies, which investigated: 1) association between FES and GM volumes (Shah et al., 2017), and 2) association between BMI and GM volumes (García-García et al., 2019). We assessed the association between FES, BMI as explanatory variables and regional GM volumes as the dependent variable. Age and sex were covariates of no interest. We used BMI as continuous variable, as this is preferable for statistical reasons and to increase sensitivity. In addition, this was the preferred approach in most previous studies (García-García et al., 2019). As BMI is also used clinically to define categories with increased

risk of adverse outcomes, based on validated cut-offs (De Backer, 2003) we also repeated the analyses with BMI as a categorical variable. In these analyses we compared normal weight (BMI<25) against overweight or obese participants (BMI>=25).

Secondary whole brain VBM analyses:

These analyses were also carried out on a combined sample of FES (N=120) and control (N=114) participants. In order to maximize brain coverage and test whether we would replicate the findings of previous studies, in FES or obesity, we conducted secondary whole brain VBM analysis investigating the association between FES, BMI as explanatory variables, and local GM volumes, with sex and age as covariates of no interest.

Additional VBM analyses:

We explored the effects of clinical, treatment-related or metabolic variables on our VBM results among the FES participants (N=120). Specifically, we tested for associations between relevant variables and average GM values from the voxels within the regions associated with FES or BMI from the primary analyses. We used individual GM modulated, smoothed images (GM probability maps) and calculated average GM values from the significant clusters. For simple, robust and conservative exploration, we subsequently used Spearman's correlation coefficient and Mann-Whitney U test to explore the association between average GM values and continuous or categorical variables respectively. We also explored associations between treatment-related parameters and metabolic variables in FES participants. We reported nominal p-values for these hypotheses generating/exploratory analyses.

3.1.2. Results

3.1.2.1. Analysis 1: Obesity, dyslipidemia and brain age in first-episode psychosis

We analyzed a sample of 120 participants with FES and 114 controls. Relative to controls, FES participants had significantly higher LDL (t=3.52, p=0.001), TG (t=2.7, p=0.008), lower HDL

(t= -3.33; p=0.001) and a significantly greater proportion of overweight/obese participants ($X^2(1)=4.01$; p=0.045), see table 1.

	First-episode schizophrenia participants	Control participants	P
N	120	114	N/A
Sex, N (%) female	46 (38.33)	61 (53.5)	0.02
Age, mean (SD) years	27.00 (4.94)	25.70 (4.01)	0.03
Duration of illness, mean (SD) months [a]	5.11 (5.43)	N/A	N/A
Duration of untreated illness, mean (SD) months [a]	3.12 (4.80)	N/A	N/A
Duration of antipsychotic treatment, mean (SD) months[a]	1.98 (2.92)	N/A	N/A
BMI, mean (SD)	23.32 (4.00)	22.60 (2.93)	NS
Overweight or obese, N (%)	38 (31.67)	23 (20.18)	0.045
Weight, mean (SD) kg	72.63 (15.07)	70.02 (13.30)	NS
Height, mean (SD) cm	176.15 (9.86)	175.46 (9.21)	NS
LDL-cholesterol, mean (SD) mmol/l [b]	2.61 (0.73)	2.24 (0.56)	<0.001
HDL-cholesterol, mean (SD) mmol/l [b]	1.34 (0.37)	1.55 (0.38)	0.001
TG, mean (SD) mmol/l [b]	1.32 (0.56)	1.10 (0.45)	0.008
Total cholesterol, mean (SD) mmol/l [b]	4.56 (0.94)	4.29 (0.72)	0.05
CRP, mean (SD) mg/l [c]	2.16 (4.11)	1.18 (1.60)	NS
Glucose,, mean (SD) mg/l [d]	4.45 (0.79)	N/A	N/A

Table 1. Sample description.

Abbreviations: BMI – body mass index, Dg - diagnosis, HDL – high density lipoprotein, LDL – low density lipoprotein, TG - triglycerides, CRP - C-reactive protein.

[a] Data available from 116 FES participants.

[b] Lipid levels were obtained in 73 FES participants and 80 controls.

[c] CRP levels were obtained in 68 FES participants and 53 controls.

[d] 3 participants had glucose>5.6mmol/l, which in all instances normalized after re-testing; data available from 96 FEP participants

3.1.2.1.1. BrainAGE results

BrainAGE scores were significantly associated with diagnosis of FES (t(232)=2.82, p=0.005), overweight/obesity category (t (232)=2.74, p=0.007) and BMI (r(232)=0.15, p=0.02, Fig. 1A-C). The association between BrainAGE score and BMI was related to association between BrainAGE score and weight (r(232)=0.17, p=0.009), not height (r(232)=0.10, p=0.13).

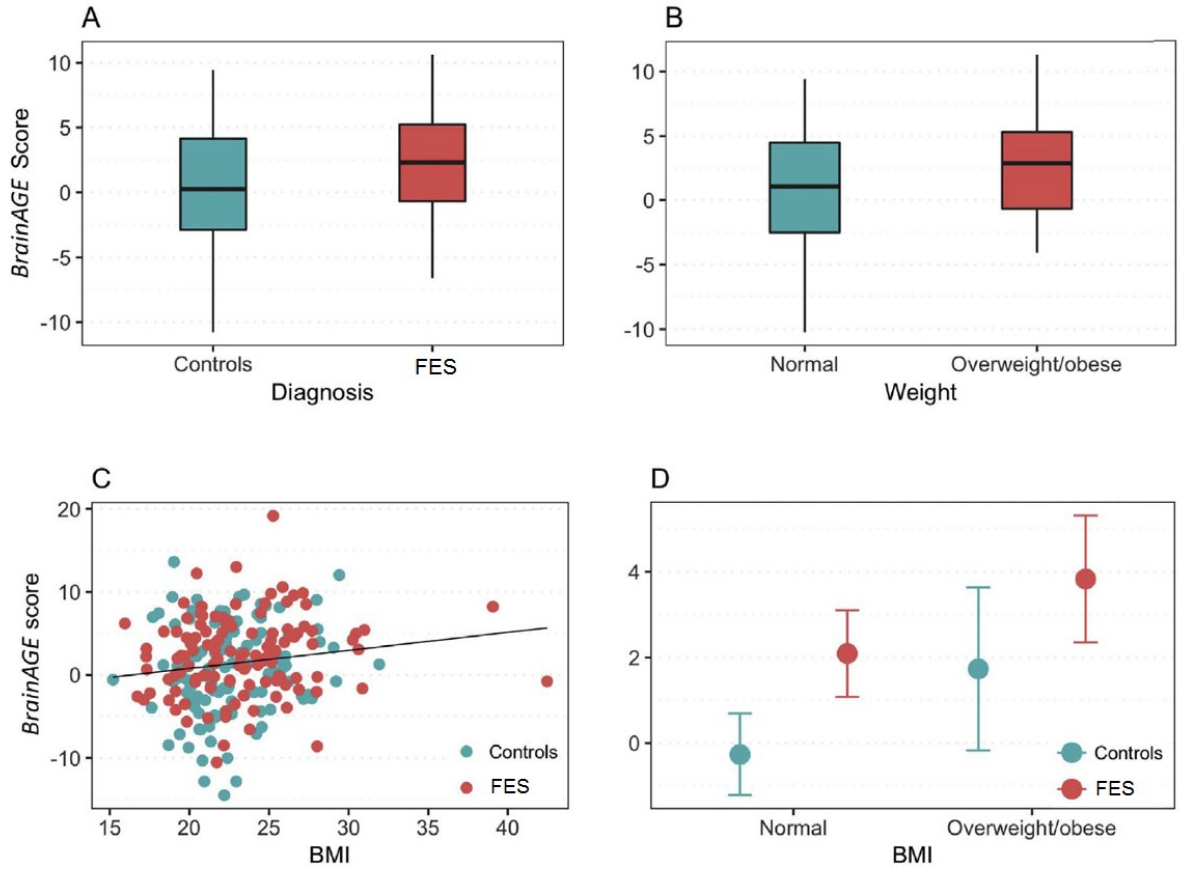

Figure 1. Associations between BrainAGE scores and psychiatric diagnosis or metabolic factors. BrainAGE scores were significantly associated with the diagnosis of first-episode psychosis (FES, panel A), overweight/obesity (panel B), body mass index (BMI, panel C). Overweight/obesity was significantly associated with BrainAGE scores additively to the effect of FES (panel D, - age adjusted mean and 95% confidence intervals).

BrainAGE scores were not associated with LDL-cholesterol category ($t(151)=-1.71$, $p=0.09$), or level ($r(151)=0.05$, $p=0.51$), HDL-cholesterol category ($t(151)=0.89$, $p=0.38$) or level $r(151)=-0.12$, $p=0.14$), TG category ($t(151)=0.16$, $p=0.87$) or level ($r(151)= -0.02$, $p=0.79$).

Among the potential confounders, BrainAGE scores were associated with age ($r(232)=-0.38$, $p < 0.001$), but not sex in either FES ($t(118)=1.53$, $p=0.13$) or controls ($t(112)=0.94$, $p=0.35$).

In multiple regression containing psychiatric diagnosis, overweight/obesity category, and age as a nuisance factor, each of the predictors was significantly and additively associated with BrainAGE scores, yielding a significant model ($R2=0.22$, $F(3, 230)=21.92$, $p < 0.001$, Table 2, Fig. 1D). There was no interaction between FES and overweight/obesity ($F(1, 229)=0.03$, $p=0.86$). BrainAGE scores were highest in participants with a combination of FES and overweight/obesity (3.83 years, 95% Confidence interval (CI)=2.35-5.31) and lowest in normal weight controls (−0.27 years, 95%CI=−1.22-0.69, Fig. 1D).

Factor	B	Standard error of B	t	p
Diagnosis of FES	1.15	0.31	3.73	< 0.001
Overweight/obesity	0.92	0.35	2.66	0.008

These analyses were corrected for age, which was significantly associated with the dependent variable ($B = -0.47$, standard error of $B = 0.07$, $t = -6.99$, $p < 0.001$).

Table 2. Results of the multiple regression analyses containing psychiatric diagnosis (first-episode psychosis (FES) vs controls), BMI category (normal weight vs. overweight/obesity), and age as a nuisance factor.

In sensitivity analyses, both overweight/obesity ($B=0.97$, SE $B=0.37$, $t=2.60$, $p=0.01$; $B=0.99$, SE $B=0.41$, $t=2.42$, $p=0.02$) and diagnosis ($B=1.21$, SE $B=0.33$, $t=3.73$, $p < 0.001$; $B=1.30$, SE $B=0.37$, $t=3.48$, $p < 0.001$) remained significantly and additively associated with BrainAGE scores in each diagnostic subgroup (schizophrenia or acute and transient psychotic disorders). Even among only FES participants (without controls), overweight/obesity remained significantly associated with BrainAGE scores ($F(1,117)=4.04$, $p < 0.05$).

3.1.2.1.2. Effects of medications

BrainAGE scores in previously medication naive participants (N=40) were greater than in controls ($F(1,151)=8.24$, $p=0.005$), comparable to previously medicated FES individuals ($F(1,117)=0.08$, $p=0.78$) and not associated with cumulative exposure to antipsychotics ($r(38)= -0.38$, $p=0.71$). The previously medication naive participants did not differ from the previously medicated ones in relevant clinical variables. Medication dosage at the time of scanning was

not associated with BrainAGE scores (r(109)=0.13, p=0.17), or BMI (r(109)=-0.02,p=0.83). BrainAGE scores were not associated with treatment with first (t(114)=-1.64, p=0.10), second generation antipsychotics (t(114)=-1.17, p=0.25), antidepressants (t(114)=-1.13, p=0.26), anticonvulsants (t(114)=1.47, p=0.15), or the number of different medication classes used (F(3,112)=1.35, p=0.26).

3.1.2.1.3. Metabolic changes during hospitalization

BMI increased significantly during hospitalization (t(111)=-3.70, $p < 0.001$), but BrainAGE scores were associated even with weight (r(110)=0.22, p=0.02) and BMI (r(110)=0.18, p=0.05) measured at admission. LDL-cholesterol levels increased significantly during hospitalization (t(35)=-5.72, $p < 0.01$), with a trend for increase in TG (t(35)=-1.85, p=0.07) and no difference in HDL-cholesterol levels (t(35)=-0.69, p=0.50). Age was significantly associated with levels of LDL-cholesterol (r(151)=0.22, p=0.007), TG (r(151)=0.27, $p < 0.001$), but not HDL-cholesterol (r(151)=-0.12, p=0.15).

3.1.2.1.4. Effects of other clinical variables

BrainAGE scores were not associated with duration of illness (r(114)=-0.08, p=0.38), duration of untreated psychosis (r(114)= -0.07, p=0.48), current symptoms (r(118)=0.04, p=0.63), systolic (r(113)=-0.009, p=0.93), diastolic (r(113)=-0.11, p=0.23), pulse pressure (r(113)=0.10, p=0.29), personal history of hypertension (t(118)=-1.19, p=0.24), glucose levels (r(94)=-0.13, p=0.20), substance abuse/dependence (t(117)=-0.64, p=0.52), current cigarette smoking (t(113)=-0.72, p=0.47) or marijuana abuse (t(117)=-0.64, p=0.52).

3.1.2.2. Analysis 2: Higher body-mass index and lower grey matter volumes in first episode of psychosis

3.1.2.2.1. Primary VBM analyses

When focusing on regions previously associated with FES or obesity, we found an association between FES and lower GM volume, while controlling for BMI, in a) cluster including left IFG-STG-temporal pole-insula-operculum (d=0.55; t_{max}=4.19; pTFCE=0.008; 395 voxels), b) left postcentral gyrus (d=0.43; t_{max}=3.34; pTFCE=0.043; 13 voxels). We also found an

association between higher BMI and lower GM volume, when controlling for FES, in the left cerebellum (d=0.74; t_{max}=5.30; pTFCE<0.001, 144 voxels); see Fig.2. The results remained unchanged, when using BMI as categorical predictor (normal weight vs. overweight/obese).

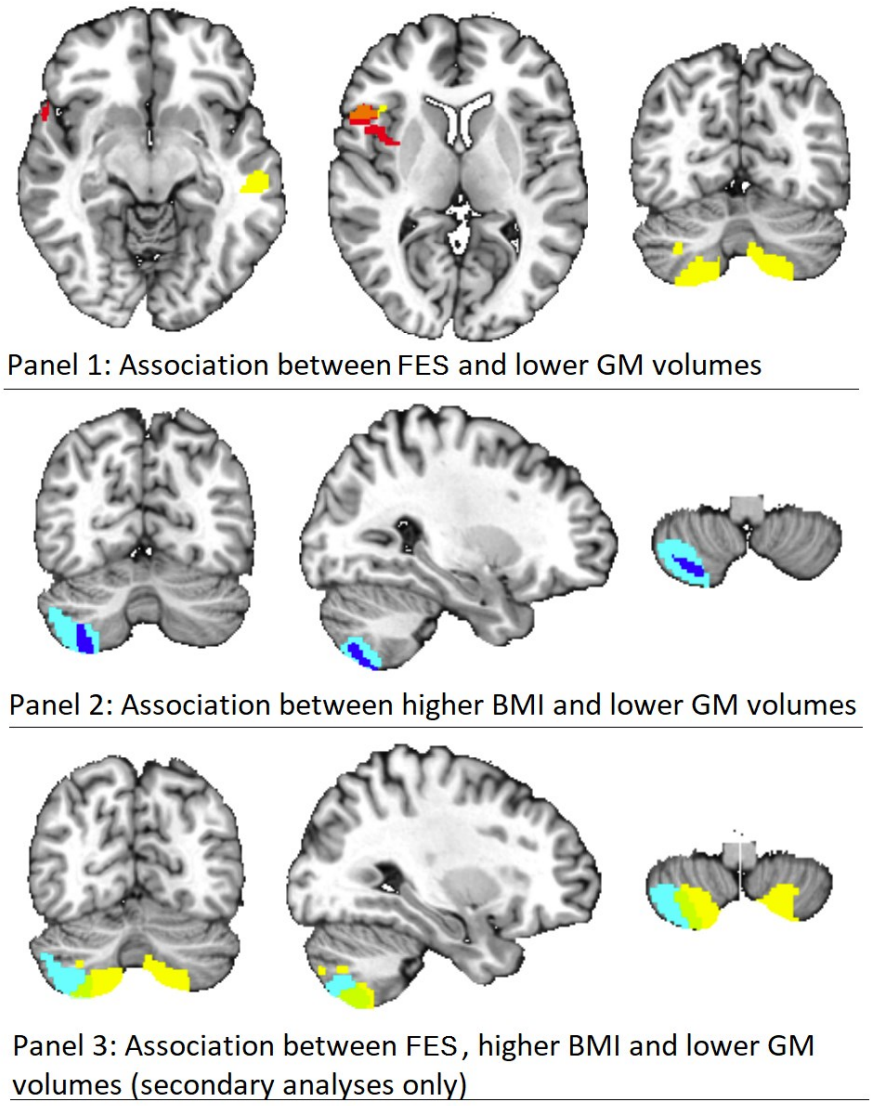

Figure 2. VBM analyses results.

Panel 1: Associations between FES and lower GM volumes; primary analyses (red), secondary whole brain analyses (yellow). Overlap between primary and secondary analyses (orange). Panel 2: Associations between higher BMI and lower GM volumes; primary analyses (dark blue), secondary whole brain analyses (light blue). Panel 3: Associations between FES, higher BMI and lower GM volumes from secondary analyses only; association with FES (yellow), association with BMI (light blue), overlap between FES and BMI (green). TFCE corr. p<0.05. Results are displayed superimposed on the Colin 27 T1 template.

3.1.2.2.2. Secondary VBM analyses

At the whole brain level and when controlling for BMI, we found associations between FES and lower GM in the a) right cerebellum (d= 0.57; t_{max}=4.39; p_{TFCE}=0.004; 1242 voxels), b) left cerebellum (d= 0.6, t_{max}= 4.59; pTFCE=0.004, 1207 voxels), c) cluster including left inferior frontal gyrus and superior temporal gyrus (d=0.62; t_{max}=4.7, pTFCE=0.024, 151 voxels), d) right temporal cortex (d=0.56; t_{max}= 4.25; pTFCE=0.031, 110 voxels). When controlling for FES, higher BMI was associated with lower GM volume in the cerebellum (d= 0.71; t_{max}= 5.1; p_{TFCE}=0.004; 858 voxels). There was overlap between findings of primary and secondary analyses. Both FES and BMI were negatively associated with GM in the left cerebellum, see Fig.2.

3.1.2.2.3. Additional VBM analyses

Average GM values from voxels associated with BMI from primary analyses were negatively correlated with low density lipoprotein cholesterol - LDL (r_s= -0.255, p=0.030), high sensitive C-reactive protein - CRP (r_s= -0.327, p=0.006), positively correlated with high density lipoprotein cholesterol - HDL (r_s= 0.269, p=0.021). None of the other clinical/treatment-related/metabolic variables were associated with average GM values from the voxels within the regions associated with BMI or FES.

BMI was negatively associated with HDL (r_s= -0.479, p<0.001), positively with TG (r_s= 0.424, p<0.001) and CRP (r_s= 0.586, p<0.001). CRP was also positively associated with LDL (r_s= 0.252, p=0.039) and TG (r_s= 0.392, p=0.001). HDL was further negatively correlated with TG (r_s= -0.374, p=0.001), and LDL was positively correlated with TG (r_s= 0.253, p=0.031).

There was no association between treatment-related variables (duration of antipsychotic treatment, medication status prior to hospitalization, chlorpromazine equivalent antipsychotic dose at MRI, cumulative medication exposure until MRI) and BMI, HDL, LDL, TG or CRP.

3.2. Study 2: Insulin resistance is associated with verbal memory impairment in bipolar disorders

3.2.1. Methods

3.2.1.1. Sample description

This multicenter study was conducted in the outpatient clinics of University hospitals in Milan (Italy), Turin (Italy), and Prague (Czech Republic), between February 2017 and October 2018. Outpatients with diagnosis of BD type I or II (verified by SCID-I) in euthymic phase of the disorder consecutively admitted to the study centers were asked to participate. To be enrolled, patients had to be in euthymic state (HAM-D-17 $\leq$ 7; YMRS $\leq$ 5; CGI-BP $\leq$ 3) and free from significant mood symptoms at least two months before the index visit. Psychiatrists administered the diagnostic interview and rating scales. Patients were excluded if they had dementia, borderline personality disorder, diabetes mellitus or current alcohol/substance use disorder. Other comorbid psychiatric disorders were allowed. Study procedures were explained in detail, and patients were asked to read and sign an informed consent. The study was conducted according to the Declaration of Helsinki and approved by the Independent Ethics Committee of participating centers.

3.2.1.2. Study procedures

During the study visit, a blood draw measuring basal insulin, glucose, total cholesterol, HDL cholesterol and triglycerides (TG) was performed in fasting condition. The samples were analyzed in hospital laboratories using standard methods of clinical biochemistry. We also collected anthropometric measures (weight, height). Patients were then asked to undergo assessment by psychiatrist and cognitive testing within one month from the blood sampling. During the interview we systematically assessed for the following socio-demographic and clinical variables, including age, gender, education, marital and occupational status, diagnosis, age at onset, number of previous episodes, pharmacological treatment. Participants underwent neuropsychological testing, which consisted of the California Verbal Learning Test (CVLT) and the Digit Span forward and backward (DS). The CVLT is a test of verbal learning, recall (encoding and retrieval) and recognition of the learned content. A list of 16 words (belonging to four semantic categories) is read five times, and the patient has to recall the words in the list

after each trial (trials 1-5). After the fifth trial, an interference list is read and the patient is asked to recall it. A short delayed recall test is conducted immediately after recalling the interference list, where the participant is asked to recall the words in the first list of words (trial 6). Cues are then provided for the four semantic categories to facilitate recall (trial 7). After 20 minutes in which the participants performed the DS, a long delayed recall test is presented (trial 8). Cues are again provided for the four semantic categories to facilitate recall (trial 9). Finally, a yes-no recognition list consisting of 44 words is read to the patient, who has to correctly retrieve the 16 words (recognition). The DS is a test evaluating auditory attention and working memory. In the DS a sequence of digits is read aloud at a rate of one digit per second, and the participant must repeat the sequence. The sequences start at a length of two digits, and two sequences of each length are read out. The sequence length increases by one digit until the participant recalls correctly at least one sequence of the same length. In the DS forward, the patient must recall the sequence in the same order that was read by the experimenter; in the DS backward, the patient must recall the sequence in the reverse order. Insulin resistance (IR) was estimated with the homeostatic model assessment of insulin resistance (HOMA-IR = [fasting plasma insulin (mU/L) x fasting plasma glucose (mmol/L)]/22.5). The HOMA-IR correlates well with estimates using the euglycaemic clamp method and it is a well-accepted measure of IR (Pillinger et al., 2017; Wallace et al., 2004). The HOMA scores used as cutoff to define IR vary across studies, ranging from 1.7 to 3.875 (Tang et al., 2015). Nevertheless, the World Health Organization (WHO) defines IR as a value equal or greater than the 75th percentile value for non-diabetic subjects (Alberti and Zimmet, 1998). As all subjects in our study were non-diabetic, we employed the WHO definition and diagnosed IR in those with a HOMA-IR score ≥ 3.5, corresponding to the 75th percentile in HOMA scores in our sample.

3.2.1.3. Statistical analyses

We used standard descriptive statistics to document the socio-demographic and clinical characteristics of the sample. To limit the number of comparisons and thus to preserve statistical power, we converted the cognitive measures to z-scores and calculated composite scores separately for verbal and working memory, according to a previously published method (Bruehl et al., 2010; Laws et al., 2017). The verbal memory composite scores were calculated from CVLT subtests, which were available in all participants, including trials 1-5, trial 6, and trial 8 (total recall, short-delayed recall, long-delayed recall).

Verbal and working memory composite scores were then calculated as follows:

- composite verbal memory score = (trials 1-5 z-score + trial 6 z-score + trial 8 z-score) / 3
- composite working memory score = (DS forward z-score + DS backward z-score) / 2

These composite verbal and working memory scores were separately entered as dependent variables into a general linear model with IR (yes, no) as predictor, age as covariate and center as a random factor. To explore the extent to which the individual subtests contributed to the association between IR and cognitive performance, we repeated equivalent models, but with raw scores from individual subtests as the dependent variables and calculated eta squared as the measure of effect size. We also explored associations between individual biochemical, clinical, demographic predictors and individual composite cognitive scores, while controlling for age and site. Variables, which were significantly associated with cognitive performance were then included in a model together with IR. All analyses were performed using IBM SPSS 20.0 software (Armonk, NY).

3.2.2. Results

We recruited 111 euthymic BD participants. Eleven patients were excluded from the final sample: 5 had current alcohol or substance abuse, 4 had borderline personality disorder comorbidity, 2 had type 2 diabetes mellitus. Thus, we analyzed data from 100 euthymic BD participants. 51% of participants in the whole sample were females, mean age was 45.2 ± 13.3 years, age at onset 25.8 ± 8.7 years and 56.7% had bipolar disorder type I. Mean BMI was 26.5 ± 5.4 kg/m2 , and mean HOMA-IR was 2.9 ± 4.0. Patients with IR were older and less educated than patients without IR. Age of onset of BD was higher in patients with IR. BMI and TG levels were greater in patients with IR. Patients with IR were more frequently treated with mood stabilizers, while exposure to antipsychotics (aripiprazole, olanzapine, quetiapine) did not differ between the two groups Socio-demographic and clinical correlates of IR are shown in Tab.3.

	IR *N* = 24	No IR *N* = 71	*P*
Sex (female), n (%)	10 (41.7)	37 (52.1)	0.38
Age (years), mean ± *sd*	**49.2 ± 9.3**	**43.7 ± 14.3**	**0.04**
Education (years), mean ± *sd*	**12.9 ± 3.3**	**14.9 ± 2.7**	**<0.01**
BD type I, n (%)	13 (54.2)	46 (66.7)	0.27
Age of onset (years), mean ± *sd*	**29.3 ± 10.3**	**24.5 ± 7.5**	**0.05**
Duration of illness (years), mean ± *sd*	19.9 ± 14.4	19.3 ± 13.4	0.87
N. of manic episodes, mean ± *sd*	4.8 ± 4.3	3.9 ± 3.7	0.33
N. of depressive episodes, mean ± *sd*	4.6 ± 3.9	4.8 ± 4.7	0.66
At least one lifetime suicide attempt, n (%)	4 (16.7)	20 (29)	0.23
BMI, mean ± *sd*	**29.3 (5.5)**	**25.9 (5.1)**	**<0.01**
Triglycerides, mmol/l	**3.3 (2.1)**	**1.8 (1.0)**	**<0.01**
HDL cholesterol, mmol/l	1.3 (0.5)	1.4 (0.4)	0.21
Total cholesterol, mmol/l	4.7 (1.3)	4.8 (1.0)	0.55
Psychotropic medication, n (%) *Antipsychotics* ***Mood stabilizers*** *Antidepressants*	18 (75) **24 (100)** 7 (29.2)	39 (57.4) **56 (82.4)** 9 (13.2)	0.13 **0.03** 0.08

Table 3 Socio-demographic/clinical characteristics of patients with and without IR.

3.2.2.1. Cognitive functions and insulin resistance

When controlling for age and center, participants with IR displayed worse composite verbal memory score (-0.38 vs 0.17; F(1, 8.23)=17.90; p=0.003, partial eta squared=0.69). Among the individual subtests, short delayed free recall showed the largest effect size (partial eta squared=0.73), whereas CVLT long delayed free recall showed the lowest effect size (partial eta squared=0.48) for differences between those with and without IR (Tab.4).

Composite working memory scores were comparable in patients with or without IR (-0.20 vs 0.07; F(1,6.05)=1.64; p=0.25, partial eta squared=0.21).

	IR	No IR	Partial eta squares
CVLT scores			
CVLT total recall (trial 1–5)	42.2 (9.7)	50.0 (11.6)	0.688
CVLT short delayed free recall (trial 6)	9.6 (2.3)	11.1 (3.0)	0.727
CVLT long delayed free recall (trial 8)	9.0 (3.0)	10.6 (3.2)	0.478
DS scores			
DS Forward	6.4 (1.4)	6.5 (1.4)	0.002
DS Backward	4.3 (1.4)	5.0 (1.4)	0.502

Table 4. Exploratory analyses of association between IR and individual cognitive subtests.

3.2.2.2. Exploratory analyses

Composite verbal memory scores were nominally associated with TG (Beta=-0.21, t(92)=-2.02, p<0.05), HDL (Beta=0.20, t(91)=2.13, p=0.04), but not with total cholesterol (Beta=-0.03, t(85)=-0.26, p=0.80), BMI (Beta=0.02, t(83)=0.21, p=0.84), exposure to antipsychotics (F(1, 2.07)=5.95, p=0.13) or mood stabilizers (F(1,1.03)=0.10, p=0.80), or years of education

(Beta=0.08, t(61)=0.70, p=0.49). In the model, which controlled for age, site, TG and HDL, IR remained significantly associated with composite verbal memory scores (F(1, 47.99)=9.82, p=0.003), whereas the association between TG or HDL and composite memory scores became non-significant (F(1,82)=0.07, p=0.79; F(1,82)=3.52, p=0.06, respectively). Composite working memory scores were nominally associated with years of education (Beta=0.37, t(59)=3.05, p=0.004), but not with HDL (Beta=0.14, t(82)=1.31, p=0.19), TG (Beta=-0.21, t(83)=-1.86, p=0.07), total cholesterol (Beta=0.03, t(76)=0.25, p=0.80), BMI (Beta=0.07, t(75)=0.63, p=0.53), exposure to antipsychotics (F(1,2)=0.28, p=0.65) or mood stabilizers (F(1,1)=0.004, p=0.96). The association between IR and composite working memory scores remained non-significant (F(1, 47.75)=3.43, p=0.07), even when we controlled for site, age and years of education.

4. SECTION 2. BRAIN IMAGING DIFFERENCES BETWEEN BD AND SZ

We performed 2 studies focusing on brain structural differences between schizophrenia and bipolar disorder. First, we used the same brain imaging method as described above, i.e. BrainAGE, to capture multivariate neurostructural alterations in early stages of SZ or BD (Study 3). This study was published in Schizophrenia Bulletin (Hajek et al., 2019). In addition, we studied both SZ and BD across different disease stages, and focused on cerebellar anatomy. The findings were published in Acta Psychiatrica Scandinavica, 2019 (Laidi et al., 2019).

4.1. Study 3: Brain Age in Early Stages of Bipolar Disorders or Schizophrenia

4.1.1. Methods

4.1.1.1. Sample description

We analyzed the data from two related studies and aimed at identifying neurobiological alterations in the early stages bipolar disorder (BD) or schizophrenia (SZ).

Study 3A:

This was a part of the ongoing Early Stages of Schizophrenia study (Spaniel et al., 2016), for more details please see previous description from Study 1 above and related article (Hajek et al., 2019). To limit the effects of medication and illness burden, we focused on individuals with first episode schizophrenia who where medication naive prior to the first admission.

Study 3B:

Participants were recruited from an ongoing Offspring Risk for Bipolar disorders Imaging Study—ORBIS31 in Halifax, Canada and from a parallel arm of the study performed in Prague, Czech Republic. To isolate biological risk factors for BD, we recruited offspring from families of well-characterized adult patients with BD, as described previously (Hajek et al., 2013). Families were identified through adult patients with BD, who had participated in: previous genetic and high-risk studies (Lopez et al., 2010; Duffy et al., 2002) for the Halifax sample; the Czech Bipolar Disorder Case Registry (Hajek et al., 2010) for the Prague sample. Only the offspring from these families, not the probands/parents, were a part of the MRI study. In keeping with previous studies (Duffy et al., 2002; Todd et al., 2010), we included participants with BD type I or type II, but not with BD NOS as probands for this study. The average genetic liability among unaffected offspring of BD patients decreases with age, as an increasing proportion of those with higher liability become affected. Therefore, we focused on individuals around the typical age of onset, who remain at a substantial risk of future onset of BD (Duffy et al., 2009; Immonen et al., 2017). Thus, the main inclusion criterion for all groups in both centers was age between 15 and 35 years. The offspring of BD patients were divided into 2 subgroups. (1) The high-risk (HR) unaffected group, which consisted of offspring with no lifetime Axis I diagnosis of mood disorders (ie, a personal history of at least one episode of depression, hypomania, or mania meeting full DSM-IV criteria). These individuals were at an increased risk for BD because they had one parent affected with a primary mood disorder (Whiteford et al., 2013). The affected familial group, which consisted of offspring who met criteria for a lifetime Axis I diagnosis of mood disorders (ie, a personal history of at least one episode of depression, hypomania, or mania meeting full DSM-IV criteria) and had one parent affected with a primary mood disorder. This definition stems from clinical HR studies by us and others, which clearly showed, that the index mood episode in majority of offspring of

bipolar parents is typically depression and that young participants with personal history of depression and family history of BD often develop BD later in life (Duffy et al., 2009; Shaw et al., 2005; Henin et al., 2005; Hillegers et al., 2005). Not combining the unaffected and affected participants and focusing on fully unaffected group, allowed us to maximize the main advantage of a genetic high-risk design, which is the ability to study participants who carry the genetic risk, but have not been exposed to the effects of the illness episodes or treatment.

Control participants without any personal or family history of DSM-IV Axis I psychiatric disorders, were recruited from similar socioeconomic background. Common exclusion criteria for all groups in both centers included any serious medical/neurological disorders, substance abuse/dependence during the last 6 months and any MRI contraindications. Probands, offspring and control subjects were interviewed by pairs of clinicians (psychiatrists and/or nurses) using Schedule for Affective Disorders and Schizophrenia–Lifetime version (Endicott and Spitzer, 1978) or Schedule for Affective Disorders and Schizophrenia for School-Age Children (Kaufman et al., 1997) in participants under 18 years of age. Diagnoses were made based on DSM-IV (American Psychiatric Association; *Diagnostic and Statistical Manual;* 4th Edition) in a blind consensus review, by an independent panel of senior clinical researchers using all available clinical materials.

4.1.1.2. Image processing

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

Study 3B. Participants were scanned at 2 sites, Prague and Halifax. At both sites, all MR acquisitions were performed with a 1.5 Tesla General Electric Signa scanner and a standard single-channel head coil. We acquired T1-weighted SPGR (Spoiled Gradient Recalled) scans: flip angle = 40°, TE = 5 ms, TR = 25 ms, FOV = 24 cm × 18 cm, matrix = 256 × 160 pixels, NEX = 1, no inter-slice gap, 124 coronal, 1.5 mm thick slices.

Brain age estimation:

We applied a BrainAGE method, detailed description is provided in previous BrainAGE estimation section (Study 1; Franke et al., 2010; Franke et al., 2013; Franke and Gaser, 2012).

4.1.1.3. Statistical analyses

All statistical analyses were conducted in R Studio (R version 3.3.2). To compare clinical and demographic variables, we used t test, 1-way ANOVA or chi-square test, as appropriate. Our primary outcome measure in both studies was the whole brain BrainAGE score. In each study, we initially tested for association between age or sex and BrainAGE scores, to select, which demographic variables to control for. In Study 3A we then performed analysis of covariance with BrainAGE scores as the dependent variable, status (FEP, control) as the grouping variable, while covarying for demographic variables, which were significantly associated with BrainAGE scores (primary analysis # 1). To compare brain and chronological age within subjects, we used paired t test. In Study 3B, we performed analysis of covariance with BrainAGE scores as the dependent variable, status (HR unaffected, affected familial, control groups) and site (Halifax, Prague) as the grouping variables, while covarying for demographic variables, which were significantly associated with BrainAGE scores (primary analysis # 2). To compare brain and chronological age within subjects, we used repeated measures ANOVA with site (Halifax, Prague) as the grouping factor and type of age (chronological, brain) as the repeated measure. To calculate effect size in the primary analyses, we used Cohen's d when comparing 2 groups (Study 3A, FES vs control participants) and $\eta 2$ when comparing 3 groups (Study 3B, HR unaffected, affected familial, control participants). To explore association between BrainAGE scores and clinical variables, we utilized Pearson correlations or 2 sample t tests, where appropriate. To further control for sex, we repeated the primary analyses with sex as additional covariate. In post hoc analyses, we separately compared the GM and WM BrainAGE scores between the groups in each site. For tissue types, showed between group differences in BrainAGE scores, we also performed voxel based morphometry analyses, using the preprocessed scans, to identify regions, which were associated with BrainAGE scores. As these analyses primarily served for visualization, we used uncorrected P value of .001, cluster extent of 50 voxels. To quantify the agreement between brain and chronological age, we calculated the ICC estimate and 95% CIs in controls using psych package, ICC command in R based on a mean-rating, as we used both chronological and brain age for calculation of BrainAGE scores, consistency-agreement, 2-way mixed-effects model. In the primary and post hoc analyses, we corrected the P values for multiple comparisons. The remaining analyses were exploratory.

4.1.2. Results

4.1.2.1. Study 3A: BrainAGE in early stages of schizophrenia

For Study 3A, we recruited 86 participants, including 43 previously unmedicated individuals with FES and 43 age and sex matched controls, see Tab.58. BrainAGE scores were associated with age ($r(84) = -.43$, $P < .001$), but not sex ($t(84) = -0.44$, $P = .66$). We thus adjusted for age in the following analyses. Participants with FES had higher BrainAGE scores relative to controls ($F(1, 83) = 8.79$, corrected $P = .008$, Cohen's $d = 0.64$). The proportion of participants who had a greater biological than chronological age was higher among the FES patients (74.41%) than controls (46.51%, $\chi2(1) = 7.00$, $P = .008$). The brain age in participants with FES was higher than their chronological age by an average of 2.64 ± 4.15 years (matched $t(42) = 4.36$, $P < .001$), see Fig.3. BrainAGE scores were not associated with duration of illness ($r(41) = .01$, $P = .97$) or, duration of untreated psychosis ($r(41) = 0.02$, $P = .89$). There were no differences in BrainAGE scores between the diagnoses ($t(41) = 0.19$, $P = .85$). When we controlled for both age and sex, the differences in BrainAGE scores between FES and controls remained significant ($F(1, 82) = 8.70$, $P = .004$).

	FES	Control Participants	*P*
N	43	43	N/A
Sex, *N* (%) female	17 (39.53)	17 (39.53)	NS
Age, mean (SD) years	27.09 (4.93)	27.05 (4.40)	NS
Diagnosis schizophrenia/acute and transient psychotic disorders, *N*(%)	25(58.14)/18(41.86)	N/A	N/A
Illness duration mean (SD) months	4.61 (5.39)	N/A	N/A
Duration of untreated illness, mean (SD) months	3.38 (5.05)	N/A	N/A
Duration of treatment, mean (SD) months	1.23 (0.95)	N/A	N/A
Proportion of participants with greater brain than chronological age, *N* (%)	32 (74.41)	20 (46.51)	.008
BrainAGE score, mean (SD), years[a]	2.64 (4.15)	−0.01 (4.15)	.004

Note: *BrainAGE*, brain-age gap estimate.
[a]Means adjusted for age.

Table 5. Study 3A description.

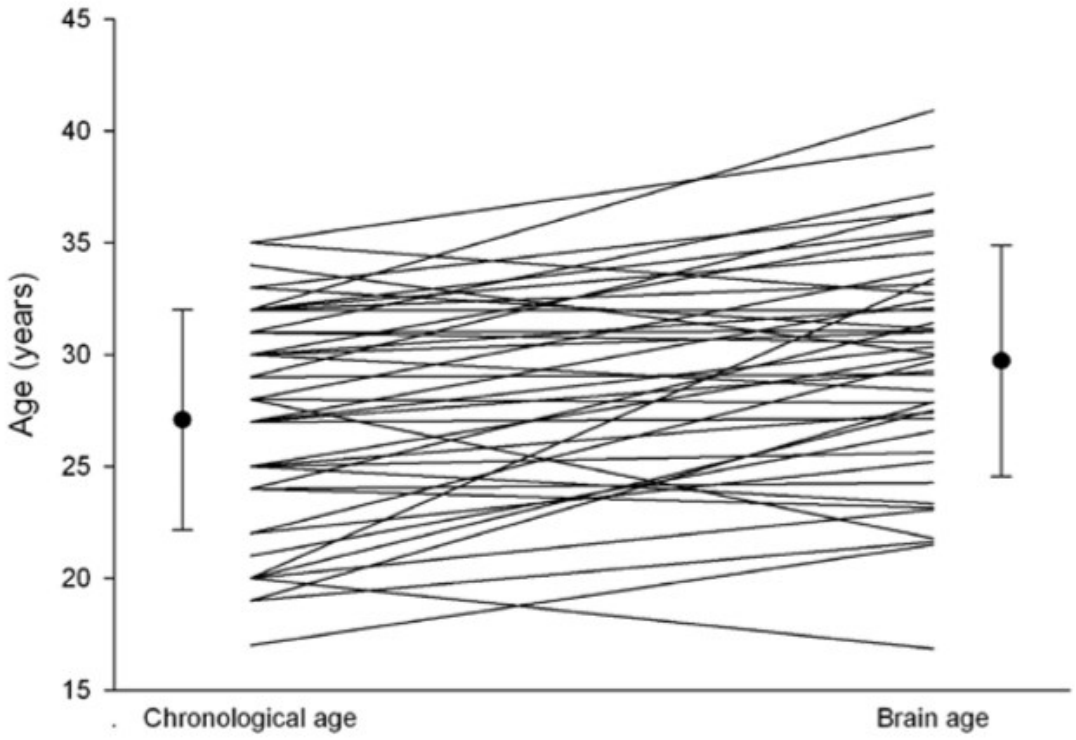

Figure 3. Comparison of brain age and chronological age in participants with first episodes of schizophrenia (individual subject data and mean ± SD).

Post hoc analyses showed that participants with FES differed from controls in BrainAGE scores estimated from GM ($F(1, 83) = 8.21$, corrected $P = .01$), but not WM ($F(1, 83) = 4.71$, corrected $P = .06$). The BrainAGE scores were negatively associated with GM volume diffusely throughout the brain, see Fig.4. There was no positive association between BrainAGE scores and GM even at an uncorrected threshold of $P = .001$.

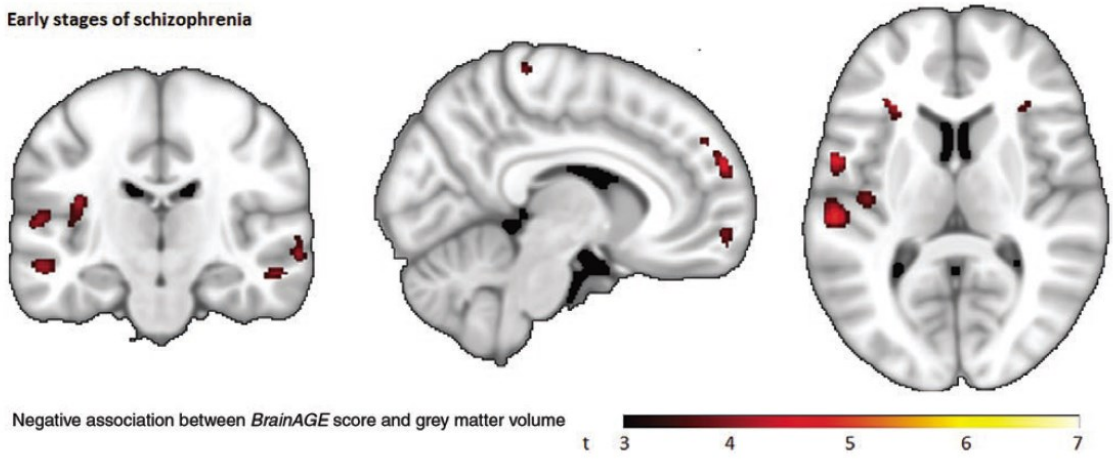

Figure 4. Negative association between gray matter volume and brain-age gap estimate (BrainAGE score) in participants with first episodes of schizophrenia ($P \leq .001$, cluster extent = 50).

4.1.2.2. Study 3B: BrainAGE in early stages of bipolar disorder

We recruited 156 participants, including 48 HR unaffected, 48 affected familial and 60 control subjects, see Tab.6. BrainAGE scores were associated with age ($r(154) = -.24$, $P = .002$), but not sex ($F(1, 152) = 2.79$, $P = .10$). We thus adjusted for age in the following analyses. BrainAGE scores were comparable between HR unaffected, affected familial and control participants ($F(2,149) = 1.04$, corrected $P = .70$, $\eta 2 = 0.01$), with no differences between the 2 acquisition sites ($F(1,149) = 0.39$, $P = .53$) and no site by group interaction ($F(2,149) = 0.04$, $P = .96$). The proportion of participants who had a greater brain than chronological age did not differ between the groups ($\chi 2(2) = 0.83$, $P = .66$, see Tab.6). The brain age in the HR unaffected ($F(1,46) = 0.50$, $P = .48$) or in the affected familial participants ($F(1,46) = 1.46$, $P = .23$) was comparable to their chronological age, see Fig.5. BrainAGE scores were not associated with number of episodes ($r(43) = -.28$, $P = .07$), number of hospitalizations ($r(46) = -.09$, $P = .55$) or duration of illness, when controlling for age ($B = 0.04$, SE of $B = 0.25$, $t = 0.16$, $P = .87$). There were no differences in BrainAGE scores between the diagnoses ($F(2,45) = 1.75$, $P = .19$) or between participants with vs without lifetime history of lithium treatment ($t(46) = -1.21$, $P = .23$), although only 7 participants had a lifetime history of Li treatment. When we controlled for both age and sex, the differences in BrainAGE scores between the groups remained nonsignificant ($F(2, 148) = 0.97$, $P = .38$).

Halifax	Unaffected HR Participants	Affected Familial Participants	Control Participants	*P*
N (Halifax/Prague)	48 (28/20)	48 (33/15)	60 (42/18)	N/A
Sex, *N* (%) female	29 (60.42)	33 (68.75)	36 (60.00)	NS
Age, mean (SD) years	20.91 (4.15)	23.09 (4.51)	23.41 (2.93)	.002
Diagnosis	N/A	MD = 26, BDI = 10, BDII = 7, BD NOS = 2, Psychosis NOS = 1, ADO = 2	N/A	N/A
Treatment at the time of scanning, *N* (%)	N/A	24 (50.00)	N/A	N/A
Medication Type at the Time of Scanning	N/A	AC = 5,AD = 11, AP = 9, Li = 2	N/A	N/A
Lifetime history of Li treatment	N/A	7 (14.58)	N/A	N/A
Age of onset, mean (SD), years[a]	N/A	17.39 (3.58)	N/A	N/A
N Episodes, mean (SD)[b]	N/A	3.04 (3.18)	N/A	N/A
N hospitalizations, mean (SD)	N/A	0.60 (1.25)	N/A	N/A
Personal history of psychotic symptoms, *N* (%)	N/A	7 (14.58)	N/A	N/A
Family history of psychotic symptoms in probands, *N* (%)	17 (35.41)	15 (31.25)	N/A	NS
Proband diagnosis, bipolar I *N* (%) / bipolar II *N* (%)	37 (77.08)/11 (22.92)	36 (75.00)/12 (25.00)	N/A	NS
Proportion of participants with greater brain than chronological age, *N* (%)	21 (43.75)	19 (39.58)	29 (48.33)	NS
BrainAGE score mean (SD), years[c]	−1.02 (5.02)	−0.96 (5.18)	0.25 (5.27)	NS

Note: AC, anticonvulsants; AD, antidepressants; ADO, adjustment disorder with depressed mood; AP, antipsychotics; BD, bipolar disorder; HR, high risk; Li, lithium; MD, major depression; NOS, not otherwise specified; N/A, not applicable; NS, not significant; *BrainAGE*, brain-age gap estimate.
[a]Data missing in 2 participants.
[b]Data missing in 3 participants.
[c]Means adjusted for age and site.

Table 6. Study 3B description.

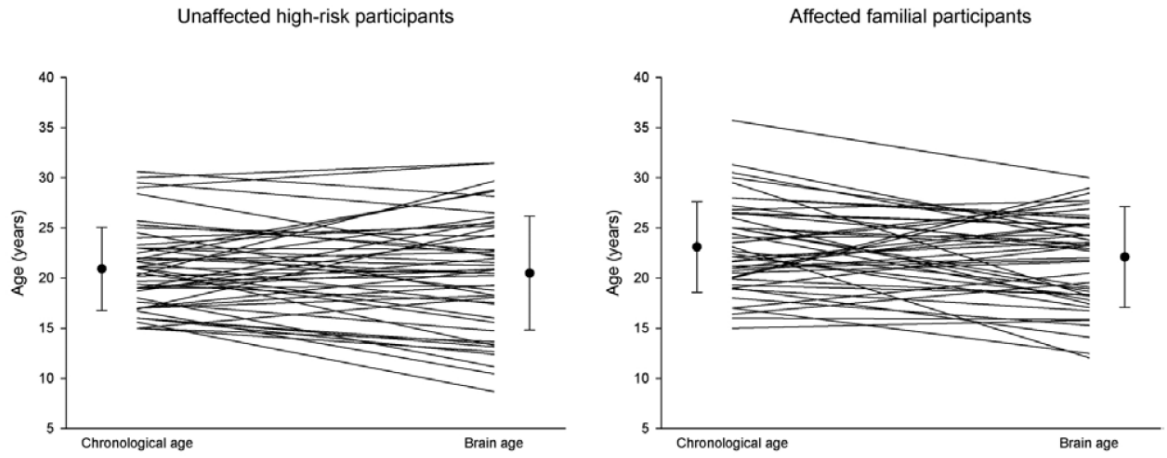

Figure 5. Comparison of brain age and chronological age in participants at genetic risk (unaffected high-risk participants) and early in the course of bipolar disorders (affected familial participants) (individual subject data and mean +/- SD).

Post hoc analyses showed no differences between the groups in BrainAGE scores estimated from GM ($F(2,149) = 1.43$, corrected $P = .48$) or WM ($F(2,149) = 1.93$, corrected $P = .30$).

4.2. Study 4: Cerebellar parcellation in schizophrenia and bipolar disorder

4.2.1. Methods

4.2.1.1. Sample description

Participants: Patients with SZ spectrum disorder and controls were recruited in 3 different sites located in France (Créteil), Czech Republic (Prague) and the USA (New Mexico). Patients with BD and controls were recruited in 5 different centers in USA (Pittsburgh), Germany (Mannheim), Italy (Udine) and 2 sites in France (Créteil and Grenoble). For more details about inclusion criteria, see original article (Laidi et al., 2019). Demographic characteristics are reported in Tab.7, 8. Only one center (Créteil, France) recruited patients with SZ, BD and controls. All other centers recruited either SZ and controls or BD and controls. As a part of this multicenter study, our center recruited 86 patient with FES and 88 controls (Early Stages of Schizophrenia study; Spaniel et al., 2016).

	Patients (n = 182)	Controls (n = 198)	Statistical test	Statistics, p-value
Mean age (std)	32 (11)	33 (11)	Student t-test	t = - 0.16, p = 0.87
Sex: Male / Female	122 / 60	96 / 102	Chi-2 test	q = 13.3, p < 0.001
Site of Inclusion	COB = 57 PRA = 86 CRE = 39*	COB = 58 PRA = 88 CRE = 52	-	-

COB = COBRE dataset

PRA = Prague, Czech Republic

CRE = Créteil, France

*: including 3 patients with schizo-affective disorder

Table 7. Demographic characteristic of participants with SZ

	Patients (n = 144)	Controls (n = 176)	Statistical test	Statistics, p-value
Mean age (std)	38 (11)	35 (10)	Student t-test	t = 2.41, p = 0.02
Sex: Male / Female	53 / 91	68 / 108	Chi-2 test	q = 0.11, p = 0.73
Site of Inclusion	CRE = 31 MAN = 37 PIT = 51 GRE = 13 UDI = 12	CRE = 52 MAN = 36 PIT = 23 GRE = 10 UDI = 55	-	-

CRE = Créteil, France

MAN = Mannheim, Germany

PIT = Pittsburgh, USA

GRE = Grenoble, France

UDI = Udine, Italy

Table 8. Demographic characteristic of participants with BD.

4.2.1.2. Image processing, cerebellar grey matter volume analyses

All participants underwent a T1 weighted MRI (T1) with a full coverage of the cerebellum. Details on acquisition sequences are reported in original article (Laidi et al., 2019). All T1 images were processed using the CERES pipeline that performs a fully automated segmentation and parcellation of the cerebellum (Romero et al., 2017) following the protocol described in Park et al. paper (Park et al., 2014). Afterwards, we divided the cerebellar grey matter in 6 regions of interest: lobule I-V, lobule V, Crus I, Crus II, lobule VIIb and the postero-inferior lobe (lobules VIII to X). We chose these regions of interest because the resolution on standard T1 images do not allow to visually differentiate the five first (lobules I to V) and the three last lobules (lobule VIII to X) of the cerebellum. We extracted the grey matter volume of these 6 regions of interest (ROIs) and the global cerebellar grey matter volume.

Quality control: All segmentations were visually inspected by an examiner (CL) blind of the diagnoses. Each segmented cerebellum (3D volume) was inspected in axial, coronal and sagittal views using Brainvisa/Anatomist software (http://brainvisa.info). First, the examiner checked the quality of the segmentation, to ensure that no extra cerebellar tissue was labeled as cerebellar tissue and vice-versa. Second, the examiner inspected the quality of the lobular parcellation. Last, CL inspected the global brain segmentation to ensure the validity of the total intracranial measure (ICV), included as a covariate in the statistical analysis. All images not meeting our quality criteria were excluded of the study.

4.2.1.3. Statistical analyses

We used a Chi-square test to test for significant differences in the proportion of males and females and a Student t-test to compare ages between patients and controls (Tab.8, Tab.9).
To compare the size of the global cerebellar volume and ROIs in the cerebellum between patients and controls, we performed a linear model with (i) age and ICV as covariates and (ii) sex, diagnosis and site as cofactors. Before performing pairwise comparisons (t-tests) between patients and controls, we ensured that the standardized residuals were normally distributed, as assessed by the Shapiro–Wilk test ($p > 0.05$) and a QQ-plot. We applied a false discover rate correction (FDR –Benjamini Hochberg correction) to control multiple testing. We present both uncorrected (presented as "p" value) and corrected p values (presented as "p corrected"). Results that survived correction for multiple comparisons were considered as significant. We conducted our statistical analyses separately on the SZ and the BD sample. Similarly, we compared the size of the global cerebellar volume and ROIs in patients with BD medicated vs not medicated with lithium, with a linear model including (i) age and ICV as covariates and (ii) sex, lithium status and site as cofactors. We conducted several supplementary analyses. Because of the exploratory nature of theses analyses, we did not correct our results for multiple comparisons. Changes in cerebellar volume could be related to the lifetime dose of medication or to the duration of the illness. We thus repeated our analysis on the significant regions previously identified in the subsample of first episode patients with SZ spectrum disorder and controls recruited in Czech Republic (n = 174). We studied the association between the severity of schizophrenia (assessed with the Positive and Negative Symptoms Schizophrenia (PANSS)

scale) and the regions of interest in the cerebellum. The PANSS scale was available in patients recruited in France (n = 35) and Czech Republic (n = 79). Tests were conducted with the Z-score of PANSS total, negative, positive and general psychopathology scores. We performed linear models with (i) age, ICV and PANSS Z scores as covariates and (ii) sex and site as cofactors.

Clinical, genetic and neuroimaging studies 21 suggested that there might be distinct patterns between patients with BD (n = 53) with and without psychotic features (n = 56). We thus repeated our analysis on patients with BD with and without psychotic features. In this analysis, patients were recruited in Créteil, France (n = 19), Germany (n = 34), USA (n = 39), Grenoble, France (n = 13) and Italy (n = 4). Alcohol dependence is known to have a damaging effect on the cerebellum: cerebellar ataxia is frequent in alcoholics and prenatal exposure to alcohol affects the cerebellum 22. Thus, alcohol dependence might be a confounding factor in our study. We repeated our analysis to ensure that our results remained significant when considering only patients without alcohol dependence.

Likewise, it has been proposed that cannabis could affect the structure of the cerebellum 23. Thus, we conducted an analysis in the sample recruited in Czech Republic to study the effect of cannabis consumption, during the month prior to the inclusion, on the cerebellum. We performed a linear model, considering age and intracranial volume as covariates and sex and cannabis status as cofactors. Antipsychotics are known to affect brain structures and could be also a potential confounding factor, explaining the structure differences in the cerebellum between patients with schizophrenia and controls. To address this question, we repeated our analyses in a sample of first episode patients with schizophrenia, with limited exposure to antipsychotics. In addition we conducted a linear model, in our population of patients with schizophrenia recruited in Czech Republic to study the effect of medication load (computed in chlorpromazine equivalent dose) on our regions of interest in the cerebellum. We considered age, ICV and medication load as covariates and sex as a cofactor.

4.2.2. Results

4.2.2.1. Total cerebellar volume and lobular analysis in schizophrenia

One hundred and eighty-two patients with SZ and 198 controls were included in this analysis. The global cerebellar volume, Crus II and lobule VIIb were significantly smaller in patients compared to controls (Tab.9 and Fig.6).

Grey matter volumes (cm3)	p-value	FDR corr. P value	t-value	95% confidence interval
Total cerebellum	0.0003	**0.001 ***	-3.62	[-4.16 ; -1.23]
Lobule I-V	0.0828	0.097	-1.74	[-0.48 ; 0.03]
Lobule VI	0.0459	0.074	-2.00	[-0.81 ; -0.01]
Crus I	0.1928	0.19	-1.30	[-1.03 ; 0.21]
Crus II	0.0008	**0.002 ***	-3.38	[-1.06 ; -0.28]
Lobule VIIb	0.0000	**0.0001 ***	-4.33	[-0.64 ; -0.24]
Lobule VIII - X	0.0535	0.074	-1.94	[-1.09 ; 0.01]

Table 9. Effect of diagnosis on cerebellar anatomy in patients with SZ compared to controls.

* significant results after FDR correction

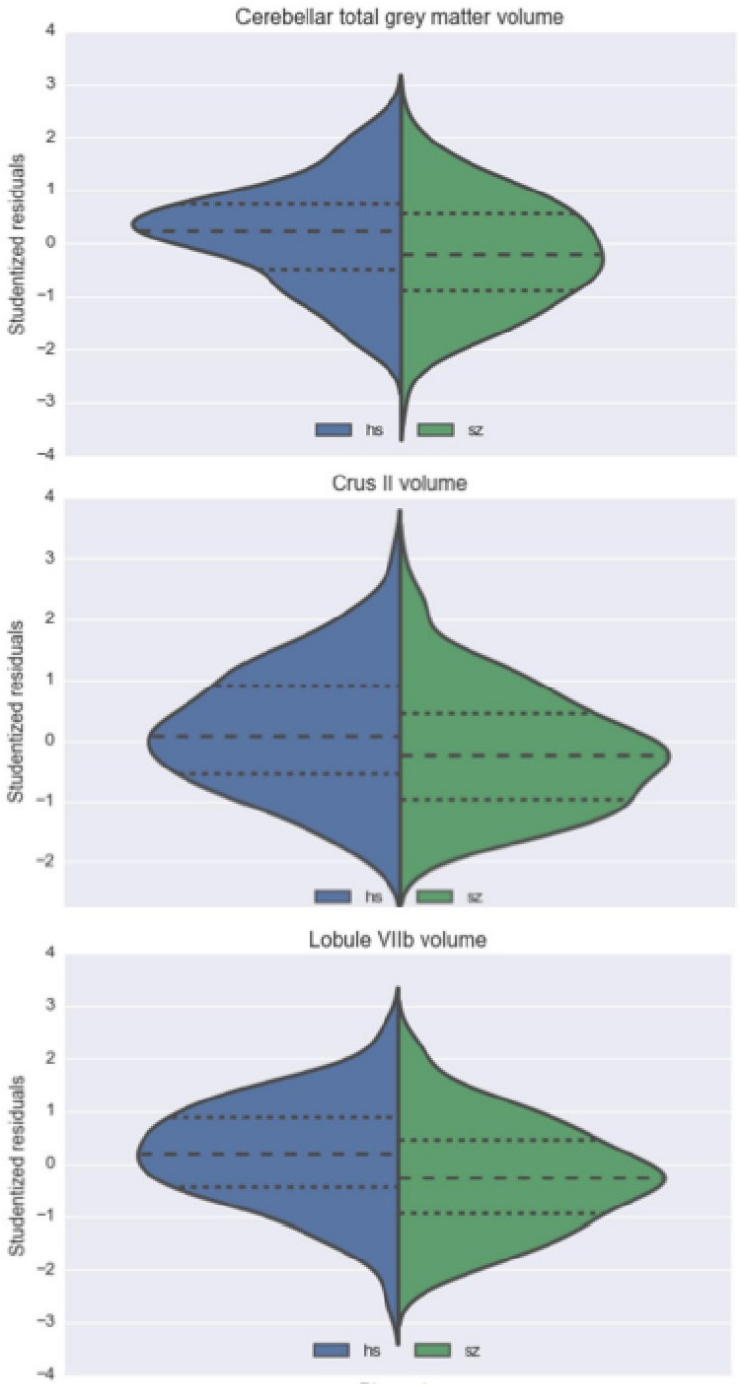

Figure 6: Grey matter volume of the cerebellum, Crus II and lobule VIIb in patients with SZ and controls: partial residual plot.
Legends: hs, healthy subjects; sz, patients with schizophrenia; comparison of studentized residuals after regressing the effect of site, age, sex and intra cranial volume. Hashed lines delineate quartiles of the distribution; the central hashed line refer to the mean of the distribution

4.2.2.2. Total cerebellar volume and lobular analysis in bipolar disorder

One hundred and forty four patients with type I BD and 176 controls were included in this analysis. Demographic characteristics are reported in Tab.9. We did not find any significant difference between patients and controls for any of the regions of interest. Results are reported in Tab.13. BD participants treated with Li at the time of scanning (n=56) had significantly larger volume of the left anterior cerebellum grey matter volume than participants not treated with Li (n = 86).

Grey matter volumes (cm3)	p-value	FDR corr. P value	t-value	95% confidence interval
Total cerebellum	0.6327	0.82	-0.48	[-2.10 ; 1.28]
Lobule I-V	0.0993	0.34	I.65	[-0.05 ; 0.52]
Lobule VI	0.8048	0.82	-0.25	[-0.49 ; 0.38]
Crus I	0.0579	0.34	-1.90	[-1.30 ; 0.02]
Crus II	0.5407	0.82	-0.61	[-0.62 ; 0.33]
Lobule VIIb	0.5811	0.82	0.55	[-0.16 ; 0.29]
Lobule VIII - X	0.8285	0.82	0.22	[-0.49 ; 0.61]

Table 10. Effect of diagnosis on cerebellar anatomy in patients with BD compared to controls.

4.2.2.3. Exploratory analyses

Cerebellar volume in the sample of first episode patients with schizophrenia

We found a decreased volume in patients compared to controls in the total cerebellar volume (p= 0.0005), Crus II (p = 0.0006) and lobule VIIb (p = 0.0036). This suggests that the size reduction in the cerebellum is present since the beginning of the illness and is not related to its evolution.

Influence of PANSS score in patients with schizophrenia

We found a negative correlation between the volume of Crus I and the PANSS general psychopathology score (p = 0.007). In addition, we found a negative correlation between the volume of Crus I and the PANSS total score (p = 0.047).

Influence of psychotic features in patients with bipolar disorder

We compared patients with BD with and without psychotic features. We did not find any significant difference between the two groups for any of our regions of interest.

Influence of alcohol dependence

Patients recruited in France and Czech Republic did not suffer from alcohol dependence. However this information was lacking in patients recruited in the USA. Thus, we repeated our analyses in patients with schizophrenia recruited in France and Czech Republic. Our results remained significant in the total cerebellar ($p = 0.0001$; t-value = - 3.9), Crus II ($p = 0.0002$; t-value = - 3.8) and lobule VIIb ($p = 0.0004$; t-value = -3.6) volumes.

Influence of cannabis use

Sixteen patients with schizophrenia recruited in our center (Czech Republic) had a history of cannabis consumption in the month prior to the inclusion. However, there was no effect of cannabis history in the last month prior to the inclusion on the volume of the total cerebellar (p-value = 0.60; t-value = - 0.57), Crus II (p-value = 0.12; t-value = -1.57) and lobule VIIb (p-value =0.41; t-value = - 0.81) volumes.

Influence of medication load in patients with schizophrenia

There was no significant effect of medication load on the volume of the total cerebellar ($p = 0.41$; t-value = - 0.82), Crus II ($p=0.79$; t-value = - 0.26) and lobule VIIb ($p = 0.19$; t-value = 1.33) volumes.

5. DISCUSSION

5.1. Metabolic factors and brain structure

5.1.1. Overweight/obesity and brain structure

The primary goal of this work was to assess the effects of metabolic parameters and psychosis on brain structure. We confirmed that overweight/obesity was more frequent in patients with FES than in controls. The study also for the first time suggested that overweight/obesity, may

contribute to neurostructural changes already early in the course of illness. Specifically, using BrainAGE analyses, we found that the brains of participants with FES appeared on average 2.64 years older than their chronological age. Weight and BMI were also significantly positively associated with advanced brain age. Consequently, BrainAGE scores were highest in participants with a combination of FES and overweight/obesity, where the average discrepancy between brain and chronological age reached 3.83 years. The average difference between brain and chronological age among normal weight controls was−0.27 years. Importantly, the effect of overweight/obesity on brain structure was additive to the effect of FES. In addition, both overweight/obesity and diagnosis remained significantly and additively associated with BrainAGE scores in each diagnostic subgroup, i.e. schizophrenia or acute and transient psychotic disorders.

These results are congruent with our a-priori hypotheses. Previous studies have reported neurostructural alterations and advanced brain age already in FES (Boos et al., 2007; Kempton et al., 2010; De Peri et al., 2012; Cooper et al., 2014; Koutsouleris et al., 2014; Schnack et al., 2016), as well as in participants with high BMI (Debette et al., 2010; Tiehuis et al., 2014; Masouleh et al., 2016). Furthermore, overweight/obesity is a risk factor for advanced brain ageing, as found in neurodegenerative disorders (Xu et al., 2015). In keeping with other studies (Hajek et al., 2014, Hajek et al., 2015), our sensitivity analyses have suggested that the negative effects of metabolic disorders on the brain occur regardless of a specific psychiatric disorder.

As BrainAGE use machine learning algorithm to analyze brain structure, it is not possible to localize obesity-related alterations using this technique. Thus, to address this knowledge gap, we followed up on the previous analysis and explored the effects of overweight/obesity and psychosis on regional brain volumes. We found that both FES and BMI were negatively associated with local grey matter volumes. Some regions of lower GM volumes were found only in FES (frontotemporal areas, right cerebellum) or only in participants with higher BMI (areas in the left cerebellum), whereas a cluster of lower GM volumes in the left cerebellum was additively associated with both FES and BMI. Our results are congruent with our a-priori hypotheses and expand our previous study demonstrating effects of BMI on BrainAGE.

The findings of association between FES and lower GM in fronto-temporal areas and the association between BMI and cerebellar regions are in line with previous meta-analyses

(García-García et al., 2019; Leung et al., 2011; Radua et al., 2012; Shah et al., 2017). Interestingly, even our whole brain results fell into regions, which were associated with FES or obesity in previous meta-analyses, thus providing strong replication and increasing the chance of true positive findings.

Previous neurostructural findings regarding cerebellum in early stages of schizophrenia are less consistent and more heterogeneous. In keeping with our results, a number of individual studies reported lower GM volumes of cerebellum in all stages of SZ (Dean et al., 2014; He et al., 2019; Moberget et al., 2018; Pantelis et al., 2003; Venkatasubramanian et al., 2010; Wang et al., 2017; Zhang et al., 2020). We confirmed lower cerebellar volumes in large dataset of 182 patients with SZ (Laidi et al., 2019). However, cerebellar findings from meta-analyses exploring GM volume abnormalities in FES are inconsistent, with some reports finding cerebellar alterations only in certain subgroups or not at all (Leung et al., 2011; Radua et al., 2012; Shah et al., 2017). Previous studies did not control for BMI, which appears to be negatively associated with cerebellar volume independent of the effects of psychosis. Perhaps, the uncontrolled presence of overweight/obesity may contribute to heterogeneity in cerebellar volumes between studies in FES.

5.1.2. Obesity related metabolic factors contributing to neurostructural alterations

As obesity is a complex phenomenon, it is important to explore which obesity associated factors are particularly relevant to the brain alterations found in obese/overweight participants. BrainAGE scores were not associated with lipid blood levels, VBM analyses showed that among FES participants, LDL levels were negatively and HDL levels positively associated with GM within the cluster showing association with BMI. As VBM analyses were restricted to brain regions previously associated with BMI, this analysis may have better chance to detect the signal. On the other hand, lack of association between BrainAGEscores and cholesterol or lipids may also be related to the relatively young age (18-35 years), absence of other pathology or relatively recent onset of lipid abnormalities in our study. Perhaps the dyslipidemia related alterations at this age are not diffuse enough to affect a global measure of brain structure. Although strongly associated, obesity and dyslipidemia have partly differing biological underpinnings (Ipsen et al., 2016) and may also differ in their effects on brain structure. Previous studies have suggested a positive association between HDL and gray matter volume

in participants over 40 years of age or among the elderly (Whalley et al., 2003; Ward et al., 2010; Schwarz et al., 2018). Dyslipidemia is a known risk factor for cerebrovascular disease (Pikula et al., 2015), has pathoplastic effects on brain structure in participants with manifest atherosclerosis (Tiehuis et al., 2014) or in those with additional vascular risk factors, such as diabetes or hypertension (Schwarz et al., 2018). The increase of LDL-cholesterol and TG during hospitalization and the association between age and LDL-cholesterol or TG, suggest a recent onset of lipid abnormalities in our cohort. Thus, we cannot rule out that longer exposure to dyslipidemia on brain could lead to negative effects, detectable also by the BrainAGE method.

5.1.3. Brain structure, obesity and low-grade inflammation

Obesity is frequently associated with low-grade systemic inflammation (Wisse, 2004) and higher levels of pro-inflammatory cytokines are also documented in drug-naive FES patients (Miller et al., 2011; Perry et al., 2019; Upthegrove et al., 2014). Abdominal visceral obesity is one of the main potential contributors to the low-chronic inflammatory state, which is often found in FES (Fontana et al., 2007; Minichino et al., 2017). In keeping with this, we found a positive correlation between CRP and BMI, LDL or TG in FES participants. Correlation with BMI was particularly strong (r_s= 0.586, $p<0.001$). Importantly, CRP was also negatively correlated with average GM values from the cerebellar cluster associated with BMI (r_s= -0.327, p=0.006). Interestingly, animal studies showed that cerebellum is prone to obesity-driven neuroinflammation and blood–brain barrier dysfunction (Guillemot-Legris et al., 2016; Guillemot-Legris and Muccioli, 2017; Tapia-González et al., 2011). This study thus adds support to previously postulated hypothesis that overweight/obesity in FES may contribute to worsening of the low-grade chronic inflammatory status, with relevant consequences for brain structure (Minichino et al., 2017).

5.1.4. Obesity and atherosclerosis

Overweight/obesity may impact brain health indirectly, by increasing the risk of atherosclerosis. Obesity is a well-known risk factor for atherosclerosis (Yoo et al., 2014).

Adipokines released by adipose tissue induce hypercoagulability, endothelial dysfunction and systemic inflammation, which may contribute to atherosclerosis (Rocha and Libby, 2009). Also dyslipidemia, common feature associated with obesity, can promote atherosclerosis, as oxidized LDL in vessel wall leads to an inflammatory cascade that activates atherogenic pathway (Ellulu et al., 2016). Atherosclerosis was associated with lower brain volumes (Geerlings et al., 2010). In keeping with previous, we found that main contributors to atherosclerosis, higher LDL and CRP levels, were negatively associated with GM within the cluster showing association with obesity. However, a significant contribution of cerebrovascular disease among young, diabetes free participants with low rates of hypertension seems less likely.

5.1.5. Multifactorial etiology of obesity

Additional alternative explanations pertain to the multifactorial etiology of obesity in psychosis. Aside from effects of medications, genetics, lifestyle factors, including high-fat diets, alcohol, smoking, and lack of exercise, psychosocial factors, including poverty and disparities in health care/monitoring may all play a role (Newcomer, 2007; Manu et al., 2015). We cannot rule out spurious associations between the more distal factors, brain health and metabolic alterations (Rais et al., 2008; Pajonk et al., 2010; Zipursky et al., 2013; McEwen et al., 2015). Some of these factors, including diet, exercise or chronic stressors are difficult to quantify. Others, such as history of substance abuse, were not associated with BrainAGE scores or GM volumes. In addition, the negative effects of obesity on the brain may be linked to increased levels of cortisol or to decreased levels of brain-derived neurotrophic factor (Minichino et al., 2017). Similar mechanisms have also been implicated in the pathophysiology of psychosis (Hoschl and Hajek, 2001; Andreazza et al., 2008; Gubert et al., 2013). Importantly, the additive association between variables argues against confounding by a spurious third factor.

The interpretation is also complicated by the unclear direction of association between brain and metabolic alterations. Prospective studies indicate that changes in BMI precede and lead to changes in brain volumes (Bobb et al., 2014; Honea et al., 2016; Tuulari et al., 2016; Mueller et al., 2015; Yokum and Stice, 2017). Cross-sectional studies suggest that prefrontal gray matter volumes mediate the association between genetic factors and obesity (Opel et al., 2017; Wolf et al., 2017) and that obesity and brain alterations share common genetic

underpinnings (Weise et al., 2017). Whereas the genetic contributions are regionally highly specific (Opel et al., 2017; Wolf et al., 2017), BrainAGE scores reflect diffuse alterations (Franke et al., 2010, 2013). If a common genetic effect contributed to both obesity and psychosis by altering brain structure, then these 2 factors would not be additively and independently associated with BrainAGE scores.

5.2 Insulin resistance and cognition

Participants recruited from our outpatient Bipolar disorders clinic at National Institute of Mental Health in Klecany, allowed us to also study possible clinical/functional consequences of obesity-related abnormalities. Specifically, in collaboration with Department of Neuroscience in Milan, we conducted a multicenter study of association between insulin resistance (IR) and cognition in subject with BD (Study 2; Salvi et al., 2020). We demonstrated that among remitted BD participants without diabetes mellitus, IR was significantly associated with verbal memory performance, even when we controlled for other relevant metabolic or treatment variables. Importantly, the association between IR and verbal memory was not confounded by exposure to antipsychotics, which were not associated with worse cognitive performance. Similar association between IR and verbal memory was recently documented in schizophrenia (Wijtenburg et al., 2019). Our study is also in keeping with previous cross sectional as well as prospective reports documenting the negative association between IR and cognitive functioning in participants without psychiatric disorders (Young et al., 2006; Bruehl et al., 2010; Laws et al., 2017).

For example, participants with hyperinsulinemia showed declarative memory impairments and greater cognitive decline over a 6-year follow-up (Young et al., 2006). Bruehl and colleagues showed worse performance in declarative memory and executive functions in participants with versus without IR (Bruehl et al., 2010). In a larger study of cognitively normal adults, higher HOMA-IR was associated with poorer performance on measures of verbal episodic memory, executive function and global cognition (Laws et al., 2017). Among the verbal memory subtests, total and short delay free recall were most sensitive to IR. This pattern of verbal

memory alterations among euthymic BD participants with IR was generally in keeping with the patterns of alterations in euthymic/subsyndromal BD participants (Cardoso et al., 2016; Chepenik et al., 2012; Martínez-Arán et al., 2004; Sumiyoshi et al., 2017;Vasconcelos-Moreno et al., 2016). In addition, among the CVLT subtests, total immediate recall is most strongly associated with lower hippocampal volumes in BD (Chepenik et al., 2012). In a previous study Hajek and colleagues reported lower hippocampal volumes in BD participants with relative to those without IR (Hajek et al., 2014).

We did not find association between IR and working memory. This observation is in line with a previous study, where the effects of IR on declarative memory were three times higher than the effects of IR on working memory (Bruehl et al., 2010). This is very much in keeping with the effect sizes for verbal (partial eta squared=0.69) and working memory (partial eta squared=0.21) in our study.

The effects of IR on brain function are not surprising. Insulin acts not only peripherally but also on the brain: it is actively transported through the blood-brain barrier and binds to its receptors, which are widely distributed throughout the olfactory bulb, cerebral cortex, hippocampus, hypothalamus, amygdala, septum and cerebellum (Kullmann et al., 2016; Hill et al., 1986). In rodent studies, insulin signaling in the hippocampus has been shown to promote cell survival and synaptic plasticity (Banks et al., 2012). The mechanisms underlying the connection between IR and cognition could include withdrawal of trophic factors, inhibition of insulin-responsive gene expression and impaired mitochondrial energy metabolism, which causes oxidative stress through increased production of reactive oxygen species (Andreazza et al.,2010; Brietzke et al., 2011; de la Monte, 2009; Kroner, 2009). In addition, insulin signaling appears to increase NMDA-mediated glutamatergic transmission in hippocampus, thus enhancing processes of long-term potentiation (Ferrario and Reagan, 2018). In a recent rodent study, high-fat diet induced IR led to excess of palmitic acid deposition in hippocampus, causing impairment in long-term potentiation through reduced glutamatergic synaptic currents (Spinelli et al.,2017). These mechanisms contribute to explain why both type 2 diabetes and IR are associated with specific cognitive impairment in memory, processing speed and executive functions (Moheet et al., 2015) and with reduced hippocampal volume (Hajek et al., 2014; Ursache et al., 2012).

Metabolic syndrome, which is often characterized by IR, and diabetes are frequent in BD. Yet, the screening for diabetes in BD is insufficient and IR is not monitored at all. Even a well-done routine assessment for diabetes may thus overlook the presence of IR, which typically presents with normal glucose levels. Yet, this factor appears to be associated with cognitive impairment and could contribute to poor psychiatric and brain outcomes (Calkin et al., 2015; Hajek et al., 2014). In line with previous research (Kolenic et al., 2016), our findings put more emphasis on clinical screening of insulin metabolism in BD.

5.3. Structural brain differences between SZ and BD

5.3.1. BrainAGE differences between SZ and BD

In Study 3 (Hajek et al., 2019), we found that participants with FES showed greater, whereas individuals at risk or in the early stages of BD showed comparable BrainAGE scores to controls. The brains of participants with FES appeared on average 2.64 years older than their chronological age and those results are in line with previous findings of Study 1. The higher BrainAGE scores in participants with FES were associated with smaller GM volume diffusely throughout the brain. Our findings are congruent with previous investigations using a range of techniques. Three previous studies also demonstrated greater differences between brain and chronological age in participants with schizophrenia than in controls (Koutsouleris et al., 2014; Nenadić et al., 2017; Schnack et al., 2016). The BrainAGE scores in participants with FES in our study (2.64 y), were between the BrainAGE scores of participants at clinical risk for schizophrenia (1.7 y; Koutsouleris et al., 2014) and those with established illness (3.36 y; Schnack et al., 2016 or 5.5 y; Koutsouleris et al., 2014).

In contrast to FES, the brain age in participants early in the course of BD was nonsignificantly lower than their chronological age. No previous study investigated BrainAGE scores in early stages of BD. A single previous study found no association between BrainAGE scores and BD (Nenadić et al., 2017). As this study included only 22 BD participants and did not provide information about duration of illness or medications exposure, we do not know whether brain and chronological age remain comparable even later in the course of BD. Our results are also

congruent with structural brain imaging studies and fit within a model positing a greater neurodevelopmental contribution to schizophrenia than BD. A number of cross sectional studies have found either preserved or even larger regional brain volumes in participants at risk or in the early stages of BD (Ladouceur et al., 2008; Hajek et al.,2009; Hajek et al.,2013; Roberts et al., 2016; Fusar-Poli et al., 2012). In contrast, participants at risk or in the early stages of schizophrenia typically show smaller global as well as regional brain volumes (Boos et al., 2007; Kempton et al., 2010; Cooper et al., 2014; De Peri et al., 2012). Longitudinal studies have also suggested that whereas the trajectory of brain development tends to be altered already before the onset or early in the course of schizophrenia (Shaw et al., 2010; Paus et al., 2008; Gogtay et al., 2008; Gogtay et al., 2010), similar maturational brain changes are not typically seen in the early stages of BD (Gogtay et al., 2010; Sanches et al., 2008; Hajek et al., 2005). Our cross sectional studies, closely converge with the results of previous longitudinal observations, which have suggested that accelerated brain maturation may have diagnostic specificity for schizophrenia and is not found in participants who later develop BD (Gogtay et al., 2010). More broadly, the pattern of differences observed in our study fits with epidemiological studies, which have demonstrated that premorbid academic performance was below average in those who went on to develop schizophrenia (Murray et al., 2004; Rapport et al., 2012; Rapport et al., 2005; Reichenberg et al., 2010; Trotta et al., 2015), but intact or above average in those who later developed BD (Trotta et al., 2015; MacCabe et al., 2010; Koenen et al., 2009). Similarly, cognitive functioning in participants with FES is typically impaired relative to controls (Trotta et al., 2015; Bora et al., 2014) or participants with first episode of BD, who tend to demonstrate preserved or even above average cognitive performance (MacCabe et al., 2010; Koenen et al., 2009).

The presence of diffuse structural alterations, as suggested by the elevated BrainAGE scores, already early in the course of schizophrenia is concerning. Preventing the development of these changes, which are detectable already within months from the first diagnosis, would be difficult. It puts an emphasis on studies attempting to better understand the underpinnings of these alterations (Hajek et al., 2014) and to devise methods to treat them.

The comparable BrainAGE scores in offspring of bipolar parents and controls suggest preserved brain structure early in the course of BD. Many previous studies have demonstrated that structural brain alterations are frequent later in the course of illness (Hibar et al., 2016; Hibar

et al., 2017). This puts an emphasis on studies attempting to prevent the development of brain structural alterations during the course of BD (Hajek et al., 2014). BrianAGE analyses results of Study 3 are in line with our Study 4, which was focused on the cerebellar anatomy of patients with SZ or BD (Laidi et al., 2019).

5.3.2. Cerebellar differences between SZ and BD

In Study 4 (Laidi et al., 2019), we conducted a volumetric MRI study in 648 participants with SZ, BD and healthy controls. We found a decreased volume of the total cerebellar volume, Crus II and the lobule VIIb in patients with SZ compared to controls. There was no significant difference between patients with BD and controls per se, but BD patients treated with lithium had a larger anterior cerebellar volume compared to controls. To date, this is the first multicenter study probing cerebellar differences at a lobular level in both patients with SZ and BD.

Our results are in line with findings from the previous studies (Moberget et al., 2018; Laidi et al., 2015). Moberget et al. found in a large sample of 983 patients with SZ and 1349 controls, a global volume reduction of the cerebellum compared to controls. In addition, the authors reported in a voxel and vertex wise mega analysis, a reduction of volume within the cerebellum, mostly located in lobule VIIb, Crus II, Crus I and lobule VI. The extent to which our findings replicate the previous results, despite the differences in methods of measuring cerebellar morphometry (voxel based morphometry, versus parcellation into lobules), is remarkable. Such a strong replication is relatively rare in a field which is known for preponderance of false positive findings (Ioannidis, 2011). Jointly, these findings suggest that smaller volumes of cerebellum are among the most robust findings in schizophrenia, replicable with different methodological approaches.

Moreover, we found a decreased volume in two cerebellar lobules (Crus II and lobule VIIb, adjacent to Crus II) located in the cognitive part of the cerebellum. The Crus II region is connected to the prefrontal cortex, a region that has been linked to schizophrenia. Our result supports the hypothesis of a cognitive dysmetria in schizophrenia, where the cortical-subcortical circuit between the cerebellum and the prefrontal cortex might be altered (Andreasen and Pierson, 2008). A disruption in this circuit may lead to difficulty in prioritizing,

processing and responding to information, which could account for the wide range of symptoms.

We did not find difference in the cerebellar anatomy when comparing patients with bipolar disorder and controls. Previous key studies from Hibar et al. (Hibar et al., 2018; Hibar et al., 2016) investigated the cortical and subcortical anatomy of patients with bipolar disorder in multicentric samples from the ENIGMA consortium. However the anatomy of the cerebellum was not investigated in these studies. On the other hand, Zhang and colleagues (Zhang et al., 2020) recently performed meta-analysis of VBM studies in relatives of patients with SZ, BD, and major depressive disorder (MDD) to identify overlapping and discrete structural correlates of familial risk for mental disorders. Decreased cerebellar gray matter was the only abnormality common to relatives of all three conditions. Besides the differences in studied population compares to our study (relatives versus BD), different findings may arise from different methods of measuring cerebellar morphometry (VBM versus parcellation into lobules), or from our lower sample size. Based on our previous findings about association between BMI and cerebellar volumes, perhaps this discrepancy could be explained by greater rates of obesity in the Zhang et al study.

We investigated if confounding factors could explain our results. Chronic consumption of alcohol in well known to affect the cerebellum (Cardenas et al., 2007) and can lead to its size reduction (Cardenas et al., 2007; Shear et al., 1996). Thus, our results might have been related to alcohol dependence in patients with schizophrenia. However, when repeating our analyses in a sub-sample of patients with schizophrenia without alcohol dependence, our results remained significant.

Likewise, there is evidence that cannabis could affect the cerebellar structure (Battistella et al., 2014). However, our analyses suggested that there was no effect of cannabis on our results.

As this was a multicenter study, we were unable to control for possible contribution of metabolic parameters to cerebellar alterations. Such analysis appears to be very rational, as VBM findings from our Study 1 showed in line with meta-analysis of García-García (García-García et al., 2019), that obesity is also associated with lower GM volume in cerebellum.

5.3.3. Medication and brain structure

When interpreting the findings of Study 1, we need to carefully consider the effects of antipsychotic medications on brain and metabolic markers (Andreasen et al., 2013; Tek et al., 2016; Jorgensen et al., 2017). Although BMI increased during hospitalization, BrainAGE scores were associated even with BMI from the time of admission. Thus, the contribution of medications to our findings is less likely. Furthermore, even participants who were medication naive prior to admission had greater BrainAGE scores than controls and BrainAGE scores were not associated with cumulative or current antipsychotic exposure. Also VBM analyses did not find associations between antipsychotic treatment and GM volumes. Previous studies described associations between cumulative exposure of antipsychotic medication and GM volumes (Vita et al., 2012) as well as pro-adipogenic effect of antipsychotics (Bak et al., 2014; Spertus et al., 2018). But at the same time, participants in our study had on average only 1.99 month of antipsychotic treatment and BMI was not associated with cumulative antipsychotic exposure. We cannot rule out that following a longer antipsychotic treatment, their metabolic side effects would become more relevant for association between antipsychotics and GM volumes or BrainAGE scores. The class of antipsychotic medication could also play a role. Almost all of the patients in our study received second generation antipsychotics. Previous meta-analysis of longitudinal studies found GM volume reduction mostly in participants treated with first generation antipsychotics (Vita et al., 2015). However, other studies and meta-analyses have found negative effects of antipsychotics on brain structure even in studies, which included participants treated with atypicals (Andreasen et al., 2013; Fusar-Poli et al., 2013; Van Gestel et al., 2019).

We studied the effect of medications also in Study 4 (Laidi et al., 2019), where we specifically focused on the effects of Lithium. Lithium shows neuroprotective effects (see Hajek and Weiner, 2016 for full review) and is much more often used in BD than in SZ. Consequently, it is possible that the absence of cerebellar changes in BD and their presence in SZ could be related to differential exposure to Lithium. Second, Johnson et al. (Johnson et al., 2018; Johnson et al., 2015) reported, using quantitative T1p mapping, cerebellar abnormalities in patients with BD. T1p mapping abnormalities were normalized in patients treated with lithium. Last, 5 cases of a lithium induced long-lasting cerebellar toxicity (Niethammer et al., 2007; Banwari et al.,

2016) have been reported and intention tremor, also known as cerebellar tremor, is a common side effect of lithium.

We found an increased volume in the anterior cerebellum in patients with BD medicated with lithium compared to BD patients not medicated with lithium. The anterior cerebellum is connected to the sensori-motor cortex (O'Reilly et al., 2010), which could explain the cerebellar motor syndrome described in patients medicated with lithium. However, we did not see effects of Lithium on the posterior cerebellum, which showed abnormalities in SZ. Therefore, it is unlikely that the absence of cerebellar changes in BD was related to neuroprotective effects of Lithium.

Antipsychotics could be also a potential confounding factor, explaining the structure differences in the cerebellum between patients with SZ and controls. However, when repeating our analyses in a sample of first episode patients, with limited exposure to antipsychotics, our results remained significant. In addition we did not find any association between the regions differing between patients with schizophrenia and control and the medication load.

6. LIMITATIONS

Our studies have several relevant limitations that should be acknowledged. Only prospective studies could establish the causality of the association between metabolic alterations and brain structure and functions. It is possible that obesity or IR are not the cause, but rather the consequence of brain imaging changes, which may render participants more impulsive (Miquel et al., 2016; Opel et al., 2015; Schilling et al., 2013).

In Studies 1 (Kolenic et al., 2018) and 2 (Kolenic et al., 2020, manuscript submitted for publication), we excluded participants with stroke, but cannot rule out microangiopathy or impaired vascular reactivity (Urback et al., 2017). Although no participant reported personal history or was newly diagnosed with type II diabetes mellitus, we cannot rule out effects of insulin resistance. We did not measure BMI exactly at the time of scanning in all participants, which might introduce noise and decrease the effect size. Yet, the association between BrainAGE and weigth/BMI likely reflects longer term effects and not recent changes. BrainAGE metric captures age but also maturational (Franke et al., 2012) or disease related

effects (Koutsouleris et al., 2014; Schnack et al., 2016; Ronan et al., 2016; Nenadic et al., 2017). We used BrainAGE primarily to obtain a cumulative measure of diffuse brain structural alterations. We controlled for many relevant confounders, but we were unable to quantify the effects of diet, exercise, life events or chronic stressors. Although our primary VBM analyses were testing a-priori hypotheses using preselected variables and regions of interest, additional analyses exploring associations between metabolic and inflammatory markers were exploratory/hypothesis generating and their results should be interpreted with caution.

Study 2 (Salvi et al., 2020) has also several limitations. Firstly, only a prospective study could confirm the direction of the association between IR and verbal memory. Thus, we can not rule out reverse causation, whereas impaired memory causes IR. In addition, without a control group, we can not test for interactions between BD and IR in their effects on cognitive functioning. Comparison with a control group could help disentangle the effects of Ir from those of BD on memory function. Regardless of whether this is an independent effect of only IR or an interaction between BD and IR, our data suggest that the presence of IR is an important factor, which could explain some of the variation in cognition in patients with BD. The sample size was primarily targeting differences in verbal memory and could have been underpowered to detect the association between IR and working memory. Since the studied population is at high risk for metabolic issues the chosen HOMA-IR cutoff might have underestimated IR in our study group. While HOMA-IR is the easiest and most frequently employed method to measure insulin resistance, future validation with gold-standard measurements of insulin sensitivity would provide deeper insight into the association between insulin signaling and cognition in BD. Finally, the study was carried out in three centers in different countries, where patient characteristics might have varied. However, we controlled for effects of site in statistical analyses.

Relevant limitations should be considered before interpreting our results of brain structural differences between SZ and BD. In Study 3 (Hajek et al., 2019), we applied different strategies to recruit participants in early stages of BD and early stages of SZ. This was motivated by the fact that whereas genetic high-risk design is well suited for BD, it is difficult to use in SZ, which is associated with lower fecundity (Bundy et al., 2011). Despite the differences in design, both studies focused on participants early in the course of illness and thus reduced potential sources of heterogeneity, including long-term effects of medication and illness burden. There may have

been differences in illness severity between the studies, as the FES were recruited at the point of their first hospitalization. If BrainAGE scores primarily reflected illness severity, affected offspring of BD parents would show greater BrainAGE scores than unaffected high-risk individuals; which was not the case. Consequently, it is unlikely that BrainAGE scores represented a non-specific measure of illness severity. Also, in Study 3B, data were collected at 2 acquisition sites. We controlled for differences between the sites in our statistical analyses. In addition, BrainAGE score estimation is scanner-independent and has been validated for multisite/mutiscanner setting (Franke et al., 2010). Indeed, the brain-age scores in our study did not differ between the 2 sites. In Study 3A, all data were acquired at a single site. Due to this, it would not be possible to directly compare the patient groups and control for site and study effects.

In Study 4 (Laidi et al., 2019) subjects were recruited in centers using different acquisitions parameters. For the most part, individual centers recruited participants only with SZ or only with BD, thus making a direct transdiagnostic comparison difficult. There is an overlap with previous study conducted in a sample of patient with SZ, BD and controls (Laidi et al., 2015). However our current study was conducted in a larger sample, with different software, allowing us to investigate the morphometry of the cerebellum at a lobular level. Our results suggest that Lithium has an effect on the size of the anterior cerebellum in patients with bipolar disorder. However, due to the cross-sectional nature of this study, it is not possible to draw any firm conclusion on the effect of lithium on the cerebellum. Further studies with a longitudinal design are warranted to better understand the effect of lithium on the cerebellum. We did not find size reduction in the cerebellum in patients with bipolar disorder compared to controls. Although we investigated the cerebellar anatomy in a multicenter sample of 144 patients, we cannot exclude that this negative finding might be related to a lack of power. In addition, the number of inclusion centers and the variability in the imaging acquisition protocols might as well explain some of our negative findings. We conducted several sensitivity analyses in sub-samples of our study. Because of the lack of power, our results (in particular negative findings) must be interpreted with caution. Because this study was focused on the cerebellum, we did not investigate the relations between cerebellar abnormalities and distant cerebral abnormalities. Further studies are warranted to better understand how cerebellar abnormalities could be linked to abnormalities in functionally connected regions such as the prefrontal cortex.

7. IMPLICATIONS, FUTURE PERSPECTIVES

The results of this work have several relevant clinical and methodological implications. At first, associations between higher BMI or overweight/obesity on one side and higher BrianAGE scores or lower GM volumes on the other, are clinically concerning, as the metabolic disturbances are present already early in the course of psychosis (Mitchell et al., 2013a, 2013b). The evidence for additive contribution of overweight/obesity to brain structural alterations in FES emphasizes the need to improve cardiovascular risk factor optimization in psychosis, intervene early and integrate psychiatric and medical management (Unutzer et al., 2006; Miller et al., 2013). Identification of overweight/obesity as potential risk factor for neurostructural alterations in psychosis may be the first step towards their management. Lifestyle interventions focused on psychological well-being and weight management have proven to be effective in improving cognitive, clinical and functional outcomes in many psychiatric syndromes (Fava, 2012; Goracci et al., 2016; Minichino et al., 2017). Obesity-related structural brain abnormalities might be reversible with dietary/lifestyle/surgical/medication interventions fostering weight loss and, especially in adolescents and young adults (Gomez-Pinilla, 2011; Haltia et al., 2007; Mueller et al., 2015; Shan et al., 2019; Tuulari et al., 2016). Structural neuroimaging studies have reported increases in brain volumes following aerobic exercise in healthy subjects as well as in patients with schizophrenia (Pajonk et al., 2010), which may be related to weight reduction (Honea et al., 2016; Mueller et al., 2015). Similarly, weight loss following bariatric surgery resulted in global brain tissue recovery (Tuulari et al., 2016). Also medications targeting obesity may have neuroprotective effects. Promising results have been described using antidiabetic liraglutide (Gejl et al., 2016), as also shown by the pilot trial in patients with bipolar disorder (Mansur et al., 2017a, 2017b). Other potential therapeutic options for future research include antiglucocorticoid mifepristone, which may improve cognitive dysfunction in participants with mood disorders (Watson et al., 2012) and showed also potential implications in reducing the risk of developing olanzapine/risperidone-induced weight gain (Gross et al., 2010, Gross et al., 2009). Adjuvant antiinflammatory agents could improve psychotic symptoms, augmentation with minocycline or pregnenolone were associated with cognitive improvements in patients with schizophrenia (Cho et al., 2019). Last but not least, protein deacetylase sirtuin1 (Sirt1) is protective against metabolic consequences of chronic exposure to a high-fat diet in animal models (Pfluger et al., 2008) and against signs of

accelerated ageing in animal (Alcendor et al., 2007) as well as in human studies (Wyman and Atamas, 2018).

Also, the confirmation of the association between IR on worse verbal memory in BD could pave the way for new interventions. Several studies have investigated the effects on cognition of pharmacological interventions addressing brain IR. Administration of insulin in healthy subjects positively affects memory. In a first such study, a high dose of intravenous insulin was more effective than a low dose in acutely improving the ability of remembering word lists (Kern et al., 2001). In a subsequent study conducted on healthy subjects before and after 8 weeks of intranasal insulin treatment, delayed recall of words was enhanced, yet immediate recall, non-declarative memory and selective attention were not affected by insulin administration (Benedict et al., 2004). There is also a growing evidence that several insulin-sensitizers such as rosiglitazone, liraglutide, and to some extent metformin independently improve cognitive function in mice models (Hansen et al., 2015; Patel et al., 2016; Ying et al., 2014). Liraglutide also improved memory and executive functions in individuals with mood disorders and, interestingly, the effect was moderated by baseline HOMA-IR scores (Mansur et al., 2017a).

The results may have also functional implications. Posterior cerebellar regions are connected to associative brain areas such as the prefrontal cortex and dysfunctions in the cortico-cerebellar-thalamo-cortical circuits could result in psychotic symptoms, as cerebellum acts as all-purpose modulator of movement as well as thought (Andreasen and Pierson, 2008). Additionally, posterior cerebellum is involved in cognitive and mood regulation (Buckner, 2013; Stoodley and Schmahmann, 2009). Therefore cerebellar alterations could help explain the pathoplastic effects of obesity on psychiatric outcomes, as previously documented (Calkin et al., 2009; Godin et al., 2018; Manu et al., 2014; Phillips et al., 2015).

Results of lower GM volumes of cerebellum region in subjects with SZ may also have therapeutic implications. The cerebellum is connected to almost every region of the brain, with the exception of the visual cortex and might represent a potential therapeutic target. For example, transcranial direct current stimulation (tDCS) has been applied in patients with non-clinical psychosis to improve their skills in procedural learning (Gupta et al., 2017).

Understanding the exact location of the cerebellar alterations in SZ is important since the location of the cerebellar stimulation influence the effect of brain stimulation in the cerebellum and distant cortical regions (Farzan et al., 2016).

Cross diagnostic brain imaging studies, especially those focusing on early stages of illness, are relatively rare in psychiatry. BD and SCH are often correctly diagnosed only years after the initial manifestations (Hirschfeld et al., 2003; Penttila et al, 2014) which leads to delayed treatment and contributes to poor prognosis (Penttila et al., 2014; Berk et al., 2009; Berk et al., 2011; Diaz-Caneja et al., 2015). We showed that BrainAGE scores and cerebellar volume measurement could aid in differential diagnosis between BD and SZ early in the course of illness.

Besides the clinical/functional implications, our results are relevant for methodological reasons. BMI is not usually collected or controlled for in VBM studies of SZ, although the negative effects of obesity on brain structure are robust and replicated in both psychiatric and non-psychiatric participants (Cox et al., 2019; Dekkers et al., 2019; García-García et al., 2019; Hamer and Batty, 2019). Identification of relevant contributors to GM abnormalities in SZ is an important step toward the better understanding and interpretation of neurostructural studies.

8. CONCLUSIONS

To conclude, we confirmed the assumption that metabolic disorders are more frequent in patients with psychosis already in the early stages of the disease and that they contribute negatively to the structural changes of the brain independently of the effect of the psychosis. Higher BMI and overweight/obesity were associated with lower regional GM volumes and with diffuse brain alterations manifesting as accelerated brain age. The effects of psychosis were most pronounced in frontotemporal regions, whereas both psychosis and higher BMI were additively associated with lower GM in the cerebellum. Importantly, higher BrainAGE scores and lower GM volumes in FES appeared unrelated to treatment with antipsychotic medications. This is highly clinically relevant, as FES participants have an increased risk of metabolic disorders and brain structural alterations. The additive effects of FES and BMI also suggest that comorbidity with overweight/obesity could contribute to

heterogeneity of neuroimaging findings in psychosis. Our exploratory analyses showed that dyslipidemia and elevated CRP could contribute to obesity-related neurostructural alterations. We also demonstrated that among BD participants without diabetes mellitus, IR was significantly associated with verbal memory performance, even when we controlled for other relevant metabolic or treatment variables. This is highly clinically relevant, as IR is currently not screened for. Our findings raise the possibility that early detection and treatment of metabolic disturbances, which are reversible, might improve or preserve brain structure and function in major psychiatric disorders.

Additionally, when focusing on differences between BD and SZ, we found neurostructural changes in participants with FES, which made their brains appear 2.64 years older than their chronological age. In contrast, participants in the early stages of BD had comparable BrainAGE scores to controls and comparable brain and chronological age. These findings are congruent with previous cognitive, developmental and brain imaging studies and lend further support to the model of greater neurodevelopmental contributions to schizophrenia than BD. Results were congruent with our next study, where we found lower cerebellar grey matter volume in SZ, but not in BD. Cerebellar volume reduction in SZ was located within the cognitive, posterior parts of the cerebellum including Crus II and lobule VIIb. Association between SZ and smaller cerebellar volumes is one of the most robust and replicated brain imaging findings in this disorder. Our studies support a distinct pattern of brain alterations in SZ and BD. BrainAGE method and cerebellar volume measurements could aid in early differential diagnosis between BD and SZ.

9. SHRNUTÍ

Potvrdili jsme předpoklad, že metabolické poruchy jsou častější již v raných stádiích psychóz a že mohou negativně přispívat ke strukturálním změnám mozku nezávisle na účinku samotné psychické poruchy. Jak vyšší BMI, tak nadváha/obezita, byly obě asociovány s nižším objemem šedé hmoty a také s difúzními změnami mozku, které se v MR obrazu projevovaly jako zrychlené stárnutí. Samotná psychóza byla nejvýrazněji asociována s nižším objemem šedé hmoty ve frontotemporálních regionech, zatímco psychóza i vyšší BMI byly aditivně

asociovány s nižším objemem šedé hmoty mozečku. Nepozorovali jsme souvislost mezi antipsychotickou léčbou a vyšším skóre BrainAGE, případně nižším objemem šedé hmoty mozku. Naše výsledky jsou z klinického hlediska důležité, neboť pacienti s psychózou mají zvýšené riziko metabolických poruch, co může negativně přispívat k neurostrukturálním mozkovým změnám. Rozdílné zastoupení nadváhy/obezity v jednotlivých studiích zameřených na zkoumání negativního efektu psychóz na mozkové struktury pak může zvyšovat heterogenitu nálezů. Naše exploratorní analýzy naznačují, že jak dyslipidémie, tak zánět (zvýšená hladina CRP) by se na obezitou navozených strukturálním změnám mozku mohly spolupodílet. Dále jsme prokázali významnou asociaci mezi inzulínovou rezistencí a nižším výkonem verbální paměti u pacientů s bipolární afektivní poruchu (BD), a to bez komorbidity s cukrovkou. Nález je důležitý taky z hlediska monitorování metabolických parametrů u BD, nakolik stanovení inzulínové rezistence je v běžné klinické psychiatrické praxi prováděno raritně. Naše výsledky naznačují, že prevence nebo včasná léčba metabolických komorbidit u BD nebo SZ by mohla zpomalit neurostrukturální změny a snížit negativní dopad na kognitivní funkce. Zajímavé a důležité výsledky přineslo taky zkoumání neurostrukturálních rozdílů mezi SZ a BD. U pacientů s první epizodou schizofrenie (FES) jsme v MR obrazu pozorovali znaky imponující jako zrychlené stárnutí mozku, v průměru o 2,64 roku ve srovnání se skutečným biologickém věkem. Naproti tomu účastníci v riziku nebo v raných stádiích BD nevykazovali rozdíl mezi odhadovaným a biologickým věkem, stejně tak se nelišili od zdravých kontrol. V následné multicentrické studii jsme pozorovali menší globální objem mozečku u SZ, ale nikoliv u BD. Naše pozorování jsou ve shodě s předchozími kognitivními, neurovývojovými a neurozobrazovacími studiemi a podporují model závažnější neurovývojové zátěže u SZ ve srovnání s BD. Asociace mezi SZ a narušenou strukturou mozečku patří k nejrobustnějších a nálezům u pacientů se schizofrenii. Výsledky naších studii naznačují, že jak metoda BrainAGE, tak měření objemu mozečku by mohly pomoci při včasné diferenciální diagnostice mezi SZ a BD.

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11. PUBLICATIONS

Publications in extenso, that constitute the basis of the PhD thesis:

a) with impact factor

Kolenic, M., Franke, K., Hlinka, J., Matejka, M., Capkova, J., Pausova, Z., ... & Hajek, T. (2018). Obesity, dyslipidemia and brain age in first-episode psychosis. *Journal of psychiatric research*, *99*, 151-158. (IF 3.917)

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Laidi, C., Hajek, T., Spaniel, F., **Kolenic**, M., d'Albis, M. A., Sarrazin, S., ... & Linke, J. (2019). Cerebellar parcellation in schizophrenia and bipolar disorder. *Acta Psychiatrica Scandinavica*, *140*(5), 468-476. (IF 4.694)

b) without impact factor

Kolenic, M., Capkova, J., Hajek, T. (2016). Insulin resistance, type 2 diabetes mellitus and bipolar disorders. *Psychiatrie*. *20*(3), 147-152.

2. Other publications

a) with impact factor

Sebela, A., **Kolenic,** M., Farkova, E., Novak, T., & Goetz, M. (2019). Decreased need for sleep as an endophenotype of bipolar disorder: an actigraphy study. *Chronobiology international*, *36*(9), 1227-1239. (IF 2.562)

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b) without impact factor

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12. APPENDIX - Original publications related to the thesis