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Asociace metabolických faktorů a strukturálních změn mozku u psychotických poruch

Association between metabolic factors and structural brain changes in psychoses

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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.

LIST OF ABBREVIATIONS

BD - bipolar disorder
BMI – body-mass index
CI - confidence interval
CGI-BP - Clinical Global Impressions-Bipolar Scale
CRP - C-reactive protein
CVLT - California Verbal Learning Test
DS - Digit Span
DSM-IV - Diagnostic and Statistical Manual of Mental Disorders, 4th Edition
FWE - family-wise error
FES - first episode schizophrenia
FEP- first episode psychosis
GM – gray matter
HAM-D - Hamilton Rating Scale for Depression
HC - healthy controls
HDL - high-density lipoprotein cholesterol
HOMA-IR - Homeostatic Model Assessment of Insulin Resistance
HR- high-risk
ICD-10 - International Statistical Classification of Diseases and Related Health Problems 10th Revision
IR- insulin resistance
IXI - Information eXtraction from Images
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
YMRS - Young Mania Rating Scale

1. INTRODUCTION

Bipolar disorders (BD) and schizophrenia (SZ) are among the leading causes of morbidity and mortality worldwide (Gustavsson et al., 2011; Whiteford et al., 2013). SZ is often accompanied by affective symptomatology and BD may often present with psychotic symptoms. (Dunayevich and Keck, 2000). Both SZ and BD are often correctly diagnosed only years after the initial manifestations (Hirschfeld et al., 2003; Penttila et al., 2014). Early differential diagnosis between BD and SZ is highly important, as delayed treatment contributes to poor prognosis (Penttila et al., 2014; Berk et al., 2011). This is where detailed studies of neurobiology/neuroanatomy may play a prominent role.
SZ is frequently conceptualized as a neurodevelopmental disorder (Rapoport et al., 2012), and lower GM volumes were reported already in medication-naive participants (Shah et al., 2017). On the other hand, neurodevelopmental antecedents are mostly absent in individuals in with BD (Sanches et al., 2008) and participants in early phases of BD typically show preserved brain structure (Hajek et al., 2005; Hajek et al., 2009; Hajek et al., 2013). But many of the brain changes progressively worsen in both SZ and BD (Andreasen et al., 2011; Vita et al., 2012; Abé et al., 2020) and this is likely related to accumulation of certain clinical variables (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 (van Erp et al., 2018; Hibar et al., 2018).
Another key characteristic of neuroimaging literature in BD or SZ is heterogeneity of findings (Wang et al., 2019; Shah et al., 2017). Better understanding of the clinical factors which contribute to brain alterations is important first step towards prevention or treatment of neurobiological changes. One of the potential sources of neuroimaging abnormalities in BD and SZ could be the comorbidity with medical conditions known to affect the brain.

Overweight or obesity are disproportionately frequent in SZ and BD (Correll et al., 2014; Foley and Morley, 2011; Galletly et al., 2012). 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; Angst et al., 2002). 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; Farruggia and Small, 2019; Godin et al., 2018; Rashid et al., 2013; Fagiolini et al., 2004).

Neurostructural alterations are frequently reported in participants with obesity (Cherbuin et al., 2015; Masouleh et al., 2016) 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; Shah et al., 2017; Willette and Kapogiannis, 2015; Wang et al., 2019; Opel at al., 2020, van Erp et al., 2018; 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 (Yau et al., 2014), possibly as a result of systemic low-grade inflammation, which is frequently associated with obesity (Wisse, 2004), as well as brain changes (Guillemot-Legris and Muccioli, 2017). 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).

There is a replicated evidence showing that obesity is negatively associated also with cognitive functions in non-psychiatric subjects (Prickett et al., 2015; Gunstad et al., 2010). 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). 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; 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). 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. AIMS, OBJECTIVES, HYPOTHESES

Brain imaging may provide potential support for early differential diagnosis between SZ and BD. 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 disproportionally frequent metabolic abnormalities in SZ and BD.
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. METHODS

We diveded analyses in to 2 separate sections. In Section 1, we analyzed association between metabolic factors and brain structural or functional abnormalities. For that reason we performed 2 studies. In Study 1, we focused on the effects of psychosis and obesity on a composite index of brain structure (BrainAGE). In Study 2, using VBM, we investigated the localization of obesity-related neurostructural alterations and whether these directly overlap with regions associated with psychosis. In Study 2, we studied association between insulin resistance and cognition in subject with BD. In Section 2, we analyzed brain structural differences between schizophrenia and bipolar disorder**. For that reason, we p**erformed 2 additional studies. In Study 3, we used the BrainAGE to capture multivariate neurostructural alterations in early stages of SZ or BD. In Study 4 we studied both SZ and BD across different disease stages, and focused on cerebellar anatomy. Brief overview of methods are decribed below.

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

3.1.1. Sample description

We analyzed a sample of 120 participants with FES and 114 controls (Early Stages of Schizophrenia study, Spaniel et al., 2016). 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), 3) had <24 months of untreated psychosis, 4) were 18–35 years old. Patients with psychotic mood disorders, were excluded from the study. Healthy controls, 18–35 years old, were recruited using the following exclusion criteria: 1) lifetime history of any psychiatric disorders, 2) psychotic disorders in first or second-degree relatives.

3.1.2. Brain imaging analyses

3.1.2.1. Analysis 1: Brain age estimation. BrainAGE machine learning method estimates the biological age of the brain from MRI (Franke et al., 2013; Koutsouleris et al., 2014). The difference between brain age and chronological age, called BrainAGE score, captures diffuse, multivariate neurostructural alterations into a single number (Franke et al., 2010; Franke et al., 2012). We trained the model using an independent sample of 504 healthy individuals from the IXI database. Our outcome measure was the BrainAGE score (Franke et al., 2010).

3.1.2.2. Analysis 2: Voxel-based morphometry analyses. We conducted optimised VBM protocol (Good et al., 2001). Voxel-wise general linear model was used to compute associations between local GM volume and studied variables (status - FES/controls, BMI, age, sex). Permutation-based non-parametric testing, correcting for multiple comparisons across space, was applied. The threshold was set to $p<0.05$ using threshold-free cluster enhancement (TFCE) and 5000 permutations.

3.1.3. Statistical analyses

3.1.3.1. Analysis 1, BrainAGE

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. We also explored the association between BrainAGE scores and relevant clinical variables.

3.1.3.2. Analysis 2, VBM

We performed primary VBM analysis with small volume corrections to regions which have been previously associated with FES or obesity (Shah et al., 2017; García-García et al., 2019). We assessed the association between FES, BMI as explanatory variables and regional GM volumes as the dependent variable. Secondly, we performed whole brain VBM analysis. Additionally, we explored the effects of clinical, treatment-related or metabolic variables on our VBM results among the FES participants.

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

3.2.1. Sample description

This multicenter study enrolled outpatients with diagnosis of BD 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.

3.2.2. 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. Participants underwent neuropsychological testing (California Verbal Learning Test - CVLT and the Digit Span forward and backward - DS). 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).

3.2.3. Statistical analyses

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. 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.

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

3.3.1. 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 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). 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). 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. 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 and had one parent affected with a primary mood disorder. Control participants without any personal or family history of DSM-IV Axis I psychiatric disorders, were recruited from similar socioeconomic background.

3.3.2. Image processing

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

3.3.3. Statistical analyses

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. 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. 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.

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

3.4.1. Sample description

Patients with SZ spectrum disorder, BD and controls were recruited in Czech Republic, USA, Germany, Italy and France. For more details about inclusion criteria, see original article (Laidi et al., 2019).

3.4.2. Image processing, cerebellar grey matter volume analyses

All T1 MRI 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). We extracted the grey matter volume of 6 cerebellar regions of interest (ROIs) and the global cerebellar grey matter volume.

3.4.3. Statistical analyses

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. Results that survived correction for multiple comparisons were considered as significant. We conducted our 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 studied the association between the severity of schizophrenia and the regions of interest in the cerebellum.

4. RESULTS

4.1. SECTION 1. ASSOCIATION BETWEEN METABOLIC FACTORS AND BRAIN STRUCTURAL ABNORMALITIES

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

4.1.1.1. Analysis 1: Obesity, dyslipidemia and brain age in first-episode psychosis
We analyzed a sample of 120 participants with FES and 114 controls (Kolenic et al., 2018). 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).

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).

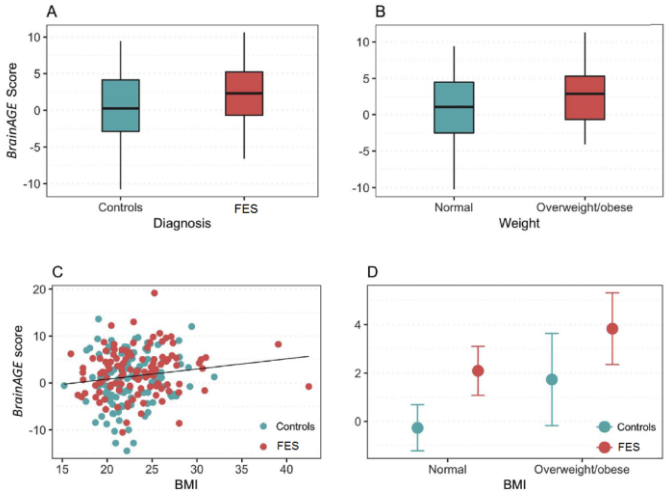

Figure 1. Associations between BrainAGE scores and psychiatric diagnosis or metabolic factors. BrainAGE scores were significantly associated with the diagnosis of first-episode psychosis (FES, panel A), overweight/obesity (panel B), body mass index (BMI, panel C). Overweight/obesity was significantly 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, HDL-cholesterol, TG.

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 ($R2=0.22$, $F(3, 230)=21.92$, $p < 0.001$). 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).
BrainAGE scores in previously medication naive participants (N=40) were greater than in controls, comparable to previously medicated FES individuals and not associated with cumulative exposure to antipsychotics. BrainAGE scores were not associated with duration of illness, duration of untreated psychosis, current symptoms, systolic or diastolic pressure, personal history of hypertension, glucose levels, substance abuse/dependence, current cigarette smoking, or marijuana abuse.

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

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).

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, b) left cerebellum, c) cluster including left inferior frontal gyrus and superior temporal gyrus, d) right temporal cortex. When controlling for FES, higher BMI was associated with lower GM volume in the cerebellum. 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.

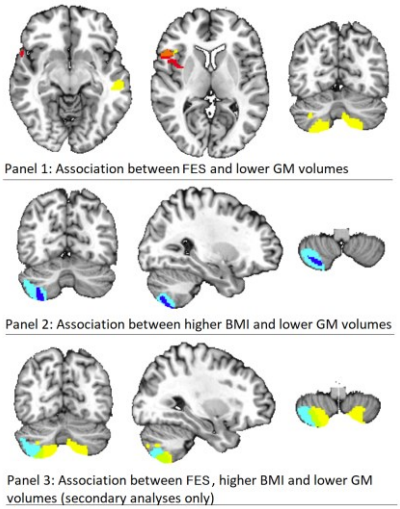

Figure 2. VBM analyses results. Panel 1: Associations between FES and lower GM volumes; primary analyses (red), secondary whole brain analyses (yellow). Overlap between primary and secondary analyses (orange). Panel 2: Associations between higher BMI and lower GM volumes; primary analyses (dark blue), 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. $p<0.05$.

Additional VBM analyses. Average GM values from voxels associated with BMI from primary analyses were negatively correlated with LDL (r_s= -0.255, p=0.030), CRP (r_s= -0.327, p=0.006), positively correlated with high 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 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). 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.

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

We analyzed data from 100 euthymic BD participants (Salvi et al., 2020). 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. 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).

Exploratory analyses

Composite verbal memory scores were nominally associated with TG, HDL, but not with total cholesterol, BMI, exposure to antipsychotics, mood stabilizers, or years of education. In the model, which controlled for age, site, TG and HDL, IR remained significantly associated with composite verbal memory scores, whereas the association between TG or HDL and composite memory scores became non-significant.

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

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

4.2.1.1. 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. Participants with FES had higher BrainAGE scores relative to controls ($F(1, 83) = 8.79$, corrected $P = .008$, Cohen's $d = 0.64$). The brain age in participants with FES was higher than their chronological age by an average of 2.64 ± 4.15 years (matched $t(42) = 4.36$, $P < .001$). When we controlled for both age and sex, the differences in BrainAGE scores between FES and controls remained significant ($F(1, 82) = 8.70$, $P = .004$).

4.1.1.2. 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 comparable between HR unaffected, affected familial and control participants ($F(2,149) = 1.04$, corrected $P = .70$, $\eta2 = 0.01$), 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 brain age in the HR unaffected or in the affected familial participants was

comparable to their chronological age. BrainAGE scores were not associated with number of episodes, number of hospitalizations or duration of illness, when controlling for age.

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

4.2.2.1. Total cerebellar volume and lobular analysis in schizophrenia

182 patients with SZ and 198 controls were included. The global cerebellar volume, Crus II and lobule VIIb were significantly smaller in patients compared to controls (Fig.3).

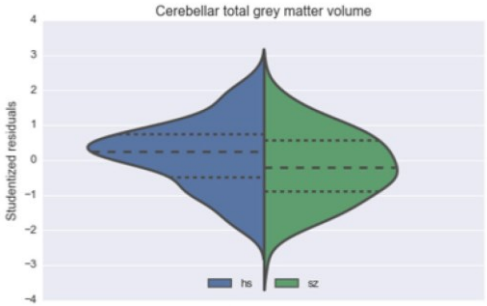

Figure 3: Grey matter volume of the cerebellum in patients with SZ and controls: partial residual plot.
Legends: hs, healthy subjects; sz, patients with schizophrenia; comparison of studentized residuals after regressing the effect of site, age, sex and intra cranial volume. Hashed lines delineate quartiles 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

144 patients with type I BD and 176 controls were included. We did not find any significant difference between patients and controls for any of the regions of interest. 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). 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 ($p = 0.047$).

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.
There was no significant effect of medication load on the volume of the total cerebellar, Crus II and lobule VIIb volumes.

5. DISCUSSION

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. 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. Importantly, the effect of overweight/obesity on brain structure was additive to the effect of FES. We also 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.

Previous studies have reported neurostructural alterations and advanced brain age already in FES (Koutsouleris et al., 2014), as well as in participants with high BMI (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). 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; Shah et al., 2017). Perhaps, the uncontrolled presence of overweight/obesity may contribute to heterogeneity in cerebellar volumes between studies in FES.

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. Dyslipidemia is a known risk factor for cerebrovascular disease (Pikula et al., 2015) and has pathoplastic effects on brain structure in participants with manifest atherosclerosis (Tiehuis 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. Importantly, CRP was also negatively correlated with average GM values from the cerebellar cluster associated with BMI (r_s= -0.327, p=0.006).

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 (Pajonk et al., 2010; Zipursky et al., 2013). 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. The interpretation is also complicated by the unclear direction of association between brain and metabolic alterations.

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. Our study is also in keeping with previous reports documenting the negative association between IR and cognitive functioning in participants without psychiatric disorders (Wijtenburg et al., 2019; Bruehl et al., 2010). 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).

The effects of IR on brain function are not surprising. Insulin is actively transported through the blood-brain barrier and binds to its receptors, which are widely distributed throughout the brain (Kullmann et al., 2016). 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). 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 line with previous research (Kolenic et al., 2016), our findings put more emphasis on clinical screening of insulin metabolism in BD.

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 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 (Koutsouleris et al., 2014; Nenadić et al., 2017). 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. Our results are also congruent with structural brain imaging studies (Hajek et al.,2009; Hajek et al.,2013; Fusar-Poli et al., 2012) and 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).

In Study 4 (Laidi et al., 2019), 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). 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.

When interpreting the findings, we need to carefully consider the effects of antipsychotic medications on brain and metabolic markers (Andreasen et al., 2013; 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 (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.

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).

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). 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). Importantly, obesity-related structural brain abnormalities might be reversible with dietary, lifestyle, surgical or medication interventions fostering weight loss (Gomez-Pinilla, 2011; Haltia et al., 2007; Mueller et al., 2015; Shan et al., 2019; Tuulari et al., 2016). Also medications targeting obesity may have neuroprotective effects. Promising results have been described using antidiabetic liraglutide (Gejl et al., 2016),(Mansur et al., 2017a, 2017b). Other potential therapeutic options for future research include antiglucocorticoid mifepristone, (Watson et al., 2012), adjuvant antiinflammatory agents (Cho et al., 2019) or protein deacetylase sirtuin1 (Sirt1; Wyman and Atamas, 2018).

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., 2011). 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.

6. 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.

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8. 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)

Hajek, T., Franke, K., **Kolenic,** M., Capkova, J., Matejka, M., Propper, L., ... & Kopecek, M. (2019). Brain age in early stages of bipolar disorders or schizophrenia. *Schizophrenia bulletin*, *45*(1), 190-198. (IF 7.575)

Salvi, V., Di Salvo, G., Korčáková, J., Torriero, S., Aragno, E., **Kolenič,** M., ... & Hajek, T. (2020). Insulin resistance is associated with verbal memory impairment in bipolar disorders. *Journal of Affective Disorders*, *266*, 610-614. (IF 4.084)

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

Kolenič M., Čapková J., Hájek T. Insulin resistance, type 2 diabetes mellitus and bipolar disorders; Psychiatrie, 2016 (3)

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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