Psychoneuroendocrinology 97 (2018) 135–142

Contents lists available at ScienceDirect

Psychoneuroendocrinology

journal homepage: www.elsevier.com/locate/psyneuen

Obesity influences white matter integrity in schizophrenia

Marco Spangaro[a,1], Elena Mazza[a,1,*], Sara Poletti[b,c], Roberto Cavallaro[a,b], Francesco Benedetti[b,c]

[a] IRCCS San Raffaele Scientific Institute, Department of Clinical Neurosciences, Milan, Italy
[b] University Vita-Salute San Raffaele, Milan, Italy
[c] C.E.R.M.A.C. (Centro di Eccellenza Risonanza Magnetica ad Alto Campo), IRCCS San Raffaele Scientific Institute, Milan, Italy

ARTICLE INFO

Keywords:
White matter
Schizophrenia
Body mass index (BMI)
Obesity
Diffusion tensor imaging (DTI)
Tract-based spatial statistics (TBSS)

ABSTRACT

Background: White matter (WM) alterations have been consistently described in patients with schizophrenia and correlated with the severity of psychotic symptoms and cognitive impairment.

Obesity has been reported in over 40% of patients with schizophrenia and has been associated with cognitive deficits, cardiovascular diseases, metabolic alterations, and overall mortality. Moreover, studies among healthy subjects and subjects at risk for psychosis reported an influence of Body Mass Index (BMI) on structural connectivity. We therefore hypothesized that obesity and overweight could further disrupt WM integrity of patients affected by schizophrenia.

Methods: Eighty-eight schizophrenia patients were evaluated for BMI. We divided the sample in overweight/obese and normal weight groups. We then performed whole brain tract-based spatial statistics in the WM skeleton with threshold-free cluster enhancement of DTI measures of WM microstructure: axial (AD), radial (RD), and mean diffusivity (MD), and fractional anisotropy (FA).

Results: A significant difference between the two groups was observed: normal weight patients showed higher AD and a higher FA trend compared to obese patients in several fibers' tracts including longitudinal fasciculus, uncinate fasciculus, corona radiata, thalamic radiation, fronto-occipital fasciculus, cingulum and corpus callosum.

Conclusions: Elevated BMI might contribute to WM disruption of schizophrenia by hampering structural connectivity in critical cortico-limbic networks, known to play a crucial role in neurocognitive functioning, emotional processing and psychopathology whose dysfunction are prominent features of the disorder.

1. Introduction

Schizophrenia associates with metabolic alterations and increased risk of cardiovascular diseases (CVDs), obesity, metabolic syndrome (MetS), type 2 diabetes, various cancers, and overall mortality (Vancampfort et al., 2013). Possibly due to unhealthy life-style and antipsychotics side-effects (Mitchell et al., 2013), patients with schizophrenia have an increased weight or comorbid obesity in 40–60%. Metabolic alteration are detectable at the earliest stages of illness, and their incidence increases in multi-episode patients (Minichino et al., 2017).

Besides its role in increasing risk for CVDs, obesity has been associated with an alteration of neural substrates and functioning. Previous studies reported a widespread reduction of grey matter volumes (GM) and white matter (WM) integrity among non-psychiatric obese and overweight individuals (Raji et al., 2010; Stanek et al., 2011). Specifically, obese healthy subjects showed GM and WM atrophy localized to frontal lobes, anterior cingulate gyrus, hippocampus, and thalamus, as well as a reduction in WM integrity throughout the brain (Verstynen et al., 2012). Alteration of neural substrates associated to obesity also negatively affects cognition and daily functioning (Cohen, 2010). Furthermore, obesity was shown to lead to a higher risk of mild cognitive impairment and dementia in the elderly (Bocarsly et al., 2015). In rodents, diet-induced obesity leads to microglial alterations, decreased dendritic spine density and synaptic marker expression, and neurocognitive impairment (Bocarsly et al., 2015).

Meta-analytic evidence associates schizophrenia with spread alterations of Diffusor Tension Imaging (DTI) measures of WM microstructure (Vitolo et al., 2017), including lower fractional anisotropy (FA) and axial diffusivity (AD), and increased mean diffusivity (MD) and radial diffusivity (RD) in different white matter tracts and regions (Canu et al., 2015). FA reflects organization, directional coherence,

* Corresponding author at: Department of Clinical Neurosciences, IRCCS San Raffaele Scientific Institute, Via Stamira d'Ancona 20, 20127 Milano, Italy.
E-mail address: elena-mazza@hotmail.it (E. Mazza).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.psyneuen.2018.07.017
Received 21 January 2018; Received in revised form 9 July 2018; Accepted 10 July 2018

and/or integrity of the fibers (Cherubini et al., 2010), and FA and AD positively correlate with development of working memory capacity, reading ability, information processing speed and motor speed (Vernooij et al., 2009). MD, representing the mean molecular diffusion, increases with reduced membrane density, such as in tissue degeneration after injury (Sen and Basser, 2005). It can be a sensitive indicator of the overall developmental changes in brain tissue, demonstrating changes in fiber coherence and tortuosity (Basser and Pierpaoli, 2011). Higher RD has been found to accompany reduced FA in WM tracts in schizophrenia, possibly due to demyelination or changes in the axonal cytoskeleton (Takahashi et al., 2011). All together, lower FA/AD and higher MD/RD suggest abnormal microstructure of myelin sheaths and axons in Schizophrenia. The WM bundles reporting the worst disruption in DTI studies in schizophrenia are long projection fibers, callosal and commissural fibers, part of motor descending fibers, and fronto-temporal-limbic pathways (Vitolo et al., 2017). Interestingly, many of the brain regions that were reported as altered in schizophrenia, are often disrupted in obesity as well.

Several biological pathways are disrupted both, in weight-related processes, and in psychosis (Lopresti and Drummond, 2013), and could provide a common biological underpinning for shared brain imaging abnormalities. Both obesity and schizophrenia are characterized by increased oxidative stress, hypothalamus-pituitary-adrenal axis disturbances, neurotransmitter imbalances, mitochondrial alterations, and dysregulated inflammatory pathways. It was suggested that the co-occurrence of these diseases may increase the severity of brain structural abnormalities associated with core features of the psychiatric disorder, through a synergistic and disruptive effect (Minichino et al., 2017). In particular, chronic inflammation associated with obesity could affect brain plasticity and signaling processes, known to be altered in schizophrenia, by increasing the level of circulating cytokines and adipokines (Kiliaan et al., 2014)

This hypothesis is also consistent with clinical studies reporting (a) worse prognostic outcomes among obese and overweight psychotic patients (Rashid et al., 2013); (b) an association between elevated body mass index (BMI) and poorer verbal memory performance among both patients with schizophrenia and healthy subjects (Friedman et al., 2010); and (c) significant relationships between cognitive impairment and each of the components of MetS (hypertension, dyslipidemia, abdominal obesity and diabetes) (Bora et al., 2017).

Despite these intriguing evidences, the relationship between BMI, metabolic alterations and neural substrates in schizophrenia has been scarcely investigated. One study attempted to investigate possible associations between BMI and WM integrity in schizophrenia, reporting negative results (Tang et al., 2011). However, this study used a Region of Interest (ROI) approach, which only analyzes a limited and specific number of WM tracts. More recently, decreased FA and increased RD were associated with high BMI in several brain areas among young adults at risk for psychosis, free of antipsychotic medications, compared to non at risk healthy subjects, thus supporting the hypothesis of a negative neurobiological interaction between obesity and schizophrenia (Koivukangas et al., 2016).

Given the convergence of neurobiological alterations between diseases and the negative effects on connectivity reported in literature, we then hypothesized that obesity and overweight could further disrupt WM integrity of patients affected by schizophrenia. The aim of the present study is to investigate the association between DTI parameters and BMI in a sample of patients affected by schizophrenia, using tract-based spatial statistics (TBSS). Moreover, in order to better understand the relationship between metabolic status and WM integrity, we analyzed possible effects of triglycerides, cholesterol, and glucose blood levels on DTI measures as well.

2. Methods

2.1. Participants and clinical assessment

The sample included 88 patients (28 females, 60 males) with a diagnosis of schizophrenia [DSM-IV-TR criteria - Structured Clinical Interview (SCID-I) interview], recruited at the psychiatric ward of San Raffaele Turro Hospital in Milan. Severity of symptoms was rated on the Positive and Negative Syndrome Scale (Kay et al., 1987).

All patients were on antipsychotic therapy: 31 patients were taking clozapine, 16 patients risperidone and others 16 haloperidol, 11 patients were taking olanzapine, 9 paliperidone and 5 aripiprazole. All the doses of the antipsychotics were converted into chlorpromazine equivalents and mean administered doses were calculated (Gardner et al., 2010); patients were being administered a mean dose of 380.03 (S.D. = 211.89) mg chlorpromazine equivalents of antipsychotic drugs.

Blood samples were then drawn early in the morning for all patients (fasting) within a week of MRI scan, and processed for analysis of serum lipid levels of total cholesterol, glucose and triglycerides. Lipid concentrations were measured on a Cobas 8000 modular analyzer (Roche Diagnostics - Rotkreuz, Switzerland).

Inclusion criteria were absence of other diagnoses on Axis I; absence of mental retardation on Axis II; absence of pregnancy, history of epilepsy, major medical and neurological disorders; absence of history of drug or alcohol abuse or dependency dependency within the previous year. Physical examination, laboratory tests and electrocardiograms were performed at admission. After complete description of the study to the participants, written informed consent was obtained. All research activities have been approved by the local ethical committee.

2.2. Image acquisition

Diffusion tensor imaging was performed on a 3.0 T scanner (GyroscanIntera, Philips, Netherlands) using SE Eco-planar imaging (EPI) and the following parameters: TR/TE = 8753.89/58 msec, FoV (mm) 231.43 (ap), 126.50 (fh), 240.00 (rl); acquisition matrix 2.14 × 2.71 × 2.31; 55 contiguous, 2.3-mm thick axial slices reconstructed with in-plane pixel size 1.88 x 1.87 mm; SENSE acceleration factor = 2; 1 b0 and 35 non-collinear directions of the diffusion gradients; b value = 900 s/mm2. Fat saturation was performed to avoid chemical shift artefacts. It was performed through Spectral Presaturation with Inversion Recovery (SPIR), a hybrid technique that combines a fat-selective RF-pulse and spoiler gradient together with nulling of the residual longitudinal fat magnetization through an inversion delay mechanism (http://mriquestions.com/spir.html). On the same occasion and using the same magnet 22 Turbo Spin Echo (TSE), T2 axial slices (TR = 3000 ms; TE = 85 ms; flip angle = 90°; turbo factor 15; 5-mm- thick, axial slices with a 512 × 512 matrix and a 230 × 230 mm2 field of view) were acquired to rule out brain lesions.

2.3. Data processing and analyses

Image analyses and tensor calculations were done using the “Oxford Centre for Functional Magnetic Resonance Imaging of the Brain Statistical Library” (FSL 4.1.4; www.fmrib.ox.ac.uk/fsl/index.html) (Woolrich et al., 2009). First, each of the 35 DTI volumes was affine registered to the T2-weighted b = 0 volume using FLIRT (FMRIB's Linear Image Registration Tool) (Jenkinson and Smith, 2001). This corrected for motion between scans and residual eddy–current distortions present in the diffusion-weighted images. Anisotropy can be estimated through the application of diffusion-sensitizing gradients and the calculation of elements of the diffusion tensor matrix, i.e. the three eigenvalues λ_1, λ_2 and λ_3. The tendency to diffuse along the principal direction of the fibre (AD, λ_1) reflects the integrity of axons and myelin sheaths, and the bundle coherence of WM tracts (Boretius et al., 2012). An increase in radial diffusivity (RD, the average of λ_2 and λ_3),