Journal of Affective Disorders 241 (2018) 305–310

Contents lists available at ScienceDirect

Journal of Affective Disorders

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

Research paper

Microglial markers in the frontal cortex are related to cognitive dysfunctions in major depressive disorder

Hua Li[a], Aadi P. Sagar[a], Szabolcs Kéri[a,b,c,*]

[a] Nyírő Gyula National Institute of Psychiatry and Addictions, Budapest, Hungary
[b] Department of Cognitive Science, Budapest University of Technology and Economics, Budapest, Hungary
[c] Department of Physiology, University of Szeged, Faculty of Medicine, Szeged, Hungary

ARTICLE INFO

Keywords:
Major depression
Inflammation
PET
Translocator protein
Cognition

ABSTRACT

Background: Evidence suggests that microglia-mediated processes are implicated in the pathophysiology of major depressive disorder (MDD). The relationship between these processes and cognitive dysfunctions has not been explored.

Methods: We recruited 50 never-medicated patients with MDD and 30 healthy control subjects. We used [^{18}F]-FEPPA positron emission tomography (PET) to examine translocator protein total distribution volume (TSPO V_T), a marker of microglia. Cognitive functions were evaluated with the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (attention, immediate and delyed memory, language, and visuospatial functions).

Results: Patients with MDD showed elevated TSPO V_T in all regions of interest (white matter, grey matter, frontal cortex, temporal cortex, and hippocampus) and were impaired on the attention and delayed memory domains of the RBANS. In the frontal cortex, increased TSPO V_T was associated with lower scores on the RBANS attention domain when the analysis was corrected for age, gender, education, and depressive symptoms.

Limitations: Affective functions were not investigated, the specificity of [^{18}F]-FEPPA binding is limited, TSPO may reflect microglia/macrophage density rather than activation, and the sample was not balanced (more patients were included than controls).

Conclusions: Attentional dysfunctions may be associated with microglial pathology in the frontal cortex of untreated patients with MDD.

1. Introduction

In response to an increased attention paid to cognitive dysfunctions in major depressive disorder (MDD), numerous recent studies explored the characteristics and clinical significance of impairments in several cognitive domains. In the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, the majority of patients with MDD reported subjective difficulty with attention and decision making (Sinyor et al., 2010). Moreover, residual cognitive symptoms pose a serious challenge even in euthymic patients (Bora et al., 2013; Hasselbalch et al., 2011; Nierenberg et al., 2010), necessitating the achievement of cognitive remission (Bortolato et al., 2016). Although the cumulative disease burden is important in the emergence of cognitive dysfunctions (Hasselbalch et al., 2013), deficits can be observed in individuals experiencing their first major depressive episode (Lee et al., 2012). In a meta-analysis of the literature examining first-episode MDD, Lee et al. (2012) found cognitive deficits with small to medium effect size for psychomotor speed, attention, visual learning and memory, and executive functions. Psychomotor speed and memory functions were related to the actual clinical state of the patients, meanwhile attention and executive dysfunctions might be trait markers (Lee et al., 2012). However, the neurobiological correlates of cognitive dysfunctions are not clearly understood.

The inflammatory model of MDD may provide a heuristic framework to better understand cognitive dysfunctions (Allison and Ditor, 2014; Carvalho et al., 2014). Several studies demonstrated that cytokines and other inflammatory mediators display an altered level of expression in MDD, which may interact with the hypothalamic-pituitary-adrenal gland (HPA) stress axis, the metabolism of monoamine neurotransmitters, and cellular and synaptic plasticity in the brain (Dantzer et al., 2008; Furtado and Katzman, 2015; Miller et al., 2009; Singhal and Baune, 2017). These biological pathways show a highly

* Corresponding author at: Department of Physiology, University of Szeged, Faculty of Medicine, Szeged, Hungary.
E-mail addresses: szkeri@cogsci.bme.hu, keri.szabolcs@kzc-opai.hu (S. Kéri).

https://doi.org/10.1016/j.jad.2018.08.021
Received 19 May 2018; Received in revised form 14 July 2018; Accepted 7 August 2018
Available online 08 August 2018

interactive relationship. The hyperactivity of the HPA axis, an increased production of pro-inflammatory cytokines, mitochondrial dysfunctions, and an insufficient neurotrophic support with deficient synaptic plasticity may all contribute to cognitive deficits in MDD (Carvalho et al., 2014; Czarny et al., 2018).

Taking into consideration the paucity and controversy of neuropathological data, (Dean et al., 2010; Shelton et al., 2011; Steiner et al., 2011; Thomas et al., 2000), in vivo positron emission tomography (PET) methods allow at least an indirect assessment of pathophysiological mechanisms linked to neuroinflammation with a special reference to microglial cells. Microglia have a multifaceted role in inflammation, synaptic pruning, and neuronal plasticity. Critically, in addition to canonical stimuli (e.g., infectious agents, trauma, and toxins), these cells also react to psychological stress (Johnson and Kaffman, 2018; Mondelli et al., 2017; Singhal and Baune, 2017). Microglia, together with astrocytes and endothelial cells, express TSPO 18 KDa (translocator protein or peripheral benzodiazepine receptor) in the outer mitochondrial membrane. Increased TSPO binding may reflect heightened cell density, or, in rodent models, pro-inflammatory activation resulting in perturbed oxidative phosphorylation, generation of reactive oxygen species, and abnormal adenosine triphosphate (ATP) production (Alam et al., 2017; Dupont et al., 2017; Gulyas et al., 2012; Liu et al., 2014; Owen et al., 2017).

In a PET study, Setiawan et al. (2015) reported elevated TSPO total distribution volume (TSPO V_T) in various cortical and subcortical regions in MDD, which was especially pronounced in patients with longer disease duration without treatment (Setiawan et al., 2018). In the anterior cingulate cortex, which is implicated in cognitive control and emotion regulation, higher TSPO V_T was linked to more severe depressive symptoms (Setiawan et al., 2015) and suicidal thinking (Holmes et al., 2017). Increased TSPO V_T was normalized during cognitive-behavioral therapy, suggesting that microglial activation or density is a state marker of the illness and may be reduced in parallel with the amelioration of depressive symptoms (Li et al., 2018).

The present study was designed to investigate the relationship between TSPO V_T and cognitive functions in first-episode, non-medicated patients with MDD. Our hypothesis was that higher levels of microglial markers (TSPO V_T) would be linked to worse cognitive performance in multiple domains (immediate/delayed memory and attention) (Lee et al., 2012). Regarding the regional distribution of TSPO V_T and its relationship with cognition, we expected a marked association between neuropsychological performance and microglial markers in the frontal cortex and hippocampus (Arnone et al., 2016).

2. Methods

2.1. Participants

We enrolled 50 drug-naïve patients with MDD and 30 healthy control subjects matched for age, gender, education, body mass index (BMI), and hip-to-waist ratio (Table 1). From this sample, 40 patients and 20 control subjects were included in our previous study (Li et al., 2018). The present paper reports data from a baseline assessment when the patients did not participate in treatment. The study was coordinated at the National Institute of Psychiatry and Addictions, Budapest, Hungary. The procedure of recruitment and clinical assessment were described previously (Li et al., 2018) (Fig. 1.). For clinical and social evaluation, we used the Structured Clinical Interview for DSM-IV Axis I Disorders, Clinician Version (SCID-CV) (First et al., 1996), the Hamilton Rating Scale for Depression (HAM-D) (Hamilton, 1980), and the Hollingshead Four-Factor Index (socioeconomic status) (Hollingshead, 1975). There were three major inclusion criteria: (i) first diagnosis of current major depressive episode and MDD according to DSM-IV, (ii) age above 18 years, (iii) no history of psychopharmacological or psychotherapeutic treatment. The exclusion criteria were as follows: psychotic, manic, or mixed symptoms, family history of bipolar disorder and psychoses, severe suicidality, substance misuse, smoking, non-steroid anti-inflammatory drugs (NSAIDs), and oral contraceptive use (Fig. 1.). We also measured peripheral low-grade inflammation (C-Reactive Protein, CRP), BMI, and waist-to-hip ratio to control the potential effect of obesity on inflammation (Hotamisligil, 2006) (Table 1). The study was done in accordance with the Declaration of Helsinki, approved by the national and institutional ethics boards. All participants gave written informed consent.

Table 1
Characteristics of the participants.

	Major depressive disorder (N = 50)	Control subjects (N = 30)
Gender (male/female)	25/25	15/15
Age (years)	28.7 (9.0)	27.4 (9.0)
Education (years)	11.8 (5.0)	12.1 (5.6)
Hamilton Rating Scale for Depression (HAM-D)	20.6 (5.2)	–
Body mass index	24.5 (6.9)	24.3 (5.4)
Waist-to-hip ratio (central obesity)	0.68 (0.09)	0.67 (0.06)
C-Reactive Protein (CRP) (mg/L)$^+$	1.6 (0.5)	0.9 (0.3)

Data are mean (standard deviation) with the exception of gender ratio. $^+p < 0.01$.

2.2. Brain image acquisition and processing

We used [^{18}F]-FEPPA PET as described previously (Li et al., 2018) (High Resolution Research Tomograph, Siemens Medical Solutions, Knoxville, TN; spatial resolution: 2.5 mm; axial length of the imaging field of view (FOV): 25.2 cm, transaxial FOV: 31.2 cm, duration of scanning: 125 min). We administered [^{18}F]-FEPPA as an intravenous bolus injection (180 MBq, SD = 15; radiochemical purity: > 95%; specific activity: 120 TBq/mmol, SD = 115) (Wilson et al., 2008) and collected arterial blood samples manually and automatically for the kinetic analysis (Rusjan et al., 2011) (PBD-101 Programmable Blood Sampler, Bright Technologies Ltd, Sheffield). A filtered back projection algorithm (Hann filter at Nyquist cutoff frequency) was used for the reconstruction of PET images. To improve image quality and accuracy, we applied attenuation correction (single photon point source, 137Cs, $T_{1/2}$ = 30.2 years, Eg = 662 keV). The total volume of distribution (V_T) was calculated as a measure of radioligand binding by using time activity curves in a two-tissue compartment model (Rusjan et al., 2011).

T1-weighted magnetic resonance imaging (MRI) was also performed (Siemens Trio 3T scanner; 256 × 256 matrix, 176 sagittal slices with a thickness of 1 mm, TR 2530 ms, TI 1100 ms, TE 1.64/3.5/5.36/7.22 ms, bandwidth 651 Hz, non-selective excitation at 7°). We used Statistical Parametric Mapping-5 (SPM5, Wellcome Trust Centre for Neuroimaging, London, UK) for realignment, segmentation, and co-registration with PET images. The FreeSurfer software (version 5.0) was applied to delineate grey matter, white matter, frontal cortex, temporal cortex, and hippocampus (Collste et al., 2016; Schain et al., 2014), which were the regions-of-interest (ROIs) for TSPO V_T analysis. We focused on these ROIs because they were successfully applied in previous TSPO PET studies in MDD, providing reliable information on microglia activation or density (Li et al., 2018; Setiawan et al., 2018; Setiawan et al., 2015).

We genotyped each participant for a single nucleotide polymorphism of the TSPO gene (rs6971 in exon 4, C →T) affecting [^{18}F]-FEPPA binding (Mizrahi et al., 2012). Mixed and low affinity binders (Ala147/Thr147) (n = 5) were excluded from the study.

2.3. Cognitive functions

A trained neuropsychologist administered the Repeatable Battery