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Preliminary data indicating a connection between stress-induced prefrontal dopamine release and hippocampal TSPO expression in the psychosis spectrum

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ABSTRACT

Prolonged stress can cause neuronal loss in the hippocampus resulting in disinhibition of glutamatergic neurons proposed to enhance dopaminergic firing in subcortical regions including striatal areas. Supporting this, imaging studies show increased striatal dopamine release in response to psychosocial stress in healthy individuals with low childhood maternal care, individuals at clinical high risk for psychosis (CHR) and patients with schizophrenia. The prefrontal cortex (PFC) is connected to the hippocampus and a key region to control neurochemical responses to stressful stimuli. We recently reported a disrupted PFC dopamine-stress regulation in schizophrenia, which was intact in CHR. Given the available evidence on the link between psychosocial stress, PFC dopamine release and hippocampal immune activation in psychosis, we explored, for the first time in vivo, whether stress-induced PFC dopamine release is associated with hippocampal TSPO expression (a neuroimmune marker) in the psychosis spectrum. We used an overlapping sample of antipsychotic-naïve subjects with CHR ($n = 6$) and antipsychotic-free schizophrenia patients ($n = 9$) from our previously published studies, measuring PFC dopamine release induced by a psychosocial stress task with [^{11}C]FLB457 positron emission tomography (PET) and TSPO expression with [^{18}F]FEPPA PET. We observed that participants on the psychosis spectrum with lower stress-induced dopamine release in PFC had significantly higher TSPO expression in hippocampus ($\beta = -2.39$, $SE = 0.96$, $F(1,11) = 6.17$, $p = 0.030$). Additionally, we report a positive association between stress-induced PFC dopamine release, controlled for hippocampal TSPO expression, and Global Assessment of Functioning. This is the first exploration of the relationship between PFC dopamine release and hippocampal TSPO expression in vivo in humans.

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1. Introduction

Schizophrenia is a debilitating mental disease with a complex etiology, believed to be caused by a combination of genetic and/or environmental factors such as stress (van Os et al., 2010). The neural diathesis-stress model suggests that the relationship between stress and psychosis is mediated by the hypothalamic-pituitary-adrenal (HPA) axis and hippocampus leading to neurotransmitter imbalance, including alterations in dopamine signalling (Walker and Diforio, 1997). Preclinical studies showed that prolonged stress can lead to neuronal loss in the hippocampus (Sapolsky, 1996) proposed to result in hyperactivity of hippocampal pyramidal neurons, which is believed to underlie, at least partially, schizophrenia psychopathology (Heckers and Konradi, 2015). The increased hippocampal drive is proposed to enhance tonic dopamine firing in striatal areas leading to a hyper-responsive dopamine state, supported by studies using the methyl azoxymethanol acetate (MAM) animal model (Grace, 2016). In humans, positron emission tomography (PET) studies support these preclinical data, showing increased striatal dopamine release in response to psychosocial stress in healthy individuals with low childhood maternal care (Pruessner et al., 2004) and in patients with schizophrenia or those at clinical high risk for psychosis (CHR) (Mizrahi et al., 2012a).

The prefrontal cortex (PFC) is a key brain region for controlling neurochemical responses to emotional stimuli, including stress and anxiety (Rosenkranz et al., 2003), and is directly connected to the hippocampus (Godsil et al., 2013). Dopaminergic function in PFC is suggested to be reduced in schizophrenia (Weinstein et al., 2017)

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supported by preclinical models (Burke et al., 2010; Watt et al., 2009) and a recent PET study reporting significantly blunted dopamine release in dorsolateral PFC (dlPFC) following an amphetamine challenge in first-episode psychosis (FEP) as compared to healthy volunteers (Slifstein et al., 2015). In line with Hernaus et al. (2015), who showed a comparable dopamine release in medial PFC (mPFC) between patients with non-affective psychotic disorder and healthy volunteers, we did not observe any difference in PFC (dlPFC and mPFC) dopamine release in response to an acute psychosocial stress challenge among schizophrenia, CHR and matched healthy volunteers (Schifani et al., 2018).

Neuroinflammation and abnormal immune response are suggested to contribute to the pathogenesis of schizophrenia (Barron et al., 2017; Kirkpatrick and Miller, 2013). Immunological abnormalities might be involved in the aberrant hippocampal function as post-mortem studies reported an increased microglia staining (Busse et al., 2012) and loss in volume (Adriano et al., 2012) in the hippocampus in schizophrenia. Additionally, preclinical studies suggest that maternal immune activation can lead to brain abnormalities in the early development of offspring (Knuesel et al., 2014), which together with adolescent stress exposure can result in elevated immune activation in hippocampus and mesolimbic dopamine hyper-responsivity in adult animals associated with a behavioral phenotype relevant to schizophrenia (Giovanoli et al., 2013). Brain immune activation can be studied in vivo via PET imaging of the 18 kDa translocator protein (TSPO), which is overexpressed in activated glia (Sandiego et al., 2015b). While recent imaging studies, mostly using second-generation TSPO radioligands, failed to detect a significant increase in TSPO expression in schizophrenia or CHR (Bloomfield et al., 2015; Coughlin et al., 2016; Di Biase et al., 2017; Hafizi et al., 2017; Hafizi et al., 2016; Kenk et al., 2015; Van Der Doef et al., 2016), and even show a decrease (Collste et al., 2017; Plaven-Sigray et al., 2018), some have reported positive associations between hippocampal TSPO expression and severity of symptoms, including apathy, state anxiety and cognitive deficits in individuals on the psychosis spectrum (Hafizi et al., 2017; Hafizi et al., 2016). Supporting these neuroimaging data, post-mortem studies have linked increased hippocampal immune activation to schizophrenia subsamples with increased distress including individuals with paranoid schizophrenia (Busse et al., 2012) or those who committed suicide (Steiner et al., 2008; Steiner et al., 2006).

Although previous literature proposed a link between psychosocial stress, PFC dopamine release and neuroinflammation in psychosis (for a review see Mizrahi, 2016), no human in vivo study has directly explored the association between these factors. This preliminary report aims to explore -for the first time- whether PFC stress-induced dopamine release is associated with hippocampal TSPO expression. We measured dopamine response to a validated psychosocial stress challenge in PFC and TSPO expression in hippocampus of participants on the psychosis spectrum including those with CHR and schizophrenia. Based on the neural diathesis-stress model, we proposed a negative association between dopamine release in response to stress and TSPO expression. Additionally, we explored the relationship with global functioning and severity of symptoms with no directional hypothesis in this pilot investigation.

2. Methods

2.1. Participants

Our study included an overlapping sample of subjects with CHR (n = 6) and schizophrenia (n = 9) which were enrolled and scanned in two independent studies, measuring PFC dopamine release in response to a psychosocial stress challenge with [^{11}C]FLB457 PET (2 PET scans per subject) and TSPO expression with [^{18}F]FEPPA PET (1 arterial PET scan per subject), included in 3 previous publications (Hafizi et al., 2017; Hafizi et al., 2016; Schifani et al., 2018). Inclusion and exclusion criteria as well as study and scan parameters/procedures for the dopamine release study and TSPO expression study are described in detail in those articles.

CHR individuals met the diagnostic criteria for prodromal syndrome as per the Criteria of Prodromal Syndromes (COPS) (Miller et al., 2003), had no current Axis I disorder, determined with the Structured Clinical Interview for DSM-IV (SCID) (First et al., 2002), and had no history of or current treatment with antipsychotic medication (antipsychotic-naïve). Schizophrenia patients had a diagnosis of schizophrenia, schizoaffective, delusional, or schizophreniform disorder as determined with the SCID, with no current treatment with antipsychotic medication (antipsychotic-free or -naïve), and no concurrent Axis I disorder. Participants were excluded from the study for current diagnosis of substance abuse/dependence or positive urine drug screen (tested at baseline), pregnancy or currently being breastfeeding, clinically significant medical illness, and the presence of metal implants precluding a magnetic resonance imaging (MRI) scan.

The severity of (attenuated) psychotic symptoms was evaluated with the Structured Interview for Psychosis-risk Syndromes (SIPS) and the Scale of Psychosis-risk Symptoms (SOPS) (Miller et al., 2003) (CHR group) or the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) (schizophrenia group) and functioning was quantified with the Global Assessment of Functioning scale (GAF) which rates the level of functioning based on overall psychological, social, and occupational functioning (Endicott et al., 1976).

Both studies were approved by the Research Ethics Board at the Centre for Addiction and Mental Health and were conducted in accordance with the Declaration of Helsinki. All subjects signed written informed consent after study procedures were fully explained.

2.2. Montreal Imaging Stress Task

Psychosocial stress was induced with the validated Montreal Imaging Stress Task paradigm (Pruessner et al., 2004), used in numerous PET and functional MRI studies (Lederbogen et al., 2011; Mizrahi et al., 2012a; Pruessner et al., 2004; Schifani et al., 2018) and described in detail before (Schifani et al., 2018). In brief, all participants were scanned twice on separate days while performing either a Sensory Motor Control Task (referred to as “control”, always done first) or the Montreal Imaging Stress Task (referred to as “stress”). Following the PET scan sessions, participants' subjective perception of stress was evaluated using an abridged version of the State Anxiety Questionnaire (SAQ) (Spielberger et al., 1977).

2.3. Image acquisition and reconstruction

Each participant underwent MRI to obtain a structural image (proton density-weighted, PD), necessary for delineation of individual regions of interest (ROIs) and co-registration with the PET image. For details see (Hafizi et al., 2017; Hafizi et al., 2016; Schifani et al., 2018). PET images were obtained using either a 90 minute acquisition for [^{11}C]FLB457 (two scans per person) or a 125 minute acquisition for [^{18}F]FEPPA (one scan per person) following intravenous bolus injection of ~9–11 mCi [^{11}C]FLB457 or ~4.5–5.5 mCi [^{18}F]FEPPA using a high-resolution PET-CT scanner Siemens-Biograph HiRez XVI or a high-resolution research tomograph scanner (Siemens Molecular Imaging, Knoxville, TN, USA), respectively. For [^{18}F]FEPPA scans, arterial blood samples were collected to determine radioactivity in blood and plasma, and the relative proportion of radiolabeled metabolites. The dispersion and metabolite-corrected plasma input function was generated as described before (Rusjan et al., 2011). No blood sampling was performed for [^{11}C]FLB457 scans. Further details on image acquisition and reconstruction were reported before (Hafizi et al., 2017; Hafizi et al., 2016; Schifani et al., 2018).

2.4. PET data analyses

Time-activity curves (TACs) were extracted for the PFC and hippocampus using both hemispheres (for [^{11}C]FLB457 and [^{18}F]FEPPA scans, respectively) as well as cerebellar cortex (for [^{11}C]FLB457 scans) using a validated in-house imaging pipeline (the ROMI software). All ROIs were delineated using the individual PD images and transferred to the PET images (Rusjan et al., 2006). Binding estimates per tracer were assessed as follows using our in-house software fMOD:

2.4.1. [^{11}C]FLB457

An estimate of binding potential (BP_{ND}) of [^{11}C]FLB457 in the ROIs was calculated using the Simplified Reference Tissue Model (SRTM) in which BP_{ND} is proportional to the parameters receptor number (B_{max}) and affinity (K_d) [$BP_{ND} \propto B_{max}/K_d$] (Lammertsma and Hume, 1996). Instead of an arterial input function, this model uses a within-brain reference region (cerebellar cortex excluding vermis). It is a validated method and commonly used to quantify [^{11}C]FLB457 kinetics (Ito et al., 2001; Narendran et al., 2009; Olsson et al., 1999). Few studies discussed small amounts of specific binding of [^{11}C]FLB457 in cerebellum (Narendran et al., 2011; Vandehey et al., 2010), however, no alterations in cerebellar distribution volume were apparent when participants were challenged with amphetamine and methylphenidate (Montgomery et al., 2007; Narendran et al., 2009). Several previous [^{11}C]FLB457 studies have successfully estimated BP_{ND} using the SRTM and cerebellum as reference region (MacDonald et al., 2009; Mizrahi et al., 2007; Schifani et al., 2018) and moreover, a recent study verified SRTM to be a valid modeling approach to estimate the percentage change in [^{11}C]FLB457 BP_{ND} ($\Delta BP_{ND} = 1 - BP_{ND}^{Stress}/BP_{ND}^{Control}$) (Sandiego et al., 2015a). Both hemispheres per ROI were combined to create a single TAC for BP_{ND} calculation. The same correction for injected mass was applied as reported in detail in our previous publication (Schifani et al., 2018). The corrected change in BP_{ND} was calculated based on (Gallezot et al., 2017):

$$\Delta BP_{ND}^{c} = \frac{\Delta BP_{ND}\left(1 + \left(\mu^{Stress}/ED_{50}\right)\right) + \left(\left(\mu^{Control} - \mu^{Stress}\right)/ED_{50}\right)}{1 + \Delta BP_{ND}\left(\mu^{Stress}/ED_{50}\right) + \left(\left(\mu^{Control} - \mu^{Stress}\right)/ED_{50}\right)}.$$

μ and ED_{50} equal the ratio mass of injected radioligand to body weight or the mass injected which would reduce $BP_{ND}^{Control}$ by 50%, respectively (Schifani et al., 2018).

2.4.2. [^{18}F]FEPPA

The total volume of distribution (V_T) for hippocampus was calculated with the two-tissue compartment model and arterial plasma input function, as previously validated for [^{18}F]FEPPA (Rusjan et al., 2011).

Participants were genotyped for the TSPO rs6971 polymorphism and based on that categorized as high-affinity (C/C), mixed-affinity (C/T), and low-affinity (T/T) binders (Mizrahi et al., 2012b; Owen et al., 2012). Details about genotyping procedures are provided elsewhere (Hafizi et al., 2017; Hafizi et al., 2016).

2.5. Statistical analysis

All statistical analyses were performed using SPSS version 22.0 (IBM, Armonk, NY, USA).

To test the association between stress-induced PFC dopamine release ([^{11}C]FLB457 ΔBP_{ND}) and hippocampal TSPO expression ([^{18}F]FEPPA V_T) a general linear model (GLM) with [^{11}C]FLB457 ΔBP_{ND} in PFC as the dependent variable and [^{18}F]FEPPA V_T in hippocampus as the independent variable was used, while controlling for the effects of clinical group and TSPO genotype.

We also explored the associations between the residuals of the GLM (i.e. after partialling out TSPO binding, genotype and group) and 1) clinical status quantified as severity of symptoms (including SOPS total score and 4 subscores as well as PANSS total score and 3 subscores) and 2) global functioning using bivariate correlations.

Differences in demographics between groups were assessed using Student *t*-tests (continuous variables) or Pearson's chi-squared tests (categorical variables). Differences in SAQ scores for each task were analyzed using a two-way ANOVA with repeated measures with study group as a between-subject factor, followed by post hoc ANOVAs using Bonferroni correction for multiple comparisons.

All analyses were two tailed with the conventional $\alpha = 0.05$. We considered results to be significant at $p \leq 0.05$ and at trend level at $p \leq 0.1$.

3. Results

Our analysis comprised a sample of 6 antipsychotic-naïve CHRs and 9 antipsychotic-free patients with schizophrenia (45 PET scans in total). Details about demographics, clinical characteristics and PET parameters are visualized in Table 1. There was a trend for a difference between groups in sex ($p = 0.057$) and a significant difference in age, with schizophrenia patients being older than CHR participants ($p = 0.045$). The average time since psychosis onset in the schizophrenia group was 43.44 ± 52.19 (mean ± SD) months, with six patients being below 60 months and three above.

[^{11}C]FLB457 scans (control vs stress) were performed 8.67 ± 6.88 (mean ± SD) days apart. All participants completed both tasks during the [^{11}C]FLB457 scans successfully. The [^{11}C]FLB457 and [^{18}F]FEPPA scans were performed 63.93 ± 93.74 (mean ± SD) days apart (first [^{11}C]FLB457 scan vs [^{18}F]FEPPA scan). There was no significant difference among groups in any of the PET scan parameters.

As expected, SAQ total score (positive items reversed scored) was significantly elevated following the stress task in comparison to the control task (effect of task: $F(1,13) = 38.90$, $p < 0.0001$, Bonferroni-corrected $p < 0.05$ for each group), suggesting that the stress paradigm was effective (Schifani et al., 2018).

For our primary analysis, we observed a significant negative association between [^{11}C]FLB457 ΔBP_{ND} in PFC and [^{18}F]FEPPA V_T in hippocampus (controlled for TSPO genotype) (Fig. 1; $\beta = -2.39$, $SE = 0.96$, $F(1,11) = 6.17$, $p = 0.030$) suggesting that participants on the psychosis spectrum with lower stress-induced PFC dopamine release had higher hippocampal TSPO expression.

For our exploratory analyses, we observed a positive association between residuals of the GLM and GAF score (Fig. 2; $r = 0.60$, $p = 0.018$) suggesting that participants on the psychosis spectrum with lower stress-induced PFC dopamine release, controlling for hippocampal TSPO expression, had lower global functioning. This association was absent when stress-induced PFC dopamine release was not controlled for hippocampal TSPO expression ($r = 0.44$, $p = 0.10$). There were no associations between residuals of the GLM and symptom severity including SOPS and PANSS total and subscores ($p > 0.05$).

4. Discussion

Our preliminary results suggest a negative association between PFC dopamine release in response to an acute psychosocial stress challenge and hippocampal TSPO expression in the psychosis spectrum, including patients with schizophrenia and individuals at CHR. To the best of our knowledge, this is the first in vivo study exploring this association.

Lower dopamine release in PFC regions (significant in dlPFC only) in FEP compared to healthy volunteers was shown in a previous study in response to an amphetamine challenge using [^{11}C]FLB457 (Slifstein et al., 2015). In contrast, using a psychosocial stress challenge and [^{18}F]fallypride PET, Hernaus et al. (2015) did not observe a significant difference in mPFC dopamine release between patients with non-affective psychotic disorder and healthy volunteers,

Table 1
Participants' demographics, clinical characteristics and PET scan parameters.

	CHR (N = 6)	Schizophrenia (N = 9)	Statistics
Demographics			
Gender (male/female)	1/5	6/3	$\chi^2 = 3.62$, p = 0.057
Age (years (SD))	21 (2.76)	27 (6.14)	t = 2.22, df = 13, p = 0.045[a]
Genotype (HAB/MAB)	5/1	7/2	$\chi^2 = 0.069$, p = 0.79
Clinical characteristics			
Age of onset (years (SD))	–	23.00 (6.46)	–
Duration of illness (month (SD))	–	43.44 (52.19)	–
SOPS (mean (SD))			
Positive	11.33 (3.20)	–	–
Negative	11.17 (7.14)	–	–
Disorganized	4.00 (2.28)	–	–
General	9.67 (1.75)	–	–
Total	36.17 (10.70)	–	–
PANSS (mean (SD))			
Positive	–	16.78 (3.07)	–
Negative	–	13.78 (6.70)	–
General	–	34.78 (8.33)	–
Total	–	64.78 (14.45)	–
GAF (mean (SD))	55.67 (3.98)	53.67 (5.27)	t = 0.79, df = 13, p = 0.45
Antipsychotic free/naïve	0/6	3/6[b]	–
Current medication			
Antidepressants	1	1	–
Low dose antipsychotics	0	1[c]	–
PET parameters ([^{11}C]FLB457)			
Amount injected (mCi (SD))			
Control task	10.11 (0.65)	10.13 (0.50)	t = −0.094, df = 13, p = 0.59
Stress task	10.10 (0.54)	10.17 (0.84)	t = −0.17, df = 13, p = 0.72
Specific activity (mCi/μmol (SD))			
Control task	3737.89 (1586.04)	2358.52 (706.56)	t = 2.32, df = 13, p = 0.22
Stress task	3264.08 (1722.15)	2857.69 (1291.90)	t = 0.52, df = 13, p = 0.53
Mass injected (μg (SD))			
Control task	1.11 (0.34)	1.72 (0.50)	t = −2.60, df = 13, p = 0.25
Stress task	1.37 (0.55)	1.54 (0.63)	t = −0.54, df = 13, p = 0.75
PET parameters ([^{18}F]FEPPA)			
Amount injected (mCi (SD))	5.03 (0.26)	5.15 (0.30)	t = −0.83, df = 13, p = 0.42
Specific activity (mCi/μmol (SD))	3053.65 (2324.03)	3926.85 (3708.95)	t = −0.51, df = 13, p = 0.62
Mass injected (μg (SD))	1.04 (0.77)	0.76 (0.37)	t = −0.96, df = 13, p = 0.36

Abbreviations: CHR, clinical high risk for psychosis; GAF, Global assessment of functioning; HAB, high-affinity binder; MAB, mixed-affinity binder; PANSS, Positive and Negative Syndrome Scale; PET, positron emission tomography; SD, standard deviation; SOPS, Scale of Psychosis-risk Symptoms.
[a] Significant difference between groups ($p \leq 0.05$).
[b] Recruited before commencing antipsychotic medications or following their refusal, no patient was washed out of their antipsychotic medications in this study.
[c] Quetiapine (100 mg) taken only after the PET scan session.

similar to our study where we reported no significant differences in stress-induced dopamine release either in dlPFC or mPFC between antipsychotic-free schizophrenia patients and matched healthy volunteers using [^{11}C]FLB457 (Schifani et al., 2018). Those three studies were conducted under different conditions including varying challenges (amphetamine vs psychosocial stress), tracers ([^{18}F]fallypride vs [^{11}C]FLB457), and clinical populations, which could have

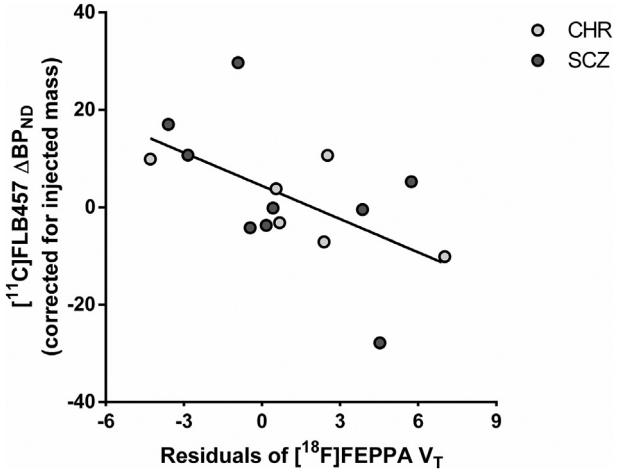

Fig. 1. Association between stress-induced dopamine release ([^{11}C]FLB457 ΔBP_{ND}) in PFC and TSPO expression (residuals of the linear regression of [^{18}F]FEPPA V_T on TSPO genotype) in hippocampus in subjects on the psychosis spectrum. The line represents the best linear model fit of the data of the whole sample. Pearson correlation was significant (r = −0.57, p = 0.026). CHR, clinical high risk for psychosis; SCZ, schizophrenia.

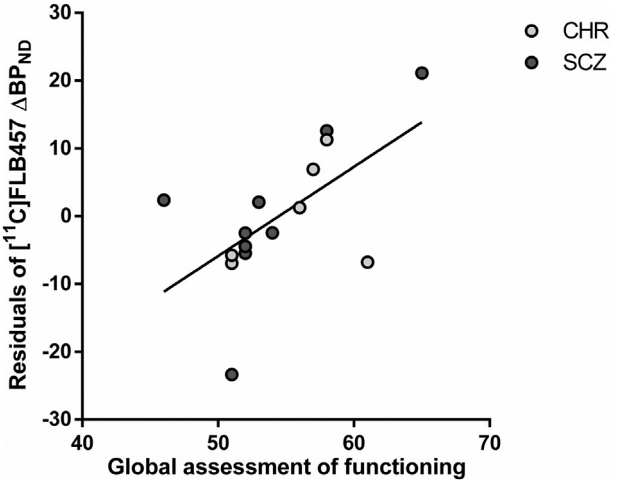

Fig. 2. Association between the residuals of the general linear model (residuals of [^{11}C]FLB457 ΔBP_{ND} in PFC controlled for [^{18}F]FEPPA V_T in hippocampus, TSPO genotype and clinical group) and global assessment of functioning (GAF) in subjects on the psychosis spectrum. The line represents the best linear model fit of the data of the whole sample. Pearson correlation was significant (r = 0.60, p = 0.018). CHR, clinical high risk for psychosis; SCZ, schizophrenia.

explained the varying results (recently reviewed by Schifani et al., 2017). As part of the same study, we observed no difference in dopamine release in PFC (dlPFC and mPFC) between CHR and healthy volunteers (Schifani et al., 2018), supported by another study reporting comparable dopamine release in the ventromedial PFC in response to a similar psychosocial stress challenge in first degree relatives of individuals with a psychotic disorder and matched controls using [^{18}F]fallypride PET (Lataster et al., 2014).

Early PET studies, using the first-generation TSPO PET tracer [^{11}C]PK11195, reported increased TSPO expression in total gray matter or hippocampus in patients with schizophrenia (Doorduin et al., 2009; Van Berckel et al., 2008). However, most of the recent studies, using second-generation TSPO radioligands (including [^{11}C]PBR28, [^{11}C]DPA-713 and [^{18}F]FEPPA), observed no significant alterations in hippocampal TSPO expression in CHR (Hafizi et al., 2017), FEP (Coughlin et al., 2016; Hafizi et al., 2016) or chronic schizophrenia (Kenk et al., 2015) with one study and a recent meta-analysis reporting a significant decrease (Collste et al., 2017; Plaven-Sigray et al., 2018) as compared to healthy volunteers. Interestingly, post-mortem studies linked an increased hippocampal immune activation in schizophrenia to subsamples with increased distress including individuals with paranoid schizophrenia (Busse et al., 2012) or those who committed suicide (Steiner et al., 2008; Steiner et al., 2006).

Previous studies have reported an aberrant functional coupling between hippocampus and mPFC during rest (in the default mode network) (Zhou et al., 2008) and working memory (Meyer-Lindenberg et al., 2005; Wolf et al., 2009) in schizophrenia. Furthermore, schizophrenia patients seem to exhibit an abnormal activation in both hippocampus and mPFC associated with the severity of paranoid symptoms (Goghari et al., 2010). Interestingly, aberrant functional coupling between hippocampus and PFC was already reported in patients with FEP and those at CHR (Benetti et al., 2009) suggesting that this might indicate a vulnerability to the disease (trait marker) rather than chronicity of the illness (state marker) (Godsil et al., 2013). Additionally, patients with schizophrenia display deficits in emotional regulation (Holt et al., 2009) that may depend on the integration between hippocampus and mPFC (Kalisch et al., 2006; Milad et al., 2007).

Hippocampus and mPFC exert regulatory control over the stress pathways and are themselves influenced by stress (Franklin et al., 2012). For instance, chronic stress is associated with loss in dendritic material in mPFC (Holmes and Wellman, 2009) and hippocampus (McEwen et al., 2016). A recent study by Gomes and Grace (2016) suggests that early deficiency of the mPFC might underlie the stress vulnerability following early life adversity. They reported that early (postnatal day (PND) 25) mPFC lesion via bilateral infusion of ibotenic acid combined with mid-to-late adolescent (PND 31–40) repeated stress resulted in a mesolimbic dopamine hyper-responsivity in adult rats (including increased locomotor response to amphetamine and ventral tegmental area (VTA) dopamine population activity) similar to what is reported in schizophrenia, whereas the adolescent stressor alone did not induce any of these alterations (Gomes and Grace, 2016). The mPFC is believed to exert its stress-regulatory role via inhibition of the amygdala (Hariri et al., 2003; Rosenkranz and Grace, 2002; Rosenkranz et al., 2003) and amygdala activation is associated with a loss of inhibitory parvalbumin-expressing interneurons in the hippocampus (Berretta et al., 2004). Loss of parvalbumin interneurons is related to hippocampal hyperactivity which is suggested to underlie the mesolimbic hyper-responsive dopamine state of schizophrenia (Heckers and Konradi, 2015; Lodge et al., 2009). Mid-to-late adolescence is a critical period for PFC and hippocampus development and the maturation of inhibitory circuitry (Caballero et al., 2013; Caballero et al., 2014) which is sensitive to stress (Czeh et al., 2005; Holland et al., 2014; Zaletel et al., 2016). Therefore, heightened stress sensitivity following mPFC dysfunction and disruption in the regulation of amygdala reactivity to stress during adolescence might lead to hippocampal dysfunction followed by mesolimbic dopamine system hyper-responsivity (Grace, 2016). Furthermore, a recent study assessing the effects of early developmental stress linked decreased parvalbumin-expression to immune activation (Lukkes et al., 2017).

Our present data suggests, that not all individuals on the psychosis spectrum have a disrupted phenotype of decreased stress-induced PFC dopamine release and increased hippocampal TSPO expression but rather a subset of them. This suggestion would be in line with our preceding publications, where we observed that higher distress and anxiety were associated with lower PFC dopamine release and cortisol response (Schifani et al., 2018) and higher hippocampal TSPO expression (Hafizi et al., 2017) in CHR.

Since our overlapping sample of participants did not comprise any healthy volunteers, we can only make assumptions about the relationship between stress-induced PFC dopamine release and hippocampal TSPO expression in this group.

Additionally, we observed a positive association between residuals of the GLM and GAF score suggesting that participants on the psychosis spectrum with lower stress-induced PFC dopamine release, controlled for hippocampal TSPO expression, had lower global functioning. Consistent with this observation, various studies reported that lower neuronal activity (or rather hemodynamic response) in PFC areas in response to a cognitive task, measured with near-infrared spectroscopy, was associated with lower global functioning scores in chronic schizophrenia (Kinou et al., 2013; Koike et al., 2011; Takeshi et al., 2010; Takizawa et al., 2008).

4.1. Strength and limitations

This is the first human in vivo study investigating the relationship between PFC dopamine release in response to a validated stress challenge and hippocampal TSPO expression in the same cohort.

The current study has the following limitations. First, our sample is fairly small ($n = 15$, with $n = 6$ CHR and $n = 9$ schizophrenia, comprising a total of 45 PET scans, 3 per participant). Although we believe this is sufficient for this initial exploration, these results do not imply causation for the explored associations and need to be replicated in an adequately powered sample to definitely test these associations; barring the methodological complexities of scanning antipsychotic-free/naïve patients on three occasions, including arterial blood sampling. Furthermore, as the associations with functioning and symptom severity were exploratory, we did not apply Bonferroni's p-value correction for the number of associations with scales (GAF, SOPS, PANSS) or subscales (subscales of SOPS and PANSS), which would not have survived in this small sample. Second, while PET scans for [^{11}C]FLB457 and [^{18}F]FEPPA were acquired on separate days (63.93 ± 93.74 (mean ± SD) days apart), we do not believe that this affected our findings as both [^{11}C]FLB457 (Narendran et al., 2013; Sudo et al., 2001) and [^{18}F]FEPPA (Park et al., 2015; Rusjan et al., 2011) have satisfactory test-retest reliability. Third, our psychosis spectrum group included a CHR sample, which is inherently a heterogeneous group (exhibiting a conversion to psychosis rate of about 26% over a mean follow-up period of 2.35 years) (Fusar-Poli et al., 2013), and patients with schizophrenia. Acknowledging the limitations of merging both groups, we believe that it harnesses the variability in the psychosis spectrum to investigate the tested relationship. Nonetheless we want to highlight the preliminary nature of the present findings, but also its remarkable support from preclinical models (Burke et al., 2010; Giovanoli et al., 2013; Watt et al., 2009). Fourth, we acknowledge that including a control group would have been beneficial to compare their relationship between stress-induced PFC dopamine release and hippocampal TSPO expression to our individuals on the psychosis spectrum. Unfortunately, the sample of healthy volunteers was not overlapping with the present studies. Finally, limitations of [^{11}C]FLB457 and [^{18}F]FEPPA PET imaging were discussed elsewhere (Hafizi et al., 2017; Hafizi et al., 2016; Schifani et al., 2018).

4.2. Conclusion

This is the first study observing a negative association between stress-induced PFC dopamine release and hippocampal TSPO expression in a sample comprising participants with schizophrenia and CHR. These results give preliminary indication for the interplay between these two molecular systems -prefrontocortical dopamine and immune activation in the hippocampus- in psychosis.

Contributors

Author RM designed the study. Authors CS, SH, MK, HT and CG managed the literature searches and analyses. Author CS undertook the statistical analysis and wrote the first draft of the manuscript, together with SH and RM. All authors contributed to and have approved the final manuscript.

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Conflict of interest

All other authors declare that they have no conflicts of interest.

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