European Neuropsychopharmacology (2019) 29, 1023–1032

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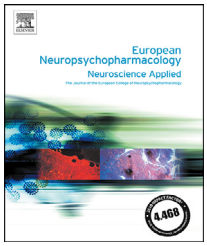

Prefrontal cortical dopamine release in clinical high risk for psychosis during a cognitive task: a [^{11}C]FLB457 positron emission tomography study

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Received 19 December 2018; received in revised form 1 May 2019; accepted 10 June 2019

KEYWORDS
Schizophrenia;
Prodromal;
Cognition;
WCST;
Imaging

Abstract
Research suggests decreased cortical dopamine is a neural correlate of cognitive deficits in schizophrenia. Evidence of impaired cognitive task-induced cortical dopamine release was demonstrated in patients with psychosis. However, whether cortical dopamine release in response to a cognitive task in clinical high risk for psychosis (CHR) is also impaired, is currently unknown. We aimed to test dopamine release in the dorsolateral prefrontal cortex (DLPFC) and the anterior cingulate cortex (ACC) in antipsychotic-free CHR participants and healthy controls

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https://doi.org/10.1016/j.euroneuro.2019.06.004

(HC) performing the Wisconsin Card Sorting Task (WCST). Two [^{11}C]FLB457 PET scans were conducted for 13 CHR and 15 HC while performing the WCST and the sensorimotor control task (SMCT), respectively. A magnetic resonance image was acquired for anatomical delineation. Percentage change in binding potential (ΔBP_{ND}) in ACC and DLPFC in WCST were compared with the SMCT between CHR and HC. Mixed model analysis revealed no statistically significant differences in the cognitive task induced ΔBP_{ND} in any ROIs. There were no main effect of group ($F(1, 26) = 0.348$; $p = 0.560$) or ROI ($F(1, 26) = 1.080$; $p = 0.308$) and no significant Group x ROI interaction ($F(1, 26) = 0.049$; $p = 0.826$). Our findings suggest no statistically significant difference between CHR and HC in cognitive task-induced cortical dopamine release. This is the first in vivo study to illustrate that the cortical hypodopaminergic state observed in schizophrenia may not be present in its putative high-risk state.

1. Introduction

Schizophrenia is a debilitating disorder affecting ~1% of the population and consists of positive and negative symptoms and cognitive deficits (McGlashan and Fenton, 1992). Cognitive impairments are a core feature of the disease, precede illness onset (Addington and Addington, 1999), persist throughout the course of the disease, and predict functional outcome (Green, 2006; Green and Harvey, 2014; Greenwood et al., 2005). The prefrontal cortex (PFC) and its subregions are a highly-connected network (Miller and Cohen, 2001; Ongur and Price, 2000), and involved in the regulation of executive functioning in response to changing environmental demands (Baddeley, 1986; Goldman-Rakic, 1995). Succinctly, the dorsolateral PFC (DLPFC) is strongly involved in working memory function, planning and inhibition, the anterior cingulate cortex (ACC) is involved in awareness and attention (Baddeley, 1986).

Dopamine is unequivocally implicated in reward, stress and cognitive processes (Egerton et al., 2009; Mizrahi, 2015). Schizophrenia is characterized by a striatal hyperdopaminergic state and cortical hypodopaminergic state, the former being more heavily studied in schizophrenia research. Various lines of evidence, including preclinical (Arnsten et al., 1994; Sawaguchi and Goldman-Rakic, 1991) and clinical (Carter et al., 2001; Laurens et al., 2003; MacDonald et al., 2005) studies, suggest decreased cortical (dopamine) activity to be related to the cognitive deficits observed in schizophrenia (Rao et al., 2018). However, direct evidence of a PFC hypodopaminergic hypothesis in living humans, particularly in young individuals, is still limited. To date, there are four Positron Emission Tomography (PET) imaging studies that have explored cortical dopamine release in schizophrenia. While two studies reported no differences in stress-induced dopamine release in medial and dorsolateral PFC between healthy controls (HC) and patients experiencing psychosis (Hernaus et al., 2015; Schifani et al., 2018), Slifstein et al. (2015) used an amphetamine challenge paradigm and reported a blunted cortical dopamine release in first-episode psychosis as compared to HC, which was significantly different in the DLPFC only. Furthermore, decreased dopamine release was associated with decreased working memory-related activation of the DLPFC in the first-episode psychosis population. Consistent with this study, Rao et al. (2018) has recently reported a reduction in PFC dopamine release in response to a cognitive challenge, supporting the cortical hypodopaminergic hypothesis in schizophrenia.

Cognitive deficits are present before illness onset (Cotter et al., 2014; Fusar-Poli et al., 2013; Lee et al., 2015) and knowledge about alterations in dopamine signaling during this critical period preceding the diagnosis of schizophrenia, is still very limited. Such knowledge is highly relevant for the development of biomarkers for disease progression. To date, only one study explored cortical dopamine response to a psychosocial stress task in individuals in prodromal psychosis (CHR) as compared to HC and found no differences between groups (Schifani et al., 2018). However, no PET imaging data is available on dopamine release in cortical brain regions in response to a cognitive task in CHR. Based on our previous study showing blunted cortical dopamine release in the ACC and DLPFC in response to a cognitive task in schizophrenia (Rao et al., 2018), this study aimed to examine cognitive task-induced cortical dopamine release in CHR individuals using the same Wisconsin Card Sorting Task (WCST) (Berg, 1948). We hypothesize a decrease in cognitive task-induced dopamine release in the main regions of interest (ROI): DLPFC and ACC in CHR, as compared to HC. Further, we explored differences in [^{11}C]FLB457 binding (BP_{ND}) across groups and sessions in main ROIs and exploratory ROIs: medial prefrontal cortex (MPFC) and orbitofrontal cortex (OFC). Lastly, we also explored the relationship between cognitive task-induced cortical dopamine release and symptomatology and cognitive performance.

2. Experimental procedures

2.1. Participants

Twenty-nine participants (58 scans) were included in this study, comprising fourteen CHR participants recruited from the Focus on Youth Psychosis Prevention (FYPP) clinic at the Center for Addiction and Mental Health (CAMH), and 15 matched HC data from a previous publication (Rao et al., 2018). One CHR participant was excluded from the analysis as they did not complete the cognitive task while in the scanner. CHR participants were between the ages of 18 and 33 years old, mean age was 22.92 ± 4.25. All were free of substance use corroborated by clean urine drug screens, and all were antipsychotic free, while 5 of them were also antipsychotic naïve. All CHR met Attenuated Prodromal Syndrome Criteria as per diagnostic Criteria of Prodromal Syndromes (Miller et al., 2003), with no concurrent disorder in the axis I spectrum as determined with the

Structured Clinical Interview for DSM-IV (SCID) (First et al., 2002) and no history (or current) treatment with antipsychotic medication for at least 21 days prior to study participation. HC participants were between the ages of 18 and 34 years old, mean age was 25.13 ± 4.93. HC did not meet criteria for any prodromal syndrome and had no history of psychiatric illness as determined by the SCID or psychoactive drug use, and had no first-degree relatives with a major mental disorder. Exclusion criteria for all participants were as follows: claustrophobia, currently breast feeding or pregnant, positive urine drug screen or current diagnosis of substance dependence/abuse, a clinically significant physical illness, any metal implants on or in the body precluding a magnetic resonance imaging (MRI) scan.

2.2. Assessments

Clinical status and severity of psychosis-risk symptoms of CHR participants was noted using the SIPS (McGlashan, 2001; Miller et al., 1999, 2003) by trained research staff and overseen by attending psychiatrist (RM) at CAMH before study participation. All participants were administered the Global Assessment of Functioning (GAF) scale to assess level of functioning based on overall psychological, social and occupational functioning (Endicott et al., 1976) and the Clinical Global Impression scale (CGI), a standardized clinician-rated evaluation to assess current illness state (Guy, 1976). All participants underwent neuropsychological assessment using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (Randolph et al., 1998). The study was approved by the Research Ethics Board at (CAMH) in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants after being informed of all study procedures.

2.3. Wisconsin card sorting task and sensory motor control task

All participants performed the Wisconsin Card Sorting Task (WCST) during the PET scan (Berg, 1948), which is well validated by prior functional magnetic resonance imaging and PET studies (Ko et al., 2009; Monchi et al., 2006a, 2006b) and described in detail elsewhere (Rao et al., 2018).

2.4. PET image acquisition

PET scans were performed using a high-resolution PET-CT, Siemens-Biograph HiRez XVI (Siemens Molecular Imaging, Knoxville, TN, U.S.A.), to measure radioactivity in 81 brain sections with a thickness of 2.0 mm each. A thermoplastic mask was made for each participant and used in conjunction with a head fixation system during PET measurements to reduce head movement. PET data were obtained for 90 min following an intravenous bolus injection of [^{11}C]FLB457. The images were reconstructed using 2D filter back projection algorithms with a ramp filter at Nyquist cut-off frequency.

2.5. MRI acquisition

All participants underwent an MRI session using a Discovery MR750 3T MRI (General Electric, Milwaukee, WI, USA) scanner to obtain a proton density-weighted image with the following parameters (imaging mode - 3D; sagittal plane; FSPGR sequence; 8 channel head coil; TR=6.7 s; TE=3 s; Flip angle - 8; frequency - 256; slice thickness - 0.9 mm). These MR images were used for delineation of individual ROI after co-registering with the PET image.

2.6. PET data analysis

Percent change in [^{11}C]FLB457 binding was used to quantify dopamine release in response to the cognitive task. [^{11}C]FLB457 is a high-affinity radiotracer and a validated tool to quantify cortical dopamine release (Narendran et al., 2011b). It is reported to have ≤15% test-retest variability (Narendran et al., 2011b) and is preferable to other cortical D2 receptor radioligands such as [^{11}C]fallypride as it displays a higher signal-to-noise ratio in cortical areas (Narendran et al., 2009). PET data analysis was carried out using our validated in-house software ROMI (Rusjan et al., 2006), as previously described (Rao et al., 2018; Schifani et al., 2018).

The Simplified Reference Tissue Model (SRTM) was applied to obtain a quantitative binding estimate from each Time Activity Curve (TAC) (Lammertsma and Hume, 1996) using the in-house software fMOD. Instead of an arterial input function, the SRTM uses a within-brain reference region, cerebellar cortex (without vermis) in this case. SRTM provides an approximation of the radiotracer binding potential (BP_{ND}), which is proportionate to the more fundamental parameters of receptor number (B_{max}) and affinity (K_d) [$BP_{ND} \approx B_{max}/K_d$]. This is a validated method and is frequently used with [^{11}C]FLB457 (Ito et al., 2001; Narendran et al., 2009; Olsson et al., 1999). A small number of studies suggest minor specific binding in cerebellum with [^{11}C]FLB457 (Narendran et al., 2011b; Vandehey et al., 2010), with no changes in cerebellar distribution volume observed following amphetamine and methylphenidate challenges (Montgomery et al., 2007; Narendran et al., 2009), (Sandiego et al., 2015), and previous studies using the [^{11}C]FLB457 radiotracer have effectively used SRTM with cerebellum as the reference region (Ko et al., 2009; MacDonald et al., 2009; Mizrahi et al., 2007).

The right and left anatomical regions were averaged together and used to derive radiotracer BP_{ND} in each ROI. However, as there are challenges with quantifying [^{11}C]FLB457, partially due to potential mass effects, a novel correction was applied in this study, as described elsewhere (Schifani et al., 2018). The correction accounts for competition between radioligand and dopamine in the WCST session while assuming negligible levels of occupied receptors in the SMCT session. These assumptions are supported experimentally as variations in cortical [^{11}C]FLB457 binding has not been observed in a dopamine depletion study (Frankle et al., 2010) while ~1000% increase of dopamine has been measured with microdialysis following 0.3 mg/kg amphetamine in non-human primates (Narendran et al., 2014). The corrected change in cortical [^{11}C]FLB457 BP_{ND} was calculated as follows (Gallezot et al., 2017):

$$\Delta BP_{ND}^{C} = \frac{BP_{ND}\left(1 + \left(\frac{\mu^{WCST}}{ED_{50}}\right)\right) + \left(\frac{(\mu^{SMCT} - \mu^{WCST})}{ED_{50}}\right)}{1 + \Delta BP_{ND}\left(\frac{\mu^{WCST}}{ED_{50}}\right) + \left(\frac{(\mu^{SMCT} - \mu^{WCST})}{ED_{50}}\right)}$$

where μ is the ratio mass of radioligand injected to body weight and ED_{50} is the mass injected that would reduce $BP_{ND}^{Control}$ by 50%. The ED_{50} was estimated as described elsewhere (Schifani et al., 2018).

2.7. Statistical analysis

Statistical analyses were completed using SPSS, (version 24.0; IBM Corporation, Armonk, NY, USA). Groups differences in demographics, GAF and scan parameters, cognitive task performance and SMCT [^{11}C]FLB457 binding (BP_{ND}) in each individual ROI were calculated using independent t-tests (continuous variables) or Pear-

Table 1 Participant's demographics, clinical characteristics and ragioligand injection parameters.

			HC ($n=15$)	CHR ($n=13$)	Results	P
	Age		25.13 ± 4.93	22.92 ± 4.25	$t=1.26$	0.22
Gender	Male		8	9	$X^2=0.738$	0.39
	Female		7	4		
Smoking Status	Smoker		3	3	$X^2=0.039$	0.84
	Non-Smoker		12	10		
Antipsychotic Free				8		
Antipsychotic Naïve				5		
Drug Free Duration (months)				8.25 ± 7.26		
Chlorpromazine Equivalent Dose (mg)				11.23 ± 7.78		
Total Years of Education			15.20 ± 2.15	14.58 ± 1.68	$t=0.85$	0.41
Clinical	SOPS Positive			11.00 ± 4.71		
Measures	SOPS Negative			11.92 ± 5.36		
	SOPS Disorganized			5.00 ± 2.12		
	SOPS General			7.00 ± 3.98		
	SOPS Total			34.92 ± 10.41		
GAF			84.50 ± 4.95	51.82 ± 6.95	$t=6.26$	
						0.000*
PET Measures	Amount Injected (MBq)	SMCT	370 ± 28.51	367.30 ± 23.44	$t=0.27$	0.79
([^{11}C]FLB457)		WCST	364.45 ± 19.77	364.08 ± 20.67	$t=0.02$	0.99
	Mass Injected (μg)	SMCT	1.43 ± 0.42	1.51 ± 0.66	$t=0.40$	0.69
		WCST	1.39 ± 0.51	1.32 ± 0.68	$t=0.32$	0.75
	Specific Activity (MBq/nmol)	SMCT	104229 ± 33781	129352 ± 85507	$t=1.05$	0.30
		WCST	106227 ± 29452	123728 ± 77034	$t=0.82$	0.42

*p is significant at <0.05 (two-tailed).
Abbreviations: HC, healthy controls; CHR, clinical high risk for psychosis; SOPS, Scale of Prodromal Symptoms; GAF, Global Assessment of Functioning; SMCT, Sensory Motor Control Task; WCST, Wisconsin Card Sorting Task.

son's chi-squared tests (categorical variables). To test the primary hypothesis of group differences in cognitive task-induced dopamine release ([^{11}C]FLB457 ΔBP_{ND}), a linear mixed models with the main effects of group (2-levels, CHR, HV), ROI (2 levels, DLPFC, ACC) and their interaction, as the independent variables, with ΔBP_{ND} value as the dependent variable was used. This model includes main effects of group and ROI. Significant group x ROI interactions were followed up using contrasts of regression β values between groups. If the interaction term was not significant, it was removed from the model. Significant main effect of ROI were followed up by independent t-tests to test differences between groups at α=0.025 in each ROI (2 ROIs).

To explore differences in [^{11}C]FLB457 binding (BP_{ND}) across groups and with regions, a linear mixed models with effect of group (2-levels, CHR, HV), session (2 levels, SMCT, WCST) and their interaction, as the independent variables, with BP_{ND} value per ROI as the dependent variable was used. This model includes main effects of group and session. Significant group x session interactions were followed up using contrasts of regression β values between groups, when statistically significant. If the interaction term was not significant, it was removed from the model. A significant group x session interaction indicates the group differences of cognitive task-induced change in [^{11}C]FLB457 binding (BP_{ND}) in ROIs, as more simply exemplified by [^{11}C]FLB457% displacement (ΔBP_{ND})

The relationship between cognitive task-induced dopamine release ([^{11}C]FLB457 ΔBP_{ND}), clinical assessments and cognitive measures (percent errors, Perseverative Errors and Categories Completed on the WCST and RBANS scores) were explored using separate general linear models, with ΔBP_{ND} value per ROI as the dependent variable while controlling for group and cognitive measures and including an interaction for group x cognitive measure scores. The analysis was then followed by Pearson's linear correlations. As this analysis was considered exploratory, we did not control for multiple comparisons.

3. Results

3.1. Demographics and PET scan parameters

Demographics, clinical characteristics, PET scan parameters and medication history can be found in Table 1. There were no differences in age, sex, smoking status, total years of education and scan parameters among groups. Furthermore, attenuated psychotic symptoms measured before and after SMCT and WCST sessions for the CHR group were not different between and within sessions. PET scans were performed 10.14 ± 20.52 days apart.

3.2. Cognitive task paradigm

Cognitive performance details can be found in Table 2. There was no statistically significant difference between groups in the SMCT and WCST performance accuracy (SMCT: $t=1.19$, $p=0.25$; WCST: $t=0.47$, $p=0.65$). As expected, both groups made significantly more errors in the WCST session than the SMCT session ($F(1, 27)=63.26$, $p<0.0001$), suggesting that the WCST was sufficiently sensitive in exerting cognitive effort in all participants. Furthermore, there were no statistically significant differences between CHR and HC in the number of Perseverative Errors ($t=0.13$,

Table 2 Participant's performance on cognitive measures.

		HC ($n=15$)	CHR ($n=13$)	t	p
SMCT	% Correct	97.92 ± 1.66	96.32 ± 4.88	1.19	0.25
	% Error	2.08 ± 1.66	3.66 ± 4.88	1.19	0.25
WCST	% Correct	87.72 ± 3.33	86.96 ± 5.12	0.47	0.65
	% Error	12.27 ± 3.33	13.03 ± 5.12	0.47	0.65
	Perseverative Responses	52.64 ± 4.40	51.41 ± 7.61	0.54	0.60
	Perseverative Errors	13.54 ± 3.25	13.38 ± 3.60	0.13	0.90
	Categories Completed	6.93 ± 2.03	7.55 ± 1.47	0.91	0.37
RBANS	Immediate Memory	93.60 ± 11.96	102.00 ± 15.57	1.61	0.12
	Visuospatial Memory	95.67 ± 19.30	91.46 ± 13.20	0.66	0.51
	Language	95.33 ± 23.21	106.00 ± 16.24	1.39	0.18
	Attention	96.40 ± 15.06	115.15 ± 19.49	2.87	0.01*
	Delayed Memory	98.13 ± 10.06	95.46 ± 12.71	0.62	0.54
	Total Scale	94.20 ± 13.54	103.31 ± 16.43	1.61	0.12

*p is significant at <0.05 (two-tailed).
Abbreviations: HC, healthy controls; CHR, clinical high risk for psychosis; SMCT, Sensory Motor Control Task; WCST, Wisconsin Card Sorting Task; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status.

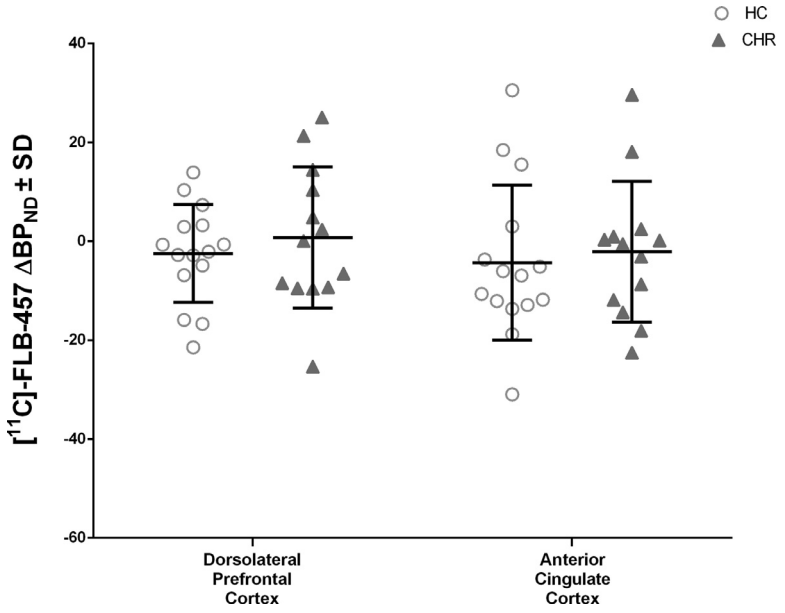

Fig. 1 No differences in cognitive task-induced dopamine release between groups (ΔBP_{ND} of [^{11}C]FLB457) in main ROIs. Graph shows cognitive task-induced dopamine release indexed by ΔBP_{ND} of [^{11}C]FLB457 of both groups (HC in circles and CHR in triangles) in DLPFC and ACC. $p > 0.05$ in all ROIs. ROI, regions of interest, DLPFC, dorsolateral prefrontal cortex, ACC, anterior cingulate cortex.

$p=0.90$), Perseverative Responses ($t=0.54$, $p=0.60$) and Categories Completed ($t=0.91$, $p=0.37$) in WCST.

3.3. Cognitive task-induced dopamine release

Details of cognitive task-induced dopamine release as indexed by [^{11}C]FLB457 ΔBP_{ND} can be found in Fig. 1. There were no main effect of group ($F(1, 26)=0.348$; $p=0.560$) or ROI ($F(1, 26)=1.080$; $p=0.308$) and no significant group x ROI interaction ($F(1, 26)=0.049$; $p=0.826$).

3.4. Exploratory analysis examining differences in [^{11}C]FLB457 binding (BP_{ND}) across groups and sessions

Details of [^{11}C]FLB457 binding across groups and sessions are summarized in Fig. 2. There was a main effect of group in DLPFC ($F(1, 52)=7.339$, $p=0.009$), ACC ($F(1, 52)=7.266$, $p=0.009$) and exploratory region MPFC ($F(1, 52)=7.445$ $p=0.009$). The CHR group had higher binding in both the SMCT and WCST sessions than HC. We observed no statistically significant difference in [^{11}C]FLB457 BP_{ND} between ses-

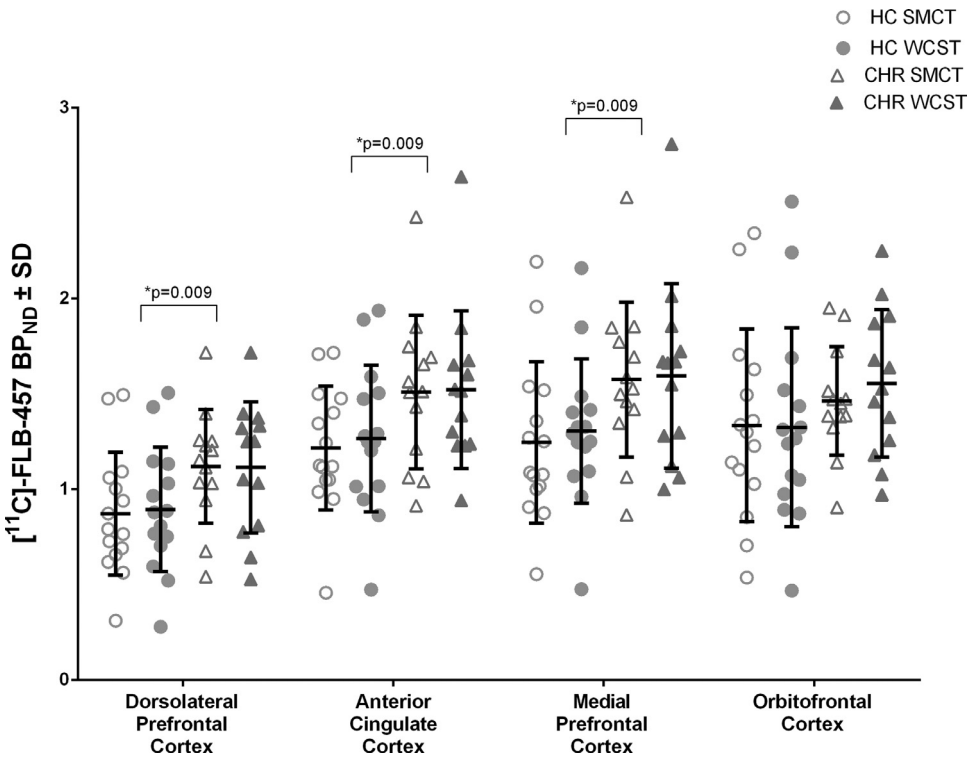

Fig. 2 Significant differences in main effect of group on cortical BP_{ND} in all ROIs except OFC with higher binding values in the CHR than HC. Graph shows cognitive task-induced binding potential (BP_{ND}) of [^{11}C]FLB457 in HC (circles) and CHR (triangles) for main (DLPFC and ACC) and exploratory (MPFC and OFC) regions of interest. DLPFC, dorsolateral prefrontal cortex, ACC, anterior cingulate cortex, MPFC, medial prefrontal cortex, OFC, orbitofrontal cortex, HC, healthy controls, CHR, clinical high risk for psychosis.

sions (SMCT vs. WCST) (main effect of session per ROIs: all $p > 0.1$) and no significant group x session interactions in any of the ROIs (all $p > 0.1$), consistent with no group differences in cognitive task-induced dopamine release (ΔBP_{ND}) reported above.

3.5. Exploratory associations between cognitive task-induced dopamine release and cognitive performance in main ROIs

The relationship between WCST Categories Completed (Fig. 3A) and [^{11}C]FLB457 ΔBP_{ND} was significantly different between groups in the DLPFC [omnibus test: $F(3, 24)=3.86$, $p=0.02$, $\eta^2=0.326$; interaction between group and WCST Categories Completed: $F(1, 24)=8.47$, $p=0.008$, $\eta^2=0.261$]. The effect on WCST Categories Completed on [^{11}C]FLB457 ΔBP_{ND} was significant in CHR participants (slope=6.76, $t=3.29$, $p=0.003$, $\eta^2=0.311$) but not in HC (slope=−0.44, $t=0.32$, $p=0.754$, $\eta^2=0.004$). No significant effects were present in ACC.

3.6. Exploratory associations between cognitive task-induced dopamine release and cognitive performance in exploratory ROIs

The relationship between WCST Categories Completed (Fig. 3B) and [^{11}C]FLB457 ΔBP_{ND} was significantly different between groups in the exploratory region OFC [omnibus test: $F(3,24)= 3.21$, $p=0.04$, $\eta^2=0.287$; interaction between group and WCST Categories Completed $F(1, 24)=7.26$, $p=0.001$, $\eta^2=0.232$]. The effect on WCST Categories Completed on [^{11}C]FLB457 ΔBP_{ND} was significant in CHR participants (slope=9.05, $t=2.81$, $p=0.008$, $\eta^2=0.262$) but not in HC (slope=−1.39, $t=0.65$, $p=0.524$, $\eta^2=0.017$).

There were no statistically significant associations between RBANS subscales and [^{11}C]FLB457 ΔBP_{ND} in any of the main ROIs. However, the relationship between RBANS Delayed Memory performance and [^{11}C]FLB457 ΔBP_{ND} was significantly different between groups in the exploratory region OFC [omnibus test: $F(3,24)=5.39$, $p=0.006$, $\eta^2=0.402$; interaction between group and Delayed Memory performance: $F(1,24)=12.19$, $p=0.002$, $\eta^2=0.337$]. The effect on RBANS Delayed Memory performance on [^{11}C]FLB457 ΔBP_{ND} was significant in CHR participants (slope = 1.17, $t=3.44$, $p=0.002$, $\eta^2=0.331$) but not in HC (slope = −0.66, $t=1.65$, $p=0.096$, $\eta^2=0.116$).

Further, the relationship between RBANS Immediate Memory performance and [^{11}C]FLB457 ΔBP_{ND} revealed a trend towards significance between groups in the OFC [omnibus test: $F(3,24)=2.55$, $p=0.079$, $\eta^2=0.242$; interaction between group and RBANS Immediate Memory performance: $F(1,24)=2.08$, $p=0.163$, $\eta^2=0.080$]. The effect on RBANS Immediate Memory performance on [^{11}C]FLB457 ΔBP_{ND} was significant in CHR participants (slope = 0.79,

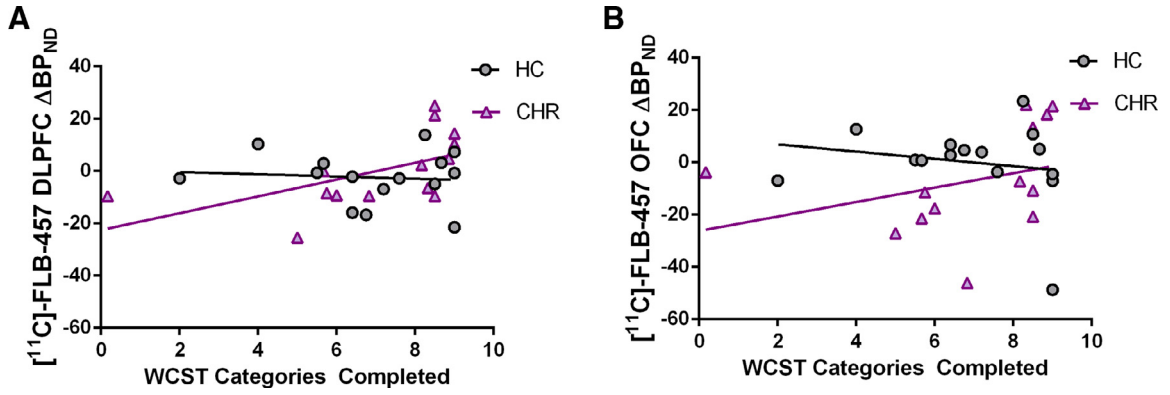

Fig. 3 Associations between [^{11}C]FLB457 ΔBP_{ND} and WCST Categories Completed in healthy controls (HC) and clinical high risk for psychosis (CHR). Lines represent the best linear model fit of the data per group (HC: gray line, CHR: purple line). The correlations were significant in CHR in DLPFC, not in OFC (A: $r = 0.310$, $p = 0.04$; B: $r = 0.111$, $p = 0.24$) but not in HC in either DLPFC or OFC (A: $r = 0.008$, $p = 0.75$; B: $r = 0.032$, $p = 0.52$). WCST, Wisconsin Card Sorting Task, [^{11}C]FLB457 ΔBP_{ND}, binding potential, DLPFC, dorsolateral prefrontal cortex, OFC, orbitofrontal cortex.

$t = 2.52$, $p = 0.019$, η^2=0.209) but not in HC (slope = 0.083, $t = 0.22$, $p = 0.828$, η^2=0.3370).

4. Discussion

Based on our previous work that showed blunted cortical dopamine release in the ACC and DLPFC in response to a cognitive task in schizophrenia (Rao et al., 2018), we sought to examine cognitive task-induced cortical dopamine release in CHR individuals using the same WCST. We anticipated a decrease in cognitive task-induced dopamine release in the DLPFC and ACC in CHR as compared to HC. Although patients with schizophrenia demonstrated blunted cognitive task-induced cortical dopamine release, no such effect was observed in the present study in CHR. This is the first study examining dopamine release in cortical brain regions in response to a cognitive challenge in CHR suggesting that the cortical hypodopaminergic state of psychosis may not be present in its putative high-risk state. This is in line with a recent study exploring cortical dopamine release in response to psychosocial stress in CHR (Schifani et al., 2018).

Although increased striatal dopamine signalling in psychosis is well supported by preclinical, post-mortem and imaging evidence, cortical in-vivo dopamine signaling (Hernaus et al., 2015; Rao et al., 2018; Schifani et al., 2018; Slifstein et al., 2015; Weinstein et al., 2017) is only now being investigated. This may be attributed to the methodological challenges in using PET radiotracers that are sensitive enough to quantify the lower density of dopamine $D_{2/3}$ receptors in cortex as compared to striatal brain regions. Our study adds to the growing body of literature particularly focusing in cortical dopamine release in CHR. When exploring differences in [^{11}C]FLB457 binding (BP_{ND}) across groups and sessions, we observed that the CHR group had numerically higher [^{11}C]FLB457 binding in the DLPFC, ACC and in the exploratory region MPFC, as compared to the HC group (regardless of session). This generally higher [^{11}C]FLB457 binding might suggest an increased expression of cortical $D_{2/3}$ receptors, which would be consistent with the previously observed upregulation of cortical D1 receptors in drug-naïve patients with schizophrenia (Abi-Dargham et al., 2011; Cervenka, 2018); although inconsistent with other studies with [^{11}C]FLB457 in psychosis (Rao et al., 2018; Slifstein et al., 2015).

In terms of cognitive abilities, there is a lot of heterogeneity in CHR, and there is also emerging evidence pointing towards a subgroup of individuals that experience attenuated psychotic symptoms but do not display cognitive deficits (Heinrichs and Awad, 1993; Hill et al., 2002; Lewandowski et al., 2014). Recent research from the North American Prodrome Longitudinal Study cohort reported that CHR individuals have poorer social functioning and cognitive abilities than HC, and this finding applies regardless of conversion to psychosis (Addington et al., 2018; Barbato et al., 2015; Fusar-Poli et al., 2013; Seidman et al., 2010, 2016). However, in this study there was no statistically significant differences in cognitive task performance between groups. One possible explanation may be compensatory mechanisms during memory retrieval and cognitive processes in PFC in our CHR group. A recent fMRI study by Cao et al. (2018) reports hyper-activation in cognitive control and attention areas in the brain when performing cognitive tasks in CHR. Areas of over-activation suggest residual inefficiencies during these cognitive processes. The increased activation could potentially indicate the need for excessive control in information retrieval in CHR, particularly in those that transition to psychosis. Research in schizophrenia also reports altered retrieval in cortical regions (Lepage et al., 2006; Öngür et al., 2006). It is also possible that the lack of significant differences between groups in either cognitive performance or cortical dopamine release may be related to the heterogeneity inherent to this population. In this small sample, we could not investigate who transitioned to psychosis, which may further explain the present lack of differences between groups.

In our study, dopamine release in the DLPFC and OFC was positively associated with WCST Categories Completed. Categories Completed is an indication of performance on

the WCST and better performance on the WCST is signified via a higher number of Categories Completed (Nyhus and Barceló, 2009). Therefore, a decreased cognitive-task induced dopamine release was associated with fewer categories completed in our CHR sample. Additionally, cognitive task-induced dopamine release in the OFC was positively associated with RBANS Immediate and Delayed memory subscale scores in CHR. Decreased cognitive task-induced dopamine release was associated with poorer cognitive performance on the RBANS. While these associations must be considered exploratory, they nonetheless suggest a critical role of cortical dopamine on cognitive performance, which must be further tested in future studies.

There are some limitations that should be considered. First, our results are also presented using a novel method (Schifani et al., 2018) to account for the fact that the mass of the [^{11}C]FLB457 may not be at a tracer dose (Narendran et al., 2011). Even though in our present sample, there were no effect of mass injected, weight or age between the two groups, we applied the correction to further confirm that the mass of the radiotracer did not affect ΔBP_{ND} comparisons between groups. Second, radiotracer uptake in the cerebellar cortex between SMCT and WCST scans exhibited nearly complete overlap (data not shown) suggesting no cerebellar contribution to our results. Third, the exploratory associations between clinical and cognitive measures and ΔBP_{ND} did not survive multiple comparisons using Bonferroni correction. As mentioned previously, they require verification using a larger sample and must be considered exploratory. This is especially important as post hoc analyses revealed that the correlations between dopamine release and RBANS Immediate and Delayed Memory subscales were mainly driven by two participants as the interaction no longer survives upon conducting leave one-out analysis. Fourth, in neurochemical brain imaging studies, relatively small sample sizes represent a potential limitation, however, we have at least 13 participants in each group and only 2 ROIs which is sufficient power to detect group differences in our setting. Despite this, type 2 error cannot be fully ruled out. Fifth, the practice effects associated with re-administration of the WCST between the two sessions should be considered (Basso et al., 2001; McCaffrey et al., 1992). Practice can affect neuropsychological test scores when a test is taken more than once, thus improving, superficially an overall score. Although the WCST itself was administered for one not both scans, the SMCT is essentially the same as the WCST without the classification rules. However, the order of the sessions were counterbalanced to minimize such effects. Sixth, only 5 CHR participants were antipsychotic-naïve but all participants were antipsychotic free at the time of study participation. While antipsychotics use is known to affect dopamine activity, in our sample, the participants that were previously exposed to antipsychotics were taking dosages below therapeutic level (Table 1). Further, there were no statistically significant differences in the exploratory comparisons of dopamine release in CHR participants that were antipsychotic-free and -naïve (data not shown). Additionally, results do not change when taking smoking status into account. Individuals that were smokers in our sample had only very infrequent use as they only smoked cigarettes during social occasions and report no regular daily/weekly smoking habits.

4.1. Conclusion

Our results show no significant difference between CHR and HC in cognitive task-induced cortical dopamine release. Associations between cortical dopamine release and cognitive performance on WCST and RBANS, though exploratory, highlight the need for further studies exploring cognitive deficits in CHR which may have important clinical implications for functional outcome or clinical staging.

Role of the funding source

This work was supported by the Canadian Institutes of Health Research (Canada Hope 116290 to NR and RM).

Contributors

R.M. and P.R. designed the study and wrote the protocol. A.T., N.R., and H.H.T. helped in data collection and data analyses. A.T. and C.S. carried out the statistical analysis and A.T. managed the literature searches and wrote the first draft of the manuscript. All authors have edited and approved the final manuscript for publication.

Conflict of interest

The authors declare no conflict of interest in relation to this work.

Acknowledgements

We thank the staff of the Centre for Addiction and Mental Health (CAMH) Research Imaging Centre and Focus on Youth Psychosis Prevention (FYPP) Clinic for their technical assistance.

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