DOI:
10.1038/s41386-019-0541-2

Document Version
Publisher's PDF, also known as Version of record

Neuropsychopharmacology www.nature.com/npp

ARTICLE OPEN

Glutamatergic and dopaminergic function and the relationship to outcome in people at clinical high risk of psychosis: a multi-modal PET-magnetic resonance brain imaging study

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Preclinical models of psychosis propose that hippocampal glutamatergic neuron hyperactivity drives increased striatal dopaminergic activity, which underlies the development of psychotic symptoms. The aim of this study was to examine the relationship between hippocampal glutamate and subcortical dopaminergic function in people at clinical high risk for psychosis, and to assess the association with the development of psychotic symptoms. ^{1}H-MRS was used to measure hippocampal glutamate concentrations, and ^{18}F-DOPA PET was used to measure dopamine synthesis capacity in 70 subjects (51 people at clinical high risk for psychosis and 19 healthy controls). Clinical assessments were undertaken at baseline and follow-up (median 15 months). Striatal dopamine synthesis capacity predicted the worsening of psychotic symptoms at follow-up ($r = 0.35$; $p < 0.05$), but not transition to a psychotic disorder ($p = 0.22$), and was not significantly related to hippocampal glutamate concentration ($p = 0.13$). There were no differences in either glutamate ($p = 0.5$) or dopamine ($p = 0.5$) measures in the total patient group relative to controls. Striatal dopamine synthesis capacity at presentation predicts the subsequent worsening of sub-clinical total and psychotic symptoms, consistent with a role for dopamine in the development of psychotic symptoms, but is not strongly linked to hippocampal glutamate concentrations.

Neuropsychopharmacology (2019) 0:1–8; https://doi.org/10.1038/s41386-019-0541-2

INTRODUCTION

Psychotic disorders are typically preceded by a prodromal period of 1–5 years, characterised by worsening sub-clinical psychotic symptoms and a decline in overall functioning [1]. Operationalised criteria have been developed on the basis of symptoms, functional decline and family history of psychosis to identify people who may be in the prodrome and are at high risk of developing psychosis in the next few years [2]. People meeting these operationalised criteria are referred to as being at clinical high risk of psychosis. Psychotic disorders are associated with considerable burden once they have developed, and current treatments are limited by poor tolerability and effectiveness in many patients [3]. There is thus considerable interest in understanding the pathophysiology underlying the development of psychotic symptoms to help develop new treatments [4].

The dopamine and glutamate hypotheses are two leading theories for the pathophysiology of psychosis [3]. Although initially developed separately, the hypotheses have been integrated to propose that glutamate dysregulation in cortical regions, including the hippocampus, leads to striatal dopamine dysfunction, which, in turn, underlies the development of psychotic symptoms [3, 5–9]. Supporting this, preclinical evidence indicates that hippocampal hyperactivity leads to mesostriatal dopamine dysfunction [10–12], and implicates glutamatergic neuron dysregulation in the hippocampus in this process [13]. Moreover, a number of clinical studies have shown altered hippocampal structure, function and perfusion in psychotic disorders, and people at risk of psychosis [13–20]. However, to our knowledge, only one study has investigated the relationship between hippocampal glutamatergic measures and striatal dopamine function in people at high risk for psychosis [21]. This study found levels of glutamate, in the hippocampus, were inversely related to striatal dopamine synthesis capacity in people at clinical risk of psychosis, particularly in the subgroup who went on to develop a psychotic disorder. This suggests the hypothesis that dysfunction in hippocampal glutamatergic drive dysregulates striatal dopaminergic function. As the number of subjects in the one in vivo study in patients to date was relatively modest ($n = 14$), the first aim of this study was to test the hypothesis that striatal dopamine synthesis capacity and hippocampal glutamate

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Received: 17 June 2019 Revised: 20 September 2019 Accepted: 23 September 2019
Published online: 16 October 2019

measures are related in an independent and larger sample of clinical high-risk subjects.

In vivo imaging studies of dopaminergic function show that dopamine synthesis and release capacity are elevated in patients with psychosis [22, 23], and some [24, 25], but not all [26, 27], studies have found this to be associated with the severity of psychotic symptoms. Striatal dopamine-release capacity has also been associated with the induction of psychotic symptoms by amphetamine [27]. Elevated dopamine synthesis and release capacity have also been reported in people at clinical high risk of psychosis [28–30], but not in other groups experiencing sub-threshold psychotic symptoms who do not meet criteria for a psychotic disorder [31]. Raised dopamine synthesis capacity has also been shown to be specific to those individuals who associated with an increased risk of transition to psychosis [32, 33]. Taken together, this evidence suggests that dopaminergic dysfunction may underlie the development of psychotic symptoms. However, it is not known if dopamine synthesis capacity predicts the worsening of sub-clinical psychotic symptoms in people at risk of psychosis. Therefore, the second aim of our study was to test the hypothesis that increased striatal dopamine synthesis capacity would predict an increase in the severity of psychotic symptoms, as well as the onset of a psychotic disorder.

METHODS

Study design

The study comprised a case–control comparison of patients with healthy controls with a longitudinal, naturalistic clinical follow-up of patients to determine the relationship between baseline imaging measures and clinical outcome. All volunteers received clinical and imaging measures. In addition, the patients received follow-up to determine clinical outcome as described below. Ethical permission was given by the local research ethics committee. All participants provided written informed consent to participate.

Participants

Patients were recruited from services for people at clinical high risk of psychosis in South England. Inclusion criteria were (1) met operationalized criteria for being at clinical high risk of psychosis based on a standardised, semi-structured clinical assessment as described by Yung et al. [34]; (2) no history of current or past psychotic disorder assessed using the structured clinical interview for diagnosis [35] and (3) antipsychotic naive or antipsychotic-free for at least 6 weeks.

Healthy controls were recruited from the same geographical area via adverts in the local media and met the following inclusion criteria: (1) no history of current or past mental disorder assessed using the structured clinical interview for diagnosis [35]; (2) no criteria for being at clinical high risk of psychosis as described by Yung et al. [34] (3) antipsychotic naive or antipsychotic-free.

Exclusion criteria for all subjects were any of (1) a history of significant head trauma, (2) dependence on illicit substances, (3) medical co-morbidity (other than minor, self-limiting illnesses) and (4) contraindications to scanning (such as pregnancy).

Clinical measures

At baseline, all subjects were assessed using the Global Assessment of Function (GAF [36]) to measure social and occupational function, and the National Adult Reading Test (NART) to estimate premorbid IQ [37]. In addition, all patients received symptom measures rated using the Positive and Negative Syndrome Scale (PANSS [38]) and the Comprehensive Assessment of At Risk Mental States (CAARMS [34]) rating scales at baseline and at clinical follow-up.

Clinical follow-up

Patients received a follow-up assessment at a median of 15.0 (interquartile range (IQR) = 11–23) months post baseline measures. Transition to a psychotic disorder was determined using the structured clinical interview for diagnosis [35]. The percentage change in CAARMS-positive symptom (unusual thought content, bizarre ideas, perceptual abnormalities and disorganised speech) severity rating from baseline to follow-up was calculated as follows:

$$100 \times (\text{symptomratingatfollowup} - \text{symptomratingatbaseline}) / (\text{symptomratingatbaseline})$$

where CAARMS scores were not available for patients ($n = 3$), PANSS-positive severity ratings (after subtracting seven to correct for the non-zero floor [39]) were used in their place to calculate the percentage change in positive symptoms.

PET imaging acquisition and analysis

All participants received a PET scan to index dopamine synthesis capacity at baseline. Subjects were asked not to eat or drink (except water), and refrain from alcohol for 12 h prior to scan and not to smoke for 2 h prior to the scan [40]. Imaging data were obtained on a Siemens Biograph 6 HiRez PET scanner (Siemens, Erlangen, Germany) in three-dimensional mode. To prevent formation of radiolabelled metabolites that may cross the blood–brain barrier, participants received 400 mg of entacapone, a peripheral catechol-o-methyl-transferase inhibitor, and 150 mg of carbidopa, a peripheral aromatic acid decarboxylase inhibitor, 1 h before scan. Participants were positioned in the scanner with the orbitomeatal line parallel to the transaxial plane of the tomograph. Head position was marked and monitored, and a CT scan was conducted for attenuation correction. Approximately 150 MBq of ^{18}F-DOPA was administered by bolus intravenous injection 30 s after the start of the dynamic PET scan. PET data were acquired in 32 frames of increasing duration, over the 95-min scan (frame intervals: 8×15, 3×60, 5×120, 16×300 s). Our primary measure was the whole striatal influx constant (K_i^{cer}, described as Ki in some earlier publications [28]).

Image analysis was conducted blind to group status. A mutual information algorithm was used to correct for head movement [41]. SPM8 was used to automatically normalise a tracer-specific ^{18}F-DOPA template [42], together with a striatal brain atlas using the definition described by Martinez et al., which includes dividing the striatum into three subdivisions based on the predominant origin of projections to the striatum from limbic, associative and sensorimotor brain regions, respectively [43]. The whole striatum was our primary region of interest. However, given recent findings that the elevation in dopamine synthesis capacity in psychosis may be more marked in the associative striatum [23], we conducted additional exploratory analyses using the subdivisions for completeness. Following visual inspection of the time-activity curves, K_i^{cer} was calculated using the Patlak–Gjedde graphical approach adapted for a reference tissue input function [44]. We have previously shown this approach to have good reliability, with intraclass correlation coefficients for the whole striatum of over 0.8 [45].

MRS acquisition

Scanning was conducted on a General Electric (Milwaukee, Wisconsin, USA) Signa HDxt 3Tesla MRI scanner. Structural images were acquired using a whole-brain three-dimensional sagittal T1-weighted scan, with parameters based on the Alzheimer's Disease Neuroimaging Initiative (ADNI) (TE = 2.85 ms; TR = 6.98 ms; inversion time = 400 ms; flip angle = 11°; voxel size $1.0 \times 1.0 \times 1.2$ mm; for full details see http://adni.loni.usc.edu/methods/mri-analysis/mri-acquisition/). Structural T1 images were segmented into grey matter, white matter and cerebrospinal fluid (CSF) using Statistical

Parametric Mapping software (SPM8; Wellcome Trust Centre for Neuroimaging, London, UK) to allow correction of the ^{1}H-MRS data for partial volume CSF contamination. ^{1}H-MRS spectra (PRESS–Point RESolved Spectroscopy; TE = 30 ms; TR = 3000 ms; 96 averages) were acquired in the left hippocampus (voxel dimensions: 20 × 20 × 15 mm (right–left, anterior–posterior, superior–inferior); see Supplementary Fig. 1). We employed the standard GE probe (proton brain examination) sequence, which uses a standardised chemically selective suppression (CHESS) water suppression routine. Unsuppressed water reference spectra (16 averages) were also acquired as part of the standard acquisition. Shimming and water suppression were optimised, with auto-prescan performed twice before each scan.

LC-model 6.3-I0 [46] was used to estimate glutamate levels. Following visual inspection of spectra quality, metabolite analyses were restricted to spectra with linewidths at full-width at half-maximum ≤0.1 ppm, Cramér–Rao lower bounds ≤20% and signal to noise ratio ≥5. Model metabolites and concentrations used in the basis set are fully detailed in the LC-Model manual (http://s-provencher.com/lcmodel.shtml). An in-house script was used to identify the relative distribution of white matter, grey matter and cerebrospinal fluid in the voxel. Metabolite values were corrected for the CSF content of the voxel using the formula Mcorr = M × (WM + 1.28 GM + 1.55 CSF)/(WM + GM), where M is the uncorrected metabolite value, and WM, GM and CSF are the white matter, grey matter and cerebrospinal fluid fractions of the voxel, respectively [47]. The ^{1}H-MRS data are a sub-set of a larger sample recently reported [48], but the PET and the integration of the PET and ^{1}H-MRS data have not been previously reported. The voxel tissue content and imaging quality control variables are summarised in Supplementary Table 9.

Statistical analysis

All statistical analyses were performed using R version 3.3.2 [49]. Significance was set at $p < 0.05$ (two tailed). Baseline clinico-demographic variables were compared using independent *t* tests or ANOVA for the continuous data, and the chi-square test for categorical variables.

To test our first hypothesis that there was an inverse relationship between glutamate and dopamine in the high-risk sample as a whole, a linear regression analysis was performed with whole striatal dopamine synthesis capacity as the dependent variable, and glutamate concentrations as the predictor. We investigated whether this relationship was altered following the addition of potentially confounding variables (age, sex and ethnicity) to the model, given possible effects of age [50], sex [51, 52] and ethnicity [53], on the imaging measures.

To test our second hypothesis that dopamine synthesis capacity at baseline predicted worsening of symptoms, we performed linear regressions, analysing both the relationship between dopamine synthesis capacity and percentage change in symptoms. Given possible effects of age [50], sex [51, 52] and ethnicity [53], on the imaging measures, we conducted secondary exploratory analyses that adjusted for these co-variates.

In addition, we conducted exploratory analyses to determine if dopamine synthesis capacity predicted persistent functional impairment. We also investigated whether baseline dopamine levels were different from controls using independent *t* tests and ANCOVA.

RESULTS

Fifty-one patients and 19 controls participated in the study. Forty-seven patients received both PET and MRI scans (one received only an MRI scan and three received only a PET scan), and all controls received both PET and MRI scans. Time between scans was similar for patients (median 17.7 weeks, IQR 13.4–33.3) and controls (median 11.6 weeks, 4.3–23.3) (Mann–Whitney U Test, $p = 0.82$). There were no significant differences between patient and control groups in terms of age, gender, ethnicity or estimated premorbid IQ (see Table 1). Of the 51 patients, 35 were followed-up clinically, while 16 were lost to follow-up. There were no significant differences in clinico-demographic variables between the subjects with follow-up and those lost to follow-up (Table 2).

Table 1. Clinico-demographic details of study participants

	Controls	Patients	*P*
n	19	51	
Age	25.1(4.3)	23.0 (4.0)	0.06
% male	47	57	0.66[a]
% white ethnicity	79	73	0.81[a]
PANSS-positive	n/a	14.6 (4.8)	–
PANSS-negative	n/a	12.9 (4.7)	–
PANSS general	n/a	31.5 (9.7)	–
PANSS total	n/a	59.1 (16.9)	–
CAARMS-positive	n/a	10.4 (4.4)	–
CAARMS total	n/a	42.3 (20.9)	–
GAF	92.7 (5.7)	56.4 (9.6)	<0.001
Premorbid IQ estimate	102.0 (12.7)	105.1 (13.7)	0.41
Hippocampal glutamate concentration	8.06 (1.09)	8.27 (1.43)	0.57
Striatal K_i^{cer}	0.0128 (0.0011)	0.0126 (0.0010)	0.53

PANSS Positive and Negative Syndrome Scale, *CAARMS* comprehensive assessment of the at-risk mental state, *GAF* general assessment of functioning, *IQ* intelligence quotient estimated from national adult reading test
Values are mean (SD). *P*- values refer to control–patient comparison. *P*-values refer to *t* test unless otherwise indicated
[a]Chi-square test

Imaging results in the total clinical high-risk sample relative to controls

There were no significant differences between the total patient and control groups in terms of dopamine synthesis capacity ($t = 0.63$, df = 67, $p = 0.53$) or hippocampal glutamate concentrations ($t = 0.57$, df = 65, $p = 0.52$; see Fig. 1, Supplementary Fig. 2), and this remained the case after controlling for the influence of age, gender and ethnicity (group effect on dopamine synthesis capacity: $F = 0.39$, df = 64, $p = 0.54$; and on glutamate concentrations: $F = 0.39$, df = 62, $p = 0.54$). There were also no significant differences in dopamine synthesis capacity between groups for any of the striatal subdivisions (see Supplementary Information, Supplementary Tables 1, 2).

Relationship between striatal dopamine synthesis capacity and hippocampal glutamate levels

Figure 2 shows the relationship between hippocampal glutamate concentrations and striatal dopamine synthesis capacity in patients and controls. The bivariate regression showed that there was no significant association between hippocampal glutamate concentrations and striatal dopamine synthesis capacity in patients (beta = -1.60×10^{-4}, SE = 1.05×10^{-4}, $R^2 = 0.05$, $p = 0.13$), including in the adjusted model (when age, gender and ethnicity were added to the model (beta = -1.92×10^{-4}, SE = 1.14×10^{-4}, $p = 0.10$)), or in controls in either the bivariate (beta = -1.01×10^{-4}, SE = 2.40×10^{-4}, $R^2 = 0.01$, $p = 0.68$) or adjusted (beta = 5.92×10^{-4}, SE = 2.85×10^{-4}, $p = 0.98$) models. No significant relationships were seen for any of the striatal subdivisions either, in either patients or controls (see Supplementary Information, Supplementary Tables 5–8).

Table 2. Clinico-demographic details of patients with and without clinical follow-up

	Sample with follow-up	Lost to follow-up	*P*
n	35	16	
Age	23.1 (3.9)	22.7 (4.5)	0.75
% male	60	50	0.72[a]
% white ethnicity	71	75	0.99[a]
PANSS-positive	14.1 (4.4)	15.8 (5.5)	0.25
PANSS-negative	12.2 (4.5)	12.3 (5.2)	0.52
PANSS general	31.9 (9.9)	30.7 (9.5)	0.70
PANSS total	59.3 (16.3)	58.7 (18.8)	0.91
CAARMS-positive	10.8 (4.4)	9.36 (4.31)	0.30
CAARMS total	43.4 (20.9)	42.4 (23.1)	0.89
GAF	55.0 (9.5)	59.4 (9.6)	0.14
Premorbid IQ estimate	107.0 (10.7)	101.1 (18.2)	0.16
Hippocampal glutamate concentration	8.26 (1.5)	8.29 (1.4)	0.95
Striatal K_i^{cer}	0.0127 (0.001)	0.0125 (0.001)	0.50

PANSS Positive and Negative Syndrome Scale, *CAARMS* comprehensive assessment of the at-risk mental state, *GAF* general assessment of functioning, *IQ* intelligence quotient estimated from national adult reading test
Values are mean (SD) or % in case of sex and ethnicity. *P*-values refer to *t* test unless otherwise indicated
[a]Chi-square test

Relationship between dopamine synthesis capacity and subsequent worsening of symptoms

Dopamine synthesis capacity at baseline was associated with subsequent worsening of psychotic (positive) symptoms (beta = 1.6×10^4, SE = 7.9×10^3, $R^2 = 0.12$, df = 32, $p < 0.05$) (see Fig. 3), and this remained significant when age, gender and ethnicity were added to the model (beta = 1.9×10^4, SE = 8.5×10^3, df = 29, $p < 0.05$). The relationship was significant for the associative subdivision, but not sensorimotor or limbic subdivisions (see Supplementary Information, Supplementary Tables 3, 4). The relationship was similar when the total symptom rather than the positive symptom scores were examined, in both unadjusted (beta = 4.5×10^4, SE = 1.8×10^4, df = 32, $p < 0.05$) and adjusted models (beta = 4.8×10^4, SE = 2.0×10^4, df = 29, $p < 0.05$).

Transition to a psychotic disorder

Ten individuals (19.6% of the total high-risk sample) developed a psychotic disorder during the follow-up period after the PET and MRS scans. There was no significant difference in baseline dopamine synthesis capacity between the transition (mean (SD): 0.0122 (0.001)) and non-transition (mean (SD): 0.0127 (0.001)) subgroups ($t = 1.3$, df = 48, $p = 0.28$).

DISCUSSION

Our first main finding is that in people at clinical high risk for psychosis, striatal dopamine synthesis capacity predicted the worsening of psychotic symptoms. This adds to evidence that dopamine synthesis and release capacity are positively correlated with psychotic symptom severity [54–56], and treatment response [57] in patients with a psychotic disorder. Although the relation-

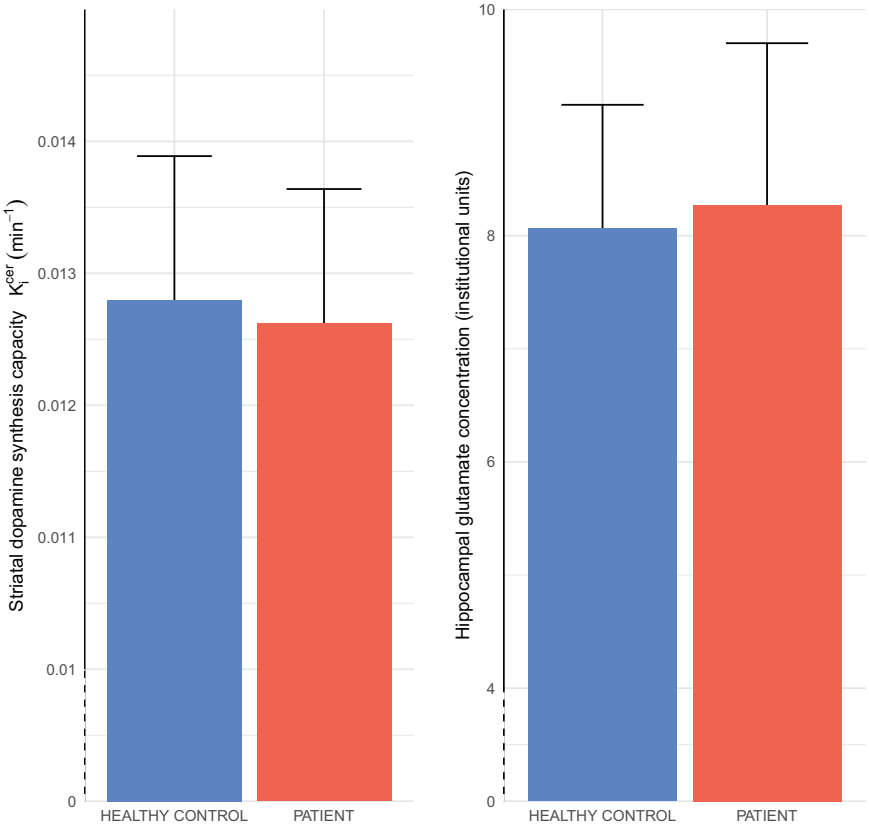

Fig. 1 Mean (SD) striatal dopamine synthesis capacity and hippocampal glutamate concentrations are not significantly different between patients and controls ($p = 0.55$ and $p = 0.52$, respectively)

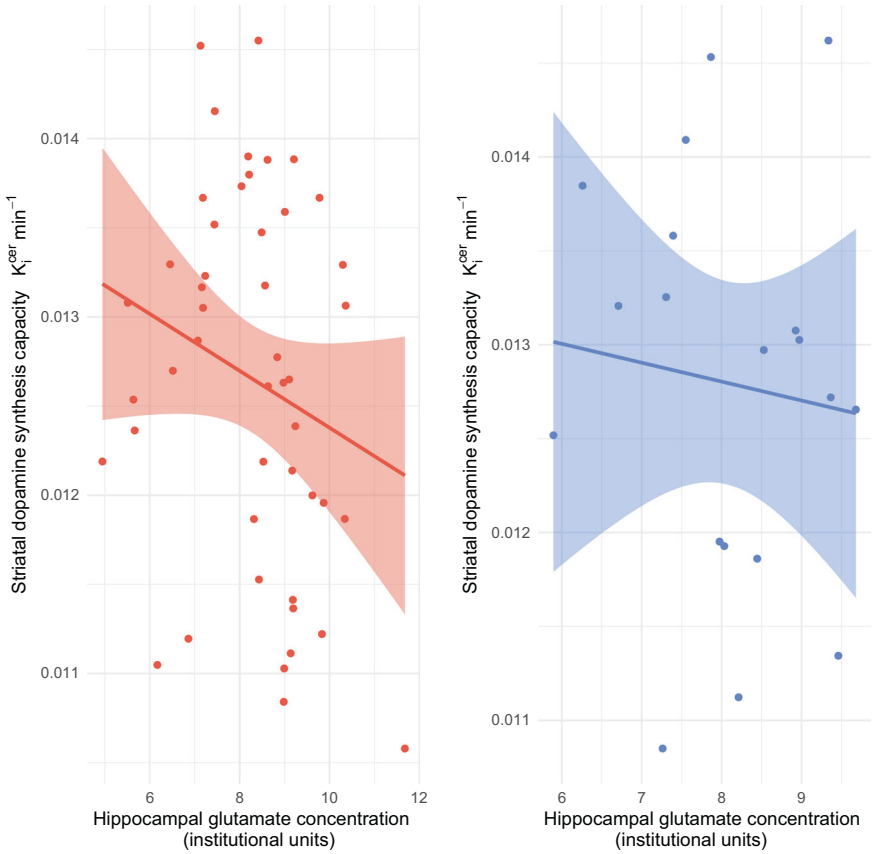

Fig. 2 Hippocampal glutamate concentration is not significantly related to striatal dopamine synthesis capacity in patients (red; $p = 0.13$) or controls (blue, $p = 0.68$)

ship was strongest for the associative subdivision, specificity to this region remains to be established given the high degree of collinearity between dopamine measures for all three subdivisions and that we did not test for an interaction. However, there was no significant difference between patients who later developed a psychotic disorder relative to those who did not, contrary to our previous findings [32]. This could be due to the fact that the difference between receiving a diagnosis of a psychotic disorder or not can come down to small differences in duration or severity of symptoms, for example, the difference between 7 days versus 6 days of psychotic symptoms [34]. It has been argued that these differences are unlikely to be clinically meaningful, and that a dimensional approach to psychosis may be more appropriate [58]. This is also consistent with evidence that there is a dimensional relationship between dopamine dysregulation and the induction of psychotic symptoms in healthy volunteers as well [59–61]. Factors other than symptom levels may also influence the diagnostic process, such as the patient's coping skills and level of functioning. It should also be noted that some patients in the non-transition group showed a greater worsening of symptoms than patients in the transition group (see Supplementary Fig. 3), and that some individuals develop a psychotic disorder up to 10 years after [62], indicating that further follow-up is required to determine if there are any transitions in the non-transition group. Notwithstanding this, taken together, our findings that there was a relationship between dopaminergic dysfunction and worsening of symptoms, but not transition to psychosis, indicate that dopamine dysfunction is more strongly linked to the development of symptoms than a diagnosis of a psychotic disorder. These findings add to other evidence that alterations in subcortical dopamine function in subjects with mental health problems may be more related to psychotic symptoms than to diagnostic categories per se [26, 54]. For example, patients with psychotic bipolar disorder show a similar elevation of striatal dopamine synthesis capacity to patients with a schizophreniform psychosis [54].

Our finding that there was no significant relationship between hippocampal glutamate levels and striatal dopamine synthesis capacity contrasts with our previous finding in subjects at clinical high risk of psychosis, which found a negative relationship with $r = 0.54$ [21]. It is possible that our failure to detect a relationship in the current study is due to a type II error. However, the patient sample in this study ($n = 51$) was much larger than in the previous study ($n = 14$), and had >80% power to detect the anticipated moderate or larger ($r > 0.4$) relationship between dopamine and glutamate indices. Thus, our study was well powered to detect the anticipated effect size, although it is possible that there is a smaller effect. It should be recognised that the MRS glutamate signal at 3 T is a composite of intra and extrasynaptic glutamate, and glutamine [3, 63]. Thus, we cannot exclude the possibility that alterations in synaptic glutamate levels are masked by other components of the signal, or indeed, that there are alterations in glutamate receptor levels. Notwithstanding these caveats, our findings are not consistent with the model that increased hippocampal glutamate levels dysregulates striatal dopamine function. They do not, however, rule out the alternative hypothesis suggested by preclinical models and clinical findings of hippocampal overactivity in psychosis [8, 12, 13, 18–20], that it is disinhibition of glutamate output neurons, and not altered glutamate drive in the hippocampus, that leads to subcortical dopaminergic dysregulation. This disinhibition could occur secondary to reduced GABAergic interneuron function, or other mechanisms affecting glutamatergic neuronal excitability that occur without concomitant measurable differences in glutamate concentrations in the hippocampus. In this case, one would not

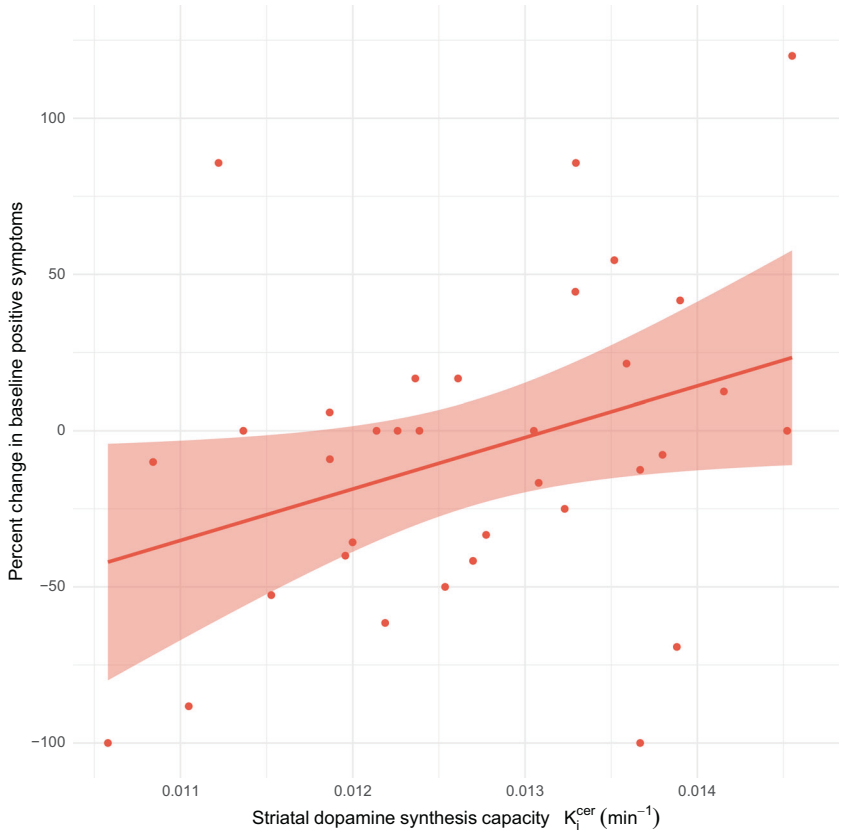

Fig. 3 Striatal dopamine synthesis capacity at baseline is directly associated with subsequent increase (worsening) of psychotic (positive) symptoms ($r = 0.35$, $p < 0.05$) in people at clinical risk of psychosis

predict a relationship between hippocampal glutamate levels and striatal dopaminergic function, as it would be glutamate levels at the site of the projections' termination (i.e., the striatum) that would show an association with dopamine function. A recent study has reported an inverse relationship between glutamate concentration in the anterior cingulate cortex and striatal dopamine synthesis capacity in patients with first-episode psychosis [64], and this has been seen also in healthy controls along with a direct association between striatal glutmate levels and striatal dopamine synthesis capacity [65]. Unfortunately, we did not measure glutamate concentration in the striatum or anterior cingulate cortex in this study. Further studies are warranted to test the relationship between striatal dopamine function and glutamate concentration in other brain regions in high-risk subjects.

However, an alternative hypothesis is that it is disinhibition of hippocampal glutamatergic output neurons, as opposed to glutamatergic drive in the hippocampus, that leads to striatal dopaminergic dysregulation [8],

We did not find a difference in striatal dopaminergic function between clinical high-risk subjects overall and controls, in contrast to previous findings [28, 29, 66]. This difference could reflect changes in the population referred to early detection services over time, with evidence indicating that subjects are referred earlier in the at risk period in more recent cohorts compared with earlier cohorts [67]. This is consistent with the transition rate in the present sample, which was ~19%, compared with ~35% in earlier samples [28, 32]. Transition rates similar to those in our current sample have also been reported in more recent cohorts from clinical studies around the world [2, 62], indicating that our current sample is likely to be representative of subjects currently referred to at risk services. Nevertheless, the lower transition rate and evidence that there may be transitions up to 10 years after presentation [62], indicates that the current finding of no difference in dopamine synthesis capacity should be considered as preliminary pending long-term follow-up of our current sample. The potential lack of generalisability to cohorts, where transition rates are greater, is a limitation that pertains to all the negative findings reported. We also did not detect a significant difference in hippocampal glutamatergic function between the high-risk subjects and controls, in contrast to our previous findings in a larger study that included the current cohort [48], although in agreement with previous studies in smaller samples that also did not detect significant differences [21, 68]. Thus, the difference between the Bossong et al. finding [48] and our current results may reflect the lower power in the current sample.

Methodological considerations

A number of subjects were lost to follow-up, which could introduce bias into the outcomes. However, the clinical and demographic characteristics of these subjects were not significantly different from those in the other groups, indicating this unlikely to be a major bias. It should be recognised that some non-transition subjects might subsequently develop a psychotic disorder. However, as the peak period for transition to psychosis is within the first year of follow-up [2], it is likely that we have identified the majority of transitions. Although it was not significant, there was a trend for the controls to be older than the patients. However, including age as a covariate in analyses did not have a major effect on findings.

Implications

Our finding that dopamine synthesis capacity predicted the worsening of psychotic symptoms but was not linked to transition suggests that other factors are involved in the diagnosis of psychotic disorder. One interpretation could be that dopamine

dysfunction underlies the development of psychotic symptoms, but whether these have a functional impact depends on additional factors, such as the coping skills, and psychological response of the individual, and their social support, consistent with psychosocio-biological models of psychosis [69–71]. Another possibility is that in the at-risk period, small differences in dopamine drive short-term psychotic-like experiences, but whether these become long-lasting and more severe depends on the development of further dopamine dysregulation. These possibilities are not mutually exclusive and a combination of both is possible [69].

Our finding that hippocampal glutamate is not linked to striatal dopamine dysfunction does not support the hypothesis that elevated hippocampal glutamatergic drive is driving striatal dopamine dysfunction, but is consistent with models that disinhibition of glutamatergic projections could drive striatal dopamine dysregulation. This predicts increased glutamate levels in targets of glutamatergic projections from the hippocampus, including the striatum. Elevated glutamate levels have been reported in the striatum in people at risk of psychosis, and linked to the transition to psychosis [72, 73]. Unfortunately, we did not measure striatal glutamate levels due to time constraints. New methods to index inhibitory regulation of hippocampal projection neurons, and MRS studies involving the targets of hippocampal projection neurons, are needed to test this further.

CONCLUSIONS

Striatal dopamine synthesis capacity predicts worsening of psychotic-like symptoms, but is not strongly related to transition to psychosis or hippocampal glutamate levels, indicating a role for dopamine in the development of symptoms but that other factors contribute to the transition to a psychotic disorder.

FUNDING AND DISCLOSURE

This study was funded by Medical Research Council-UK, and Wellcome Trust grants and the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. Dr Howes has received investigator-initiated research funding from and/or participated in advisory/speaker meetings organised by Angellini, Astra-Zeneca, Autifony, Biogen, BMS, Eli Lilly, Heptares, Jansenn, Lundbeck, Lyden-Delta, Otsuka, Servier, Sunovion, Rand and Roche. Neither Dr Howes nor his family have been employed by or have holdings/a financial stake in any pharmaceutical company. The other authors have no relevant conflicts of interest.

ADDITIONAL INFORMATION

Supplementary Information accompanies this paper at (https://doi.org/10.1038/s41386-019-0541-2).

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