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Transition to Psychosis Associated With Prefrontal and Subcortical Dysfunction in Ultra High-Risk Individuals

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Background: **People at ultra high risk (UHR) of psychosis have an elevated risk of developing a psychotic disorder, but it is difficult to predict which individuals will make a transition to frank illness. We investigated whether functional magnetic resonance imaging (fMRI) in conjunction with a phonological fluency task at presentation could distinguish subjects who subsequently developed psychosis from those who did not.** ***Methods:*** **Sixty-five subjects (41 with an UHR and 24 healthy controls) were assessed at clinical presentation using fMRI, in conjunction with a verbal fluency task. [18F]-DOPA positron emission tomography (PET) data were also available in a subgroup of 21 UHR and 14 healthy controls subjects. UHR subjects were followed clinically for at least 2 years.** ***Results:*** **Compared with UHR subjects who did not become psychotic, UHR subjects who subsequently developed psychosis showed increased activation in bilateral prefrontal cortex (PFC), brainstem (midbrain/basilar pons), the left hippocampus, and greater midbrain-PFC connectivity. Furthermore, exploratory analysis of [18F]-DOPA PET data showed that transition to psychosis was associated with elevated dopaminergic function in the brainstem region.** ***Conclusions:*** **In people at high risk of psychosis, increased activation in a network of cortical and subcortical regions may predict the subsequent onset of illness. Functional neuroimaging, in conjunction with clinical assessment and other investigations, may facilitate the prediction of outcome in subjects who are vulnerable to psychosis.**

Key words: prodromal psychosis/schizophrenia/prefrontal cortex/dopamine/MRI/18F-DOPA PET

Introduction

The onset of psychotic disorders is usually preceded by a prodromal phase, characterized by attenuated psychotic symptoms and a decline in social and occupational function.[1] Approximately 20%–30% of people with these features, termed an ultra high risk (UHR), develop frank psychosis usually within 24 months.[2] However, it is not always possible to identify which individuals will later develop psychosis on the basis of the presenting clinical features. There is thus a need for biomarkers that may help to predict which UHR subjects will later become psychotic.

The most robust functional neuroimaging findings associated with schizophrenia are altered prefrontal cortex (PFC), anterior cingulate cortex (ACC), and temporal lobe activation, particularly during the performance of tasks that engage executive functions, such as verbal fluency (VF) paradigms.[3,4] These alterations, particularly in PFC response, are thought to underlie impairments in the performance of VF and other executive tasks in patients with schizophrenia.[5] Neuropsychological studies also report impaired executive function in UHR cohorts,[6,7] and imaging studies show qualitatively similar alterations in PFC, ACC, and medial temporal lobe function.[8–10] However, the samples of UHR subjects in these imaging studies were too small to permit assessment of whether functional alterations were associated with later transition to psychosis, and it is not known if alterations in region underpinning executive function are more markedly altered in the subgroup that later develop psychosis. To date, only one functional magnetic resonance imaging (fMRI) study has included a sufficiently large sample of UHR subjects to permit a comparison of the data from subjects who did and did not go on to develop psychosis.[11] Although the task used by Sabb and colleagues[11] was not designed to examine executive function, increased neural activity in the bilateral PFC and anterior cingulate is reported. Furthermore, increased activity in the superior temporal gyrus, caudate, and left PFC distinguished those who subsequently developed psychosis from those that did not.

The aim of the present study was to use fMRI, in conjunction with a verbal fluency task (VFT), to compare functional activation in UHR who subsequently transitioned to psychosis and UHR subjects who did not. Based on our previous results,[9] we first predicted that the UHR group as a whole would show altered activation, particularly in the PFC and ACC, during a VFT relative to healthy controls. We then tested the hypothesis that UHR subjects who subsequently developed psychosis would show a more marked functional alteration in these regions than those who did not. Existing [18F]-DOPA positron emission tomography (PET) data, available in a subgroup of our sample, were used to explore the possibility that presynaptic dopamine synthesis was altered in regions associated with transition to psychosis.

Methods

Participants

Sixty-five subjects (24 healthy controls and 41 at UHR of psychosis) participated in the study. All were right-handed (apart from 1 UHR subject), native English speakers, and had no history of neurological illness, drug, or alcohol dependence. The sample included 17 UHR subjects and 15 controls whose fMRI data have been reported previously.[9] The study had National Health Service UK Research Ethics Committee (CoREC) approval, and all participants gave informed consent. All subjects had an estimated premorbid IQ in the normal range as assessed using the National Adult Reading Scale.[12] Handedness was assessed using the Lateral Preference Inventory.[13] Gender, mean age, and estimated premorbid IQ are reported in table 1.

UHR subjects ($n = 41$) were recruited via Outreach and Support in South London.[14] The UHR diagnosis was made using the Comprehensive Assessment of At-Risk Mental States (CAARMS[1]). Subjects met one or more of the following criteria: (*a*) attenuated psychotic symptoms (*b*) brief limited intermittent psychotic symptoms (a history of one or more episodes of frank psychotic symptoms that resolved spontaneously within 1 week in the past year), or (*c*) a recent decline in function, together with either the presence of schizotypal personality disorder or a family history of psychosis in a first-degree relative. The mean Global Assessment of Function score of the group at initial assessment was 57 (SD = 11.86). Psychopathology on the day of scanning was assessed using the Positive and Negative Syndrome Scale (PANSS[15]), and ratings are presented in table 1. The self-reported ethnicity of the sample was 28 White British, 6 Black, 4 Asian, and 3 of mixed origin. Four of the UHR subjects were being treated with low doses (less than 1.5 mg haloperidol equivalents per day) of antipsychotic medication. Healthy controls ($n = 24$) were recruited from the local community. Participants with a history of medical or psychiatric disorders or who were receiving prescription medications were excluded. Their self-reported ethnicity was 15 White British, 8 Black, and 1 of Asian origin. Both Controls and UHR subjects were excluded if they met *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, criteria for a substance misuse or dependence disorder or if there was a history of neurological disorder. Any participants reporting recent recreational drug use (use of cannabis, stimulants, hallucinogens, or opiates in the 2 weeks prior to the MRI scan) were excluded. Prior to PET imaging, a urine screen was performed to exclude subjects who had engaged in recent drug use.

Clinical Follow-up

All UHR subjects were followed clinically for at least 24 months subsequent to initial referral (mean duration = 24.67 mo). During the follow-up period, 7 UHR subjects (17%) made a transition to psychosis. Transition was defined according to the criteria in the CAARMS[1] and required the presence of one or more of the following for at least a week: (*a*) abnormal thoughts held with delusional intensity, (*b*) true hallucinations, (*c*) formal thought disorder to the degree of incoherence and/or loose associations. The mean duration between scanning and transition was 8.5 months. None of the transition cases were receiving antipsychotics at the time of scanning, although one was taking antidepressant medication. Four of the transition cases received a diagnosis of schizophrenia, 1 a diagnosis of schizoaffective disorder, and 2 cases have yet to receive a formal diagnosis but are receiving antipsychotic medication. None of the UHR subjects who did not make a transition received a new psychiatric diagnosis during the follow-up period. Of the 7 transition cases, 5 had received both fMRI and [18F]-DOPA PET imaging at baseline.

Verbal Fluency Task

Functional MRI data were acquired while subjects performed a VFT. In the experimental condition, the subjects were instructed to overtly generate a word in response to a visually presented letter. A full description of the task is provided elsewhere.[9] Briefly, experimental conditions were presented in blocks lasting 28 seconds, with 7 presentations of a given letter per block and 5 blocks of each condition. The experimental condition alternated with a control condition, in which the word "REST" was presented at the same rate and participants were asked to repeat this word overtly (word repetition [WR]). Incorrect responses were defined as pass responses, as were words that were proper names, repetitions, or grammatical variations of previous words.

Image Acquisition

For all the subjects, MRI scans were acquired on a 1.5-T Magnet (Signa LX; GE, Milwaukee, WI). VF was studied using a T2*-weighted echo-planer image sequence (TR

Table 1. Mean (SD) Subjects Demographics and Symptom Rating

	Controls	UHR	Controls vs UHR	UHR-nt	UHR-t	UHR-nt vs UHR-t
fMRI sample						
Subjects	24	41		34	7	
Age in years	25.46 (4.42)	24.24 (5.13)	$P = .33$	24.44 (5.28)	23.11 (3.12)	$P = .52$
Gender	16M:8F	27M:14F	$\chi^2 = .91$	22M:12F	5M:2F	$\chi^2 = .93$
Handedness	24R:0L	39R:2L	$\chi^2 = .42$	33R:1L	6R:1L	$\chi^2 = .45$
Premorbid IQ	107.20 (7.80)	102.18 (11.71)	$P = .11$	102.47 (11.72)	100.50 (13.09)	$P = .26$
Antipsychotic medication	—	4		4	0	—
Antidepressant medication	—	6		5	1	—
GAF score		57.00 (11.86)		57.00 (11.20)	56.00 (18.50)	$P = .86$
PANSS positive		12.44 (4.48)		12.51 (4.73)	12.00 (2.96)	$P = .79$
PANSS negative		10.63 (4.38)		10.40 (4.30)	12.00 (5.06)	$P = .42$
PANSS general		25.15 (6.63)		24.97 (6.60)	26.17 (6.68)	$P = .68$
PANSS total		48.02 (11.92)		47.66 (11.8)	50.17 (13.16)	$P = .64$
fMRI and [18F]-DOPA PET sample						
Subjects	14	21		16	5	
Age in years	25.4 (3.60)	26.24 (5.4)	$P = .67$	25.51 (5.81)	26.32 (4.22)	$P = .91$
Gender	10M: 4F	12M:9F	$\chi^2 = .26$	9M:7F	3M:2F	$\chi^2 = .39$
Handedness	14R: 0L	19R:2L	$\chi^2 = .42$	15R: 1L	4R:1L	$\chi^2 = .45$
Premorbid IQ	104.64 (9.05)	99.62 (13.44)	$P = .24$	98.50 (13.23)	101.34 (12.17)	$P = .43$
Antipsychotic medication	—			2	0	
Antidepressant medication	—			2	0	
GAF Score		57.26 (10.86)		59.53 (10.11)	48.98 (10.34)	$P = .08$
PANSS positive	—	12.10 (4.33)		12.50 (4.81)	10.90 (2.28)	$P = .46$
PANSS negative	—	10.10 (3.50)		9.44 (2.60)	12.20 (5.35)	$P = .12$
PANSS general	—	25.10 (5.40)		25.38 (7.70)	24.20 (7.05)	$P = .76$
PANSS total	—	47.38 (11.91)		47.56 (11.62)	46.80 (14.02)	$P = .90$

Note: UHR, ultra high risk—all subjects with UHR regardless of outcome; UHR-nt, subjects with UHR that did not transfer into psychosis; UHR-t, subjects with UHR that did transfer into psychosis; fMRI, functional magnetic resonance imaging; PET, positron emission tomography; GAF, Global Assessment of Function; PANSS, Positive and Negative Syndrome Scale.

4000 ms, TE 40 ms) with each acquisition compressed into the first 2000 ms of the repetition time, creating a 2000 ms silent period in which subjects could articulate a response in the absence of scanner noise. Compressed acquisition sequences are also effective in reducing motion artifact due to head movement during articulation.[16] Each volume contained 22 axial 5 mm slices with a 0.5 mm gap between each slice (voxel size = 3.75 × 3.75 × 5.5 mm).

fMRI Analysis

Preprocessing of functional data was performed using SPM5 software (http//www.fil.ion.ucl.ac.uk/spm), running in Matlab (Mathworks Inc., Sherbon, MA), and is described in our previous study.[17] The first-level multiregression analysis was performed for each subject to test the correlation between the MRI signals and our fitted model. Low-frequency noise was removed using a high-pass filter with a cutoff of 128 seconds. We modeled 4 regressors: easy VF blocks, hard VF blocks, error responses, and WR. We specified first-level contrasts (*a*) easy VF > WR and (b) hard VF > WR. Error responses were treated as a nuisance regressor and were not explicitly modeled in first-level contrasts. One-sample *t* tests were used to examine the main effect of task (easy and hard VF > WR) in control and UHR groups separately. A random effects 2 × 3 factorial ANOVA was used to examine the main effects of task (easy vs hard VF), group (controls, UHR who did not develop psychosis [UHR-nt], and UHR subjects that made a transition to psychosis [UHR-t]), and interaction effects.

The context-dependent contributions of the brainstem region (identified by random-effects analysis, see results) to

brain regions elsewhere were assessed by psychophysiological interactions (PPIs[18]). Subject-specific time series were obtained from the midbrain region of the brainstem (using an anatomical mask of this regions in WFU pickatlas to ensure subject-specific eigenvariates were restricted to the anatomical region of interest [ROI]) by extracting the first principle component with a 6 mm sphere from the peak voxel within the anatomically defined region using the effect of interest. After these time series had been obtained for each subject, the actual PPI analysis was conducted using the midbrain region as the seed. The PPI term was computed with a vector coding for the main effect of task (ie, easy + hard VF [+1] <> WR [−1]). The PPI term for each region was then used in a first-level multiregression analysis. Subject-specific contrast images were then entered into a second-level random effects model. All statistical inferences from random effects models were made at a corrected cluster level ($P < .05$, with a standard voxel-level threshold of $P < .001$) unless otherwise stated.

[18F]-DOPA PET—Imaging

Within our sample, [18F]-DOPA PET imaging data were available in a subgroup of control (n =14), UHR-nt (n = 16), and UHR-t (n = 5) subjects. Due to the fMRI finding of increased activation (UHR-t > UHR-nt) in the brainstem (see results), we performed an exploratory and post hoc analysis to examined dopamine synthesis capacity in this region. A full description of the [18F]-DOPA PET procedure is provided elsewhere.[19] 18F-DOPA PET images were processed using fully automated methods as previously described.[19] Standardized ROI in Montreal Neurologic Institute space were defined in the cerebellum (the reference region) and in the brainstem. Dopamine synthesis capacity (k_i^{cer}) was determined in an anatomical brainstem ROI that included midbrain (ventral tegmental area, substantia nigra) and pons using a graphical analysis with the cerebellum as the reference region. The ROI were applied in a fully automated procedure using the HAMNET maximum probability atlas, a commercially available atlas of standard brain regions.[20]

Results

Behavioral Results

All subjects performed the task with a high degree of accuracy. Mean errors (SD) during easy VF trials were: controls = 3.45 (3.60), UHR-nt = 5.43(4.50) and UHR-t = 4.56 (6.80). Mean errors (SD) during hard VF trials were: controls = 7.21(6.11), UHR-nt = 10.12 (5.93) and UHR-t = 8.75 (6.47). There was a main effect for load, with all subjects making more errors in response to hard compared with easy letters (F = 34.03, df = 1.62 $P < .001$). There was no significant main effect for group (F = 1.13 df = 1,62 P = .33) and no significant group by load interaction (F = .14 df = 1.62 P = .87).

fMRI Results

Effect of Task: VF vs WR. In control subjects, there was activation in the left superior frontal, precentral and inferior frontal gyrus (pars operculum), the left insula, and the thalamus bilaterally. In UHR subjects, there was activation in the left middle frontal gyrus, the left pre- and postcentral gyrus, frontal operculum and insula, the superior frontal gyri, and the right insula, caudate, and brainstem. There was no significant main effect of load (easy vs hard VF) in either group.

Effect of Group: UHR vs Controls. There was greater activation in the UHR group relative to controls in the right middle frontal gyrus and superior frontal sulcus (table 2 and figure 1a), but no areas where controls showed more activation than UHR subjects.

UHR-t vs Controls. UHR who subsequently developed psychosis showed greater activation than controls in the right middle frontal and bilateral superior frontal gyrus/sulcus (table 2 and figure 1b). No areas showed greater activation in control relative to UHR-t subjects.

UHR-nt vs Controls. No clusters survived correction. At an uncorrected voxel-level threshold ($P < .001$), relative to controls, the UHR-nt group showed greater activation in the left middle temporal gyrus and the right middle frontal gyrus. No areas showed greater activation in control relative to UHR-nt subjects.

UHR-t vs UHR-nt. Relative to the UHR-nt group, the UHR-t group showed greater activation in the left superior frontal gyrus, the bilateral middle frontal gyrus, the brainstem including the midbrain and the basilar pons, and the left hippocampus including the subiculum (table 2 and figure 1c). No areas showed greater activation in UHR-nt relative to UHR-t subjects. The differential midbrain/basilar pons activation seen in the UHR-t relative to UHR-nt motivated a post hoc functional connectivity analysis to establish if transition to psychosis was associated with altered connectivity between the midbrain and cortical regions. Using the midbrain region as the seed, we observed greater negative functional connectivity in the UHR-t relative to both the UHR-nt and the control groups in the left superior frontal and right middle frontal gyri (table 2 and figure 2a). This effect was due to greater functional connectivity between the midbrain and PFC regions in UHR-t subjects during WR trials (ie, the negative interaction term; figure 2b).

[18F]-DOPA PET Exploratory Analysis. In the subgroup of subjects who underwent both fMRI and [18F]-DOPA PET scanning (table 1), there was no significant difference in mean brainstem [18F]-DOPA k_i^{cer} between controls and the UHR group as a whole (t = −.80 df = 33 P = .42). However, in the UHR-t subjects (n = 5),

Table 2. (i) Group Differences in Regional Activation (fMRI) During Verbal Fluency, (ii) Group Contrasts (Negative) for PPI Analysis With Midbrain Seed Region

Contrasts	Side	*Z*	*x*	*y*	*z*	Region
(i) fMRI contrasts						
UHR > controls	R	4.54	32	50	14	Middle frontal gyrus
	R	3.84	28	36	38	Superior frontal sulcus
UHR < controls						No supra threshold effect
UHR-t > controls	R	4.80	32	50	14	Middle frontal gyrus
	R	4.13	16	54	12	Superior frontal sulcus
	L	3.97	−14	50	2	Superior frontal gyrus
UHR-t < controls						No supra threshold effect
UHR-nt > controls						No supra threshold effect
UNR-nt > controls						No supra threshold effect
UHR-t > UHR-nt	R	5.09	32	60	14	Inferior frontal gyrus/middle frontal sulcus
	R	4.50	2	−12	−10	Brainstem (midbrain/pons)
	L	4.20	−2	−24	−18	Brainstem (midbrain/pons)
	L	4.17	−28	−7	−20	Hippocampus
	L	4.36	−14	50	4	Superior frontal gyrus
	L	4.20	−36	58	10	Middle frontal gyrus
UHR-t < UHR-nt						No supra threshold effect
(ii) PPI contrasts						
UHR-t > controls	L	4.29	−16	50	4	Middle frontal gyrus
		3.92	−12	60	12	
Controls > UHR-t						No supra threshold effect
UHR-t > UHR-nt	L	3.37	−24	50	38	Superior frontal gyrus
		3.68	−16	50	4	
	R	3.91	14	56	10	Middle frontal gyrus
UHR-nt > UHR-t						No supra threshold effect

Note: The *x*, *y*, *z* coordinates of local maxima are listed according to the MNI coordinate system. All results reported at ($P < .05$ cluster corrected). UHR-nt, subjects with UHR that did not transfer into psychosis; UHR-t, subjects with UHR that did transfer into psychosis; fMRI, functional magnetic resonance imaging; PPI, psychophysiological interaction.

there was a significant elevation in brainstem [18F]-DOPA k_i^{cer} relative to UHR-nt subjects ($n = 16$; $t = -3.2$, $df = 19$ $P < .01$) and a trend for an elevation relative to control subjects ($t = -1.70$, $df = 17$, $P = .10$) (figure 3).

Discussion

All subjects performed the VFT with a high degree of accuracy, and, consistent with previous functional imaging studies of VF, there was activation in supplementary motor area, medial frontal gyrus, cingulate cortex, insula, inferior frontal gyrus, precentral gyrus, and temporal lobe,[3,4] independent of group. Activation in this network of regions during VF is thought to support speech production and executive language processes,[21] and activation in the ventrolateral PFC, specifically the inferior frontal gyrus (IFG), is associated with word selection.[22] The UHR subjects showed greater activation than controls in the right middle and superior frontal gyri, with most of the differential response in the dorsolateral PFC. This region, is critical for executive functioning,[23] and during word production, plays a role in planning appropriate responses.[24,25] This finding adds to previous imaging studies that report altered PFC activation that is associated with vulnerability for psychosis.[8,10,11] These results replicate some of the findings from our previous study,[9] which were based on a subsample ($n = 17$ UHR and $n = 15$ controls) of that studied here. The previous study identified areas of relatively increased PFC activation in UHR subjects, but also prefrontal areas where activation was relatively reduced[9]: the latter was not evident in the present study. However, in the previous study, the analysis was constrained to regions where there was a linear or quadratic relationship across first episode, UHR, and control groups.

Our main prediction that there would be differences in PFC activation between UHR subjects who subsequently developed psychosis and those who did not was confirmed. Relative to the UHR-nt group, the UHR-t subgroup showed greater activation in the right inferior frontal, bilateral middle frontal, and left superior frontal gyri. The basis of the increased PFC activation in this

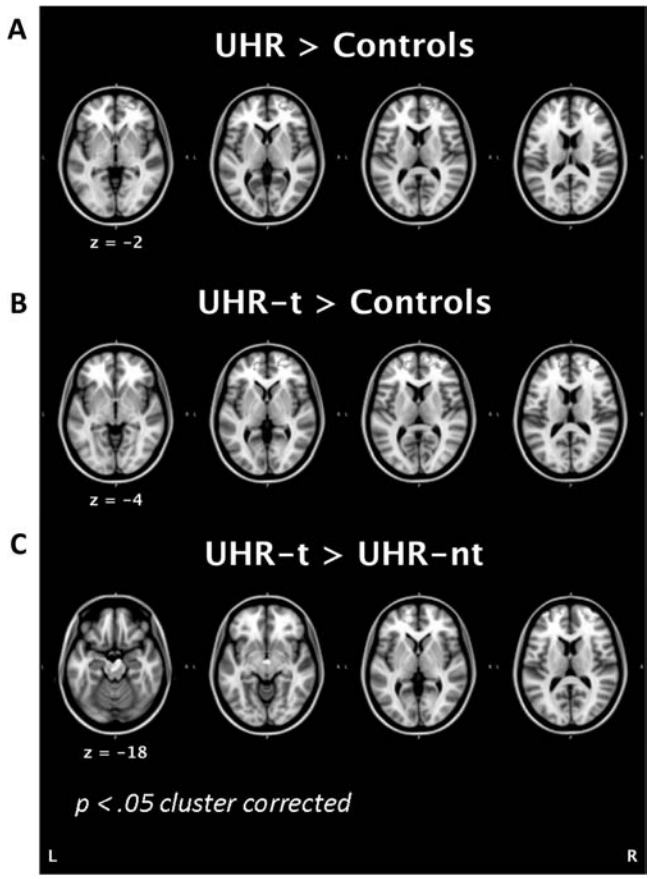

Fig. 1. Statistical Parametric Maps (SPMs) showing regions of greater activation during verbal fluency (easy + hard trials) in (A) ultra high risk (UHR) > controls, (B) subjects with UHR that did transfer into psychosis (UHR-t) > controls, and (C) UHR-t > subjects with UHR that did not transfer into psychosis (UHR-nt).

context is unclear, but it may reflect inefficient prefrontal function[26] or a compensatory response to impaired executive function[27] in UHR subjects. Our finding of increased PFC activation is consistent with a previous study examining functional activations in a UHR group according to clinical outcome[11] and may be indicative of neural inefficiency in vulnerable individuals.[28]

Unlike the study by Sabb and colleagues[11], increased lateral temporal activation was not observed in the UHR-t subgroup nor did activation differ in the ACC. However, increased activation in the brainstem (including the midbrain and pons) and the left hippocampus did distinguish UHR-t and UHR-nt groups. These differences are of particular interest, as the midbrain includes the site of brain dopaminergic neurons. The medial temporal region is thought to be critical to the pathophysiology of psychosis[29–32] and has been specifically linked to the onset of psychosis in UHR subjects.[33] A recent circuit-based model proposes that in schizophrenia, a disruption of interneuronal regulation of the ventral subiculum (part of the anterior hippocampus) leads to an overdrive of the dopamine system in the midbrain and striatum[34] and that dysregulation in this circuit is critical to the onset of psychosis.[35] Further work is needed to test this hypothesis properly in humans; however, the results of the present study appear to provide some preliminary support this model.

To examine if increased midbrain activation was related to altered activation in cortical regions, we conducted a post hoc functional connectivity analysis with the midbrain as seed region. An increase in midbrain-PFC functional connectivity was seen in UHR-t subjects relative to UHR-nt and controls. Although functional connectivity analyses do not permit inferences regarding causality, the results demonstrate an association between activation in the midbrain and PFC that is particular to UHR subject who subsequently develop psychosis. The correlation between time series in the midbrain and PFC was due to increased connectivity between theses regions during WR trials (baseline condition) in the UHR-t group suggesting enhanced midbrain-PFC coupling when the task demands were low. Given the midbrains's involvement in the mesolimbic system, this finding is consistent with studies by our own group reporting an association between altered PFC activation and elevated striatal dopamine function in UHR subjects (eg, Fusar-Poli et al[17]). To directly investigate the involvement of the dopamine system, we were able to examine midbrain presynaptic dopamine synthesis in a subgroup of our sample using [18F]-DOPA PET. The UHR-t subjects showed a significant elevation in [18F]-DOPA uptake relative to UHR-nt subjects. Although exploratory, this result extends our previous finding that dopamine synthesis capacity in the striatum is also increased in UHR subjects who later develop psychosis and increases further longitudinally as they develop psychosis.[36] [18F]-DOPA k_i^{cer} indexes dopamine synthesis and storage capacity and is presumably positively related to somatodendritic dopamine release in the midbrain. Increases in [18F]-DOPA k_i^{cer}[19] could thus result in a hypodopaminergic state in the PFC[37] via D2 receptor autoinhibitory feedback mechanisms.[38] However, due to the small sample size ($n = 5$), we were unable to robustly explore the relationship between [18F]-DOPA uptake and PFC activation in our UHR-t subgroup.

One limitation of the present study is the small number of subjects in the UHR-t subgroup. However, in functional neuroimaging studies, the use of a random effect approach with small sample sizes typically results in reduced sensitivity rather than false positive results; a small sample size will result in a small number of degrees of freedom, resulting in a less sensitive statistical analysis.[39] The findings are unlikely to reflect differential task performance because there were no group differences at the behavioral level and only data from trials associated with correct response were used in the analysis. Similarly, they are not attributable to effects of medication, as all but 4 of the UHR subjects were medication naive, and only one of the transition subgroup had

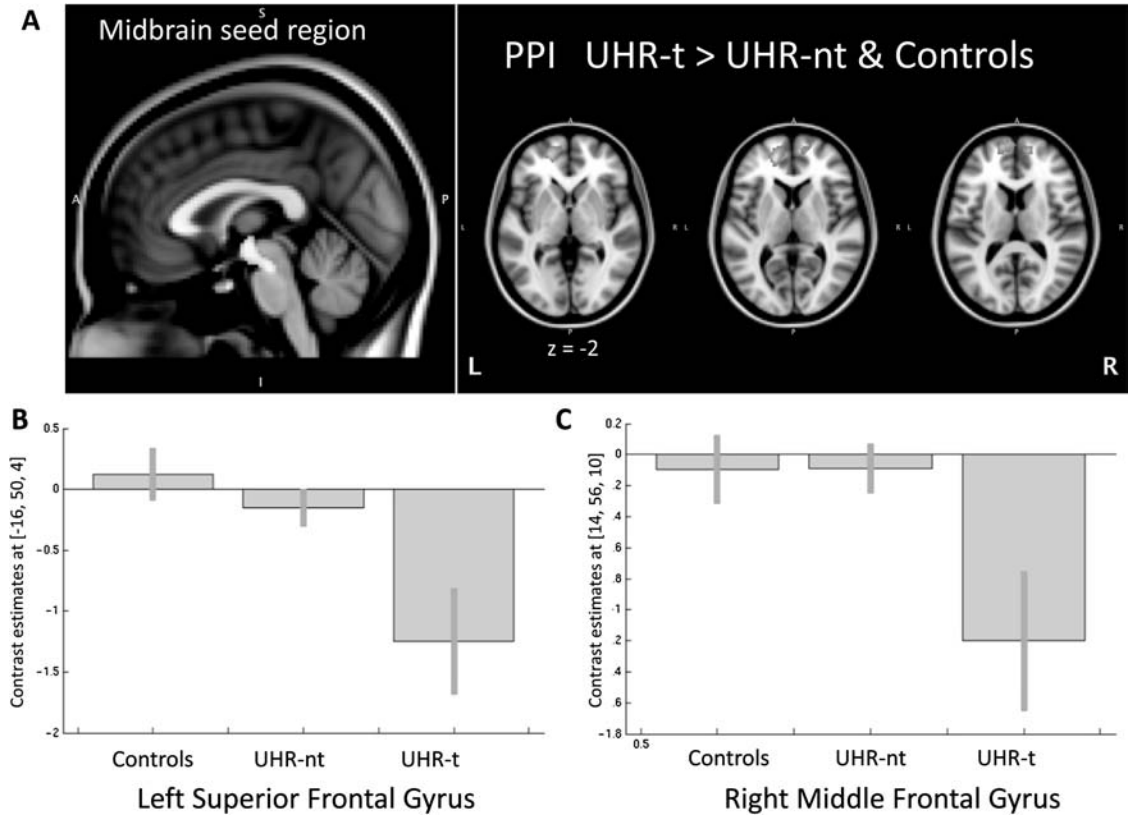

Fig. 2. (A) Psychophysiological interaction (PPI) seed region in midbrain and statistical parametric map (SPM) of PPI group negative effect in subjects with ultra high risk (UHR) that did transfer into psychosis (UHR-t) > subjects with UHR that did not transfer into psychosis (UHR-nt) in prefrontal cortex ($P < .05$ cluster corrected) and plots showing significantly greater negative (word repetition > verbal fluency) PPI contrast estimates in UHR-t subjects in (B) left superior frontal gyrus, and (C) right middle frontal gyrus.

been exposed to medication. It is also unlikely that the subjects from the UHR-t group already had an undetected psychotic disorder at the time of scanning, as there was no difference in PANSS score between the 2 UHR subgroups and in all but one of the UHR-t group, frank psychosis was not diagnosed until more than 6 months after they were scanned. However, in order to avoid possible confounding effects on the blood oxygen level dependent (BOLD) signal, UHR subjects with substance misuse and dependence disorders were excluded from the present study. The number of UHR subjects meeting these criteria is generally low,[14] and exclusion of these subjects is unlikely to have made our sample unrepresentative. Finally, although the ROI used in the PET analysis includes the midbrain dopaminergic nuclei of the substantia nigra and ventral tegmentum, it also includes other monoaminergic nuclei, in particular the raphe nucleus and locus coerulus, which may contain aromatic L-amino acid decarboxylase and metabolise DOPA. As such the k_i^{cer} values reported for this region may reflect a contribution from serotoninergic and noradrenergic neurons as well as dopaminergic neurons.[40] At present, the extent of this contribution is not clear.

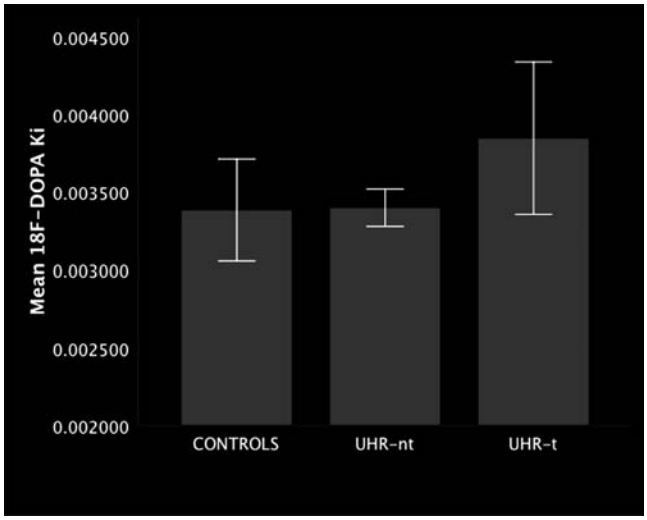

Fig. 3. Mean brainstem [18F]-DOPA k_i^{cer} by group (error bars = 95% CI).

In summary, in people at high risk of psychosis, increased activation in a network of cortical and subcortical regions and increased midbrain-PFC connectivity may predict the subsequent onset of illness. Functional neuroimaging, in conjunction with clinical assessment and other investigations, may facilitate the prediction of outcome in subjects who are vulnerable to psychosis.

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The authors have declared that there are no conflicts of interest in relation to the subject of this study.

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