

# Abnormal Frontostriatal Interactions in People With Prodromal Signs of Psychosis

## A Multimodal Imaging Study

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**Context:** Alterations in dopaminergic neurotransmission and function of the prefrontal cortex are thought to be central to the pathophysiology of schizophrenia, but the relationship between these factors in the development of psychosis is unclear.

**Objective:** To investigate the relationship between striatal dopamine activity and prefrontal function in people at ultra high risk of psychosis.

**Design:** Subjects were studied using functional magnetic resonance imaging while performing a working memory (N-back) task. Positron emission tomography with fluorine 18-labeled fluorodopa was used to investigate presynaptic striatal dopamine activity.

**Setting:** Outpatient service for people with prodromal signs of psychosis.

**Patients and Other Participants:** Thirty-four subjects participated in the study: 14 healthy volunteers and 20 subjects with an at-risk mental state (ARMS).

**Main Outcome Measures:** Regional brain activation (blood oxygen level–dependent response), Ki for [<sup>18</sup>F]fluorodopa uptake, and objective ratings of psychopathology at the time of scanning.

**Results:** In the associative part of the striatum, the Ki for [<sup>18</sup>F]fluorodopa was higher in the ARMS group than in the controls. During the N-back task, ARMS subjects displayed less activation in the right middle frontal gyrus, the medial frontal gyri, and the left superior parietal lobule than controls. The Ki for [<sup>18</sup>F]fluorodopa was positively correlated with activation in the right middle frontal gyrus in controls but negatively correlated with activation in this region in the ARMS group.

**Conclusions:** In people with prodromal signs of psychosis, there are direct correlations between altered prefrontal cortical function and subcortical dopamine synthesis capacity, consistent with the notion that frontostriatal interactions play a critical role in the pathoetiology of schizophrenia.

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**A**BNORMAL PREFRONTAL CORtical function during cognitive tasks and elevated striatal dopaminergic transmission are 2 of the most robust pathophysiological features of schizophrenia,<sup>1,2</sup> but the relationship between them in the development of the disorder remains to be established. Prefrontal dysfunction appears to underlie many of the cognitive impairments seen in schizophrenia, particularly deficits in working memory function.<sup>3,4</sup> Both alterations in prefrontal activation<sup>5</sup> and impairments in working memory<sup>6</sup> are also evident in individuals with an at-risk mental state (ARMS), who present with “prodromal” symptoms of psychosis and have a very high risk of developing psychosis within the following

2 years.<sup>7</sup> Furthermore, there is some evidence that within an ARMS sample, the severity of working memory impairments predicts subsequent onset of schizophrenia.<sup>8</sup>

Working memory is normally mediated by a distributed neural network that includes the parietal and prefrontal cortex,<sup>9,10</sup> with consistent engagement of the dorsolateral prefrontal regions.<sup>10</sup> Working memory function is normally modulated by central dopaminergic activity.<sup>11</sup> Thus, the pharmacological manipulation of dopamine activity in experimental animals<sup>12,13</sup> and healthy subjects<sup>14</sup> alters prefrontal function at both the neuronal and regional level during working memory tasks. Systemic administration of dopamine agonists can enhance working memory performance<sup>15</sup> and modulate task-

dependent neuronal activity within the prefrontal cortex,<sup>16,17</sup> while in Parkinson disease<sup>15</sup> and in animal models,<sup>18</sup> the loss or depletion of dopamine neurons is associated with impaired performance. Prefrontal function during working memory tasks appears to be most efficient at a particular level of afferent dopamine activity and suboptimal if dopamine activity is either too low or too high.<sup>19</sup> This relationship can be described as following an inverted U-shaped curve.<sup>19</sup>

Schizophrenia is associated with overactivity of the subcortical dopaminergic system, leading to increased dopamine activity and release in the striatum and to the development of psychotic symptoms.<sup>20-22</sup> These findings are also evident in subjects with an ARMS<sup>23</sup> and in individuals at high familial risk of psychosis.<sup>22,24</sup> The relationship between alterations in striatal dopamine activity and changes in prefrontal and working memory function in the development of schizophrenia is unclear.<sup>12</sup> However, as dopamine activity normally modulates the efficiency of prefrontal function, it has been suggested that altered prefrontal activation in schizophrenia may be related to an abnormal level of dopamine activity. To our knowledge, only 1 previous positron emission tomography (PET) study has examined both prefrontal activation and striatal dopamine function in schizophrenia. Reduced prefrontal blood flow during the Wisconsin Card Sorting Test was correlated with elevated striatal dopamine function in patients with chronic schizophrenia, a correlation that was not evident in healthy controls.<sup>25</sup>

The aim of the present study was to examine the relationship between dysfunction in the prefrontal cortex and in the striatal dopamine system in the development of psychosis. We studied medication-naïve subjects with prodromal signs for psychosis (ARMS), measuring prefrontal activation during a working memory task (the N-back) with functional magnetic resonance imaging (fMRI) and dopamine synthesis capacity in the striatum with fluorine 18-labeled fluorodopa PET. On the basis of previous studies,<sup>22,26</sup> we first hypothesized that the ARMS subjects would be associated with both reduced prefrontal activation and elevated striatal dopamine function relative to controls. Following the findings of Meyer-Lindenberg et al,<sup>25</sup> we then tested our main hypothesis that the relationship between prefrontal activation and striatal dopamine function in the ARMS subjects would be significantly different from that in controls.

## METHODS

### SUBJECTS

#### ARMS Group (n=20)

Individuals meeting PACE criteria for the ARMS<sup>27</sup> were recruited from Outreach and Support in South London.<sup>28</sup> The diagnosis was based on assessment by 2 experienced clinicians using the Comprehensive Assessment of At-Risk Mental States (CAARMS)<sup>29</sup> and a consensus meeting with the clinical team. All subjects were antipsychotic naïve at the time of the scanning. Two subjects were receiving an antidepressant treatment. The group was representative of the local population of people presenting with an ARMS in terms of age, sex, ethnicity, and duration and intensity of symptoms.<sup>28</sup>

### Controls

Healthy volunteers (n=14) were recruited via advertisements in the local media. Subjects were excluded if there was a history of neurological disorder or they met *DSM-IV* criteria for a substance dependence or abuse disorder or other axis I psychiatric diagnosis.

All subjects in both groups were native speakers of English and were right handed, as evaluated using the Lateral Preference Inventory.<sup>30</sup>

### CLINICAL MEASURES

The severity of symptoms in the ARMS group was assessed at the time of scanning using the CAARMS<sup>29</sup> and the Positive and Negative Syndrome Scale.<sup>31</sup> The first 3 items on the CAARMS, which cover delusions, hallucinations, and thought disorder, were summed to give a total score for attenuated "positive" psychotic symptoms. Consumption of illicit substances, tobacco, and coffee/tea was evaluated using a modified version of the Cannabis Experience Questionnaire.<sup>32</sup> Premorbid intelligence was assessed using the National Adult Reading Test.<sup>33</sup> The effect of group on demographic and clinical measures was tested using analyses of variance for parametric variables, and Mann-Whitney *U* tests were used to compare individuals with ARMS with controls for nonparametric variables after checking for equality of variance with the Levene test.

### fMRI SCANNING

#### Image Acquisition

Images were acquired on a 1.5-T Signa (GE Healthcare, Milwaukee, Wisconsin) system at the Maudsley Hospital, London, England. T2\*-weighted images were acquired using a gradient echo sequence (repetition time=2000 milliseconds and echo time=40 milliseconds) with 3-mm slices and a 0.3-mm gap in 14 axial planes. Images were acquired while subjects performed an N-back task. Subjects were presented with series of letters that they viewed using a prismatic mirror. The interstimulus interval was 2 seconds. During a baseline (0-back) condition, subjects were required to move a joystick to the left when the letter X appeared. During 1-back and 2-back conditions, participants were required to press a button on the joystick with their right index finger if the currently presented letter was the same as that presented 1 or 2 trials beforehand, respectively. The 3 conditions were presented in 10 alternating 30s blocks, matched for the number of target letters per block (ie, 2 or 3) in a pseudorandom order. Reaction time and response accuracy were recorded online. To facilitate anatomical localization of activation, a high-resolution inversion recovery image data set was also acquired, with 3-mm contiguous slices and an in-plane resolution of 3 mm (repetition time=1600 milliseconds, inversion time=180 milliseconds, echo time=80 milliseconds).

#### Image Analysis

Functional MRI data were analyzed using Statistical Parametric Mapping (SPM5; Wellcome Department of Cognitive Neurology, London) running in MATLAB7.1 (The MathWorks, Natick, Massachusetts). All volumes were realigned to the first volume, corrected for motion artifacts, mean adjusted by proportional scaling, normalized into standard stereotactic space (template provided by the Montreal Neurological Institute), and smoothed using a 6-mm full-width-at-half-maximum gaussian kernel. The time series was high-pass filtered to eliminate low-frequency components (filter width 128 seconds) and adjusted for systematic differences across trials. In the first-level

analysis, the onset times (in seconds) for each trial were convolved with a canonical hemodynamic response function. Because no significant effect of cognitive load on regional activation was observed, each task condition (1-back, 2-back) was then contrasted against the baseline condition (0-back) in each subject. Because performance differences have been shown to represent a strongly moderating variable when comparing neural correlates of working memory, the analysis was restricted to images associated with correct responses. To test the hypothesis that there were between-group differences in activation, we performed a second-level analysis comparing activation during N-back, independent of task demand (1-back + 2-back combined vs 0-back) between the 2 groups, using an independent-samples *t* test. The whole-brain voxelwise threshold was set at  $P < .05$ , familywise error corrected.

## PET SCANNING

### Image Acquisition

Images were acquired using a 3-dimensional PET scanner (ECAT/EXACT3D; Siemens/CTI, Knoxville, Tennessee), which has a spatial resolution of  $4.8 \pm 0.2$  mm and a sensitivity of 69 cps/Bq/mL.<sup>34</sup> Images of the whole brain were reconstructed from 95 planes with a slice spacing of 2.425 mm. All subjects received 150 mg of carbidopa and 400 mg of entacapone orally 1 hour prior to scanning to reduce the formation of radiolabelled metabolites,<sup>35-37</sup> which may potentially cross the blood-brain barrier.<sup>38</sup> Subjects were positioned with the orbitomeatal line parallel to the transaxial plane of the tomograph. Head position was marked and monitored via laser crosshairs and a camera. A 5-minute transmission scan was carried out before radiotracer injection using a 150-MBq cesium 137 rotating point source to correct for attenuation and scatter. Approximately 150 MBq of [<sup>18</sup>F]fluorodopa was administered by intravenous injection immediately following a 30-second background frame. The emission scan lasted 95 minutes with 26 time frames (comprising a 30-second background frame and four 60-second, three 120-second, three 180-second, and finally fifteen 300-second frames). The PET data from 8 of the subjects with an ARMS and 5 of the control subjects have been previously reported as part of a separate study.<sup>23</sup>

### Image Analysis

Movement correction was conducted by denoising the nonattenuated dynamic image<sup>39</sup> and realigning the frames to a single frame acquired 6 minutes postinjection using a mutual information algorithm.<sup>40</sup> The transformation parameters were then applied to the corresponding attenuation-corrected frames and the realigned frames combined to create a movement-corrected dynamic image for the regions of interest (ROI) analysis.<sup>41</sup> The ROI analysis was carried out blind to group status by one of us (O.D.H.). Standardized regions in Montreal Neurological Institute space were defined in the cerebellum using a probabilistic atlas<sup>42</sup> and in the whole striatum delineated using the criteria described by Mawlawi et al,<sup>43</sup> drawn on a healthy control MRI in Montreal Neurological Institute space. This ROI atlas was then normalized to each individual PET summation image (native space) together with the [<sup>18</sup>F]fluorodopa template used in a previous study<sup>44</sup> (constructed from images acquired using the ECAT/EXACT3D scanner) using Statistical Parametric Mapping (SPM2; Wellcome Department of Cognitive Neurology). Using the [<sup>18</sup>F]fluorodopa template improves the normalization of the ROI atlas.<sup>45</sup> Striatal subdivisions were delineated according to the criteria used by Martinez et al<sup>46</sup> to yield limbic, associative, and sensorimotor subregions.<sup>46</sup> These subdivisions reflect the topographical arrangement of corticostriatal projections, with projections to the limbic subregion from areas such as the hip-

pocampus and amygdala, projections to the associative subregion from associative areas such as the dorsolateral prefrontal cortex, and projections to the sensorimotor subregion from the motor cortex and premotor and supplementary motor cortex.<sup>47</sup> Graphical analysis was used to calculate influx constants (*K<sub>i</sub>* values) for the whole striatal ROI and the functional subdivisions relative to uptake in the reference region for the left and right sides combined.<sup>48</sup> The cerebellum was used as the reference region because it has been shown to have little or no specific [<sup>18</sup>F]fluorodopa uptake and the lowest uptake in the brain.<sup>49</sup> An analysis of variance was used to determine whether there was an effect of group on *K<sub>i</sub>* value.

## INTEGRATION OF fMRI AND PET DATA

The fMRI and PET scans in each subject were performed as close together as was practically possible. In many subjects, both scans were performed in the same week, but restrictions on the availability of scanning slots meant that this was not always possible. To explore the correlation between the prefrontal blood oxygen level-dependent response during the N-back task and striatal dopamine function, *K<sub>i</sub>* values from the PET data were entered as covariates in the fMRI group analysis. The whole-brain results were then masked with the activation map corresponding to the main effect of the working memory task (1-back + 2-back combined vs 0-back). Results were reported at  $P < .05$  familywise error corrected for multiple comparisons. We also completed a post hoc analysis of potential interactions between blood oxygen level-dependent signal and [<sup>18</sup>F]fluorodopa uptake by extracting the  $\beta$  values and testing them in a regression model in SPSS (SPSS Inc, Chicago, Illinois) ( $P < .05$ ). The Cook distance test was used to assess the effect of potential outliers on the correlations. In a second step, we tested if there was a differential neural response between ARMS subjects with a high *K<sub>i</sub>* ( $n >$  median) and ARMS subjects with a low *K<sub>i</sub>* ( $n <$  median). Across the whole group (ARMS and control subjects), we also compared subjects with mid *K<sub>i</sub>* values (25 percentiles  $< n >$  75 percentiles) with those with high or low *K<sub>i</sub>* values ( $n <$  25 percentiles and  $n >$  75 percentiles). Because of the exploratory aim of these post hoc comparisons, we used a threshold of  $P = .001$ , uncorrected.

## RESULTS

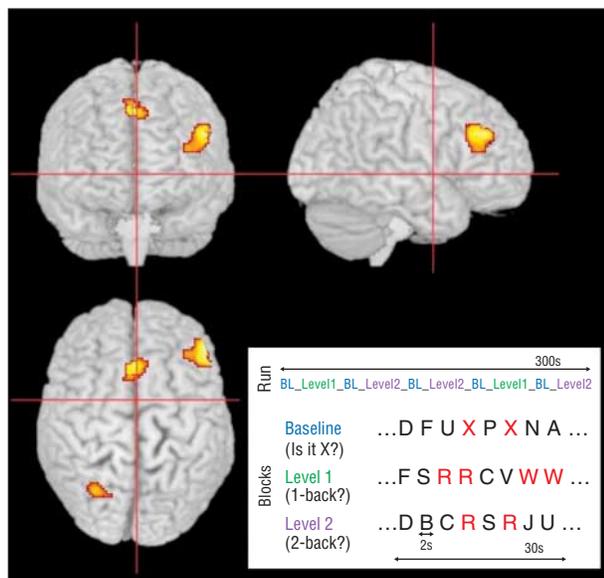
### CLINICAL AND DEMOGRAPHIC CHARACTERISTICS OF THE SAMPLE

The 2 groups were matched in terms of age (ARMS subjects, mean [SD] = 26.6 [5.0] years; controls, mean [SD] = 25.5 [3.6] years;  $t = -0.68$ ;  $P = .50$ ), estimated premorbid IQ (ARMS subjects, mean [SD] = 101.29 [12.29]; controls, mean [SD] = 103.62 [8.92];  $t = 0.574$ ;  $P = .57$ ), and history of cannabis use (cannabis cigarettes smoked per week,  $t_{32} = -1.28$ ;  $P = .21$ ). As expected, there was a significant group difference in the severity of psychopathology, both when rated using the CAARMS (total scores:  $t_{32} = -4.50$ ;  $P < .001$ ; disorders of thought content:  $t_{32} = -7.38$ ;  $P < .001$ ; perceptual disorders:  $t_{32} = -4.18$ ;  $P < .001$ ; speech disorders:  $t_{32} = -5.91$ ;  $P < .001$ ) and the Positive and Negative Syndrome Scale (total scores:  $t_{32} = -3.25$ ;  $P = .003$ ; positive scores:  $t_{32} = -4.93$ ;  $P < .001$ ; negative scores:  $t_{32} = -3.18$ ;  $P = .003$ ; general scores:  $t_{32} = -3.74$ ;  $P < .001$ ). We did not try to subdivide the ARMS sample according to whether they developed psychosis subsequent to scanning, as the sample is still undergoing clinical follow-up. At least 2 years'

**Table. Foci of Brain Activation During the N-back Task**

Brain Region	Side	MNI Coordinates			No. of Voxels	z Scores
		x	y	z		
Main effect of task (independent of group)						
Middle frontal gyrus	R	44	30	32	2707	6.10
Middle frontal gyrus	R	36	34	24		5.91
Inferior frontal gyrus	R	54	8	18		5.34
Middle frontal gyrus	L	-42	26	30	1507	6.00
Middle frontal gyrus	L	-40	-2	44		5.15
Inferior frontal gyrus	L	-48	2	24		5.05
Medial frontal gyrus	R	6	20	46	166	4.89
Superior frontal gyrus	L	-6	10	54		4.53
Medial frontal gyrus	L	-2	22	44		4.32
Insula	L	-34	22	0	94	4.91
Inferior parietal lobule	R	38	-52	50	2719	6.83
Inferior parietal lobule	R	32	-48	42		6.52
Superior parietal lobule	R	32	-66	48		6.15
Superior parietal lobule	L	-28	-58	48	1794	6.68
Inferior parietal lobule	L	-32	-50	42		6.15
Precuneus	L	-26	-64	38		5.76
Controls>ARMS group						
Middle frontal gyrus	R	54	34	28	89	3.93
Medial frontal gyrus	L	-2	24	44	41	3.69
Superior parietal lobule	L	-28	-66	58	34	3.56

Abbreviations: ARMS, at-risk mental state; MNI, Montreal Neurological Institute.



**Figure 1.** Reduced prefrontal and parietal activation in subjects with an at-risk mental state relative to controls during the N-back task ( $P < .05$ , familywise error corrected). The left side of the brain is shown on the left side of the Figure.

follow-up is needed to determine which individuals will develop psychosis.<sup>50</sup>

### N-BACK TASK

There were no differences in response accuracy between the ARMS (mean=93.96) and control (mean=94.57) groups during the N-back task ( $F_{32}=0.01$ ;  $P = .71$ ) and no differences in reaction time ( $F_{32}=1.765$ ;  $P > .05$ ).

## fMRI RESULTS

### Main Effect of Task

During the task, relative to baseline, there was bilateral activation in the middle, inferior, and medial frontal gyri and the inferior and superior parietal lobule and left-sided activation in the superior frontal gyrus and insula (**Table**) ( $P < .05$ , corrected).

### ARMS Subjects vs Controls

The ARMS group showed less activation in the right middle frontal gyrus, left medial frontal gyrus, and left superior parietal lobule than the controls (Table and **Figure 1**) ( $P < .05$ , corrected). There were no brain areas that showed greater activation in the ARMS group than the control group.

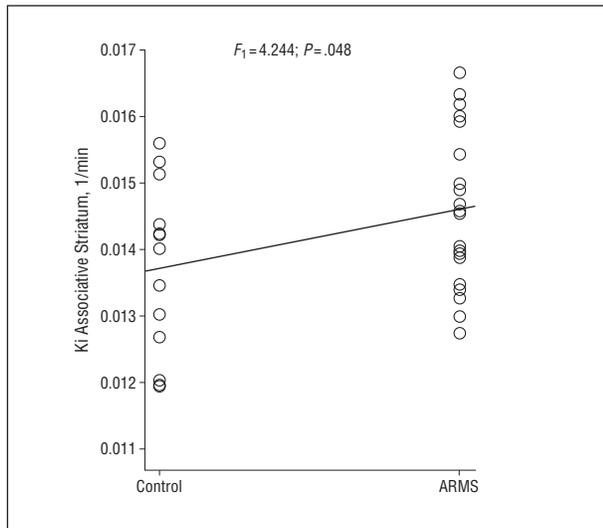
## PET RESULTS

A significant group effect was observed for the associative subdivision of the striatum ( $F_1=4.244$ ;  $P = .048$ ), but not for the limbic ( $F_1=3.650$ ;  $P > .05$ ) or the sensorimotor subdivisions ( $F_1=0.660$ ;  $P > .05$ ) (**Figure 2**). The Ki in the associative striatum was elevated by 6.33% (Cohen  $d$  effect size, associative striatum=0.75) in the ARMS group relative to the control group. There was no interaction between laterality and group for any of the striatal subdivisions or for the striatum as a whole ( $F=0.987$ ;  $P > .05$ ).

### RELATIONSHIP BETWEEN PREFRONTAL ACTIVATION AND STRIATAL DOPAMINERGIC FUNCTION

Within the network of areas engaged by the task (defined earlier), there was a significant difference in the relation-

ship between [<sup>18</sup>F]fluorodopa uptake in the associative subdivision of the striatum and activation in the right middle frontal gyrus in the 2 groups ( $x=48, y=32, z=24; z=5.03; P=.02$ , corrected) (**Figure 3**). In this region, there was a positive correlation between activation during the N-back task (1-back + 2-back vs 0-back) and the Ki in the associative striatum in controls ( $r=0.758; F=16.183; P=.002$ ) (Figure 3). Conversely, in the ARMS group, this correlation was negative, with increasing striatal Ki linked to decreasing activation ( $r=-0.717; F=18.024; P=.001$ ). These correlations were not driven by effects of outliers, as tested by the Cook D. Post hoc analyses revealed that the neural response in this area was not correlated with performance during the N-back task ( $r=0.146; P>.05$ ).



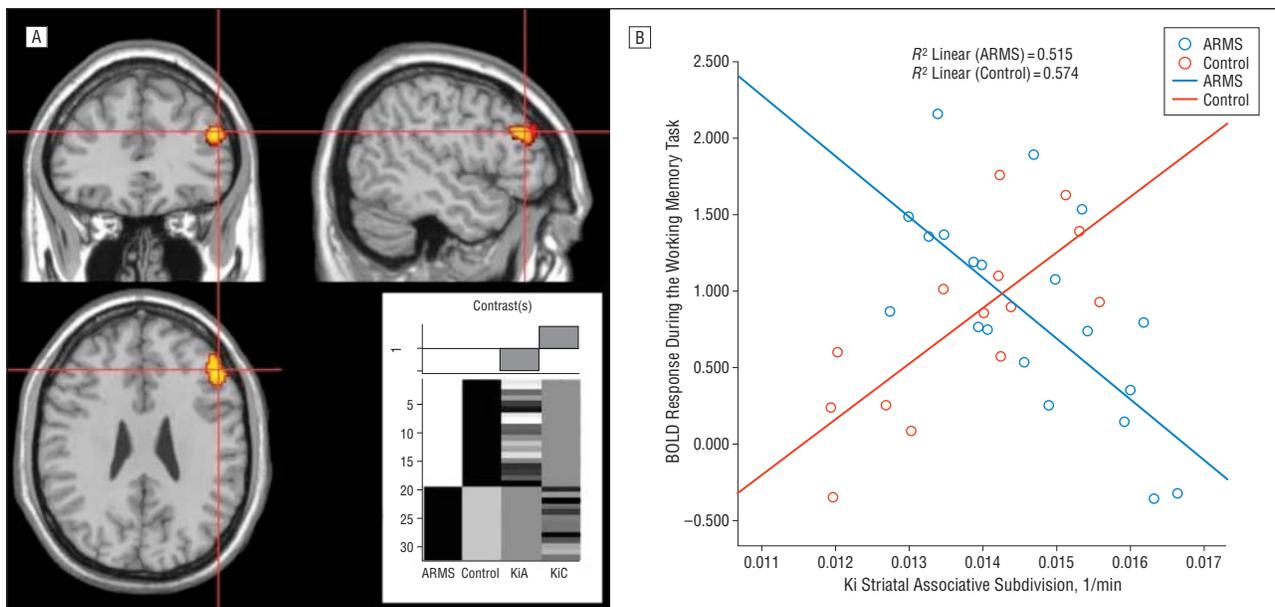
**Figure 2.** Elevated Ki for fluorine 18-labeled fluorodopa in the associative subdivision of the striatum in the at-risk mental state (ARMS) group relative to controls.

A post hoc quadratic regression analysis across all subjects (ARMS and controls) explained 42% of the variance in the data ( $R^2=0.422$ ) (**Figure 4**). Within the whole sample (ARMS and control groups combined), subjects with midrange Ki values (25 percentiles  $< Ki > 75$  percentiles; 25 percentiles = 0.0133, 75 percentiles = 0.0152) were compared with subjects with either high or low Ki values ( $Ki < 25$  percentiles and  $Ki > 75$  percentiles). Those with midrange values showed greater activation in the right middle frontal gyrus ( $x=52, y=32, z=14; Ke [cluster extent]=88; z=3.02; P=.001$ , uncorrected) than those with either low or high Ki (Figure 4). This region is similar to that where there was a group difference in the correlations between prefrontal activation and dopamine function (see earlier). Subjects with either high or low Ki values showed greater activation in the left precuneus ( $x=-24, y=-58, z=52; Ke=68; z=3.61; P=.001$ , uncorrected) and in the right superior parietal lobule ( $x=4, y=-66, z=54; Ke=124; z=3.22; P=.001$ , uncorrected) than subjects with midrange Ki values (Figure 4).

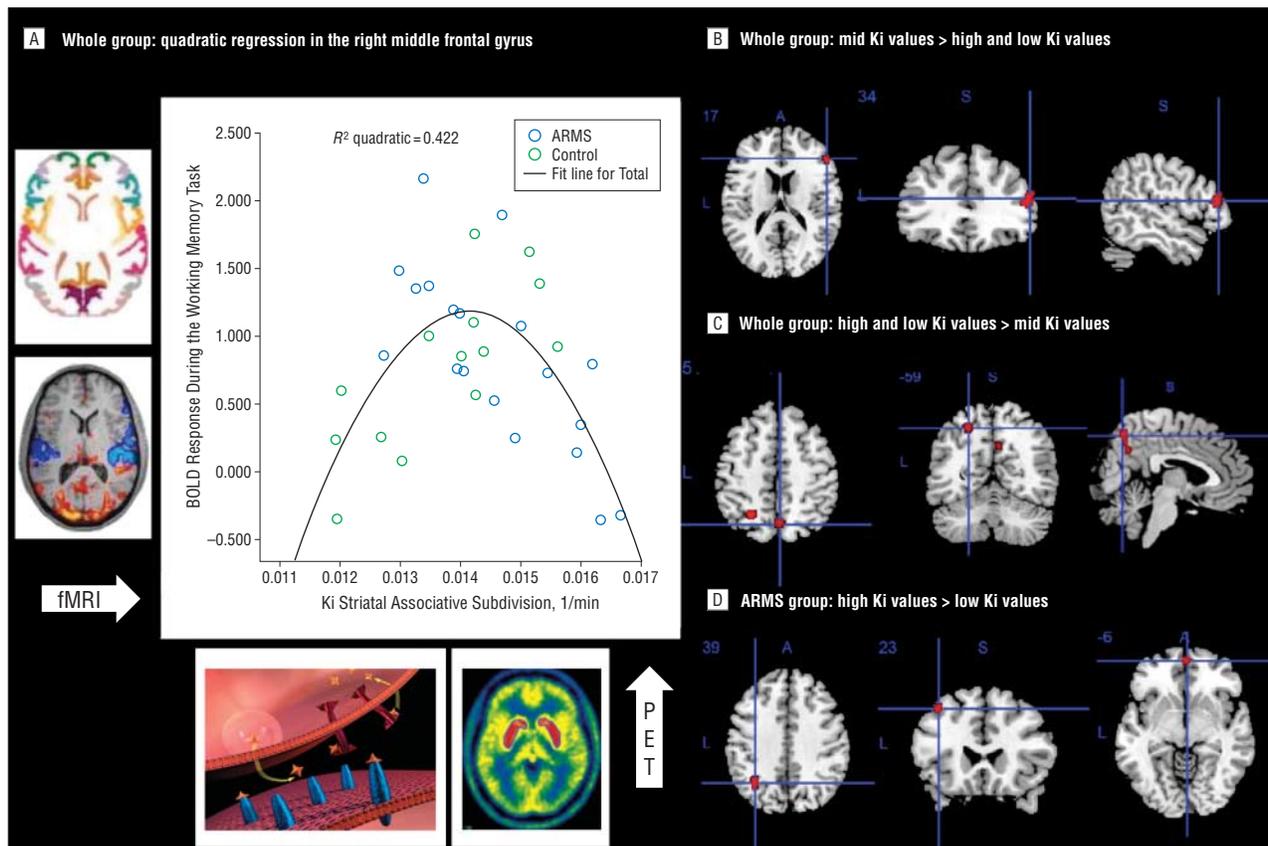
Within the ARMS group, the subjects with the most elevated Ki (greater than the group median;  $Ki=0.0146/min$ ) showed greater activation than those with a less marked elevation in Ki (lower than the group median;  $Ki=0.0146/min$ ) in the left superior frontal gyrus ( $x=-38, y=24, z=50; z=3.29; Ke=38; P=.001$ , uncorrected), medial frontal gyrus ( $x=0, y=60, z=-6; z=3.03; P=.001$ , uncorrected), and inferior parietal lobule ( $x=-35, y=-64, z=36; z=3.56; Ke=96; P<.001$ , uncorrected) (Figure 4).

#### COMMENT

We combined fMRI and PET to examine the relationship between prefrontal cortical activation and striatal dopamine function in people with an ARMS. These sub-



**Figure 3.** Group differences in the relationship between prefrontal activation during the N-back task (A) and striatal dopamine function. There was a positive correlation between right middle frontal activation and fluorine 18-labeled fluorodopa uptake in the associative striatum in controls (red) but a negative correlation in the at-risk mental state (ARMS) group (blue) (B). The left side of the brain is shown on the left side of the Figure ( $P<.05$ , familywise error corrected). BOLD indicates blood oxygen level dependent; and KiA, Ki value for ARMS group; and KiC, Ki value for controls.



**Figure 4.** A, Quadratic regression (black line) showing the relationship between right middle frontal activation and dopamine function in the associative striatum, independent of group. B, Across the whole sample, there was greater prefrontal activation in subjects with midrange Ki values compared with subjects with relatively high or low Ki values. C, The converse applied in the left precuneus and in the right superior parietal lobule. D, Across the at-risk mental state (ARMS) group, the subjects with the most elevated Ki values showed greater activation than those with a less marked elevation in Ki in the left superior frontal gyrus, medial frontal gyrus, and inferior parietal lobule. The left side of the brain is shown on the left side of the Figure. BOLD indicates blood oxygen level dependent; fMRI, functional magnetic resonance imaging; and PET, positron emission tomography.

jects had attenuated psychotic symptoms that had developed in the context of a decline in social and vocational function<sup>51</sup> associated with a very high risk of developing psychosis and were naive to antipsychotic medication. Consequently, the findings cannot be secondary to effects of psychotic illness or its treatment.

The ARMS group differed from controls in terms of both prefrontal activation and striatal dopamine function. The fMRI data revealed that the ARMS group showed a relatively reduced blood oxygen level–dependent response in the dorsolateral and medial prefrontal cortex. Because the differential activation we observed was evident in the context of comparable response accuracy, and the analysis was restricted to images associated with correct responses, it is unlikely to be related to group differences in task performance and may instead reflect a true difference at the neurophysiological level. Abnormalities in prefrontal activation during cognitive tasks have previously been described in the ARMS<sup>5,52</sup> and have consistently been reported in the early phases of schizophrenia.<sup>26</sup> Structural imaging studies in the ARMS have identified reductions in gray matter volume in a number of prefrontal, medial temporal, and lateral temporal regions. Reductions in prefrontal regions appear to be more marked in the subgroup of subjects who later develop psychosis,<sup>53,54</sup> suggesting that prefrontal abnormalities may be particularly

related to the later onset of psychosis.<sup>54–58</sup> The ARMS group also showed a significant increase in the Ki (<sup>18</sup>F)fluorodopa uptake) in the associative subdivision of the striatum. Increased Ki functionally represents increases in dopamine synthesis capacity as previously observed in a cohort of ARMS subjects,<sup>23</sup> some of whom also participated in the study reported herein, and in schizophrenia.<sup>59</sup>

Our principal hypothesis was that the relationship between prefrontal activation and striatal dopamine function would be different in the ARMS group compared with controls. This hypothesis was confirmed. In the ARMS group, the degree of prefrontal activation during the working memory task was negatively correlated with the level of dopamine function in the associative striatum, whereas in controls, the correlation was positive. Thus, within the ARMS group, the severity of the prefrontal abnormality (in this case, an attenuation of activation) was directly related to the severity of the striatal dopamine dysfunction (an elevation of Ki). The localization of the fMRI findings to the lateral prefrontal cortex is consistent with localization of the dopaminergic findings to the associative striatum, as these regions are anatomically connected.<sup>60</sup>

A quadratic regression analysis of the relationship between prefrontal activation and striatal dopamine function across the whole sample, independent of group, indicated that this followed an inverted U-shaped curve

(Figure 4). Thus, prefrontal activation was maximal in subjects with midrange levels of dopamine function, but less marked in subjects in whom dopamine function was either relatively low or relatively high. This relationship is similar to the inverted U relationship between prefrontal cortical function during working memory tasks and afferent dopamine activity described in experimental animals and in healthy human subjects.<sup>11,19,61</sup> According to this model, there is a dopamine activity level that is optimal for efficient working memory function, corresponding to the peak of the inverted U curve.<sup>19,62,63</sup> The opposite direction of the correlations between Ki and prefrontal activation in the ARMS and control groups can be interpreted as reflecting their different positions on the putative inverted U curve. In the ARMS group, in whom dopaminergic function is relatively elevated, most subjects would tend to lie to the right of the curve's peak, where the efficiency of prefrontal function is relatively low. Within this group, the greater the Ki, the further the subject lies to the right of the curve, the less efficient their prefrontal function, and the weaker the activation.<sup>64</sup> Conversely, in the controls, most subjects lie to the left of the curve's peak. Within this group, the greater the Ki, the closer the subject lies to the peak of the curve, the greater the prefrontal efficiency and the level of activation. While we observed a significant correlation between striatal dopamine function and prefrontal activation, there was no evidence of a correlation between dopamine function and performance of the N-back task. Although the inverted U-shaped curve that relates prefrontal function to dopamine activity was originally defined on the basis of neurophysiological, rather than behavioral, measures of prefrontal function,<sup>63</sup> a relationship between dopamine activity and performance of another task putatively mediated by prefrontal cortex (the Wisconsin Card Sorting Test) has also been reported.<sup>25</sup> Task performance can be seen as an indirect measure of the underlying prefrontal physiology and may be influenced by a range of additional factors. It is thus not surprising that we were able to detect a relationship between dopamine function and prefrontal activation, but not with task performance. The latter might have been evident if there had been significant group differences in task performance and if the study had been powered to detect differences at the behavioral, as opposed to the physiological, level. In line with this neurochemical pattern, we found that, within the ARMS sample, those lying to the right of the peak of the inverted U-shaped curve showed greater recruitment of superior frontal, medial frontal, and parietal areas than those positioned on the left side of the peak. The greater engagement of these areas can be interpreted as a compensatory response to maintain normal task performance in the face of elevated dopamine activity. The finding that prefrontal function is related to the level of striatal dopamine function in controls as well as in patients, and that the relationship in both groups may follow a common curve, suggests that there is a continuum across controls and subjects with an ARMS with respect to prefrontal and dopamine function. This may reflect the composite psychopathological status of the ARMS group, which includes subjects with true prodromal signs (who will later develop psychosis) and sub-

jects who are at high risk but will not develop psychosis.<sup>65</sup> The participants in the present study have not yet been followed up for a sufficient period (at least 2 years is required<sup>50</sup>) to determine their long-term clinical outcome, and the extent to which the findings relate to the subsequent onset of psychosis remains to be determined. Clinical follow-up of the ARMS sample may clarify whether subjects who subsequently develop psychosis lie furthest to the right of the curve's peak.

These data extend previous findings in patients with established schizophrenia<sup>25,66</sup> by showing that an alteration in the relationship between prefrontal cortical function and striatal dopamine function is evident when people have prodromal symptoms, prior to the full clinical expression of the disorder. The cross-sectional nature of the present study precludes assessment of the direction of causality between the prefrontal and striatal findings. However, basic research indicates that activity in dopaminergic projections to the striatum is influenced by the prefrontal cortex.<sup>67,68</sup> The prefrontal cortex regulates subcortical dopamine transmission via projections to the ventral tegmental area, caudate, and nucleus accumbens.<sup>69</sup> In rats, experimental depletion of dopamine in the medial prefrontal cortex leads to enhanced dopamine turnover and use in the striatum,<sup>70</sup> while prefrontal lesions induce a striatal increase in D<sub>2</sub> messenger RNA.<sup>71</sup> Similarly, excitotoxic prefrontal lesions in marmosets influenced neurochemical and molecular indexes of striatal dopamine function.<sup>72</sup> A primary dysfunction of the prefrontal cortex could thus lead to increased subcortical dopaminergic function<sup>25</sup> and the development of psychosis. However, selective disruption of dopamine function in the striatum in mice can impair working memory performance and alters dopamine levels and D<sub>1</sub> receptor function in the prefrontal cortex,<sup>73</sup> suggesting that changes in striatal dopamine function can have secondary effects in the prefrontal cortex. Longitudinal neuroimaging studies of prefrontal and dopamine function in ARMS subjects may clarify the chronology of the respective changes.

In conclusion, we found that prefrontal dysfunction during performance of a working memory task was directly related to elevated striatal dopamine function in people at ultra high risk of psychosis. Furthermore, the relationship between prefrontal activation and dopamine function was the opposite to that found in controls. These findings support the hypothesis that abnormal frontostriatal interactions underlie the development of cognitive impairments and psychotic symptoms in schizophrenia and provide the first evidence, to our knowledge, that altered frontostriatal interactions predate the onset of illness. Available evidence indicates that both dopamine function<sup>74-76</sup> and the blood oxygen level-dependent signal in the prefrontal cortex<sup>77-80</sup> are sensitive to antipsychotic manipulation. In addition, clinical trials suggest that treatment with antipsychotic medication may improve the prodromal symptoms<sup>81</sup> and reduce the risk of transition to psychosis in subjects with an ARMS.<sup>82,83</sup> Our data, which indicate that the ARMS is associated with dopamine dysfunction and that this is related to prefrontal dysfunction, provide a neurophysiological rationale for the use of treatments that act on the brain dopamine system in this group.

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