Altered Striatal Functional Connectivity in Subjects With an At-Risk Mental State for Psychosis

Orwa Dandash1, Alex Fornito1–4, Jimmy Lee5–6, Richard S. E. Keefe7,8, Michael W. L. Chee8, R. Alison Adcock9, Christos Pantelis1,10, Stephen J. Wood8,11, and Ben J. Harrison1

1Melbourne Neuropsychiatry Centre, Department of Psychiatry, The University of Melbourne, Melbourne, Australia; 2Centre for Neural Engineering, The University of Melbourne, Melbourne, Australia; 3The Victorian Research Laboratory National ICT Australia Ltd, Victoria, Australia; 4Monash Clinical and Imaging Neuroscience, School of Psychology and Psychiatry and Monash Biomedical Imaging, Monash University, Clayton, Australia; 5Department of General Psychiatry 1 and Research Division, Institute of Mental Health, Buangkok, Singapore; 6Office of Clinical Sciences, Graduate Medical School, Duke-National University of Singapore, Singapore, Singapore; 7Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, NC; 8Neuroscience and Behavioral Disorders Program, Graduate Medical School, Duke-National University of Singapore, Singapore, Singapore; 9Department of Psychiatry and Behavioral Sciences and Center for Cognitive Neuroscience, Duke University, Durham, NC; 10Melbourne Health, Melbourne, Australia; 11School of Psychology, University of Birmingham, Edgbaston, Birmingham, UK

*To whom correspondence should be addressed; School of Psychology, University of Birmingham, Edgbaston, Birmingham, B15 2TT, UK; tel: 44 121 414 4917, fax: 44 121 414 4897, e-mail: s.j.wood@bham.ac.uk

Recent functional imaging work in individuals experiencing an at-risk mental state (ARMS) for psychosis has implicated dorsal striatal abnormalities in the emergence of psychotic symptoms, contrasting with earlier findings implicating the ventral striatum. Our aims here were to characterize putative dorsal and ventral striatal circuit-level abnormalities in ARMS individuals using resting-state functional magnetic resonance imaging (fMRI) and to investigate their relationship to positive psychotic symptoms. Resting-state fMRI was acquired in 74 ARMS subjects and 35 matched healthy controls. An established method for mapping ventral and dorsal striatal functional connectivity was used to examine corticostriatal functional integrity. Positive psychotic symptoms were assessed using the Comprehensive Assessment of At-Risk Mental State and the Positive and Negative Syndrome Scale. Compared with healthy controls, ARMS subjects showed reductions in functional connectivity between the dorsal caudate and right dorsolateral prefrontal cortex, left rostral medial prefrontal cortex, and thalamus, and between the dorsal putamen and left thalamic and lenticular nuclei. ARMS subjects also showed increased functional connectivity between the ventral putamen and the insula, frontal operculum, and superior temporal gyrus bilaterally. No differences in ventral striatal (ie, nucleus accumbens) functional connectivity were found. Altered functional connectivity in corticostriatal circuits were significantly correlated with positive psychotic symptoms. Together, these results suggest that risk for psychosis is mediated by a complex interplay of alterations in both dorsal and ventral corticostriatal systems.

Key words: ARMS/fMRI/resting state/striatum

Introduction

The onset of psychosis is commonly preceded by a prodromal period characterized by subthreshold symptomatology and functional decline.1 These symptoms have been construed as reflecting an at-risk mental state (ARMS), which is associated with an enhanced risk of converting to frank psychosis within 2 years.2,3 A number of anatomical, functional, and neurochemical brain changes thought to be crucial to the pathogenesis of the disease have been associated with the ARMS.4–6 Chief among these is elevated dopamine transmission in the striatum,7,8 a brain region rich in dopamine D2 receptors targeted by most antipsychotic drugs.9,10

Many pathophysiological models of psychosis ascribe a prominent role to the striatum, comprising the caudate and putamen, given its rich interconnectivity with other regions known to be dysfunctional in psychosis, such as the prefrontal cortex.11–14 In particular, animal studies have emphasized dysfunction of a ventral (limbic) circuit, linking ventral striatum (nucleus accumbens) with medial prefrontal cortex, a system implicated in the mesolimbic dopaminergic pathway.15,16
Recently, however, in vivo positron emission tomography research has demonstrated elevated dopaminergic activity in the dorsal but not the ventral striatum of patients with established schizophrenia and ARMS subjects. These elevations correlate with the severity of positive psychotic symptoms and prefrontal activation in the latter group. Thus, in contrast to animal models, human data implicate dorsal striatal dysfunction in the emergence of psychosis. They also suggest that abnormalities may not be restricted to the striatum but propagate throughout interconnected corticostriatal circuitry, consistent with the idea that psychotic disorders arise as a result of aberrant brain connectivity or “dysconnectivity.”

Despite this possibility, no study to date has directly examined corticostriatal dysfunction in ARMS individuals from a systems-level perspective in order to characterize putative, circuit-based risk biomarkers for psychosis. Resting-state functional magnetic resonance imaging (fMRI) provides a powerful probe of the functional integrity of corticostriatal circuitry by mapping networks of brain regions showing coherent fluctuations of spontaneous neural activity. These fluctuations are under strong genetic control and are thought to represent an intrinsic property of brain functional organization. In this study, we used this technique to investigate the functional connectivity of dorsal and ventral striatal regions (caudate nucleus and putamen) with the rest of the brain in a well-characterized, relatively large sample of ARMS subjects recruited in a community-based setting in Singapore.

The aims of this study were 2-fold. First, we sought to systematically examine functional connectivity within dorsal and ventral corticostriatal circuits to evaluate whether the ARMS is associated primarily with alterations in the dorsal circuit, ventral circuit, or both. Second, we sought to characterize circuit-level abnormalities related to psychotic symptoms, independently of any covariance with depression and anxiety, which are often present in ARMS individuals. Based on recent neuroimaging work, we hypothesized that participants would show altered striatal functional connectivity in the dorsal circuit compared with healthy controls. We also hypothesized that altered functional connectivity would be associated with more severe psychotic symptoms.

**Methods**

**Participants**

Eighty help-seeking individuals were recruited from the Longitudinal Youth At Risk study, a research study based at the Institute of Mental Health (IMH), Singapore. Individuals were recruited from psychiatric clinics at IMH, the Singapore Armed Forces, and from community mental health services run by trained counselors. Comprehensive Assessment of At-Risk Mental State (CAARMS) was used to establish at-risk status for the development of psychosis. Included individuals had no history of psychotic disorder, neurodevelopmental disorder, serious medical disorders, or mental retardation and no current substance use. Baseline symptoms were assessed with the Positive and Negative Syndrome Scale (PANSS) of schizophrenia, the Calgary Depression Scale for Schizophrenia (CDSS), and the Beck Anxiety Inventory (BAI). Overall functioning was assessed using the Global Assessment of Functioning (see online supplementary table 1 for further information). All assessments were carried out by trained psychologists ($N = 14$, CAARMS interrater reliability $\kappa = 0.99$).

At intake, 25 ARMS subjects were receiving antidepressants (tricyclic or serotonin reuptake inhibitors); 2 were receiving antianxiety treatment (benzodiazepines); 12 were receiving both antidepressants and benzodiazepines; and 2 received low-dose antipsychotic treatment (chlorpromazine 50 mg and seroquel 25 mg). Repeating analyses after excluding the last 2 subjects did not alter the findings, so we report on the full sample here. Subsequent to MRI scan, 6 ARMS subjects made a transition to psychosis as outlined by the CAARMS (see online supplementary table 2 for further information).

Forty subjects with a similar sociodemographic background to ARMS subjects matched for age, gender, handedness, and educational attainment were recruited as healthy controls. Sample characteristics were compared between the groups (table 1) using univariate ANOVA in the Statistical Package for the Social Sciences (v.20). Educational attainment was assessed by the Primary School Leaving Examination, a standardized multidisciplinary test of scholastic achievement. Exclusion criteria were history of severe head injury, personal history of psychotic or neurologic disorders, and substance or alcohol dependence assessed with the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, fourth edition. All participants gave their written and informed consent approved by the ethics review board of the Singaporean National Healthcare Group.

**Image Acquisition**

T2*-weighted echo-planar images were acquired for each subject in the resting condition with a 3.0 T MRI scanner (Siemens Magnetom, Trio Tim) that is equipped with a 12-channel array coil. Subjects were instructed to lie still with their eyes closed and not to fall asleep. Functional volumes were acquired in 3 mm$^3$ voxel size, with a time to repetition (TR) of 2000 ms, time to echo (TE) of 30 ms, flip angle of 90° in 64 × 64 matrix size, and 192 mm field of view (FOV). For 7 control subjects, 320 volumes were acquired with 28 slices each. For the remaining participants, 240 volumes comprising 36 slices...
each were obtained. Repeating analyses after excluding the 7 subjects did not significantly alter the findings, so we report on the full sample here. For registration of functional images, high-resolution anatomical T1 images were acquired using a 3-dimensional magnetic-prepared rapid gradient echo (MPRAGE) sequence and multiecho MPRAGE. One hundred and ninety-two contiguous sagittal slices of 1.0 mm thickness using a TR of 2300 ms, TE of 2980 ms, flip angle of 9°, and a FOV of 256 mm in 256 × 256 matrix were acquired with a voxel size of 1.0 mm³.

Preprocessing
A validated resting-state functional connectivity mapping procedure was used to characterize ventral and dorsal corticostriatal systems via primary seed regions of interest located in ventral and dorsal areas of the caudate nucleus and putamen (see Di Martino et al for anatomical delineation of these regions and Harrison et al and online supplementary text for a full description of the methodology implemented herein).

First-Level, Within-Subjects Analysis
Functional connectivity maps were estimated for each participant by including the striatal region time series and nuisance signals as predictors of interest/no-interest in whole-brain, linear regression analyses in SPM8 for each hemisphere. Prior to model estimation, a high-pass filter set at 128 seconds was used to remove low-frequency drifts. Each of the 3 nuisance covariates were orthogonalized (using an iterative Gram-Schmidt method) and then removed from each seed’s time series along with 6 head-motion parameters (3 translation and 3 rotation) by linear regression, resulting in a general linear model that comprised “noise-cleaned” regions and 9 nuisance variables. Contrast images were generated for each participant by estimating the regression coefficient between all brain voxels and each region’s time series.

Second-Level, Between-Group Analysis
For each striatal region, participants’ contrast images were included in a random effects 2 × 2 factorial design (Group [control, ARMS] by Hemisphere [left, right]) in SPM8. Within-group statistical maps were thresholded at a false discovery rate of \( P < .05 \) for the whole-brain volume (figure 1). Between-group effects (main effects of group and group × hemisphere interactions) were mapped by implicitly masking t contrasts (1 tailed) with a global conjunction of the within-subjects effect calculated for both groups for the combined left and right hemispheres. Nuisance covariates included age, gender, and 4 additional summary measures of head motion to further

<table>
<thead>
<tr>
<th>Table 1. Demographics and Clinical Characteristics of the At-Risk Mental State (ARMS) Group and the Healthy Comparison Group</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Characteristics</strong></td>
</tr>
<tr>
<td>Age (y)</td>
</tr>
<tr>
<td>Educational attainment</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Gender</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Handedness</td>
</tr>
<tr>
<td>Left</td>
</tr>
<tr>
<td>Mixed</td>
</tr>
<tr>
<td>Right</td>
</tr>
<tr>
<td>Clinical scores</td>
</tr>
<tr>
<td>CAARMS positive symptoms scale</td>
</tr>
<tr>
<td>Unusual thought content</td>
</tr>
<tr>
<td>Nonbizarre ideation</td>
</tr>
<tr>
<td>Perceptual abnormality</td>
</tr>
<tr>
<td>Disorganized speech</td>
</tr>
<tr>
<td>PANSS</td>
</tr>
<tr>
<td>PANSS total</td>
</tr>
<tr>
<td>PANSS positive</td>
</tr>
</tbody>
</table>

Note: CAARMS, Comprehensive Assessment of At-Risk Mental State; PANSS, Positive and Negative Syndrome Scale.

aThe data of 4 (5.4%) ARMS subjects were not available at the time of the analysis.
bSummed across intensity and frequency measures.

each were obtained. Repeating analyses after excluding the 7 subjects did not significantly alter the findings, so we report on the full sample here. For registration of functional images, high-resolution anatomical T1 images were acquired using a 3-dimensional magnetic-prepared rapid gradient echo (MPRAGE) sequence and multiecho MPRAGE. One hundred and ninety-two contiguous sagittal slices of 1.0 mm thickness using a TR of 2300 ms, TE of 2980 ms, flip angle of 9°, and a FOV of 256 mm in 256 × 256 matrix were acquired with a voxel size of 1.0 mm³.
remove residual head-motion effects: (1) the number of significant micromovements (instances of >0.10 mm relative displacement between adjacent volumes); (2) mean head displacement; (3) maximum head displacement; and (4) mean head rotation. Between-group statistical maps were thresholded using a $P < .05$ (family-wise error) cluster-wise corrected threshold determined using a permutation-based framework (1000 permutations with a cluster-forming threshold of $P < .01$ uncorrected), as implemented in the REST toolbox.

**Symptom Correlates of Striatal Functional Connectivity**

We investigated associations between striatal functional connectivity and measures of positive symptom severity taken from the CAARMS and PANSS positive symptom scale in ARMS subjects ($N = 70$). Secondary associations with CDSS and BAI scales were also performed to test the specificity of findings to positive symptoms. These scores were entered as covariates into separate general linear models, which also included age, gender, and the 4 head motion derivatives as nuisance covariates. Correlations between clinical ratings and connectivity measures were masked by the between-group difference observed between ARMS and control subjects (figure 2) to identify the symptom correlates of striatal functional dysconnectivity observed in ARMS subjects. All results were displayed at $P < .05$ (FWE) cluster-wise corrected, with appropriate correction for the search volume employed.

**Results**

*Functional Connectivity Analyses*

Across groups, functional connectivity of the dorsal and ventral striatum (figure 1) recapitulated previous
results and was consistent with known anatomical connectivity. When functional connectivity was compared between groups, significant differences were observed for the dorsal caudate, dorsal putamen, and ventral putamen seed regions (figure 2; table 2). With regard to the dorsal caudate, ARMS subjects demonstrated significantly reduced functional connectivity with the right dorsolateral prefrontal cortex, left rostral medial prefrontal cortex, and thalamus bilaterally (figure 2A). For the dorsal putamen seed region, ARMS subjects demonstrated reduced functional connectivity with the left lenticular nucleus and the medial dorsal, ventral lateral, and ventral anterior thalamic nuclei (figure 2B). ARMS subjects demonstrated increased functional connectivity between ventral putamen seeds and lateral superior temporal gyrus, frontal operculum and the insula bilaterally (figure 2C). There were no significant group differences for the ventral striatal (nucleus accumbens) seed, nor were there any significant group × hemisphere interactions for any seed region.

Brain-Behavior Associations

In ARMS participants, higher scores on the CAARMS nonbizarre ideation subscale predicted lower functional connectivity between the dorsal caudate and the left rostromedial prefrontal cortex (figure 3A). Higher scores on the perceptual abnormality subscale predicted lower functional connectivity between the dorsal caudate and right dorsolateral prefrontal cortex (figure 3A). Additionally, higher unusual thought content (CAARMS) and PANSS positive scores predicted lower functional connectivity between the dorsal putamen and the medial dorsal, ventral lateral, and ventral anterior thalamic nuclei (figure 3B). Finally, higher unusual thought content scores (CAARMS) predicted higher functional connectivity between ventral putamen and language areas, superior temporal gyrus and the insula bilaterally, whereas higher PANSS positive scores predicted higher functional connectivity with the left inferior frontal gyrus (figure 3C).

No further significant associations with CAARMS or PANSS positive scores were identified.

Repeating the analysis while covarying for CDSS and BAI ratings did not significantly alter the correlation between corticostriatal functional connectivity and positive symptom severity. To control for medication effects, we ran a separate analysis in which we investigated differences in functional connectivity of striatal seeds (that showed significant between-group differences) between ARMS subjects receiving antidepressants (n = 34) and those who did not (n = 36), masked by the observed pattern of group differences. No significant differences were found. To further exclude the effect of diagnosis and/or treatment, we repeated the between-group analysis after excluding subjects with Axis-I diagnosis of depressive and/or anxiety disorder in addition to subjects receiving antidepressants and/or benzodiazepines. Despite lower power, the same effects were observed (P < .01 uncorrected), indicating our results are not attributable to diagnosis or treatment effects (see online supplementary figure 1).

Discussion

It remains controversial whether psychotic symptoms emanate from primary alterations of dorsal or ventral corticostriatal circuitry. To address this question, we systematically characterized the functional integrity of dorsal and ventral corticostriatal circuits at a systems level with resting-state fMRI in a large sample of ARMS subjects experiencing attenuated psychotic symptoms. ARMS subjects showed a selective reduction of functional connectivity in dorsal corticostriatal circuits and increased functional connectivity between ventral putamen and brain regions largely involved in language, including the superior temporal and transverse gyri, insula, and frontal operculum bilaterally. No functional connectivity changes were found for the ventral striatum/nucleus accumbens seeds. The magnitude of both dorsal and ventral circuit alterations correlated significantly with
the severity of positive psychotic symptoms as measured by the positive symptoms scales of the CAARMS and the PANSS.

The alterations of corticostriatal functional connectivity in ARMS subjects are in strong agreement with accumulating evidence of functional and neurochemical changes in these structures prior to the onset of frank psychosis\textsuperscript{40-42} (reviewed in Fusar-Poli, McGuire, Borgwardt\textsuperscript{5}) and their general role in the pathophysiology of schizophrenia.\textsuperscript{13,43} In addition, our findings confirm and extend the findings of resting-state fMRI studies in first episode\textsuperscript{44} and established schizophrenia patients\textsuperscript{45} (reviewed in Fornito and Bullmore\textsuperscript{20} and Pettersson-Yeo et al\textsuperscript{46}) by showing that functional dysconnectivity is evident in subjects

### Table 2. Brain Regions Demonstrating Significant Between-Group Differences in Functional Connectivity and Association With Positive Psychotic Symptoms in ARMS Subjects

<table>
<thead>
<tr>
<th>Main Effect</th>
<th>Anatomical Region</th>
<th>Hemisphere</th>
<th>MNI Coordinates $(x, y, z)$</th>
<th>$z$ ($df = 1,208$)</th>
<th>Voxels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dorsal caudate</td>
<td>Rostral medial prefrontal cortex</td>
<td>Left</td>
<td>$-8, 74, 8$</td>
<td>3.34</td>
<td>215</td>
</tr>
<tr>
<td>Dorsal caudate</td>
<td>Dorsal lateral prefrontal cortex</td>
<td>Right</td>
<td>$26, 18, 62$</td>
<td>3.60</td>
<td>298</td>
</tr>
<tr>
<td>Thalamus</td>
<td>Left</td>
<td>$-6, -12, 14$</td>
<td>4.12</td>
<td>828</td>
<td></td>
</tr>
<tr>
<td>Thalamus</td>
<td>Right</td>
<td>$8, -22, 12$</td>
<td>4.30</td>
<td>580</td>
<td></td>
</tr>
<tr>
<td>Dorsal putamen</td>
<td>Lentiform nucleus</td>
<td>Left</td>
<td>$-26, -8, 0$</td>
<td>4.19</td>
<td>239</td>
</tr>
<tr>
<td>Thalamus</td>
<td>Left</td>
<td>$-12, -10, 16$</td>
<td>3.07</td>
<td>316</td>
<td></td>
</tr>
<tr>
<td>Thalamus</td>
<td>Right</td>
<td>$58, -14, 10$</td>
<td>4.59</td>
<td>629</td>
<td></td>
</tr>
<tr>
<td>Dorsal putamen</td>
<td>Thalamus</td>
<td>Left</td>
<td>$-58, -24, 24$</td>
<td>3.83</td>
<td>238</td>
</tr>
<tr>
<td>Thalamus</td>
<td>Left</td>
<td>$-48, 18, -4$</td>
<td>3.77</td>
<td>239</td>
<td></td>
</tr>
<tr>
<td>Thalamus</td>
<td>Right</td>
<td>$-56, -6, 6$</td>
<td>3.64</td>
<td>629</td>
<td></td>
</tr>
<tr>
<td>Thalamus</td>
<td>Right</td>
<td>$-44, -6, -4$</td>
<td>3.23</td>
<td>239</td>
<td></td>
</tr>
<tr>
<td>Ventral putamen</td>
<td>Doperculum</td>
<td>Left</td>
<td>$-56, 10, 6$</td>
<td>3.15</td>
<td>27</td>
</tr>
<tr>
<td>Ventral putamen</td>
<td>Insula</td>
<td>Left</td>
<td>$-44, -4, 2$</td>
<td>2.72</td>
<td>27</td>
</tr>
<tr>
<td>Ventral putamen</td>
<td>Insula</td>
<td>Right</td>
<td>$48, -4, 4$</td>
<td>3.32</td>
<td>27</td>
</tr>
<tr>
<td>Ventral putamen</td>
<td>Insula</td>
<td>Left</td>
<td>$-48, 18, -4$</td>
<td>3.77</td>
<td>239</td>
</tr>
<tr>
<td>Ventral putamen</td>
<td>Insula</td>
<td>Left</td>
<td>$-56, -6, 6$</td>
<td>3.64</td>
<td>629</td>
</tr>
<tr>
<td>Ventral putamen</td>
<td>Thalamus</td>
<td>Left</td>
<td>$-12, -12, 16$</td>
<td>3.40</td>
<td>27</td>
</tr>
<tr>
<td>Ventral putamen</td>
<td>Thalamus</td>
<td>Left</td>
<td>$-12, -12, 20$</td>
<td>3.04</td>
<td>17</td>
</tr>
<tr>
<td>Positive Symptoms Association</td>
<td>Anatomical Region</td>
<td>Hemisphere</td>
<td>MNI Coordinates $(x, y, z)$</td>
<td>$z$ ($df = 1,131$)</td>
<td>Voxels</td>
</tr>
<tr>
<td>Dorsal caudate</td>
<td>Dorsal lateral prefrontal cortex</td>
<td>Right</td>
<td>$32, 38, 44$</td>
<td>3.10</td>
<td>35</td>
</tr>
<tr>
<td>Dorsal caudate</td>
<td>Rostral medial prefrontal cortex</td>
<td>Left</td>
<td>$-10, 72, 8$</td>
<td>3.04</td>
<td>17</td>
</tr>
<tr>
<td>Dorsal putamen</td>
<td>Thalamus</td>
<td>Left</td>
<td>$-12, -10, 16$</td>
<td>3.40</td>
<td>27</td>
</tr>
<tr>
<td>Dorsal putamen</td>
<td>Thalamus</td>
<td>Left</td>
<td>$-12, -12, 16$</td>
<td>3.04</td>
<td>17</td>
</tr>
<tr>
<td>Ventral putamen</td>
<td>Insula</td>
<td>Right</td>
<td>$48, -4, 4$</td>
<td>3.32</td>
<td>27</td>
</tr>
<tr>
<td>Ventral putamen</td>
<td>Insula</td>
<td>Left</td>
<td>$-48, 18, -4$</td>
<td>3.77</td>
<td>239</td>
</tr>
<tr>
<td>Ventral putamen</td>
<td>Thalamus</td>
<td>Left</td>
<td>$-56, 10, 6$</td>
<td>3.15</td>
<td>27</td>
</tr>
</tbody>
</table>

Note: ARMS, at-risk mental state; FWE, family-wise error. Results are viewed at $P < .05$ (FWE) cluster-wise corrected.

Fig. 3. $z$ scores statistical maps of significant brain-behavior association between estimates of functional connectivity of striatal seeds and positive psychotic symptoms on the Comprehensive Assessment of At-Risk Mental States (unusual thought contents, nonbizarre ideation, and perceptual abnormality) and the PANSS positive scales in at-risk mental state subjects ($N = 70$). Results are masked with the between-group difference (main effect) mask and displayed at a $P < .05$ (FWE) cluster-wise corrected. See table 2 for more information and online supplementary figure 2 for scatter plots.
experiencing positive psychotic symptoms characteristic of the psychosis prodrome and that it is not a secondary effect of antipsychotic treatment, comorbidity, or illness chronicity.

The involvement of dorsal corticostriatal circuitry is consistent with recent reports indicating that the ARMS is associated with elevation of dopamine transmission specifically in the dorsal, so called "associative," regions of the caudate nucleus. In past work, this elevation was associated with severity of psychotic symptoms and altered prefrontal function. Our findings extend these results by demonstrating a functional disconnection in the form of reduced connectivity between dorsal striatal and prefrontal regions while also highlighting an important role for the ventral putamen in this circuit-level abnormality.

It is as yet unclear whether altered striatal dopamine is a cause or consequence of the apparent functional disconnection reported herein. Certainly, there is evidence that pharmacological manipulation of dopamine transmission can alter brain functional connectivity. In one study, acute depletion of dopamine precursors (tyrosine and phenylalanine) in healthy controls led to a reduction in frontostriatal functional connectivity, whereas administration of l-Dopa, another dopamine precursor, enhanced it. Neither of these agents represent pharmacological models of psychosis, thus the effects of these drugs need not necessarily mimic our findings, though they do suggest that general increase in dopamine leads to increased frontostriatal functional connectivity. This observation seems to be at odds with our report of reduced functional connectivity, coupled with other findings of increased striatal dopamine in ARMS subjects. However, it is well known that there is an inverted U-shaped relationship between dopamine levels and optimal cortical function and behavior. and well-established models posit that deviations from optimal dopamine levels in either direction (ie, too much or too little) will increase the noise of information processing in neural systems. Adding noise to 2 variables (eg, regional fMRI time series) will generally decrease the correlation between them. Thus, both abnormal increases and decreases in dopamine could plausibly lead to reduced functional connectivity.

Accumulating neuroimaging evidence in subjects at clinical high risk for psychosis shows significant neuroanatomical alterations in cortical regions before the onset of psychosis. Similar changes have generally not been observed in striatal or thalamic regions (reviewed in Fusar-Poli et al and Fusar-Poli, McGuire, Borgwardt). The strong connectivity of cortical afferents with the striatum and their role in controlling subcortical dopaminergic pathways imply that cortical alterations may precede and influence striatal dopamine transmission as a result of disrupted functional connectivity between these regions. Importantly, disinhibition of subcortical dopamine and the concomitant emergence of psychotic symptoms have historically been viewed as the final step in a common pathway arising from aberrant cortical afferents. It is therefore plausible that disruption of corticostriatal functional connectivity is driven by cortical abnormality. Our observed association between corticostriatal dysconnectivity and positive psychotic symptoms (figure 3), as well as other work implicating the prefrontal cortex in mediating aspects of psychotic symptoms, is in support of this notion, though further work is required to establish causal influences of this perturbation.

Alterations in striatothalamic connectivity are consistent with models implicating cortical disinhibition of subcortical dopamine in the emergence of psychotic symptoms. These models posit that disinhibition of subcortical dopamine increases the flow of sensory information to the thalamus, which results in a failure of the thalamus to “filter out” irrelevant stimuli before they reach the cortex, thus predisposing an individual to psychotic symptoms. Given that the thalamus receives the bulk of striatal output via GABAergic projections to the medial dorsal, ventral anterior, and ventral lateral nuclei, it was perhaps not surprising that ARMS subjects experiencing more severe positive psychotic symptoms showed disrupted functional connectivity between the dorsal putamen and these nuclei (figure 3B).

The selective localization of striatothalamic dysconnectivity to the left hemisphere is also in agreement with previous reports showing neurochemical abnormalities in the left thalamus in ARMS subjects. Importantly, reduced thalamic glutamate correlated with altered activation and electrophysiological response in the prefrontal cortex and superior temporal gyrus, as well as reduced gray matter volume in the lateral temporal, inferior frontal, and insular cortices, brain regions that showed increased functional connectivity with the ventral putamen (figure 2C). These findings suggest that the abnormal increase in functional connectivity of the ventral putamen may reflect an abnormal increase in cortical glutamatergic tone that could potentially be caused by thalamocortical disinhibition of pyramidal cells. Alternatively, the ventral putamen could be in overdrive to compensate for a primary dorsal corticostriatal abnormality. Recent evidence in ARMS subjects points to alteration in ventral striatal and medial temporal areas function that is not present in control subjects, and our more recent observation in unaffected siblings of first-episode psychosis patients shows reduced dorsal and increased ventral corticostriatal connectivity. Thus, dorsal frontostriatal hypoconnectivity may be a generic risk biomarker for psychosis, while ventral system hyperconnectivity may emerge as a compensatory response or secondary consequence.

Despite the relatively large sample of ARMS subjects, between-group differences in functional connectivity may be an underestimate of the actual underlying...
Altered Striatal Connectivity in ARMS Subjects

disturbance given the smaller sample size of healthy controls. A major strength, however, is the absence of substance abuse problems due to the generally low prevalence of substance use in Singapore. In particular, cannabis use, which is often more common in ARMS individuals, can influence dopamine levels and corticostriatal function and thus represents a major confound in imaging studies. Though nearly half of our ARMS sample were taking antidepressants, the association we observed between corticostriatal functional connectivity and psychotic symptoms was evident independent of depressive symptom, and there were no differences between participants on/off these medications. These findings support a specific involvement of corticostriatal dysconnectivity in the emergence of psychotic symptoms. The lack of outcome data in our analyses prevents any inferences concerning the specific risk for psychosis in our sample. Nonetheless, the robust association observed with positive symptom severity in individuals deemed to be at risk for psychosis, as defined using extensively validated operational criteria, suggests that this circuit-level disruption is intimately related to the expression of psychotic symptoms. This assertion is further supported by our recent finding of similar dorsal circuit changes in patients with first-episode psychosis and their unaffected relatives. Six individuals in our ARMS group have since made the transition to psychosis, and we are presently following up the remainder of participants to clarify clinical outcomes and more accurately characterize risk levels.

In summary, our results indicate that the ARMS is associated with a disruption of dorsal and ventral corticostriatal functional connectivity and that this disruption correlates with the severity of positive psychotic symptoms. These findings converge with recent evidence that dopamine elevations are present specifically in dorsal striatal regions of ARMS subjects and patients with schizophrenia while also highlighting a role for ventral corticostriatal circuitry. Further work examining the utility of this phenotype in predicting transition to psychosis will be critical in determining its clinical relevance.

Supplementary Material

Supplementary material is available at http://schizophreniabulletin.oxfordjournals.org.

Funding

National Research Foundation Singapore under the National Medical Research Council Translational and Clinical Research Flagship Program (NMRC/TCR/003/2008). The Australian Postgraduate Award (2010); the Melbourne Neuropsychiatry Centre Research Higher Degree Award (2010) to O.D.; CR Roper Fellowship and National Health and Medical Research Council Project Grant (1050504 to A.F.); Department of Veteran's Affair; Feinstein Institute for Medical Research; GlaxoSmithKline; National Institute of Mental Health; Novartis; Psychogenics; Research Foundation for Mental Hygiene, Inc; the Singapore National Medical Research Council (to R.S.E.K.); National Health and Medical Research Council of Australia Senior Principal Research Fellowship (628386 to C.P.); National Health and Medical Research Council of Australia Program Grant (566529 to C.P.); National Health and Medical Research Council of Australia Clinical Career Development Award (628509 to B.J.H.).

Acknowledgments

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

References


50. Meyer-Lindenberg A, Miletich RS, Kohn PD, et al. Reduced prefrontal activity predicts exaggerated striatal...


