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The neural correlates of performance in adolescents at risk for schizophrenia: Inefficiently increased cortico-striatal responses measured with fMRI

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Abstract

Background—fMRI studies indicate that schizophrenia patients and their adult relatives require greater prefrontal activation to maintain performance at levels equal to controls, but studies have not established if this pattern of inefficiency is observed in child and adolescent offspring of schizophrenia patients (SCZ-Off).

Methods—Using a task with visual working memory demands, we investigated activation in cortico-striatal networks and dorsal prefrontal modulation of regions underlying visual working memory in a group of SCZ-Off (n=19) and controls with no family history of psychosis (n=25 subjects) using an event-related design. Trials were divided based on memory performance (correct vs. incorrect) to specifically identify the neural correlates of correct working memory performance.

Results—Whereas groups did not differ in terms of behavioral accuracy, SCZ-Off demonstrated significantly increased fMRI-measured activation in dorsal prefrontal cortex and the caudate nucleus during correct, relative to incorrect memory performance. Whereas activation in SCZ-Off was high and independent of performance in each region, in controls the fMRI response was related to behavioral proficiency in the caudate. Further, exploratory analyses indicated that this inefficiency in the dorsal prefrontal cortex response increased with age in SCZ-Off (but in no other regions or group). Finally, these differences were not based in differences in dorsal prefrontal modulation of other regions during successful performance.

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Discussion—These results are consistent with observed patterns in adult patients and first-degree relatives. Inefficient fronto-striatal responses during working memory may characterize the schizophrenia diathesis and may reflect the effects of the illness and vulnerability for the illness.

Keywords

Schizophrenia; Offspring; Inefficiency; Development; Vulnerability; fMRI

Background

Cortical-striatal hypo-functionality constitutes a central and enduring cognitive impairment in schizophrenia and in relatives of schizophrenia patients (Faraone et al., 1999; Goldman-Rakic, 1999; Touloupoulou et al., 2003). *In vivo* imaging studies indicate that cortico-striatal hypo-functionality in working memory in particular is expressed by greater *inefficiency* of the fronto-striatal response, both in schizophrenia patients (Callicott et al., 2000; Jansma et al., 2004) and in adult siblings and first-degree relatives of patients (Callicott et al., 2003; Whitfield-Gabrieli et al., 2009). That is, when performance is matched across groups (Manoach, 2003), patients and relatives in general so an increased fMRI response comparable to controls. Such inefficiency indicates that brain responsivity in the schizophrenia diathesis is fundamentally altered; patients and individuals with a family history of the illness must demand greater resources to sub-serve behavior. By extension, cognition is most likely affected in the illness because demand for cortico-striatal resources during complex tasks may exceed the capacity of the underlying neurocircuitry to sub-serve demand. This inefficiency has been linked to impaired fronto-striatal dopamine (Simpson et al., 2010) and reduced gamma-aminobutyric acid (GABA) neurotransmission (Lewis et al., 2005), providing translation between molecular and systems' hypotheses in schizophrenia.

The question of performance inefficiency has not generally been addressed in adolescent offspring of schizophrenia patients (SCZ-Off) with fMRI. Of all the groups with increased vulnerability to schizophrenia, child and adolescent SCZ-Off provide a unique opportunity to investigate both neurodevelopmental (Lewis & Levitt, 2002) and genetic vulnerability in the schizophrenia diathesis (Diwadkar et al., 2001; Diwadkar et al., In Press). Working memory provides a particularly useful domain for assessing functional inefficiencies in SCZ-Off in part because such paradigms can be tractably administered in young subjects (Casey et al., 1995), and because this behavioral domain recruits diverse cortico-striatal regions, and relies and collaborative activity across these structures (Schweinsburg et al., 2005; Smith et al., 1998; Wager & Smith, 2003). Furthermore, neurodevelopment in adolescence in large part is based on the optimization and specialization of cortico-striatal systems for working memory and control (Durstun & Casey, 2006; Edin et al., 2007; Luna et al., 2004), and genetic vulnerability to schizophrenia is likely to impact intra-cortical and cortico-striatal interactions (Harrison & Weinberger, 2005), and prefrontal function in particular (Tan et al., 2007). Recent evidence from verbal working memory studies suggests that SCZ-Off are characterized by inefficiencies in cortico-striatal interactions during both easy and complex levels of task-demand (Bakshi et al., In Press).

Working memory is primarily subserved by the dorsal prefrontal cortex, the basal ganglia (in particular the caudate nucleus) and the parietal cortex (Wager et al., 2003). These regions appear to be involved independent of the modality or the nature of stimuli used in working memory tasks. Additional regions appear to be recruited based on their relative specialization for the content of the memoranda employed (e.g., faces or letters) (Braver et al., 1997; Druzgal & D'Esposito, 2003; Phelps, 2006). Furthermore, interactive or collaborative processing, particularly between frontal cortex and other regions (Diwadkar et al., 2000; Gazzaley et al., 2004) appears to reflect the relatively distributed architecture of this cognitive domain.

The expansion of working memory competence and capacity is particularly marked during adolescence (Bunge & Wright, 2007). This expansion is closely associated with changes in the structural maturation of the frontal cortex (Gogtay et al., 2004), and the development of fronto-striatal connections that have been documented in diffusion tensor MRI studies (Lebel et al., 2008; Stevens et al., 2009). As a result of functional and connective maturation, working memory efficiency increases with age. Therefore, it is plausible that developmentally mediated derailment of fronto-striatal function in SCZ-Off may lead to inefficiencies in working memory implementation. Here we investigated the generality of previous findings to the domain of visual working memory (Honey & Fletcher, 2006). We specifically focused on fMRI responses underlying correct as opposed to incorrect performance. First we contrasted activation for correctly judged against activation for incorrectly judged items during a continuous visual memory task providing the most appropriate characterization of the neural correlates of correct responding. Then SCZ-Off and HC were compared in second level analyses to assess differences in performance efficiency and investigate if SCZ-Off required more cortico-striatal resources to subservise behavioural response levels comparable to controls. We also analyzed if dPFC modulation of cortico-striatal regions during correct performance distinguished SCZ-Off from HC (Diwadkar et al., 2000; Edin et al., 2007) using psycho-physiological interaction (Friston et al., 1997). Psycho-physiological interaction provides a measure of effective connectivity between the seed and target regions (Stephan, 2004) characterizing the modulatory effects of the former on the latter during task-relevant conditions. Analyses were focused on cortical, limbic and sub-cortical regions most closely associated with visual working memory related function, including the dorsal prefrontal cortex (dPFC), the superior parietal cortex (Diwadkar et al., 2000), the basal ganglia (Grahn et al., 2009), the fusiform gyrus (Druzgal et al., 2003) and the amygdala (Phelps, 2006).

Methods

Subjects

All protocols were approved by the Human Subjects Investigative Committee (HIC) of Wayne State University. A total of 44 subjects provided consent or assent to participate and received monetary compensation for their participation. Of these, nineteen were offspring of schizophrenia patients (7 females, mean age=14.3 yrs [8–19 yrs]) and twenty-five healthy control (HC) subjects (8 females, mean age=14.6 yrs [10–19 yrs]). Groups did not differ in IQ (SCZ-Off: 94 vs. HC: 93; $p>.25$) (Wechsler, 1987). Subjects were recruited from the

greater Detroit area through advertisements and patient services at the Wayne State University School of Medicine. Rule outs were achieved through telephone and personal interview, and screening questionnaires, to ascertain if subjects had a history of psychotic illness in first-degree relatives. Diagnoses for parents of offspring were reached using the Structured Clinical Interview for DSM-IV schizophrenia (First et al., 1997). All HC and SCZ-Off were clinically evaluated using the Schedule for Affective Disorders and Schizophrenia-Child Version (Kaufman et al., 1997) and the SCID. Assessments were administered by a trained interviewer (U.R., A.J.). In addition, the assessment of clinical function in SCZ-Off was based on the Global Assessment of Function (GAF) sub-scale of the Structured Interview for Prodromal Symptoms (Miller et al., 2003). The GAF is a reliable index of the psychological, social, and occupational functioning of individuals, providing a measure of the extent of clinical impairment in subjects. Sub-scale scores reflect largely absent symptoms (>80) or transient to severe symptoms (<80) (Diwadkar et al., 2011). SCZ-Off had slightly lower GAF scores than HC (76 vs. 85, $p<.05$) suggesting slightly elevated increases in the incidence of symptoms. Four SCZ-Off were diagnosed with non-exclusionary disorders including Separation Anxiety Disorder ($n=1$), Attention Deficit Hyperactivity Disorder hyperactive type ($n=1$), Attention Deficit Hyperactivity Disorder NOS ($n=1$) and Social phobia ($n=1$).

Task

During the task faces were presented successively in pseudo-random order (3 s/face) with subjects indicating if the affective valence signalled by a face matched the previous face in the sequence. A jittered event-related design was employed (jitter: 3–5 s. in 0.5s increments) to maximize the efficiency of recovering contrast (Josephs & Henson, 1999). Eighty normatively rated (Ekman & Oster, 1979) photographs depicting positive (happy), negative (angry, fearful, sad) and neutral emotions were used. In addition, we also employed 16 control stimuli which consisted of pixilated faces, providing a control for the visual aspects of the task. Therefore, the task consisted of ninety six trials. Data were acquired during a single fMRI session (11.5 mts) and within this session subjects were given intermittent breaks (fixation marker) before a new sequence began. Stimuli were only presented once to avoid repetition effects on the BOLD response (Gilaie-Dotan et al., 2008). Intermittent breaks were provided to allow subjects to rest before the next uninterrupted sequence of trials began. A schematic of the task including how trials were assigned based on a hypothetical set of responses is depicted in Figure 1a.

fMRI

fMRI was performed on a Bruker MedSpec 4T system at the MR Research Center in the Wayne State University School of Medicine. For each subject, a total of 345 echoplanar imaging (EPI) scans were acquired using a gradient-echo sequence with 24 axial slices (TR=2000 ms, TE=30 ms, FOV=240x240 mm, voxel size= $3.75 \times 3.75 \times 4$ mm, matrix size= 64×64). Data were analyzed using SPM8. Raw images were realigned with the AC-PC orientation, co-registered with the first image in the sequence and corrected for susceptibility-by-movement interactions. Following realignment, images were normalized to a standard EPI template (Montreal Neurological Institute). The six motion parameters (planar and angular) were employed as covariates of no interest in all first-level analyses.

Trials were designated by response type (correct or incorrect). Activity associated with each of these response types was modeled by convolving box-cars (3s) with the canonical hemodynamic response function. Intra-subject contrasts (Correct > Incorrect) were used to model activation differences at the first level, providing separation of activation associated with correct responses, from activation associated with incorrect responses.

In addition to the analyses of activation, modulatory interactions using a dPFC seed was assessed using psycho-physiological interaction (Friston et al., 1997) or PPI. PPI is a valuable method of evaluating the modulatory effects of an *a priori* defined seed region (e.g., dPFC) on target regions during a psychological contrast of interest (e.g., correct responding vs. incorrect responding). PPI provides a *directional connectivity* map between the seed and targets, with the strength of this connectivity parametrically encoded voxel-wise within intra-subject maps. When thresholded in second level random effects analyses (Friston et al., 1997) PPI can reveal differences between groups in the modulatory effects of the seed on targets. For these analyses, time series (one per hemisphere) from the dPFC from each subjects' effects of interest map ($p < .05$) were convolved with the contrast of interest (Correct > Incorrect). To assess the facilitatory effects of activity in the seed region (dPFC) on targets during the task (i.e. contrast) of interest, the convolution term was weighted positively (Das et al., 2005).

Group differences were assessed at the 2nd level based on first-level images. For analyses of activation differences, Correct > Incorrect first level contrasts were used. For analyses of PPI, positive interaction contrast images were used. Age and gender were used as covariates in all analyses to account for the wide range in the age of subjects (8 yrs age 20 yrs). Regions of interest were anatomically defined in stereotactic space using established methods (Maldjian et al., 2003). Cluster level correction ($p < .05$) was applied to identify significant clusters (Ward, 2000). All fMRI analyses were replicated excluding SCZ-Off (n=4) with non-exclusionary clinical criteria.

Results

Behavior

Behavioral results (% correct performance) were analyzed to assess whether groups differed in accuracy. Groups did not differ in terms of proportion correct across the experiment (HC: mean=.77 sd=.09; SCZ-Off: Mean=.74, sd=.1; Figure 1b). Separate regression analyses indicated that performance was independent of age in each of HC and SCZ-Off ($r = .08$ and $r = .2$ respectively, $p > .5$). Because the assignment of fMRI images to conditions in the event-related analyses was predicated on performance, this equivalence also ensured that across groups, on average the number of fMRI images assigned to each condition (Correct vs. Incorrect) were equivalent across groups.

fMRI (Activation)

Significant main effects of group were observed in the dorsal prefrontal cortex, and within the dorsal striatum in the head of the caudate nucleus. Figure 2 and Table 1 depict clusters projected on dorsal and medial views of the cortical surface. Radiating graphs depict mean

normalized signal change, under the significance peaks of interest (2 mm radius) listed in Table 1, indicating significantly *increased* BOLD in SCZ-Off relative to controls. Effects in other regions did not reach significance.

To assess the effects of age and clinical characteristics on the signal change data, data from each of the caudate and the dPFC clusters were submitted to analyses of covariance. These analyses employed two factors: Group and Developmental Group. To assign subjects to developmental group, we used a median split of age to classify subjects based on early adolescence and late adolescence (HC: Older Adolescents, $n=13$; SCZ-Off: Older Adolescents, $n=10$). These analyses allowed us to investigate group differences and potential group by development interactions in a General Linear Model framework. To model clinical characteristics of the sample the GAF score was used as covariate in these analyses.

These analyses revealed significant main effects of group in the Caudate, $F_{1,39}=4.97$, $p<.05$, $MSe=.215$ and the dPFC, $F_{1,39}=5.42$, $p<.05$, $MSe=.328$ with moderate effect sizes on each, partial $\eta^2=.11$ and $\eta^2=.12$ respectively (Cohen, 1988). No effects of GAF score were observed in either region ($p>.5$). Finally, no effects of Developmental Group or interactions were observed ($p>.4$). Figure 3 depicts data from these analyses depicted as a function of Group and Developmental Group.

Age-related effects were further explored using locally weighted polynomial regression (LOESS)(Cleveland & Devlin, 1988). LOESS allows for better exploration of trends in data because unlike parametric curve fitting techniques that use *a priori* defined functions or the GLM methods previously employed, the method involves iterative fitting of polynomials to each individual data point using weighted least squares (Hastie et al., 2001). The regression function for the data series is only completed after regression function values have been computed for each of the data points. The resultant curve fit does not possess a single mathematical form but reflects the trend that best captures the form of the data. Weighted nearest neighbor kernel functions are employed to weigh the neighbors of the current data point in the analyses based on distance, with nearest neighbors weighted more than points further away in the entire data set. LOESS allows for a better characterization of the spread in data, has proved valuable in deriving differences in developmental trends in cross-sectional data in pediatric populations including healthy and ADHD subjects (Stanley et al., 2008), and is less sensitive to outliers (unlike parametric curve fitting techniques). For the present analyses, we employed the Epanechnikov kernel function which strikes an optimal balance between weighting nearest versus distant neighbors of the data point (Hastie et al., 2001). To minimize effects of differential sampling density of values around different ages in each of the groups, the maximal band width was applied to the kernel to weight all the points at each local fit.

The four LOESS fits (for each group and for each of the two regions of interest) are depicted in Figure 4 showing differences in age-related trends across the regions of interest. Control subjects evinced largely age-invariant fits in the dPFC (Fig 4a) and caudate (Fig 4c). In SCZ-Off, LOESS suggested an increase in the dPFC response from the middle of, and continuing through late, adolescence (Fig 4b), with no clear trend in the caudate (Fig 4d).

Performance and fMRI response—The continuous relationship between performance and the fMRI response in the largest clusters in each of the dPFC and basal ganglia was explored using linear regression. To limit the effects of outliers in the data, performance values that exceeded 2.5 standard deviations from the mean (Tukey, 1977) were excluded from each group. The resultant data (HC: $n=24$; SCZ-Off: $n=19$) were analyzed. Across panels, Figure 5 depicts the relationships between performance and activation in each of HC and SCZ-Off. In the dPFC (Fig 5a & 5b), within groups fMRI activity was independent of performance ($r=.03$ and $r=.19$, $p>.2$ respectively). A performance-dependent relationship in HC was observed in the caudate ($r=.38$), $F_{1,22}=3.65$, $p<.05$, one-tailed, $\beta=.45$ (Cohen, 1992). The fMRI response in SCZ-Off was independent of performance, $r=.04$. Differences in correlation coefficients and the slopes of the observed regression functions between HC and SCZ-Off were not significantly different (Cohen & Cohen, 1983).

fMRI (Modulatory Interactions with PPI)

Analyses of modulatory interactions using bidirectional contrasts did not reveal differences between SCZ-Off and HC ($p>.2$). That is, there were no differences between groups in the degree of dPFC modulation of working memory-related regions during correct (relative to incorrect) responding. To confirm significant overlap across groups in dPFC modulation of the evaluated circuit, we conducted a conjunction analyses on first level maps in each of SCZ-Off and HC. Thresholded image maps using the minimum inference statistic (Nichols et al., 2005) are depicted in Figure 6 (with significance peaks in Table 2). Significant clusters are rendered for the bilateral parietal lobe (k_E 469 voxels; cluster volume 1876 mm³), the bilateral basal ganglia (k_E 64 voxels, cluster volume 256 mm³), the bilateral amygdala (k_E 19 voxels, cluster volume 76 mm³) and the bilateral fusiform gyrus (k_E 48 voxels, cluster volume 192 mm³).

Discussion

Four observations were noted in the analyses: a) When assessing activation specifically associated with correct responses, SCZ-Off showed increased activation compared to HC, in the dPFC and the caudate nucleus of the basal ganglia (Figure 2). Activation differences were not observed in the other regions evaluated in the working memory network including the parietal lobe, the putamen, the amygdala or the fusiform gyrus; b) No clear developmental trends were observed in the cross-sectional analyses. Interactions between developmental stage and group were not significant (Figure 3) suggesting inefficiencies were in evidence in young and old SCZ-Off relative to HC. Exploratory curve fitting analyses using LOESS suggested that in SCZ-Off, the dPFC response underlying correct responding increased with age, with the increase appearing from approximately the middle of adolescence (Figure 4). These results must be treated as speculative as LOESS analysis is sensitive to local but not general trends in the data, is subject to the density of points sampled, and does not permit classical inferences of differences between groups. Nevertheless, these results suggest that inefficiencies in the fronto-striatal response in SCZ-Off do not normalize with age, suggestive of a pervasive development deficit; c) In HC, but not SCZ-Off, caudate activation was linearly predicted by performance, whereas the dPFC response in either group was unrelated to performance (Figure 5); d) Finally, the modulatory

effects of the dPFC on other regions during correct responding was comparable across groups (Figure 6). These effects in the fMRI data were observed in the face of performance characterized based on item-analyses of comparable behavioral responses (Figure 1).

The average age of this sample (14 yrs) provides unique convergence with previously documented studies in patients and adult siblings. Inefficient recruitment of fronto-striatal resources may be an important and general characteristic of vulnerability and disease in the schizophrenia spectrum. Taken together, these results imply that selective hyperactivity of the fronto-striatal core of working memory is required to maintain memory performance in SCZ-Off at levels comparable to HC.

Working Memory in the dPFC and Caudate

As with previously used paradigms (Postle et al., 2003), the current task allowed us to assess differences between groups in modality-specific and modality-independent regions for face-related visual working memory, as well as extend previous work in SCZ-Off (Bakshi et al., In Press). The role of the dPFC in working memory has been well established, and recent evidence suggests highly complementary memory-related functions within the caudate (Grahn et al., 2008; 2009). This complementarity reflects the intricate mapping between regions of the dPFC (particularly Brodmann Areas 9 & 46) and the head of the caudate nucleus (Calzavara et al., 2007). Cellular studies indicate that phasic dopamine release and neuronal activity during memory retention is a primary mechanism employed by frontal neurons to maintain information online (Fuster, 1989). The anterior caudate, in receiving working memory signals from the dPFC, subserves the integration of function across the working-memory related networks during acquisition, maintenance and control (Chang et al., 2007), rendering this region more sensitive to task-proficiency. The specificity of the observed effects across the network, and within sub-regions of the network is notable. In particular, the observed hyper-activity in SCZ-Off was specific to the hetero-modal regions of cortico-striatal structures, suggesting that memory-related inefficiency in the schizophrenia diatheses is modality-independent. Furthermore, within the basal ganglia, the specificity of the effect to the head of the caudate is notable, given that regions such as putamen or the caudate tail are implicated in stimulus response mapping and movement (Menon et al., 2000) or processes of pattern recognition (Nakano, 2000) respectively.

Fronto-striatal dopamine is essential for the efficient working memory function and capacity (Castner & Williams, 2007); hyper- or hypo-dominergia disrupts the receptive field properties of frontal neurons (Vijayraghavan et al., 2007). An imbalance in prefrontal and striatal dopamine has been implicated in working memory deficits (Goldman-Rakic et al., 2004; Goldman-Rakic & Selemon, 1997). Striatal (in particular caudate) dopamine is highly predictive of working memory capacity (Landau et al., 2009), and the abnormal fronto-striatal dopaminergic pathway has been implicated in the observed patterns of inefficient working memory performance in patients (Tan et al., 2007) and also in at-risk populations (Fusar-Poli et al., 2009; Hirvonen et al., 2005). Disrupted dopamine signalling in turn may underlie reduced synaptic plasticity in the frontal cortex (Goto et al., 2010; Jay, 2003), thereby depressing synaptic facilitation and the capacity of working memory in schizophrenia (Gore et al., 2010) and in groups vulnerable to schizophrenia. In development,

selectively reduced dopamine innervation to the prefrontal cortex impairs working memory function (Diamond, 1996), a mechanism which has been implicated in developmental models of schizophrenia (Weinberger, 1987). Furthermore, the Val158Met polymorphism of the Catechol-O-methyl transferase gene that significantly reduces synaptic dopamine has been associated with impaired working memory efficiency and prefrontal cortical function (Egan et al., 2001; Harrison et al., 2005). In this context, selective fronto-caudate hyperactivity in SCZ-Off is suggestive of developmentally mediated influences on decreasing fronto-striatal working memory efficiency. The current studies do not offer direct support for the fronto-striatal dopamine hypothesis, though the fronto-striatal specificity of the results and their consistency with other studies is notable.

Learning related deficits are also a hallmark of the schizophrenia diathesis (Diwadkar et al., 2008) and have been linked to deficits in visuo-spatial memory as well (Wood et al., 2002). In general, working memory and executive processes may be central to several cognitive domains including associative learning, which does rely on the temporary maintenance of memoranda (relying on frontal activity) before items can be consolidated in longer-term memory (Bunge et al., 2004; Ranganath et al., 2004). In this context, the current results suggest the frontal (and striatal) inefficiencies in the schizophrenia diathesis may substantially impact associative learning. Indeed, as recently demonstrated using Dynamic Causal Modeling (Banyai et al., In Press) associative learning in schizophrenia patients is particularly associated with reduced fronto-hippocampal coupling, indirectly suggesting that frontal hyper-activation is a reflection of dysconnection that may lead to the inefficient functional hyper-specialization. Whereas we have not collected associative learning data in children at risk for schizophrenia, we speculate that learning related deficits in this group would reflect those observed in adult patient studies.

Collaborative activity underlying working memory

In the present analyses, no differences were observed in the modulatory effects of the dPFC on other regions in the network during correct responding. Animal and human fMRI studies have emphasized the collaborative effects of inter-cortical function during working memory (Chafee & Goldman-Rakic, 2000; Diwadkar et al., 2000; Wager et al., 2003). The elimination in adolescence, of overproduced synapses has been associated with more efficient intra-regional processing and more systematic inter-regional collaboration (Klingberg, 2006). Differences in modulatory effects revealed by psycho-physiological interaction suggest either that the activity in the seed region changes the responsivity of the target regions during the task or that the inputs from the seed are different between groups (Friston et al., 1997). The lack of modulatory differences and the significant overlap observed across groups (Figure 2) suggest that selective hyper-activation observed in SCZ-Off reflects local processing demands during correct memory performance. In general, the lack of modulatory differences may reflect the relatively low demands of a task that did not generate variation in collaborative demands (Bakshi et al., In Press; Koshino et al., 2005).

Schizophrenia Offspring: Vulnerability and Development

SCZ-Off are highly vulnerable both to developmental deviations in bio-behavioral signals (Barbour et al., 2010; Diwadkar et al., 2001; Diwadkar et al., 2006), and most likely as a

consequence of these deviations, to psychiatric disorders (Paus et al., 2008). Incidence rates of schizophrenia-related or not otherwise specified psychosis in offspring of schizophrenia patients range from 8 to 20%, that is up to twenty times higher than the incidence in the general population (Erlenmeyer-Kimling & Cornblatt, 1987). While conversion rates may be seen as relatively low, other measures point to pervasive deficits in neuropsychological and brain function during childhood and adolescence. Through adolescence, SCZ-Off show altered trajectories of development in key frontal lobe domains including working memory and executive function (Diwadkar et al., 2006), as well as increased incidence of Axis I psychopathology (Keshavan et al., 2008). In general, impairments have been observed in psychological domains subserved by fronto-striatal function, including working memory and sustained attention. In addition structural, metabolic and membrane phospholipid alterations in fronto-striatal circuitry (Keshavan et al., 2009; Keshavan et al., 2003) provide evidence of the neuronal bases of these psychological impairments. However, psychological and structural MRI related impairments in SCZ-Off are subtle with effect sizes that often require large samples. The study of brain function provides a potentially richer framework to identify functional measures of risk and vulnerability in the adolescent brain even using more modest sample sizes (Diwadkar & Keshavan, 2002).

Limitations in sample size (that are expected in groups such as SCZ-Off who are difficult to recruit and assess) might hinder generalization of the findings. Furthermore, the cross-sectional nature of the study limits the understanding of their relevance for the eventual emergence of psychopathology. Finally, given the role of specific genetic polymorphisms in working memory and schizophrenia (Tan et al., 2009), the absence of genetic characterization of our cohort limits our ability to relate these findings to more specific molecular underpinnings. These limitations notwithstanding, the present results provide compelling evidence of latent fronto-striatal dysfunction in adolescents vulnerable to schizophrenia.

Development, risk and psychiatric illness form an inextricably linked chain of life events existing in the neo-natal state onward (Gilmore et al., In Press), and studying the integrity of the brain's functional responses constitutes a central strategy for the understanding of, and intervention in, groups at risk for psychiatric illness. From this perspective, understanding the neural correlations of accurate performance provides insight into the functional brain response in an experimental setting. It reflects an inherent inefficiency to cognitive demand in adolescents at risk for schizophrenia, the observed cortico-striatal hyper-activity suggests that the vulnerable brain may be ill developed to respond to complex demand characteristics of the real world. In this way our fMRI studies suggest a pathway for the documented increases in psychopathology and cognitive deficits in this population (Keshavan et al., 2004) in the functional neurobiology of the adolescent brain.

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Figure 1.

(a) The task employed is depicted. Stimuli (faces or pixilated images) were presented for 3 s with a randomly jittered 3–5 s inter-stimulus interval. For exposition, possible responses on trials are denoted “same/different” and in the context of the stimuli used, the correctness of the response is underlined beneath. In the analyses, Correct responses were separated from Incorrect responses and first-level contrasts (Correct > Incorrect) were used to isolate the neural correlates of correct working memory performance. (b) Proportion correct responses depicted for each of HC and SCZ-Off groups did not differ. Error bars are $\pm$ sem.

Figure 2.

Significant clusters in bilateral dorsal (a) and medial (b) views under the main effect depict differences in activity associated with correct responding in SCZ-Off and controls. Hyperactivity was restricted to the dorsal prefrontal cortex and the caudate nucleus. Radiating graphs of normalized signal change under each of the significance peaks indicate that SCZ-Off hyper-activate each of the dPFC and caudate to sub-serve comparable performance (See Table 1; error bars: $\pm$ sem).

Figure 3.

Signal change data from each of the Caudate and dPFC are plotted as a function of Group and Developmental Group (Early Adolescence vs. Late Adolescence). As seen, SCZ-Off show inefficiently increased activity associated with correct responses at each developmental stage.

Figure 4.

(a) – (d). LOESS fits are depicted separately for each of the groups (a–c: HC; b–d: SCZ-Off) for data drawn from each of the peaks of significance (Figure 2 and insets). As seen in SCZ-Off, the LOESS fits suggest that the dPFC response during correct responding increases with age from the middle of adolescence (arrow) onward. Trends in controls are dissimilar to SCZ-Off, and are either age invariant (caudate) or decreasing (dPFC).

Figure 5.

Signal change in each of groups under the significant cluster of interest (Fig 2) is depicted as a function of proportion correct responses in each group. Solid lines are linear regression with mean confidence interval. As seen in SCZ-Off, in each of the (b) dPFC and (d) caudate, the fMRI response remains elevated and independent of performance. In controls, the response in the dPFC (a) remains elevated and independent of performance, whereas the response in the caudate (b) was proportionally related to performance.

Figure 6.

Conjunction analyses of PPI maps indicate significant overlap across groups in the degree of dPFC during correct responding (Nichols et al., 2005). Significant conjunction clusters are overlaid on dorsal (a), medial (b) and ventral (c) views (Significance peaks across the regions of interest are presented in Table 2).

Table 1

Clusters with significantly increased activity ($p_u < .05 / p_c < .05$) in SCZ-Off compared to HC were observed in dPFC, and the head of the caudate (Figure 2). Cluster extent thresholds based on 10^4 Monte Carlo simulations ($p_c < .05$, $p_u < .05$) were dPFC: 82 voxels (656 mm³) and Caudate: 52 voxels (416 mm³).

Region	Hemi	k_E	Statistic ($F_{1,40}$)	MNI (x,y,z)
dPFC	Right	655	12.18	34,2,38
Caudate (Head)	Left	122	7.62	-12,2,22

Table 2

Conjunction analyses with the minimum inference statistic revealed significant overlap in positive modulation by the dPFC during correct responding in HC and SCZ-Off (Fig 5). Maximum peaks from each of the regions assessed are detailed.

Region	Statistic $\text{SPM}\{T_{g2}^{2\{\text{Ha:k} \geq 1\}}\}$	MNI (x,y,z)
Parietal (Supramarginal Gyrus)	3.35	54,-54,22
Amygdala	3.16	26,4,-18
Basal Ganglia	3.13	-18,0,2
Fusiform Gyrus	3.08	20,-86,-20