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Dysfunctional striatal systems in treatment-resistant schizophrenia.

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Abstract

The prevalence of treatment-resistant schizophrenia points to a discrete illness subtype but to date its pathophysiologic characteristics are undetermined. Information transfer from ventral to dorsal striatum depends on both striato-cortico-striatal and striato-nigro-striatal sub-circuits, yet while the functional integrity of the former appears to track improvement of positive symptoms of schizophrenia, the latter have received little experimental attention in relation to the illness. Here, in a sample of individuals with schizophrenia stratified by treatment-resistance and matched controls, functional pathways involving four foci along the striatal axis were assessed to test the hypothesis that treatment-resistant and non-refractory patients would exhibit contrasting patterns of resting striatal connectivity. Compared with non-refractory patients, treatment-resistant individuals exhibited reduced connectivity between ventral striatum and substantia nigra. Furthermore, disturbance to corticostriatal connectivity was more pervasive in treatment-resistant individuals. The occurrence of a more distributed pattern of abnormality may contribute to the failure of medication to treat symptoms in these individuals. This work strongly supports the notion of pathophysiologic divergence between individuals with schizophrenia classified by treatment-resistance criteria.

1. Introduction

Establishing why current antipsychotic medication fails to assuage hallucinations (aberrant perceptions) or delusions (fixed, false beliefs) in approximately 30% of schizophrenia patients (Lieberman *et al*, 2005) is a key clinical problem and relies on identifying core neural features that predict treatment resistance. Current medication for schizophrenia principally targets the striatum (Seeman and Lee, 1975); and clinical potency is predicted by its binding to and blockade of the dopamine D_2 receptor (Creese *et al*, 1976). However, the observation that responders and treatment-resistant individuals exhibit virtually identical D_2 receptor occupancy levels (Wolkin *et al*, 1989) suggests that occupancy alone is insufficient to produce symptomatic alleviation. More recent observations that treatment-resistant patients differ from responders in terms of both dopamine concentrations in the limbic and associative striatal subdivisions and glutamate concentration in the anterior cingulate cortex (ACC)(Demjaha *et al*, 2014; Demjaha *et al*, 2012) suggest the presence of discrete pathophysiologic subtypes. Nevertheless, the mechanisms underlying treatment resistance remain incompletely resolved.

Information appears to flow from ventral striatum - where basic stimulus features such as anticipated reward value are encoded - to dorsal structures, where distinct parallel circuits facilitate this transfer, and refine information content for subsequent appropriation by learning and action processes(Botvinick *et al*, 2009; Croxson *et al*, 2009; Haber and Knutson, 2010). Striato-cortico-striatal loops predominantly involving prefrontal cortex (PFC) projections have been delineated in nonhuman primates (Alexander *et al*, 1986), and confirmed in humans with diffusion tensor imaging (Leh *et al*, 2007; Lehericy *et al*, 2004) and resting-state functional magnetic resonance imaging (rs-fMRI) (Di Martino *et al*, 2008). These loops include: a ventral circuit anchored in the inferior limbic subdivision of the striatum and comprising connections with orbitofrontal cortex (OFC), ventro-medial PFC, medial thalamus and limbic regions, which is fundamental to associative learning and reward-mediated decision making (Knutson and Cooper, 2005); and a dorsal circuit, including the associative subdivision of the striatum, dorsolateral PFC and medio-dorsal and ventro-anterior thalamus, which maintains information relating to reward outcomes (O'Doherty *et al*, 2004). Furthermore, there is convergent evidence for the complementary involvement of these corticostriatal networks in psychotic illness. Compromised ventral circuit function has been well established by consistently reduced activation of ventral striatum and PFC during reward processing in schizophrenia (Heinz and Schlagenhauf, 2010; White *et al*, 2013), structural changes of ventro-medial PFC after or during the transition to a first illness episode (Mechelli *et al*, 2011), and an up-regulation of ventral striatum dopamine concentration in psychotic individuals (Fusar-Poli and Meyer-Lindenberg, 2013). However, preferential elevation of dopamine in dorsal striatum has also been reported in both unmedicated patients and individuals in an at-risk mental state (ARMS) for developing psychosis(Howes *et al*, 2009; Kegeles *et al*, 2010).

Sub-circuits comprising pathways between striatum and substantia nigra (SN) are less publicised but equally pivotal for information flow through the striatum; playing a seemingly crucial role in

instrumental learning and habit formation(Belin and Everitt, 2008). These projections are more broadly distributed than cortico-striatal pathways (Haber and Knutson, 2010). Despite this inter-mingled, clustered arrangement, ventral tegmental area and medial SN are generally associated with ventral striatum, and central and ventrolateral SN with associative and sensorimotor striatum respectively (Haber and Fudge, 1997; Haber et al, 2000; Nauta and Domesick, 1978; Somogyi et al, 1981). While ventral striatum receives sparse SN input, it projects to a large region of midbrain and is therefore a strong modulator of SN activity. By contrast, dorsal striatum (caudate/putamen) receives diverse and numerous afferent connections from SN, and is therefore heavily influenced by SN, but itself extends limited reciprocal projections. Individuals with schizophrenia have been recently shown to exhibit reduced nigro-striatal connectivity(Yoon et al, 2013; Yoon et al, 2014), but striato-nigro-striatal connections have not yet been investigated in relation to treatment resistance.

Studying functional connectivity (FC) in striatal circuits at rest circumvents issues of performance (e.g. inter-subject differences, practice and ceiling/floor effects), which confound task-based functional imaging investigations. As yet, no robust structural or functional brain correlates have been associated specifically with treatment-resistant schizophrenia (Nakajima *et al*, 2015). Investigation of multiple cortico-striatal circuits has, however, revealed complex, subtle alterations in association with both vulnerability to psychosis and clinical features of the disorder. ARMS individuals display hypoconnectivity (as compared with control subjects) in the circuit involving dorsal caudate, right DLPFC, medial PFC and thalamus, but hyperconnectivity between ventral putamen, fronto-insular cortex and superior temporal gyrus (Dandash *et al*, 2014). Similarly, in individuals with first-episode psychosis (FEP) and their first-degree relatives, functional connectivity is enhanced for the ventral circuit and reduced for the dorsal circuit (Fornito *et al*, 2013). These findings, together with the assumed importance of striatal networks for treatment response and the growing evidence for a dissociable neurophysiologic foundation for treatment-resistant schizophrenia, guided our interest in clarifying whether treatment-resistant individuals are differentiable from other individuals with schizophrenia on the basis of their striatal connectivity.

If pharmacological blockade of striatal $D_{2/3}$ receptors effects clinical improvement and normalisation of brain activity in some patients but not others, it is likely that treatment-responsive and resistant patients differ in terms of their striatal network function. A recent study has used this idea to examine prospective treatment response, identifying changes in striatal connectivity with prefrontal and limbic regions as important in symptomatic alleviation (Sarpal *et al*, 2015). Guided by these observations, the rationale that treatment-resistant individuals would differ from non-refractory patients in these brain substrates that track clinical improvement, and the idea that treatment-resistant individuals would exhibit striatal FC abnormalities indicative of their specific cognitive and behavioural impairments, we addressed two principal hypotheses: First, that treatment-resistant individuals with schizophrenia would display reduced connectivity along nigro-striatal pathways compared with non-refractory individuals,

since learning and its influence on action can be impaired in treatment-resistant individuals (Dratcu *et al*, 2007; Kolakowska *et al*, 1985), and related processes are regulated by striatum and substantia nigra (Braver *et al*, 1999a; Braver and Cohen, 1999b; D'Ardenne *et al*, 2012). Second, that fronto-striatal disruptions observed when comparing patients with healthy individuals (Quide *et al*, 2013; Sarpal *et al*, 2015) would differ as a function of treatment resistance. In addition, as the persistence of positive symptoms is fundamental to treatment resistance, and with the aim of building on previous FEP observations (Fornito *et al*, 2013), we assessed the extent to which current positive symptom severity predicted striatal FC in treatment-resistant and non-refractory patients.

2. Materials and Methods

2.1 Participants

Thirty-eight right-handed individuals satisfying DSM-IV criteria for schizophrenia took part in this fMRI study. These individuals were stratified according to their documented response to antipsychotic treatment in electronic medical records: 16 met modified Kane criteria for treatment-resistant schizophrenia on the basis of: 1) completion of at least two sequential 4-week antipsychotic trials at a daily dose of 400-600 mg chlorpromazine (or equivalent); 2) persistent psychotic symptoms of at least moderate severity (as indexed by Positive and Negative Syndrome Scale (PANSS) scores (Kay *et al*, 1987) on one or more positive subscale measure); and 3) impaired occupational functioning (as indexed by a score ≤59 on the Global Assessment of Function (Conley and Kelly, 2001; Demjaha *et al*, 2012). Patients not satisfying all treatment resistance-related criteria were assigned to the non-refractory schizophrenia group. Medication compliance was assessed by review of pharmacy and medical records. This recruitment strategy, in contrast to the selection of treatment-resistant and treatment-responsive patients (with alleviated symptoms), permitted between patient-group matching in terms of current symptom severity, which presented the capability to dissociate effects of treatment resistance from those of current illness state. Patient groups were group-matched for age, sex, and parental socio-economic status (Rose and Pevalin, 2001) with each other and a sample of 20 healthy volunteers. Healthy participants were recruited by local poster advertisement. Respondents were excluded from study if: they reported a personal history of psychiatric or neurological illness; a recent history of illicit substance use; or a history of psychotic illness in a first-degree relative; or exhibited a major current physical illness. Details of these participants' demographics, clinical characteristics are presented in Table 1. Ethical approval was provided by Central London Research and Ethics Committee 3. All participants provided informed written consent and were given a monetary inconvenience allowance for participation.

2.2 Design

All patients participated in one MRI session and experienced no amendment to their ongoing antipsychotic treatment regimen.

2.3 fMRI data acquisition

fMRI data for each scanning session comprised 300 gradient-echo echo-planar images (TR/TE: 2000/30 ms, flip angle: 75°, matrix: 64 x 64) acquired on a 3 Tesla GE Signa MR scanner (GE Healthcare, USA) at the Institute of Psychiatry, London. Each whole-brain image contained 37 non-contiguous slices of 2.4-mm thickness separated by a distance of 1 mm, and with in-plane isotropic voxel resolution of 3.4 mm. Participants were instructed to remain still with gaze fixed on a central cross for the duration of this ten-minute resting-state scan. A high-resolution T1-weighted structural scan was acquired for each

participant using a fast-spoiled gradient-echo pulse sequence (repetition time = 9.4 ms, echo time = 3.8 ms, flip angle = 12°, time to inversion= 450 ms).

2.4 fMRI analysis

fMRI data were preprocessed using SPM8 (Statistical Parametric Mapping, Wellcome Department of Imaging Neuroscience, University of London, UK). Data were slice-time corrected and realigned to the first image of each series, normalised via unified segmentation of subject-specific anatomical data coregistered to the SPM-T1 template, and smoothed using a 6-mm full-width at half maximum Gaussian kernel. Segmented white matter (WM) and cerebrospinal fluid (CSF) images were thresholded at 50% tissue probability and binarised to create nuisance variable masks.

To facilitate potential comparisons with recent related findings, further processing and seed definition followed procedures outlined elsewhere (Dandash *et al*, 2014; Fornito *et al*, 2013). Seeds were defined in both hemispheres as 3.5-mm radius spheres at the following stereotaxic coordinates: dorsal caudate (DC; x = ±13, y = 15, z = 9); ventral striatum/nucleus accumbens (VS; x = ±9, y = 9, z = -8); dorsal-caudal putamen (dcP; x = ±28, y = 1, z = 3); and ventral-rostral putamen (vrP; x = ±20, y = 12, z = -3)(Dandash *et al*, 2014). To complement di Martino and colleagues' original investigation(Di Martino *et al*, 2008), effects were additionally modelled in relation to their remaining two seeds, but as per previous work(Dandash *et al*, 2014), experimental focus was placed upon the former four seeds. Component-based correction (CompCor) of temporal confounds relating to head movement and physiological noise was performed using the CONN toolbox (v.14) (Whitfield-Gabrieli and Nieto-Castanon, 2012). Under the rationale that related noise effects are not spatially uniform, and that regional signals encode temporally distinct linear combinations of them, CompCor parses signals measured within specified masks into linearly additive temporal components whose effects on connectivity metrics can all be mitigated. Accordingly, the first 5 principal components of the WM- and CSF-mask signals were calculated, and the first eigenvariate of activity within each of the 6 bilateral seeds was estimated after regressing out linear effects of the 6 realignment parameters, their first derivatives and the 10 noise components. Preprocessed data were temporally bandpass-filtered (0.01-0.1 Hz).

First-level FC analyses were performed using general linear models, as implemented in SPM8. These modelled individual-specific co-variation between the activity of each seed and the rest of the brain,and comprised regressors for the 6 seed regions' time-courses, 6 realignment parameters and their first derivatives, and the 10 noise components. Second-level models were estimated according to our explicit hypotheses. First, to test whether FC between each striatal seed and the rest of the brain differed between individuals with treatment-resistant and non-refractory schizophrenia, independent-samples T-tests were conducted for these groups for each seed. To permit dissociation of effects relating to, and those independent from, the severity of current psychotic illness, covariates included the positive, negative

and general PANSS sub-scores. To further account for potential motion effects on connectivity estimates, the effects of 4 summary measures of head movement were added as covariates (Fornito *et al*, 2013; Van Dijk *et al*, 2012) in these and all subsequent between-group, second-level analyses. Second, to examine potential idiosyncrasies in connectivity specific to each patient group, independent samples T-tests were conducted to compare their whole-brain connectivity patterns with those of the healthy individuals. Third, to evaluate patient-group specific relationships between current schizophrenic symptomatology and whole-brain striatal FC, analyses of covariance (ANCOVA) models were estimated for each of the four seeds, independently for treatment-resistant and non-refractory schizophrenia. These models included the 3 PANSS sub-scores as predictors, and the 4 summary measures of head movement and CPZ dosage as covariates. The inclusion of negative and general symptom sub-scores allowed detection of effects specific to the positive symptom sub-score.

Finally, ANCOVA tests were used to investigate the extent to which striatal FC was predicted by antipsychotic medication dosage in individuals with schizophrenia. Effects were assessed via within-group models because, as shown in Table 1, there was a significant difference in CPZ dosages between the patient groups. Covarying out the effects of variables which differ between groups does not statistically equate to conducting the same experiment in individuals matched on that variable, as has been elegantly and repeatedly discussed elsewhere (see, for example, Suckling, 2011). With this in mind, independent ANCOVA tests were run for the treatment-resistant and non-refractory individuals with schizophrenia. The effects of medication dosage on each seed's functional connectivity were examined separately in models incorporating subject-specific contrast images for the functional connectivity of that seed and covarying out effects of the 3 PANSS sub-scores, the 4 summary measures of head movement and the four summary measures of head movement. Importantly, on account of the between-group differences in CPZ dosage, the covariates were not mean centred. This ensured that the effects of each particular dosage were consistently described across both groups.

For all analyses significance was ascribed according to a family-wise error corrected cluster-wise threshold determined using the AlphaSim permutation procedure implemented in the REST toolbox (http://pub.restfmri.net) in a manner identical to previous investigations of striatal FC in psychosis(Dandash *et al*, 2014; Fornito *et al*, 2013). To reduce Type 1 error, the conventional family-wise error corrected cluster threshold of .05 was further Bonferroni corrected to reflect the number of seeds tested. Significant between-patient group effects are reported only in those voxels judged significant in the healthy individuals. Seed-specific masks were constructed from the results of one-sample T-tests conducted on the healthy-group contrast images, covarying for effects of the summary measures of head movement, and using the cluster-level significance criterion described above (Figure S1). These were selected under the rationale that they represent the core connectivity circuit for each seed. (Figures S2 and S3 illustrate overlap between healthy group findings and significant clusters in non-refractory and treatment-resistant schizophrenia respectively.).

3. Results

3.1 Divergent functional connectivity in treatment-resistant and non-refractory schizophrenia

In comparisons with healthy individuals, the patient groups exhibited divergent patterns of corticostriatal abnormality. The treatment-resistant patients displayed reduced FC between VS and middle frontal gyrus, between DC and sensorimotor cortex, and in terms of striato-striatal connectivity of circuits involving the vrP seed (Figure 1; Table 2). By contrast, significantly reduced functional connectivity was found between the DC and rostral PFC extending into dorsolateral PFC, and DC and visual cortex in non-refractory patients as compared with healthy controls (Figure 1; Table 2). Between-group comparisons for the other seeds produced non-significant results. Compared with non-refractory patients, treatment-resistant individuals with schizophrenia exhibited reduced striato-nigral FC between VS and substantia nigra, and reduced FC between dcP and the pulvinar of the thalamus. In addition, they exhibited enhanced functional connectivity between DC and medial and superior PFC compared with non-refractory individuals (Figure 2; Table 2).

3.2 Relationships between FC and positive symptoms of schizophrenia

In treatment-resistant schizophrenia, increased positive PANSS sub-score was associated with reduced functional connectivity between VS and parietal midline structures and middle frontal gyrus. In the same group, increased positive PANSS sub-score was also associated with increased FC between dorsal striatum seeds and regions including precuneus, posterior cingulate and medial prefrontal cortex. In non-refractory schizophrenia, positive PANSS sub-score was positively associated with FC between VS and anterior cerebellum (Figure 3; Table 3). No other relationships between positive PANSS score and functional connectivity were significant. (Details of the relationships between antipsychotic medication dosage and striatal FC are presented in Supplementary Materials and Methods.)

3.3 Relationships between FC and antipsychotic dosage

In treatment-resistant schizophrenia CPZ dosage significantly positively predicted FC of the striatum with several cortical regions, including lingual gyrus (Table 4). Significant inverse relationships between medication and striatal FC were limited to the findings relating to the VS seed, whereby medication inversely predicted connectivity with regions including posterior cingulate gyrus, lingual gyrus, cerebellum, and prefrontal cortex (Table 4).

By contrast, for non-refractory individuals with schizophrenia, no significant positive associations between CPZ dosage and FC were observed for any of the striatal regions investigated. However, CPZ dosage inversely predicted FC with prefrontal cortex for the DC, dcP and vrP seeds (Table 4).

4. Discussion

Alleviating the persistent symptoms of treatment-resistant schizophrenia is contingent on understanding their neurophysiologic provenance. There is evidence that treatment-resistant individuals differ from responsive patients in terms of striatal dopamine synthesis capacity and prefrontal glutamate availability (Demjaha et al, 2014; Demjaha et al, 2012). In view of these findings, this study investigated functional connectivity with a focus on these brain structures in individuals with schizophrenia stratified by treatment resistance and healthy control subjects. It identifies potential idiosyncrasies of treatment-resistant schizophrenia on two principal fronts. First, patients with schizophrenia with treatment resistance exhibited reduced connectivity between VS and SN; reduced connectivity between the dcP and thalamus; and elevated connectivity between DC and medial PFC (Figure 2; Table 2). We thereby identify diminished cross-talk between VS and SN as a potential mechanism for treatment resistance. In light of the relative abundance of connections from VS to SN (Haber et al, 2010), it is likely that this finding represents a diminution of the influence of VS on other brain structures in treatment-resistant schizophrenia.

The current data also emphasises specific corticostriatal pathways along which information flow within cortico-basal ganglia reward systems differs between these patient groups. Specifically, coupling between DC and superior and medial prefrontal cortex is reduced in non-refractory compared with treatment-resistant patients (Figure 2; Table 2). These notable differences at multiple sites along the putative ventral-dorsal transfer axis suggest that there may be differential dysfunction, impacting the feedback systems that process and integrate reward-related information with cognition and action. Second, as compared with healthy control subjects, the schizophrenia groups displayed varying differences in striatal FC, which were for the most part demonstrative of reduced cortico-striatal and striato-striatal connectivity in patients. Treatment-resistant individuals exhibited reduced connectivity of the VS with orbito-frontal cortex, between DC and sensorimotor regions, and between vrP and a striatal cluster encompassing caudate head and putamen. By contrast, significant differences in striatal FC in non-refractory patients were limited to the DC, whose connectivity with regions including rostro-lateral PFC, occipital cortex and cerebellum was attenuated (Figure 2). These findings imply that corticostriatal dysconnectivity is more anatomically distributed in treatment-resistant individuals, which could in part explain the reduced efficacy of medication in these individuals. However, neuroimaging data in treatment-resistant schizophrenia reported to date, which have failed to uncover robust correlates of poor response to medication (Nakajima *et al*, 2015), do not support this interpretation.

This work upholds and adds to recent observations from FEP and ARMS cohorts of hypoconnectivity (as compared with controls) of dorsal corticostriatal circuits (Dandash *et al*, 2014; Fornito *et al*, 2013). In our study however, reduced functional connectivity (compared with controls) between DC and PFC was specific to non-refractory patients. Furthermore, treatment-resistant individuals displayed elevated connectivity between DC and medial PFC when compared with non-refractory patients, suggesting that fronto-striatal hypoconnectivity is a less useful disease marker for treatment-resistant individuals; providing a further point of neurophysiologic distinction between patients stratified by response.

Contrary to previous investigations, we found little evidence for ventral corticostriatal hyperconnectivity in schizophrenia. However, while ventral-circuit hyperconnectivity provides an elegant candidate mechanism for cognitive features of psychotic illness relating to aberrant salience attribution (Kapur *et al*, 2005), its empirical support is presently equivocal. In fact, there are numerous reports of reduced functional connectivity of ventral-circuit PFC regions in schizophrenia (Backasch *et al*, 2014; Diaconescu *et al*, 2011; He *et al*, 2013; Lynall *et al*, 2010; Tomasi and Volkow, 2014). While these discrepant findings may be attributable to factors including clinical heterogeneity, a more complete understanding of schizophrenia-related abnormalities in these networks can be assisted by examining reported effects in the context of a more comprehensive characterisation of the individuals involved (Insel, 2014), and with reference to specific abnormalities in task-related behaviour.

One of the fundamental cornerstones of clinical practice is to increase the dosage of medication following insufficient clinical improvement in patient symptoms. This can be observed clearly in our sample, where the prescribed medication dose in the treatment-resistant group exceeds that of the non-refractory group (Table 1). However, it does pose a confound for the investigation of treatment-resistant schizophrenia. Covarying out effects of medication dosage across groups is not a valid solution - this would not equate to measuring FC in groups matched for medication dosage - as has been elegantly argued elsewhere (Suckling, 2011). As such, the extent to which the reported between-group differences are purely pathophysiological or the result of pharmacological confounds cannot be definitively detailed, and this limits the current findings. Nevertheless, the analyses of the relationships between CPZ and striatal FC imply that the between-group differences were not solely attributable to differences in current medication level. While medication effects in non-refractory schizophrenia were limited to inverse associations with prefrontal cortex, distributed drug effects were found in the treatment-resistant group, with the most robust associations between dosage and striato-occipital connections. It is possible that the relative scarcity of drug effects in the non-refractory group reflects reduced medication dosage in this group. For the most part the observed regional drug effects did not exhibit spatial correspondence with the regions whose FC was found to differ between the patient groups or between the healthy and patient groups. However, it is noteworthy that medication was inversely related with connectivity between DC and postcentral gyrus in treatment-resistant individuals and that connectivity between DC and an anatomically proximal region of postcentral gyrus was reduced in treatment-resistant individuals

as compared with controls, suggesting that this may be a pharmacologically-driven between-group effect rather than a direct effect of the disorder.

Further support for the notion that the current effects are not purely medication derived is provided by the regional disparity between the current between patient group FC effects, and recent observations in responsive patients following medication (Sarpal *et al*, 2015). However, an incomplete understanding of the consequences of long-term antipsychotic treatment and inter-individual variation in related phenomena limits this work. Similarly, the possibility that medication with clozapine influenced connectivity in the treatment-resistant group cannot be wholly discounted. Investigating the direct effects of current clozapine treatment on striatal connectivity, and connectome differences specific to individuals with persistent positive symptoms despite clozapine treatment (termed 'ultra-resistant psychosis') are hugely pertinent areas for future work. Unfortunately, the size of the current subsamples precluded their adequate investigation with this dataset (Supplementary Information). However, one benefit of having a majority (n=11) of clozapine treated patients in the treatment-resistant group is that their treatment is accompanied by monitoring of serum blood levels to ensure that minimum therapeutic levels are achieved during dose titration. This provides a metric for antipsychotic dosage compliance, which can otherwise be a concern in these patients.

Previous inverse associations between positive PANSS sub-scores and striatal functional connectivity (Fornito *et al*, 2013) were not replicated. In the non-refractory patient group no significant negative relationships were found. The treatment-resistant individuals did, however, exhibit significant negative relationship between positive symptom severity and connectivity between the VS seed and the cingulate and middle frontal gyrus. In this latter group, those individuals with more severe positive symptoms also displayed enhanced connectivity between dcP and expansive regions including precuneus, cingulate gyrus and superior parietal lobule, and between DC and cuneus, medial frontal and middle temporal gyrus. It would be speculative to suggest on the basis of these relationships that the mechanistic foundations of positive symptoms differ between these patient groups; the observed relationships may, however, represent mechanisms responsible for prolonging these disease features. Particularly noteworthy are the observations of enhanced connectivity between posterior cingulate gyrus, precuneus and inferior parietal lobule - core regions of the default mode network - and dcP in the treatment-resistant group, which intimate aberrant interconnections between processes of salience attribution and internal monitoring (Fox *et al*, 2005; Kapur *et al*, 2005; Raichle *et al*, 2001).

While it is advantageous to detect discrepant brain-system features stratified on the basis of past treatment response - since this can potentially improve our understanding of the neural basis of treatment resistance – predicting which individuals are unlikely to respond prior to chronic ineffective medication is of greater import. Long-term medication has been suggested to produce D_2 receptor up-regulation and associated supersensitivity to dopamine (Ginovart et al, 2009; Samaha et al, 2007), in

turn reducing the effective potential of subsequent treatments. Furthermore, ineffective treatment adds to the functional and social incapacitation of long-term illness. As such, tracking the occurrence and timing of differences of cerebral structure and function, such as those currently identified, from the early stages of illness may help identify individuals unlikely to respond to treatment. Future longitudinal work geared towards establishing whether the detected features are a primary component of a treatment-resistant illness sub-type, or a secondary feature of long-term illness or ineffective pharmacologic treatment, is warranted. The current study provides evidence of physiologic substrates related to treatment resistance in schizophrenia; however, while it is likely that both genetic (Frank *et al*, 2015) and environmental (Hassan and De Luca, 2015) factors underlie treatment resistance and its associated mechanisms, the causative factors remain inadequately explained. Characterising the treatment-resistance phenotype in terms of clinical and cognitive features has the potential to improve our understanding of the key aetiological determinants (Gonzalez-Rodriguez *et al*, 2014).

By finding that striatal functional connectivity selectively differs between treatment-resistant and non-refractory patients, and that these differences cannot be directly attributable to symptomatic severity at time of study, this work advocates the notion that contrasting medication response reflects divergent pathophysiologic mechanisms in these individuals. More specifically, variations in corticostriatal association are seen in relation to treatment response in line with recent related findings (Sarpal *et al*, 2015); and striato-nigral dysconnection is identified as a distinct feature of treatment-resistant illness. There is increasing interest in examining glutamatergic treatment options in schizophrenia (Papanastasiou *et al*, 2013) and elevated glutamate function has been observed in association with treatment resistance (Demjaha *et al*, 2014). Given recent accounts that the N-methyl-d-aspartate receptor antagonist, ketamine - which disinhibits glutamatergic stimulation of non-NMDA receptors (Moghaddam *et al*, 1997) - modulates functional connectivity of ventral striatum (Dandash *et al*, 2014), striato-nigral disconnection is a viable mechanism for targeted treatment of refractory schizophrenia. This work marks a potentially important bridge towards dealing with this chronically incapacitating aspect of the illness.

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References

Alexander GE, DeLong MR, Strick PL (1986). Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annual review of neuroscience* **9**: 357-381.

Backasch B, Sommer J, Klohn-Saghatolislam F, Muller MJ, Kircher TT, Leube DT (2014). Dysconnectivity of the inferior frontal gyrus: implications for an impaired self-other distinction in patients with schizophrenia. *Psychiatry research* **223**(3): 202-209.

Botvinick MM, Huffstetler S, McGuire JT (2009). Effort discounting in human nucleus accumbens. *Cognitive, affective & behavioral neuroscience* **9**(1): 16-27.

Braver TS, Barch DM, Cohen JD (1999a). Cognition and control in schizophrenia: a computational model of dopamine and prefrontal function. *Biological psychiatry* **46**(3): 312-328.

Braver TS, Cohen JD (1999b). Dopamine, cognitive control, and schizophrenia: the gating model. *Progress in brain research* **121**: 327-349.

Conley RR, Kelly DL (2001). Management of treatment resistance in schizophrenia. *Biol Psychiatry* **50**(11): 898-911.

Creese I, Burt DR, Snyder SH (1976). Dopamine receptor binding predicts clinical and pharmacological potencies of antischizophrenic drugs. *Science* **192**(4238): 481-483.

Croxson PL, Walton ME, O'Reilly JX, Behrens TE, Rushworth MF (2009). Effort-based cost-benefit valuation and the human brain. *The Journal of neuroscience : the official journal of the Society for Neuroscience* **29**(14): 4531-4541.

D'Ardenne K, Eshel N, Luka J, Lenartowicz A, Nystrom LE, Cohen JD (2012). Role of prefrontal cortex and the midbrain dopamine system in working memory updating. *Proceedings of the National Academy of Sciences of the United States of America* **109**(49): 19900-19909.

Dandash O, Fornito A, Lee J, Keefe RS, Chee MW, Adcock RA*, et al* (2014). Altered striatal functional connectivity in subjects with an at-risk mental state for psychosis. *Schizophrenia bulletin* **40**(4): 904-913.

Demjaha A, Egerton A, Murray RM, Kapur S, Howes OD, Stone JM*, et al* (2014). Antipsychotic treatment resistance in schizophrenia associated with elevated glutamate levels but normal dopamine function. *Biological psychiatry* **75**(5): e11-13.

Demjaha A, Murray RM, McGuire PK, Kapur S, Howes OD (2012). Dopamine synthesis capacity in patients with treatment-resistant schizophrenia. *The American journal of psychiatry* **169**(11): 1203-1210.

Di Martino A, Scheres A, Margulies DS, Kelly AM, Uddin LQ, Shehzad Z, *et al* (2008). Functional connectivity of human striatum: a resting state FMRI study. *Cerebral cortex* **18**(12): 2735-2747.

Diaconescu AO, Jensen J, Wang H, Willeit M, Menon M, Kapur S, *et al* (2011). Aberrant Effective Connectivity in Schizophrenia Patients during Appetitive Conditioning. *Frontiers in human neuroscience* **4**: 239.

Dratcu L, Grandison A, McKay G, Bamidele A, Vasudevan V (2007). Clozapine-resistant psychosis, smoking, and caffeine: managing the neglected effects of substances that our patients consume every day. *American journal of therapeutics* **14**(3): 314-318.

Fornito A, Harrison BJ, Goodby E, Dean A, Ooi C, Nathan PJ, *et al* (2013). Functional dysconnectivity of corticostriatal circuitry as a risk phenotype for psychosis. *JAMA psychiatry* **70**(11): 1143-1151.

Fox MD, Snyder AZ, Vincent JL, Corbetta M, Van Essen DC, Raichle ME (2005). The human brain is intrinsically organized into dynamic, anticorrelated functional networks. *Proceedings of the National Academy of Sciences of the United States of America* **102**(27): 9673-9678.

Frank J, Lang M, Witt SH, Strohmaier J, Rujescu D, Cichon S, *et al* (2015). Identification of increased genetic risk scores for schizophrenia in treatment-resistant patients. *Molecular psychiatry* **20**(7): 913.

Fusar-Poli P, Meyer-Lindenberg A (2013). Striatal presynaptic dopamine in schizophrenia, part II: meta-analysis of [(18)F/(11)C]-DOPA PET studies. *Schizophrenia bulletin* **39**(1): 33-42.

Ginovart N, Wilson AA, Hussey D, Houle S, Kapur S (2009). D2-receptor upregulation is dependent upon temporal course of D2-occupancy: a longitudinal [11C]-raclopride PET study in cats. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology* **34**(3): 662-671.

Gonzalez-Rodriguez A, Molina-Andreu O, Imaz Gurrutxaga ML, Catalan Campos R, Arroyo MB (2014). A descriptive retrospective study of the treatment and outpatient service use in a clinical group of delusional disorder patients. *Revista de psiquiatria y salud mental* **7**(2): 64-71.

Haber SN, Knutson B (2010). The reward circuit: linking primate anatomy and human imaging. *Neuropsychopharmacology* **35**(1): 4-26.

Hassan AN, De Luca V (2015). The effect of lifetime adversities on resistance to antipsychotic treatment in schizophrenia patients. *Schizophrenia research* **161**(2-3): 496-500.

He Z, Deng W, Li M, Chen Z, Jiang L, Wang Q, *et al* (2013). Aberrant intrinsic brain activity and cognitive deficit in first-episode treatment-naive patients with schizophrenia. *Psychological medicine* **43**(4): 769-780.

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Heinz A, Schlagenhauf F (2010). Dopaminergic dysfunction in schizophrenia: salience attribution revisited. *Schizophr Bull* **36**(3): 472-485.

Howes OD, Montgomery AJ, Asselin MC, Murray RM, Valli I, Tabraham P*, et al* (2009). Elevated striatal dopamine function linked to prodromal signs of schizophrenia. *Archives of general psychiatry* **66**(1): 13-20.

Insel TR (2014). The NIMH Research Domain Criteria (RDoC) Project: precision medicine for psychiatry. *The American journal of psychiatry* **171**(4): 395-397.

Kapur S, Mizrahi R, Li M (2005). From dopamine to salience to psychosis--linking biology, pharmacology and phenomenology of psychosis. *Schizophrenia research* **79**(1): 59-68.

Kay SR, Fiszbein A, Opler LA (1987). The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophrenia bulletin* **13**(2): 261-276.

Kegeles LS, Abi-Dargham A, Frankle WG, Gil R, Cooper TB, Slifstein M*, et al* (2010). Increased synaptic dopamine function in associative regions of the striatum in schizophrenia. *Archives of general psychiatry* **67**(3): 231-239.

Knutson B, Cooper JC (2005). Functional magnetic resonance imaging of reward prediction. *Current opinion in neurology* **18**(4): 411-417.

Kolakowska T, Williams AO, Jambor K, Ardern M (1985). Schizophrenia with good and poor outcome. III: Neurological 'soft' signs, cognitive impairment and their clinical significance. *The British journal of psychiatry : the journal of mental science* **146**: 348-357.

Leh SE, Ptito A, Chakravarty MM, Strafella AP (2007). Fronto-striatal connections in the human brain: a probabilistic diffusion tractography study. *Neuroscience letters* **419**(2): 113-118.

Lehericy S, Ducros M, Van de Moortele PF, Francois C, Thivard L, Poupon C*, et al* (2004). Diffusion tensor fiber tracking shows distinct corticostriatal circuits in humans. *Annals of neurology* **55**(4): 522-529.

Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO*, et al* (2005). Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *The New England journal of medicine* **353**(12): 1209-1223.

Lynall ME, Bassett DS, Kerwin R, McKenna PJ, Kitzbichler M, Muller U*, et al* (2010). Functional connectivity and brain networks in schizophrenia. *The Journal of neuroscience : the official journal of the Society for Neuroscience* **30**(28): 9477-9487.

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Mechelli A, Riecher-Rossler A, Meisenzahl EM, Tognin S, Wood SJ, *et al* (2011). Neuroanatomical abnormalities that predate the onset of psychosis: a multicenter study. *Arch Gen Psychiatry* **68**(5): 489-495.

Moghaddam B, Adams B, Verma A, Daly D (1997). Activation of glutamatergic neurotransmission by ketamine: a novel step in the pathway from NMDA receptor blockade to dopaminergic and cognitive disruptions associated with the prefrontal cortex. *J Neurosci* **17**(8): 2921-2927.

Nakajima S, Takeuchi H, Plitman E, Fervaha G, Gerretsen P, Caravaggio F, *et al* (2015). Neuroimaging findings in treatment-resistant schizophrenia: A systematic review: Lack of neuroimaging correlates of treatment-resistant schizophrenia. *Schizophrenia research* **164**(1-3): 164-175.

O'Doherty J, Dayan P, Schultz J, Deichmann R, Friston K, Dolan RJ (2004). Dissociable roles of ventral and dorsal striatum in instrumental conditioning. *Science* **304**(5669): 452-454.

Papanastasiou E, Stone JM, Shergill S (2013). When the drugs don't work: the potential of glutamatergic antipsychotics in schizophrenia. *The British journal of psychiatry : the journal of mental science* **202**: 91-93.

Quide Y, Morris RW, Shepherd AM, Rowland JE, Green MJ (2013). Task-related fronto-striatal functional connectivity during working memory performance in schizophrenia. *Schizophrenia research* **150**(2-3): 468-475.

Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL (2001). A default mode of brain function. *Proceedings of the National Academy of Sciences of the United States of America* **98**(2): 676-682.

Rose D, Pevalin DJ (2001). *The national statistics socio-economic classification: unifying official and sociological approaches.*

Samaha AN, Seeman P, Stewart J, Rajabi H, Kapur S (2007). "Breakthrough" dopamine supersensitivity during ongoing antipsychotic treatment leads to treatment failure over time. *The Journal of neuroscience : the official journal of the Society for Neuroscience* **27**(11): 2979-2986.

Sarpal DK, Robinson DG, Lencz T, Argyelan M, Ikuta T, Karlsgodt K, *et al* (2015). Antipsychotic treatment and functional connectivity of the striatum in first-episode schizophrenia. *JAMA psychiatry* **72**(1): 5-13.

Seeman P, Lee T (1975). Antipsychotic drugs: direct correlation between clinical potency and presynaptic action on dopamine neurons. *Science* **188**(4194): 1217-1219.

Suckling J (2011). Correlated covariates in ANCOVA cannot adjust for pre-existing differences between groups. *Schizophrenia research* **126**(1-3): 310-311.

Tomasi D, Volkow ND (2014). Mapping small-world properties through development in the human brain: disruption in schizophrenia. *PloS one* **9**(4): e96176.

Van Dijk KR, Sabuncu MR, Buckner RL (2012). The influence of head motion on intrinsic functional connectivity MRI. *Neuroimage* **59**(1): 431-438.

White TP, Gilleen J, Shergill SS (2013). Dysregulated but not decreased salience network activity in schizophrenia. *Frontiers in human neuroscience* **7**: 65.

Whitfield-Gabrieli S, Nieto-Castanon A (2012). Conn: a functional connectivity toolbox for correlated and anticorrelated brain networks. *Brain connectivity* **2**(3): 125-141.

Wolkin A, Brodie JD, Barouche F, Rotrosen J, Wolf AP, Smith M*, et al* (1989). Dopamine receptor occupancy and plasma haloperidol levels. *Archives of general psychiatry* **46**(5): 482-484.

Table 1. Sample demographic and clinical characteristics. Bracketed values denote standard deviations.

Variable	Treatment-resistant schizophrenia (n=16)	Non-refractory schizophrenia (n=22)	Healthy (n=20)	Between-group comparisons
Age (years)	36.69 (7.86)	37.55 (9.60)	36.30 (9.38)	P >.5 for all comparisons
Sex (male/female)	12/4	19/3	17/3	P >.5 for all comparisons
Parental socio-economic status (NS-SEC)	2.69 (1.49)	2.64 (1.65)	2.35 (1.59)	P >.5 for all comparisons
Intelligence quotient (WASI)	96.81 (17.82)	99.09 (12.57)	111.67 (17.40)	TR vs. NR: T(36)=0.46, P=.646 TR vs. HC: T(34)=2.46, P=.020 NR vs. HC: T(40)=2.65, P=.012
Positive PANSS Negative PANSS General PANSS	17.88 (5.90) 17.50 (7.00) 34.88 (11.00)	15.32 (3.87) 18.45 (5.68) 29.91 (6.66)		TR vs. NR: T(36)=1.61, P=.115 TR vs. NR: T(36)=0.46, P=.646 TR vs. NR: T(36)=0.73, P=.092
Age at onset of illness (years)	21.34 (4.40)	25.57 (5.88)		TR vs. NR: T(36)=2.41, P=.022
Duration of illness (years)	15.47 (6.41)	11.86 (10.35)		TR vs. NR: T(33.79)=1.30, P=.201
Current antipsychotic medication	Clozapine (n=11), Aripiprazole (n=2), Olanzapine (n=2), Amisulpride (n=1), Haloperidol (n=1), Palliperidone (n=1), Quetiapine (n=1), Zuclopenthixol (n=1)	Olanzapine (n=9), Aripiprazole (n=3), Risperidone (n=3), Amisulpride (n=1), Fluphenazine decoate (n=1), Haloperidol (n=1), Pipotiazine (n=1), Quetiapine (n=1), Venlafaxine (n=1), Zuclopenthixol (n=1)		
Antipsychotic medication dosage (mg/day; CPZ)	764.06 (339.15)	281.68 (299.14)		TR vs. NR: T(36)=4.64, $P=5x10^{-4}$
Antidepressant medication	Citalopram (n=1)	Citalopram (n=1) Fluoxetine (n=1)		

TR, treatment-resistant schizophrenia; NR, non-refractory schizophrenia; HC, healthy controls; NS-SEC, National Statistics Socio-Economic Classification (Rose and Pevalin, 2001); WASI, Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999); PANSS, Positive and Negative Syndrome Scale for schizophrenia (Kay et al., 1987); CPZ, chlorpromazine equivalent

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Table 2. Significant grey matter foci of between-group differences in striatal resting-state functional connectivity

Contrast	Seed	Brain structure (Brodmann Area)	Coordinates			T-value	k_E
			x	y	z		
TR < HC	VS	Middle frontal gyrus (47)	32	40	-6	3.26	156
	DC	Postcentral gyrus (2)	50	-30	44	3.83	363
		Precentral gyrus (4)	58	-10	50	3.35	363
	dcP	None					
	vrP	Caudate head	-14	20	0	3.72	151
		Lentiform nucleus, putamen	-20	8	-2	3.70	151
TR > HC	VS	None					
	DC	None					
	dcP	None					
	vrP	None					
Non-TR < HC	VS	None					
	DC	Cuneus (19)	-2	-92	26	4.32	526
		Cuneus (18)	4	-80	26	4.22	526
		Lingual gyrus (18)	-12	-74	-8	3.33	157
		Fusiform gyrus (19)	-26	-70	-16	4.13	191
		Superior frontal gyrus (10)	-16	66	18	4.08	211
		Middle frontal gyrus (10)	-30	64	10	3.60	232
		Cerebellum, posterior lobe	-28	-64	-20	4.18	191
	dcP	None					
	vrP	None					
Non-TR > HC	VS	None					
	DC	None					
	dcP	None					
	vrP	None					
TR < non-TR	VS	Mammillary body	-2	-8	-12	4.81	270
		Substantia nigra	-14	-22	-6	3.94	270
	DC	None					
	dcP	Thalamus, pulvinar	24	-32	8	3.48	231
	vrP	None					
TR > non-TR	VS	None					
	DC	Superior frontal gyrus (8)	24	34	50	5.12	218
		Superior frontal gyrus (9)	-4	58	36	3.85	177
		Superior frontal gyrus (8)	-6	38	56	4.31	157
		Superior frontal gyrus (8)	-2	36	50	3.75	157
		Medial frontal gyrus (10)	-10	66	14	3.41	177
	dcP	None					
	vrP	None					

TR, treatment-resistant schizophrenia; HC, healthy controls; VS, ventral striatum; DC, dorsal caudate; dcP, dorso-caudal putamen; vrP, ventro-rostral putamen

Table 3. Relationships between positive PANSS sub-score and striatal resting-state functional connectivity in treatment-resistant and non-resistant schizophrenia

Group	Seed	Direction	Brain structure (Brodmann Area)	Coordinates			T-value	k_E
				x	y	z		
TR	VS	Positive	None					
		Inverse	Cingulate cortex (31)	-10	-48	42	3.52	172
			Precuneus (7)	-8	-58	48	3.51	172
			Middle frontal gyrus (9)	34	26	38	4.59	162
	DC	Positive	Cuneus (18)	18	-100	2	11.02	240
			Cuneus (17)	18	-96	0	9.84	240
			Medial frontal gyrus (6)	8	-30	64	7.18	262
			Medial frontal gyrus (6)	-2	-24	56	5.09	262
			Middle temporal gyrus (39)	-46	-70	8	5.25	285
	dcP	Positive	Precuneus (7)	6	-68	48	14.10	328
			Precuneus (7)	-8	-62	46	7.94	328
			Cingulate cortex (31)	4	-44	38	7.77	1306
			Inferior parietal lobule (40)	38	-48	40	4.52	1306
			Superior parietal lobule (7)	-22	-70	46	4.62	178
			Precuneus (7)	40	-74	38	5.97	260
			Superior parietal lobule (7)	38	-72	44	5.13	260
		Inverse	None					
	vrP	Positive	None					
		Inverse	None					
non-TR	VS	Positive	Cerebellum, anterior lobe	14	-28	20	5.10	156
		Inverse	None					
	DC	Positive	None					
		Inverse	None					
	dcP	Positive	None					
		Inverse	None					
	vrP	Positive	None					
		Inverse	None					

TR, treatment-resistant schizophrenia; non-TR, non-refractory schizophrenia; VS, ventral striatum; DC, dorsal caudate; dcP, dorso-caudal putamen; vrP, ventro-rostral putamen

Table 4. Regions in which striatal resting-state functional connectivity was significantly related to antipsychotic dosage.

A)Treatment-resistant schizophrenia (n=16)							
Contrast	Seed	Brain structure (Brodmann Area)	Coordinates			T-value	k_E
			x	y	z		
Positive relationship	VS	None					
	DC	Lingual gyrus (18)	-32	-76	-16	7.71	382
		Lingual gyrus (18)	-22	-80	-16	6.54	382
		Lingual gyrus (18)	-20	-76	-12	5.79	382
		Cerebellum, declive	24	-56	-16	6.21	457
		Fusiform gyrus (19)	30	-68	-16	5.73	457
		Occipital lobe (19)	16	-58	-8	4.69	457
	dcP	Lingual gyrus (18)	-12	-74	-10	8.38	302
		Lingual gyrus (19)	-16	-64	-10	5.65	302
		Lingual gyrus (18)	-2	-86	-4	4.64	302
		Lingual gyrus (18)	-6	-82	-8	4.53	302
		Cuneus (18)	4	-88	14	5.56	222
		Lingual gyrus (18)	6	-78	-6	5.29	222
	vrP	Medial frontal gyrus (8)	-8	28	44	5.97	277
Inverse relationship	VS	Posterior cingulate gyrus (30)	-6	-68	8	5.31	490
		Lingual gyrus (19)	-22	-64	-2	4.59	490
		Middle frontal gyrus (9)	40	34	42	6.11	375
		Middle frontal gyrus (8)	26	26	46	5.52	375
		Middle frontal gyrus (9)	32	24	38	5.30	375
		Lingual gyrus (18)	26	-76	-8	7.75	376
		Cerebellum, declive	16	-68	-20	5.07	376
		Cerebellum, culmen	12	-50	-20	5.03	376
		Lingual gyrus (19)	10	-58	2	5.53	154
		Medial frontal gyrus (8)	14	24	46	4.87	157
	DC	Postcentral gyrus (2)	-36	-32	40	5.85	182
	dcP	None					
	vrP	None					

B) Non-refractory schizophrenia (n=22)							
Contrast	Seed	Brain structure (Brodmann Area)	Coordinates			T-value	k_E
			x	y	z		
Positive relationship	VS	None					
	DC	None					
	dcP	None					
	vrP	Medial frontal gyrus (6)	6	-2	62	5.81	172
		Paracentral lobule (5)	16	-40	52	4.12	214
		Precentral gyrus (4)	28	-32	52	3.95	214
Inverse relationship	VS	None					
	DC	Medial frontal gyrus (8)	-18	32	30	3.76	732
		Anterior cingulate gyrus (24)	-2	4	40	5.04	732
	dcP	Medial frontal gyrus (6)	4	-12	66	5.04	271
		Medial frontal gyrus (6)	6	-16	54	3.87	271
		Paracentral lobule (5)	10	-40	54	3.73	271
	vrP	None					

VS, ventral striatum; DC, dorsal caudate; dcP, dorso-caudal putamen; vrP, ventro-rostral putamen

Figure legends

Figure 1. Specific disease-related reductions in striatal connectivity, showing: reductions in resting functional connectivity (FC) between the dorsal caudate (DC) seed and prefrontal cortex (top row); reductions in FC between the ventral striatum (VS) and middle frontal gyrus (second row); reductions in FC between DC and sensorimotor cortex (third row); and reductions in FC between ventro-rostral putamen (vrP) and proximal stuctures of the striatum (bottom row). All results are thresholded at a family-wise error corrected cluster threshold of .0125 (to correct for the investigation of four seeds) and overlaid on a standardised T1-weighted template image.

Figure 2. Significant differences in striatal connectivity between treatment-resistant and non-refractory individuals with schizophrenia, controlling for effects of current psychiatric symptom severity and movement. Left column shows the seeds for which the subsequent results within each row apply. Blue scale denotes regions significantly less connected in non-refractory patients as compared with the treatment-resistant individuals; and yellow scale denotes regions significantly more connected with seed in non-refractory individuals. All results are thresholded at a family-wise error corrected cluster threshold of .0125 (to correct for the investigation of four seeds) and overlaid on a standardised T1-weighted template image. VS, ventral striatum; DC, dorsal caudate; dcP, dorso-caudal putamen; vrP, ventro-rostral putamen.

Figure 3. Significant associations between current positive symptom severity and striatal connectivity in treatment-resistant schizophrenia. Left column shows the seeds for which the subsequent results within each row apply. Blue scale denotes regions whose connectivity with the seed was significantly inversely related to symptoms severity; and yellow scale denotes whose connectivity with the seed was significantly positively related to symptoms severity. All results are thresholded at a family-wise error corrected cluster threshold of .0125 (to correct for the investigation of four seeds) and overlaid on a standardised T1-weighted template image. VS, ventral striatum; DC, dorsal caudate; dcP, dorso-caudal putamen.