ORIGINAL INVESTIGATION

A naturalistic study of grey matter volume increase after early treatment in anti-psychotic naïve, newly diagnosed schizophrenia

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Abstract

Background Anti-psychotic treatment appears to be associated with striatal volume increase, but how early this change occurs is still unknown.

Methods A single prospective cohort of 20 anti-psychotic-naïve patients, newly diagnosed with schizophrenia, underwent magnetic resonance imaging brain scan at baseline. This was repeated following up to 8 weeks of anti-psychotic treatment. Ten patients had repeat scan within only 3 weeks. The choice of anti-psychotic medication was naturalistic, i.e., clinician-led. Well-matched healthy individuals were also scanned to control for non-specific changes over a 3-week period.

Results After 3 weeks of anti-psychotic treatment, significant grey matter volume increase in the right caudate, superior and inferior frontal gyrus, precentral gyrus, and left inferior parietal lobule was noted. However, after 8 weeks of anti-psychotic treatment, volume increase in the right thalamus and bilateral cerebellum was observed. Significant grey matter reduction was detected in the left medial frontal gyrus at both 3- and 8-week intervals.

Conclusions Early increase in striatal volume change occurs as early as 3 weeks after anti-psychotic treatment, whilst thalamic volume increase is apparent later, by 8 weeks of treatment. We speculate that drug-mediated neuroplasticity may provide a biomarker for clinical recovery.

Keywords Caudate · Anti-psychotics · First episode · Drug naïve · Longitudinal · Naturalistic

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Introduction

Anti-psychotic treatment is known to modulate brain morphology, and schizophrenia per se is associated with structural brain abnormalities such as cerebral ventricular enlargement and smaller brain volume especially in limbic regions (Wright et al. 2000). For example, caudate volume deficits have been reported in first-episode schizophrenia prior to anti-psychotic exposure (Chua et al. 2007; Lui et al. 2009), but after 18 months of fluphenazine or other anti-psychotic treatment, caudate volume increases (Chakos et al. 1994). Similarly, up to 12 weeks first-time exposure to either olanzapine (Okugawa et al. 2007) or risperidone (Massana et al. 2005), for the first time, the basal ganglia were also noted to enlarge. Lieberman et al. (2005b) replicated the direction of these findings in patients treated with 6 months of haloperidol, but not olanzapine, which was associated with a generalized increased in brain volume.

Since anti-psychotics demonstrate clinical efficacy within 3 weeks (Johnstone et al. 1978), we previously characterized the effect of anti-psychotic drugs on brain structure during this early phase of clinical recovery. We reported that compared to anti-psychotic naïve patients, caudate volume was larger in the patients who had 3 weeks anti-psychotics exposure (Chua et al. 2009). However, these might arguably have been due to biological variations between the two different patient groups. Therefore, we

planned to study a naturalistic longitudinal cohort of first-episode, anti-psychotic drug-naïve patients with schizophrenia to capture the brain structural response to treatment in the same individuals. We chose a naturalistic design (i.e., choice of anti-psychotic was entirely clinician-led and unrestricted by medication protocol) so that it could be representative of patients in a clinical setting. We hypothesized that (1) anti-psychotic medication would increase caudate volume in previously anti-psychotic drug-naïve patients with first-episode schizophrenia as early as 3 weeks and (2) volume increase would subsequently extend to other subcortical-limbic regions over time. If so, the basal ganglia might hold critical clues to the mechanism of pathology and recovery in schizophrenia and could potentially provide a biomarker of neuroplasticity for both onset (Chua et al. 2007) and clinical recovery in schizophrenia.

Materials and methods

Subjects

A consecutive series of patients was screened for eligibility to join the study within the first day of presenting to the Department of Psychiatry through clinic or Accident and Emergency services as previously described (Chua et al. 2007; Chua et al. 2009). Briefly, inclusion criteria were age 16–50 years, no previous history of any anti-psychotic medication; first experience of psychotic symptoms (i.e., hallucinations and/or delusions and/or thought disorder, with decline in daily functioning), according to the Diagnostic and Statistical Manual of Mental Disorders-IV (American Psychiatric Association 1994) and assessed by two independent specialists in Psychiatry; no significant mood/organic disorder; and capable of full informed written consent to participate. Exclusion criteria were any history of neurological problems; loss of consciousness; persistent headaches; head trauma; electroconvulsive therapy; any history of psychostimulant use, including cannabis; and special school attendance. Healthy controls were recruited from the local community as described previously (Chua et al. 2007) and balanced for age, gender, height, and handedness to the patient sample. The well-matched healthy controls were a newly recruited sample and did not overlap with the subjects from our previous study (Chua et al. 2007). Each participant gave written informed consent to participate according to the Declaration of Helsinki. The study received the approval of the Institutional Review Board of the hospital concerned.

We decided to use a naturalistic design for medication, so that anti-psychotic treatment was entirely the decision of the responsible clinician, in accordance with clinical need and local practice guidelines. The clinician-led choice of the range of available anti-psychotics, atypical or typical, was an important feature in facilitating subject enrollment. The first magnetic resonance imaging (MRI) scan for patients was performed according to protocol, before anti-psychotic medication commenced. Re-scan was scheduled 3 weeks after starting anti-psychotic medication for the first time. For those patients who could not return within 3 weeks, re-scan was scheduled up to 8 weeks. The positive and negative syndrome scale (PANSS; Kay et al. 1987) was used to assess patients' psychopathology on the day of the first baseline MRI scan and during follow-up (but not necessarily coincident with the second scan). All patients were followed up for at least 6 months to confirm the diagnosis of schizophrenia. The healthy controls followed the same MRI scanning protocol and were scheduled for re-scan at 3 weeks to control any spurious volume changes generated by repeated scans. Demographics of different group subjects were compared by one-way analysis of variance (ANOVA), and the symptom score changes within patients after treatment were analyzed by two-tailed paired t tests in Statistical Package for the Social Sciences 16.0.

Magnetic resonance imaging (MRI) acquisition

All subjects were scanned on a GE Sigma 1.5 Tesla system (General Electric, Milwaukee, WI, USA). The scan lasted for 20 min. A consultant radiologist, blind to diagnosis, reviewed each MRI scan for any gross anomalies. Scans aligned to the anterior commissure-posterior commissure line were acquired across the whole brain. A fast SPGR 3D sequence was used, with 124 slices, contiguous, 1.2 mm thick, Nex=1, time to repetition (TR) 11.4 s, time to echo (TE) 4.2 ms, flip angle 15°, field of view 24×24, and matrix 256×256. Dual-echo fast spin echo (PD/T2) images covering the whole brain were collected, with 3 mm thick, TR 5–6 s, TE 20/80 ms, and matrix 256×192.

Image pre-processing and analysis

Image pre-processing was performed using Statistical Parametric Mapping-2 (SPM2; Wellcome Department of Cognitive Neurology, Institute of Neurology, London, UK), running in MATLAB 6.5 (The MathWorks, Inc., Natick, MA, USA). For each individual, there were three scans per each time point: T1, T2, and PD. The follow-up scans at time point 2 were first co-registered to the baseline scans at time point 1. The images at each time point were then segmented using the expectation maximization segmentation (EMS) toolbox (http://www.medicalimagecomputing.com/downloads/ems.php).

EMS is a fully automated algorithm that uses information from multiple sequence modalities, so that bias correction can be enhanced (Van Leemput et al. 1999a, b).

Accurate bias estimation is very important in longitudinal studies (Leow et al. 2006). Grey, white, and cerebrospinal fluid tissue maps, and a bias-free T1 image were obtained after this segmentation. Following tissue classification, images were further preprocessed according to (Moorhead et al. 2007). The bias-free T1 image at follow-up was mapped to the baseline image using high-dimensional (HD) wrapping in SPM2. The parameters from this step were applied to the follow-up grey matter map to minimize the shape difference between the tissue maps of the two time points. The HD-wrapped image was modulated with the Jacobian determinants of the wrap to retain the intensity information at native space. A "difference map" for each individual, reflecting tissue density changes between the two time points, was calculated by subtracting the baseline image from the follow-up image. This difference map was then normalized to a customized template with optimized method (Good et al. 2002) and smoothed with an 8-mm full-width half-maximum kernel for statistical analysis in SPM2.

Difference maps of the 3-week group, the 8-week group, and the control group were analyzed by two-way ANOVA. Output was in the form of SPM with the Montreal Neurological Institute (MNI) coordinates, based on a height threshold $p < 0.001$ and extent threshold of 50 contiguous voxels.

Results

Demographic and clinical comparison between groups

A consecutive series of 25 anti-psychotic naïve patients newly diagnosed with schizophrenia was eligible to participate. Five patients were excluded (two declined to participate, one remitted spontaneously and declined repeat MRI scan, and two declined to have a follow-up scan). Therefore, 20 patients (80% of the eligible sample) underwent MRI scan before and after treatment, of which, ten had received 3 weeks of anti-psychotic treatment. The rest exceeded this duration because they preferred to attend

follow-up or be scanned after 3 weeks had elapsed. For the entire sample, median duration of treatment was 37 days, range of 15–92 days. The anti-psychotic treatment history of the patient group is presented in Table 1. Briefly, six patients were assigned typical anti-psychotic drugs, including Flupenthixol, Trifluoperazine, and Haloperidol. Two of them were later switched to atypical Amisulpride by their responsible clinical doctors before MRI re-scanned. The rest were all treated by atypical anti-psychotic drugs, and nine of them were under Amisulpride. None of them was treated concurrently with lithium. After early anti-psychotic treatment, PANSS score significantly decreased (from 72.7 (15.22) to 47.3 (13.01), $t = 5.769$, $p < 0.001$), as did positive PANSS (from 19.5 (6.21) to 10.4 (4.02), $t = 6.085$, $p < 0.001$) and general psychopathology PANSS (from 33.4 (8.33) to 21.6 (4.76), $t = 5.495$, $p < 0.001$). There was no significant change in negative PANSS score (from 15.2 (7.40) to 12.1 (7.62), $t = 1.556$, $p = 0.136$). The subgroup of ten patients re-scanned within only 3 weeks was comparable in demographic and clinical parameters (PANSS scores or drug dosage equivalents) from those re-scanned beyond 3 weeks. Eleven healthy controls balanced for age, height, gender, and handedness were scanned and re-scanned after 3 weeks (Table 2).

Grey matter volume analysis

Compared to the control group, patients within only 3 weeks anti-psychotic treatment showed significantly increased grey matter volume in the right caudate, superior frontal gyrus, inferior frontal gyrus, precentral gyrus, and left inferior parietal lobule. Grey matter reduction occurred in the left medial frontal gyrus, middle frontal gyrus, and right cerebellum (Fig. 1a; Table 3). In the patient group treated for more than 3 weeks, grey matter volume increase compared to controls was noted mainly in the right thalamus, extending to the left precentral gyrus, fusiform gyrus, superior parietal gyrus, right superior occipital gyrus, and bilateral cerebellum, and grey matter reduction in the left medial frontal gyrus (Fig. 1b). When compared to the

Table 1 Anti-psychotic treatment histories ($n=20$)

Medication	Patient	Dose (mg)			Length of treatment (days)	
		Mean	Range	CPZ equivs (mg)	Mean	Range
Amisulpride	9	200	100–400	100	42	16–92
Olanzapine	1	20	20	400	19	19
Risperidone	2[a]	1	1	50	25.5	16–33
Quetiapine	2[a]	125	50–200	170	56.5	53–60
Trifluoperazine	3[a]	8	5–15	160	26	4–38
Flupenthixol	2[a]	3	3	100	19	7–31
Haloperidol	1[b]	3	3	100	23	23

CPZ equivs chlorpromazine equivalent dosage (Woods 2003)

[a] One of the patients was later switched to Amisulpride by the responsible clinician

[b] The patient was later switched to Perphenazine by responsible clinician

Table 2 Demographics of subjects

Variable	Healthy controls (n=11)	Patient re-scan within 3weeks (n=10)	Patient re-scan beyond 3weeks (n=10)	ANOVA F	p value
MRI re-scan time (days; median)	21	22	55	36.844	0.000[a]
Dosage equivalents to 100 mg oral CPZ/day (mg/day; mean, SD)	n/a	160 (108)	115 (71)	1.105	0.284
Type of anti-psychotics (typical:atypical:mix)	n/a	2:7:1	2:7:1	n/a	n/a
Age (years; mean, SD)	28.0 (11.7)	29.9 (13.5)	26 (10.0)	0.338	0.716
Height (cm; mean, SD)	164.9 (9.5)	167 (12.0)	163 (7.6)	0.241	0.789
Handedness (% right-handed)	73%	94%	86%	1.419	0.262
Sex (M:F)	5:6	4:6	5:5	0.092	0.912
Baseline total PANSS score (mean, SD)	n/a	76.6 (17.9)	68.7 (11.6)	1.172	0.256

[a] Significant difference ($p < 0.001$) between groups, one-way ANOVA

3-week treatment group, the longer treated group had grey matter volume increases in the right thalami, inferior frontal gyrus, hippocampus, lingual gyrus, and bilateral cerebellum; and grey matter volume decreases in the right hemisphere, including caudate, ventral lateral nucleus thalamus, superior frontal gyrus, inferior frontal gyrus, precentral gyrus, and middle temporal gyrus (Fig. 1c).

To capture the time window for regionally specific anti-psychotic drug response, we extracted the absolute volume changes in the right caudate and thalamus in SPM. Caudate volume increase was significant in 90% of patients scanned at 3 weeks. There was no increase after around 40 days of treatment. In contrast, thalamus volume did not significantly change in the first 3 weeks but increased after 40 days
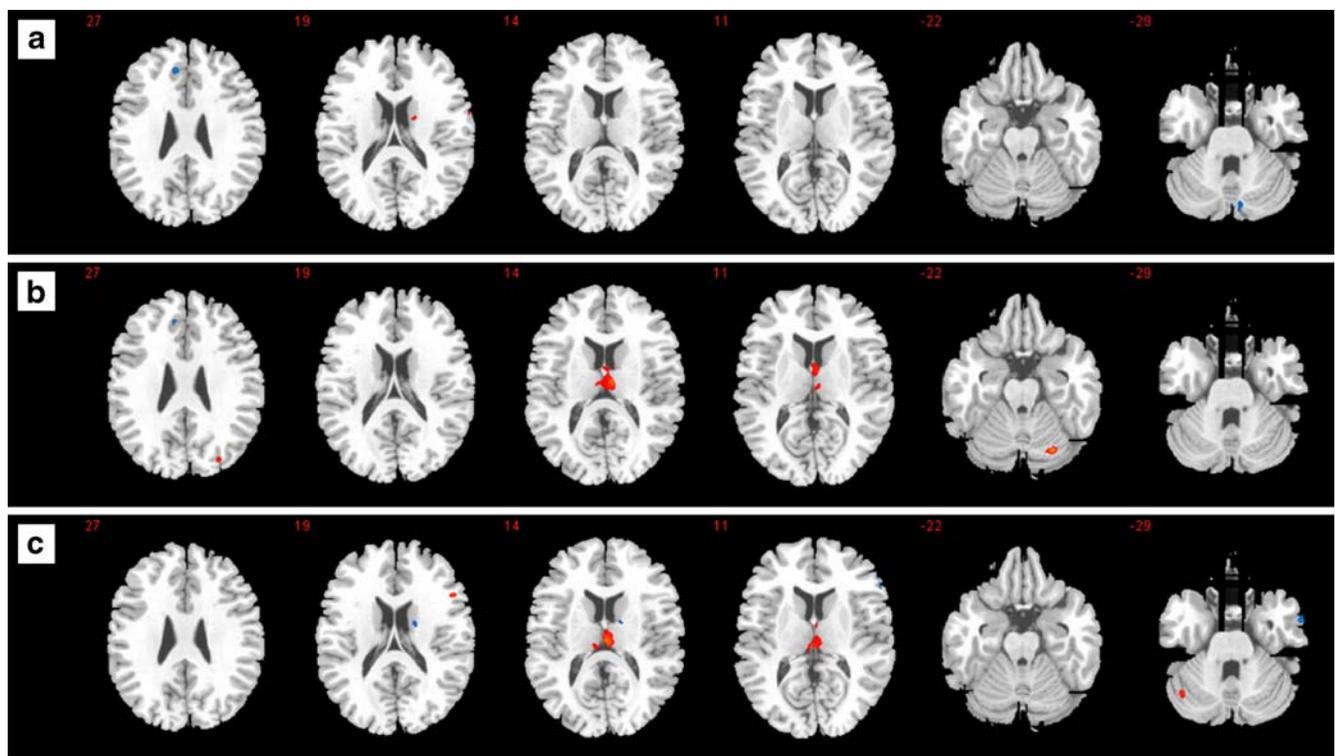
Fig. 1 Regional grey matter changes after early weeks of anti-psychotic drug treatment. The right side of the brain corresponds to the right side of the figure. The z coordinate for each axial slice in standard Talairach and Tournoux space is given in millimeters. **a** Grey matter significant increase (*red*)/decrease (*blue*) in patients within only 3 weeks anti-psychotic drug treatment (n=10) compared to controls (n=11). **b** Grey matter significant increase (*red*)/decrease (*blue*) in patients beyond 3 weeks anti-psychotic drug treatment (n=10) compared to controls (n=11). **c** Compared to the within 3 weeks treatment group (n=10), more (*red*)/less (*blue*) grey matter increase beyond 3 weeks anti-psychotic treatment (n=10)

Table 3 Regional grey matter changes after early anti-psychotic drug treatment

Between group comparison	Region	MNI coordinates (mm)			Voxels	*p* value
		X	Y	Z		
Within 3 weeks treatment compared to controls	Increase					
	Subcortical					
	R caudate	17	−2	18	54	0.000
	Frontal lobe					
	R superial frontal gyrus	11	−6	73	250	0.000
	R superial frontal gyrus	67	−21	44	86	0.000
	R inferior frontal gyrus (BA46)	51	46	2	50	0.000
	R precentral gyrus (BA6)	65	2	17	59	0.000
	R precentral gyrus (BA6)	67	−12	31	75	0.000
	Parietal lobe					
	L inferior parietal lobule (BA40)	−32	−44	44	55	0.000
	Decrease					
	Frontal lobe					
	L medial frontal gyrus (BA9)	−8	39	27	226	0.000
	L middle frontal gyrus (BA6)	−28	13	48	55	0.000
	L middle frontal gyrus (BA6)	−3	11	53	61	0.000
	Cerebellum					
	R posterior lobe	9	−78	−29	50	0.000
Beyond 3 weeks treatment compared to controls	Increase					
	Subcortical					
	R thalamus (anterior)	8	−13	14	783	0.000
	Frontal lobe					
	L precentral gyrus (BA9)	−44	5	38	65	0.000
	Temporal lobe					
	L fusiform gyrus (BA20)	−60	−20	−25	63	0.000
	Parietal lobe					
	L superior parietal lobule (BA7)	−29	−57	46	57	0.000
	Occipital lobe					
	R superior occipital gyrus (BA19)	30	−80	27	55	0.000
	Cerebellum					
	L posterior lobe	−8	−53	−31	54	0.000
	R posterior lobe	28	−72	−22	168	0.000
	R anterior lobe	12	−52	−6	165	0.000
	Decrease					
	Frontal lobe					
	L medial frontal gyrus (BA9)	−8	40	27	74	0.000
Beyond 3 weeks treatment compared to only within 3 weeks treatment	More increase					
	Subcortical					
	R thalamus (medial dorsal)	3	−19	15	686	0.000
	Frontal lobe					
	R inferior frontal gyrus (BA45)	52	21	18	99	0.000
	Temporal lobe					
	R hippocampus	27	−39	−2	50	0.000
	Occipital lobe					
	R lingual gyrus (BA18)	12	−84	−13	171	0.000
	Cerebellum					
	R anterior lobe	9	−35	−6	126	0.000
	L posterior lobe	−40	−64	−29	104	0.000

Table 3 (continued)

Between group comparison	Region	MNI coordinates (mm)			Voxels	_p_ value
		X	Y	Z		
	Less increase					
	Subcortical					
	R caudate	16	−1	17	139	0.000
	R thalamus (ventral lateral)	9	−14	4	157	0.000
	Frontal lobe					
	R precentral gyrus (BA6)	19	−20	70	76	0.000
	R inferior frontal gyrus (BA46)	56	36	9	271	0.000
	R superior frontal gyrus (BA6)	18	−2	66	62	0.000
	Temporal lobe					
	R middle temporal gyrus (BA21)	62	0	−28	99	0.000

A sample Montreal Neurological Institute coordinate (x, y, z) is given for the approximate center of each 3-D cluster, but the 3-D cluster is not confined to this area alone. The volume of grey matter within each cluster is shown for the groups in milliliter. $p < 0.001$, extent threshold of 50 contiguous voxels

treatment in 90% of the patients scanned at the later time point (Fig. 2).

Discussion

Our principal finding was that after 3–8 weeks anti-psychotic drug treatment, previously drug-naïve patients presenting with their first episode of schizophrenia had grey matter volume _increases_ in the fronto-striatal and temporo-limbic regions, extending to bilateral cerebellum. Specifically, as early as 3 weeks after anti-psychotic treatment, we noted right caudate volume increase, but thalamic and temporo-limbic- parietal volumetric increase was detected later at 3 to 8 weeks after treatment. To our knowledge, our study is the first to report time-specific regional brain morphological changes during the early weeks of anti-psychotic treatment.

Fig. 2 Grey matter volume change in different regions depending on the duration of anti-psychotic drug treatment (*n*=20). **a** Caudate (R) volume change in the whole patient group. **b** Thalamus (R) volume change in the whole patient group
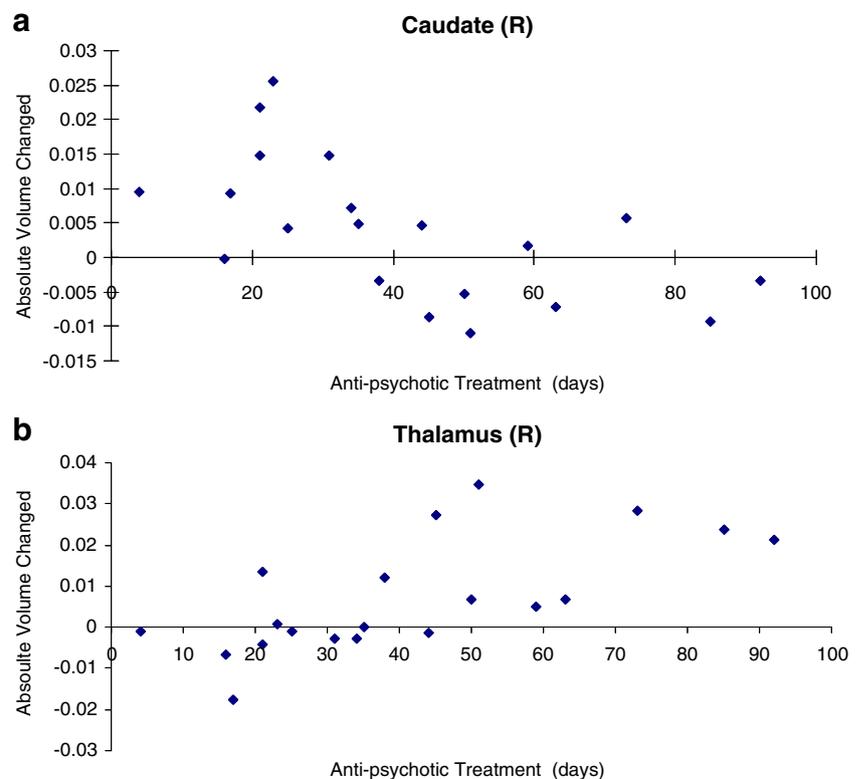
We used a naturalistic treatment design in a single prospective cohort, and the MRI follow-up rate (80%) was high, thus, we believe these findings can be generalized to the clinical setting. Most patients (nine out of 20) were prescribed Amisulpride (an atypical D3 antagonist without serotonin/noradrenaline affinity (Tyson et al. 2004)) which was not included in the Clinical Antipsychotic Trials of Intervention Effectiveness study (Lieberman et al. 2005a) but widely used in European and Asian countries. Though various different types of anti-psychotic drugs were prescribed in this study, the number of patients exposed to typical and atypical treatments was the same in two patient groups (Table 2), thereby minimizing the effect of different drug types. The confounding effects of previous exposure to medication and illness chronicity on neural response to anti-psychotic were also avoided in this sample. Previous studies of caudate volume changes after treatment have been equivocal: some found no difference (Choi et al. 2005); others found a significant difference (Chua et al. 2009; Corson et al. 1999b; Shihabuddin et al. 1998) following drug treatment. Choi et al. (2005) examined a mix of drug-naïve and previously treated patients, while Corson et al. (1999a) only included drug-naïve patients. Shihabuddin et al. (1998) found that caudate volumes were significantly smaller in drug-naïve patients compared to healthy controls but were largest in previously medicated drug-free patients. Thus, in this sample of completely anti-psychotic-naïve first-episode schizophrenia patients, we have shown that brain morphology can be modulated by treatment after just 3 weeks. We also showed that, while increase in caudate volume occurred in the first 3 weeks of anti-psychotic drug treatment, a subsequent *increase* in thalamic volume could be detected at up to 8 weeks of treatments. Therefore, the subcortical response to anti-psychotic therapy appears to critically depend on the duration of exposure to treatment, although it may well reflect the degree of symptomatic recovery too.

Neuroplasticity induced by anti-psychotic drugs

Grey matter increase in the D2 receptor-rich basal ganglia after anti-psychotic treatment is consistent with previous reports of anti-psychotic drug-induced hypertrophy in caudate nucleus (Chua et al. 2009; Massana et al. 2005; Shihabuddin et al. 1998), putamen, and thalamus (Gur et al. 1998b). Dopaminergic drugs such as amphetamine or L-dopa, which increase dopaminergic transmission, can induce a state indistinguishable from paranoid schizophrenia (Laruelle and Abi-Dargham 1999). The mechanism of how anti-psychotic drugs work in schizophrenia remains to be fully elucidated, but all anti-psychotic drugs, whether typical or atypical, are dopamine antagonists (Carlsson 1978). The cellular processes responsible for striatal volume increase in anti-psychotic medicated patients are obscure (Konradi and Heckers 2001), but neuropathological studies show changes in the synaptic organization of the striatum, particularly the caudate nucleus (Beckmann and Lauer 1997; Lauer and Beckmann 1997). Thus, anti-psychotic drugs might act to reverse pathology in the dopaminergic pathway in schizophrenia in the early treatment phase. Our findings help substantiate a critical interaction between anti-psychotics and neurodevelopmental alterations of brain function and structure in patients with schizophrenia (Horacek et al. 2006).

Consistent with this, neurogenesis, in terms of increased number of striatal neurons, has been reported in human schizophrenic postmortem brain tissues (Beckmann and Lauer 1997; Lauer and Beckmann 1997) and in anti-psychotic simulated animal models (Wakade et al. 2002; Wang et al. 2004). For example, 3 weeks of Olanzapine treatment in adult male rats increased the number of newly generated cells in the prefrontal cortex and dorsal striatum (Wang et al. 2004). New cell proliferation and division in the subventricular zone (Wakade et al. 2002) has also been observed. Dopamine is known to play an important role in the regulation of endogenous neurogenesis (Borta and Hoglinger 2007) and synaptic plasticity (Konradi and Heckers 2001) in the adult mammalian brain. In vitro experiments have shown that D2 receptor stimulation inhibits neural stem cell proliferation, and that this can be reversed by anti-psychotic drugs, like Haloperidol (Kippin et al. 2005). Taken together, the weight of evidence indicates that dopamine specifically inhibits neuroplasticity and dopamine-blockading agents are capable of reversing this action. We speculate that re-modelling of synapses and development of new neuronal circuit connections could have a role in anti-psychotic drug action.

We were intrigued to note that beyond 3 weeks of anti-psychotic treatment, grey matter *increases* were detected in the right thalamus (see Fig. 1). Though previous studies reported that the volume of thalamus could be modulated under anti-psychotic drug treatment from as early as weeks (Dazzan et al. 2005) to several years (Gur et al. 1998a; van Haren et al. 2007), most of them focused on the effects of typical and atypical agents rather than the timing of this modulation occur. Atypical anti-psychotic treatments were reported to be particularly associated with the thalami enlargement (Dazzan et al. 2005) (Scherk and Falkai 2006), while other studies have found reduced thalamic volume in chronic patients treated from typical to Olanzapine (Khorram et al. 2006) or failed to detect significant thalamic volume change in medicated schizophrenic patients (Deicken et al. 2002). However, Lewis and Lieberman contend that different anti-psychotic drugs appear to perform more similarly than previously thought (Leucht et al. 2009, 2003). In this view, like the controversial findings in caudate, the inconsistencies in the literature may be due to different duration of treatment

exposure rather than the different mechanisms triggered by typical and atypical anti-psychotics. Scherk and Falkai (2006) reviewed the effects of anti-psychotics on brain structure and concluded that patients who switched from typical to atypical anti-psychotics had prior increases in caudate volume reversed. In our study, caudate volume significant increased only in the first 3 weeks of anti-psychotic exposure and then reduced, suggesting that the time course of the treatment is an important but overlooked consideration.

Grey matter reductions were also detected in our study, mainly in the left frontal cortex. Compared to the within 3-week treatment group, with up to 8 weeks anti-psychotic treatment, patients showed less grey matter reductions in the left medial frontal gyrus, middle frontal gyrus, superior frontal gyrus, and the cerebellum. We speculate that in the first 3 weeks, anti-psychotic actions primarily target dopaminergic receptors-rich areas, like caudate, affecting other regions later. On the other hand, these grey matter reductions could be due to the steady progression of disease or potentially signal some degree of drug-associated neurotoxicity. The latter possibility is supported by Dean's review, which suggested that both acute and longer-term anti-psychotic exposure may induce excitotoxicity and cell apoptosis (Dean 2006). For example, cell viability decrease, membrane blebs, and retraction of cell extensions have been observed in Fluphenazine-treated rat primary hippocampal neurons (Sram et al. 1990) and Haloperidol-treated clonal mouse hippocampal cells (Lezoualc'h et al. 1996). A decrease in neurotrophic factors induced by anti-psychotics could be another mechanism of neurotoxicity, leading to grey matter volume reduction.

However, to put the question of neurotoxicity in perspective, it is noteworthy that the bulk of evidence suggests anti-psychotic treatment does not worsen cognitive impairment and may even improve it (Keefe et al. 1999; Lieberman 1999; Meltzer et al. 1996). Moreover, the cognitive difficulties suffered by patients prior to treatment are reported to be proportional to their duration of untreated psychosis, suggesting anti-psychotic drug are generally beneficial (Lappin et al. 2007). Thus, whether anti-psychotic exposure has neurodegenerative impact is a controversial issue but provides stimulus for further research into both neurotoxicity and neuroplasticity associated with anti-psychotic drugs, as well as possible avenues of neuro-protection early in the disorder (Lieberman et al. 2007).

Limitation

One limitation of our study is that the PANSS scores were collected at various times during follow-up and, unfortunately, were not coincident with the second MRI scans, though symptoms in all patients improved following the anti-psychotic treatment. This prevented us testing whether caudate and thalamus changes were directly associated with PANSS improvement. Associations between volume increases in striatum and positive symptom reduction in schizophrenia have been reported before (Taylor et al. 2005). Dopamine excess has been seen as a trigger which inappropriately activates subsets of neurons in the prefrontal-ventral, striatal-ventral, pallidal-mediodorsal, and thalamic-prefrontal loops associated with positive symptoms (O'Donnell and Grace 1998). Thus, we believe that early clinical recovery related to *restoration* of normal brain morphology, at least in the basal ganglia region, is a reasonable proposition and is the focus of on-going work.

Since the study was a naturalistic one, we did not specifically compare typical and atypical anti-psychotics. We decided that unrestricted choice of drug prescription by the responsible clinician would facilitate subject recruitment as well as enable us to address the core question of how the brain responds to early treatment. Nine out of 20 patients in this study were treated on Amisulpride, a distinctive anti-psychotic which blocks both D3 and D2 receptors. In further studies with a larger cohort, we plan to further explore the extent to which use of this particular drug contributed to the good treatment response and brain changes observed here. Only six out of 20 patients received typical or typical-atypical mix anti-psychotics, so any comparison between typical and atypical drugs would have been unbalanced. Of these six patients on typical medication, three of them were scanned at 3 weeks, and three after 3 weeks, so medication profile was unlikely to explain the differences between the 3- and 8-week groups. In our previous work, we reported larger caudate volumes in patients treated for 3 weeks compared to drug-naïve patients (Chua et al. 2009). In that study, two out of three of the patients were treated with typical anti-psychotics, suggesting that the effect on caudate size at least is not especially drug-specific. Possibly, D2R blockade by either typical or atypical anti-psychotics may be the common factor in this brain response to treatment.

Summary

In summary, grey matter increases were detected early in the course of treatment in a naturalistic study of previously anti-psychotic drug-naïve patients with first-episode schizophrenia. Patients after 3 weeks treatment had significant grey matter *increases* in the right caudate and frontal gyrus. However, after a longer period, up to 8 weeks of anti-psychotic treatment, the *increases* in caudate disappeared and were found in the right thalamus and bilateral cerebellum instead. This study successfully captured the time window of early anti-psychotic effects on grey matter volume changes. It contributes to the growing evidence that

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anti-psychotic drugs may possibly have a role in mediating neural plasticity during the early phase of clinical recovery. However, this is speculative and would benefit from further attention using animal models of schizophrenia and anti-psychotic action. In future studies, we plan to confirm our findings in a larger group and explore indices of neuronal growth using magnetic resonance spectroscopy and gene expression analysis. The hope is that markers for prognosis and treatment response in early psychosis can be established to aid future treatment strategies in the disorder.

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