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Amygdalohippocampal neuroplastic changes following neuroleptic treatment with quetiapine in first-episode schizophrenia

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Abstract

Schizophrenia is a severe, debilitating, chronic disease that is accompanied by morphologic changes within the brain. However, it is unclear to what extent alterations of grey and white matter in schizophrenia are linked to the disease itself, or whether they are a consequence of neuroleptic treatment. Typical and atypical antipsychotics exert differential effects on brain structure. Moreover, atypical antipsychotics may have distinct profiles with respect to grey matter in schizophrenic patients. Findings on drug-induced grey matter changes are heterogeneous due to variation in stage of illness, duration of treatment and use of multiple antipsychotics. Using voxel-based morphometry applied to high-resolution magnetic resonance images, we show that monotherapy with the atypical agent quetiapine (mean daily dose=445 mg±200 S.D.) may induce structural brain changes in first-episode schizophrenia patients (N=20) within 21 d of treatment. Specifically, we demonstrate longitudinal macroscopic changes (i.e. grey matter increases) in the left amygdalohippocampal region that were predicted by drug plasma levels but not daily doses. These structural alterations were accompanied by a clinical improvement of schizophrenic symptoms. Comparison with healthy controls (n=30) showed that grey matter amount in the respective amygdalar region was significantly reduced in unmedicated first-episode schizophrenia patients. These findings suggest that drug-induced neuroplastic changes in schizophrenia can occur quickly and are dependent on pharmacokinetics.

Introduction

Schizophrenia is a brain disorder with multifactorial aetiology. Environmental risk factors such as urbanicity (McGrath et al., 2004; Krabbendam and van Os, 2005) and genetic components (see work by Rodriguez-Murillo et al. (2012) for an overview) may interact with altered brain function in schizophrenia patients. In particular, amygdala function is likely influenced by such extrinsic and intrinsic factors (Cousijn et al., 2010; Lederbogen et al., 2011). However, dysfunctional amygdala activity in schizophrenia patients is related to clinical state rather than to genetic predisposition (Rasetti et al., 2009).

In addition to functional abnormalities, a broad range of structural alterations has been demonstrated in patients with schizophrenia. Also, *structural* abnormalities of the amygdala–hippocampus complex have been found to be associated with psychopathology (Rajarethinam et al., 2001; Tomasino et al., 2011). In general, the neuroanatomical changes in schizophrenia are by no means static but progress with the disease, as revealed by a recent meta-analysis (Chan et al., 2011). Reviewing 41 voxel-based morphometry (VBM) studies, Chan and colleagues found strong evidence that in patients suffering from a first episode of schizophrenia, the fronto-temporal, striatal and cerebellar grey matter (GM) amount is lower than in individuals at high risk for schizophrenia. Furthermore, disease progression from the first episode to chronic schizophrenia was shown to be associated with GM decrease in the anterior cingulate cortex (ACC), right insula, left amygdala and thalamus. Thus, the authors summarized that schizophrenia seems to represent a progressive cortico-striato-thalamic loop disorder. In addition, the results may also be seen as consistent with the notion of schizophrenic 'cognitive dysmetria' due to a dysfunctional prefrontal-thalamic-cerebellar

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circuitry (Andreasen et al., 1996; Andreasen, 1999). Another recent meta-analysis (Olabi et al., 2011), specifically focusing on longitudinal volumetric studies using region-of-interest structural magnetic resonance imaging, suggested that potential schizophrenia-related alterations in the amygdala–hippocampus complex are not progressive. However, it revealed significantly greater decreases in frontal grey and white matter, parietal white matter and temporal white matter volume over time in schizophrenia patients compared with healthy controls.

This provides evidence of progredient GM changes in schizophrenia, but leaves a critical question unclear: whether these changes are related to the disease itself or rather attributable to medication. While there is consensus that treatment with antipsychotics affects brain structure, the relationship between type of medication and neuroanatomical location still remains a matter of debate. Initially, an increased volume of the basal ganglia, particularly the caudate nuclei, following antipsychotic treatment has been described (Chakos et al., 1994). Subsequent studies indicated differential effects of typical and atypical agents. Typical agents were assumed to increase basal ganglia GM, whereas atypicals seemed to reverse such effects (Gur et al., 1998; Corson et al., 1999; Smieskova et al., 2009). In addition, treatment with atypical neuroleptics has been found to lead to GM increase in the thalamus (Gur et al., 1998; Tomelleri et al., 2009). However, the absence of GM changes following atypical neuroleptic treatment has also been reported (McClure et al., 2008). This may be explained by distinct neuroplastic or neurotoxic effects of different drugs. Different atypical antipsychotics appear to exhibit specific effects on brain structure. Increases of GM in the caudate and nucleus accumbens, in the superior temporal gyrus (STG) and in the parietal as well as the occipital lobes have been described after treatment with risperidone (Massana et al., 2005; Molina et al., 2005; Girgis et al., 2006), and a decrease in the basal ganglia and an increase in the orbitofrontal cortex (OFC) and ACC after treatment with quetiapine (Stip et al., 2008, 2009). However, even with the same compound, conflicting results emerged: olanzapine, for instance, has been reported to leave GM unaffected (Lieberman et al., 2005) but also to be associated with GM decrease in the frontal and parietal regions (Molina et al., 2007). In summary, there is a considerable variability in magnetic resonance imaging data in schizophrenia (Honea et al., 2005). With respect to drug-induced structural brain alterations, differential effects between the typical and atypical antipsychotic groups seem to provide only a partial explanation of this variability. Hence, the categorization into typical and atypical antipsychotics may represent an oversimplification in this regard.

Synopsis and interpretation of these heterogeneous findings are complicated by the involvement of different patient samples (e.g. first-episode vs. chronic schizophrenia patients), uneven duration of treatment, small sample sizes and the employment of a priori hypotheses deduced from previous neuro-imaging studies in schizophrenia, which may have led to bias. This implies a strong need for further prospective investigations of longitudinal GM changes associated with antipsychotics, at best accounting for drug-dependent variability in neuroplastic effects.

Hence, the present work sought to explore whether an atypical antipsychotic, quetiapine, is capable of inducing neuroplastic changes in unmedicated patients with first-episode schizophrenia. Placebo-controlled studies have shown that clinical improvement may be expected within 2–3 wk of quetiapine treatment (Buckley, 2004). Accordingly, we hypothesized that quetiapine-related neuroplastic changes, possibly linked to symptom reduction, would likewise be traceable after such a time period. Based on preclinical literature pointing to a neuroplastic effect of quetiapine on the amygdalohippocampal complex (Xu et al., 2002; Fumagalli et al., 2004; Luo et al., 2005; Park et al., 2006), it seemed likely that changes would also occur in this region in schizophrenia patients.

Method

Subjects

Forty-three patients with a suspected first episode of schizophrenia according to both DSM-IV-TR (American Psychiatric Association, 2000) and ICD-10 (World Health Organization, 1994) were included. Patients had been screened according to the following criteria: included were female and male patients aged from 18 to 65 yr with no history of previous intake of antipsychotics. Female patients of childbearing age had to be on secure contraception, and gravidity was excluded by a pregnancy test. Patients fulfilling the criteria of any other psychiatric disorder than schizophrenia, especially drug-induced psychosis, and suicidal patients were excluded. Furthermore, patients with a known history of intake of antipsychotics, an intolerance of quetiapine fumarate, or the concomittant intake of cytochrome P450 inductors/inhibitors or psychotropic medication (e.g. antidepressants, anticonvulsants, etc.) except for hypnotics and benzodiazepines, were non-eligible. Special care was taken during the whole trial to ensure that exclusion criteria were not violated and that patients were treated with quetiapine monotherapy. In the case of necessity of indispensable co-medication, the patient was excluded. In addition, quetiapine plasma levels were measured at baseline assessment to eliminate the possibility that patients had recently taken quetiapine (contrary to their claims). Moreover, patients suffering from an unstable somatic comorbidity, with epilepsy, brain malformation, history of traumatic brain injury, an absolute neutrophil count $<1.5 \times 10^9 \, l^{-1}$ or an HbA1c value $>8.5\%$ were excluded. Finally, patients who had taken part in another clinical trial within the last 30 d before screening were not included in the study.

Table 1. Patients' (*n*=20) characteristics

	Baseline	Follow-up	*df*	*t* value	*p* value
Age (y)	27.75±7.10				
Sex: female/male	5/15				
Treatment duration (d)	21.40±4.83				
Cumulative quetiapine dose (mg)	9308.75±4055.08				
Daily quetiapine dose (mg)	444.50±199.99				
Quetiapine level (*n*=19) (ng/ml)		331.05±288.31			
CGI-I		2.55±1.23			
GAF	43.40±11.25	53.80±11.62	19	3.62	0.002
BPRS: Total score	54.65±12.52	45.85±16.16	19	2.87	0.010
PANSS: Total score	95.10±19.36	84.30±24.21	19	1.98	0.062
PANSS: Positive syndrome	21.65±5.17	17.80±5.13	19	3.15	0.005
PANSS: Negative syndrome	26.50±5.73	24.00±6.22	19	1.83	0.084
PANSS: General psychopathology	46.95±11.01	42.50±15.07	19	1.27	0.221

Values are given as mean±S.D.

Degrees of freedom (df), *t* and *p* values correspond to a paired *t* test on the scales for Global Assessment of Functioning (GAF) (Caldecott-Hazard and Hall, 1994), Brief Psychiatric Rating (BPRS) (Overall and Gorham, 1962), and Positive and Negative Syndrome (PANSS) (Kay et al., 1987) performed in SPSS (PASW Statistics 18, release version 18.0.0, SPSS, Inc., 2009, USA, http://www.spss.com). CGI-I, Clinical Global Impression Improvement (Guy, 1976).

'Baseline' was defined as the time-point of magnetic resonance imaging (MRI) on the day of first administration of quetiapine; imaging was performed before quetiapine intake. 'Follow-up' was defined as the time-point of the MRI scan performed after treatment with quetiapine; imaging was also performed before quetiapine intake. One patient's quetiapine level data were lost.

All patients provided written informed consent to participate in the study (ClinicalTrials.gov Identifier: NCT00554658). The protocol was approved by the local ethics committee and was therefore in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Four patients dropped out between screening and baseline assessment (i.e. before quetiapine intake) due to acute worsening of their psychopathological symptoms or a panic attack in the MRI scanner. Another nine patients had to be taken out of the trial after baseline assessment because of comedication (*N*=2, duloxetine/perazine), side effects (*N*=2), drug noncompliance (*N*=1), revocation of consent form (*N*=2) or loss of contact with the patient (*N*=2). After end of treatment, another ten patients had to be excluded due to diagnoses other than schizophrenia. Diagnoses included adjustment disorder, acute and transient psychotic disorder, bipolar affective disorder, depressive episode, disturbance of activity and attention, emotionally instable personality disorder, harmful use of cannabinoids, mixed personality disorder, obsessive–compulsive disorder and schizoaffective disorder. The characteristics (before and after treatment) of the remaining 20 patients suffering from a first episode of schizophrenia are given in Table 1.

Thirty healthy and medication-free subjects served as a comparison group and were matched for age and gender to the patients. Mean age was 30.20±7.61 y (*t*=1.15, *df*=48, *p*=0.258), the proportion female/male was 11/19 (χ^2=0.75, *df*=1, *p*=0.386). Inclusion of these controls was specifically intended for testing whether the potential GM changes after quetiapine intake were observed in regions altered in first-episode schizophrenia patients when compared with healthy subjects.

Image acquisition

Structural magnetic resonance imaging at baseline and follow-up was performed on a 1.5 T scanner (MAGNETOM Sonata, Siemens Medical Solutions, Germany), yielding T1 weighted, high-resolution brain images. A 3D magnetization-prepared rapid acquisition with gradient echo sequence was adopted: repetition time 1880 ms, echo time 3.42 ms, flip angle 15°, matrix size 256×256, 176 sagittal slices, voxel size 1 mm×1 mm× 1 mm. Data were analysed by means of VBM8 (http://dbm.neuro.uni-jena.de/vbm/), integrated as a toolbox into SPM8 (Wellcome Trust Centre for Neuroimaging, UK).

Image processing

To assess GM changes over time, the default longitudinal preprocessing approach implemented in the VBM8 toolbox was applied. After registration of the follow-up image to the baseline image for each subject separately, intra-subject bias correction was applied. Then, images were segmented into different tissue classes, followed by affine (i.e. linear) and non-linear registration (i.e. Dartel (Ashburner, 2007)) of the segments. The segment approach is based on a maximum *a posteriori* (MAP) technique (Rajapakse et al., 1997) and employs a partial volume estimation (PVE (Tohka et al., 2004)). Moreover, a spatially adaptive non-local means (SANLM) filter (Manjón et al., 2010) and a classical Markov Random

Table 2. Grey matter (GM) decreases and increases during antipsychotic treatment in first-episode schizophrenia

Laterality	Macroanatomical region	Cytoarchitectonic region	Cluster size in voxels	MNI coordinates			Z score
				x	y	z	
GM decreases							
R	Cerebellum, Lobule VIIa Crus I (Hem) Cerebellum, Lobule VIIa Crus II (Hem)		1117	39	−66	−38	4.55
L	Cerebellum, Lobule VIIa, Crus I (Hem) Cerebellum, Lobule VI (Hem)		285	−33	−64	−36	3.93
R	Inferior frontal gyrus (VLPFC)	BA 47	69	30	27	−12	3.65
GM increases							
R	Cerebellum, Lobule VIIa Crus I (Hem) Cerebellum, Lobule VIIa Crus II (Hem)		301	52	−57	−45	4.54
L	Parahippocampal gyrus	Amyg (LB) Hipp (EC)	275	−28	−1	−33	4.19
R	Temporal pole	BA 38	133	21	10	−45	4.42
R	Superior temporal gyrus (STG)	TE 1.0	60	52	−16	−2	4.18
R	Thalamus (Th-Prefrontal/Temporal)		50	12	−10	10	3.53

Thresholded at a voxelwise uncorrected $p<0.001$ with a cluster size $k \geqslant 46$ voxels (number of expected voxels according to the random field theory).

Amyg (LB), Amygdala (laterobasal); BA, Brodmann area; Hipp (EC), Hippocampus (entorhinal cortex); L, left; MNI, Montreal Neurological Institute; R, right; VLPFC, ventrolateral prefrontal cortex.

Detailed information on cerebellar and cyto-architectonics is available for: EC, LB (Amunts et al., 2005), Th-Prefrontal, Th-Temporal (Behrens et al., 2003), Lobule VIIa Crus I/II (Diedrichsen et al., 2009), and TE 1.0 (Morosan et al., 2001).

Field (MRF) approach (Rajapakse et al., 1997) were used for denoising. Finally, the realigned and normalized GM segments were smoothed using an isotropic Gaussian kernel of 8 mm full width at half maximum (FWHM). Similarly, for group comparisons, images were registered using affine and non-linear registration (Ashburner, 2007) and segmented into three tissue types. Also here, segmentation was refinded by PVE, a SANLM filter and a MRF approach (Rajapakse et al., 1997; Tohka et al., 2004; Manjón et al., 2010). The modulated GM images were then smoothed with an isotropic Gaussian 8 mm FWHM kernel.

Statistical analysis

The resulting (longitudinal) GM images were entered into a repeated measures ANOVA with the factors subject and time (baseline and follow-up) to test for GM decreases and increases following 3 wk of antipsychotic treatment. Firstly, we applied an uncorrected cluster-forming threshold of $p<0.001$ to the resulting t-maps to maintain high sensitivity to longitudinal structural brain changes. To eliminate minor, presumably incidental, findings, only clusters exceeding the number of expected voxels according to the random field theory (Worsley et al., 1992) were reported at this threshold.

In a second step we investigated the relationship between quantitative parameters of quetiapine treatment and GM changes. To this end, baseline images were subtracted from follow-up images for each participant, respectively. The difference images were then fed into separate multiple regression analyses on the regressors 'cumulative quetiapine dose', 'daily quetiapine dose' and 'quetiapine plasma level'. Each patient's 'cumulative quetiapine dose' was calculated by summing up the doses of every single day, and 'daily quetiapine dose' in turn by dividing 'cumulative quetiapine dose' by the number of days between baseline and follow-up assessment. The regression analysis was restricted to the clusters showing significant GM change (i.e. clusters in Table 2) according to the previously computed ANOVA (inclusive masking, $p<0.05$). We then tested whether the observed GM increases related to quantitative quetiapine parameters were significant using a small volume correction (SVC) with a sphere of 6 mm diameter (centred at the local maximum within the respective cluster) on a statistical threshold of $p<0.05$, FWE corrected (Worsley et al., 1996). Cluster correlation coefficients (Pearson's r) were calculated by means of SPSS (PASW Statistics 18, release version 18.0.0, SPSS, Inc., 2009, USA, http://www.spss.com) after extracting data based on the regression design matrix with MarsBar (Brett et al., 2002).

Third, we compared grey matter of first-episode schizophrenia patients at baseline and of healthy controls in two-sample t-tests to assess whether the longitudinal GM changes occurred in regions altered in schizophrenia patients. Similarly to the approach regarding quantitative quetiapine parameters, this analysis was restricted

to the clusters showing longitudinal GM change in the schizophrenia patients; likewise, SVC was used, and the statistical threshold was set to $p < 0.05$, FWE corrected.

A reference image at an optimum threshold was created from all available baseline and follow-up images, serving as an explicit mask in all analyses (Ridgway et al., 2009). Due to the non-isotropic smoothness of VBM data, correction for non-stationarity was applied.

We chose VBM since it allows for assessment of grey matter in whole-brain analyses in a rapid and automated manner. However, we are aware that, although VBM results may be compatible with and extend the findings of volumetric ROI analyses (Job et al., 2002), VBM does not make manual ROI-based analyses redundant. As both methods may provide complementary information, especially in the context of schizophrenia (Giuliani et al., 2005), future volumetric ROI analyses based on the results of the present study are recommended.

Anatomical labeling

Resulting brain regions were macroanatomically and cytoarchitectonically labeled by means of the Anatomy Toolbox (Eickhoff et al., 2005, 2006, 2007), assigning GM changes to the most probable histological area. Areas not included with the Anatomy Toolbox were labeled by reference to the Talairach Daemon (Lancaster et al., 2000). We report this probabilistic and histology-based anatomical allocation in Table 2 and provide references to details of the cytoarchitecture in the table note.

Results

Both CGI-I ratings obtained at follow-up and an increase of GAF scores ($p < 0.01$) indicated an average symptom improvement from baseline to follow-up. A mean decrease of BPRS total scores also reached significance ($p < 0.05$), whereas improvement according to PANSS total scores was only observed as a trend ($p < 0.1$). Nevertheless, there was a significant decrease of scores on the positive syndrome subscale ($p < 0.01$) (see Table 1 for details).

VBM differentiated several decreases and increases of GM in schizophrenia patients following 3 wk of treatment with quetiapine (cf. Table 2). GM reduction was found in the cerebellum in both hemispheres as well as in the right ventrolateral prefrontal cortex (VLPFC; Brodmann area (BA) 47). An increase of GM amount was observed in the right cerebellum (distinct from the cluster showing decrease), thalamus, STG and temporal pole ($p < 0.001$, uncorrected).

Regression analysis revealed no significant positive or negative relationship between cumulative quetiapine dose or average daily quetiapine dose with GM increases or decreases in any brain region. In contrast, quetiapine plasma level correlated positively with GM increase in the amygdalohippocampal cluster, in particular the laterobasal amygdalar subdivision (peak voxel coordinates in Montreal Neurological Institute (MNI) space, cluster size k in voxels: $x = -22$, $y = -3$, $z = -26$, $k = 59$). SVC indicated that quetiapine level-related GM increase in the amygdala was significant on voxel level ($p_{SVC} < 0.05$, FWE corrected) (cf. Fig. 1). The corresponding cluster r was 0.493 (see Fig. 2 for a scatter plot). No significant positive or negative relationship between quetiapine plasma level with GM increases or decreases was found in any other brain region.

The comparison of schizophrenia patients with healthy controls revealed that GM amount in the laterobasal amygdala was significantly reduced in schizophrenia patients before quetiapine treatment ($x = -22$, $y = -3$, $z = -23$, $k = 93$; $p_{SVC} < 0.05$, FWE corrected). This analysis also showed that GM in the right (lobule VIIa, crura I and II) and left (lobule VIIa, crus I; lobule VI) cerebellum, both regions where longitudinal substance loss was observed, had already significantly been impaired in schizophrenia patients at baseline ($x = 39$, $y = -58$, $z = -36$, $k = 546$ and $x = -27$, $y = -63$, $z = -32$, $k = 278$; $p_{SVC} < 0.05$, FWE corrected). No areas of increased GM amount compared to healthy controls were found in schizophrenia patients.

Discussion

This is the first study to demonstrate longitudinal GM changes in first-episode schizophrenia after neuroleptic monotherapy within only 3 wk. These structural alterations indicate highly dynamic neural processes at the initial stage of schizophrenia after initiation of neuroleptic treatment with quetiapine. There is evidence that GM changes induced by quetiapine after 5 months of treatment correlate with changes in clinical condition (Stip et al., 2009; Ebdrup et al., 2010). It is intriguing that structural brain changes related to treatment with quetiapine can already be detected within 21 d. This time period is in line with the onset of action of antipsychotics in the treatment of psychoses (Agid et al., 2003; Leucht et al., 2005, 2007; Zedkova et al., 2011). Thus, our results further support the notion that neuroplasticity at a structural level may be involved in mediating clinical improvement (May et al., 2006).

In summary, we observed longitudinal GM increase in the amygdalohippocampal region that correlated with drug plasma levels and GM decrease bilaterally in the cerebellum without a relationship with quantitative drug parameters. Both changes occurred in areas showing reduced GM in unmedicated schizophrenia patients compared with healthy controls, according to a baseline brain scan. The progressive GM loss in the cerebellum observed after 3 wk is in line with the most recent quantitative meta-analysis of structural brain changes in schizophrenia linked to illness progression (Chan et al., 2011). This study indicated a convergence of GM reduction foci in the right hemisphere of the cerebellum when
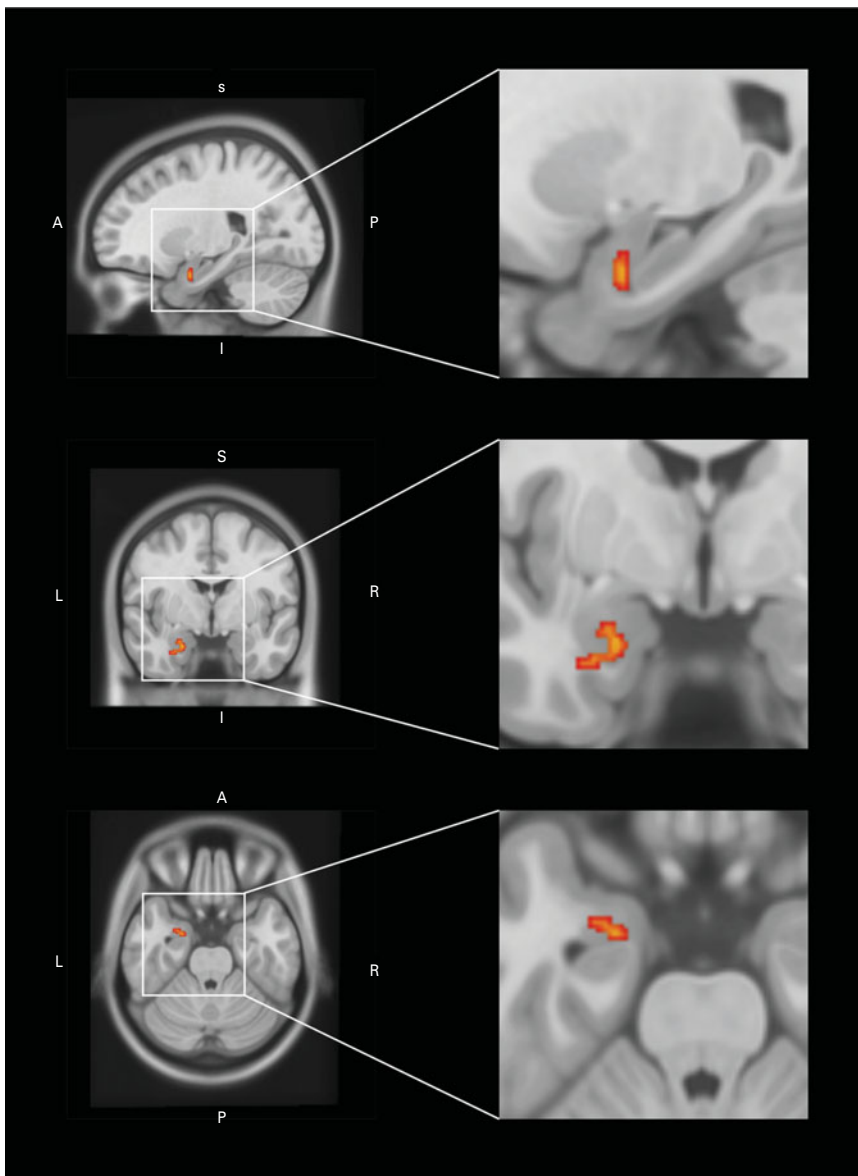
Fig. 1. Grey matter (GM) increase in the left amygdala positively correlated with patients' quetiapine levels. GM increase is superimposed on sagittal, coronal and axial slices of an average standard brain. The left column shows the whole brain, whereas the right column displays a part of the same slice at 3×magnification. A, anterior; I, inferior; P, posterior; S, superior.
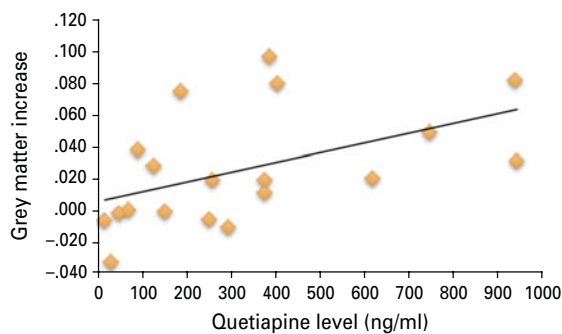
Fig. 2. Scatter plot of the relationship between the mean cluster grey matter increase and quetiapine plasma level obtained at follow-up. Pearson's $r=0.493$, $p<0.05$ (two-sided).

comparing first-episode schizophrenia patients with healthy controls. Furthermore, it suggested a decrease of GM in the left cerebellum advancing with transition of the disease from the first episode to a chronic stage. Here, we found no relationship of the longitudinal structural changes in the cerebellum with quantitative quetiapine parameters. The comparison with healthy controls revealed GM reductions in right and left cerebellar structures in unmedicated, first-episode schizophrenia patients. Both findings suggest that GM loss in these areas is linked to the disease (progress) rather than to drug treatment. In this context, the trend of GM increase in another distinct area in the cerebellum seems puzzling. This finding may suggest regionally selective effects of quetiapine on brain structure, and is in line with the

results of Deng et al. (2009), who found progrediently increasing GM during treatment with various antipsychotics in the cerebellum. Caution is warranted, however, as we observed no relationship between cerebellar changes and quantitative quetiapine parameters.

Apart from the cerebellum, structural GM alterations related to illness progress have also been reported by the respective meta-analysis in several other areas (Chan et al., 2011). Thus, longitudinal GM reductions in the cerebellum in first-episode schizophrenia patients without previous regular intake of antipsychotics point to the importance of these structural alterations, particularly at the initial stage of the disease. The observation that these GM changes occur as early as within 3 wk underlines the rapidity of neuroanatomical changes in both regions. Notably, the cerebellar area where patients in our study exhibited GM loss (lobule VII, crus I/II) corresponds to the cognitive region of the cerebellum (Stoodley and Schmahmann, 2009). Considering emerging evidence for the role of the cerebellum (Stoodley, 2012) in cognition and known structural abnormalities of this region in schizophrenia patients (Andreasen and Pierson, 2008; Kühn et al., 2012), the observed GM loss in these regions may reflect cognitive impairment in schizophrenia.

GM deficits of the left amygdala, as observed in the present sample of first-episode patients compared with healthy controls, are in accord with VBM studies assessing GM alterations in schizophrenia. More specifically, such structural changes are consistently seen in individuals at high risk for schizophrenia, as well as at the initial and chronic stages of the disease (Chan et al., 2011). Generally, amygdala pathology in schizophrenia seems to be lateralized to the left hemisphere (Joyal et al., 2003; Leung et al., 2011). Quetiapine might be able to reverse these GM deficits of the left amygdala, as indicated by the observed GM increase after 3 wk of treatment and the positive correlation between quetiapine plasma levels and the degree of increase. The observation that there was a relationship between GM change and quetiapine plasma levels, but not doses, is not surprising, given the only weak relationship between dose and plasma concentration of quetiapine (Wittmann et al., 2010; Sparshatt et al., 2011). Besides increasing amygdala GM, patients also showed an improvement of (particularly positive) symptoms. The observed structural changes might represent a basis for known relatedness of amydala activity in schizophrenia to clinical state (Rasetti et al., 2009).

Nevertheless, the value of quetiapine plasma concentration monitoring in clinical practice is still considered controversial (Mauri et al., 2007). While some authors doubt its usefulness in the context of clinical routine (Sparshatt et al., 2011), others argue in favour of measuring quetiapine levels to optimize individual pharmacotherapy (Wittmann et al., 2010). The only weak relationship of dose with plasma levels might at least

partly be explained by differences in individual clearance and polymorphisms in the ABCB1 gene (Wittmann et al., 2010; Nikisch et al., 2011). This gene encodes the P-glycoprotein transporter (P-gp), which in turn may influence both the blood and brain drug concentrations (Nikisch et al., 2011). In general, high D_2 receptor occupancy during pharmacotherapy is positively correlated with clinical improvement in schizophrenia (Yilmaz et al., 2012). This may also hold true for quetiapine (Pávics et al., 2004), but the relationship between quetiapine plasma level and D_2 occupancy seems not entirely clear (Sparshatt et al., 2011). Therefore, it has been suggested that further research on the relationship between quetiapine plasma concentration and clinical response is necessary (Sparshatt et al., 2011). The observed dependence of GM increase in the amygdala on quetiapine plasma levels, together with the concomitance of these structural brain changes with clinical improvement, may provide an indirect argument for the relevance of quetiapine plasma levels for clinical outcome.

The entorhinal cortex, located adjacent to the amygdala in the medial temporal lobe, likewise showed GM increase after 3 wk of treatment. Structural pathology in the entorhinal cortex volume is frequently observed in schizophrenia patients (Pearlson et al., 1997; Joyal et al., 2002; Turetsky et al., 2003; Prasad et al., 2004; Baiano et al., 2008) and assumed to contribute to psychopathology and cognitive disturbances of the disease (Baiano et al., 2008). Structural alterations in the entorhinal cortex are not likely to reflect disease chronicity or exposure to antipsychotics, but are associated with positive symptoms (Prasad et al., 2004). The concomitance of GM changes in the entorhinal cortex and significant changes on the PANSS positive subscale in the present sample of first-episode schizophrenia patients is in line with this observation.

VBM is not capable of disclosing the mechanism of the underlying longitudinal GM changes. In general, an increase in cell size, neural or glial cell genesis, spine density or even changes in blood flow or interstitial fluid have been discussed as a basis for GM increases (May et al., 2006). On a molecular level, D_2 receptor blockade induces reversible remodeling of GM in cortical–striatal circuits within hours (Tost et al., 2010). Such synaptic remodeling, as well as neuronal growth, are affected by immediate effector proteins such as brain-derived neurotrophic factor (BDNF) (Tost et al., 2010). Quetiapine has been shown to upregulate the glial cell line-derived neurotrophic factor (GDNF) (Di Benedetto et al., 2012) and BDNF (Xu et al., 2002; Fumagalli et al., 2004; Luo et al., 2005; Park et al., 2006). More specifically, quetiapine promotes neuroplasticity by inducing upregulation of BDNF expression in hippocampal regions in rats (Xu et al., 2002; Fumagalli et al., 2004; Luo et al., 2005; Park et al., 2006). This effect seems to be drug-specific and was not observed with the conventional antipsychotic agent haloperidol (Fumagalli et al., 2004). BDNF contributes to the

etiology of schizophrenia and is modulated by neuroleptic treatment (Angelucci et al., 2005; Szeszko et al., 2005); schizophrenia in turn is related to GM abnormalities in amygdaloparahippocampal regions (Chan et al., 2011). Moreover, deficits in prepulse inhibition of startle, which is also impaired in schizophrenia, are reversed by quetiapine in rats with lesions of the basolateral amygdala (Shoemaker et al., 2003), even though this effect was not observed for short-term quetiapine treatment in schizophrenia patients (Molina et al., 2011). Recently, there is growing empirical support for BDNF-dependent modulation of neural plasticity in the amygdala (Cowansage et al., 2010). Alternative explanations for the observed volume increases, such as acute cell swelling, e.g. through quetiapine-related mitochondrial damage (Modica-Napolitano et al., 2003) leading to increased osmotic pressure, cannot be excluded, but seem unlikely. Thus, our finding of prominent longitudinal increase of amygdala GM correlating with quetiapine plasma levels supports the notion that quetiapine-induced neuroplasticity is mediated by neurotrophic factors.

One limitation of this study is the modest sample size. Therefore, we cannot exclude effects other than the reported ones being overlooked. In this regard, the relatively high number of drop outs ($N = 23$) has also to be considered. However, only a minor number of patients ($N = 5$) had to be excluded due to reasons that might be seen in the context of quetiapine treatment (comedication, side effects, noncompliance). Most drop-outs were due to the fact that the suspected diagnosis of schizophrenia could not be confirmed. In this context, it has to be considered that no structured diagnostic instruments were applied at the time of screening. The subsequent application of strict diagnostic criteria according to the ICD-10, however, ensured that all included patients in fact suffered from a first episode of schizophrenia. At the same time, the sample was not restricted to a particularly compliant sample or to treatment responders. However, it should be kept in mind that the findings are restricted to unmedicated first-episode patients. Future studies should investigate whether the reported GM changes can also be observed in chronic patients. Another limitation of the study is the lack of a placebo control. However, the main finding of the study, the correlation between GM increase in the amygdalohippocampal complex and quetiapine plasma levels, is unaffected by the lack of a placebo control. Nevertheless, it cannot be excluded that the observed longitudinal GM changes are independent of quetiapine treatment, even if this seems rather unlikely. Last but not least, it has to be considered that we do not have information on socioeconomic status, education levels or (premorbid) IQ estimates. Although a previous VBM study (Haier et al., 2004) suggests that at least general intelligence is not correlated with GM volume in the amygdalo-hippocampal region, these variables might have affected the results of the group comparison.

In summary, the present results provide evidence for a quetiapine-related increase of GM volume in the amygdalohippocampal complex in patients suffering from first-episode schizophrenia, and show that this increase is predicted by quetiapine plasma levels but not by quetiapine doses. These neuroanatomical changes are already detectable after 21 d. These findings suggest that drug-induced structural neuroplasticity in schizophrenia can occur quickly, and is likely to depend on pharmacokinetics.

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