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ORIGINAL PAPER

Progressive pathology is functionally linked to the domains of language and emotion: meta-analysis of brain structure changes in schizophrenia patients

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Abstract Schizophrenia is a neuropsychiatric disorder entailing progressive psychotic, cognitive and affective symptoms. Several imaging studies identified brain structure abnormalities in schizophrenia patients, particularly in fronto-temporal regions and evidence for progressive anatomical changes. Here, we synthesised these findings by quantitative coordinate-based meta-analysis, assessing regions of consistently reported brain structure changes, their physiological functions and the correlation of their likelihood with disease duration. The meta-analysis revealed four significant clusters of convergent grey matter reduction, while one cluster indicated higher grey matter values in patients. A voxel-wise analysis revealed a correlation between grey matter reduction and disease duration in the left anterior insula. Functional characterisation revealed significant association with reward, affective processing and language functions. The current analysis allowed the identification of consistent morphometric changes across a large sample of studies in regions that are associated with neurophysiological functions that are altered as hallmarks of schizophrenia psychopathology. The observation that the location of presumably progressive pathology is functionally linked to language and emotion is well in line with increasing deficits in these domains with disease progression in schizophrenia.

Keywords Schizophrenia · Brain structure · Anatomical likelihood estimation · Disease duration · Structure–function relationship · BrainMap

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Introduction

Schizophrenia is a neuropsychiatric disorder that goes along with progressively debilitating symptoms. While its exact pathogenesis remains unclear, a large number of neuroimaging studies found compelling evidence for brain morphology changes in schizophrenia [1]. Besides global atrophy and ventricular enlargement, most studies implicated a fronto-temporally pronounced pattern of alterations, where medial temporal lobe structures, the superior temporal gyrus and inferior frontal regions show volume reductions in affected individuals [1]. Since brain structure changes also can be found in first episode, drug-naïve patients [2] or unaffected first-degree relatives [3], the interpretation of these results as gross morphological correlates of disease-specific neuropathology seems plausible

[4]. Matching disease development, progressive structural abnormalities have also been described [5, 6].

While these results might raise the idea of progressive fronto-temporal brain atrophy as a central feature in schizophrenia, there are several serious limitations to this conclusion. Findings on brain structure changes in schizophrenia are often inconsistent and sometimes contradictory over studies. The magnitude of the reported changes is rather small with considerable overlaps between a patient group and a healthy population [4]. Finally, most studies—in particular with longitudinal designs—are based on relatively small sample sizes.

We here report results from an anatomical likelihood estimation (ALE)-based meta-analysis [7, 8] of thirty-eight peer-reviewed articles, involving a total of 1,736 schizophrenia patients and 1,915 healthy controls. The purpose of our ALE meta-analysis was to provide a quantitative summary of the existing findings on brain structure changes in schizophrenia, to investigate whether the likelihood of finding regional atrophy correlates with disease duration and relate the identified regions to mental functions.

Methods

Literature search and selection

The PubMed (http://www.ncbi.nlm.nih.gov/pubmed/) database was searched using the following search strings "schizophrenia + vbm", "schizophrenia + voxel", "schizophrenia + morphometry" and "schizophrenia + voxel-based" to identify morphometric MRI studies investigating schizophrenia. Additional studies were identified by reference tracing and through review articles, and all results were manually verified for inclusion criteria [9]. In total, 38 studies published 2001–2011 were included in the meta-analysis, 26 of which gave information on disease duration (see supplementary Table 1).

Anatomical likelihood estimation meta-analysis procedure

The meta-analysis was carried out using the activation likelihood estimation (ALE) approach for coordinate-based meta-analysis of neuroimaging results [10, 11]. The resulting non-parametric p-values were thresholded at a cluster level corrected threshold of $P < 0.05$ and transformed into Z-scores for display. We then used the SPM Anatomy Toolbox v1.5 [12] to compare the localisation of the significant effects to histological areas. Regions that have not yet been histologically examined were labelled using the "Harvard-Oxford cortical and subcortical structural atlas" [13].

Correlations between disease duration and likelihood of grey matter changes

We investigated whether the probability of finding regional atrophy in schizophrenia was related to the disease duration of the assessed patients. Thus, modelled anatomical effects values were correlated on a voxel-wise level with mean disease duration as reported in the original studies using Spearman rank correlation ($P < 0.05$). All 26 studies that reported duration of disease were included in this analysis, which was constrained to the regions showing a significant convergence of reported atrophy across studies.

Functional characterisation by behavioural domains

To determine possible functional consequences of structural changes in schizophrenia, we analysed the behavioural domain metadata associated with each obtained cluster by reference to the BrainMap database (http://brainmap.org/) to determine frequency of domain hits relative to its distribution across the whole brain (i.e. the entire database) [8, 14].

Results

Convergent atrophy in schizophrenia patients

We found 4 clusters of convergent evidence for regional atrophy in patients relative to controls. The largest of these four clusters (−46, 14, −3, $k = 457$) was located fronto-temporally in the left periinsular region. It was extended from the inferior frontal gyrus (opercular part, not encroaching BA 44 or BA 45) across the anterior insula to the superior temporal gyrus.

The maximum of the second largest cluster was located in the left thalamus (−4, −20, 9, $k = 146$), while the cluster extended over the mid-line into the right thalamus and was allocated to regions of the thalamus projecting to prefrontal and temporal lobes according to the thalamic connectivity atlas [15]. A third cluster (−22, −10, −17, $k = 126$) was found in the left medial temporal lobe. Allocation by cytoarchitectonic probabilistic mapping showed that this region of convergent atrophy was attributed mainly to the laterobasal (LB) complex of the amygdala. Smaller parts were located in the superficial (SF) amygdala, the entorhinal cortex and the subiculum. Finally, we found convergent evidence for grey matter decreases in the left basal forebrain/ventral striatum (−4, 6, −3, $k = 118$). (Figure 1a, Supplementary Table 2).

In contrast to these findings, we also observed one cluster located in the left putamen (−26, −2, 13, $k = 156$) of convergent evidence for significantly increased grey

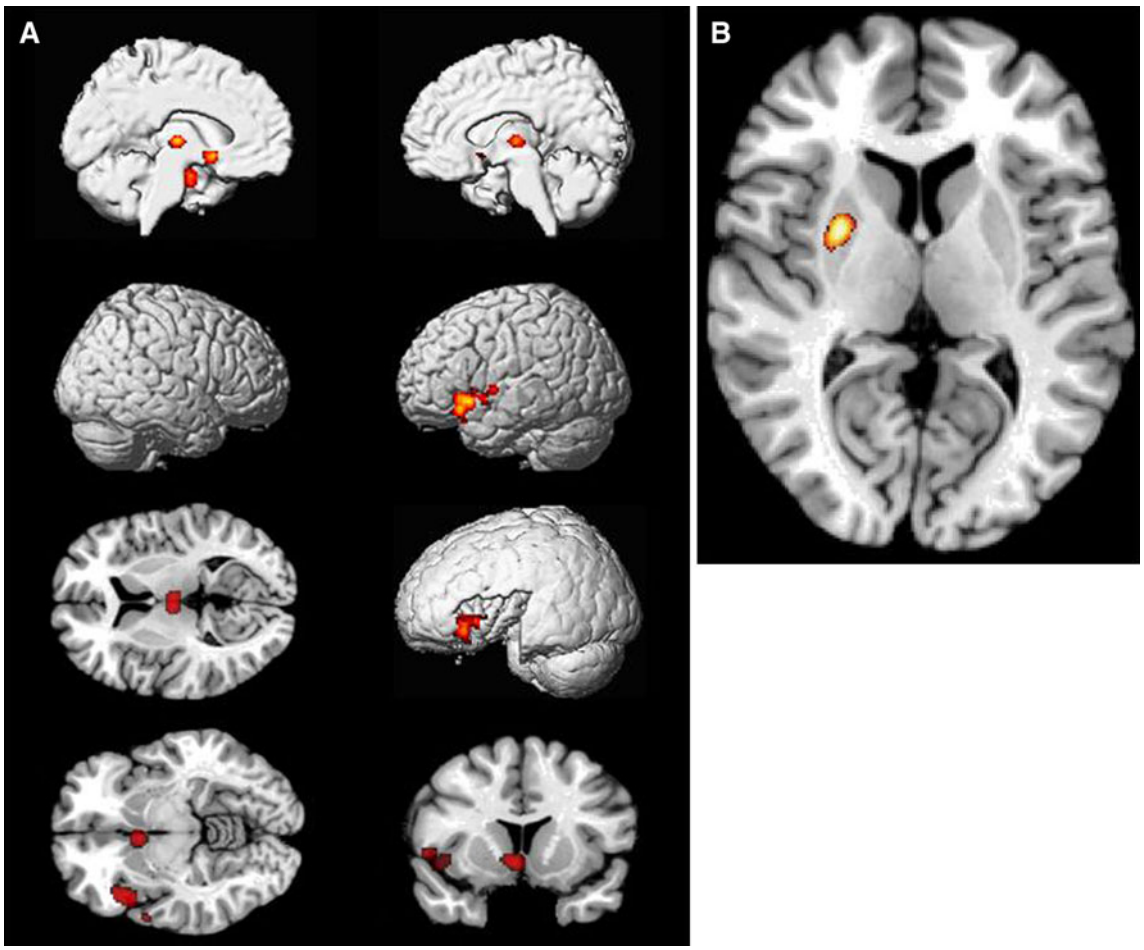

Fig. 1 **a** 4 clusters indicated convergent regional atrophy in schizophrenia patients. Clusters were located in the *left* periinsular region, the bilateral thalamus, the *left* medial temporal lobe (mainly the laterobasal amygdala) and the *left* basal forebrain/ventral striatum. **b** Only one cluster indicating significantly increased grey matter was found. It was located in the *left* putamen

matter in patients relative to healthy controls (Fig. 1b, Supplementary Table 2).

Correlation of regional atrophy with duration of disease

Correlating the probability of finding differences between patients and controls to the mean disease duration of the patients included in the particular sample yielded one cluster of significant positive association located in the left anterior temporo-insular cortex (-46, 8, -7, $k = 34$). We did, however, not find any significant clusters indicating a correlation between regional grey matter increases and disease duration. (Fig. 2, Supplementary Table 2).

Functional analysis by behavioural domains

All of the behavioural domains and paradigms that were significantly ($P < 0.05$, Bonferroni-corrected for multiple comparisons) associated with the left periinsular cluster were related to language, speech and music processing. Experiments activating the amygdala/medial temporal lobe cluster were significantly associated with affective and emotional processing as well as face perception, olfaction and memory. Experiments featuring activation in the basal forebrain featured significant association with emotional and in particular reward processing. Functional associations were least strong for the thalamic cluster, related to interoception and reward.

The only cluster of significantly increased grey matter volume, finally, was associated with action (execution) related tasks, including finger tapping and overt speech.

Discussion

This study confirms and extends recent summaries on brain morphology changes [16–18] in schizophrenia by demonstrating the affection of frontal, temporal and thalamic regions. While one of the first publications in this field compared first episode with chronic schizophrenia patients

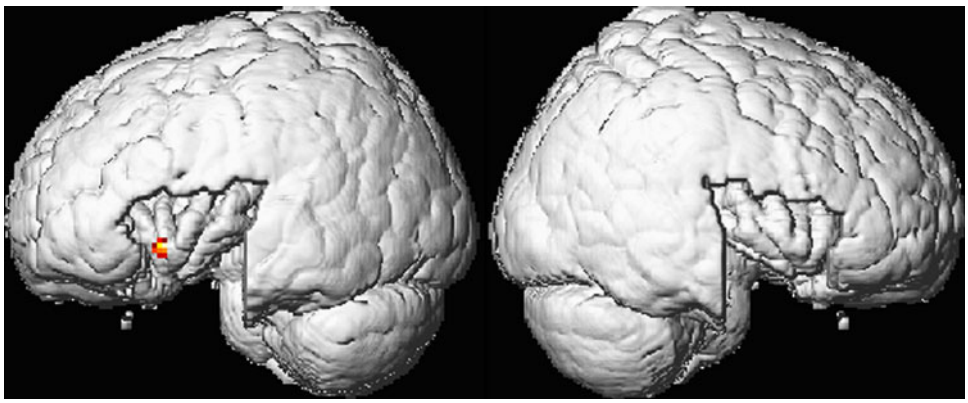

Fig. 2 A voxel-wise analysis assessing whether the probability of finding differences between patients and controls was related to the mean disease duration of the patients included in the particular sample yielded one cluster located in the *left* temporal pole

[16], to our best knowledge, this is the first approach to assess the influence of disease duration on the likelihood of observing differences in regional brain structure. Moreover, we demonstrated an observer-independent data-driven approach to assess structure–function relationship of affected brain regions by reference to the BrainMap database.

The observed fronto-temporal predilection for brain structure abnormalities is in line with several independent lines of evidence. Functional MRI and EEG studies have shown that the synchronisation of frontal and temporal regions is attenuated in schizophrenia patients, and that this strongly predicts their likelihood of experiencing hallucinations [19]. These findings have led to the hypothesis of a fronto-temporal dysconnectivity as a pathophysiological key mechanism underlying core symptoms such as auditory hallucinations. The present data indicate that atrophy of structures on the frontal operculum and the speech-sensitive anterior insula [20] may be considered a neuroanatomical correlate of such symptoms. This view, which highlights the role of structures beyond Broca's region (BA 44/45), would be in line with a recent meta-analysis on the functional localisation of auditory hallucinations [21].

An affection of the medial temporal lobe in schizophrenia has been largely replicated by the volumetric literature [1]. We here were able to demonstrate structural alterations in particular of the laterobasal group within the amygdala complex. They are considered key structures for the affective evaluation of incoming sensory, in particular auditory and visual, stimuli [22]. In this context, it is not only worthwhile to point to aberrant amygdala activation of patients with schizophrenia in response to emotional stimuli [23].

Thalamic regions have also been repeatedly implied in the pathophysiology of schizophrenia. The fact that thalamic atrophy is mainly found in nuclei projecting into the prefrontal and the temporal neocortex further corroborate the hypothesis of dysfunctional fronto-temporo-thalamic networks as a key component in the pathophysiology of schizophrenia [16–18]. Interestingly, aside from these bilateral changes in the thalamus, all clusters of convergence were located in the left hemisphere. Deficits of cerebral lateralisation have been discussed as a key pathophysiological component in schizophrenia both on a functional [24] and on an anatomical level [4, 24]. The lateralised character of our own findings goes along with these results.

In the current meta-analysis, we only observed a single cluster of convergent increased grey matter values, in the left putamen. Volume increases of the basal ganglia have been described as a result of antipsychotic treatment [25], a notion challenged by others [26]. Moreover, disturbances of action control are frequently found in schizophrenia [27]. We would hence tentatively suggest that the observed disturbance of basal ganglia structure might reflect genuine (patho-)physiological processes attributable to the disorder itself rather than to a secondary pharmacological phenomenon.

Physiologically, the affected regions are linked to cognitive functions involved in language processing (including listening, semantics or speech) or affect. Clinically, disturbances of speech are a hallmark of schizophrenia and emphasised by the fact that the DSM-V rates "disorganised speech" as one of the 5 major diagnostic criteria. Moreover, auditory verbal hallucinations are a frequent feature of schizophrenia psychopathology. Our results point to a potential correlate of these symptoms by neuroanatomical changes in regions contributing to language, speech and semantics. Likewise, we demonstrated structural affection of regions physiologically involved in affective processes including reward, which matches behavioural and functional changes of emotion processing in schizophrenia [28]. These seem to be directly related to functions that may be subserved by the structurally altered regions found in this study, in particular the medial temporal cluster. Moreover, the affection of reward-related regions may mirror the negative symptoms of lack of drive and motivation.

The analysis on the influence of disease duration only yielded a small cluster in the left anterior insula, again in its cognitive/language-related part. Thus, our results suggest a

qualitatively stable pattern of regions involved over the course of the disorder that enrols fronto-temporal, limbic and thalamic brain regions. It needs to be emphasised though that our approach may not track progressive volume loss in a given brain region but only describes whether there is an increased likelihood of finding atrophy with higher (mean) duration of disease in the investigated sample. In summary, integrating across studies on presumably heterogeneous populations that were defined by different diagnostic criteria, we demonstrate consistent evidence for brain structure changes in regions associated with reward, emotional and language processes in schizophrenia patients, which is qualitatively stable over the course of the disease.

Conflict of interest The authors declare that they have no conflict of interest.

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