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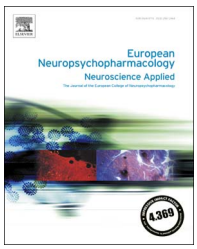

Cortical folding abnormalities in patients with schizophrenia who have persistent auditory verbal hallucinations

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Abstract
In schizophrenia temporal cortical volume loss differs between patients presenting with persistent auditory verbal hallucinations (pAVH) in contrast to those without hallucinatory symptoms (nAVH). However, it is unknown whether this deficit reflects a neural signature of neurodevelopmental origin or if abnormal temporal cortical volume is reflective of factors which may be relevant at later stages of the disorder. Here, we tested the hypothesis that local gyrification index (LGI) in regions of the temporal cortex differs between patients with pAVH (n=10) and healthy controls (n=14), and that abnormal temporal LGI discriminates between pAVH and nAVH (n=10). Structural magnetic resonance imaging at 3T along with surface-based data analysis methods was used. Contrary to our expectations, patients with pAVH showed lower LGI in Broca´s region compared to both healthy persons and nAVH. Compared to nAVH, those individuals presenting with pAVH also showed lower LGI in right Broca's homologue and right superior middle frontal cortex, together with increased LGI in the precuneus and superior parietal cortex. Regions with abnormal LGI common to both patient samples were found in anterior cingulate and superior frontal areas. Inferior cortical regions exhibiting abnormal LGI

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in pAVH patients were associated with overall symptom load (BPRS), but not with measures of AVH symptom severity. The pattern of abnormal cortical folding in this sample suggests a neurodevelopmental signature in Broca's region, consistent with current AVH models emphasizing the pivotal role of language circuits and inner speech. Temporal cortical deficits may characterize patients with pAVH during later stages of the disorder.

1. Introduction

Auditory verbal hallucinations (AVH) are a highly relevant clinical feature of schizophrenia that has attracted extensive clinical, phenomenological and neurobiological interest. Yet treating these symptoms, especially in persons suffering from persistent AVH (pAVH) which do either not or not sufficiently respond to psychopharmacotherapy, is still a major clinical challenge. AVH are a core symptom of schizophrenia and related spectrum-disorders, but they also frequently occur in other psychiatric entitities and in the non-psychiatric population (Diederen et al., 2013). The clinical features of AVH may also characterize distinct nosological entities within the schizophrenia-spectrum (Mauri et al., 2008), which could be more prone to treatment-resistance (Gonzalez et al., 2006), and which may differ from patients without AVH in terms of brain volume abnormalities (Gaser et al., 2004; Shapleske et al., 2002; van Swam et al., 2013).

Across neuroimaging studies temporal cortical volume loss is one of the most consistent finding in patients with pAVH in schizophrenia (Allen et al., 2007, 2008). Most structural data derived from voxel-based morphometry (VBM) studies, which reported an association between AVH severity and bilateral superior temporal gray matter volume loss (reviewed by Modinos et al. (2013)). In a previous report, using a multivariate statistical technique for structural data analysis, we have shown lower volume of a network including medial/inferior frontal and bilateral superior temporal regions in pAVH patients compared to both controls and to non-hallucinating patients with schizophrenia (nAVH) (Kubera et al., 2014). These data also supported a specific role of this structural network in the expression of specific symptom characteristics, such as symptom duration or symptom frequency and intensity (Kubera et al., 2014). Yet it is unclear so far whether disrupted temporal cortical integrity reflects a stable trait of the disorder, or if may evolve over time during the course of the illness.

Cortical gyrification is thought to be determined before and around birth and undergo only minor changes during childhood and adolescence (Zilles et al., 2013). Regarding the neurodevelopmental hypothesis of schizophrenia, which postulates that abnormal neurodevelopmental processes starts years before disease onset (Rapoport et al., 2012) cortical folding patterns are practicable to investigate early brain development and represent a stable morphological feature of the brain not prone to state dependent effects, medication and environmental factors (Nenadic et al., 2015; Zilles et al., 2013). For measuring cortical folding the gyrification index (GI), i.e. the ratio between the folded cortical surface and an outer cerebral surface have been applied (Zilles and Rehkämper, 1998). In schizophrenia, several studies indicated abnormal gyrification in frontal and temporal regions, as studies alternately report both reduced and increased cortical folding (White and Hilgetag, 2011). Recent studies with larger sample sizes showed hypogyria in the left precentral gyrus, right middle temporal gyrus and right precuneus (Nesvag et al., 2014), the right transverse temporal gyrus and bilateral posterior cingulate and bilateral caudal anterior cingulate (Nanda et al., 2014). Remarkably, abnormal cortical folding patterns have been observed in first-degree relatives, even though to a lesser degree (Nanda et al., 2014). Yet, despite this progress of defining early structural changes in patients with schizophrenia, the underlying cortical folding changes of AVH are poorly defined. At present, there is a striking paucity of data addressing the specificity of abnormal gyrification for patients with treatment resistant AVH. The identification of such changes can therefore allow us to illustrate neurodevelopmental trait markers for the phenomenological dimensions of AVH in schizophrenia.

The aim of the study was to analyse neurodevelopmental indices which could provide valuable complementary information on stable neural features specifically in individuals suffering from pAVH in schizophrenia in comparison to patients without AVH and healthy controls. The development of powerful 3D-based image-processing techniques (e.g. surface-based morphometry, SBM) based on T1-weighted structural MRI scans allows an automatic computation a fine-grained quantification of local gyrification (Schaer et al., 2012, 2008). Here, we performed cortical surface reconstruction on 3 Tesla MRI data to investigate local gyrification index (LGI) differences between patients with schizophrenia presenting with and without persistent AVH, and to explore the relationship between LGI and specific symptom dimensions in hallucinating patients. We predicted that in contrast to healthy individuals and nAVH patients, pAVH individuals would exhibit more pronounced abnormalities in language related brain regions, e.g. temporal cortical gyrification according to the topography of structural alterations previously reported in VBM studies on AVH in schizophrenia. In this case, temporal cortex abnormalities would indicate both state and trait features closely associated with pAVH. In addition, we expected that abnormal temporal cortical gyrification would be also related to AVH symptom expression, as shown by our previous work (Kubera et al., 2014) and by other independent researchers (Plaze et al., 2011).

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