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Possible dysregulation of cortical plasticity in auditory verbal hallucinations—A cortical thickness study in schizophrenia

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ABSTRACT

Introduction: Investigations of gray matter changes in relation with auditory verbal hallucinations (AVH) have reported conflicting results. Assuming that alterations in gray matter might be related to certain symptoms in schizophrenia this study aimed to investigate changes in cortical thickness specific to AVH. It was hypothesized that schizophrenia patients suffering from persistent AVH would show significant differences in cortical thickness in regions involved in language-production and perception when compared to schizophrenia patients which had never experienced any hallucinations.

Methods: Using cortical thickness analysis the present study investigated ten schizophrenic patients suffering from AVH, ten non-hallucinating schizophrenic patients, and ten healthy control subjects. Anatomical data were acquired on a 3 T MRI system, transformed into standard space and cortically aligned to investigate local differences in whole brain cortical thickness between the two patient groups. Based on this comparison, brain regions with alterations specific for the patients with AVH were identified and then used as regions of interest to compare both patient groups to the healthy subjects respectively.

Results: Hallucinating patients showed gray matter reductions in the dominant hemisphere predominantly in sensory language areas relevant for speech processing. Increased cortical thickness was found in regions related to self-monitoring.

Conclusions: Gray matter reductions in chronic schizophrenic patients may be the sequel of synaptic derangement or disease-related deregulation of language circuits. In order to clarify the ambiguous information processing additional demands might be put on cortical structures responsible for self-monitoring processes leading to changes in cortical thickness in the sense of neural plasticity.

1. Introduction

The neurobiological pathogenesis of Auditory Verbal Hallucinations (AVH) is current intensively debated in schizophrenia research. Even though a number of neuroimaging studies have added important knowledge to the understanding of the neurobiological basis of AVH the exact mechanisms and the relation between brain structure and function of this intriguing phenomenon still remain unresolved and controversial discussed (McCarley et al., 1999; Shenton et al., 2001; for review see Allen et al., 2008).

Functional and structural studies have consistently reported, in addition to other regions, an involvement of language-production and perception areas including the primary auditory cortex during AVH (Dierks et al., 1999; Shergill et al., 2000). During AVH these areas were activated in the speech dominant hemisphere and white matter fibers connecting these areas (arcuate fascicle) showed a higher directionality in patients suffering from AVH when compared to non-hallucinating patients and healthy controls (Hubl et al., 2004; Shergill et al., 2007). Based on these findings it was suggested that the stronger directionality between language related areas may lead to a dysfunctional coactivation of the auditory cortex labeling self-generated inner speech as coming from outside, which then are referred to as AVH (Strik et al., 2008). However, it is still a matter of debate, whether AVH could be

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sufficiently explained by this mechanism, or if structural changes in gray matter might play an additional crucial role in the generation of AVH.

Structural changes in brain gray matter can be examined by voxel-based morphometry (VBM) allowing statistical whole brain analysis of gray matter density. A recent thorough whole brain VBM meta-analysis of gray matter alterations in schizophrenia irrespective of symptomatology, demonstrated reduced gray matter density in distributed regions, including bilateral insular cortex, anterior cingular cortex, left parahippocampal gyrus, left middle frontal gyrus, postcentral gyrus, and thalamus (Glahn et al., 2008). Studies using VBM to investigate AVH in schizophrenic patients reported structural alterations in extra-sensory regions in addition to the auditory cortex (Gaser et al., 2004; Neckelmann et al., 2006; Shapleske et al., 2002). In this context reduced gray matter has been found in the left insular cortex and the adjacent temporal pole (Shapleske et al., 2002), the thalamus and cerebellum (Neckelmann et al., 2006) and the left transversal gyrus (Heschl), the left supramarginal gyrus, and the dorsolateral prefrontal cortex in hallucinating patients (Gaser et al., 2004).

However, VBM is based on a voxel-wise comparison of local gray matter concentration, thus this method also reflects differences in surrounding tissue (partial volume effect). As a consequence the results may be influenced by the brains shape (e.g. sulcal widening or curvature) (Ashburner and Friston, 2000: Shenton et al., 2001; Narr et al., 2005; Glahn et al., 2008; for review see Honea et al., 2005; Allen et al., 2008).

Furthermore, VBM requires the segmented data to be smoothed with large Gaussian kernels in order to be used for statistical inference (Ashburner and Friston, 2000). This blurring impedes the exact estimation of gray matter structure and its comparison between groups. These facts make it desirable to use a more exact estimation of whole brain alterations of gray matter, as provided in the presented study by measures of cortical thickness obtained after cortical alignment.

Interindividual differences in cortical thickness can be related to the migration of neuronal cells and formation of synaptic contacts which occurs during development at early pregnancy (Garey, 2010; Shaw et al., 2008). Measures of cortical thickness using in vivo imaging reflect the cytoarchitecture of the cerebral cortex, as has been demonstrated in a recent study of trajectories of cortical development (Shaw et al., 2008). Thus it may be expected that gray matter alterations due to functional deficits, such as neuronal loss or loss of neuropil, will also be reflected by alterations of cortical thickness as has been shown in earlier studies (Garey, 2010).

Although regional changes in cortical thickness in patients with schizophrenia have been addressed in previous studies (Cotter et al., 2004; Hamilton et al., 2007; Kuperberg et al., 2003; Narayan et al., 2007; Narr et al., 2005; Nesvag et al., 2008; Schultz et al., 2010; White et al., 2003; Wiegand et al., 2004; Yoon et al., 2007) none of the studies has used a symptom driven approach within the diagnosis of schizophrenia. In the current study, the question was addressed, whether cortical thickness is specifically related to the phenomenon of AVH in patients with schizophrenia. To this end patients suffering from AVH and non-hallucinating patients with schizophrenia as well as healthy controls were examined. Based on the results of previous functional and white matter structure studies in AVH demonstrating the crucial role of language related brain areas in the generation of these phenomena we hypothesize that patients with AVH will exhibit reduced cortical thickness in cerebral regions responsible for speech production and perception.

2. Methods

2.1. Subjects

Thirty right handed subjects were included in the study encompassing ten subjects in three groups. Patients with chronic schizophrenia suffering from persistent auditory verbal hallucinations (AH): $n = 10$, five female (mean age (SD) 40.9 ± 9.5 years), patients with chronic schizophrenia who never had experienced auditory verbal hallucinations (NH): $n = 10$, three female (mean age (SD) 36.3 ± 5.6 years), and healthy control subjects (CC): $n = 10$, six female (mean age (SD) 40.0 ± 9.5 years). All patients were inpatients of the University Hospital of Psychiatry in Bern, Switzerland. All healthy subjects were recruited among hospital staff members. The groups did not differ significantly in demographic data considering age, education or handedness (Table 1). Inclusion criteria were a diagnosis of schizophrenia or schizoaffective disorder corresponding to the criteria of the International Classification of Diseases, 10th Revision (Bramer, 1988), for at least 5 years. Based on medical history and neurological examination only patients were included who did not present any further physical or psychiatric disorder than the one of investigation. None of the subjects reported substance abuse before hospitalization except for sporadic cannabis consumption in 4 patients. All patients were on stable neuroleptic medication and received typical or atypical antipsychotic treatment in conventional dosages (Table 1). The study was approved by the local ethical committee and written

Table 1
Demographic data and statistics of the three investigated groups are shown. CC = healthy controls, AH = hallucinating patients with schizophrenia, and NH = non-hallucinating patients with schizophrenia.

Demographic data (Mean ± SD)	Groups investigated			Statistics	
	AH	NH	CC	$F(df = 27)$	p
n	10 (5f/5m)	10 (3f/7m)	10 (6f/4m)		
Age (Years)	40.9 ± 8.8	36.3 ± 5.6	40.0 ± 9.5	0.8	0.4
Education (Years)	11.5 ± 3.0	12.3 ± 1.9	14.0 ± 2.5	2.5	0.1
Handedness (right)	100%	100%	100%		
				$t(df = 18)$	p
Age at first psychotic symptoms (Years)	27.4 ± 9.0	29.1 ± 7.6		0.7	0.4
Duration of illness (Years)	13.7 ± 10.0	7.8 ± 9.2		0.7	0.4
Medication in Clorpromazin equivalents (mg)	411.6 ± 485.7	583.11 ± 767.71		0.6	0.6
PANSS Hallucinational Score	6.0 ± 0.7	1.1 ± 0.3		14.4	0.0
PANSS positive	32.0 ± 10.3	19.3 ± 11.4		2.6	0.1
PANSS negative	20.0 ± 12.1	22.0 ± 10.6		0.1	1.0
PANSS global	33.9 ± 18.6	34.8 ± 20.1		0.4	0.7
PANSS total scores	76.9 ± 41.0	76.1 ± 42.2		0.8	0.5