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Psychosis effect on hippocampal reduction in schizophrenia

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ABSTRACT

Introduction: In schizophrenia, disruption of the neurodevelopmental processes may lead to brain changes and subsequent clinical manifestations of the illness. Reports of the progressive nature of these morphological brain changes raise questions about their causes. The possible toxic effects of repeated stressful psychotic episodes may contribute to the disease progression.
Objectives: To analyze the influence of illness duration and previous psychotic episodes on hippocampal gray matter volume (GMV) in schizophrenia.
Methods: We performed an analysis of hippocampal GMV correlations with illness duration, number of previous psychotic episodes, and age in 24 schizophrenia patients and 24 matched healthy controls.
Results: We found a cluster of GMV voxels in the left hippocampal tail that negatively correlated with the number of previous psychotic episodes, independent from the effect of age. On the other hand we found no effect of illness duration independent of age on the hippocampal GMV. Finally, we found a cluster of significant group-by-age interaction in the left hippocampal head.
Conclusions: We found an additive adverse effect of psychotic episodes on hippocampal morphology in schizophrenia. Our findings support toxicity of psychosis concept, together with etiological heterogeneity of brain changes in schizophrenia.

1. Introduction

Since Emil Kraepelin first classified it in 1899, schizophrenia had been considered a neurodegenerative process, as expressed in the term "dementia praecox". This theory was later abandoned because of the poor findings of neurodegenerative changes in the brain similar to the "classic" degenerative disorders such as Alzheimer's disease. A neurodevelopmental hypothesis became popular. The first and frequently replicated finding in the brain in schizophrenia was ventricular enlargement. As the enlargement seemed not to progress during the course of the disease (Vita et al., 1994), the predominant opinion was that there are neuropathologic conditions that should arrest early in life and not progress (de Haan and Bakker, 2004).

With the development of neuroimaging techniques, more findings of changes in several regions of the brain in schizophrenia have been reported. The most robust abnormalities of the brain that were detected in volumetric studies include lateral ventricular enlargement, third ventricle enlargement, reduction of the medial temporal lobe structures (amygdala, hippocampus, parahippocampal gyrus) and neocortical temporal lobe regions (Shenton et al., 2001). In a meta-analysis of voxel-based morphometric studies (Honea et al., 2005), the most frequently reduced areas were the left superior temporal gyrus and left medial temporal lobe. Fifty percent of the studies reported volumetric decreases in the left parahippocampal gyrus, right superior temporal gyrus, left inferior frontal gyrus, and left medial frontal gyrus. Hippocampal reduction therefore represents one of the most frequent findings in schizophrenia; however, there are reports of negative findings, especially in first episode schizophrenia patients (Kaspárek et al., 2007; Olabi et al., 2011). This might be due to the neurobiological heterogeneity of the schizophrenia concept or due to the dynamic nature of the morphological changes.

Evidence of the progression of at least some of the brain changes has gradually accumulated (Olabi et al., 2011). Natural age-related changes of gray matter volume as seen in healthy subjects follow a different trajectory in schizophrenia (van Haren et al., 2008a,b). The dynamic changes of brain morphology seem to parallel disease development: gradual hippocampal volume reduction was observed at the time of transition to psychosis with further progression in later stages of the illness (Velakoulis et al., 2000). The course of schizophrenia probably has several phases that have different effects on the brain tissue: neurodevelopmental abnormalities followed by the active phase of

Abbreviations: AAL, automatic anatomical labeling; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; BDNF, brain-derived neurotrophic factor; CA, cornu ammonis; DG, dentate gyrus; FDR, false discovery rate; FWE, family-wise errors; HPA, hypothalamo-pituitary axis; GABA, gamma-amino butyric acid; GLM, general linear model; GMV, gray matter volume; MARTA, multi-acting receptor-targeted antipsychotics; MRI, magnetic resonance imaging; NMDA, N-methyl D-aspartate; SD, standard deviation; SDA, serotonine-dopamine antagonists; SPM, statistical parametrical mapping; VBM, voxel-based morphometry; VGLUT1, vesicular glutamate transporter 1; WFU, Wake-Forrest University.

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neurodegeneration and a plateau phase. It is thought that the active phase (the window of deterioration) lasts for 5–10 years and that it begins in the prodromal phase of the disease. Most of the decline in functioning occurs during this period (McGlashan, 1998). The supposed neuroprotective effect of initial antipsychotic treatment on brain tissue could contribute to the pattern of findings (van Haren et al., 2008a). Because of the lasting imperfections of this theory, i.e., the lack of an explanation of the plateau phase and the onset of degenerative changes in the prodromal phase, Woods (1998) proposed the unitary model, based on the progressive developmental theory, that suggests involvement of abnormalities of ongoing "late" neurodevelopmental processes involved in brain plasticity and neurite remodeling, such as synaptic or neuritic pruning.

However, the nature of the progression of brain changes is still unclear. According to findings by Loebel et al. (1992), poorer outcomes in longer durations of untreated psychosis were frequently found, indicating a toxic influence of the untreated psychosis. (McGlashan, 2006). There are reports of the adverse effects of an increasing number of previous psychotic episodes on the brain, independent from the pure illness duration (Rizos et al., 2010; Seok Jeong et al., 2005). The hypothesis of neurotoxicity has been bolstered by basic discoveries about the adaptability of neuronal connections and the viability and reproducibility of neurons in the adult brain (for review, see Weinberger and McClure, 2002). Pantelis et al. (2005) suggested a number of processes occurring at different stages of development, including an early developmental lesion that may render the brain vulnerable to anomalous late (particularly postpubertal) neurodevelopmental processes. The psychosis may have an additive neurotoxic effect on the brain changes induced by neurodevelopmental processes. These anomalous processes interact with other well-known causative factors, e.g., substance use, stress and dysregulation of HPA axis function. The combination of these factors may have a neuroprogressive squeal that may be neurodegenerative.

Hippocampal volume changes dynamically during the course of the illness (Velakoulis et al., 2000). It is a structure sensitive to the neurotoxic effects of stress and glutamate hyperactivity (McEwen, 1999), and it is the subject of change in the context of antipsychotic treatment (McClure et al., 2006). The question arises whether there are several different processes that contribute to the morphological changes in schizophrenia. In order to analyze how illness – and psychosis – related processes interact with the hippocampal morphology we performed a cross-sectional MRI morphometric study and analyzed the expression and anatomical localization of disease-related changes as correlations between illness duration (as a marker of a continuous processes) and hippocampal GMV, and as correlations between hippocampal morphology and the number of previous psychotic episodes (as a marker of the neurotoxic effect of psychosis), irrespective of the effect of age. Because of the complicated hippocampal anatomy with functional and histological heterogeneity we performed a voxel-wise analysis of hippocampal GMV to study the regional heterogeneity of the different effects.

2. Methods

2.1. Subjects

In all, 24 schizophrenia patients and 24 age, sex, and handedness (all subjects were right-handers) matched healthy controls were included in this study. The diagnosis of schizophrenia was verified using the M.I.N.I. interview (Sheehan et al., 1998). Details on the demographic parameters are given in Table 1. The exclusion criteria were drug dependence (based on the M.I.N.I. interview; subjects with drug abuse, but not dependence, were included), neurological or somatic conditions affecting structure or function of the brain, and contraindications for MRI examination.

We performed a systematic analysis of health care documentation (including outpatient and inpatient records), data provided by relatives, care providers, and subjects to obtain information on illness duration (measured in years from the initial diagnosis of schizophrenia), and number of previous psychotic relapses.

Healthy subjects were recruited from the community, local staff, and medical students. They were screened for axis I psychiatric conditions using the M.I.N.I. interview. Details of the demographic parameters are given in Table 1. The exclusion criteria were drug dependence, family history of axis I psychiatric conditions, neurological or somatic conditions affecting the structure or function of the brain, and contraindications for MRI examination.

The study was approved by the local ethics committee and all subjects signed an informed consent form.

2.2. MRI measurement

All subjects underwent MRI examination of the brain in a 1.5 T Phillips Achieva scanner (T1 fast field echo 3D sequence, in-plane resolution 0.9 × 0.9 mm, acquisition matrix 300 × 234 pixels, slice thickness 0.8 mm, TR = 25 ms, TE 4.09 ms, flip angle 30 degrees).

2.3. Image postprocessing

All images were processed using SPM 8 software (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/), with VBM 8 toolbox (http://dbm.neuro.uni-jena.de/vbm8/). Non-brain voxels were identified and removed using unified segmentation method (Ashburner and Friston, 2005), brain images were registered to a high-resolution MNI template (DARTEL template in Montreal Neurological Institute stereotactic space, an implicit template of VBM8 toolbox, derived from 550 healthy control subjects of the IXI database: http://www.brain–development.org) using high-dimensional diffeomorphic non-linear transformation (Ashburner, 2007). Consequently, whole brain images were tissue segmented into gray matter images with the use of maximum a posterior technique independent from prior information on tissue probabilities that accounts for intensity inhomogeneities (Rajapakse et al., 1997), followed by a partial volume estimation with a mixed model (Tohka et al., 2004), and with employment of denoising methods of spatially adaptive non-local means denoising filter (Manjon et al., 2010) and Markov Random Field (Rajapakse et al., 1997). Gray matter images were modulated with the Jacobian determinant of the deformation field, resliced to 1.5 mm isotropic voxels, and finally convoluted with 8 × 8 × 8 mm full-width at half maximum Gaussian kernel.

2.4. Statistical analysis

We performed a voxel-wise anatomically constrained region of interest analysis focused on the left and right hippocampus. Voxels with

Table 1
Demographic characteristics.

Group	No.	Age (SD)	Gender (M/F)	Abuse (%)	FH-SCH (%)	Education P/S/U (%)	Unemployment (%)	Marital status Si/Ma/Di (%)
HC	24	31.8 (9.2)	11/13	0*	0	1/12/11* (4.2/50/45.8)	2* (8.3)	18/5/1 (75/20.8/4.2)
SCZ	24	32.8 (9.7)	11/13	5 (21)	3 (13.6)	4/17/3 (16.7/70.8/12.5)	16 (69.6)	16/4/3 (69.6/17.4/13)

HC-healthy controls, SCZ-schizophrenia patients; M-male, F-female; R-right, M-mixed, L-left; FH-SCZ-family history of schizophrenia; P-primary, S-secondary, U-university education; Si-single, Ma-married, Di-divorced. * $p < 0.05$.