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Magnetic resonance spectroscopy investigations of functionally defined language areas in schizophrenia patients with and without auditory hallucinations

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ABSTRACT

Background: Cerebral dysfunction occurring in mental disorders can show metabolic disturbances which are limited to circumscribed brain areas. Auditory hallucinations have been shown to be related to defined cortical areas linked to specific language functions. Here, we investigated if the study of metabolic changes in auditory hallucinations requires a functional rather than an anatomical definition of their location and size to allow a reliable investigation by magnetic resonance spectroscopy (MRS).
Methods: Schizophrenia patients with (AH; n = 12) and without hallucinations (NH; n = 8) and healthy controls (HC; n = 11) underwent a verbal fluency task in functional MRI (fMRI) to functionally define Broca's and Wernicke's areas. Left and right Heschl's gyri were defined anatomically.
Results: The mean distances in native space between the fMRI-defined regions and a corresponding anatomically defined area were 12.4 ± 6.1 mm (range: 2.7–36.1 mm) for Broca's area and 16.8 ± 6.2 mm (range: 4.5–26.4 mm) for Wernicke's area, respectively. Hence, the spatial variance was of similar extent as the size of the investigated regions. Splitting the investigations into a single voxel examination in the frontal brain and a spectroscopic imaging part for the more homogeneous field areas led to good spectral quality for almost all spectra. In Broca's area, there was a significant group effect ($p = 0.03$) with lower levels of N-acetyl-aspartate (NAA) in NH compared to HC ($p = 0.02$). There were positive associations of NAA levels in the left Heschl's gyrus with total ($p = 0.03$) and negative ($p = 0.006$) PANSS scores. In Broca's area, there was a negative association of myo-inositol levels with total PANSS scores ($p = 0.008$).
Conclusion: This study supports the neurodegenerative hypothesis of schizophrenia only in a frontal region whereas the results obtained from temporal regions are in contrast to the majority of previous studies. Future research should test the hypothesis raised by this study that a functional definition of language regions is needed if neurochemical imbalances are expected to be restricted to functional foci.

Introduction

^{1}H Magnetic Resonance Spectroscopy (MRS) has been used in clinical and research investigations of human brain physiology and pathology for over two decades (Barker et al., 2009). Since it is currently not possible to acquire whole brain MRS measurements with high spatial resolution in a timeframe that is endurable for (living) subjects, regions of interest (ROIs) are commonly defined. Most often, the region to be examined is chosen based on pathological structural abnormalities or in extended brain areas presumed to be involved in the targeted patho-physiologic processes. In both cases, the region of interest (ROI) is chosen using anatomic landmarks. However, from functional brain studies it is well known that besides substantial individuality of cortical morphology (Ono et al., 1990; Uylings et al., 2005), there is considerable interindividual variability in terms of the exact location of cortical activation for specific brain functions (E.A. Allen et al., 2012; Burton et al., 2001; Fedorenko et al., 2010; Xiong et al., 2000). Hence, if metabolic disturbances are hypothesized to be restricted to or most expressed in limited areas representing specific brain function, the ROIs for MRS investigations have to be defined functionally in each subject. Furthermore, because most MRS studies use either single voxel (SV) localization techniques or spectroscopic imaging (SI) of single

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slices where the ROIs must be known and defined at the time of data acquisition, the functional definition of the ROI must usually precede MRS. Alternatively, spectroscopic whole brain analyses by multislice or 3D techniques (Maudsley et al., 2006), where ROIs can be chosen during data analysis, could be performed without knowledge of the exact region to be targeted, but these techniques are usually not considered to be as reliable and not as time-efficient for small focused ROIs, in particular when using short echo times. Since previous studies have shown dysfunctions in circumscribed cerebral areas related to the language system we investigated auditory verbal hallucinations (AVH) as a potential case of local limited metabolic imbalance.

It is well known that AVH comprise a critical domain in schizophrenia, including a low quality of life since about 30% of patients do not sufficiently respond to medication (Copolov et al., 2004; Shergill et al., 1998). Notably, 25% of patients with AVH had made serious suicide attempts driven by their voices (Hor and Taylor, 2010). Thus, a better understanding of the neural underpinnings of AVH might contribute to a better treatment regime (Homan et al., 2011; Kindler et al., 2013). However, an obstacle of a more sophisticated understanding of AVH lies in the complexity of the process possibly including anatomical, functional and neurochemical aspects and the corresponding complexity of investigation approaches. Several imaging studies found an association of speech- and language related cerebral regions and AVH. In an early functional magnetic resonance imaging (fMRI) study we showed that the cerebral activity in the primary auditory cortex during the experience of internal voices is comparable to the activation caused by external auditory stimuli (Dierks et al., 1999). We propose that this dysfunctional activity may account for the belief of externality of the voices the patients hear, which may be further supported by the measurement of auditory evoked potentials in EEG, where we found higher EEG activity in left temporal regions and lower AEP amplitudes during AVH compared to phases without AVH (Hubl et al., 2007). Thus, we suggested that pre-activation of the primary auditory cortex competes for processing resources with the external stimuli (Hubl et al., 2007) and that these alterations might be the microstructural basis responsible for the dysfunctional primary auditory cortex activity. A processing failure in Wernicke's area may promote a disturbed feedback loop reflected in altered connectivity of Broca's and Wernicke's areas (Hubl et al., 2004) and a pathological activation of Heschl's gyrus.

However, EEG and MRI cannot assess the molecular basis of schizophrenia and psychotic symptoms, and our understanding of the molecular changes in schizophrenia is essentially based on the observed effects of psychoactive drugs. MRS offers a tool to measure neurochemical alterations, here with respect to AVH.

With MRS, the chemical composition of cerebral tissue is determined non-invasively by measuring the magnetic resonance signal of hydrogen in specific metabolites (Barker et al., 2009; Jansen et al., 2006). The metabolite N-acetyl-aspartate (NAA) is considered a marker of neuronal viability and/or integrity. NAA concentrations are reduced in affected areas in neurodegenerative diseases (Adalsteinsson et al., 2000) and correlate with cognitive performance (Jung et al., 1999). With respect to schizophrenia, MRS may allow to disentangle the meaning of white matter and gray matter volume reductions which may stand for neuronal loss or dysfunction (Abbott and Bustillo, 2006). Although there are inconsistencies in the literature (Steen et al., 2005), most previous research found that in schizophrenia NAA is decreased in frontal and temporal regions and in the thalamus (Brugger et al., 2011). NAA concentrations in the thalamus and the duration of positive symptoms were negatively correlated in schizophrenia patients (Theberge et al., 2003). Martinez-Granados et al. (2008) found a decreased ratio of NAA to choline ratio in the thalamus of schizophrenia patients compared to healthy controls and in the right thalamus of hallucinating patients compared to not hallucinating patients and controls. In addition, hippocampal NAA levels have been reported to be decreased in hallucinating patients (Heckers, 2001).

The metabolite myo-inositol (mI) has been shown to be present in glial but not neuronal cells in vitro (Brand et al., 1993) and since gliosis may lead to increased mI concentrations, mI has been found to be increased in neurodegenerative diseases such as Alzheimer's disease (Miller et al., 1993). With respect to schizophrenia, an increase in mI concentrations compared to healthy controls would be compatible with the neurodegenerative hypothesis but has not been found as of yet (Delamillieure et al., 2002). Instead, most studies have shown that mI levels in schizophrenia are largely unaltered (as reviewed in Schwerk et al., 2014). In addition, there do not seem to be any published investigations into potential relations of mI content and presence of AVH, so investigations of this metabolite in AVH can be done only in an exploratory fashion.

In the current study, we used a verbal fluency (VF) task in fMRI to functionally define speech related ROIs (Broca's and Wernicke's areas) in each subject for a subsequent neurochemical analysis with MRS in two patient groups (AH: schizophrenia patients with AVH; NH: schizophrenia patients without AVH for the last 12 months) and a healthy control group (HC). In addition, left and right Heschl's gyri (HG) were defined anatomically. Thus, the four target ROIs for MRS were Broca's and Wernicke's areas (both on the left side) and left and right HG. Since Broca's area lies in the frontal part of the brain, where optimizing the magnetic field homogeneity is challenging, but the other 3 areas are in relative proximity with less stringent difficulties for field homogenization, the MRS signal acquisition was split into two parts. First, Broca's area was investigated by single voxel MRS, then the other 3 ROIs were examined by SI of a single slice, the position and orientation of which were defined by these 3 ROIs.

In accordance with previous findings of NAA being decreased in schizophrenia in frontal and temporal regions and in the thalamus (Brugger et al., 2011; Martinez-Granados et al., 2008), we hypothesized to find a relative reduction of NAA in the functionally defined Wernicke's area in hallucinating schizophrenia patients compared to patients without hallucinations and controls. In an additional exploratory analysis, we tested for metabolic changes in further metabolites, like mI, choline (Cho) and glutamate (Glu) or glutamate plus glutamine (Glx).

Methods and materials

Participants

The investigation was conducted in accordance with the Declaration of Helsinki and approved by the local ethics committee (Kantonale Ethikkommission Bern). To ensure informed consent, the investigator explained the aims and procedure of the study to the potential subject verbally, providing all important information. Then the potential subject was given written instructions as well as time to ask any questions. Only then the decision whether or not to participate in the study was made, and subjects provided written consent to participate in the study.

Three groups were investigated in the current study: AH ($n = 12$), NH ($n = 8$), and HC ($n = 11$). General inclusion criteria for patients were: aged between 25 and 50 years, right handedness, ICD-10 diagnostic criteria for schizophrenia or schizo-affective disorder, a history for schizophrenia of more than 5 years, no substance use other than nicotine, and the ability to give written informed consent. AH could but did not have to perceive AVH at the time of the measurement. According to their anamnesis (patients' files and clinical interview) these patients perceived AVH in most of their acute exacerbations (90%). NH did not experience AVH at the time of investigation nor in the previous 12 months and did not perceive AVH in most of their exacerbations (less than 10%). Individual psychopathology was assessed in a clinical interview involving the assessment of the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). All 3 groups were age- and gender-matched. Inclusion criteria for HC were: no current or previous neurological or psychiatric disorder, no severe somatic-medical disorder, no substance use other than nicotine, the ability to give written