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"Who is talking to me?" — Self–other attribution of auditory hallucinations and sulcation of the right temporoparietal junction

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ABSTRACT

Brain imaging research in schizophrenia has provided a better understanding of the neural basis of auditory hallucinations (AH). Recently, renewed interest in the phenomenology of AH raised questions related to their neural substrates. Hence, the neural basis of AH self/other attribution have yet to be investigated as beliefs regarding the origin of the voices is a cardinal feature of AH phenomenology. As the right temporoparietal junction (TPJ) and the inferior parietal lobule (IPL) play a key role in disentangling the origin of sensory events and in self/other distinction, we tested the hypothesis that the morphology of the IPL/TPJ area may be involved in AH self/other attribution. Magnetic resonance images of 39 right-handed patients with persistent auditory hallucinations and 19 healthy subjects were analyzed with sulcus-based morphometry. AH self–other attribution were found to be associated with the sulcal pattern of the posterior part of the Sylvian fissure, encompassing the IPL/TPJ area. The preference for the attribution of AH to self or to others could be associated with early neurodevelopmental events as the sulcal pattern is determined during fetal life and is stable after birth. Our study also raises basic cognitive questions regarding self-consciousness and suggest that impairments at a pre-reflexive level, leading to hearing his/her thoughts as voices ('I' level or feeling of agency), and a reflexive level leading to attribution belief ('Me' level or judgment of agency) are likely involved in AH.

1. Introduction

Brain imaging for schizophrenia research over the past two decades has provided a better understanding of the brain networks involved in auditory hallucinations (AH) (Jardri et al., 2013). Recently, renewed interest in the phenomenology of AH has shed light on the richness and variability of the clinical features of AH (Laroi et al., 2012; McCarthy-Jones et al., 2013; Stephane et al., 2003) and, in turn, raises new issues regarding the neural substrates underlying AH phenomenology. In Bleuler's seminal description of schizophrenia, he states that (Bleuler, 1950) "*The subjective conception of the hallucination is very variable. As a rule the patients ascribe the voices to people talking or to apparatuses* (…). *In some cases, the patients recognize the pathological nature of their hallucinations; particularly, the connection with or origin from their own thoughts are more or less known to many patients.*" This belief regarding the origin of the voices is a cardinal feature of AH phenomenology. In line with this classical description of AH attribution to self or to others, clustering analyses (Stephane et al., 2003) have shown that this clinical feature – ranging from the conviction that the voices are solely internally generated and related to self to the conviction that voices originate from external causes – is one of the three core phenomenological dimensions of AH. The other dimensions are spatial location and language complexity. The neural substrates of the language complexity of AH and the spatial locations of AH have already been investigated in schizophrenia patients. Indeed, brain imaging studies of AH have extensively reported altered structure and function in language brain regions (Allen et al., 2012), and two recent studies have investigated the anatomical (Plaze et al., 2011) and functional (Looijestijn

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et al., 2013) substrates of AH spatial location in schizophrenia. However, to our knowledge, the specific neural substrate of AH self/other attribution remains unknown. Studies in the field of visuo-motor agency have reported that the temporoparietal junction (TPJ) and the inferior parietal lobule (IPL), notably in the right hemisphere, play a key role in disentangling the origin of sensory events (Farrer et al., 2003; Ruby and Decety, 2001). More generally, these regions are involved in self/other distinction (Blakemore and Frith, 2003; Chaminade and Decety, 2002; Decety et al., 2002; Ruby and Decety, 2001). A recent fMRI study revealed differential activation in right IPL between 'self' and 'non-self' conditions in healthy subjects (Jardri et al., 2011) that was less marked in patients with schizophrenia due to an increased activation in the 'self' condition. Notably, this increased activation in schizophrenic patients was positively correlated with symptom severity.

In this context, we hypothesized a priori that the morphological variations of IPL/TJP area, implicated in self/other distinction, would be associated with variations of AH self/other attribution. To test this hypothesis, we used sulcus-based morphometry, as in our previous investigation of the neural basis of AH phenomenology (Plaze et al., 2011), to compare structural magnetic resonance images (MRIs) of patients with AH self/other attributions that ranged from the conviction that their AH were solely internally generated and related to self to the belief that their AH originated from external agents.

2. Materials and methods

2.1. Participants

A total of 39 right-handed (Annett, 1970) patients with schizophrenia (DSM-IV-R) and persistent auditory hallucinations (24 males, mean ± SD age 33.2 ± 9.1 years, range 22–49 years) were recruited. Hallucinations were considered persistent if they had lasted for more than one year despite adequate pharmacological treatment and had occurred daily during the past three months. Exclusion criteria included substance abuse or dependence, any other DSM-IV-R axis I diagnosis, severe head injury, neurological disorders, or contraindications to MRI scanning. Study approval was provided by the Paris (Pitié-Salpétrière) ethics committee. Written consent was obtained from all participants following a complete description of the study. Auditory hallucinations were evaluated using the 11-item Auditory Hallucinations subscale of the Psychotic Symptom Ratings Scale (PSYRATS (Haddock et al., 1999)), which included a semi-structured interview by two independent senior psychiatrists (JLM, MP; inter-rater reliability R = 0.76) who assessed the items retrospectively over a 2-week period. AH self/other attribution was assessed using the 4-level PSYRATS item #5: "1: *Believes voices to be solely internally generated and related to self*", "2: *Holds <50% conviction that voices originate from external causes*", "3: *Holds ≥50% conviction (<100%) that voices originate from external causes*", "4: *Believes voices are solely due to external causes (100% conviction)*". Patients were grouped by PSYRATS score; 11 patients had a score of 1, 8 patients had a score of 2, 8 subjects had a score of 3, and 12 subjects had a score of 4. The severity of the clinical symptoms was also assessed using the Scale for the Assessment of Positive Symptoms (SAPS (Andreasen, 1984)) and the Scale for the Assessment of Negative Symptoms (SANS (Andreasen, 1983)). All patients were treated with conventional or atypical antipsychotic drugs. Details of the demographic and clinical characteristics are reported in Table 2.

2.2. MRI acquisition

High-resolution T1 anatomical images were acquired using a 1.5 T General Electric Signa System scanner (General Electric Medical Systems, Milwaukee, WI, USA) using a spoiled gradient (SPGR) sequence that provided a high contrast between gray and white matter (3-D gradient-echo inversion-recovery sequence, Ti = 2200 ms, TR = 2000 ms, flip angle 10°, FOV = 24, 124 slices of 1.2 mm thickness, acquisition time = 6 min). Conjugate synthesis combined with interleaved acquisition resulted in 124 contiguous double-echo slices with voxel dimensions of $0.85 \times 0.85 \times 1.2$ mm^3. These MRIs were adapted for the reconstruction of the fine individual cortical folds required for sulcus segmentation.

2.3. MRI analysis

The morphology of the IPL/TPJ area was described using a three-dimensional reconstruction of its sulcal folding pattern. For the raw MRI of each subject, the cortical sulci were first automatically segmented (Mangin et al., 2004) using the Brainvisa software 4.1 (http://brainvisa.info/) with the standard parameters. The cortical sulci corresponded to medial surfaces located in the cerebro-spinal fluid between the two cortical banks. This definition of the sulci provides a stable localization that is not affected by variation in the gray matter/white matter contrast or sulcus opening or thickness (Mangin et al., 2004).

The sulcal folding pattern of the IPL/TPJ area was assessed using the Steinmetz classification of the posterior part of Sylvian fissure (pSF) (Steinmetz et al., 1990) (Fig. 1). Briefly, Type I, the most frequent pSF type, has both a horizontal branch (planum temporale) that forms the superior surface of the superior temporal gyrus and a vertical branch (planum parietale) that ascends into the supramarginal gyrus. Possible pSF variants include Type II, in which the Sylvian fissure lacks a vertical branch; Type III, in which the horizontal branch extends posteriorly to the supramarginal gyrus into the angular gyrus; and Type IV, in which the horizontal branch is absent as the vertical branch connects the post-central sulcus anterior to the supramarginal gyrus. The sulcal pattern classification (inter-rater reliability: Cohen's $\kappa = 0.92$) was performed blind to the patient HAV self-attribution score.

To validate our pSF classification procedure based on the Steinmetz types, the sulcal pattern distribution from a sample of healthy subjects (19 right-handed subjects, 11 men, 8 women; mean age = 31.9 years, SD = 7.4) was compared to the normative data derived from the analysis of 20 MRI of healthy volunteers obtained by Steinmetz et al. (1990). The absence of psychiatric symptoms in healthy subjects was confirmed by a senior psychiatrist using the Mini-International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998). The healthy subject group did not differ significantly from the patients in respect to age (Student's $T = 0.66$, $df = 55$, $p = 0.51$) or gender ($\chi^2 = 0.071$, $p = 0.79$).

2.4. Statistical analysis

To examine the extent to which pSF sulcal pattern (a categorical variable, i.e., Type I, Type II, Type III, Type IV) was associated with AH self-attribution, we analyzed the sulcal pattern distribution among the four subgroups of patients, defined from the 4-level PSYRATS item #5 score, using Pearson's χ^2 test with a Monte-Carlo simulated p-value based on 2000 replicates.

We first compared the sulcal pattern distribution between patients who believe that AH are solely or mostly due to external causes ('self' and 'mostly self' subgroups) and patients who believe that AH are solely or mostly internally generated and related to self ('non self' and 'mostly non self' subgroups). Exploratory analyses were then performed to investigate differences between each subgroup pair. Finally, the sulcal pattern distribution in healthy subjects was compared to the whole patient group and to patient subgroups.

All statistical analyses were performed using the R 2.9 software (http://www.r-project.org).

3. Results

Table 1 and Fig. 2 summarize the pSF sulcal pattern distribution observed in healthy control subjects and in each subgroup of subjects.

The observed sulcal pattern distribution in the healthy control subjects was almost identical ($\chi^2 = 2.01$; $p = 0.58$) to the distribution