^{18}FDG PET in hallucinating and non-hallucinating patients

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Abstract

OBJECTIVE: The aim of the study was to detect whether the abnormal regional brain activity correlates with auditory verbal hallucination-proneness (AVH) in a group of patients with schizophrenia and schizophrenia-related psychoses.
METHODS: 15 patients with prominent AVH (score for hallucination intensity – item 3 in the PANSS ≥4) and 15 control patients without AVH (item 3 PANSS score ≤2) underwent ^{18}FDG positron emission tomography at rest.
RESULTS: SPM group analysis revealed an increased uptake of ^{18}FDG in the right middle frontal gyrus (BA46) in subjects with high verbal hallucination score compared to non-hallucinating patients ($p<0.001$, uncorrected). Resting metabolism in BA46 positively correlated with the intensity of hallucinations (Spearman $r=0.57$; $p<0.001$).
CONCLUSIONS: The observed functional recruitment of the right prefrontal cortex in subjects with high hallucination score may reflect impairment in the integration of intended actions and sensory feedback resulting in misattribution of internal events to an external source. This mechanism may form the cognitive basis for AVH.

ORIGINAL ARTICLE

Abbreviations and units:

^{18}FDG	- 18-fluoro-deoxyglucosis
AVH	- auditory verbal hallucinations
BA	- Brodmann area
CGI	- Clinical Global Impression scale
DLFPC	- dorsolateral prefrontal cortex
EEG	- electroencephalography
fMRI	- functional Magnetic Resonance
ICD-10	- International Classification of Diseases – 10th Revision
MBq/kg	- MegaBequerels per kilogram
PANSS	- Positive and Negative Symptoms Scale
PET	- Positron Emission Tomography
rTMS	- repetitive Transcranial Magnetic Stimulation
SPECT	- Single Photon Emission Tomography
SPM	- Statistical Parametric Mapping

Introduction

Auditory verbal hallucinations (AVH) are probably one of the most frequent and challenging symptoms in schizophrenia [12]. Approximately two-thirds of patients experience the symptom sometimes during the course of their illness [11]. Despite extensive research carried out over the last decades, little is known about the neurobiology underlying this phenomenon. Recent functional brain imaging studies have demonstrated the involvement of the temporal and frontal cortical regions in AVH. These functionally interconnected areas are implicated in the generation and perception of overt verbal material along with inner speech and auditory mental imagery in healthy subjects [34,35]. Based on these findings, contemporary cognitive models conceptualize the auditory verbal hallucinations as derivations from inner speech that the given person misidentifies as "alien" through defective self-monitoring [18].

The last 15 years has shown that functional neuroimaging methods (PET, SPECT, and fMRI) are sensitive tools to detect the brain abnormity underlying AVH.

The functional imaging studies on AVH can be divided into five groups according to the experimental design employed. The first group uses correlations of regional blood flow or metabolism with AVH [8,10,25,31,40]. The second approach adopts a between-subject design comparing patients with hallucinations and healthy controls [15,26,28]. The third approach involves comparison of subjects with AVH and psychotic, non-hallucinating controls [9]. The fourth group of studies employs a within-subject design during one session comparing the hallucinations with a hallucination-free periods [23,34,37,41]. Finally, the fifth type of methodology utilizes a within-subject design (comparing the sessions during acute psychosis with hallucinations and a hallucination-free period) with respect to the therapy [27,29,38].

In our study we adopted the third and first methodological approaches. We expected the differences in the ^{18}FDG uptake within cortical (fronto-temporal, hippocampal, parahippocampal, insular, anterior cingulate) and subcortical (thalamus, striatum) structures [8,9,34,37] in high-PANSS hallucination score subjects comparing to non-hallucinating subjects with schizophrenia and schizophrenia-related psychoses.

Methods

Subjects

The study subjects were 15 right-handed subjects with prominent auditory verbal hallucinations (score of hallucination intensity – item 3 in PANSS ≥4) and 15 matched controls, right-handed patients without AVH (score of hallucination intensity – item 3 in PANSS ≤2) examined with PET at the Prague Psychiatric Centre [20].

All patients were diagnosed by two trained psychiatrists according to the ICD-10 classification. All subjects were of Caucasian origin. We tried to match patients for age, gender, laterality [2], education, number of hospitalizations, type of antipsychotic medication (first or second generation) and duration of the illness. The clinical symptom severity was assessed with the Clinical Global Impression scale (CGI) and Positive and Negative Symptoms Scale (PANSS) [21]. Subjects were evaluated within ±1 day of the PET scan. The exclusion criteria were: significant medical problems, history of head trauma, alcohol or drug abuse within the last 6 months, and EEG or brain scans (magnetic resonance or computer tomography) pathology. The study design was approved by the local ethics committee and written informed consent was obtained from all participants. Demographic and clinical data of both groups are summarized in the Table 1.

PET procedure

The regional brain metabolism was investigated using the ^{18}FDG PET. Patients fasted for a minimum of 6 hours before the examination. In a dimly-lit and quiet room, 3 MBq/kg of ^{18}FDG were administered via peripheral vein catheter. The patients then rested for 30 min. in the same room. This condition was previously described as Random Episodic Silent Thinking (REST) [1]. Then a 2D "hot" transmission scan of the brain was performed, lasting between 5 and 10 minutes. Transmission scanning time was corrected to allow for decay of the transmission sources. The data were acquired using the ECAT EXACT 922 (CTI/Siemens, Knoxville, TN) PET scanner. 3D emission scanning lasted 15 minutes. The data acquired were reconstructed by iterative OS-EM algorithm (matrix: 1282, brain mode, 47 slices, zoom: 2, subsets: 16, iterations: 6, Hann filter: 5 mm) and implemented using ECAT 7.2 software.

PET data analysis and statistics

The data analysis was performed using SPM99 (http://www.fil.ion.ucl.ac.uk/spm) implemented in Matlab (Mathworks, USA). The PET scans were converted into the Analyze format, interpolated from 47 to 68 slices and normalized into standardized stereotactic space by the use of bilinear sinc interpolation. The PET images

Table 1. The demographic and clinical characteristics of the two subject groups

		High-PANSS item 3 hallucination score group (n=15) Median (CI 95%)	Non-hallucinating group (n=15) Median (CI 95%)
Gender (male/female)		5/10	6/9
Age (years)		26 (23.5–34.5)	27 (24.0–33.5)
Handedness (Annett score)		15 right-handed	15 right-handed
Education (years)		12 (10.4–12.7)	12 (11.2–12.9)
Duration of illness (months)		30 (19.3–55.6)	13.7 (13.6–62.4)
ICD-10 diagnosis		11 schizophrenia, 3 schizophreniform, 1 schizoaffective	10 schizophrenia, 5 schizophreniform
PANSS item 1 score		3 (2.6–4.2)	3 (2.3–3.7)
PANSS item 2 score		2 (1.7–3.1)	3 (2.0–2.9)
PANSS item 3 score		4 (4.2–5.0)*	1 (1.1–1.7)
PANSS item 4 score		1 (1.3–2.5)	1 (1.0–2.1)
PANSS item 5 score		1 (1.1–2.1)	1 (1.0–2.1)
PANSS item 6 score		3 (2.6–4.1)	3 (2.4–3.6)
PANSS item 7 score		1 (0.9–1.6)	1 (1.1–2.0)
PANSS (P)		17 (15.9–21.1)†	13 (12.3–16.6)
PANSS (N)		17 (13.8–21.6)	18 (14.6–21.2)
PANSS (G)		40 (33.0–43.2)	37 (32.4–38.7)
PANSS (total)		72 (64.2–83.3)	67 (62.1–73.9)
CGI score		4 (3.8–5.0)	4 (3.8–4.8)
Current antipsychotic medication	**First generation**	2 haloperidol 1× perphenazine 1×	2 fluan×ol 2×
	Second generation	12 risperidone 3× quetiapine 2× clozapine 2× olanzapine 2× sulpiride 1× zotepine 1× ziprasidone 1×	10 risperidone 8× quetiapine 2×
	drug-naive	1	3

* - Mann-Whitney U Test p <0.001, † - Mann-Whitney U Test p <0.005

were smoothed with an isotropic Gaussian filter (full width at half maximum of 12 mm). The data-preprocessing procedure resulted in the generation of a spatially normalized image of ^{18}FDG uptake for every voxel in 68 horizontal slices through the brain.

The two sample t-test was used to determine the differences in the PET ^{18}FDG uptake between the high-AVH group and non-hallucinating patients. Global intensity differences were corrected using proportional scaling (global mean to 50, analysis threshold 0.8) and global calculation was performed by the mean voxel value. Statistical parametric maps of T-values were created and the anatomical locations of the activated areas were determined in normalized space. Every peak was defined by the number of contiguous significant voxels that constitute the peak and by the standard coordinates of the Montreal Neurological Institute (MNI). Locations reported by SPM in MNI coordinates were converted into Talairach coordinates [39] by the transform specified in the mni2tal.m program. These coordinates were used to determine the nearest gray matter (region and corresponding Brodmann area) using the Talairach Daemon program version 1.1 [22].

Voxels at a threshold of p<0.001 (uncorrected) were displayed as significant. The voxel clusters surviving thresholds smaller than 10 voxels were excluded.

To eliminate unexpected between-group differences in domains other than hallucinations, correlation analysis

(Spearman correlation) of regional glucose metabolism with the individual PANSS item 3 hallucinatory score was carried out. The analysis was restricted to voxels in which the group comparison revealed differences at p<0.001, uncorrected. Mann-Whitney U Test was used to compare demographic and clinical data of both groups.

Results

There were no between-group differences in age, gender, laterality, years of education, number of hospitalizations, type of antipsychotic (first or second generation), duration of schizophrenia or in the PANSS scores other than AVH, or CGI score. As expected, both groups differed significantly only on PANSS item 3 and the positive sub score of PANSS (Mann-Whitney U test, two sided p exact <0.001 and <0.005 respectively) (Table 1).

SPM group analysis revealed increased uptake of ^{18}FDG in the right middle frontal gyrus (Figure 1) in the high-AVH group compared to the non-hallucinating group (BA46, Talairach coordinates 46 42 22, p<0.001 uncorrected, Z score 4.01, cluster size *(k)* 224). The intensity of hallucinations positively correlated with the ^{18}FDG uptake in this region (Spearman r= 0.57; p<0.001). We did not detect any decreased ^{18}FDG uptake in the high-AVH subjects compared to the non-hallucinating patients

Discussion

The study was designed to explore the differences in cerebral metabolism between the two groups of right-handed patients with schizophrenia who differ solely according to the presence or absence of auditory hallucinations. Our data suggest that extreme severity of auditory verbal hallucinations is accompanied by increased glucose metabolism within the right middle frontal gyrus (BA46) of dorsolateral prefrontal cortex (DLPFC).

Our study results differ from the findings of many previous studies involving subjects with AVHs. Although activation of the DLFPC along with other cortical and subcortical structures was previously reported in acutely hallucinating patients with schizophrenia compared to healthy controls [10] or to psychotic, non-hallucinating controls respectively [8, 9], majority of studies confirmed evidence for the prominent involvement of the temporal cortex mainly in the left hemisphere, including primary and secondary auditory areas in the experience of AVHs [23,34,36,37].

Nevertheless, in those studies the activation of auditory cortices has been detected during acute experience of AVHs. It is presumed that in the temporal course of AVHs, activation in widely distributed cortical regions may precede the engagement of regions implicated in the perception of auditory verbal material residing in the sensorial cortex within both temporal gyri [36]. The differences in the abovementioned findings presumably stem from the methodological approach adopted in our study, since we intended to examine whether the long-term background metabolic brain activity correlates can be attributed to AVH-proneness, rather than to determine the metabolic correlates of an acute hallucinatory state.

There is considerably less consistency concerning the involvement of a network of brain regions beyond the temporal cortex that correlate with the generation of AVH. Regions repeatedly implicated include the left hippocampal formation [13,37], the striatum and thalamus [37,42], and the anterior cingulate cortex [23,37].

The isolated right-hemisphere activation in the DLPFC found in our study thus warrants closer scrutiny.

Previous studies in healthy subjects have shown the critical role of the right hemisphere in discrimination of representations that pertain to self-intended actions from those that refer to actions executed or intended by others. In a fMRI experiment, a right fronto-parietal network was selectively activated when a sudden mismatch between one's own observed and performed hand action occurred and establishment of self-attribution of visually observed actions was violated [24]. Right parietal areas have been associated with discriminating self and others in mental imagery tasks in a PET study [30]. In another PET study with healthy subjects, the activity of the inferior part of the parietal and frontal lobe, specifi-

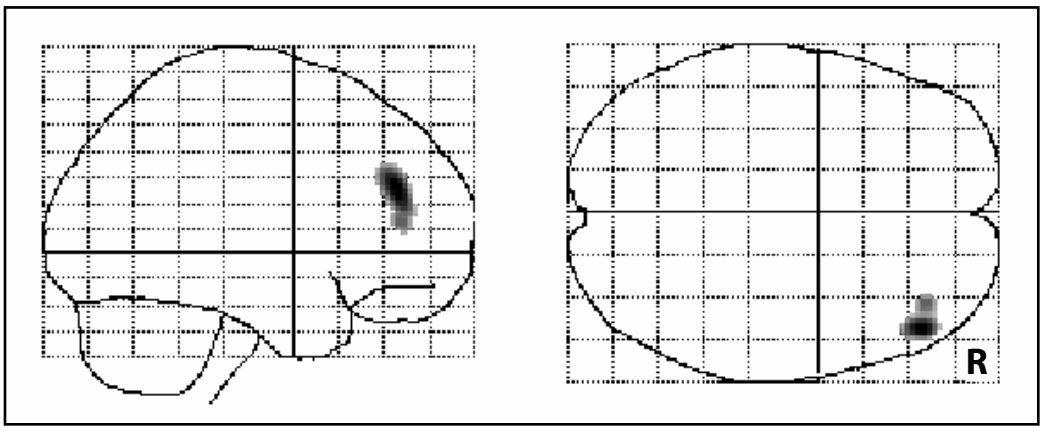

Figure 1. Statistical parametric map (SPM) showing area of significant difference in the right middle frontal gyrus (BA46) between the high-PANSS item 3 hallucination score subjects compared to non-hallucinating patients (p<0.001, uncorrected). "R" indicates the right side.

cally on the right side, was modulated by the degree of discrepancy between the movement executed and the movement of a virtual hand presented on the screen [16].

There is also a possibility that the frontal and parietal areas in a network mediating self-attribution subserve different functions. Although bilateral recruitment of the DLPFC is associated with a wide scope of cognitive functions (especially in linking short-term memory representations to goal-directed motor behavior), the strongly lateralized right DLPFC activity in right-handed subjects may probably underlie a detection of conflicts between intentions and the senses [24]. In a series of sophisticated experiments conducted by Gereon Fink and colleagues [17], healthy volunteers practiced Luria's bimanual co-ordination task under manipulation by a mirror of visual feedback from both hands. Using PET, authors primarily addressed the question, which brain regions are involved in actively monitoring the match between current intention and distorted sensory feedback. The study confirmed the pivotal role of the right DLPFC (BA 9/46) in monitoring conflict between motor intentions and their sensory/perceptual consequences. During the task the right DLPFC was specifically engaged independent of the hemispace to which attention was directed. Additional cues on the specific role of the right prefrontal cortex stem from extensive functional imaging research done in a verbal episodic memory domain. These results fit well with the assumption that the right prefrontal cortex is involved in monitoring operations, including the evaluation and verification of recovered information [7]. These findings are also consistent with the notion of a specific role of the right DLPFC (BA 9, 46) together with right frontopolar (BA 10) and ventrolateral areas (BA 47) in the attribution of familiarity of objects during the memory retrieval process [14].

Taken together, the activity seen in the right DLPFC in the abovementioned studies could be related to the feeling of loss of agency (and thus familiarity) associated with the discrepancy between intended actions and sensory feedback. In a broad sense, this particular conflict underlies hallucinatory experience. According to one of the influential cognitive models, hallucinations and other positive symptoms can be conceptualized as resulting from a breakdown in the system monitoring the current intention to make actions including the generation of inner speech [6]. As a consequence, internally generated thoughts or images are mistaken for externally generated events. This forms a basis for hallucinatory experience.

The prefrontal neuronal pathology in subjects with schizophrenia, which is mostly prominent in the dorsolateral prefrontal cortex (BA areas 9, 46) as confirmed by postmortem neuropathological studies [3,32,33] or magnetic resonance spectroscopy [4,5], underlines further the specific role of this cortical area in the neurobiology of schizophrenia.

Additionally, in a recent morphometric MRI study, the most consistent correlation between the severity of AVH in schizophrenia and volume reduction was detected in the right middle/inferior frontal gyrus (BA 45/46) together with the reduction in the left transverse temporal and inferior supramarginal gyrus [19].

There are dozens of studies using functional neuroimaging methods to find a neural correlate of hallucinations but previously only two [8,9], and now our study have used ^{18}FDG PET. The temporal resolutions of ^{18}FDG are much longer (45 min.) than those of fMRI (approx. 7 s) or PET using O^{15} (approx. 2 min.). ^{18}FDG PET reflects longer time period and thus could detect more stable brain abnormality that underlies hallucinations. Hypermetabolism in the right frontal cortex is in agreement with the previous FDG PET studies [8,9].

There are several caveats to our findings. First, we used an uncorrected threshold P value, at $p<0.001$, so we can not exclude the possibility of false positive findings. On the other hand, using the uncorrected threshold in area which is involved in the pathophysiology of hallucinations appears to be sufficient. Second, the between-group differences can be attributed to the different antipsychotics or other unidentified differences in psychopathology not measured by PANSS. Third, the raters were not blind with respect to antipsychotic therapy. Fourth, we have no co-registration MRI scans and area of detected differences can be only estimated.

In conclusion, our study suggests a role of the right DLPFC in the auditory verbal hallucination proneness. Observed increased glucose metabolism in the right DLPFC, (Brodmann area 46) in patients with high-PANSS hallucinatory score compared to non-hallucinating patients may relate to the dysfunction within this area resulting in misattribution of internal events to an external source. The identification of the impaired area can help to target novel therapeutic interventions, such as repetitive transcranial magnetic stimulations (rTMS), that lead to the inhibition of the underlying tissue.

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