Functional connectivity in healthy subjects with auditory verbal hallucinations

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Auditory verbal hallucinations (AVH) are a core feature of schizophrenia. Previous studies have provided evidence for dysfunctional integration of language regions to underlie AVH. However, schizophrenia is a complex syndrome consisting of psychotic, cognitive and negative symptoms. In order to learn whether this mechanism plays a causal role in the pathophysiology of AVH, the "pure" form of AVH should be investigated, which can be found in healthy subjects with AVH. Functional integration was assessed with psychophysiological interactions (PPI's) in 10 healthy subjects with AVH, 10 schizophrenia patients and 10 healthy controls matched for age, handedness and education. Subjects were scanned while covertly performing a paced letter fluency task. Schizophrenia patients and healthy subjects with AVH displayed dysfunctional connectivity between the left anterior cingulate cortex (ACC) and the left dorsolateral prefrontal cortex (DLPFC) and between the left inferior frontal gyrus (IFG) and the left superior temporal gyrus (STG). Additionally, dysfunctional connectivity between the left ACC and the left STG was found in the schizophrenia patients. These findings suggest a dysfunction between the production and the perception of speech in healthy subjects with AVH and schizophrenia patients. Furthermore, the difference between healthy subjects with AVH and schizophrenia patients provides an explanation why healthy subjects with AVH can execute some control over their hallucinations, in contrast to schizophrenia patients.

Keywords: Auditory verbal hallucinations, language, functional connectivity, fMRI

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1. Introduction

Auditory verbal hallucinations (AVH) are a common symptom in several psychiatric disorders and a core feature of schizophrenia in which they occur with a prevalence of 60% (Nayani & David, 1996). Clarity on the basis of the underlying pathology has not been provided yet. Previous studies have provided testable models, relating AVH to a language dysfunction (Hoffman, 1986; Frith & Done, 1988). Since elementary language functions, the production and perception of speech, are intact in subjects with AVH, disruption of functional language areas is not likely. However, the dysfunctions could well be derived from the integration of regions implicated in the production and perception of speech. One major theory looking at dysfunctional integration as the underlying basis of AVH has been proposed by Frith (1992). According to Frith (1992), hallucinations can be considered as a mis-attribution of internally generated speech to an outside agency. Evidence that speech is formed during AVH stems from studies that show that AVH are companioned by increased electro-myographic activity of the speech muscles (Grossberg, 2000) and increased activity of speech production regions (McGuire et al., 1993; Dierks et al., 1999). The mis-attribution is thought to arise from a dysfunction of the corollary discharge. The corollary discharge functions as an efferent copy of the formed speech which is send to the auditory cortex preparing it for perceiving speech as self-generated (Creutzfeldt et al., 1989). Corollary discharges are thought to be send from the frontal speech producing regions (the left inferior frontal gyrus, IFG), via the left anterior cingulate cortex (ACC) to the speech perception regions (left superior temporal gyrus, STG) through the so-called Fronto-cingulo-Temporal (FCT) circuit. In this circuit the left ACC is presumed to serve as a relay station between frontal areas sending information about produced speech and the left STG, enabling the disentanglement of external and internal speech.

The problem in this approach, however, stems from the fact that in this model the corollary discharge via the FCT circuit is necessary for speech perception and hence the AVH. If this process is dysfunctional inner speech would not arrive at the speech perception region and therefore would not be able to lead to AVH. In order to compensate for this shortcoming a second circuit is needed: the Cortico Cortical (CC) circuit. The CC circuit forms the connection crucial for the perception of self-formed speech. The CC circuit relates the left IFG to the left STG, establishing a direct connection between the speech production and perception regions. According to this hypothesis, the dual-route-self-monitoring-hypothesis, inner speech via the CC circuit generates the AVH related activity in the speech perception regions (Aleman et al., 2001). The CC circuit is then responsible for the perception of inner speech and the FCT circuit for inhibiting the perception of inner speech. The dual-route-self-monitoring-hypothesis predicts dysfunctions in both processes arising from hypo-activity of both circuits.

Functional neuroimaging studies in healthy subjects have revealed a distributed network during execution of a verbal fluency task grossly similar to the circuit mentioned in the dual-route-self-monitoring-hypothesis (Indefrey & Levelt, 2000). Verbal fluency involves the generation of words from verbal cues. The task can be presented in a variety of forms: auditory or visual; paced or unpaced; overt or covert and with random or constraint output (Curtis et al., 1998).

An additional circuit which has been implicated in prior studies exists of the connection between the left ACC and the left DLPFC (Fu et al., 2005, 2006). Previous studies on language in schizophrenia patients with AVH have provided support for the dual-route-self-monitoring hypothesis. Neurons in the STG, one of the regions implicated in the hypothesis, showed reduced responsiveness to self-produced speech in healthy subjects. (Creutzfeldt et al. 1989b; Muller-Preuss and Ploog, 1981; Frith et al., 1991b; Schlösser et al., 1998; Friedman et al., 1998; Hutchinson et al., 1999; Friston et al., 1991). This decreased responsiveness was not present in schizophrenia patients with AVH (Liddle, 1997; Frith et al., 1995; Yurgelun-Todd et al., 1996). Considering the integration of regions within this language network, several differences have been pointed out between healthy subjects and schizophrenia patients. Schizophrenia patients failed to show the pattern of connectivity present in controls between the left ACC and the left DLPFC (Spence et al., 2000; Fletcher et al., 1999). Additionally the left ACC didn't show the normal interaction with the left temporal region in schizophrenia patients. It displayed a quite different pattern characterized by widespread activation throughout prefrontal and parietal regions, with no significant activations in the primary or medial language regions in the left hemisphere (Boksman et al., 2005). The latter was replicated by Whalley et al. (2005) in subjects at high genetic risk for schizophrenia.

Additional findings on connectivity in schizophrenia originate from Diffusion Tensor Imaging studies (DTI). DTI is a technique to measure structural connectivity by assessing the osmotic movements of water within the white matter tracts. Recent studies found reduced fractional anisotropy (water diffusion) in the white matter tracts in the left Uncinate Fasciculus and reduced as well as increased fractional anisotropy in the left Arcuate Fasciculus (Burns et al., 2003; Hubl et al. 2004. The Uncinate Fasciculus is the largest of the three fiber tracts connecting the frontal and temporal lobes, and dissection studies have demonstrated that the bulk of these fibers connect the Orbital and Medial Prefrontal cortex (including ACC) to the Amygdala, Entorhinal Cortex and rostral STG (Petrides & Pandya, 1988; Morris et al., 1999). The Arcuate Fasciculus is a major association tract connecting large parts of the frontal association cortices with parietal and temporal association areas (Dejerine, 1895). It also forms the main connection between the left STG and the left IFG (Burns et al., 2003).

Summarizing the results described above, combined with the dual-route-self-monitoring-hypothesis, it can be concluded that in schizophrenia patients with AVH reductions in functional connectivity are present between the left ACC and the left DLPFC, the left ACC and the left STG and the left STG and the left IFG. These deviations may be predisposing factors for AVH. However one can not be certain that these anomalies can be derived from the AVH itself since most studies have been conducted in schizophrenia which is a complex syndrome consisting of psychotic, cognitive and negative symptoms. So far, healthy subjects with AVH as an isolated symptom have not been studied. Thus, abnormalities in schizophrenia may not be specifically related to hallucinations. In order to learn whether these mechanisms play a causal role in the pathophysiology of auditory hallucinations, the "pure" form of AVH should be investigated. This can be achieved by studying healthy subjects who experience AVH, without other psychotic or cognitive symptoms and who have no history of hospitalisation or chronic medication use. Recent studies demonstrated that 10% to 15% of individuals from the normal population report AVH (Van Os, 2000; Aleman et al., 2001). Based on these findings, it can be concluded that hallucinatory experiences form a continuum in the healthy population.

We hypothesize that the anomalies summarized above for the schizophrenia patients with AVH will also be evident in healthy controls with isolated AVH. Healthy subjects with AVH will therefore be compared to a group of schizophrenia patients with severe AVH, serving as a reference condition for our findings, and a group of control subjects. The connections expected to be dysfunctional are displayed in Figure 1. The task will consist of a verbal fluency task for comparison with previous studies (Boksman et al., 2005; Spence et al., 2000; Lawrie et al., 2002; Fu, 2005).

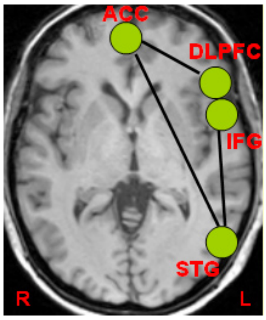

Figure 1. Graphic representation of the circuits expected to be dysfunctional in healthy subjects with AVH and schizophrenia patients.

2. Methods

2.1 Participants

Ten healthy controls without any psychotic experiences, ten healthy subjects with frequent AVH and ten schizophrenia patients were included. Participants from the first and the second group were informed about the study through a website built for this purpose. Attention to the website was drawn by means of flyers, internet links and media attention. On the website, subjects were asked to fill out an electronic questionnaire. The website contained only sparse information about the study since it could influence the answers to the questionnaire. The questionnaire consisted of 6 items relating to auditory hallucinations. Based on their scores on these items subjects were contacted and screened by telephone. When subjects fulfilled the criteria concerning age and the absence of substance abuse, they were asked to come to the UMC Utrecht where the final screening took place.

The following inclusion criteria were used for both groups. All subjects had to be aged 18-65, have no history of drugs or alcohol abuse and no diagnosis of a psychiatric disorder. These criteria were addressed in detail during the screening at the

UMC Utrecht. Screening for psychiatric disease was performed on the basis of DSM-IV as determined by an independent psychiatrist and one of the researchers using the Comprehensive Assessment of Symptoms and History (CASH) (Andreasen et al., 1992). The presence of AVH was further assessed with the Launay Slade Hallucination Scale (LSHS) (Laroi et al. 2004; Aleman et al. 2001).

Schizophrenia Patients were asked to participate by an independent psychiatrist. All were diagnosed on the basis of DSM-IV as determined by an independent psychiatrist using the CASH (Andreasen et al., 1992). All patients were using antipsychotic drugs at adequate levels, but continued to experience AVH at a frequent (daily) base.

All groups were matched for age and handedness. Healthy subjects with and without AVH were also matched for their years of education. The latter was not measured for the schizophrenia patients, since the onset of their disease interfered with their education. For safety reasons the following exclusion criteria were used: metal objects in or around the body that could not be removed (i.e. cochlear implant, surgical clips, piercings, cardiac pacemaker), history of eye trauma with a metal object, professional metal workers, alcohol abuse and possibility of pregnancy. Participants had to fill out an informed consent for participation in the study. They received an honorarium and a compensation for their traveling expenses. This study has been approved by the local hospital Medical Ethics Committee.

2.2 Experimental task

All participants were scanned using the same design and set-up. The verbal fluency task chosen in this study consisted of a letter fluency task. Letter fluency is a classical neuropsychological task of language production, which involves the generation of words beginning with a specified letter. In this paradigm the subjects were asked to covertly generate a word starting with a letter displayed on the screen in front of the subject. Since it is harder to use these letters to form words, the letters X, Q and C were excluded. Stimuli were presented in 8 activation blocks, each block lasting 30 seconds. In each activation block 10 letters were displayed at a rate of one letter every 3 seconds. As a reference condition for functional MRI image analysis, a baseline condition was presented in which a cross was projected on the screen in order to correct for visual input. Activation blocks were alternated with the reference condition. Presentation of letters was randomized in each block.

Apart from the covert word generation of the experimental trial, a short trial consisting of only two blocks, in which subjects had to generate words overtly, was used in order to measure behavioral performance of the subjects while subjects were still in the scanner. Subjects thought these blocks were part of the actual study in order to keep their performance steady. All participants performed the task correctly. However, the change from covert articulation to overt articulation was confusing for the schizophrenia patients. Therefore these behavioral blocks were not used during patient scans. Patients were trained extensively before the actual scanning started. Only patients capable of performing the task correctly were included.

2.3 Data acquisition

Activation maps were obtained using a Philips Achieva 3 Tesla Clinical MRI scanner at the University Medical Centre (UMC) in Utrecht. 400 weighted echo-planar images, depicting BOLD contrast, were acquired with the following parameter settings: 20 (axial) slices EPI, TE/TR 1200/35 ms , flip angle 35° , FOV 256x80x208, matrix 64x64x20, voxelsize 4 mm isotropic. After completion of the functional scans, a high resolution anatomical scan, with the following parameters TR/TE: 25/ 1.68 ms, 1x1x1 voxels, flip angle 30°, was acquired to improve localisation of the functional data. A mirror allowed the participant to view a screen, which facilitated the presentation of the letter fluency paradigm via a LCD projector outside the RF cabin. Head movement was minimized by a

Group	N	Age	Sex		Handedness		Years of Education
		Mean/(SD)	M	F	L	R	
Controls	**10**	45/(13)	4	6	1	9	6.5/ (.5)
AVH	**10**	44(11)	1	9	1	9	5.3/ (2)
Schizophrenia	**10**	39(11)	10	0	1	9	

Table 1. Demographic variables of the participant groups.

forehead strap and subjects wore noise insulated ear protectors.

2.4 Data analysis

FMRI data were analyzed using statistical parametric mapping (SPM2; Welcome Department of Cognitive Neurology, London, UK). Preprocessing included reorientation and within subject image realignment with rigid-body transformations using the first image as reference. This procedure corrected images for any three-dimensional head movement that occurred between scans, and hence improved the sensitivity of analyses by reducing the amount of artefactual signal intensity changes present in the image series due to movement. Afterwards, coregistration of the functional and anatomical image took place, followed by spatial normalization to a standard template. Finally, images were smoothed using an 8-mm full width at half maximum (FWHM) Gaussian kernel to increase signal-to-noise ratio, accommodate normal variability in functional and gyral anatomy, and facilitate intersubject averaging of measured BOLD signal changes.

2.5 Statistics

2.5.1 Main effects

Functional images were analyzed on a voxel by voxel basis using multiple regression analysis (Worsley and Friston 1995) with one factor coding for activation (task versus rest), and 6 for movement related activation extracted from the realignment parameters. The threshold corresponded to a p-value of 0.001. The 6 movement related regressors were used as covariates in the analysis. Following first level analysis, second level random-effects analyses were conducted for within group effects (t-tests) with a p-value of $p < 0.01$. All p-values were uncorrected for multiple comparisons.

2.5.2 Psychophysiological interactions

The basic idea behind psychophysiological interactions (PPI's) is that the activity of one area is regressed on the activity of a second region. The slope of this regression reflects the correlation between the first and the second region. The way in which this slope changes under influence of the psychological condition baseline versus language is called the psychophysiological interaction. It is a measure of how the slope is modulated by the experimental factor. Using PPI's we can determine which regions are functionally connected during language as compared to during baseline (Friston et al., 1997). In order to perform PPI analysis three vectors have to be established. The first vector consists of the first eigenvariate time series from the seed region. From each seed region a voxel is chosen to represent the activity in this region. The standard procedure, used in this study, is to select the highest activated voxel in a ROI across all subjects. A second vector consists of the psychological variable representing the experimental paradigm (language versus baseline). Finally a third vector has to be constructed representing the interaction between the first and the second vector. This third vector represents the interaction between the activity in the seed region and every other region in the brain modulated by the psychological factor. These vectors, extracted from each subjects individual dataset, are then entered into a second analysis for each subject with the first two vectors as covariates of interest and the third vector as the vector of interest with a contrast of 0 0 1. Afterwards, second level random effect analyses are conducted for within group effects separately for every seed region yielding the PPI maps for each group. A significant effect means that the covariance between the source and other regions during language is significantly different from that during the baseline condition. Important in this routine is deconvolving the BOLD signal since the interactions are expressed at the neuronal level. This deconvolving is already present in the PPI routine in spm2.

3. Results

3.1 Phenomenology of AVH

A comparison made between the AVH reported by the schizophrenia patients and the AVH reported by the healthy subjects revealed both differences and similarities. Statements are based upon the CASH interview (Andreasen et al., 1992). Therefore they are mostly qualitatively instead of quantitatively. Both groups reported that the voices they experienced sounded very real, as coming from a person standing next to them. In addition both the schizophrenia patients and the healthy subjects with AVH localized the voices as

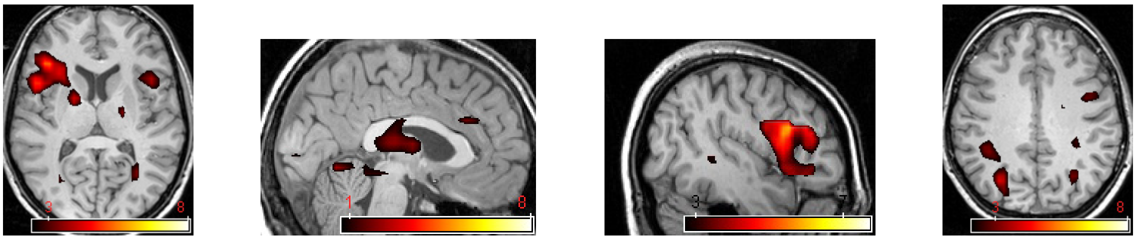

Figure 2A. SPM(T)'s for the healthy controls.

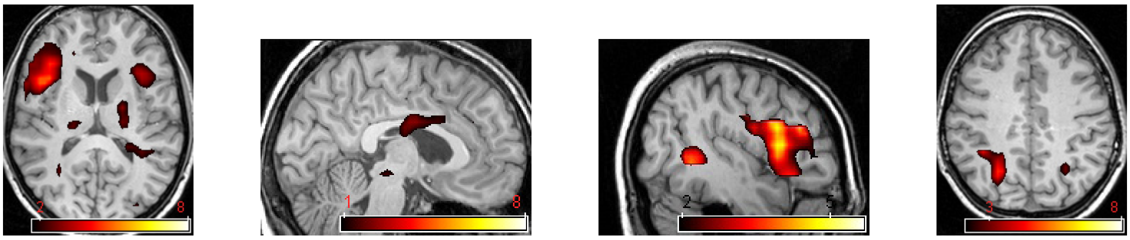

Figure 2B. SPM(T)'s for the healthy subjects with AVH.

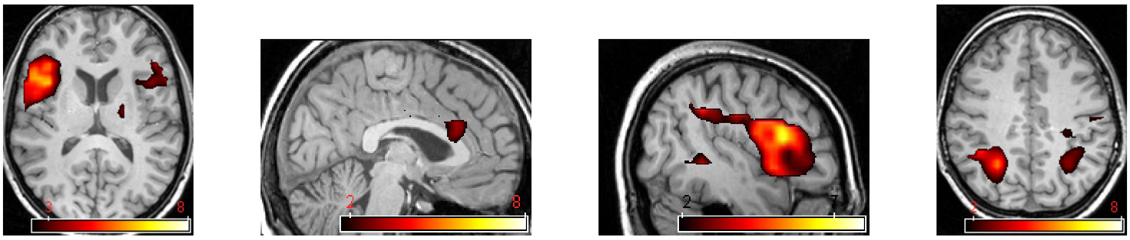

Figure 2C. SPM(T)'s for the schizophrenia patients.

coming from 'the outside world'. Also all subjects experienced up to 6 different voices, mostly the voices of relatives, friends or other acquaintances. Differences were apparent in the frequency of the experienced hallucinations, the amount of positive versus negative content and the control the subjects could execute over their hallucinations. While the frequency of the hallucinations varied from multiple times per hour till once every three months in the healthy subjects with AVH, the schizophrenia patients experienced hallucinations almost constantly. Furthermore, all of the schizophrenia patients reported that the hallucinations made them either anxious or uncomfortable. Only one of the healthy subjects reported the hallucinations to be fearful occasionally. The same person reported the content of the voices to be negative sporadically. For the schizophrenia patients the content of the voices was negative, regularly. Moreover, the healthy subjects with AVH claimed to be able to execute come control over their hallucinations, meaning they could stop the hallucinations whenever they interfered with their daily activities. This was not the case for the schizophrenia patients. The only control they could execute was by focusing their attention on something different in which they succeeded occasionally.

During the verbal fluency task both groups reported the absence of hallucinations.

3.2 ROI Main-effects Analysis

Figures display activation in the ROI's only. Images are in neurological orientation. Figure 2 shows the SPM(T)'s of the group averages of the control subjects (Figure. 2A), the healthy subjects with AVH (Figure. 2B) and the schizophrenia patients (Figure. 2C) after applying a threshold of $p < 0.01$. These results demonstrate that greater activity was observed in the left ACC, left IFG, left STG and left DLPFC during language relative to rest in all groups ($p < 0.01$).

3.3 Psychophysiological interaction analysis

3.3.1 Left ACC

Significant functional connectivity between the left ACC and the left temporal lobe, mainly the STG was found for both the controls subjects and the healthy subjects with AVH. This pattern was not found for the schizophrenia patients. The latter only showed one localized region of significant functional connectivity with the left ACC consisting of the right cingulate gyrus. This

Group	Coordinates			Z score	P value
	X	*Y*	*Z*		
Control subjects					
R DLPFC	12	51	16	2.63	0.004
L Middle Temporal Gyrus	-51	-64	20	2.18	0.015
R Cingulate Gyrus	8	-45	35	1.97	0.025
L DLPFC	-8	48	20	1.81	0.035
R Middle Temporal Gyrus	51	-65	20	1.81	0.035
Corpus Callosum	4	27	2	1.77	0.038
R Medial Frontal Gyrus	8	59	11	1.68	0.047
L Superior Temporal Gyrus	-51	-61	21	2.18	0.015
R Superior Temporal Gyrus	51	-61	21	1.68	0.046
AVH					
R Thalamus	12	-34	13	3.07	0.001
R Postcentral Gyrus	44	-26	34	2.76	0.003
L Lateral Ventricle	-20	-34	16	2.71	0.003
R Middle Temporal Gyrus	51	-66	7	2.71	0.003
R Precentral Gyrus	40	-2	33	2.69	0.004
L Claustrum	-28	12	7	2.63	0.004
L Middle Temporal Gyrus	-36	-65	18	2.43	0.008
R Caudate	20	-2	30	2.22	0.013
Interhemispheric	0	12	7	2.05	0.020
L Superior Frontal Gyrus	-20	48	4	2.19	0.014
R Superior Temporal Gyrus	40	-38	17	2.56	0.005
L Superior Temporal Gyrus	-48	-20	-2	1.96	0.025
Schizophrenia Patients					
R Cingulate Gyrus	8	-26	31	2.19	0.014

Table 2. Summary of psychophysiological interaction analyses for the left ACC.

connection was not present in the other groups. For the control subjects significantly greater activity for the interaction between the left ACC and the left DLPFC was observed during letter fluency relative to the baseline condition. This finding was not replicated for the subjects with AVH and the schizophrenia patients. Furthermore the subjects with AVH displayed multiple widespread nonlocalized covarying activity with the left ACC. The SPM(T)'s from this analysis are shown in Figureure 4 and table 3 provides the location of the maximum activated voxels in these regions. Images are in neurological orientation. Results for the schizophrenia patients are displayed in saggital instead of transverse view in order to show the localized interaction with the cingulate gyrus. Using a transverse view this cannot be visualized very well.

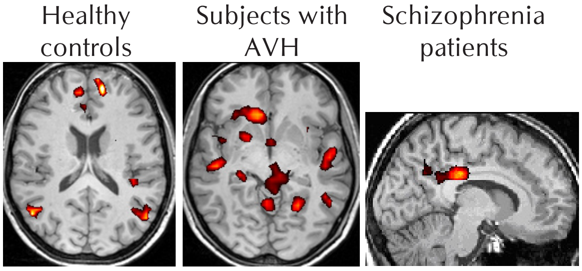

Figure 3. SPM(T)'s for the PPI analyses for the left ACC.

3.3.2 Left STG

The hypothesized interaction between the left STG and the left IFG was found in the control subjects. The healthy subjects with AVH and the schizophrenia patients failed to show this Interaction. The SPM(T)'s of this analysis are shown in Figure 5 and in table 4 the locations of the maximally activated voxels are shown. Images are in neurological orientation.

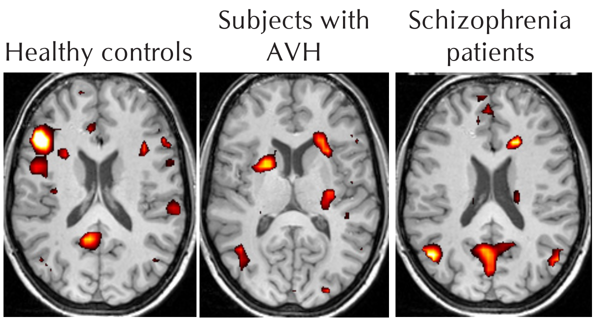

Figure 4. SPM(T)'s for the PPI analyses for the left STG.

4. Discussion

To date, language connectivity has not been examined in healthy subjects experiencing AVH. We examined this group in order to be able to study this symptom in isolation. Hallucinating healthy subjects were compared to non-hallucinating healthy subjects as well as to hallucinating schizophrenia patients.

The functional connectivity analysis that tested for the interaction between activity in the left ACC and word fluency task performance in the healthy controls revealed a clear interaction with the left STG. Healthy subjects with AVH showed the same interaction with the left STG, however, they showed a more widespread pattern throughout the brain which is in agreement with Boksman et al. (2005). In their study, the schizophrenia patients didn't show any interaction with the temporal cortex. In the current study, the only interaction the schizophrenia patients displayed with the left ACC as the seed region consisted of the right cingulate gyrus. This is in accordance with Boksman et al. (2005) in which never treated schizophrenia also displayed an interaction with the right cingulate gyrus. In the current study an interaction between the left ACC and the right cingulate gyrus was observed in the control subjects as well, but not in the healthy subjects with AVH. The cingulate gyrus has been reported to be involved in attention, executive processes, word generation, and memory (Petersen et al., 1988). Verbal fluency tasks are besides a measure of language, a measure of executive function and working memory. According to the dual-route-self-monitoring-hypothesis, the ACC functions as a control center, interacting with regions crucial in adequate execution of the experimental task. The isolated interaction with the right cingulate gyrus in the schizophrenia patients could be implying the high demands placed on these subjects in order to carry out the task correctly. The widespread pattern of activation covarying with ACC activation in the healthy subjects with AVH could be indicative of the inability of the ACC to monitor recruitment and activation of other area's, effectively, leading to recruitment of regions of less interest in execution of the task.

The healthy people with AVH differ from the schizophrenia patients not solely on the basis of the multitude of symptoms but also on the way they regulate the hallucinations. The first group claims that they are generally able to stop the hallucinations or call on them. The ACC plays a major role in executive cognitive, attention and motor functioning as well as mediating emotions (Devinsky et al., 1995; Paus, 2001; Yucel et al., 2003). Since our subjects with AVH have the ability to regulate their hallucinations, connectivity with the left temporal region is perhaps not disrupted in this subgroup. In order to determine this relationship further research should focus on comparing people with AVH on the basis of the criterion control versus no control over the hallucinations. A different explanation is that differences in connectivity between the schizophrenia patients and the healthy subjects are related to the frequency of the hallucinations or to the general cognitive decline present in the schizophrenia patients. Secondly, the healthy controls showed a focal localized interaction between the left ACC and the left DLPFC. This pattern was not found in the other groups. Fletcher et al. (2001) established dysfunctional connectivity between the left prefrontal cortex and the left ACC and the left STG in schizophrenia patients during the performance of a language task. Their interpretation was dysfunctional cingulate modulation of prefrontal influence of the left STG. Since we did not find prefrontal-STG dysconnectivity their findings could also be interpreted as a dysfunction of both ACC-prefrontal dysconnectivity and ACC-STG dysconnectivity. This interpretation is in agreement with Spence et al. (2000) who demonstrated reduced functional connectivity between the left DLPFC and the left ACC in schizophrenia patients, but not between the left DLPFC and the left STG.

For the PPI analysis with the left STG as the seed region a localized interaction was found with the left IFG for the healthy controls. For the healthy subjects with AVH and the schizophrenia patients this connection was absent as was also found by Burns et al., (2003) using structural connectivity analysis (e.g. DTI). Our findings point to a disruptive or dysfunctional connection between language areas for execution and perception of speech. These disruptions could be the basis for the liability to AVH, since they are possibly responsible for differentiating between self formed speech and external speech.

From the results described above it can be concluded that the dysfunctional connections present in the schizophrenia patients replicate the results of previous studies. Considering the healthy subjects with AVH the same dysconnections are present apart from the connection between the left ACC and the left STG. These findings are partly in agreement with the dual-route-self-monitoring-hypothesis. The interaction between the left IFG and the left ACC as predicted in the dual-route-self-monitoring-hypothesis was not present in either of the groups. However, there was a clear interaction between the left DLPFC and the left ACC.

The anatomical boundaries of the DLPFC have not been precisely defined. The term DLPFC is commonly used to refer to part of the frontal lobe and comprises of the inferior frontal gyrus the middle frontal gyrus and the lateral aspect of the superior frontal gyrus (John et al., 2006). Brodmann area 46 which is generally accepted to be part of the DLPFC, as was the case in our study, is often referred to be part of the IFG. With this in mind one could argue in favor of the dual-route-self-monitoring-hypothesis. Nevertheless, in future research, one should focus on the relation between the DLPFC and the IFG.

4.1 Limitations and suggestions for future research

The results of this study should be interpreted with caution for multiple reasons. Firstly we only studied a small sample of participants in each group due to the fact that recruiting healthy subjects with AVH is quite challenging.

Secondly the participant groups were not matched for sex. The group of schizophrenia patients existed of 9 male and only one female participant, while the group of healthy people with AVH was comprised of only one male participant. This was due to the fact that most schizophrenia patients volunteering were males and almost all healthy participants that responded to our website were females. Furthermore, of the schizophrenia patients volunteering for this study, all but one woman had to be excluded because of scanner anxiety. Considering the healthy subjects experiencing AVH, the researchers are not aware whether the higher amount of women volunteering was due to a response bias or whether the percentage of women experiencing AVH without meeting the criteria for a psychiatric diagnose, is actually higher. A future study should attempt to seek out which is the case. Therefore, we focused on exact matching of our subgroups on other characteristics. However, a study by Weiss et al. (2003) showed that men and women, that did not differ significantly in verbal fluency task performance. showed a very similar pattern of brain activation. Also differences in language lateralization between men and women are absent (Sommer et al., 2004).

Thirdly since our scanning protocol consisted of a 20 slice EPI our analysis was limited to our regions of interest. Additional regions with the possibility of differential activations could not be mentioned in this study. Using a larger scanning protocol would enable us to have a look at additional regions such as the cerebellum.

Also the measures of behavioral performance used are qualitative in origin. Therefore a direct relationship between the performance level and the measured activation cannot be determined. A quantitative measure could solve this.

Finally there are some limitations to the method used. In the PPI routine it is assumed that the task represented by an experimental condition is mediated by a network of interacting brain regions and those different tasks correspond to different functional networks. The problem however lies in the fact that large covariances in interregional activity can come about by both direct and indirect effects. Two regions' activities may have a large correlation if they are anatomically linked, and if that link is functional in a specific task. However, they also could have a large correlation if they receive inputs from a common region. Most likely, a combination of both direct and indirect effects occurs at the same time, presenting a major interpretation problem for the covariance paradigm (Horwitz et al., 1999). Furthermore, it is not possible to determine the weight of the correlation coefficients between interacting regions. Different methods like structural equation modeling should be used in addition to determine direct and indirect effects and the path coefficients between interconnected regions.

Also, even though the contrast used as the psychological factor differs in a meaningful way, language versus baseline, it is only informative about language in a broad sense. Interpretations about how the differences are related to AVH are rather loose. Therefore it would be meaningful to study execution versus perception of language a contrast which is believed to be important in the origin of AVH.

In summary, schizophrenia patients and healthy subjects with AVH display dysfunctional connectivity between the regions important in the perception and production of speech. Furthermore, the presence of a functional connection between the left ACC, important in executing cognitive control, presumes that healthy subjects with AVH can execute some control over their hallucinations. Future research should focus on more sophisticated methods to study the integration between brain regions important in the perception and production of speech in subjects with AVH.

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