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Attentional modulation of source attribution in schizophrenia: behavioral and neural correlates

Aufmerksamkeitskontrolle von Attributionsprozessen in Schizophrenie: behaviorale und neuronale Grundlagen

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To Joseph and Amelie

1. Introduction

1.1 Diagnosis of schizophrenia and functional magnetic resonance (fMRI) imaging

Although schizophrenia is discussed as if it is a single disease, it probably comprises a group of disorders with heterogeneous etiologies, and it includes patients whose clinical treatment, response and courses of illness vary (B. J. Sadock, Kaplan, & Sadock, 2007). According to DSM- IV (*Diagnostic and statistical manual of mental disorders*, 1994) patient's disorder is diagnosed as schizophrenia when the patient exhibits two of the following symptoms each present for a significant portion of time during a 1-month period (or less if successfully treated):

1) delusions
2) hallucinations
3) disorganized speech (e.g. frequent derailment or incoherence)
4) grossly disorganized or catatonic behavior
5) negative symptoms (i.e. affective flattening, alogia or avolition)

Other important criteria for establishing the diagnosis of schizophrenia are social occupational dysfunction, such as work, interpersonal relations, or self-care which should be markedly below the level achieved prior to onset of illness (B. J. Sadock et al., 2007). In addition, continuous signs of the disturbance noted above should persist for at least 6 months.

Schizoaffective disorder and mood disorder with psychotic features should be ruled out because no major depressive, manic or mixed episodes have occurred concurrently with the affective-phase symptoms. Importantly, the disturbance diagnosed as schizophrenia should not be due to direct psychological effect of a substance (e.g. a drug abuse, a medication) or a general medical condition. If there is a history of autistic disorder or another pervasive developmental disorder, the additional diagnosis of schizophrenia is made only if prominent. Delusions or hallucinations should also be present for at least a month. DSM-IV-TR classifies the subtypes of schizophrenia as paranoid, disorganized, catatonic, undifferentiated, and residual, based predominantly on clinical presentation. The 10th revision of *Interational Statistical Classification of Diseases and Related Problems* (Dilling, Mombour, & Schmidt, 2004), by contrast uses nine subtypes: paranoid schizophrenia, hebephrenia, postschizophrenic depression, residual schizophrenia, simple schizophrenia, other schizophrenia, and schizophrenia unspecified, with eight possibilities for classifying the course of the disorder, ranging from continuous to complete remission.

In 1980., T.J. Crow proposed a classification of schizophrenia into types I and II, on the basis of the presence or absence of positive (or productive) and negative (or deficit) symptoms (B. J. Sadock et al., 2007). The positive symptoms include delusions and hallucinations. The negative symptoms include affective flattening or blunting, poverty of speech or speech content, blocking, poor grooming, lack of motivation, anhedonia and social withdrawal. Type I patients tend to have mostly positive symptoms, normal brain structures on CT scans and relatively good response to treatment. Type II patients tend to have mostly negative symptoms, structural brain abnormalities on CT scans, and poor response to treatments.

Previous investigations on schizophrenia are as complex and disperse as this psychiatric entity on its own. Important advances in the understanding of schizophrenia have occurred in several major areas. The advances in neuroimaging techniques, especially magnetic resonance imaging (MRI), and refinements in neuropathological techniques have focused much interest on certain brain areas as central to the pathophysiology of schizophrenia. Research on schizophrenia in last two decades had been trying to cover aspects relevant for detection of neurobiological causes of schizophrenia (e.g. dopamine hypothesis), brain areas and neural circuits central for the pathophysiology of the disorder, drug efficiency (e.g. atypical antipsychotic as clozapine), followed by research on psychosocial intervention strategies used in the treatment and rehabilitation of schizophrenic patients (B. J. Sadock et al., 2007). Especially up to date are studies on cognitive impairment in schizophrenia (M. F. Green, Kern, Braff, & Mintz, 2000; Rocca et al., 2006), in relationship to genetics and biochemical research (Bhattacharyya et al., 2012; Prata et al., 2012).

Despite a number of appealing functional imaging studies of patients with positive and negative symptoms only few studies have investigated positive symptoms of schizophrenia and more particularly how attention is modulating the perception of reality in these patients (Ilankovic et al., 2011; Maruff, Danckert, Pantelis, & Currie, 1998; U. Schneider et al., 2002). Thus, a better understanding of the cognitive and neurological alterations that accompany the positive form of schizophrenia and how these differ from those seen in the negative or chronical form of the illness may be useful in establishing and refining cognitive treatments.

1.2 Schizophrenia and self–processing deficits: an historical overview

A variety of self disorders in schizophrenia have always been recognized as the essential components of its clinical picture. In the nineteenth century it has been already widely spoken about the ‘disorders of self’, but this list was as long as it was heterogeneous (‘desintegration’, ‘blurring of boundaries’, ‘discordance’, ‘intrapsychical ataxia’, ‘schizophrenia’) (T. Kircher & David, 2003).

Kraepelin (Kraepelin, 1896) introduced the concept of dementia praecox in the fifth edition of manual, the term that emphasized the distinct cognitive process and early onset of the disorder. Rather intriguingly, Kraepelin does not say anything about the disorders of the self.

Eugen Bleuler used the term schizophrenia to express the presence of schisms between thought, emotion and behavior in patients with the disorder. In his book on schizophrenia he only discussed the disorders of the self in the sections on “Die Person” (Bleuler & Aschaffenburg, 1911). His examples of self- disorders centre on cases suffering from delusions of being someone else or having ‚made’ emotions, actions and feelings. At the beginning of the twentieth century, the concept of “Ich-Störungen” developed (Jaspers, 1913), which included what nowadays would be called passivity feelings (first-rank symptoms schizophrenia, (K. Schneider, 1959)), disorders of body schema, and even depersonalization.

A contemporary of Bleuler and Kraepelin, Joseph Berze (Berze, 1914) was the first explicitly to propose that a basic alteration of self-consciousness was a primary disorder of schizophrenia. Jaspers suggested activity, unity, temporal-diachronic identity and me/not me demarcation as four experiential modes in which self is aware of itself and can be affected in any of them due to the illness (Jaspers, 1913).

Kurt Schneider (K. Schneider, 1959) addressed self-disorders in his description of passivity phenomena and according to him, first rank symptoms refer to a state where patients interpret their own thoughts or actions as due to alien forces or to other people and feel they are controlled or influenced from others. First rank symptoms might reflect the disruption of a mechanism which normally generates consciousness of one's own action and thoughts and allows correct attribution to their source. Phenomenologists have also identified 'transitivistic' phenomena as central features of basic self-disturbance (Parnas & Handest, 2003; Parnas et al., 2005). These phenomena refer to a loss or permeability of the self-world boundary, reflected as confusion between self and other people (e.g., whether oneself or another person had a certain thought or experience, confusion about whether a mirror image is of oneself or another person, etc.), being threatened by bodily contact, or being in a passive position in relation to other people.

Up to nowadays it remains considered, that in no other mental disorder, but in schizophrenia, the self is so exposed and impaired (Nelson et al., 2009).

1.3 Self-disturbance in phenomenology and empirical research

The self-disturbance model is based on the combination of empirical research, clinical experience and phenomenological considerations. Before discussing in which particular way is the sense of self impaired in schizophrenia, I will give a brief overview of selfhood on phenomenological and neurobiological level.

Several levels of types of selfhood are being distinguished on the phenomenological level (T. Kircher & David, 2003):

1. pre-reflective, minimal or basic self "ipseity"

2. reflective, extended self, self as invariant and persisting subject of experience and action

3. social or narrative self (personality, habits, style)

Also, several levels of types of selfhood are suggested on the neurobiological level (Nelson et al., 2009):

1. Proto or bodily self-sensory processing

2. Core self- self referential processing

3. Autobiographical self- higher order cognitive processing

The phenomenological model of self-disturbance in schizophrenia- spectrum disorders suggests that the disorder of self occurs at the first (or most basic) level of self-awareness (''ipseity''), in contrast to the disordered self in non-schizophrenia- spectrum personality disorders, such as borderline or narcissistic personality disorder, in which the self is disturbed on the level of the narrative self, with a more basic sense of self remaining intact (Parnas & Handest, 2003).

The types of anomalous experience affecting ipseity, which are evident in the prodromal period, include disturbed sense of presence, corporeality (anomalous bodily experiences, such as perceived morphological change or motor disturbances), stream of consciousness (anomalous cognitive processes, such as thought interference, thought pressure, or thought block), self-demarcation (loss or permeability of self-world boundary, such as confusion between oneself and other people), and existential reorientation (fundamental reorientation with respect to worldview, such as self reference or solipsistic phenomena), all of which are intimately interrelated (Parnas, 2005; Sass & Parnas, 2003).

Another important distinction for understanding self-disturbance is between two kinds of self awareness, the first one being a sense of subjectivity and the second one called sense of agency. The first one is the brain's capacity to distinguish it's mind from the rest of the world while the later one refers to the ability to distinguish between self initiated thoughts. From this perspective schizophrenia would be a disorder that affects sense of agency of a person, but leaves his or her sense of subjectivity intact (T. Kircher & David, 2003).

My study on source attributions is addressing disturbance of reflexive self on the phenomenological level and disturbance of core self on the neurobiological level.

1.4 Self- disturbance in neuroscientific models

1.4.1 Self-monitoring of inner speech and corollary discharge

Several cognitive neuroscientific models of self-disturbance have also been proposed (Ditman & Kuperberg, 2005; Seal, Aleman, & McGuire, 2004) and while they vary somewhat in their details, they share the formulation that the fundamental disturbance causing psychotic symptoms is a difficulty distinguishing between the origins of endogenously and exogenously generated stimuli, commonly referred to as a *deficit in source or self-monitoring.* Thus, positive symptoms such as auditory hallucinations and passivity phenomena are thought to result from the misattribution of internal thoughts and actions (e.g., inner speech or motor commands) to external sources. Such abnormalities have been characterized as reflecting an *'autonoetic agnosia'*: a difficulty identifying self-generated events (Keefe R.S.E., Courtney M., Bayan U.J., Harvey P.D., & McEvoy J.M., 1998). As auditory verbal hallucinations (AVH) are one of the most common symptoms experienced by patients with schizophrenia and are usually associated with delusions (Liddle, 1987) a considerable amount of theoretical and behavioral work examining source and self-monitoring in schizophrenia has been undertaken to explain AVH and delusions in schizophrenic patients (P. Allen, Aleman, & McGuire, 2007; Seal et al., 2004). According to the model of Frith (C. D. Frith, 1987) AVH result from defective monitoring of thoughts/inner speech, as they are generated, leading to misidentification of self-generated thoughts as external ‚alien' voices. This is usually referred to as a breakdown in the monitoring of the intention to generate inner speech, through a loss of the '*efference copy'* associated with the generation of verbal material. This efference copy or "corollary discharge" serves to inform an internal monitor of forthcoming action and may thus help to distinguish self generated from externally generated verbal material (Blakemore, Oakley, & Frith, 2003). Although typically associated with sensorimotor systems, corollary discharge might also apply to inner speech or thought, which can be regarded as our most complex motor act. In the absence of this signal, inner speech may thus be misidentified as 'alien' and perceived as externally generated voices (Feinberg, 1978; C. D. Frith & Done, 1988). Hallucinations have therefore been conceptualized as resulting from a breakdown in the systems monitoring the current intention to make actions (C. D. Frith & Done, 1988);(See figure 1.1).

Frith’s model is supported by data from studies that have engaged verbal self-monitoring by experimentally manipulating auditory verbal feedback while patients with AVH spoke aloud (Cahill C., Silbersweig D., & Frith C., 1996; L. C. Johns et al., 2001). Altering the acoustic characteristics of their speech introduced a disparity between what subjects expected to hear and what they actually perceived. In both studies patients who are experiencing hallucinations and delusions (H/D patients) were more likely than controls to make errors of misattribution, towards misidentifying their own speech as alien when it was distorted. Allen et al. (P. Allen et al., 2004) adapted the paradigm used by Johns et al. (L. C. Johns, Gregg, Allen, & McGuire, 2006; L. C. Johns et al., 2001) in that way that participants made judgments about the source of pre-recorded speech rather than speech that was generated online. As participants were simply required to indicate when they recognized their own voice, the putative self-monitoring of self-generated speech was bypassed. Despite this H/D patients were still more likely to claim their own distorted voice as that of another person than patients without hallucinations (and significantly lower levels of delusions) and healthy controls. This finding suggests that the external misattribution of source may reflect impairment in not only verbal self-monitoring, but also in the appraisal of ambiguous sensory material (P. Allen et al., 2007).

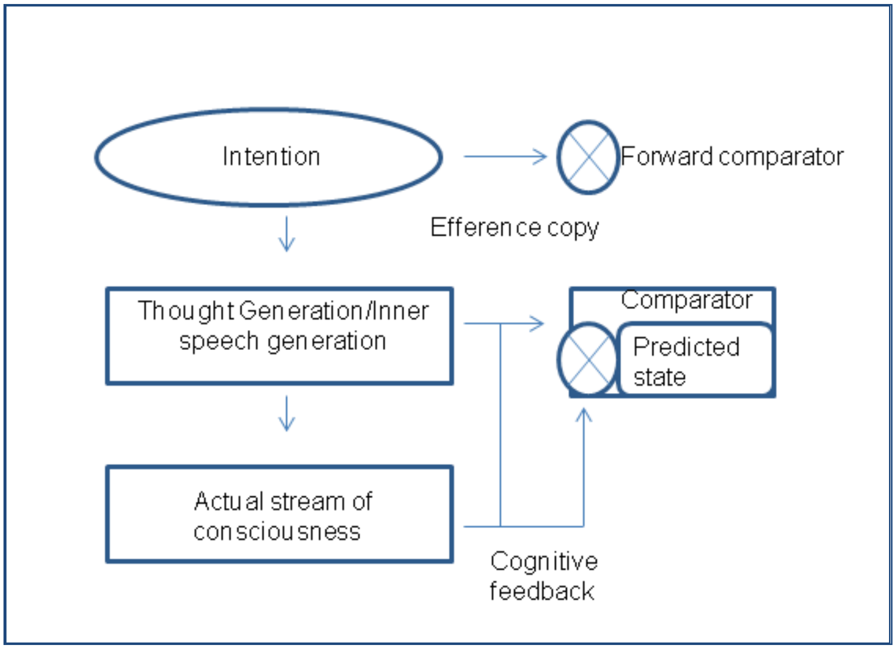

Figure 0.1 Efference copy, example on thought insertion (adapted from Gallagher et al., 2000). Normally, an efferent copy of the intention to think or speak is sent to the comparator or central monitor, which also registers the occurrence of thinking, and matches up intention and thought or intention to speak. So if the intention (the efferent copy) is somehow blocked from reaching the central monitoring mechanism, thought/voice occurs which seems not to be generated by the subject. If the efferent copy is blocked or is not properly generated, thinking or speaking still occurs, but it is not registered as under my control- it appears to be an alien voice or inserted thought.

Recent event-related brain potentials studies (J. M. Ford, 2001; Heinks-Maldonado et al., 2007) found that hallucinators performed poorly both during self-monitoring their own speech and when the putative self-monitoring of self-generated speech was bypassed. Thus they suggested that the self-monitoring of speech may have failed to develop appropriately, resulting in uncertainty about the source of current perceptions. According to these studies, misattributions therefore may result from a “coping” strategy learned over time to navigate through life.

1.4.2 Source/ reality monitoring

It has also been suggested that positive symptoms, e.g. hallucinations and delusions, are related to a more general deficit in reality and/or source monitoring leading to confusion between imagined and perceived items (Blakemore, Smith, Steel, Johnstone, & Frith, 2000; Blakemore, Wolpert, & Frith, 2002; Brébion et al., 2000). Much of the experimental evidence is consistent with this idea as patients with hallucinations and delusions (H/D patients) in general tend to misattribute to an external source the items they had produced themselves on a variety of experimental tasks (P. Allen et al., 2004; Bentall, Baker, & Havers, 1991; Bentall, Kinderman, & Kaney, 1994; Brébion et al., 2000; Brébion, Gorman, Amador, Malaspina, & Sharif, 2002; L. C. Johns et al., 2006, 2001). One of the first reality monitoring tasks (Brébion, Amador, Smith, & Gorman, 1997) showed that schizophrenic patients were impaired in discriminating old items from new and have a higher bias than controls toward reporting new items as if they were old (false alarms). In the task twenty-four items were produced, either orally by the experimenter, orally by the subjects, or seen as pictures. Subjects were later read a list of 48 items and were asked to indicate if each item was new, self-generated, experimenter-generated, or presented as a picture. Patients were impaired in discriminating self-generated items from externally generated items, with a higher bias than controls toward attributing self-generated items to an external source. The bias toward remembering orally produced items as pictures was correlated with positive symptomatology and was significantly higher in patients than in controls with high levels of positive symptoms. This suggests that mental imagery may play a role in positive symptomatology. Later on, in one of the experimental tasks patients with schizophrenia were administered several memory tasks including free recall of lists of words, recognition and source memory. The authors (Brébion et al., 2002) studied the associations of the memory errors with positive symptoms and with a broad range of negative symptoms. All the memory errors were positively associated with at least one positive symptom. On the other hand, these errors were inversely associated with certain negative symptoms reflecting lack of emotion or lack of social interactions. Authors concluded that positive and negative symptomatologies appear to have opposite links to the source monitoring errors observed in patients with schizophrenia (Brébion et al., 2002).

These findings demonstrate the relevance of studying decision biases along with discrimination performance for better understanding of the mechanisms of reality monitoring impairment in schizophrenia.

1.4.3 Is defective self-monitoring specific to AVH?

Later studies on self-monitoring found that the misattribution of self speech to an external source was not specific to patients with AVH and that patients with only delusions but no hallucinations also demonstrate a significant tendency to misattribute their own speech (L. C. Johns et al., 2006). The specificity of such a deficit to AVH is therefore equivocal as most studies report that patients with delusions also tend to make external misattributions when listening to their own distorted speech (P. Allen et al., 2007). However, the tendency to make misattribution errors in patients currently experiencing AVH in the context of an affective psychosis was not identical to the one that was seen in patients experiencing AVH in the context of schizophrenia. Namely, they did not misattribute their own speech when it was distorted, but they tended to be unsure about the speech source. Hence, the misattribution bias was not observed in patients who had a history of hallucinations but were hallucination-free for a month.

Finally, it has been suggested that the external misattribution of the source is related to the general acute psychotic state rather than to a predisposition to hallucinations (L. C. Johns et al., 2006).

1.4.4 Neural correlates of self –monitoring

Early functional imaging studies attempted to directly measure brain activity occurring whilst patients were experiencing hallucinations. A number of PET and fMRI studies reported hallucination-related activity in language-related areas, especially Broca's area, that is involved in speech production, and to a lesser extent, activity was also found in the anterior cingulate, that is involved in attentional processes, and in the left temporal cortex that is involved in auditory perception and memory processes (Ait Bentaleb, Beauregard, Liddle, & Stip, 2002; P. K. McGuire, Shah, & Murray, 1993; Shergill, Brammer, Williams, Murray, & McGuire, 2000). Importantly, the observed activity in Broca's area during AVH implicates the involvement of inner-speech and/or auditory verbal imagery. (P. K. McGuire et al., 1995) used PET imaging to study the neural correlates of inner speech and verbal imagery in healthy controls and schizophrenia patients with and without hallucinations. In the inner speech task subjects were asked to imagine speaking particular sentences in their own voice as this was thought to require the generation of inner speech, but relatively little internal speech monitoring. In the auditory verbal imagery task they were asked to imagine similar sentences but spoken in another person's voice, which was thought to entail the monitoring of inner speech to a greater extent, as well as the generation of inner speech. During the verbal imagery task, hallucinators showed reduced activation in the left middle temporal gyrus (MTG) and the rostral supplementary motor area (SMA). These regions were strongly activated by both healthy controls and nonhallucinators. In a similar study using fMRI (Shergill et al., 2000) investigated the functional anatomy of auditory verbal imagery in patients with AVH. Patients with schizophrenia and a history of prominent AVH and healthy controls were scanned while generating inner speech or imagining external speech. Patients again showed no differences from controls while generating inner speech in their own voice, which in both groups was associated with activation in the left inferior frontal cortex (IFC) and insula. However, patients experienced a relatively attenuated response in the posterior cerebellar cortex, hippocampi, lenticular nuclei, right thalamus, temporal cortex and left nucleus accumbens during verbal imagery. The authors concluded that these differences in activation were consistent with altered function in regions implicated in the monitoring of inner speech, particularly the temporal cortex. A further study (S. S. Shergill et al., 2003) studied participants while they generated inner speech at different rates, the rationale being that the greater the rate, the greater the demands on the generation and monitoring of inner speech. Furthermore, the study engaged monitoring in an automatic 'non-conscious' way, distinct from earlier imagery studies, where the participants were required to deliberately inspect an auditory percept. Both healthy controls and patients with AVH showed activation in brain regions involved in left IFC and left temporal cortex during the task, but as the rate of inner speech generation increased patients prone to hallucinations showed an attenuation of the normal response in the temporal, parahippocampal and cerebellar cortex. These findings could be interpreted as further evidence for defective self-monitoring of inner-speech in patients experiencing hallucinations. However, as a non hallucinating patient group was not studied, group differences could have been related to schizophrenia generally or the effects of medication, as opposed to AVH per se.

A small number of studies have attempted to directly address the neural correlates of explicit source/self-monitoring in healthy individuals and patients with and without hallucinations. According to the self-monitoring model of (C. D. Frith, 1987), if the speech signal predicted on the basis of the motor output (via a corollary discharge) matches what is actually perceived, then there is no change in activation in the areas that mediate the sensory processing of speech (the lateral temporal cortices. (P. K. McGuire, Silbersweig, Wright, et al., 1996) implemented a verbal self-monitoring task in a PET study with six healthy controls in which auditory verbal feedback was altered. In the first condition subjects were visually presented with single words and asked to read them aloud. In a second condition subjects were asked to silently read a word and heard the investigator saying the word instead of themselves (alien feedback). There were no differences in temporal cortical responses between these two feedback conditions. In half the trials the speech that the subjects heard was distorted by elevating the pitch. Distortion of the subjects' speech while they read aloud led to a bilateral activation of the lateral temporal cortex with a greater response on the right than the left. A similar pattern of activation was evident when subjects read aloud, but the word they heard was spoken by someone else. The authors concluded that the monitoring of self-generated speech involves the temporal cortex bilaterally and engages areas concerned with the processing of speech which has been generated externally. A subsequent fMRI study using a modified version of the task in a healthy control group confirmed the finding that temporal activation was increased when participants spoke aloud and perceived their own distorted voice or the voice of another person (Fu et al., 2006). An advantage of the task used in this study was that participants were able to make judgments about the source of perceived speech on-line. Behaviorally, participants made more misattribution responses when the feedback was their own distorted voice. These authors also reported that external misattributions during self-distorted feedback were associated with significantly reduced bilateral superior temporal activation relative to correct attributions. Therefore, they conclude that the findings support the self-monitoring hypothesis. Moreover they suggest that impairments in the fronto-temporal network could erase the volitional signature of subjective perceptual awareness, and lead to hallucinations that are experienced as involuntary.

In the following study authors (Kumari et al., 2010) had an intention to disentangle performance, illness, and symptom-related effects in speech monitoring task with help of fMRI imaging using a self-monitoring task. In this study in which participants were instructed to read each word aloud the verbal feedback was (a) their own voice (self-undistorted), (b) their own voice lowered in pitch by 4 semitones (self-distorted), (c) voice of another person matched on participant's sex (alien-undistorted), or (d) another person's voice with the pitch lowered by 4 semitones (alien-distorted). The authors also detected brain abnormalities during monitoring of self- and externally generated speech in schizophrenia. They concluded in their study on speech monitoring that hypoactivation of a neural network comprised of the thalamus and fronto-temporal regions underlies impaired speech monitoring in schizophrenia. It seems that positive symptoms and poor monitoring share a common activation abnormality in the right superior temporal gyrus (STG) during processing of distorted speech whereas altered striatal and hypothalamic modulation to own and others' voice characterizes emotionally withdrawn and socially avoidant patients.

Another relevant study (P. Allen et al., 2005) investigated whether patients with a history of auditory verbal hallucinations would misattribute their own speech as external and show differential activation in brain areas implicated in hallucinations compared with people without such hallucinations. The task activated a network of inferior frontal, temporal and cingulated regions as well as areas in the brain-stem and cerebellum. The hallucinator group differed from controls in the effect of the source of speech on activation in left STG. In this region controls showed increased activation when listening to alien speech compared to self speech, whereas the activation in hallucinator group was relatively unaffected by the source of speech. Also, distortion was associated in the control group with the engagement of anterior cingulate cortex (ACC), but this effect was absent in the hallucinator group.

I mentioned already that this study (P. Allen et al., 2005) is the most relevant for my research as participants made judgments about the source of pre-recorded speech rather than about speech that was generated online. As participants were simply required to indicate when they recognized their own voice, the putative self-monitoring of self-generated speech was bypassed. Despite this H/D patients were still more likely to claim their own distorted voice was that of another person than patients without hallucinations (and significantly lower levels of delusions) and healthy controls.
This finding suggests that the external misattribution of source may reflect impairment in not only verbal self-monitoring, but also in the appraisal of ambiguous sensory material.

1.4.5 Facial self recognition

Facial self-recognition in children and non-human primates has been linked to the emergence of self-awareness. In the following study of the ability to recognize the own face as an indicator of certain aspects of self-awareness was investigated in patients with schizophrenia ((T. Kircher, Seiferth, Plewnia, Baar, & Schwabe, 2007)).

Standardized facial pictures of the participants (20 patients with DSM-IV schizophrenia and 20 healthy controls) were presented on a computer screen serially in three forced choice identity recognition experiments. In one of the experiments patients with schizophrenia exhibited higher error rates for their own face presented to the right hemifield whereas there was no effect for the control subjects. Additionally, self-face recognition was related to hallucinations in the patients. The authors concluded that results support the notion of a specific self-face processing dysfunction in schizophrenia.

Conversely, another study (J. Lee, Kwon, Shin, Lee, & Park, 2007) came to different results. They investigated self-face recognition in patients with schizophrenia, using a visual search paradigm with three types of targets: objects, famous faces and self-faces. Schizophrenic patients showed increased reaction time (RT) for detecting targets overall compared to normal controls but they showed faster RT for self-face compared with the Famous-face condition. For healthy controls, there was no difference between self- and famous-face conditions. Thus, visual search for self-face is more efficient than for famous faces and self-face recognition is spared in schizophrenia. These findings suggest that impaired self-processing in schizophrenia may be task-dependent rather than ubiquitous.

1.5 Attentional modulation

1.5.1 Top-down and bottom-up attention

I suggest that misattribution of speech in patients with positive symptoms suggests more than a “coping strategy”. In my point of view impairment of attention, that has been cited as a fundamental clinical feature of schizophrenia (Kraepelin, 1919; Posner, Early, Reiman, Pardo, & Dhawan, 1988) plays an important role in the misattribution of external speech in patients with positive symptoms. Abnormalities of visual (James Danckert, Saoud, & Maruff, 2004; P Maruff et al., 1998; Sereno & Holzman, 1995)(Rocca et al., 2006) and auditory (D. H. Mathalon, 2004) attention processing are frequently reported in patients with schizophrenia. In particular, attention impairment had been previously shown to correlate with positive symptoms of schizophrenia (Rocca et al., 2006). Both cognitive deficits in bottom-up and top-down processing have been reported in patients with schizophrenia (Fuller et al., 2006; Gold, Fuller, Robinson, Braun, & Luck, 2007).

Interestingly, neural deficits underlying impaired cognitive performance, support 'bottom-up dysregulation' more than the top-down cortical dysregulation (Butler et al., 2007; Leavitt, Molholm, Ritter, Shpaner, & Foxe, 2007).Specifically, bottom–up or exogenous attentional control is stimulus-driven, i.e. attention is spontaneously oriented towards an incoming stimulus. In contrast, top–down or endogenous attentional control is intentional and cognitively (schema/script) driven, i.e. directed by knowledge, expectation and current goals. Importantly, 'top-down' and 'bottom-up' processes represent overlapping organizational principles rather than dichotomous constructs, and in most situations, top-down and bottom-up processes interact to optimize attentional performance (Sarter, Givens, & Bruno, 2001). Deficits in magnocelullar, visual processing in schizophrenia suggest a dysfunction even within the early regions of the visual pathway, which may lead to 'bottom-up' driven dysregulation of higher cortical function (Butler et al., 2007). A recent study in auditory processing in schizophrenia reflects analogous findings that the earliest afferent input to the primary auditory cortex which arrives from subcortical regions already show evidence of dysfunction in patients with schizophrenia, arguing for a bottom-up model of auditory processing deficits (Leavitt et al., 2007). Although there have been few investigations of top-down and bottom-up attentional processes in patients with positive symptoms, one study observed a correlation between the severity of hallucination ratings and top-down influences on auditory perception. This is consistent with the notion that hallucinations may result from an increased influence of top-down sensory expectations on conscious perception (André Aleman, Böcker, Hijman, de Haan, & Kahn, 2003). It has been also shown in previous studies that when bottom-up and top-down processes conflict, patients with schizophrenia exhibit significantly worse performance than healthy controls (P Maruff et al., 1998).

1.5.2 Other attention deficits in schizophrenia

Schizophrenia is also associated with deficits in using context to establish prepotent responses in complex paradigms and failures to inhibit prepotent responses once established (J. M. Ford et al., 2004). Patients with schizophrenia exhibit difficulties with inhibition and cue processing (Arce et al., 2006) impaired cue recognition in a social context, particularly in those with positive symptoms (Hall et al., 2004). It is noteworthy that clinical states of paranoia are characterized by elevated suspiciousness and heightened perception of social threat (M. J. Green & Phillips, 2004), qualities consistent with increased vigilance toward cues. There is growing evidence about selective attentional impairment in patients with schizophrenia suffering from positive symptoms e.g. relationship with Stroop index color-word (Rocca et al., 2006). In line with that is the finding that patients with schizophrenia show increased rates of false alarms to invalidly cued targets (Javitt, Rabinowicz, Silipo, & Dias, 2007).

1.5.3 Neuroimaging in attention and schizophrenia

Neuroimaging research indicates that different attentional mechanisms, bottom-up and top-down, produce distinct patterns of neuronal activation. Additionally, results from previous studies showed that neural networks that mediate auditory and visual attention show differences and similarities in patterns of neural activation. In general, visual and auditory attention appears to be mediated by similar ventral frontoparietal network including the inferor parietal lobe (IPL) and frontal oculomotor areas (Corbetta & Shulman, 2002; Hahn, Ross, & Stein, 2006; Mayer, Harrington, Adair, & Lee, 2006; Pessoa, Rossi, Japee, Desimone, & Ungerleider, 2009; Salmi, Rinne, Koistinen, Salonen, & Alho, 2009). Auditory attention (reorienting) has not been shown to be as right hemisphere lateralized as the visual reorienting (Mayer et al., 2006).

Previous studies on visual attention (Corbetta & Shulman, 2002; Hahn et al., 2006) suggested that partially segregated areas of the cerebral cortex are involved in bottom-up and top-down controlled shifts of attention. See figure 1.2. The ventral attention system that is involved in bottom-up triggered visual attention includes temporo-parietal junction (TPJ, i.e. inferior parts of the IPL and posterior parts of superior and middle temporal lobe) and posterior parts of the inferior/middle frontal gyrus (IFG/MFG).

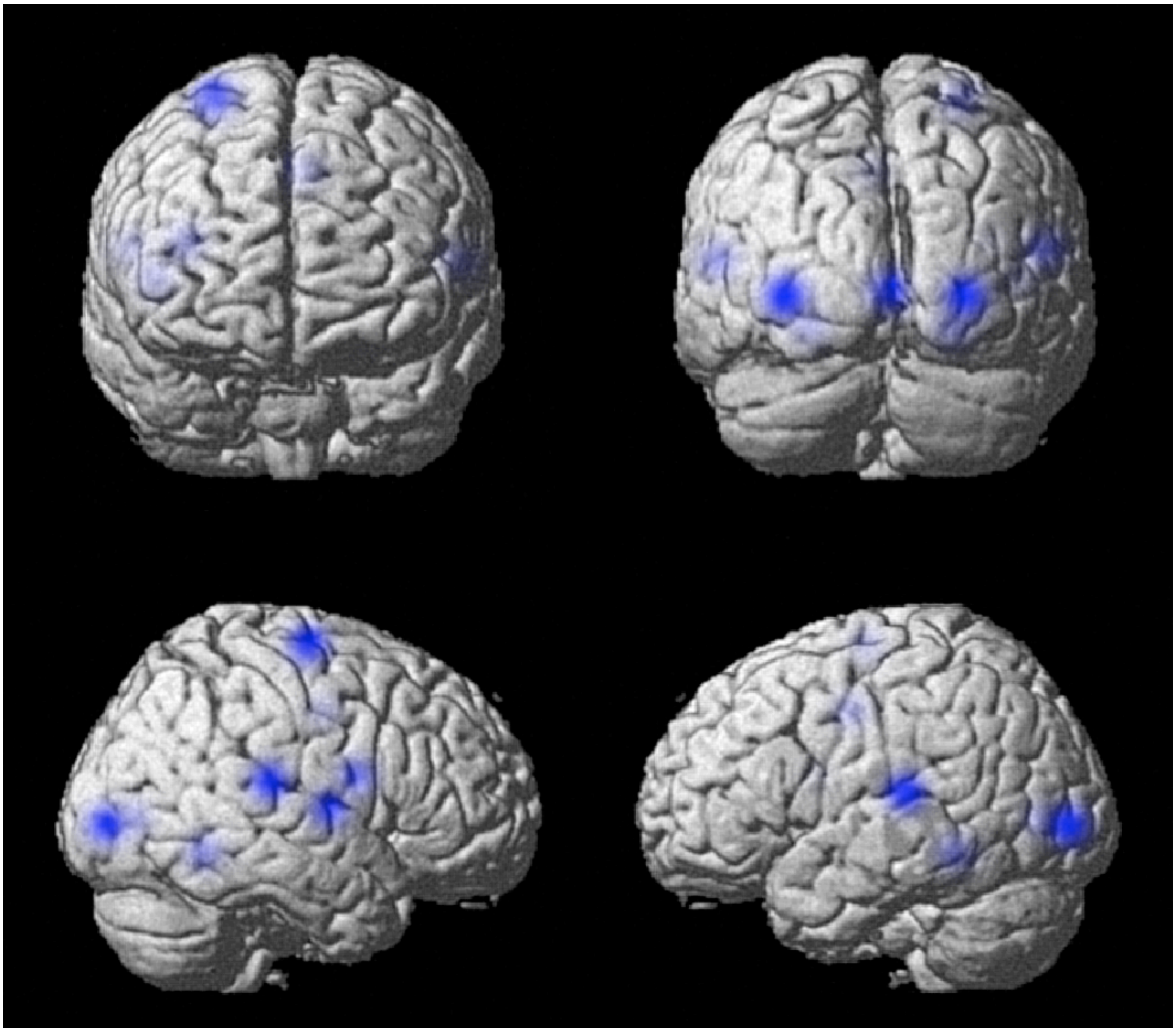

Figure 0.2 Schematic illustration of brain areas involved in bottom-up modulation of visual attention (according to Hahn et al., 2006). The regions that are referred to (in blue color): Superior temporal gyrus (STG)-temporoparietal junction (TPJ), anterior insula and precentral gyrus, posterior insula, fusiform gyrus, midcingular gyrus, lingual gyrus, cuneus, middle occipital gyrus (MOG). The left side of the brain is showed on the right side of the image and the right side of the brain is showed on the left side of the image. Note that the blobs with higher color intensity are closer to the brain surface.

Superior parietal areas, i.e. intraparietal sulcus (IPS) and superior parietal lobule (SPL) and the frontal eye fileds (FEF) in the posterior parietal cortex, in turn constitute the dorsal attention system, involved in top-down visual attention. However, many fMRI studies have reported substantial overlap between the areas associated with bottom-up triggered and top-down controlled visual attention (Serences & Yantis, 2007). These studies also suggest there is a bigger overlap between ventral and dorsal attentional system in auditory than in the visual domain (Salmi et al., 2009). In addition, these findings also suggest that different areas of SPL might have different roles in auditory attention, since the IPS and superior parts of the SPL are activated by specifically top-down controlled attention shifting, while the ventromedial SPL is activated also by bottom-up attentional modulation (distractors), auditory duration and deviation changes.

In contrast to automatic, stimulus-driven activity, activation in more posterior parts of the superior temporal cortex (near the TPJ) most likely is also modulated by top-down influences from prefrontal and parietal cortices.

The results of the first study to examine endogenous (top-down) attention within auditory modality (Mayer et al., 2006) increased activation in a temporal-prefrontal network, including left superior and right middle temporal cortex, right FEF and left IFG, but also the right precuneus (Pc). This network may not be specific to processing auditory information, but rather generally involved in shifts of attention irrespective of stimulus modality.

Other authors (Pessoa et al., 2009) have investigated control of attention involved in cue-related information within the visual modality. In general, this study suggests that the MFG and FEF in frontal cortex, and the IPS in parietal cortex are important for the top-down updating of cue-related information. Unexpected finding is related to stronger activity found in the right middle temporal gyrus (MTG) and superioduring the top-down control. These regions of the temporal parietal lobe have been more frequently reported to be involved in the bottom-up (stimulus-driven) attentional control.

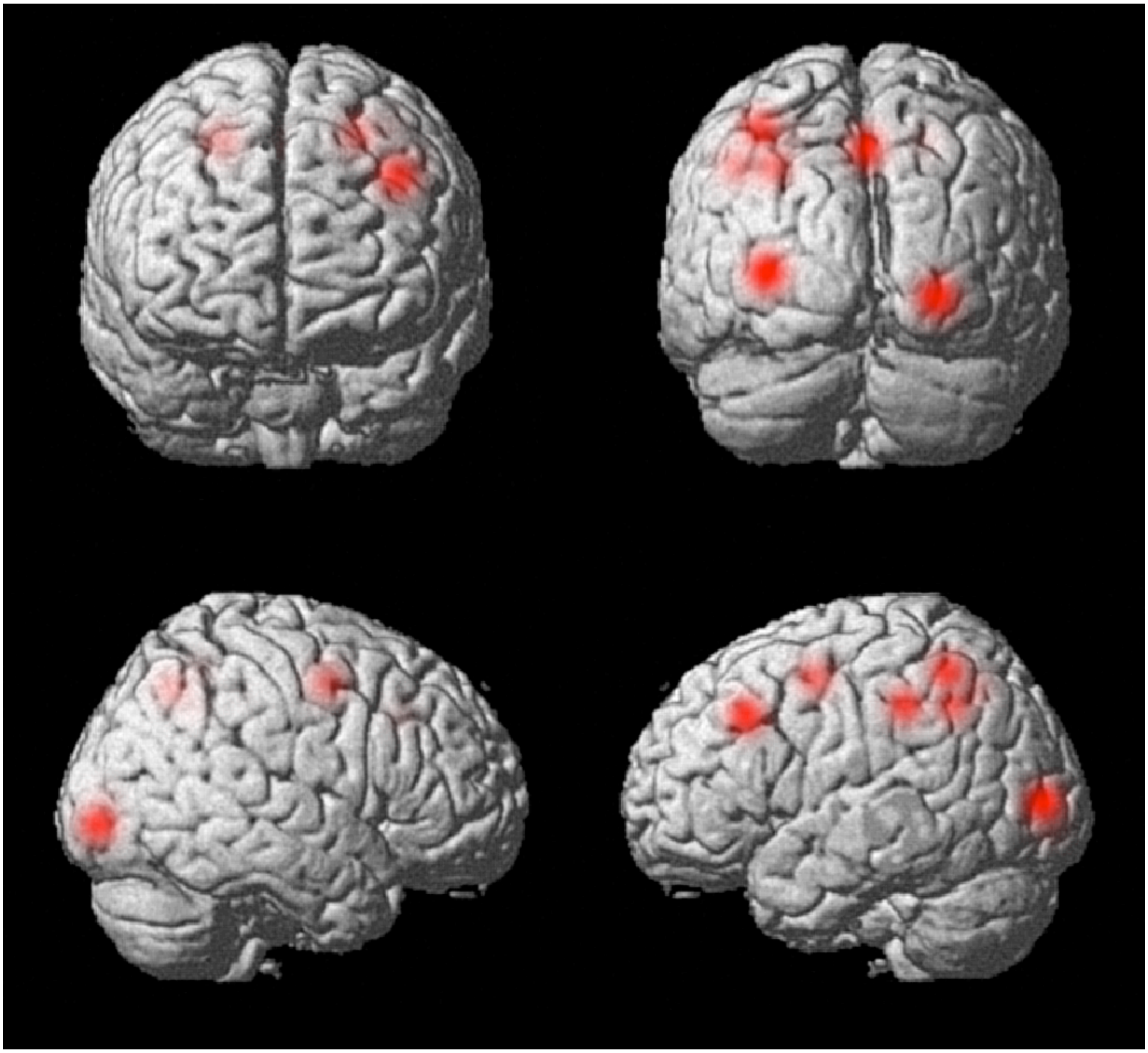

Figure 0.3 **Schematic illustration of brain areas involved in top-down modulation of visual attention (according to Hahn et al., 2006). The regions referred to are (in red color): intraparietal sulcus (IPS), superior/inferior parietal lobule inferior parietal lobule (SPL/IPL), precuneus (Pc), middle frontal gyrus (MFG), superior frontal sulcus (SFS). The left side of the brain is showed on the right side of the image and the right side of the brain is showed on the left side of the image. Note that the blobs with higher color intensity are closer to the brain surface.**

1.5.4 Audio-visual intergration and divided attention

Another relevant aspect for my study is the audio-visual integration in neuroimaging research. One of the recent studies suggesting brain areas involved in cross modal binding (Saito et al., 2005) was using audio-visual speech integration task (matching voice with lip movement). Brain areas found to be involved in cross modal matching compared with the unimodal matching task are lateral parietal lobe (LPs), dorsolateral prefrontal cortex (DLPFC) bilaterally, the left IPS, right cerebellum (Saito et al., 2005) The ventral IPS is a well known polymodal area as the fundus of the IPS is known to contain cells with distinct polysensory receptive fields (in macaque monekys). Another study (Calvert, Campbell, & Brammer, 2000) showed that posterior poles of the middle occipital gyri (MOG), left and right superior temporal sulcus (STS), left primary auditory cortex (BA 41/42), MFG, inferior parietal cortex (IPC; BA 40) exhibited strong activation in congruent audio-visual trials. In contrary, responses to incongruent auditory and visual stimulation were located as well in the left STS, left and right inferior frontal region (BA 44/45), the premotor areas (BA6), the right STG (BA22) and the anterior cingulate gyrus (ACG). Other studies (Bushara et al., 2002) found that cross modal binding was associated with higher activity in insula/ frontal operculum, DLPFC and medial prefrontal cortex (mPFC), posterior parietal cortex (PPC), posterior thalamus, superior colliculus and posterior cerebellar vermis.

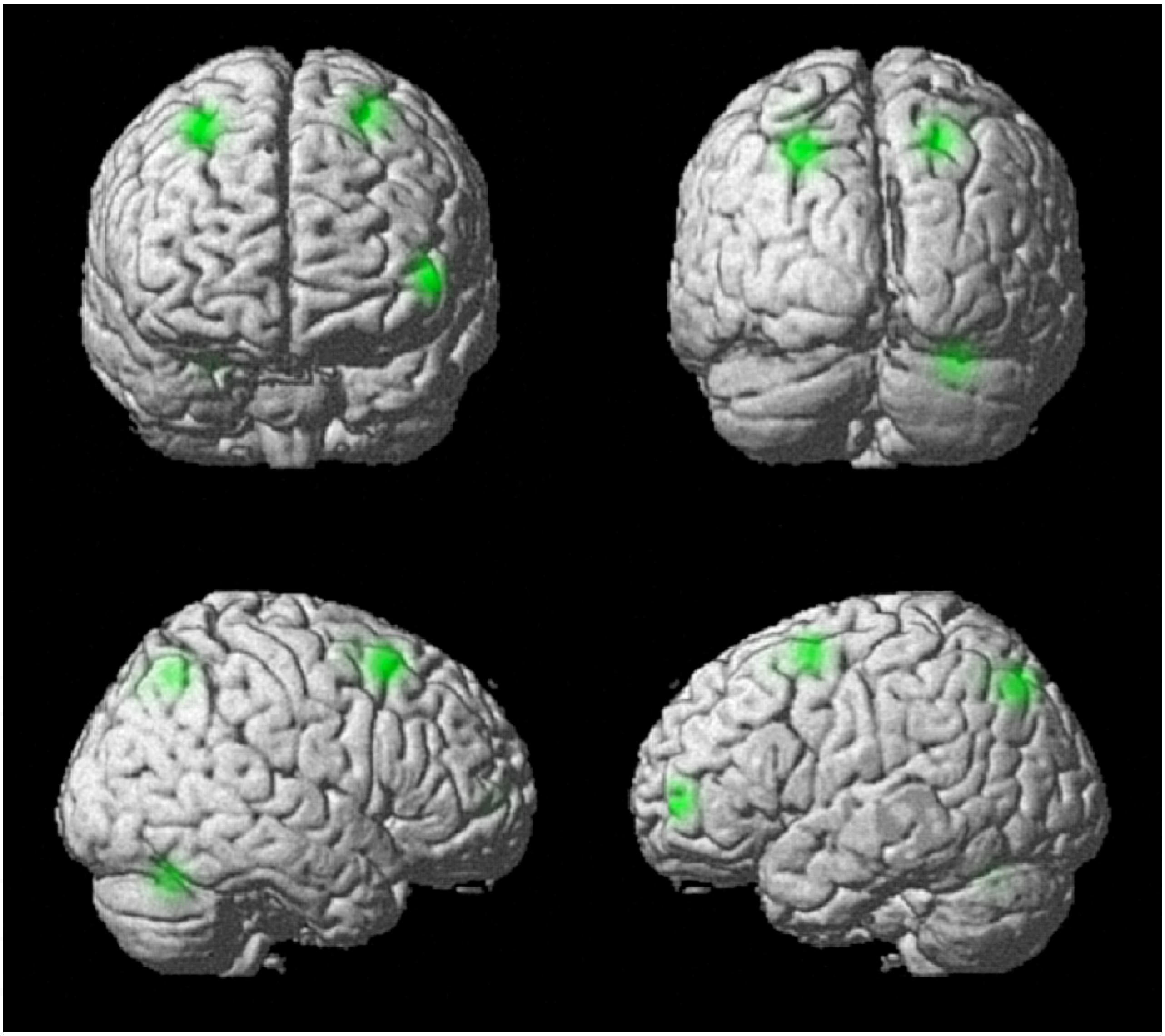

Figure 0.4 Schematic illustration of brain areas involved in audio-visual integration (according to Saito et al., 2009). The regions referred to are (in green color): intraparietal sulcus (IPS), superior parietal lobule (SPL), dorsal premotor cortex. The left side of the brain is showed on the right side of the image and the right side of the brain is showed on the left side of the image. Note that the blobs with higher color intensity are closer to the brain surface.

Importantly, neural substrates of cross modal binding are closely related to those for divided attention (J. A. Johnson & Zatorre, 2006). One of the studies investigating this relationship was using simultaneous auditory and visual events. Subjects in an fMRI scanner simultaneously heard novel melodies and viewed abstract shapes with instruction to attend either to the melodies or shapes (selective attention) or attend to both modalities (divided attention). This study found no involvement of heteromodal cortices in the bimodal selective attention condition, but in the bimodal divided attention condition there was activity in the middle DLPFC (area 46) and posterior DLPFC (area 9) .

Most of the studies on the neural correlates of visual and auditory visual attention during the past decade included healthy participants. Moreover, tasks engaging multimodal attentional cortices, have not been frequently used among patients with schizophrenia. To my knowledge my study is the first one to examine misattribution of source in H/D patients on the cross modal (audio–visual) level.

1.6 Neuroimaging and cortical midline structures

A recent meta-analysis (Northoff et al., 2006) identified three regions mPFC, dorsal anterior cingulate, and posterior cingulate, including the adjacent retrospelnium and Pc that showed increased activation when tasks required judgments about the self-relevance of stimuli, irrespective of the stimulus domain or sensory modality (e.g., determining whether certain personality traits are self-descriptive, or whether emotional stimuli have self relevance). These authors concluded that this system is a functional network specialized for self-referential processing, and that activity in this putative cortical midline system (CMS) may represent the neural instantiation of the core self. ((Damasio, 2000) identified the cingulate gyrus as a key region in a neural network sustaining the core self, arguing that its afferent and efferent connections placed it in the perfect position to integrate internal states with external information, the defining functional property of the core self.

The CMS may be regarded as an anatomical unit for two reasons: (1) These regions maintain strong and reciprocal projections among each other (2) they show a similar pattern of connectivity to brain regions outside the CMS. These actions include dense links to ventro-and dorsolateral prefrontal cortex, structures in the midbrain and brain stem subserving autonomic functions, and the limbic system, including hippocampus, amygdala and insula.

Many of the fMRI paradigms studied in the meta-analysis (Northoff et al., 2006) required consciously directed appraisals about the self-relevance of stimuli, corresponding more to the reflective and narrative selves, rather than pre-reflective minimal self described by phenomenologists. Hence, the authors of the meta-analysis argue that the processing of stimuli as self-referential is precisely what forms the basis of ipseity.

Thus, CMS regions are viewed as playing a pre-reflective role in self referential processing during tasks requiring active self-reflection, and recruitment of other brain regions, such as the lateral prefrontal cortex, is proposed to make these self-related evaluations the subject of reflective thought. As such, the self-referential processing mediated by the CMS (Northoff & Bermpohl, 2004; Northoff et al., 2006) represents an intermediary between sensory and higher-order cognitive processes.

The distinction is made (Northoff & Bermpohl, 2004) between representation, monitoring, evaluation and integration of self- referential stimuli. Specifically, the orbital and medial prefrontal cortex (OMPFC) seems to account for the continuous representation of self-referential stimuli. Once represented in the OMPFC, self-referential stimuli appear to me monitored in the supragenual anterior cingulate and evaluated in the DLPFC. Integration of these stimuli in the emotional and autobiographical context is related to the posterior cingulated cortex.

Together, these findings suggest the CMS, interacting with other brain areas, may play a role in both reflective and pre-reflective self-referential processing. However, the present evidence suggests CMS is fundamental to self-referent processes (Grimm et al., 2009; Modinos, Renken, Shamay-Tsoory, Ormel, & Aleman, 2010; Northoff & Bermpohl, 2004) and that CMS function is altered in patients with schizophrenia (Holt et al., 2011; Nelson et al., 2009; van der Meer, Costafreda, Aleman, & David, 2010).

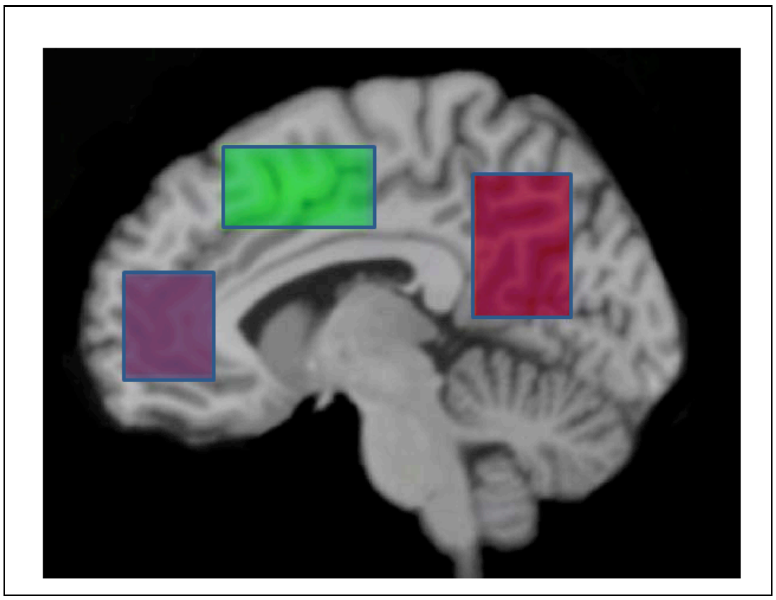

Figure 0.5 The distinction between the ventromedial prefrontal cortex VMPFC, the dorsomedial prefrontal cortex (DMPFC), and the precuneus (Pc) which might correspond to functional specialization within the CMS. Note that there are no clear anatomically defined borders between the different regions.

2. Behavioral study

2.1 Aims and hypothesis

The general aim of the behavioral part of the study was to examine the effect of attentional modulation on source decisions for pre-recorded in patients with schizophrenia, more specifically H/D patients and in healthy control (HC) group. In the previous versions of the chosen paradigm (P. Allen et al., 2004; L. C. Johns et al., 2001) disparity was used to manipulate what subjects expected to hear and what they actually perceived. I used both valid and invalid cues in a speech appraisal task (Ilankovic et al., 2011) in order to modulate the participant's expectancies about the source of speech that they heard. I used the condition in which the participant's or someone else's voice is distorted as that contributes to the ambiguity of the cue opposed to the condition in which the voice is undistorted.

I predicted that:

1) when top-down (cue preceding the voice stimuli) and bottom-up (source of the voice stimuli) mechanisms are placed in conflict (e.g. during invalid trials) H/D patients will demonstrate impaired performance relative to healthy controls. This is because patients with hallucinations and delusions are allowing top-down information to guide them at the expense of bottom-up information.

2) The patients will demonstrate a significant externalizing response bias (misidentifying their own speech as alien) that will be particularly evident on invalid cue trials when their own voice is preceded by an alien cue. Misattribution errors should be more evident in the predictive cue condition (80% valid cues and 20% invalid cues), as

the high informative power of the cue should guide source attributions stronger relative to an unpredictive cue condition (50% valid cues and 50% invalid cues).

3) Finally, in the patient group errors associated with invalid trials should correlate with severity of positive symptoms.

2.2 Method

2.2.1 Participants

Twenty-three patients who met ICD-10-GM (Band 2; World Health organization, 2008) criteria for paranoid schizophrenia recruited from a pool of volunteers from the psychiatric hospital in Munich (Department of Psychiatry and Psychotherapy, Ludwig-Maximilians-University) and twenty-three healthy German-speaking demographically-matched (gender, age, education and IQ) volunteers with no history of psychiatric illness recruited through advertisement were included in this study (see Table 2.1). All the patients were inpatients and they were tested 2-6 weeks (M=19.1 days, SD=12.3) after the admission to the hospital. They were all symptomatically stable at the time of testing and still reporting positive symptoms despite medication. They were on regular, stable doses of antipsychotic medication, either typical (19) or atypical (2) or both (2). In addition to antipsychotic medication, some patients were receiving Benzodiazepine for the treatment of anxiety (7) and Biperiden to attenuate Parkinson symptoms (4). Patients' symptoms were assessed on the day of testing using the Scale for the Assessment of Positive symptoms (SAPS; Andreason, 1984a), the Scale for Assessment of Negative Symptoms (SANS; Andreason, 1984b) and the Psychotic Symptom Rating Scale (Haddock, McCarron, Tarrier, & Faragher, 1999). Patients were selected for inclusion if they scored 3 or more on SAPS global hallucinations or delusions subscales (see Table 1). The exclusion criteria for all the subjects was the following: presence of neurological diseases, current or recent alcohol abuse or drug addiction. Only participants with an greater IQ than 85 as determined by the Wortschatztest (Schmidt & Metzler, 1992) were included. After reading a complete description of the study all participants gave written informed consent to participate, which was approved by the local research ethics committee.

Table 0.1 Demographic, psychopathological and behavioral data

	Patients with hallucinations and delusions (N=23) M (SD)	Controls (N=23) M (SD)	Analysis
Age in years	33.26 (9.30)	33.78 (9.26)	t=-.199, p=0.843
Premorbid IQ	104.87(13.28)	110.65 (12.01)	t=1.48, p=0.145
Years of education	11.91 (2.42)	12.48 (2.46)	t=.783, p=0.438
Gender ratio M/F	11/12	11/12	
Symptom ratings			
Age of onset	29.83 (7.3)		
Duration of illness	4.70 (5.1)		
Auditory Hallucinations	3.69 (3.8)		
Non-auditory Hallucinations	0.96 (2.3)		
Delusions	9 (4.2)		
Other positive symptoms [a*]	6.91 (3.3)		
Negative symptoms [b*]	8.34 (4.2)		
Attentional problems	1.57 (1.2)		
PSYRATS Auditory Hallucinations	9.26 (10.6)		
PSYRATS Delusions	13.52 (3.8)		

a*Mean of global scores for bizarre behaviour and formal thought disorder

b*Mean of global scores for alogia, anhedonia, inappropriate affect, avolation and affective flattening

*SAPS/SANS mean scores

2.2.2 Word lists

A list of 192 personal adjectives was used. The word list in the present study consisted of the majority of adjectives used by Allen et al. (P. Allen et al., 2004) derived from the study of Johns et al. (L. C. Johns et al., 2001). These words were translated into

German from the original version in English language. Three months before we had started running the experiment I started off the evaluation of the words. I created the questionnaire that we gave to 20 healthy subjects in order to evaluate the words. The questionnaire was given in order to improve reliability of the preliminary words' categorization. My 20 subjects were asked to evaluate each word from 1 to 7 on two scales (1 was standing for absolute lack of certain characteristic and 7 was standing for absolute presence of certain characteristic). First was the scale of valence (how positive or how negative some word is) and second was the arousal scale (how arousing or not some word is).

In order to choose number of words needed for the experiment after I obtained them via questionnaires, I performed statistical analysis and selected the most appropriate words by using following criteria: valence, arousal, word length and word frequency in German language. These were some mean values on different scales that had been taken into consideration before selecting the words. First, neutral words had mean value on the valence scale between 3.50 and 4.50; on arousal scale under 2.30; positive words had mean value on the valence scale above 4.50 and on arousal scale above 2; negative words had mean value on the valence scale under 3.50 and on arousal scale above 3. The sets of words presented in each condition were balanced for the number of syllables (i.e. equal amounts of one and two syllable words), word frequency and valence (equal amounts of positive, negative and neutral words). At the end I selected 96 negative words, 72 positive and 24 neutral words.

2.2.3 Auditory stimuli

1) 96 words that were the subjects own voice (i.e. self speech) and 2) 96 words that were a standardized unfamiliar male or female voice that were used to replace the voice of the subject on half of the trials (alien speech). The speech was recorded and distorted by Audacity 1.2.6. (http://audacity.sourceforge.net). The alien voice was provided by 2 members of staff at the Psychiatric Hospital in Munich, one male and one female native German speaker. The alien pictures were also provided by the same male and female stuff members that provided their alien voice to the study. I used gender matched images and voices throughout the task. The equipment I used consisted of a PC computer (Fujitsu Siemens, P19-2), Sony stereo headphones (MDR-XD300) and the microphone (UHER; MDR-XD300). Presentation software 10.3. (http://www.neurobs.com) was used to present all auditory stimuli and record the responses of the subjects. The volume levels of both the participant's speech and the alien speech were kept as close as possible by normalizing the volume to ensure that differential volume could not subsequently be used to discriminate between the two types of speech. The participants sat 60 cm in front of a 19 in. computer screen, in a semi-darkened room designated for neuropsychological tests and experiments.

2.2.4 Visual stimuli

Visual cues consisted of subjects' portrait picture (200 x 267 pixel, in full color), taken by an Olympus digital camera (D-425: 4.0 megapixel) displayed vertically in the center of the computer screen on a gray background, preceding the upcoming auditory stimuli. Pictures were matched with regard to color intensity, brightness and contrast by using Adobe Photoshop (http://www.adobe.com/de/products/photoshop/)

2.2.5 Design

There were two levels of validity (valid, invalid), two sources of speech (self, alien), two levels of distortion (0, -4 semitones) and two groups (control, patients), resulting in a 2 x 2 x 2 x 2 factorial design. Self speech preceded by a picture of the subject's own face (self picture cue) and alien speech preceded by an alien picture cue, respectively, constituted valid trials, whereas the self speech preceded by an alien face and alien speech preceded by a subject's own picture, represented invalid trials. One experimental run consisted of 50% valid cues and 50 % invalid cues (unpredictive cue condition). The other experimental run consisted of 80% valid and 20% invalid cues (predictive cue condition).

I introduced the unpredictive cue condition to be able to assess the task 'baseline', where participants' performance was neither impaired nor facilitated by the information provided by the cue, in contrast to predictive cue condition. Each run consisted of 8 possible combinations of cues (self, alien) and voices (self, alien) making a total of 192 trials (24 for each experimental condition). In the unpredictive cue condition 12 valid and 12 invalid cue trials were included whereas in the predictive cue condition 19 valid and 5 invalid cue trials were included for each experimental condition. Valid and invalid trials were pseudorandomized across subjects.

Each trial began with the appearance of the fixation cross for 1000ms. Then the cue was presented for 200 ms. The word was presented through the headphones 300 ms after the onset of the cue, followed by a response screen for 4.5 seconds. Participants wore headphones and the volume was checked to ensure that it was at the level sufficient for them to hear the speech without difficulty. The response screen with response alternatives appeared on the computer monitor after every trial to avoid the working memory load in subjects. See figure 2.1.

If the participants thought the speech they heard was their own they were instructed to press the button marked as number one on the keyboard. If they thought the speech belonged to someone else they were asked to press the button marked as number two and if they were unsure of its source they were instructed to press the button number three. After participants made their response by pressing “1”, “2” or “3” on the keyboard (‘self’, ‘other’, ‘unsure’) the new trial began. The computer recorded the response and the reaction time. In addition to the ‘self’ and ‘other’ responses, subjects were also able to register an ‘unsure’ response. This is important because when participants were in doubt about the source of speech , they were not obliged to make a forced choice between ‘self’ and ‘other’, making it more likely that when they did select either of these responses they did so with some degree of confidence.

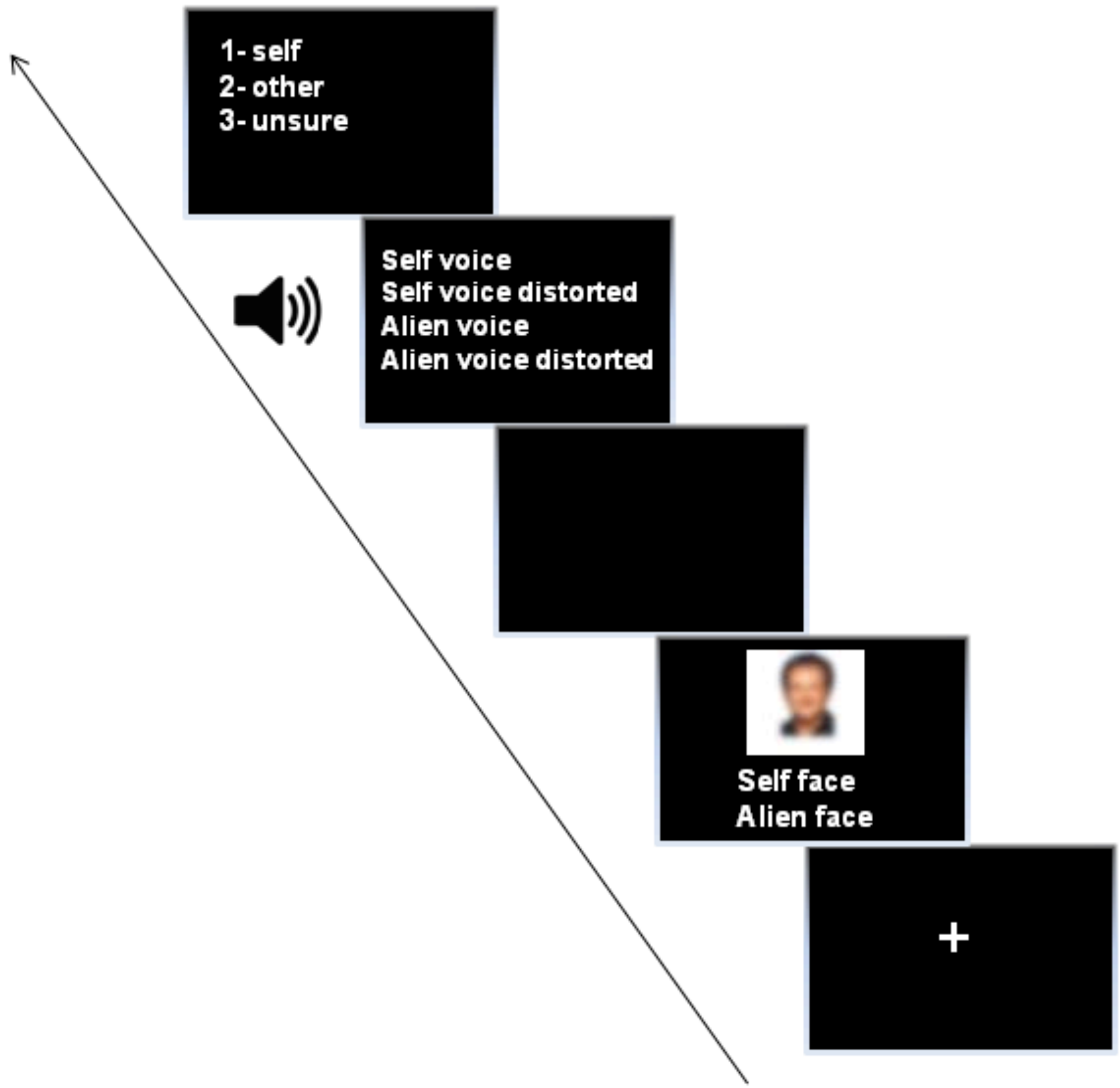

Figure 0.1 Example of trial procedure in the behavioral study

2.2.6 Procedure

Participants were informed upon recruitment that the experiment would be conducted over three sessions. I explained to me them that the first session would be used to record their speech and the second and third session would be used to administer the task.

2.2.7 First session

The participants were asked to read all 192 words in the microphone even though half would subsequently be replaced by an alien voice, to ensure that participants could not make judgments based on source information when subsequently presented with the prerecorded words. Hence to ensure that the task relied on perceptual discrimination as opposed to source memory. Before the second session 96 previously designated words (one half of the list) were replaced with the alien version of the word. Half of all self and alien words (96 words) were pitch shifted by -4 semitones. The degree of pitch was chosen because it made speaker's voice harder to recognize without making the word incomprehensible. The rest of the words were unaltered self and alien voice version (48 words each). The same words were used for the predictive and unpredictive run. The picture of the subject was always taken at the end of the session. The entire first session took about 30 minutes.

2.2.8 Second and third session

These two sessions were held on separate days in order to avoid practice effects for the participants. They took place within one week after the first session. The mean interval between the first and the second session was 2. 5 days. Participants were not informed of the level of cue predictability before each assessment, but they were given a general hint that the cue can be either valid or invalid. The testing time for the second and third session was about 15 minutes each.

2.2.9 Statistical analysis

The data were analyzed using Statistical Package for Social Science SPSS 16 (http://www.spss.com/). Separate ANOVAs for repeated measures were conducted with misattribution errors, unsure responses and reaction times as the dependent variables. Misattribution errors occurred when participants misattributed the source of the speech (i.e. responding with 'other' when the source of the speech was self and vice versa), as opposed to errors when participants responded with 'unsure' or made a null response. The within-subjects factors were source of speech (self, alien), distortion (0,-4 semitones) and cue predictability (valid, invalid). The between subjects factor was group (controls, patients). Correlation analyses were conducted using Spearman r_s statistics. All statistics were two-tailed, and reported at a significance $p<0.05$. All data were normally distributed (Leven's test).

2.3 Results

2.3.1 Misattribution errors

The groups were compared in terms of misattribution errors and unsure responses. The mean proportions for correct unsure and misattributed responses are shown in tables 2.2 and 2.3.

Table 0.2 Predictive cue condition. Mean untransformed proportions (standard deviations) for correct, unsure responses and misattribution errors according to condition and group

	Valid cue condition				Invalid cue condition			
	Self Undistorted	Self Distorted	Alien Undistorted	Alien Distorted	Self Undistorted	Self Distorted	Alien Undistorted	Alien Distorted
Controls								
Correct response	0.97	0.68	0.91	0.69	0.94	0.68	0.92	0.70
	(0.16)	(0.27)	(0.11)	(0.27)	(0.18)	(0.32)	(0.12)	(0.29)
Unsure response	0.00	0.12	0.01	0.09	0.0	0.09	0.02	0.11
	(0.00)	(0.19)	(0.04)	(0.17)	(0.02)	(0.15)	(0.06)	(0.17)
Misattributions	0.06	0.19	0.06	0.21	0.04	0.22	0.05	0.18
	(0.16)	(0.26)	(0.08)	(0.22)	(0.16)	(0.30)	(0.08)	(0.22)
Patients								
Correct response	0.90	0.27	0.80	0.68	0.86	0.25	0.77	0.71
	(0.11)	(0.30)	(0.31)	(0.36)	0.15	(0.31)	(0.31)	(0.31)
Unsure response	0.01	0.17	0.03	0.17	0.02	0.16	0.04	0.13
	(0.04)	(0.27)	(0.05)	(0.29)	(0.06)	(0.28)	(0.09)	(0.23)
Misattributions	0.07	0.54	0.16	0.10	0.10	0.57	0.17	0.14
	(0.10)	(0.37)	(0.29)	(0.15)	(0.12)	0.29	(0.29)	(0.20)

Table 0.3 Unpredictive cue condition. Mean untransformed proportions (standard deviations) for correct responses, unsure responses and misattribution errors according to condition and group

	Valid cue condition				Invalid cue condition			
	Self Undistorted	Self Distorted	Alien Undistorted	Alien Distorted	Self Undistorted	Self Distorted	Alien Undistorted	Alien Distorted
Controls								
Correct response	0.91	0.61	0.92	0.73	0.90	0.62	0.91	0.75
	(0.15)	(0.32)	(0.16)	(0.22)	(0.20)	(0.30)	(0.12)	(0.22)
Unsure response	0.00	0.11	0.06	0.11	0.01	0.14	0.02	0.10
	(0.12)	(0.20)	(0.06)	(0.17)	(0.03)	(0.23)	(0.07)	(0.15)
Misattributions	0.08	0.23	0.01	0.15	0.08	0.23	0.05	0.14
	0.15	(0.27)	(0.10)	(0.19)	(0.20)	(0.28)	(0.09)	(0.16)
Patients								
Correct response	0.90	0.29	0.78	0.72	0.89	0.26	0.77	0.71
	(0.12)	(0.29)	(0.32)	(0.34)	(0.13)	(0.27)	(0.31)	(0.31)
Unsure response	0.14	0.14	0.03	0.15	0.01	0.16	0.03	0.14
	(0.03)	(0.25)	(0.07)	(0.24)	(0.05)	(0.26)	(0.08)	(0.24)
Misattributions	0.01	0.55	0.18	0.11	0.08	0.55	0.18	0.13
	(0.10)	(0.35)	(0.30)	(0.21)	(0.10)	0.33	(0.31)	(0.20)

The effect of cue was non-significant (F=0.139, df=44, p=0.711), but there was a significant main effect of source of speech in the unpredictive (F=10.367, df=44, p=0.002) and predictive cue condition (F=6.598, df=44, p=0.014). Across both predictive and unpredictive cueing conditions all participants made more errors for self words than for alien words.

There was a significant main effect of distortion in both conditions, unpredictive (F=48.128, df=44, p=0.000) and predictive (F=50.035, df=44, p=0.000). All participants made more errors when the words were distorted than when they were not. There was also a significant interaction between source of speech, distortion and group in both cueing conditions, unpredictive (F=10.203, df=44, p<0.003) and predictive (F=10.429, df=44, p<0.002). When the words were distorted, H/D patients made significantly more misattribution errors for self words than for alien words comparing to HC (selecting 'other' when hearing their own voice). See figures 2.2.a. and 2.2.b.

In order to bolster the significance of this result, we report the effect size measure, Cohen's d, which was large for this comparison (d=1.07).

In the predictive cue condition, the main effect of cueing was not significant (F=1.48, df=44, p=0.229). However, the interaction between the cue type and group was significant (F=4.64, df=44, p=0.037). Patients with hallucinations and delusions, but not HC, made significantly more errors across all the conditions in which the cue was invalid (see Figure 2.2.b). Post hoc analysis shows that patients were particularly prone to misidentify their undistorted self-speech as alien when preceded by an invalid alien cue; whereas they did not show the tendency to misidentify their own undistorted voice when preceded by a valid face cue (t=-2.256, p=0.034). In order to assess the magnitude of this relationship within the patient's group I calculated the effect size which was moderate (d=0.27)

On the contrary, HC seem to be facilitated in the same condition, identifying undistorted self-speech when preceded by an invalid cue with more accuracy (t=2.390, p=0.026). Importantly, H/D patients did not show the opposite tendency, to make more misattribution errors when invalid cue preceded the alien undistorted voice (t=-0.362, p=0.721).

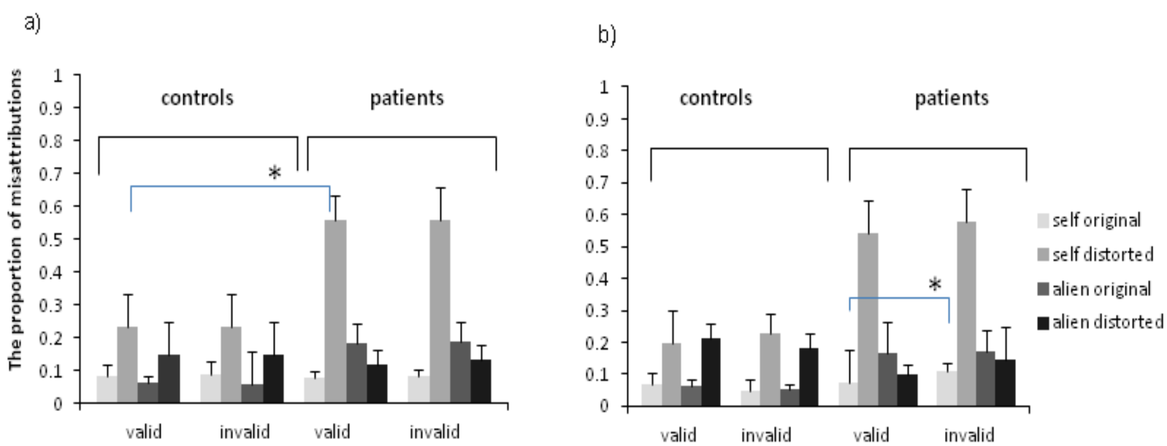

Figure 0.2 a) Mean misattribution rate across unpredictive condition b) Mean misattribution rate across predictive condition

Whereas the within-group differences in both groups in self speech condition with invalid cues were significant, the difference between the patients and the HC did not reach a significant level (t=0.346, df=44, p=0.168), though the effect size measure was moderate (d=0.42).

2.3.2 Unsure responses

The interaction between the cue type and group was not significant (F=0.440, df=44, p=0.598). Patients with hallucinations and delusions did not make significantly more unsure responses comparing to the HC. The main effect of the distortion was significant both in unpredictive (F=13.009, df=43, p=0.001) and predictive cue condition (F=0.311, df=44, p=0.001), but this was the case in both groups. All participants made more unsure responses when the words were distorted than when they were not, irrespective of the source of speech. There was a significant interaction between the cueing (invalid, valid), source of speech and distortion (F=4.255, df=43, p=0.045) in the unpredictive cue condition, showing that all subjects were particularly prone to give unsure responses for self distorted words preceded by an invalid cue (see Figure 2.3.a). In addition, I found a significant trend in interaction between cueing and distortion (F=3.953, df=44, p=0.053) in the predictive cue condition (see Figure 2. 3. b).

2.3.3 Correlation analysis

The bivariate correlation analysis was performed to examine the association between misattribution errors and symptom ratings in the patient group. In the unpredictive cue condition, the PSYRATS delusions scores were positively correlated with errors on invalid trials, in which patients listened to their distorted voice preceded by an alien face (r=0.420, p=0.046). In the predictive cue condition no correlations between errors on invalid trials and PSYRATS or SAPS scores were found. Furthermore, misattribution errors when listening to the self-distorted voice preceded by the self cue (r=0.588, p=0.003) and self-undistorted voice preceded by the alien cue were positively correlated with the SANS global attention deficit score (r=0.472, p=0.023).

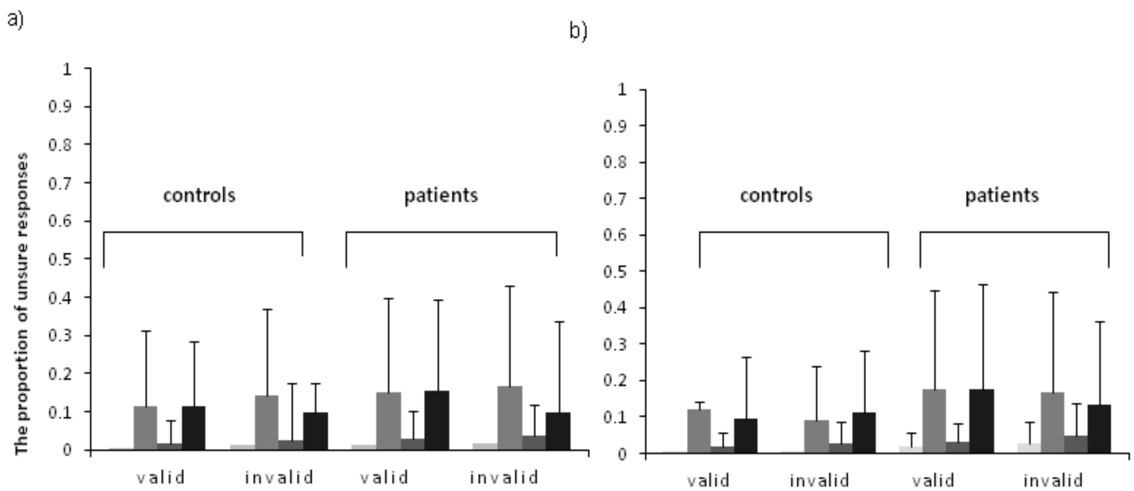

Figure 0.3 a) Mean rate of unsure responses across unpredictive condition b) Mean rate of unsure responses across predictive condition

2.3.4 Reaction times

To assess if task accuracy across groups was related to response speed, mean reaction times were calculated for correct (see Figures 2.4.a and 2.4b) and error trials (see Figures 2.5.a and 2.5b). Reaction times for correct responses on valid and invalid trials did not differ between the HC group and the patient group. However, for the misattribution errors there was a significant cueing x distortion x group interaction in the unpredictive (F=5.42, df=41, p=0.025) and predictive cue condition (F=4.24, df=41, p=0.046).

a) b)

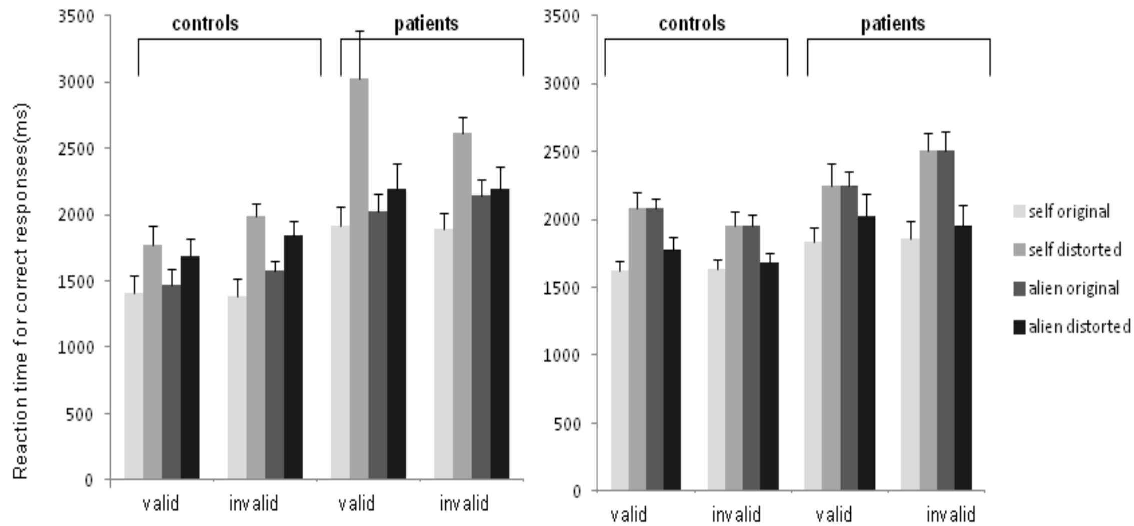

Figure 0.4 a) Mean reaction time for correct responses across unpredictive condition b) Mean reaction time for correct responses across predictive condition.

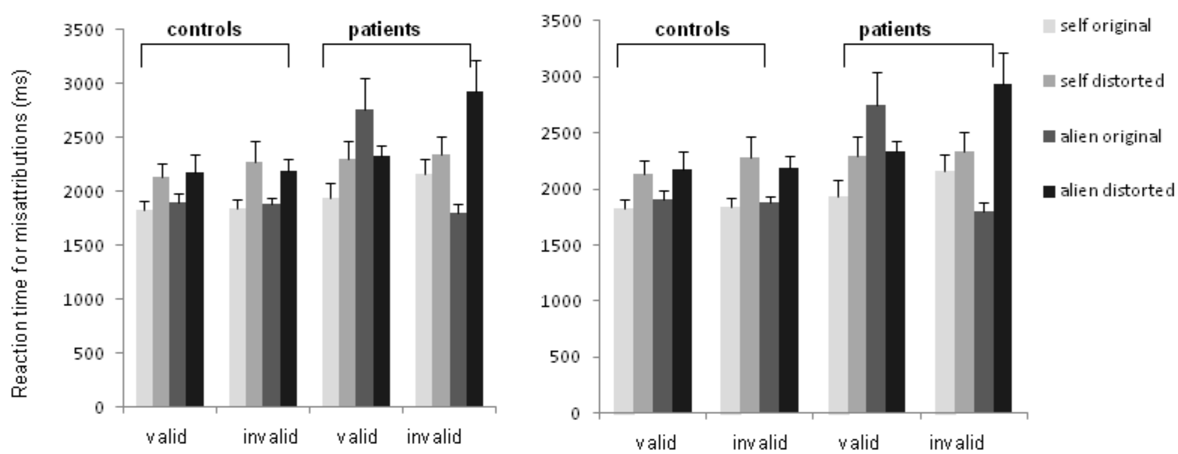

Figure 0.5 a) Mean reaction time for errors across unpredictive condition b) Mean reaction time for errors across predictive condition.

Post hoc analysis shows that H/D patients were particularly prone to misidentify their undistorted self-speech as alien when preceded by an invalid alien cue faster than the controls (t=2.289, p=0.027) in the predictive cue condition (see Figure 5b). In order to assess the magnitude of this relationship within the patient's group I calculated the effect size, which was large (d=0.71). Finally, the patients also responded faster to undistorted self-speech falsely when preceded by an invalid alien cue than when preceded by valid self cue (t=2.436, p=0.023).

2.3.5 Cross-condition effects

Across the two main conditions (unpredictive and predictive) we found a trend for patients to give less correct answers in invalid trials in the predictive cue condition comparing to the unpredictive condition. At the same time, HC were prone to give more correct responses to invalid trials in the predictive cue condition comparing to the unpredictive one (F=0.843, df=44, p=0.099).

2.4 Discussion

The aim of the behavioral part of the study was to investigate the interaction between top-down and bottom-up attention in patients with schizophrenia with predominantly positive symptoms. More specifically, I was interested in testing whether patients' source attributions for their own speech were biased by top-down information (visual cues of their own or another person's face) at the expense of bottom-up stimuli (voice stimuli), in two different versions of a cueing task. I predicted that the dominance of top-down over bottom-up mechanisms would be expressed by directing attention to the cue preceding the target, and following this cue irrespective of its predictive power.

During the unpredictive cueing task, as expected, there was no facilitation in either HC or H/D patients. The results confirmed my assumption and there is no evidence that cueing has an effect on the performance of any of the two groups in the unpredictive condition.

In line with my hypothesis, my results from the predictive cueing task show that patients were far more susceptible than HC to cue manipulation, resulting in more misattribution errors on invalid trials. This is consistent with previous studies which have demonstrated that patients with schizophrenia show increased rates of false alarms to invalidly cued targets (Javitt et al., 2007).

My findings from both predictive and unpredictive condition are consistent with previous findings using speech appraisal and monitoring task (P. Allen et al., 2004; Cahill C. et al., 1996; Judith M. Ford & Mathalon, 2005; L. C. Johns et al., 2006, 2001), that H/D-patients are more likely to make misattributions about the source of their own distorted speech than HC.

The critical issue, whether misattribution errors are augmented by invalid top-down information in the invalid trials, was confirmed. My second hypothesis that externalizing bias on invalid trials in the patient group could be source specific was not confirmed, as the interaction between cueing, source of the speech and group was not significant. The patients made significantly more errors across all the conditions in which the cue was invalid, but they were not particularly prone to misattribute undistorted self-generated speech to an external source when the voice was preceded by an alien (invalid) cue compared to HC.

However, the patients experience uncertainty during invalid cueing of the voice stimuli, especially when the majority of all cues are valid (80-20 condition). As the predictive cue condition has higher informative power to guide source attributions relative to the unpredictive cue condition, this strongly suggests that the pattern of misattribution responses does differ between patients and controls depending on the cue predictability.

Analysis of the participants' RTs showed that patients were faster when making source judgments after invalid cueing of undistorted speech relative to HC. This may reflect an overall tendency for patients to make quicker judgments based on less information. This is in accordance with patients with delusions to 'jump to conclusions' (Garety, Kuipers, Fowler, Freeman, & Bebbington, 2001). Additionally, the finding that patients were faster when making source judgments after invalid cues relative to HC is consistent with the study of (Nestor et al., 1992). They showed that patients display an abnormal rapid disengagement of attention or reduced attentional cost for invalid cues. This is presumably because patients have difficulty maintaining a mental set, which would allow them to benefit during regular, predictable sequences.

Interestingly, the tendency for patients to misattribute self-generated speech was not associated with the severity of hallucinations. However, the relationship between external misattribution of the source and hallucinations isolated from other positive symptoms has been challenged through several studies (P. Allen et al., 2007). It has been suggested that the external misattribution of the source is related to the general acute psychotic state rather than to a predisposition to hallucinations (L. C. Johns et al., 2006).The positive association between misattribution errors in the invalid cueing conditions with PSYRATS delusions scores confirms my assumption that the impaired ability to integrate top-down and bottom up information is related to an extent to the positive symptom profile.

As I mentioned before, the tendency to make misattribution errors in patients currently experiencing auditory hallucinations in the context of an affective psychosis was not identical to the one that is apparent both in patients experiencing hallucinations and patients experiencing delusions without hallucinations in the context of schizophrenia (L. C. Johns et al., 2006). They tend to make significantly more ‘unsure’ responses which makes the verbal self-monitoring deficit in this group of the patients questionable. Hence, the same study reported that defective self-monitoring was not evident in patients who had a history of hallucinations but were currently hallucination-free. Therefore, my findings together with previous reports from verbal self-monitoring studies may suggest that the patients’ response profile is rather related to psychotic state and not to a specific diagnosis.

I would like to give another look at my second hypothesis. The externalizing bias on invalid trials in the patient group was not confirmed to be source specific, as the interaction between cueing, source of the speech and group was not significant. The patients made significantly more errors across all the conditions in which the cue was invalid, but as I mentioned before they were not particularly prone to misattribute undistorted self-generated speech to an external source when the voice was preceded by an alien (invalid) cue compared to HC.

Nevertheless, as patients were not more prone to make errors in the opposite direction (i.e. when they heard alien undistorted speech preceded by a invalid self cue), I can assume that misattribution errors for undistorted self-generated speech when the voice is preceded by an alien (invalid) cue, might reach significant level in a larger sample (Cohen’s d= 2.64; effect size r= 0.79).

I would like to discuss some limitations of the study. I did not test for the specificity to positive symptoms of schizophrenia. Ideally, the relationship between cognitive deficits, psychotic state and schizophrenia as such, should be investigated in the same individuals using a longitudinal design, but this approach is logistically difficult. In this study, although the patients scored highly on the positive symptoms scales, the possibility that their impaired performance might reflected some other difference to controls cannot be excluded. The influence of medication that patients were taking could be important, but I am unable to confirm this as no studies on verbal self-monitoring have used the medication free populations. Greater sample sizes would also provide greater power to statistical analyses. As this study is the first one to integrate attentional modulation and verbal self-monitoring my results can be interpreted within the framework of negative symptoms and attentional deficit in schizophrenia (M. F. Green et al., 2000; Rocca et al., 2006). My sample comprised of patients with different lengths of illness and some of them suffered not only from positive, but also from negative symptoms. It may be that some patients experienced greater task difficulty due to again lack of capacity for attention. The correlation between the invalid condition and attentional deficit measured by the Scale for Assessment of Negative Symptoms (SANS; Andreason, 1984b) may be suggestive of such a relationship.

In conclusion, the present study is the first to dissociate bottom-up and top-down processing using a verbal self-monitoring paradigm and determine a relationship between attentional modulation and voice recognition in H/D patients. Specifically, patients with schizophrenia and this profile of symptoms have difficulty switching between top down and bottom up processing. Further, patients seem not to adequately inhibit top-down information to guide them at the expense of bottom-up information.

These results indicate that perturbed flexibility and integration of different attentional modes might be of importance regarding disturbed reality perception which may give rise to hallucinations and delusions.

3. Neuroimaging study

3.1 Aims and hypothesis

The evaluation of speech involves a network including the inferior frontal gyrus, anterior cingulate cortex (ACC), and voice selective regions in the superior temporal gyrus (STG) along the upper bank of the STS, but also bilateral middle temporal gyrus (Belin, Zatorre, Lafaille, Ahad, & Pike, 2000; Scott, Blank, Rosen, & Wise, 2000; Wang, Metzak, & Woodward, 2011). All the regions are consistently implicated in the pathophysiology of psychosis and AVH (P. Allen, Larøi, McGuire, & Aleman, 2008; Jardri, Pouchet, Pins, & Thomas, 2011; P. K. McGuire, Silbersweig, & Frith, 1996; S. S. Shergill et al., 2003, 2000). In patients with AVH and delusions the misidentification of self-generated speech is associated with reduced activation in ACC (P. Allen et al., 2007), as well as functional abnormalities in the left temporal cortex (P. Allen et al., 2007; Fu et al., 2008). Specifically, there has been significant evidence that temporal lobe (TL) regions bilaterally play a role in source attribution/monitoring (P. Allen et al., 2007; Fu et al., 2008, 2005; P. K. McGuire, Silbersweig, & Frith, 1996).

In HC, differential networks have been implicated in both top-down and bottom-up attentional processing in the visual (Giesbrecht, Woldorff, Song, & Mangun, 2003; Hahn et al., 2006; Hopfinger, Buonocore, & Mangun, 2000) and auditory (Mayer et al., 2006; Salmi et al., 2009; Shomstein & Yantis, 2004; Wu, Li, Bai, & Touge, 2009) attention studies. The IPC is crucial for the integration of bottom-up and top-down attentional demands (Corbetta & Shulman, 2002; Hahn et al., 2006). To the best of my knowledge, until now there were no neuroimaging studies investigating these attentional networks in patients with schizophrenia.

Neuroimaging studies also suggest a role for the posterior CMS in conscious awareness and integration of self-referential stimuli (T. Kircher et al., 2000; Maddock, Garrett, & Buonocore, 2003; Northoff et al., 2006).

In my neuroimaging study I aimed to examine the neural correlates of attentional modulation during a source judgment task in patients with first episode psychosis (FEP) and in HC. I chose to study FEP patients for the neuroimaging part of the study to avoid confounds associated with prolonged medication and illness chronicity associated with established schizophrenia. I adapted my behavioral task to be used in a fMRI study (Ilankovic et al., 2011).

I made the following hypothesis:

1. That during a cued source attribution task, FEP patients would make more source attribution errors than controls on trials preceded by an invalid cue.

2. I also predicted that this impairment in task performance would be associated with altered activation in the IPC and CMS and TL, regions involved in the integration of attentional demands, self-referential processes and source attributions, respectively.

3. Finally, I predicted that in FEP patients, altered activation in these regions would be associated with the severity of their positive psychotic symptoms.

3.2 Method

3.2.1 Participants

Twenty healthy, right-handed English-speaking volunteers (14 males 18 to 35 years of age) with normal hearing and corrected-to-normal vision (in 9 participants) who were matched to HC for age, gender and education participated in the experiment after giving written informed consent for a protocol approved by a Local Research Ethics Committee. Similarly as in the behavioral study none of the subjects had a history of medical disorder, drug or alcohol misuse, or was receiving medication.

Twenty patients who met DSM-IV (*Diagnostic and statistical manual of mental disorders*, 1994) criteria for psychosis were recruited through the South London and Maudsley National Health Service Trust. Clinical teams were systematically contacted with a request to identify patients with first episode psychosis who had prominent positive symptoms (hallucinations and/or delusions). This information was corroborated by careful review of the patients' clinical records. Potentially eligible patients were then approached by the investigators and assessed on the day of testing using Positive And Negative Symptom Scales (PANSS) (Kay, Fiszbein, & Opler, 1987) and the Psychotic Symptom Rating Scale (PSYRATS) (Haddock et al., 1999) (the symptom scores are reported in Table 3.1). They were on regular, stable doses of atypical (Aripriprazole, Seroquel, Olanzapine, Risperidon, Quetapine) antipsychotic medication, except for 3 patients who had ceased medication. Exclusion criteria for the patients group was the presence of an Axis II DSM-IV diagnosis or another Axis I diagnosis, a neurological disorder, history or current alcohol abuse or drug addiction. Only participants with a premorbid IQ > 80 as determined by the Wide Range Achievement Test (WRAT) (Jastak, Wilkinson, & Associates, 1984) were included in the study. Because HC had a higher premorbid IQ than the FEP group (Table 3.1) IQ scores were included as a covariate in all subsequent analyses.

Table 0.1 Demographic, psychopathological and behavioral data

	First episode patients (N=20) M(SD)	Controls (N=20) M(SD)	Statistic
Age in years	25.8 (6.3)	26.2 (6.1)	t=.17,p=0.86
Premorbid IQ	100.9 (10.6)	110.1 (7.4)	t=3.17,p=0.003*
Years of education	15.3 (3.1)	13.4 (3.2)	t=1.88,p=0.067
Gender ratio M/F	14/6	14/6	
Duration of illness	1-18 months	-	
PANSS: positive symptoms [a]	14.0 (5.5)	-	
PANSS: negative symptoms [a]	14.2 (6.0)	-	
Total Medication [b]	47243.24 (37873.96)	-	
Mean medication/day [c]	252.62 (216.57)	-	
PSYRATS Auditory Hallucinations [a]	9.50 (14.0)	-	
PSYRATS Delusions[a]	8.40 (8.2)	-	

[a] Symptom profile recorded at time of scan.
[b] Total Medication refers to the average absolute amount of medication taken by that group in standardized mg units of Chlorpromazine ± 1SD.
[c] Mean Medication/day is the average medication dosage taken by each subject during their period of treatment in standardized mg units of Chlorpromazine ± 1SD.
M = males; F = females; WRAT; PANSS = Positive and Negative Syndrome Scale.

3.2.2 fMRI task

As in the behavioral study, participants listened to speech recording of their own or another persons' speech (alien), preceded by a picture of either their own face or another person's face (alien). One hundred and sixty adjectives applicable to people were used (e.g. 'perfect', 'tall'). All the words were monosyllabic or disyllabic and were selected from lists used in the previous studies on self–monitoring and my behavioral study (P. Allen et al., 2004; Ilankovic et al., 2011). The emotional valence of these words had previously been rated by 20 healthy volunteers as negative, positive or neutral (Ilankovic et al., 2011). Thus the 160 words consisted of 70 positive, 70 negative and 20 neutral words. The sets of words presented in each condition were balanced for the number of syllables (i.e. equal amounts of one and two syllable words), word frequency and valence (equal amounts of positive, negative and neutral words).

A greyscale portrait picture (2304 x 3072 pixel size) was taken of each participant using an Olympus digital camera (D-425: 4.0 megapixel). Pictures were matched for size, colour intensity, brightness and contrast by using Adobe Photoshop Software (http://www.adobe.com/de/products/photoshop/). The picture of a male and a female researcher who were unknown to the participants was used as the "other" face picture. In line with the Eckman picture database with faces (Ekman, 1999), only the face was presented to the participants after removing the hair and neck, in order to avoid additional elements that could interfere with the face processing. The task used a factorial design with two levels of validity (valid, invalid), source of speech (self, alien), and distortion (0, -4 semitones) yielding a 2 x 2 x 2 design. Self-speech preceded by a picture of the subject's own face (self picture cue) and other (alien) speech preceded by an other person's face (alien picture cue), respectively, constituted valid trials. Self speech preceded by an alien's face and alien speech preceded by the subject's own face, represented invalid trials. The task consisted of 70% of valid and 30% of invalid cues, as when the ratio of valid to invalid cues is high, attention to the cued stimuli is purposefully allocated through top-down mechanisms (Posner, 1989). There were 28 words in each of the valid conditions and 12 words in each of the invalid conditions.

3.2.3 Procedure

Approximately 1-2 hours before scanning all participants were presented with a list of 160 words on a piece of paper and asked to read them aloud in a clear voice at a rate of approximately one word per second. Participants read all 160 words, even though half would subsequently be replaced and presented to them in another person's voice; this was to ensure that participants could not make judgments based on source memory during the task. They were not asked to remember the words. Their speech was recorded by a computer (Cool Edit 2000 for Windows XP). A male and a female researcher who were unknown to the participants recorded the words for the non-self (other) condition (80 words in total). The researchers used a neutral English pronunciation. The experimenter edited the recordings so that 80 of the words were replaced by a recording of the same word spoken in another person's voice, and 80 words (50%) of all the words (both self and other speech) were distorted using -4 semitone pitchshift. The subsets of words that were replaced and pitch shifted respectively were pre-designated (allocated so that the subsets were matched for word length, frequency and valence). The level of pitch distortion was based on findings from previous studies (P. Allen et al., 2004; Ilankovic et al., 2011; L. C. Johns & McGuire, 1999; L. C. Johns et al., 2006). The same subsets of words were used for all participants.

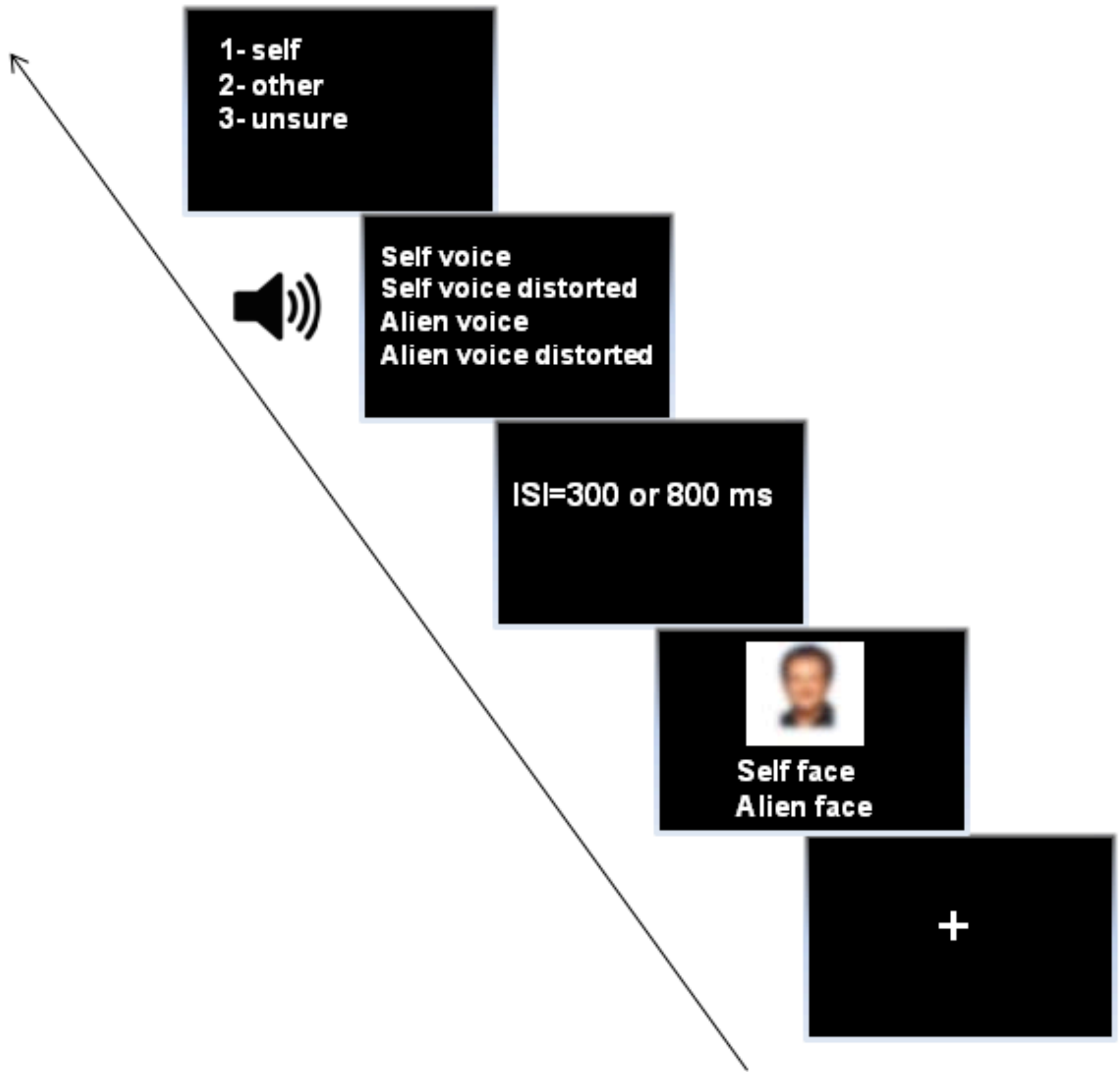

Figure 0.1 Example of trial procedure in neuroimaging study

Once participants had been placed in the scanner a standardized instruction script was read to them. Subjects were instructed to attend to each face-voice combination, but to make a decision regarding the source of the speech, not the face. Each trial started with a face picture cue that was presented for 200 ms, followed by a variable SOA (300 or 800ms) between the face picture and the voice to avoid the habituation effects . Auditory stimuli were presented via fMRI suitable headphones (Confon HP_S 01) and visual stimuli were presented via MR compatible goggles (Nordic neurolab's VisualSystem). The volume of the auditory stimuli was checked to ensure it was sufficiently loud for participants to hear the speech without difficulty. All participants reported that speech stimuli were clearly audible. The participants were able to register a response of either 'self', 'unsure' or 'other' via a joystick. See Figure 3.1. The option to register an unsure response was included to avoid the need for participants to make a forced choice between a 'self' or 'other' response when they were unsure. During rest periods participants viewed a black screen. Response accuracy and reaction times were recorded online. Participant's occasional failures to press a button were recorded as none responses.

3.2.4 MRI data acquisition

Imaging was performed with a 3.0-T whole body MRI scanner (GE Signa Excite) at the Centre for Neuroimaging Sciences, Institute of Psychiatry King's College London. A standard head coil (8 channels) was used for a radiofrequency transmission and reception. A compressed T2-weighted whole-brain echo planer pulse sequence was acquired with 744 images (axial, mode = 2D, scan timing: an effective TR of 2 seconds, composed of 1.2 seconds acquisition period and, silent period = 0.8, TE=30 ms, flip angle = 70°, matrix = 64 × 64, slice thickness = 4 mm, interslice gap=0.4 mm). The compressed sequence provided a simple and robust means of monitoring task performance in the absence of the acoustic scanner noise (Amaro et al., 2002). Of 744 images 160 were experimental and the remainder were null events (a black screen). Each whole-brain volume consisted of 24 axial slices acquired parallel to the anterior-posterior intercommissural line. Stimuli were presented in random order in an event-related design, with a variable inter-trial interval ranging from 6-8 sec in order to provide optimal hemodynamic refractoriness and avoid habituation effects (Dale, 1999). Each response time was locked to the beginning of the word presentation.

3.2.5 Behavioral analysis

The mean proportions of correct, error and unsure trials were calculated. Errors were all misattribution errors (misidentification of the source of the speech) plus unsure responses. ANCOVA was used to test for task, group and interaction effects whilst covaring for premorbid IQ. The associations between performance and PANSS/ PSYRATS scores were examined using Pearson's correlation. The data were analyzed using Statistical Package for Social Science SPSS 15 (http://www.spss.com/). All statistical tests were two-tailed, and reported at a significance $p < 0.05$.

3.2.6 Image analysis

Image processing and statistical analyses were conducted using SPM8 (Welcome Department of Cognitive Neurology, University College London, UK) running in MATLAB 7.4 (The Mathworks Inc., Natick, MA, USA). Movement correction of MRI scans was performed after the first 3 volumes were removed to allow for steady-state magnetization. The remaining 741 images were realigned to the first scan as a reference and resliced with sinc interpolation. There were no differences in the inter-scan movement parameters between groups ($p > .05$ for all parameters). Scans were spatially normalized to a standard MNI-305 template using nonlinear-basis functions. Functional data were spatially smoothed with an 8 mm full width at half maximum isotropic Gaussian kernel, to compensate for residual variability in functional anatomy after spatial normalization.

A standard first level fixed effects statistical analysis of regional responses was performed to identify regional activations in each subject independently. To remove low-frequency drifts, the data were high-pass filtered using a set of discrete cosine basis functions with a cut off period of 128 seconds. Activations at the onset of all trials, from the epoch of the face picture cue, were modeled using an event related analysis. A 1st level model with 8 regressors was specified (valid self speech, valid self distorted speech, valid alien speech, valid alien distorted, invalid self speech, invalid self distorted speech, invalid alien speech and invalid alien distorted speech). All speech trials conditions were modeled independently by convolving onset times with a canonical hemodynamic response function. Trials were modeled against a low level baseline consisting of null trials. Response estimations from the first level analysis, were entered into a series of 2nd level general linear models. First, paired t-tests were used to examine the main task effects of validity (valid vs. invalid), source (self vs. alien) and distortion (distorted vs. non-distorted) regardless of group. To examine the interaction between group and task, 1st level contrast images specifying the source x distortion interaction term, in both valid and invalid experimental conditions separately, were entered into a 2 x 2 (group x validity) flexible factorial ANCOVA with IQ as a covariate of no interest. Subsequent interaction effects were interrogated by plotting subject-specific activations extracted from voxels showing maximum effects (mean Beta values). All main and interaction effects are reported at a voxel wise corrected level (Family Wise Error, FWE, $p<0.05$). We used a whole-brain voxelwise approach, rather than a region of interest approach, to detect potential within and between-subject differences across the brain and not just in hypothesized region. A whole-brain voxelwise multiple comparisons correction is (a) stringent and (b) appropriate when no hypothesis is being tested (Friston, 1997).

Associations with symptom scores were examined using Pearson correlations with Bonferroni correction.

3.3 Results

3.3.1 Behavioral results

The groups were compared in terms of (a) total errors (misattribution errors and unsure responses taken together) and (b) unsure responses. The mean proportions for correct, unsure and total errors trials are shown in Table 3.2.

Across all participants, there were significant main effects for validity (F=4.03, df=38, p=0.05, h_p^2=0.095; invalid > valid), source (F=4.22, df=38, p=0.04, h_p^2=0.097; self-speech > alien-speech) and distortion (F=112.6, df=38, p=0.00, h_p^2=0.747; distorted-speech > undistorted-speech). The interaction between group and validity was non-significant (F=0.954, df=38, p=0.335). However, there was a trend for an interaction between validity, source and group (F=3.67, df=38, p=0.063). Post-hoc tests showed that the patients made significantly more total errors than HC when listening to their own voice preceded by an invalid cue (i.e. non-self cue) (z=-2.35, p=0.035, Figure 3.2 and 3.3). Neither the interaction between source, distortion and group (F=0.094, df=38, p=0.761), nor the interaction between validity, distortion and group was significant (F=0.034, df=38, p=0.855). The mean number of omission errors (i.e. a failure to respond) was a mean of 0.10 trials out of 160 in HC and 0.39 trials out of 160 in FEP. We found no condition specific group differences in failure to press. The main effect of distortion (F=22.950, df=38, p=0.000, h_p^2=0.603) and interaction between the source of speech and distortion (F=1.948, df=38, p=0.045, h_p^2=0.113) were significant. All participants made more unsure responses when listening to their own distorted voice. The main effects of validity and source were non-significant. There were no significant group x task interactions for unsure responses (p > 0.05 for all interactions). The main effect of validity (F=0.715, df=38, p=0.403) and the interaction between validity and the group (F=2. 624, df=38, p=0.114) were also non-significant. Mean reaction times were calculated for correct and error trials. Neither RTs for correct responses (F=.011, df=32, p=0.91) nor RTs for misattribution error trials (F=1.57, df=38, p=0.21) differed between the groups.

Table 0.2 Mean untransformed proportions (standard deviations) for correct responses, unsure responses and total errors according to condition and group

	Valid cue condition				Invalid cue condition			
	Self Undistorted	Self Distorted	Alien Undistorted	Alien Distorted	Self Undistorted	Self Distorted	Alien Undistorted	Alien Distorted
Controls								
Correct response	0.95 (0.05)	0.55 (0.35)	0.81 (0.30)	0.69 (0.26)	0.95 (0.09)	0.47 (0.35)	0.86 (0.26)	0.63 (0.28)
Unsure response	0.01 (0.03)	0.19 (0.23)	0.04 (0.08)	0.15 (0.18)	0.00 (0.00)	0.18 (0.20)	0.03 (0.09)	0.14 (0.16)
Total errors	0.04 (0.05)	0.44 (0.36)	0.13 (0.23)	0.30 (0.26)	0.02 (0.04)	0.50 (0.36)	0.13 (0.26)	0.31 (0.25)
Patients								
Correct response	0.87 (0.14)	0.54 (0.30)	0.86 (0.20)	0.62 (0.34)	0.79 (0.26)	0.25 (0.26)	0.12 (0.19)	0.64 (0.35)
Unsure response	0.05 (0.07)	0.16 (0.18)	0.03 (0.05)	0.14 (0.15)	0.10 (0.21)	0.22 (0.20)	0.06 (0.13)	0.13 (0.19)
Total errors	0.10 (0.13)	0.42 (0.28)	0.11 (0.19)	0.36 (0.33)	0.18 (0.25)	0.71 (0.26)	0.18 (0.25)	0.33 (0.34)

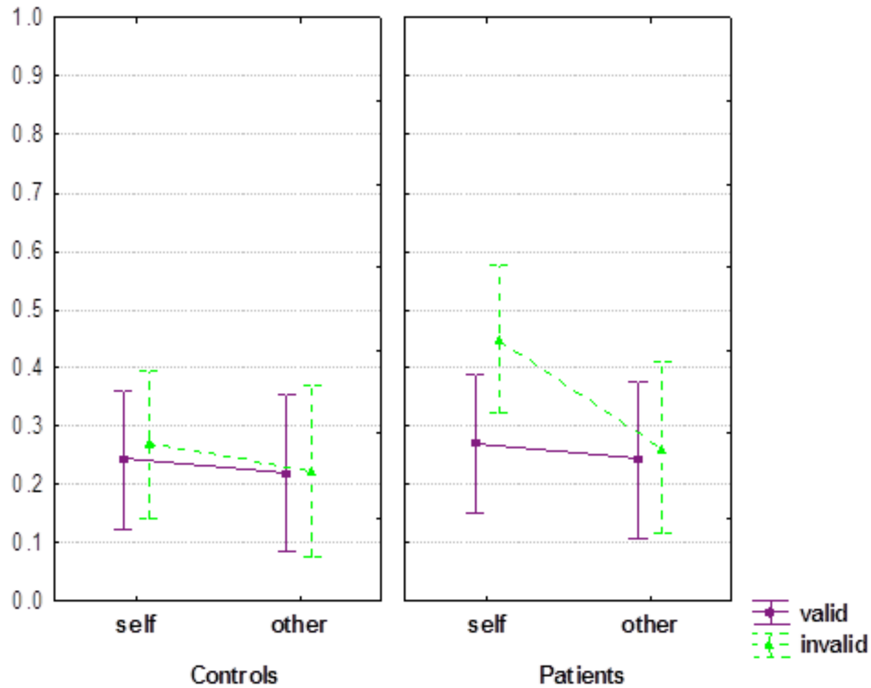

Figure 0.2 Interaction between the source of speech, validity and group with regard to the proportion of total error trials

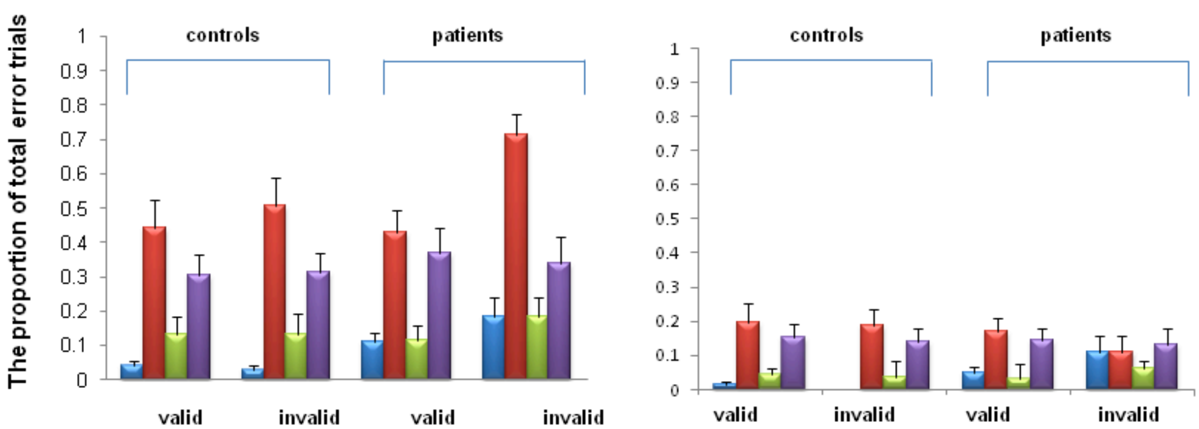

Figure 0.3 a) Proportion of the total error trials for the healthy controls and patients through the task b) Proportion of the unsure trials for the healthy controls and patients through the task.

3.3.2 Functional Magnetic Resonance Imaging

Across all conditions in all subjects, the task was associated with activation in the left postcentral, supramarginal, middle frontal, posterior cingulate, and MTG, the right insula and occipital cortex, and the supplementary motor area bilaterally.

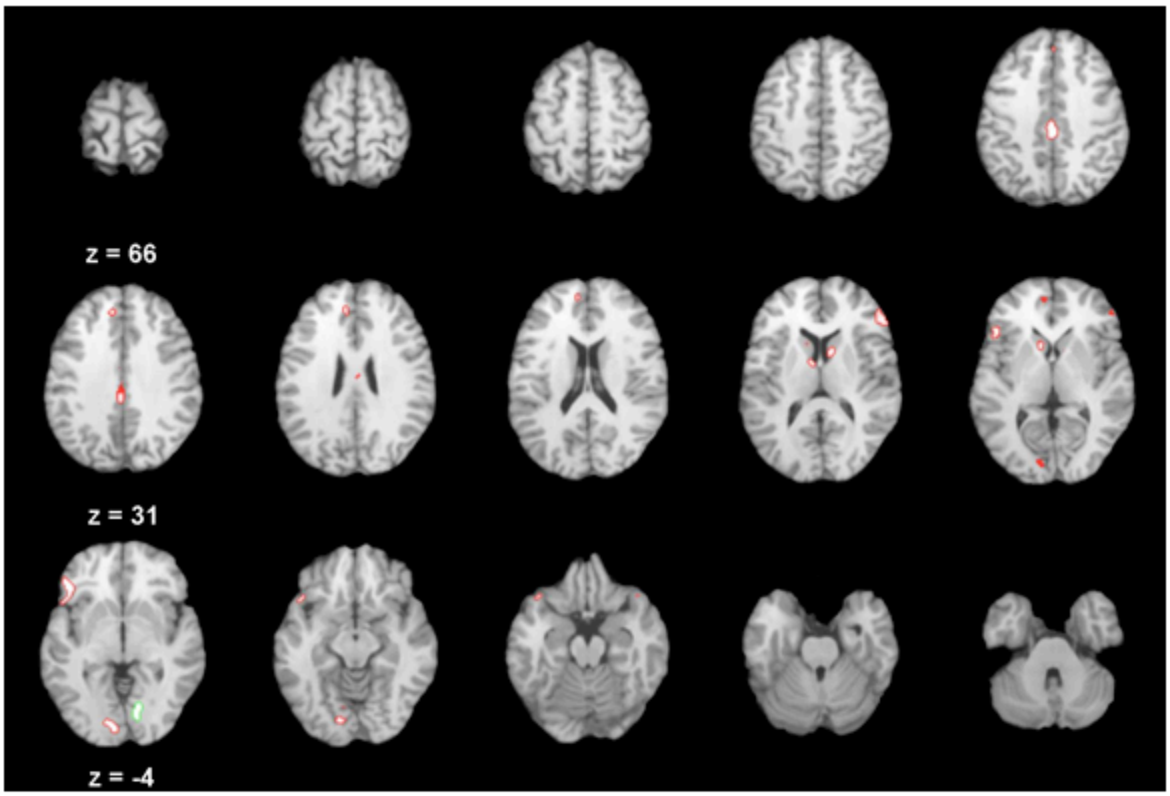

Figure 0.4 Statistical parametric maps of the main effect contrast for source of speech (self speech areas are colored red vs. alien speech areas that are colored green) The left side of the brain is showed on the left side of the images. The level of the axial section sections is indicated in Z coordinates in mm.

3.3.2.1 Main effect for source (self vs. alien trials)

Relative to alien-speech trials, listening to self-generated speech was associated with activation in the IFG, the left lingual, anterior and posterior cingulate and medial frontal gyri (mFG), the left thalamus, and the caudate nucleus bilaterally (Figure 3.4, Table 3.2).

Conversely, listening to alien-speech relative to self-speech was associated with activation in the right lingual gyrus (Figure 3.4, Table 3.2).

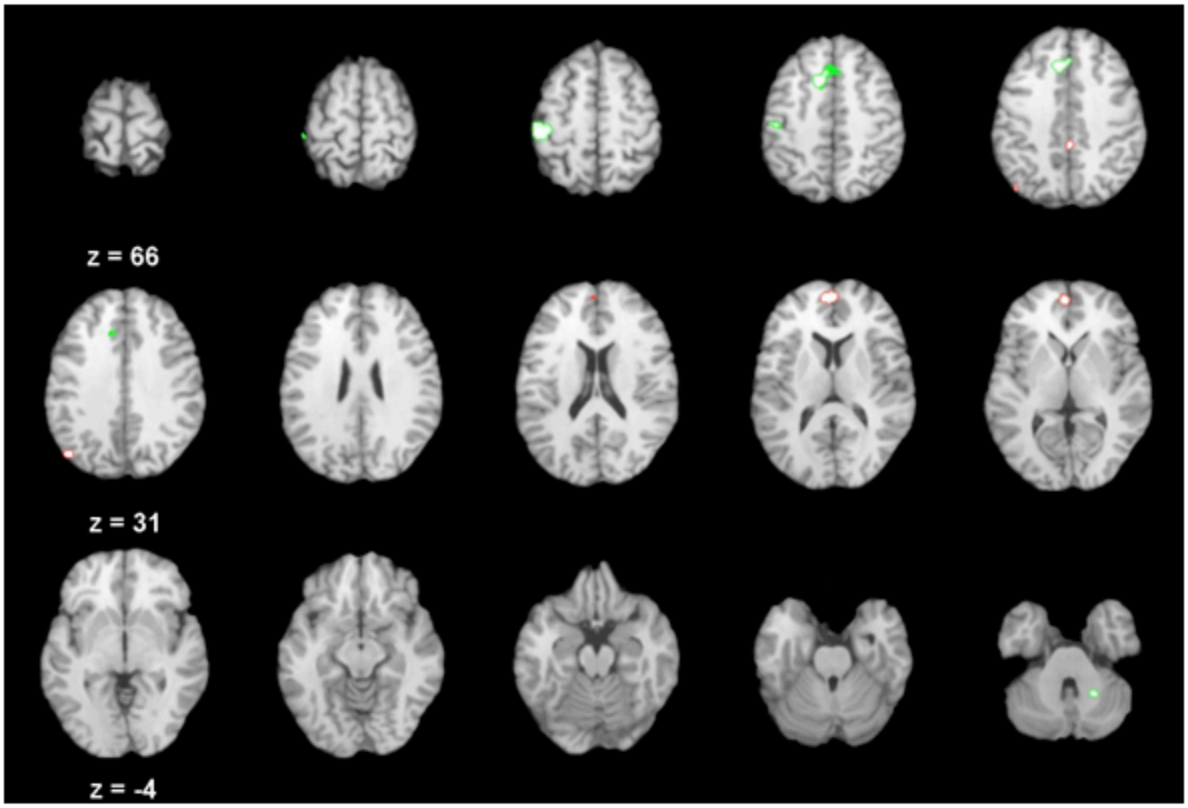

Figure 0.5 Statistical parametric maps of the main effect contrast for distortion (undistorted speech areas are colored red vs. distorted speech areas that are colored green). The left side of the brain is showed on the left side of the images. The level of the axial section sections is indicated in Z coordinates in mm.

3.3.2.2 Main effect for distortion (distorted vs. undistorted speech trials)

Relative to undistorted speech, distorted speech trials were associated with greater activation in the left postcentral gyrus, left ACC, and right cerebellum (Figure 3.5; Table 3.2). Conversely, listening to undistorted speech trials was associated with relatively greater activation in the left mFG, left angular gyrus and the right posterior cingulate gyrus (Figure 3.5, Table 3.2).

3.3.2.3 Main effect for validity (valid vs. invalid trials)

The main effect for validity did not survive correction for multiple comparisons (FEW <.05). At an uncorrected threshold (p<.001), relative to valid trials, invalid trials were associated with activation in the left ACC, the MFG bilaterally, and in the left inferior orbitofrontal gyrus (OFG). Activation in the left fusiform gyrus was seen during valid relative to invalid trials.

3.3.2.4 Interaction effects

There was a significant interaction between group, validity and source in the right MTG and in the left Pc. In both these regions, HC showed greater activation for self-speech relative to alien-speech during invalidly-cued (but not validly-cued) trials. FEP patients however, demonstrated relatively unaltered activation during both source and validity manipulations in these regions (Figure 3.6). A post-hoc analysis shows that in HC, relative to valid self-trials, invalid self-trials were associated with greater activation in the right Pc, MTG and left insula (Table 3.3). In FEP, there were no areas more active during invalid relative to valid trials. Neither the interaction between group and validity, nor the interaction between group, validity, source and distortion survived comparison for multiple comparisons (FEW<.05).

Table 0.3 Coordinates of foci of activation for the main effects. Coordinates refer to the stereotactic space as defined in the atlas of Talairach and Tournoux (1988).

Cerebral region	Side	Coordinates			Cluster size	z	BA
		x	y	z			
Main effect of source							
Self>alien							
Inferior frontal gyrus	L	-45	23	-2	173	5.75	47
	R	49	37	3	74	5.08	46
	R	43	18	-12	5	4.70	47
	R	33	16	-19	4	4.77	47
Lingual gyrus	L	-7	-85	2	123	5.51	17
Cingulate gyrus (middle)	L	0	-27	36	153	5.56	31
	L	-3	-8	31	9	4.81	24
Medial frontal gyrus	L	-5	48	3	41	5.31	10
	L	-7	49	14	9	4.75	10
	L	1	38	33	4	4.67	9
Anterior cingulate gyrus	R	-7	38	23	36	5.07	32
Thalamus(anterior nucleus)	L	-5	-3	9	13	4.78	-
Caudate (head)	L	-7	11	4	41	5.13	-
Caudate (body)	R	9	6	8	33	4.91	-
Alien>self							
Lingual gyrus	R	11	-71	-1	72	5.28	18
Main effect of distortion							
Distorted>undistorted							
Postcentral gyrus	L	-47	-26	52	227	5.78	2
Anterior cingulate gyrus	L	-7	24	31	235	5.69	32
Cerebellum (culmen)	R	21	-53	-22	29		-
Undistorted>distorted:							
Medial frontal gyrus	L	-1	50	6	153	5.53	10
Angular gyrus	L	-45	-70	29	62	5.19	39
Posterior cingulate gyrus	R	3	-33	34	32	4.83	31
Posterior cingulate gyrus	R	3	-51	9	1	4.60	29
Main effect validity							
No supra threshold effect							

Table 0.4 Coordinates of foci of activation for interactions. Coordinates refer to the stereotactic space as defined in the atlas of Talairach and Tournoux (1988)

Interactions							
Validity x source x group							
Middle temporal gyrus	R	51	-48	0	2	4.69	22
Precuneus	L	-1	-68	38	1	4.59	7
Post -hoc (self-speech trials in HC)							
(in controls and self- speech trials)							
Precuneus	L	1	-54	32	49	5.01	31
Middle temporal gyrus	R	61	-14	-11	29	4.93	21
Insula	L	-47	-39	24	18	4.73	13
Self-speech trials in FEP							
No supra threshold effect							

3.3.2.5 Symptom Correlations

In FEP patients there was a significant negative correlation between activation in the right MTG (as identified in the group x validity x source interaction) and ratings on both the PANSS positive symptoms subscale (r=-0.620, p<0.004) and the PSYRATS delusion items (r=-0.451, p<0.046). However, after correcting for multiple comparisons (Bonferroni correction), only the relationship between the right MTG and PANSS positive symptom scale remained significant (Figure 3.6.c). There were no significant correlations between right MTG or left Pc activation and PSYRATS hallucination scores (r=-0.138, p=0.561).

Since most of the patients who took part in the study were receiving antipsychotic medication, I examined if the level of medication exposure could explain the failure to activate right MTG/left Pc. No significant correlations were found for either the total current dose of medication (right MTG: r=-0.039, p=0.881, n=17/ left Pc: r=0.127, p=0.626, n=17), total duration of medication treatment (right MTG: r=0.234, p=0.365, n=17/ left Pc: r=0.290, p=0.259, n=17) or the mean daily dose over the period they had been taking antipsychotic medication (right MTG: r=-0.162, p=0.536, n=17/ r=-0.097, p=0.710, n=17).

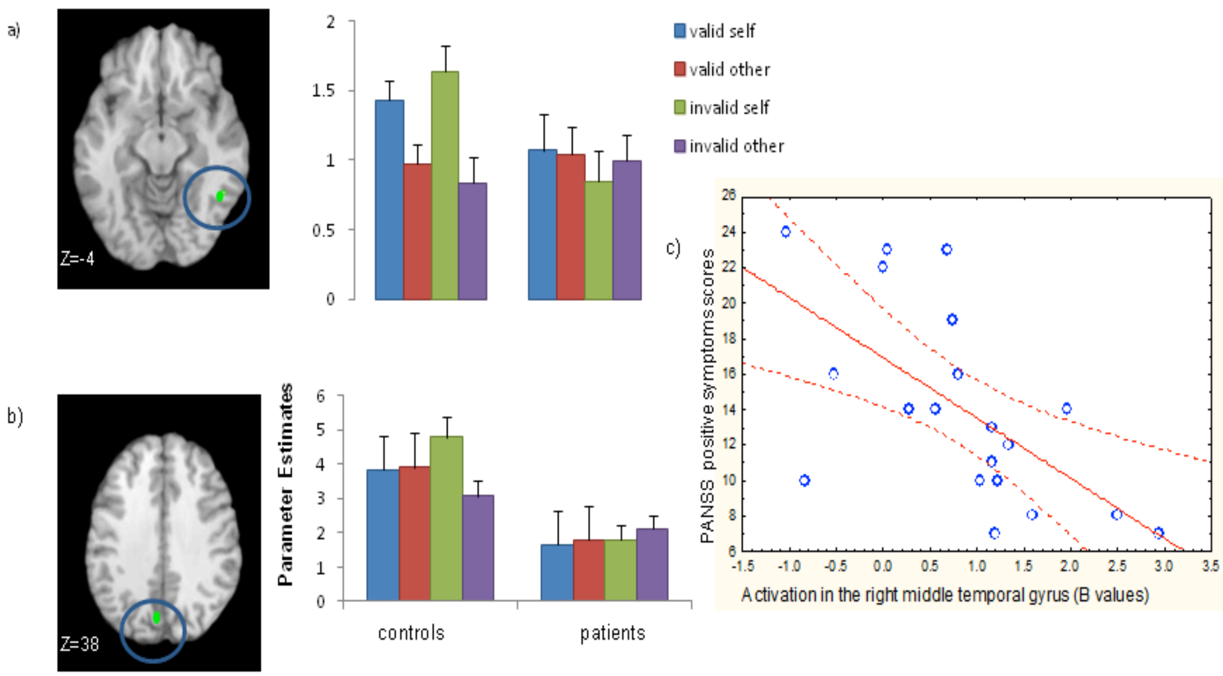

Figure 0.6 Brain activation map for the interaction between the source of speech, validity and group a) in the right middle temporal gyrus (rMTG) b) in the left precuneus (Pc) c) scatter plot showing negative correlation between beetween activation in the rMTG and PANSS positive symptoms subscale.

3.4 Discussion

3.4.1 Summary of the findings

The aims of the neuroimaging part of the study were to investigate neural correlates of attentional modulation during a source attribution task in FEP patients. Specifically, I tested if a) the FEP patients would make more source attribution errors than controls on trials preceded by an invalid cue b) the activation in IPC, CMS and TL regions was altered in FEP patients relative to HC when top-down attention (i.e. expectancy) was manipulated while participants judged the source of prerecorded speech.

Although not reaching significance FEP patients demonstrated a strong trend to misattribute their own speech to an external source when it was preceded with an invalid (non-self) cue. This is broadly in line with finding from my behavioral study, which was powered to detect group effects at a behavioral level, and suggests that the misattribution of self-generated material in patients with schizophrenia is particularly impaired when bottom-up and top-down influences conflict (P Maruff et al., 1998). Furthermore, as misattribution errors were specific to invalidly cued self-speech, rather than invalidly cued other-speech, it is unlikely that this pattern of results is due to patients being unable to learn the cuing contingency.

The fact that this interaction did not reach significant level may be due to the fact that the neuroimaging task was designed for an event related fMRI experiment rather than to show strong behavioral results.

In addition, patients were neither making more errors when listening to distorted words nor giving more unsure responses than controls. Therefore, it is even less likely that patients are exhibiting a learning deficit, but a more specific attentional impairment.

Across all conditions, the experimental task was associated with activation in a network of parietal, temporal and frontal regions, including the supramarginal gyrus, middle temporal, middle frontal and posterior cingulate gyrus. The engagement of frontal and parietal cortex is consistent with their role in top-down attentional modulation (Corbetta & Shulman, 2002; Hahn et al., 2006; Hopfinger et al., 2000; A. F. Rossi, Pessoa, Desimone, & Ungerleider, 2008). The left mFG is important for the top-down updating of cue-related information (Pessoa et al., 2009), while the MTG is commonly activated when subjects are attending to endogenous (top-down) cues, and when reorienting auditory attention (Mayer et al., 2006). Furthermore, the MTG and adjacent STS are selectively activated by voice stimuli (Belin et al., 2000) and activation in these regions is reported in previous source and speech monitoring fMRI studies (P. Allen et al., 2007; Wang et al., 2011). The left supramarginal gyrus is involved in the integration of top-down and bottom-up attention (Hahn et al., 2006), and the insula (Bushara et al., 2002), lateral temporal cortex (J.-Y. Park, Gu, Kang, Shin, Choi, Lee, & Kwon, 2010a) and IFG (Calvert et al., 2000) are involved in audiovisual integration.

In all participants, listening to self-speech was associated with activation in prefrontal regions (bilateral IFG) and CMS (cingulate, lingual and medial frontal gyri), as well as the left thalamus and bilateral caudate. Activation in the IFG (P. Allen et al., 2005) and thalamus (Kumari et al., 2010) during source attribution tasks has been reported previously, suggesting these regions may be involved in successful source monitoring (Kumari et al., 2010).

Activation seen in the cingulate gyrus and medial prefrontal cortex during self-speech trials is consistent with previous findings that CMS are involved in self-processing (C. D.

Frith & Frith, 1999; S. C. Johnson et al., 2002; Modinos, Renken, Ormel, & Aleman, 2011; Northoff & Bermpohl, 2004; Northoff et al., 2006). Activation in bilateral IFG during self-speech trials has also been reported (P. Allen et al., 2005) in HC. The role of the prefrontal cortex in source attribution is not clear but may involve the maintenance of information about different speech sources in the working memory and planning and evaluating the most appropriate response.

I was not able to confirm my second hypothesis, as the interaction between the group and validity did not survive comparison for multiple comparisons (FWE, $p<0.05$). It could be that the validity of the cue does not have any significant effect on the neural activity of the participants, unless combined with some other factor in the experimental context. More precisely, there was a significant interaction effect between group, validity and speech source. This, this interaction may suggest that validity of the cue plays an important role for attentional modulation only when the source attribution is involved.

There were differences in the effects of distortion between the FEP group and the HC, but they did survive comparison for multiple comparisons (FWE<.05). Possibly, the distortion of the voice lost the sensitivity in differentiating neural response in FEP patients relative to HC, due to the new task requirements. It is likely that in the new form of the task, other attentional requirements diminished the role that anterior cingulate had when two groups differentiated undistorted from distorted voice without a preceding cue (P. Allen et al., 2005).

As I mentioned before, there was a significant interaction effect between group, validity and speech source in the rMTG and lPc. In HC the rMTG showed greater activation during self-speech relative to alien-speech trials particularly when preceded by an invalid cue. In FEP patients however, activation in the rMTG did not appear to differentiate between self/alien or valid/invalid speech trials. Temporal lobe regions have previously been shown to facilitate source attribution in HC (P. Allen et al., 2007; Fu et al., 2005; P. K. McGuire, Silbersweig, & Frith, 1996; Wang et al., 2011), and have also been implicated in crossmodal/audiovisual integration (Driver & Noesselt, 2008; Ethofer, Pourtois, & Wildgruber, 2006; J.-Y. Park, Gu, Kang, Shin, Choi, Lee, & Kwon, 2010a). The r MTG in particular has beenshown to play an important role in audio-visual matching (Saito et al., 2005) and may be important for facilitating the integration of self-referential sensory information, a function that appears to be impaired in FEP patients. This region may therefore be particularly important for facilitating the integration of self-referential information in the auditory modality, a function that appears to be impaired in FEP patients. I did not confirm the hypothesis that impaired task performance in FEP patients would be associated with altered inferior parietal cortex activation. It is possible that integration of sensory information in the IPC is specific to the integration of spatial (Hahn et al., 2006) and/or visual (Nobre, Coull, Walsh, & Frith, 2003; Wojciulik & Kanwisher, 1999) stimuli integration. However, in HC, activation in the IPc (a part of CMS) was greater during invalid self-speech trials than during alien and validly cued speech trials. The Pc, as the postero-medial portion of the parietal lobe, has also been linked to top-down attention (Hahn et al., 2006) and is involved in the integration of self-referential information (S. C. Johnson et al., 2002; Northoff & Bermpohl, 2004), self-processing operations and the experience of agency (Northoff et al., 2006; Wojciulik & Kanwisher, 1999). Again FEP patients showed reduced activation in this region across speech and validity conditions. In FEP patients, attenuated activation in rMTG and IPc during invalidly cued self-speech trials suggests impaired integration of top-down and bottom-up information particularly when that information is self-referential. Furthermore, in FEP patients there was a negative association between rMTG activation and positive symptoms. An association between MTG dysfunction and psychosis has been reported previously is consistent with a wide body of literature and with hallucinations in particular (P. Allen et al., 2008), but the right MTG was also shown to be positively associated with other positive symptoms, such as persecution and disorganization (Kumari et al., 2010).

The fMRI study has some limitations. First, the results could not dissociate neural networks mediating top–down and bottom–up control such as in the tasks of visuospatial selective attention (Hahn et al., 2006). However, this was not the aim of my study as I sought to identify regions involved in top-down and bottom-up integration in the context of self-referential information. It is also unlikely that FEP patients were prone to misattribute facial identity as previous studies report unimpaired facial recognition in patients with schizophrenia (T. Kircher et al., 2007; J. Lee et al., 2007). Second, as the majority of the patients were receiving antipsychotic medication their symptoms were likely to have been at least partially attenuated. Third, I applied the analyses not only to correct, but to all trials, including errors and unsure trials. I did this to avoid having an uneven and/or insufficient number of correct trials in some of the participants.

3.4.2 Discussion on the main effects

Across both groups there were regions that were more activated when participants processed self generated speech compared with alien speech and vice versa. The analysis identified a widespread set of language-related areas involved when differentiating one’s own speech from the other’s (alien) speech, but also in other brain regions engaged in decision making and attention. The largest clusters were identified in the cortical area of IFG, pars triangularis, that contributes to propositional language comprehension in the dominant hemisphere, as well as to semantic word encoding (Foundas, Leonard, Gilmore, Fennell, & Heilman, 1996) but also in the orbitofrontal part of the IFG (BA 47), possibly involved in deriving source attributions (Wallis, 2007).

At last, the more rostral part of the IFG (BA 46) corresponding to the DLPFC was also more activated when participants processed self generated speech compared with alien speech. We suggest that this area is engaged, together with OFG, in maintenance of the information about different speech sources in the working memory. Additionally, planning and evaluating the most adequate decision about the speech source must have been of great importance during the task. In line with that, the lateral PFC is known to be involved in the fast adaptation and coordination of actions according to current behavioral goals, especially in situations of interfering information (Szameitat, Schubert, Müller, & von Cramon, 2002). This situation was very represented in my task since the participants had to adapt to quite fast and continuous shifts of valid and invalid trials.

The activation of cortico-basal ganglia network (caudatus-dorsomedial striatum together with hippocampus) also appears to be crucial neural substrate for learning and expression of goal-directed actions (Yin & Knowlton, 2006). In contrast, processing of other (alien) speech was associated with greater engagement of the lingual gyrus, but not the prefrontal brain structures. It is possible that processing of other (alien) speech words placed less demand on decision-making. Moreover, other (alien) speech is less familiar than self-generated speech, which required from participants to rely more on the visual information given by the cue. This might have activated the occipital lobe to a larger extent.

Further on, other regions of significance were identified in the recognition of one own's speech, in the mFG (BA 9,10). The involvement of mFG suggests the interaction of self-referential and higher order processing (S. C. Johnson et al., 2002; Modinos et al., 2011; Northoff & Bermpohl, 2004; Ochsner et al., 2005). Those previous studies on self-referential processes suggest that mFG regions could be active in determining if the stimulus or action is self- or other (alien)- generated.

Activation during the task was also influenced by the acoustic distortion of the stimuli. In accordance with previous studies on verbal self-monitoring (P. Allen et al., 2005; Fu et al., 2005), ACC activation occurred regardless of the source of speech. Its activation in association with distortion may thus have reflected increased engagement of these processes in response to stimuli that become more difficult to perceive as a result of the pitch shift. Conversely, undistorted speech evoked stronger activation in angular gyrus, near the TPJ. This finding may be suggesting that the information given by the visual cues and speech is more easily integrated when the voice is not pitch shifted.

Interestingly, distorted speech activated more anterior medial areas whereas undistorted speech activated more posterior cingulated areas. As aforementioned, the anterior medial areas are involved in monitoring and evaluation of self-referential stimuli whereas activity in posterior cingulated cortex is related to the integration of these stimuli in the emotional and autobiographical context (Northoff & Bermpohl, 2004). Therefore it seems that undistorted voice is more easily integrated with the self-referential experiences and autobiographical information than distorted speech.

4. General discussion

The general aim of my study was to determine the role of attentional modulation in source attribution in H/D patients and FEP patients, comparing to HC. This is a challenging goal due to overlapping cognitive and neural requirements associated with attention, source attribution and self processing.

Taken together the results from behavioral and fMRI study provide further evidence for external misattribution of source in H/D and FEP patients, in addition to previous studies, on the cross modal (audio-visual) level. An interaction between bottom-up and top-down processes is necessary to achieve rapid and flexible attention on a cross-modal level and this seems to be impaired in both groups of patients comparing them to HC. Further, both groups of patients showed a rudimentary disturbance of self, typically seen in “psychosis like disorders”.

In the behavioral study patients made significantly more errors across all the conditions in which the cue was invalid, but they were not particularly prone to misattribute undistorted self-generated speech to an external source when the voice was preceded by an alien (invalid) cue compared to HC.

With this finding I confirmed my first hypothesis that when top-down (cue preceding the voice stimuli) and bottom-up (source of the voice stimuli) mechanisms are placed in conflict (e.g. during invalid trials) H/D patients demonstrate impaired performance relative to HC. I concluded that this may be because H/D patients are allowing top-down information (cues) to guide them at the expense of bottom-up information.

In my investigation upon disturbed sense of self in psychosis I did not confirm the second hypothesis that patients with H/D will be misidentifying their own speech as alien on the invalid cue trials.

Fortunately, the FEP group in the fMRI study showed poorer self-recognition performance when the cues were invalid comparing to HC which gave support to this hypothesis in the imaging study.

In the context of the neuroimaging results, the most significant result about self disturbance in psychosis is the interaction effect between group, validity and speech source in the rMTG and lPc. In FEP patients however, activation in the rMTG did not appear to differentiate between self/alien or valid/invalid speech trials whereas in HC the rMTG showed greater activation during self-speech relative to alien-speech trials particularly when preceded by an invalid cue.

In FEP patients, attenuated activation in rMTG and lPc during invalidly cued self-speech trials could suggest impaired integration of top-down and bottom-up information particularly when that information is self-referential.

The third hypothesis in both behavioral and neuroimaging study was confirmed to a large extent. First, the performance of H/D patients on invalid trials was correlated with the severity of delusions. Second, there was a negative association between rMTG activation and positive symptoms in invalid trials. The negative correlation between the right MTG and positive symptoms, in particular delusions, is further supporting my hypothesis about low discrimination between the self and alien voice in the FEP group comparing to HC. Also this finding, goes in line with previous studies that the external misattribution of the source is related more to the general acute psychotic state than to a predisposition to hallucination (Johns et al., 2006).

Several brain regions that exhibited activity during the task demonstrated overlapping importance of these regions in investigating attention, source attribution and self processing.

A great significance of TL regions have previously been shown in the context of source attribution in HC (P. Allen et al., 2007; Fu et al., 2005; P. K. McGuire, Silbersweig, & Frith, 1996; Wang et al., 2011) and has also been implicated in crossmodal/audiovisual integration (Driver & Noesselt, 2008; Ethofer et al., 2006; J.-Y. Park, Gu, Kang, Shin, Choi, Lee, & Kwon, 2010b). An association between MTG dysfunction and psychosis is consistent with a wide body of literature (P. Allen et al., 2008; Honea, Crow, Passingham, & Mackay, 2005; Plaze et al., 2006). In several previous studies on auditory verbal imagery, patients showed a relatively attenuated response in the middle and superior temporal cortex (P. K. McGuire, Silbersweig, & Frith, 1996; S. S. Shergill et al., 2000), particularly those participants that were performing poor on the task (Kumari et al., 2010).

Therefore, activation in the rMTG in my study might be particularly important for facilitating the integration of self-referential information in the auditory modality, a function that appears to be impaired in FEP patients. I initially hypothesized that impaired task performance in FEP patients would be associated with altered IPC activation. However, it is possible that integration of sensory information in the inferior parietal cortex is specific to the integration of spatial (Hahn et al., 2006) and/or visual (Nobre et al., 2003; Wojciulik & Kanwisher, 1999) stimuli integration.

Analysis of fMRI data revealed another important result regarding integration of self-referential information and that is activation in Pc. As the postero-medial portion of the parietal lobe, Pc has been traditionally linked to top-down attention(Hahn et al., 2006), but lately has received a significant role in self-processing operations, namely first-person perspective taking and an experience of agency (Cavanna & Trimble, 2006; Northoff et al., 2006). The analysis I performed also suggested several other regions active in all the participants when determining if the stimulus or action was self- or alien-generated (mFG, posterior cingulate). Hence, rMTG, left Pc and insula were always more activated for self speech trials only in HC. Hereby, my results join the growing neuroimaging evidence about disturbed sense of self in psychosis (Nelson et al., 2009; Waters, Woodward, Allen, Aleman, & Sommer, 2010).

My fMRI task evoked increased activation in both temporal-prefrontal cortices involved in auditory attention, as well as in fronto-parietal attentional network which is more typical for visual attention. More precisely, the MFG is important for the top-down updating of cue-related information (Pessoa et al., 2009), the supramarginal gyrus along the temporo-parietal junction is involved in integration of top-down and bottom-up attention (Hahn et al., 2006) and the MTG is in charge of top-down attention in auditory modality (Mayer et al., 2006).

There are certain general limitations to my study. First, the results could not dissociate neural networks mediating top–down and bottom–up control such as in the tasks of visuospatial selective attention (Hahn et al., 2006). This has not been the aim of my study, as the previous studies suggested that subregions of the frontal–parietal network are highly specific for controlling spatial selective attention and that those regions are more active for spatial than for nonspatial cues that we used (Giesbrecht et al., 2003).

Second, the source recognition is not easily differentiated from attentional modulation, experimentally given overlapping cognitive and neural requirements associated with attention.

At last, the majority of the patients were on medication and due to the treatment patients' symptoms were significantly attenuated. It would be of importance to see the performance of patients with more intensive positive symptoms.

However, a remarkable consistency across studies indicates that self-recognition deficits occur across all action modalities, timing delays, and regardless of the design measuring self-recognition. The results support, though with certain constraints, the growing neuroimaging evidence about inadequate balance between the top- down and bottom-up attentional processes, especially in the context of disturbed sense of self in psychosis.

To conclude, impaired attentional modulation in FEP patients may lead to erroneous source attributions, especially when presented with self-referential stimuli. Impaired performance was associated with reduced activation in the right MTG and IPc, both regions involved in self-referential processing and integration of sensory information. Although dysfunction in these regions during these processes is associated with positive symptoms an association with AVH was not established. Future work is needed to establish the attentional hierarchy in this network.

5. Summary (English and German version)

In patients with schizophrenia, the misattribution of self-generated events to an external source is associated with self-recognition deficits and the presence of psychotic symptoms. The aim of the present study was to investigate how this misattribution is influenced by dysfunction of attentional processing, which is also impaired in schizophrenia.

I conducted two different studies. In both studies participant's expectancies were manipulated using visual cues that were either congruent (valid) or incongruent (invalid) with the speech. The source (self/alien) and the acoustic quality (undistorted/distorted) of the speech were also manipulated. First, twentythree patients with schizophrenia, with hallucinations and delusions (H/D patients) and twentythree matched healthy controls (HC) were tested for the behavioral study. Later on, twenty patients with first episode psychosis (FEP) and twenty matched healthy controls (HC) underwent functional Magnetic Resonance Imaging (fMRI) while listening to prerecorded speech.

The results of the behavioral part of the study showed that H/D patients exhibited increased error rates comparing to HC, when listening to the distorted self spoken words, misidentifying their own speech as produced by others. Importantly, patients made significantly more errors across all the invalid cue conditions. This suggested not only the presence of pathological misattribution bias, but also an inadequate balance between top-down and bottom-up attentional processes in patients, which could be responsible for misattribution of the ambiguous sensory material.

Analysis of fMRI data showed that FEP patients when listening to self-generated speech preceded by an invalid (alien) cue, relative to HC showed a strong trend to misidentify their own speech as an other person's. The patient group had reduced activation in the right middle temporal gyrus (MTG) and left precuneus (Pc) relative to HC. Within the FEP group, the level of activation in the right MTG was negatively correlated with the severity of their positive psychotic symptoms. I conclude that impaired attentional modulation in schizophrenia may contribute to the tendency for FEP patients to misattribute the source of self-generated material, and this may be mediated through the right MTG and Pc, regions that are involved in both self-referential processing and the integration of sensory information.

……………………………………….

Schizophrene Patienten neigen dazu selbstgenerierte Handlungen auf externe Quellen zu misattribuieren. Dieser Bias ist assoziiert mit kognitiven Defiziten im Bereich der Selbsterkennung sowie mit psychotischen Symptomen. Das Ziel der präsentierten Studien ist es, zu untersuchen in wie weit dieser Misattributionsbias durch Aufmerksamkeitsprozesse beeinflusst wird, welche ebenfalls in schizophrenen Patienten beeinträchtigt sind.

Ich führte zwei Studien durch in welchen die Probanden unterscheiden sollten, ob ein auditiv präsentiertes Wort in der eigenen Stimme oder einer fremden Stimme dargeboten wurde. Dabei wurden die Erwartungen der Probanden manipuliert durch visuelle Hinweisreize die entweder kongruent oder inkongruent zu einem auditiven Stimulus waren. Zudem wurde die akustische Qualität (unverzerrt / verzerrt) manipuliert.

In der ersten Studie wurden 23 Patienten mit Schizophrenie sowie 23 gesunde Probanden in einem behavioralen Design untersucht. In der zweiten Studie wurden bei 20 Patienten mit Schizophrenie sowie bei 20 gesunden Probanden das gleiche Paradigma mittels fMRT untersucht.

In der behavioralen Studie zeigte sich bei Patienten mit Schizophrenie im Vergleich zu gesunden Probanden eine erhöhte Fehlerrate und somit eine Tendenz die eigene Stimme zu missattribuieren, wenn selbstgesprochene Wörter verzerrt präsentiert wurden. Interessanterweise zeigten Patienten in allen Bedingungen mit inkongruenten Hinweisreizen eine signifikant erhöhte Fehlerrate. Dies lässt vermuten, dass bei schizophrenen Patienten ein generelles Muster kognitiver Beeinträchtigung vorliegt. Möglicherweise zeigen Patienten auf Grund einer Dysbalance von top-down und bottom-up gesteuerten Aufmerksamkeitsprozessen, eine beeinträchtigte Leistung bei der Attribuierung inkongruenter Stimuli.

In der fMRT-Studie zeigten schizophrene Patienten eine ausgeprägte Tendenz ihre eigene Stimme als eine fremde Stimme zu misattribuieren, wenn inkongruente Hinweisreize präsentiert wurden. Dabei zeigten Patienten eine reduzierte Aktivität im rechten mittleren Temporallappen sowie im linken Precuneus. Zudem zeigte sich eine negative Korrelation zwischen der Aktivität im rechten mittleren Temporallappen und der Ausprägung der positiven Symptomatik.

Daher ist anzunehmen, dass möglichweise eine beeinträchtigte Balance zwischen top-down und bottom-up gesteuerten Aufmerksamkeitsprozessen zum Misattributionbias in schizophrenen Patienten beiträgt. Zudem ist dieser Einfluss assoziiert mit Aktivität in Hirnregionen, die in der Integration sensorischer Information sowie in der Verabeitung selbstreferentieller Information involviert sind, wie der rechte mittlere Temporallappen sowie der Precuneus.

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7. Supplementary materials

The lists of words used in

a) the behavioral experiment   b) fMRI experiment

a)

Negative words			Neutral Words	Positive Words		
FAKE	SHABBY	SLEAZY	OLD	PURE	PRECIOUS	FABULOUS
CRUDE	CREEPY	TAINTED	HOT	BOLD	GORGEOUS	INVOLVED
VULGAR	BLAMED	HURTFUL	SHARP	WISE	CHARMING	GENTLE
FEARFUL	DISMAL	CROOKED	CIVIL	KIND	GRACIOUS	PREPARED
VICIOUS	AFRAID	HATED	USUAL	NICE	FRIENDLY	BALANCED
CALLOUS	PAINFUL	CRUEL	SILLY	GOOD	SPLENDID	BRILLIANT
REJECTED	FOOLISH	DAMAGED	PRIVATE	DIVINE	CARING	CLASSY
REPULSIVE	VIOLENT	BRUISED	REGULAR	HOLY	FAITHFUL	PRETTY
SHY	LOUD	STINKING	LOATHED	BROAD	HANDSOME	COSY
FAT	LAZY	CARELESS	AVERAGE	CLEAN	HUMBLE	CHERISHED
NASTY	SICK	SPITEFUL	STRAIGHT	PROUD	TRUTHFUL	PERFECT
LYING	DULL	COWARDLY	PATHETIC	REGAL	WATCHFUL	WARM
VAGUE	VILE	SINISTER	SQUARE	RAPID	SPECIAL	GLORIOUS
TIRED	EVIL	BRUTAL	PASSABLE	WITTY	FAMILIAR	AWESOME
MESSY	HOPELESS	HELPLESS	SMALL	AWARE	CLEVER	SUPERB
CRASS	WRETCHED	HEARTLESS	ROUND	LOCAL	SUPER	GIFTED
FAILED	SOROWFUL	SCABBY	CONSCIOUS	FUNNY	SUITABLE	SILENT
WICKED	PRACTICAL	SNEAKY	TALKATIVE	LOYAL	MASSIVE	EXPERT
HORRID	ILL	BEATEN	STILL	FAMOUS	PLAYFUL	COMMON
TRAGIC	ODD	FAULTY	CAREFUL	HEALTHY	ELEGANT	BRAINY
DREARY	DECAYED	SELFISH		LIGHTER	BELOVED	CHATTY
FILTHY	NERVOUS	HATEFUL		KNOWING	DYNAMIC	LOVING
GRUBBY	CORRUPT			WAKEFUL	GREAT	
FOUL	SLENDER			RELAXED	PLACID	

b)

Negative Wörter			Neutrale Wörter	Positive Wörter		
KORRUPT	FRÜCHTERLICH	GARSTIG	PATETISCH	RUHIG	WUNDERSCHÖN	MUTIG
VERSCHMUTZT	BESCHMUTZT	ABGELEHNT	GEREGELT	SEGENHAFT	NETT	WERTVOLL
WERTLOS	SELTSAM	PERVERS	NORMAL	GÖTTLICH	LEICHTER	HEIMISCH
NERVÖS	VERARMT	BESIEGT	VERBLÜFFT	SPIELERISCH	BRILLANT	PRAKTISCH
GRUSELIG	STINKEND	BRUTAL	ÜBLICH	UNGEZWUNGE N	UNBESCHÄDIGT	AUFMERKSAM
TRAGISCH	HILFLOS	GEHÄSSIG	SCHARF	UMSORGEND	GEBILDET	GROßARTIG
DÜRFTIG	SCHÄBIG	BEDAUERLICH	ALBERN	AUSGEGLICHE N	GEISTREICH	INFORMIERT
UNECHT	UNSERIÖS	VERDÄCHTIG	DURCHSCHNIT TLICH	ERFAHREN	WISSEND	FREUNDLICH
SCHMERZVOLL	KALTHÄRZIG	FEIGE	VORSICHTIG	BEACHTLICH	SCHNELL	INTELLIGENT
UNGLUCKSELIG	VULGÄR	DRECKIG	HEIß	ANMUTIG	HELIG	VORUTREILSLOS
MÜDE	VERDORBEN	ÄRMLICH	BEWUSST	LEICHTER	GEMÜTLICH	SELBSTLOS
SORGENVOLL	BEDRÜCKEND	EKELHAFT	ANNEHMBAR	TREU	BERÜHMT	LOYAL
BEHINDERT	BESTRAFT	TROSTLOS	GEWÖHNLICH	REIN	FANTASTISCH	STOLZ
SCHÜCHTERN	EINSAM	LIEBLOS	GEWAHR	GUTARTIG	LUSTIG	GUT
SCHLEIMIG	ÄRMLICH	VERLETZT	STILL	GESUND	UNPARTEIISCH	BEACHTEND
UNANGENEHM	BESCHÄDIGT	VERWIRRT	GESPRÄCHIG	VERTRAUT	DYNAMISCH	ATTRAKTIV
GEQUÄLT	BEDAUERLICH	HERZLOS	HARMLOS	BEDACHT	MAJESTÄTISCH	GÜTIG
LAUT	FEHLERHAFT	VERSTÖRT	PRIVAT	ZUFRIEDEN	UMFASSEND	GEWALTIG
ZERFALLEN	UNGEPFLEGT	EGOISTISCH	AUFGEREGT	WAHRHAFT	LIEBEVOLL	EHRENHAFT
REBELLIEREND	ABSTOßEND	UNMÖGLICH	BÜRGERLICH	ERWÜNSCHT	VORBEREITET	ELEGANT
UNEHRLICH	FURCHTSAM	GARSTIG	UNSCHÄDLICH	WEISE	WICHTIG	BEZAUBERND
INFIZIERT	UNHEIMLICH	DEFEKT	ALT	GEMEINSAM	ANSEHNLICH	WACHSAM
FAUL	BESCHULDIGT	VERLOGEN	DIREKT	UNGLAUBLICH	INVOLVIERT	ENTSPANNT
DUMM	ERSCHÜTTERT	JÄMMERLICH	REAL	GELIEBT	SAUBER	BEQUEM
ABWEICHEND	ABSCHEULICH	UNGENAU				
ÜBEL	SCHLEIMIG	DÜSTER				
ABGELEHNT	VERHASST	ÄNGSTLICH				
SCHMERZLICH	BELÄSTIGT	HEIMTÜCKISCH				
ACHTLOS	ABGETRAGEN	UNBEACHTLICH				
DÜSTER	VERFEHLT	HOFFNUNGSLOS				
AUSDRUCKLOS	SCHMUTZIG					
KRANK	UNVOLLSTÄNDIG					
CHAOTISCH	UNWILLIG					

8. Abbrevations

ACC	Anterior Cingulate Cortex
ACG	Anterior Cingulate Gyrus
AVH	Auditory Verbal Hallucinations
BA	Brodmann Area
CMS	Cortical Midline Structures
DSM-IV	Diagnostic and statistical manual of mental disorders
DLPFC	Dorsolateral Prefrontal Cortex
FEF	Frontal Eye Fields
fMRI	Functional Magnetic Resonance Imaging
FWE	Family Wise Error
H/D patients	Patients with Hallucinations and Delusions
ICD-10	International Classification of Diseases
IFC	Inferior Frontal Cortex
IFG	Inferior Frontal Gyrus
IPC	Inferior Parietal Cortex
IPS	Intraparietal Sulcus
MFG	Middle Frontal Gyrus
mFG	Medial Frontal Gyrus
MOG	Middle Occipital Gyrus
mPFC	Medial Prefrontal Cortex
MTG	Middle Temporal Gyrus
OFG	Orbitofronal Gyrus
OMPFC	Orbital and Medial Prefrontal Cortex
PANSS	Positive And Negative Symptom Scales
Pc	Precuneus
PET	Positron Emission Tomography
PPC	Posterior Parietal Cortex
PSYRATS	Psychotic Symptom Rating Scale
RT	Reaction Time
SANS	Scale for Assessment of Negative Symptoms
SAPS	Scale for Assessment of Positive Symptoms
SMA	Suppelemntary Motor Area
SPL	Superior Parietal Lobe
SPSS	Statistical Package for Social Science
STG	Superior Temporal Gyrus
STS	Superior Temporal Sulcus
TE	Time of Echo
TL	Temporal Lobe
TPJ	Temporo-parietal Junction
TR	Time of Repeat
WRAT	Wide Range Achievement Test

9. Figures and Tables

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