Cognitive and neural processes of auditory-verbal hallucinations in schizophrenia

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PART III: GENERAL DISCUSSION AND CONCLUSIONS

1. *General discussion*

1.1. *Aims and methods*

The aim of the research presented in this thesis concerned the investigation of the cognitive and neural underpinnings of auditory-verbal hallucinations (AVH) in schizophrenia. Several different methodologies were employed to test specific hypotheses with regard to the neurocognitive processes involved in AVH, and each investigation was targeted to elucidate the AVH mechanism at a different level of processing: at the level of cognition, at the level of structural brain changes, and at the level of alterations in brain function. First, we reported the findings from two behavioral experiments, designed to test whether there are measurable alterations in speech perception in subjects with (a proneness towards) hallucinations. Specifically, it was hypothesized that speech perception in these subjects is influenced to a larger extent by top-down factors such as expectations and mental imagery. However, not only external, but also inner speech has been observed to be abnormal in hallucinating subjects. In the second part of the thesis, we shifted focus to the relationship between AVH and functional and structural properties of the neural network involved in inner speech perception. The reported cognitive and neuroimaging experiments provide a correlational framework, identifying links between AVH characteristics, the underlying cognitive/perceptual processes and their neural substrates. However, from these data, causal inferences cannot be made, thus the direction of the observed relationships is unclear. In the third part of the thesis, we employed repetitive transcranial magnetic stimulation (rTMS) to tackle this issue. Temporary perturbation of neural activity by means of rTMS does allow the inference of causal links. We report on the clinical effects of a 1 Hz rTMS protocol to speech perception regions in patients with AVH, and the modulating effect on functional connectivity in the (inner) speech processing network.

1.2. *Cognitive basis of AVH: Alterations in the processing of auditory-verbal information*

The fact that auditory hallucinations usually take on a verbal form (i.e. "voices speaking"), has led researchers to suggest that they must be linked to abnormalities in the processing of speech stimuli. An early model stated that mental imagery could be too vivid, complicating the distinction between external stimuli and "perceptually rich" internally generated perceptions. Recently however, it has been proposed that AVH are due, not to pathologically enhanced imagery, but rather to an imbalance between such top-down influences and bottom-up perceptual processes. The underlying framework conceives of perception as an active process, characterized by the interaction between the processing of incoming sensory information, and existing world knowledge, as well as conscious or implicit expectations. Hallucinations may arise when a relatively higher priority is assigned to top-down factors in the determination of the final percept (Behrendt, 1998; Grossberg, 2000). Hoffman, Mazure, Quinlan & Rappaport (1999) for instance proposed that serial linguistic expectations may induce spontaneous perceptual experiences.

The first study, presented in **Chapter 4.1.**, aimed to investigate this hypothesis in a sample of healthy subjects screened for hallucination proneness. The advantage of studying a non-psychiatric population is that results are not confounded by other disease related factors, such as medication, institutionalization and cognitive deficits. Indeed, there is a growing consensus that psychotic symptoms lie on a continuum with normal experiences (Johns & van Os, 2001). Thus, within this framework, evidence of cognitive changes in a sub-clinical sample may lead the way towards a putative mechanism for AVH in schizophrenia. 351 students filled out the Launay-Slade Hallucination Scale (LSHS; Launay & Slade, 1981), a measure frequently used to assess hallucination proneness in the general population. Of these students, 42 subjects were subsequently recruited for participation in the actual experiment. These subjects represented a well distributed range of LSHS scores. Two speech discrimination tasks were designed, in which top-down influences were manipulated at two different levels: by means of sentence context ("semantic task"), or by means

of auditory imager ("phonological task"). In the former task, a sentence was presented up to the penultimate word, and the final word was presented against a background of white noise, or omitted, and only noise was presented. The sentence was either highly predictive towards the final word, or not, but in all cases grammatical violations were avoided. In the latter task, subjects were asked to imagine hearing a particular word, and subsequent detection of the same word, or a different in white noise was tested. There were no correlations between LSHS score and the performance on the phonological task, but in the semantic task, subjects with high scores on the LSHS were more likely to report hearing the expected word based on the semantic context, when it was not actually presented. We concluded that enhanced top-down processing, particularly in the form of semantic expectations may contribute to the cognitive disposition towards hallucinations.

Next, we were interested to see whether speech perception processes were abnormal and increased top-down influences were evident in patients as well (**Chapter 4.2.**). In this particular task, patients with and without hallucinations, and healthy matched controls performed a speech discrimination task. Subjects were first presented with a spoken word, embedded in white noise, and after a delay had to decide whether a second auditory stimulus was identical to the first. This task setup necessitates a matchmaking process. When the first stimulus is presented, the subject must maintain an auditory trace of it. Then, when the second stimulus appears, the subject has to compare this retained mental image with the new perception and assess the degree of overlap. Performance in this task thus measures the interaction between memorized and current perceptions, and is sensitive to the balance between top-down and bottom-up perception. We employed signal detection theory (SDT) in order to investigate the underlying cognitive-perceptual mechanisms. Interestingly, SDT allows one to distinguish perceptual sensitivity, which represents the general effectiveness of the perceptual system, and response bias, which refers to an individual's private criterion to decide whether a perceived event is an actual stimulus. In order to control for general auditory acuity, we also assessed tone perception thresholds. The results showed that, compared to healthy controls, perceptual thresholds were higher and perceptual sensitivity in the speech task was lower in both

patient groups. However, hallucinating patients showed increased sensitivity to speech stimuli compared to non-hallucinating patients. In addition, we found some evidence for a positive response bias in hallucinating patients, indicating their general tendency to reaffirm the presence of a suggested auditory stimulus. Thus, within the context of schizophrenia, patients with auditory hallucinations appear to be particularly "tuned" to auditory-verbal stimulation. The combination with a liberal criterion for deciding that a perceived event is an actual stimulus, may lead not to more perceptual errors, but rather different ones. The willingness to err on the side of false positives may result in enhanced stimulus detection, but also lead to perceptions in absence of corresponding stimulation, or hallucinations.

These two studies both implicate top-down processes in the cognitive basis of the propensity towards auditory hallucinations. In healthy subjects, this appears to take place at the level of semantic processing. In patients, changes were observed in phonological processing as well as higher order decision processes. In both cases, hallucination prone subjects seem to require less bottom-up information before accepting the identity of a particular stimulus. However, a number of important issues remain to be clarified. Firstly, we did not explicitly test perceptual processing in other modalities. Thus, the specificity of our suggestion that AVH may be linked to an increased "tuning" to auditory-verbal stimuli, and enhanced top-down influences should be verified by assessing perceptual processing in other modalities, e.g. a visual task. It is also not clear whether this cognitive predisposition actually causes AVH. Secondly, this increased tuning to auditory verbal stimuli may also be a consequence rather than a cause of hallucinations. It may well be that the frequent experience of AVH affects the perceptual system in such a way that auditory-verbal information takes on particular salience due to the personal and emotional relevance of the AVH, resulting in a cognitive system specifically geared towards speech perceptions. Increasingly, emotional processes are being considered in the pathophysiology of AVH (Kapur, 2003). We employed neutral stimuli, but future research should also assess whether perhaps the observed effects are amplified for material with negative content, as this would fit with the phenomenology of AVH.

1.3. *Neural basis of AVH: The relationship with the inner speech processing network*

The observation that abnormalities in external speech perception exist in individuals with AVH, combined with the fact that the neural processes involved in external and internal speech perception overlap to a large extent (Shergill et al., 2002; Aleman et al., 2005), as well as the similarity between AVH and inner speech, have led researchers to suggest that there may be deficits in inner speech processes and its neural substrates.

Over recent years, a number of investigations have indeed found evidence of a link between AVH and altered neural activation in a distributed network of inner speech and verbal monitoring regions in the brain (Shergill, Bullmore, Simmons, Murray, & McGuire, 2000; Shergill et al., 2003; McGuire et al., 1996). With regard to brain morphology, recent studies using Voxel-Based-Morphometry (VBM) have demonstrated regionally specific abnormalities in the inferior frontal and temporal cortex associated with AVH (Shapleske et al., 2002; Garcia-Marti et al., 2008; Neckelmann et al., 2006).

1.3.1. Structural changes in inner speech processing areas

In **Chapter 5.1.** we presented a study in which we used VBM in a sample of 26 patients with schizophrenia and medication-resistant AVH to test the hypothesis that overall severity of AVH would be associated with gray matter volume abnormalities in the inner speech network, and secondly that AVH severity would modulate structural covariance between frontal and temporal regions. Structural covariance refers to the co-variation in regional volume between different brain areas, which results from mutually trophic influences or common experience-related plasticity (Mechelli, Friston, Frackowiak, & Price, 2005). Interestingly, a number of regions express altered patterns of structural covariance in patients with schizophrenia relative to controls (Mitelman, Buchsbaum, Brickman, & Shihabuddin, 2005; Mitelman, Shihabuddin, Brickman, & Buchsbaum, 2005; Wible et al., 1995; Woodruff et al., 1997), but the relationship between these alterations and specific psychotic symptoms remains

unknown. In our patient sample AVH were characterized by means of The Auditory Hallucinations Rating Scale (AHRS; Hoffman et al., 2003), and optimized VBM was applied, using a pre-defined anatomical Regions-of-interest (ROI) approach on high resolution T-1 weighted structural MR images. A positive correlation between grey matter volume (GMV) in the left inferior frontal gyrus (IFG) and general hallucination severity was identified. Functional neuroimaging studies have indicated that the IFG is activated during hallucinations (McGuire, Shah, & Murray, 1993). Interestingly, prolonged use of a structure may result in volumetric increases (Maguire, Woollett, & Spiers, 2006). The identified left IFG region corresponds to the area where convergent input from temporal lobe regions enters the frontal lobe and has a known role in speech processing (Poldrack et al., 1999). Thus, it is not surprising that, amongst a sample of hallucinators, greater severity correlated with increased GMV therein. Secondly, the analysis of structural covariance revealed that hallucination severity modulated cortical intercorrelations between GMV of the left IFG and a number of other regions, i.e. left MTG and STG, contralateral IFG, hippocampus, and insula. Evidence exists of altered associations between left frontal and temporal regions on a structural (Mitelman et al., 2005) and functional (Lawrie et al., 2002; Ford, Mathalon, Whitfield, Faustman, & Roth, 2002) level in schizophrenia patients compared to healthy controls. Furthermore, structural covariance between fronto-temporal regions, indicating common volumetric variations, is abnormal in schizophrenia (Mechelli et al., 2007). The findings from this experiment thus extend previous results by relating altered structural covariance to the severity of a specific symptom.

1.3.2. Functional changes in inner speech processing areas

Thus, it appears that inner speech is a likely candidate process involved in the generation of AVH, at the cognitive and neural level. However, one typical aspect of AVH that is not paralleled in inner speech, concerns the "auditory" quality. AVH are perceived as "voices" with particular sensory characteristics, such as variations in loudness, accent, pitch, etc. Thus, it has been suggested that inner speech theory may be insufficient to explain the phenomenological characteristics of the sound

experience that are AVH. **Chapter 5.2.** described a study designed to assess whether these sound characteristics may nevertheless be linked to activation in brain regions that in prior research have been identified as involved in inner speech processing. FMRI scans were obtained from a group of patients with AVH, while performing a metrical stress discrimination task. This paradigm requires the subject to generate the phonological code of a visually presented word, in order to determine whether the metrical stress is on the first or second syllable of the word. It was previously shown that this task engages both the inner speech production and perception regions in healthy controls (Aleman et al., 2005). Because we were interested in the inner speech network, we defined a number or Regions-of-Interest (ROI) based on the existing literature, and correlated activity in these ROIs with measures of "loudness" and "reality" of the AVH, derived from the Auditory Hallucination Rating Scale. In addition, a language lateralization index was computed and the relationship with AVH characteristics was assessed. The results showed that louder AVH were associated with reduced task-related activity in a distributed network of areas involved in inner speech production (left inferior frontal cortex and insula), as well as inner speech perception (bilateral angular gyrus), and the monitoring of inner speech (bilateral anterior cingulate, and left middle temporal cortex). It has previously been suggested that inner speech and AVH may compete for the same neural resources (Plaze et al., 2006). Our results contribute to this interpretation by showing that variations in perceptual salience of AVH (i.e. louder AVH) lead to variable use of resources involved in inner speech, resulting in reduction of task-related activity with increasing perceptual quality of AVH. Thus, inner speech production, and the (presumably subsequent) activation of inner speech perception and monitoring are in fact involved in developing the sensory/auditory characteristics of AVH. The more subjective and multidimensional aspect of AVH "reality", however was not found to be directly of linearly related to activation in inner speech processing regions. Rather, it was shown that perceived reality correlated with reduced lateralization of task-related linguistic activity. Evidence from other structural and functional neuroimaging studies suggests that language lateralization may be reduced in schizophrenia patients as a group (Bleich-Cohen, Hendler, Kotler, & Strous, 2009; Li et al., 2007; Zhang et al., 2008;

Sommer, Aleman, & Kahn, 2003). The observation of a correlation between the "reality" of AVH and reduced lateralisation during this paradigm, suggests that enhanced contributions of the right hemisphere to inner speech may relate to misperceptions. The right hemisphere has a basic capacity for language perception, typically involving more pragmatic aspects (e.g. non literal meaning, emotional prosody), and for language production, typically consisting of short utterances of limited complexity, and negative content. If AVH represent inner speech that is provisioned with perceptual qualities through overactivation of speech perception areas of the left hemisphere, co-activation of right hemisphere language areas could further enrich the experience with non-linguistic information, such as (emotional) prosody, making it harder to distinguish the final percept from external reality.

1.3.3. *Relationship between AVH and (abnormal) inner speech*

The two studies reported in chapters 5.1. and 5.2. both add to the existing literature in support of the notion that inner speech processing and verbal monitoring neurocircuitry contribute in an important way to the generation of hallucinated speech experiences. At first glance however, the findings do not concur perfectly. Localized structural changes convergent with AVH severity were evident only in the IFG, whereas functional changes associated with the perceptual salience of AVH was observed in a more widely distributed network of inner speech processing regions. Nevertheless, assessment of the structural covariation of the IFG volume did reveal a link with a more elaborate network that largely overlapped with the functional network, i.e. both included the insula, the left medial temporal lobe and an a posterior temporal/angular area. Another difference between the studies was that the structural findings were related to a more global measure of AVH, namely, the composite score based on the AHRS subscales, which is a general measure of AVH severity. The functional data on the other hand identified a relationship specifically with the perceptual qualities of AVH, although this was also measured with subscales of AHRS. The composite AHRS score weighs frequency of occurrence more than other AVH characteristics, so it could be that gross anatomical changes are linked more to

general severity and frequency, rather than to specific characteristics such as length of AVH utterances, loudness or number of voices. The functional changes may be more sensitive to subtle differences in the perceptual or experiential qualities of the AVH.

Our finding that local changes in gray matter were restricted to IFG seems to contradict findings from previous studies, in which GMV changes in temporal regions, particularly decreases, have been reported in patients with schizophrenia. However, these changes are most often observed in comparison to control subjects and may relate to the general illness process rather than to AVH in particular (Allen, Laroi, McGuire, & Aleman, 2008), although some studies have found a link with AVH (Barta, Pearlson, Powers, Richards, & Tune, 1990; Flaum et al., 1995). The findings of our VBM study may have been limited by the relative homogeneity of our sample, which consisted of chronic patients with medication-resistant AVHs. This may have contributed to the fact that the left IFG was the only region to survive correction for multiple comparisons. In future studies perhaps larger variability in the different aspects of AVH could be considered, by a broader selection of patients. Further research could benefit also from controlling for factors such as effects of medication, which have been suggested to have neurotrophic properties which could affect cortical thickness in treated subjects compared to untreated ones (Lieberman et al., 2005). Given that regional volume alterations have also been found in VBM studies of subjects with an at-risk mental state for psychosis (Borgwardt et al., 2007; Meisenzahl et al., 2008; Pantelis et al., 2003) and functional changes in brain regions similar to those found in patients may be observed, such a population might represent an excellent opportunity to explore neuroanatomical abnormalities, and the functional substrates of hallucinations, free from potential influences of chronic antipsychotic treatment, and other illness related processes.

A more general issue that challenges the interpretation of AVH as vivid inner speech instances lies in the fact that patients with AVH do not lose the capacity for normal inner speech. They can perceive their *own* inner voice, just as non-voice hearers do, and experience only some inner speech as originating from the non-self. Additionally, from a phenomenological standpoint, their inner speech was observed to be quite similar to inner speech of healthy controls (Langdon, Jones, Connaughton,

& Fernyhough, 2008). Moreover, patients may sometimes carry on an internal dialogue with their voices, but only experience one part of this dialogue as a hallucination. A major question thus remains why certain inner speech events are disjointed from a feeling of agency and others are not, and which aspects of the experience determine the subjective perception of another person's voice, differing from the own inner voice. Moritz & Laroi (2008) recently explored the relationship between imagined (hallucinated) and real voices, and assessed the cognitive and sensory profiles of verbal thoughts, intrusions and voice-hearing in sample of psychiatric patients. To circumvent conservative response biases, an internet-based questionnaire was used, and 160 subjects completed the survey. In line with prior research, most of the patients with schizophrenia reported hearing voices. Interestingly, a significant proportion of voice-hearers (37%) admitted that their voices did not appear very real, and that they were less loud than real voices (52%). In addition, voice-hearers reported greater vividness and loudness of mental events even for normal thoughts. This suggests that enhanced mental vividness, in addition to the presence of metacognitive biases, may represent vulnerability factors for the development of hallucinations. The results therefore demonstrated that none of the traditional "four A's of hallucinations": acoustic, alien (i.e., appears as non-self), autonomous (i.e., beyond subjective control), authentic (i.e., appears like a real voice) were specific to voice-hearing in these patients. The authors concluded that differences between intrusive thoughts and voice-hearing are more quantitative than qualitative. This matches with our finding of a linear increase of activation in the "normal" inner speech network with intensifying perceptual features of AVH. Moritz & Larøi (2008) go on to suggest that post-hoc attributional processes must therefore be involved in the experience of AVH. In line with this idea, Sommer et al. (2008b) proposed that inner speech, when generated in the non-language dominant right hemisphere, may be particularly susceptible to the (mis)interpretation as an external voice, rather than a self-generated event. The fact that right hemisphere linguistic productions are typically of low linguistic complexity and may have more of an emotional component also fits with the typical content and form of AVH. We would like to advance the possibility that negatively valenced linguistic material, surfacing as

"perceptually enriched" inner speech, may lead to cognitive dissonance. By virtue of its perceptual vividness as well as its meaningful content, the perception might not be accepted as coming from the self, which promotes a post hoc (mis)attribution to an external source.

This interpretation illustrates the fact that AVH are perhaps not easily explained by a single neural deficit or a specific aberrant cognitive process. Rather, it appears that they result from a complex interplay between emotional/motivational influences, potentially both at a conscious and preconscious level, changes in cognitive/perceptual processing, such as the aberrant production, perception and monitoring of inner speech, and top-down attributions or response biases in a brain wired to experience hallucinations.

1.4. *Interventions with rTMS and the potential for causal inferences*

From the above mentioned investigations into the cognitive and neural basis of AVH, it should be clear that the evidence converges on the centrality of aberrant (inner) speech perception to the experience of AVH. It is therefore unsurprising that the posterior superior temporal gyrus, a region essential to the perception of speech, was hypothesized to be a suitable candidate region for the therapeutic application of repetitive transcranial magnetic stimulation (rTMS). Accordingly, functional neuroimaging studies have revealed enhanced activation of secondary, and occasionally primary sensory auditory cortices during AVH, particularly in the left hemisphere (McGuire et al., 1993; Suzuki, Yuasa, Minabe, Murata, & Kurachi, 1993; Van de Ven et al., 2005; Dierks et al., 1999), although a few studies found evidence of bilateral temporal involvement (Shergill, Brammer, Williams, Murray, & McGuire, 2000; Lennox, Park, Medley, Morris, & Jones, 2000b).

TMS is a non-invasive technique that enables safe, relatively painless focal brain stimulation in humans. A magnetic pulse is delivered to a specified brain area by means of a stimulating coil placed on the corresponding scalp site. In repetitive TMS (rTMS) a train of pulses of the same intensity is delivered to a single brain area at a given frequency. Low frequencies (≤ 1 Hz) can suppress excitability of cortical neurons

(Pascual-Leone, Davey, Rothwell, Wassermann, & Puri, 2002). This observation suggests a therapeutic value against the pathological neuronal hyperactivity observed in the superior temporal cortex during AVH (Hoffman & Cavus, 2002). The first study ever conducted to test the therapeutic efficiency of 1 Hz rTMS in the treatment of AVH revealed encouraging results (Hoffman et al., 1999). Stimulation of left temporoparietal cortex was compared with sham stimulation using a double-blind, cross-over design in three patients. All patients demonstrated greater improvement in hallucination severity following active stimulation compared to sham stimulation. Two of the three patients reported near total cessation of hallucinations for at least two weeks. A follow up study in a larger sample confirmed these preliminary findings: auditory hallucinations were robustly diminished after rTMS treatment relative to sham stimulation, with frequency and attentional salience showing the greatest improvement. The duration of the treatment effect ranged widely, but 52% of patients maintained improvement for at least 15 weeks. Importantly, the rTMS application was well tolerated, without evidence of neuropsychological impairment or severe side-effects. Several studies have now reported positive effects of low frequency rTMS over the left temporoparietal cortex in patients suffering from AVH (Poulet et al., 2005; Chibbaro et al., 2005; Hoffman et al., 2005; Lee et al., 2005; d'Alfonso et al., 2002), although some experimental trials have yielded null effects or mixed results (Schonfeldt-Lecuona et al., 2004; McIntosh et al., 2004). The general effectiveness of the treatment has however been supported by two recently published meta-analyses that confirmed the superiority of rTMS over placebo treatment in reducing medication-resistant AVH (Aleman, Sommer, & Kahn, 2007; Freitas, Fregni, & Pascual-Leone, 2009).

1.4.1. Clinical effects of rTMS treatment of AVH

In **Chapter 6.1.** we reported a study designed to assess whether these positive results could further be improved by applying rTMS to the bilateral temporal cortex. The underlying rationale is based on evidence of reduced language lateralization in patients with AVH (Sommer, Ramsey, Aleman, Bouma, & Kahn, 2001), as well as a

growing body of evidence implicating the involvement of both right and left language processing regions in the generation of AVH (Lennox, Park, Medley, Morris, & Jones, 2000a; Shergill et al., 2000; Sommer et al., 2008b). The role of the right temporal cortex in the processing of prosody and other "non-literal" aspects of language, matches the emotional salience and negative/derogatory form of AVH. Accordingly, we hypothesized that a bilateral treatment would contribute towards a more complete management of the symptoms, not only diminishing more objective characteristics of AVH, such as frequency, but perhaps also affecting the emotional salience. We assigned 38 patients with schizophrenia (DSM-IV) and medication-resistant AVH randomly to either 1 Hz rTMS treatment of the left temporoparietal junction (TPJ), bilateral TPJ, or placebo. Stimulation was conducted over 6 days, twice daily for 20 minutes, at 90% of the motor threshold. The treatment effect was measured at several time points before, during and after treatment, using a number of self-report questionnaires, including the Auditory Hallucination Rating Scale (AHRS), and Positive and Negative Affect Scale (PANAS). Secondly, hallucination severity was assessed before and after treatment by means of a semi-structured clinical interview (Positive and Negative Syndrome Scale; PANSS). The results showed that all groups improved to some extent on the total AHRS score. However, only the group receiving left rTMS showed a significant reduction in the frequency of AVH, which is the parameter that was identified in previous research to be most susceptible to rTMS-induced improvement. Interestingly, symptom amelioration was characterized by a slight delay of effect, becoming most evident at the follow-up measurement, one week after the final rTMS session. This is suggestive of a gradual build-up of rTMS induced changes on the underlying cortex (Valero-Cabre, Pascual-Leone, & Rushmore, 2008). The bilateral rTMS group on the other hand demonstrated a somewhat more pronounced reduction in affective responsiveness to AVH, revealing a general decrease in self-reported emotions (both in terms of negative and positive valence) during the AVH experience. In terms of clinical relevance of the findings, a modest, but significant decrease on the PANSS hallucination item was observed in the combined rTMS treatment group, whereas no change occurred in the placebo group. The left rTMS group also showed a significant, albeit modest reduction on the general

psychopathology subscale. From this we concluded that compared to bilateral or sham stimulation, rTMS of the left TPJ appears most effective in reducing auditory hallucinations, and additionally may have an effect on general psychopathology. Our findings thus support previous reports, and suggest that the left speech processing cortex is crucial to the development of AVH. However, results from the bilateral condition included in this experiment fail to clarify the exact role of the right hemisphere. The propagating effects across the brain, following local rTMS stimulation are not well understood. The possibility of interactions between the effects of stimulation of the left speech cortex and immediate and subsequent stimulation of its right sided homologue complicates the interpretation of specific rTMS induced effects on the separate regions. Further research would probably benefit from the inclusion of a condition using right sided stimulation only. The study's inherent limitations thus led us to caution against strong conclusions. The relatively small sample size and limited effects sizes, as well as the occurrence of marked improvement after sham stimulation in a number of cases, warrant a careful consideration of the observed effects.

1.4.2. *Functional connectivity: Associations with AVH and modulations by rTMS*

In **Chapter 6.2.** we reported an attempt to further investigate the therapeutic mechanism of rTMS on a neuronal level, by means of fMRI scans which were obtained before and after treatment in a subset of patients partaking in the randomized clinical trial. We were interested to see whether patterns of functional connectivity of the stimulated brain areas, i.e. the bilateral TPJ, would change as a result of rTMS application. However, first of all, this study set out to characterize the relationship between AVH and patterns of functional connectivity of the TPJ at baseline (i.e. before treatment with rTMS). It is interesting to note that recent models of schizophrenia favor a conception of the disorder in terms of a failure to integrate activity in distributed neural circuits, rather then relating schizophrenia to a (number of) localized deficit(s). Especially the disintegration of fronto-temporal connectivity during task performance has received quite a bit of attention (Lawrie et al., 2002;

Mechelli et al., 2007; Hashimoto, Lee, Preus, McCarley, & Wible, 2009). Although the use of particular tasks, especially those taxing the putative cognitive processes involved in AVH, may provide interesting clues towards the working mechanism of AVH, we reasoned that the assessment of resting state activity could also be informative. First of all, this paradigm is not confounded by potential differences in task performance between controls and patients. Secondly, the resting state represents an active default or 'idling' mode of the brain and reveals intrinsic activity. Some researchers have even suggested that this activity could be just as informative in terms of overall brain function, compared to task-evoked activity (Raichle & Gusnard, 2005). Interestingly, the intrinsic brain activity has been implicated in attention to external and internal stimulation, as well as self-referential reflective activity, specifically, episodic memory retrieval, inner speech, mental imagery, emotions, and planning future events (Gusnard, Akbudak, Shulman, & Raichle, 2001; Gusnard & Raichle, 2001; Raichle et al., 2001; Greicius, Krasnow, Reiss, & Menon, 2003; Fransson, 2005). These are all cognitive processes which have been found to be aberrant in schizophrenia patients with AVH. Thus, it seemed a reasonable assumption that patterns of functional connectivity may be associated with the predisposition towards AVH. We were able to obtain resting state fMRI scans from 27 patients with schizophrenia and AVH, and 27 matched controls. Nine patients received rTMS of the left TPJ, nine patients received bilateral rTMS and nine received a placebo treatment, by means of a sham coil. Scanning was conducted twice in the patients, namely once before and once after the complete rTMS treatment protocol, with a maximum 2 day delay. The bilateral TPJ were selected as seed regions, and functional connectivity between pairs of regions-of-interest (ROIs) was estimated by extracting and averaging the timecourse of the fMRI signal and correlating these for each pairing of a seed region with a ROI. We then assessed group differences between patients and controls. Secondly, within the patient group we looked for correlations between functional connectivity measures and AVH severity. Finally, changes in connectivity measures were assessed over time as a function of rTMS condition. The results showed that patients with schizophrenia had reduced functional connectivity between left TPJ and the right homologue of Broca, in comparison to healthy

controls. We interpreted this reduced coherence in fronto-temporal activity as a possible failure of the corollary discharge system. It has been noted that in healthy subjects, the production of inner speech leads to a corollary discharge in speech perception areas, which signals to the brain that the impending afferent "sensory" information is self-generated (Ford & Mathalon, 2004; Ford, Roach, Faustman, & Mathalon, 2007). A failure in this system will result in a loss of agency, and may cause the subsequent misattribution of the internal event to an external source, thus producing the perception of an AVH. However, as we did not include a reference group of schizophrenia patients without hallucinations, the specificity of this finding to AVH could be called into question. It is possible that this fronto-temporal connectivity deficit relates, for instance, to the entire positive symptom cluster. Other studies have however found evidence linking corollary discharge deficits to AVH (Ford & Mathalon, 2004; Ford et al., 2007), which strengthens our interpretation.

1.4.2.1. *Relationship between AVH and patterns functional connectivity of the TPJ*

Assessment of the relationship between functional connectivity measures and variability in AVH severity did allow us to identify particular changes that are specific to the presence of AVH. Within the patient group, more severe AVH were associated with reduced neural coupling between left TPJ and bilateral anterior cingulate, bilateral amygdala and the left dorsolateral prefrontal cortex. Activity in the TPJ area, as well as the anterior cingulate during the resting state probably reflects the perception and monitoring of inner speech or verbal self-referential thought (Shergill et al., 2001). As Craig (2009) suggested, when the anterior cingulate cortex fails to synchronize its activity with the generation of activity in the posterior temporal cortex, the verbal thought may become disjointed from conscious control, leading to "disembodied" language experiences. The dorso-lateral prefrontal cortex (of the left hemisphere) also showed reduced co-activation with the left TPJ, with increasing AVH severity. This area has previously been found to be deficient in schizophrenia patients with AVH (Kawaguchi et al., 2005). DLPFC has a major role in cognitive control, which further supports the former interpretation that reduced conscious control over verbal thought or imagery may be a factor in the neural underpinnings of the propensity

towards AVH. Our observation of reduced connectivity of the left TPJ to the amygdala may seem counterintuitive, as the amygdala has long been recognized as an important structure in the processing of emotions in reaction to external stimuli. As AVH often have a distinct emotional component, one might expect a stronger amygdala co-activation. Interestingly however, one study has also implicated the amygdala in the processing of self-relatedness of imagined (rather than real external) derogatory appraisals (Kim et al., 2008). We hypothesized that the observed lack of a synchronized amygdala response could be associated with a reduced sensation of self-relatedness during resting state self-reflective activity. As we suggested earlier, it is possible that this represents a cognitive mechanism by which negatively valenced verbal thoughts, especially if they are particularly abusive or derogatory, are not accepted by the patient as coming from the self. Subsequent (mis-)attributed to an external source, could then lead to an experience of an external "voice" rather than an inner thought. In sum the correlational findings suggest that activity in the left TPJ, a critical node in the speech perception/AVH network, appears to be disjointed from brain activity in areas normally involved in the attributions of agency, self-referent processing and attentional control. This constellation of reduced connections could represent the neural substrate of the cognitive predisposition towards hallucinations. We suggest that these alterations are not necessarily linked to the hallucinatory state, but putatively express the trait characteristic of hallucination proneness, as they were evident during the resting state. Admittedly, although the resting state in patients may have included epochs with AVH, it most likely does not immediately reflect actual AVH activity, as the data are averaged over the whole time period of the resting state scan.

1.4.2.2. *Modulation of functional connectivity by means of rTMS*

The third aim of the study was to assess alterations in functional connectivity in relation to rTMS treatment. Similar to the findings in the larger group reported in **Chapter 6.1.**, symptom improvement following rTMS treatment was most marked in the group receiving rTMS to the left TPJ. However, when we looked for changes in the functional connections that were associated with AVH severity in the correlational

analysis, no significant results were obtained. The group receiving rTMS of the left TPJ showed enhanced neural synchrony between the left TPJ and the right insula after rTMS treatment. The insular cortex is tightly coupled with the anterior cingulate, forming a "core control network" in the brain at rest (Dosenbach et al., 2007). Thus, we hypothesized that although the expected enhancement of the TPJ-cingulate connection was not observed, it is possible that the insula may have acted as a third covariate influence on the functional coupling between the stimulated left TPJ and the anterior cingulate, leading to symptom improvement. The clinical improvement in the bilateral group was less marked, but we did observe a trend towards a change in functional connectivity between the right TPJ and the right homologue of Broca's area. The fact that this group showed a change in connectivity in the right hemisphere, whereas the left rTMS group showed a change in connectivity with the left TPJ, fits with the expectation of local effects relative to coil positioning. In the bilateral group, it is possible that rTMS of the left TPJ, which was always conducted first, led to a disinhibition of the right TPJ. Subsequent inhibitory action on the right TPJ may have induced a corresponding decrease in activity in the right inferior frontal cortex by means of well-established fronto-temporal intrahemispheric connections. This complex interaction of opposing processes may have led to reduced synchrony between the right TPJ and right homologue of Broca's region. It appears however that these functional changes are not immediately linked to reliable decreases in AVH severity. As was mentioned before, the limited knowledge with regard to the inter- and intrahemispheric propagation of rTMS-induced effects makes it difficult to predict the neural effects of the bilateral rTMS treatment. It is not clear how the brain responds to successive stimulation of anatomically and functionally connected homologous regions, and how rTMS-induced changes in one region might influence responsivity of a functionally connected region to rTMS. Nevertheless, our results indicated that 1 Hz rTMS may have some modulating effect on functional connectivity of the stimulated region, but the association between connectivity changes observed in the resting state and clinical improvement is uncertain. The fact that the placebo group also showed some alterations in functional connectivity over the course of the treatment further complicates a clear interpretation. However, the observed changes

in the placebo group were in the opposite direction, relative to the expected alterations related to symptom improvement. For instance, rather than an enhancement, a further decrease in connectivity between the left TPJ and the left anterior cingulate and right amygdala was found after rTMS treatment.

In sum, to our knowledge this study was the first to link the symptom domain of AVH to resting state functional connectivity. Group analyses revealed a reduction in synchronized activity in fronto-temporal connectivity in patients compared to controls. Furthermore, we were able to link increasing AVH severity within the patient group to specific decreases in functional connectivity with the left TPJ. The potential of modulation of these resting state connections by means of 1 Hz rTMS was found to be minimal, but further research in larger samples and employing other (e.g. whole brain) approaches should be undertaken to further assess the potential of rTMS induced alterations in functional connectivity relative to AVH severity.

1.4.3. *Methodological remarks and implications for future research*

The two complementary and partially overlapping studies on the effects of 1 Hz rTMS at the behavioral and neural level tentatively support the critical role of the left posterior superior temporal/temporoparietal region in the genesis of AVH. The observed effects in terms of clinical importance and neuronal response were nevertheless relatively limited, which warrants a conservative interpretation of the findings. There are a number of methodological issues which may have contributed to the modest findings.

1.4.3.1. *Spatial specificity of rTMS and individual differences in neural architecture*

The first issue concerns the method used for the positioning of the coil. Although the spatial resolution of rTMS is quite coarse, within the range of 2 to 3 centimeters, precise positioning is preferable, given the fact that the magnetic field tapers off exponentially with distance from the center of the coil. In our studies, we used standard fitted EEG caps, and localization of the temporoparietal junction was based on the 10/20 international system. Neuronavigated, stereotactic methods, based on

individual anatomical or functional activation maps would no doubt decrease variability in the localization. The possibility exists that the functional area targeted in one subject does not completely match that of the next subject, and slight shifts in coil position across time and across sessions in a single subject are also likely to occur. These inaccuracies in the method may have introduced unwanted additional noise in measurements.

Related to this issue, one should take into account the presence of large inter-individual differences in the cerebral activation patterns associated with AVH. The association between AVH and activation of speech perception areas reported in the literature is based on averaged brain responses in groups of hallucinating patients. Individual subjects may nevertheless show quite variable networks of AVH-related activity, in which the posterior temporal regions may or may not be of critical importance. This implies that the "blind" application of rTMS on the anatomically defined STG/TPJ region may not be the optimal method. The use of fMRI-guided rTMS could be helpful in identifying the specific targets for rTMS application in the individual patient (Sommer et al., 2007), but this method needs further validation and is not feasible in all patients. In order to obtain workable activation maps, the patient needs to present discrete epochs of AVH activity and "silent" epochs within the time frame of one fMRI session. Intermittent hallucinators are relatively rare, and the method is not applicable to either continuous or infrequent hallucinators. And even for those patients for whom activation maps may be reconstructed, AVH-related "hot spots" may not always be adequate targets for rTMS application. For instance, certain cortical and of course subcortical areas are not immediately within reach of the rTMS apparatus.

Furthermore, with regard to interindividual variability in neuroanatomy, it should be noted our patient sample was not selected on handedness. It has been shown that handedness relates to differences in cerebral lateralization (Khedr, Hamed, Said, & Basahi, 2002), which means that this again may have harbingered unwanted variability in the area that we presumed to target with rTMS. Future studies should either include only right handed individuals, or perform separate group analyses in left

and right handed participants. Alternatively, functional indices of language lateralisation could be obtained to group the subjects.

1.4.3.2. *The effects of medication*

Our rTMS trial, in accordance with previous studies, included only subjects with medication-resistant AVH. However, we did not specifically select patients based on the type of antipsychotic and adjunctive medication. It is likely that antipsychotic medication, as well as the concurrent use of other psychoactive drugs interacts with the rTMS administration (Hoffman et al., 2000; Poulet et al., 2005). Specifically, benzodiazepines may reduce cortical excitability (Palmieri et al., 1999) or increase cortical inhibition (Daskalakis et al., 2002), thereby potentially diminishing the effect of TMS. All of our patients were receiving stable doses of antipsychotics, and one third of the patients in the active rTMS conditions received benzodiazepines as an adjunctive treatment. However, medication effects most likely do not explain group differences in terms of rTMS effects, as the number of patients receiving regular benzodiazepine treatment were equally distributed across groups. It may nevertheless have contributed to the overall relatively modest effect sizes. There is also evidence that different antipsychotics may also have variable effects on cortical excitability. For instance, Fitzgerald et al. (2002) employed a TMS paradigm on motor excitability to asses differential effects of antipsychotics and found that olanzapine and risperidone differ subtly in their effects on inhibitory mechanisms. Again, it is unlikely that group differences would be due to these medication effects, since there was as much variability within groups as between groups, in terms of the type of antipsychotic used. No studies to date have assessed the effect of rTMS treatment, in isolation from concurrent pharmacological treatment. It is considered to be unethical to withdraw chronic schizophrenic patients from medication for the duration of the rTMS treatment, as it may provoke psychotic relapse. However, studying medication naïve, first episode patients with AVH could lead to new insights. It is possible that in these patients the neural substrate of AVH may be more susceptible to rTMS induced neuroplasticity. It would therefore be interesting to asses both clinical treatment

effects, as well as functional alterations in the neural systems underlying the symptom.

1.4.3.3. *Variations in rTMS parameters*

Our study, as others have done, employed fairly conservative parameters. Stimulation was performed at 90% of the individual motor threshold, and the treatment duration of 6 days is relatively short. There is evidence of a dose-dependency effect of rTMS, implying that longer series of pulses and perhaps particularly stimulation at higher intensities would have either stronger or longer lasting effects. Nahas et al. (2001) for instance, observed a dose-related response when studying the local effect of 1 Hz rTMS on activity in the dorso-lateral prefrontal cortex in healthy subjects. A measurable change in BOLD response was present only at higher intensities. Gershon, Dannon & Grunhaus (2003) reviewed rTMS treatment studies of depression, and attempted to discern the influence of patient and technical characteristics on treatment response. They suggested that studies with longer overall treatment duration (> 10 days), with higher intensities (100-110% of the motor threshold) and more pulses per session appeared to have stronger effects. For the treatment of auditory hallucinations, such a detailed and systematic evaluation has not yet been performed. It is however conceivable that these parameters may play an important role in this instance as well. Given the relatively clean side-effect profile of 1 Hz rTMS (Machii, Cohen, Ramos-Estebanez, & Pascual-Leone, 2006) stimulation at supra-threshold intensities could be advocated. The duration of the treatment could also be extended, both in terms of session duration and in total number of sessions, especially since there appears to be a gradual build-up of the effect over the course of subsequent sessions. Interestingly, in their meta-analysis of rTMS trials of AVH treatment, Aleman et al. (2007) did observe that those studies which failed to find a positive effect were on average quite short in duration, or did not use continuous stimulation. Our own study protocol was characterized by a two day delay halfway in the treatment (i.e. a weekend hiatus). In addition, due to technical restrictions, the bilateral stimulation condition had a short time lag halfway in the session, as at this point the coil had to be switched from the left tot the right hemisphere. This may have

contributed to our finding of a modest clinical effect especially in the bilateral group. Another parameter that could be varied, is the frequency of stimulation. The presumed inhibitory effects of 1 Hz rTMS are thought to counteract pathological overactivity in the speech cortex. Interestingly, a recent case study reported beneficial effects of 20 Hz rTMS (Dollfus et al., 2008). A larger follow-up open study (Montagne-Larmurier, Etard, Razafimandimby, Morello, & Dollfus, 2009) in 11 patients revealed a significant reduction in global severity and frequency of AVH between baseline and post-treatment day 12. Subjects were treated for 2 days with 20 Hz rTMS. The target area was identified by fMRI as the highest activation cluster along the posterior part of the left superior temporal sulcus from the BOLD signal of each subject during a language task. When subjects were re-assessed 6 months after rTMS treatment, complete cessation of AVH was maintained in 2 patients. The authors explain their observations by referring to the potential of high frequency rTMS to induce inhibitory effects. In addition, they compare the findings with the effects observed in patients with tinnitus, in whom the effect of high frequency rTMS over the left temporoparietal region was found to be equivalent to that of low frequency rTMS .However, the lack of a placebo group in this study precludes strong conclusions. In sum, it is evident that clinical rTMS trials will benefit from a detailed investigation of the specific effects of the different parameter settings.

1.4.3.4. *Duration of rTMS effects*

Another issue of particular clinical and practical relevance in rTMS treatment studies is the durability of the rTMS-induced changes. In our study we do not report on symptom scores past the one week post-treatment follow up assessment, and the effect on brain response was measured at just one time point post treatment. Previous trials have observed clinical improvements lasting about 15 weeks in half of the subjects (Hoffman et al., 2005). In further research it would be informative to continue to assess patients during maintenance treatment, after the first effective rTMS treatment phase. Fitzgerald, Benitez, Daskalakis, De Castella & Kulkarni (2006) observed that a repeat course of rTMS led to marked improvements in AVH severity. Another case study confirmed this finding (Thirthalli et al., 2008), tentatively

suggesting that the protocol has potential in terms of long term maintenance treatment of AVH. Evidently, further research is necessary to verify these results in larger samples.

1.4.3.5. *Potential working mechanisms of rTMS*

Finally, a general issue that pertains to all clinical applications of rTMS concerns the fact that the working mechanism of rTMS is still poorly understood. Its effects have been likened to long term potentiation and depression (Pascual-Leone et al., 2002). The general consensus is that frequencies of 1 Hz or less have inhibitory influences on the underlying cortex, whereas frequencies of 5 Hz or more have excitatory effects. However, patterns of neuronal response may be more complex, as a recent study showed that short TMS pulse trains led to an initial period of excitation, followed by prolonged suppression of the neural response (Allen, Pasley, Duong, & Freeman, 2007). Furthermore, alternative protocols, such as theta-burst stimulation (Franca, Koch, Mochizuki, Huang, & Rothwell, 2006; Nyffeler et al., 2006; Stefan, Gentner, Zeller, Dang, & Classen, 2008) and enhanced inhibitory effects due to priming with high frequency stimuli (Iyer, Schleper, & Wassermann, 2003) illustrate that the assumption of cortical inhibition or excitation at certain frequencies is probably too simple. Also, the effect of rTMS appears to be highly dependent on the state of the stimulated cortex (Siebner et al., 2004; Silvanto, Muggleton, & Walsh, 2008; Silvanto, Muggleton, Cowey, & Walsh, 2007). Pasley et al. (2009) for instance, observed that higher pre-TMS activity predicted larger post-TMS responses in the visual cortex. They further remark that this feature could actually be used to a certain advantage in the treatment of clinical disorders. It is conceivable that one could manipulate the activity of the stimulated cortex in real time during the treatment, e.g. by having the subject perform a particular task. Beyond the synaptic effects, TMS might have consequences on other neuronal processes, such as genetic and protein regulation, and circuit-level patterns, such as oscillatory activity in functional networks. Furthermore, TMS might have non-neuronal effects, such as changes in blood flow, which are still poorly understood.

Complex interactions between local responses and propagations of rTMS induced alterations across the brain are likely to have repercussions in terms of clinical effects. The future for TMS research and its clinical utility lies in the further clarification of its neurophysiological and molecular effects on the neural architecture, in order to enable the optimization of treatment parameters.

2. *Final remarks*

2.1. *Contributions of this thesis to AVH research*

The work described in the present thesis was designed to contribute to the rich research tradition on AVH, and comprised investigations into the cognitive and neuro-psycho-biological profile of the hallucinating patient. Firstly, we showed that the predisposition to experience AVH is associated with changes in the perception and evaluation of external speech stimuli. Particularly, it appears that the speech perception of hallucinating individuals is influenced to a larger extent by internal factors, such as expectations based on the current context, and processes of mental imagery. Secondly, in this thesis we reported results form structural and functional neuroimaging studies, implicating regional variations in anatomy and hemodynamic response in the inner speech processing network in relation to AVH. In another study, we also observed evidence of alterations in functional connectivity in this network, as a function of AVH severity. These studies demonstrate that alterations in certain cognitive and neural processes covary with the propensity to hallucinate, and may point towards potential targets for cognitive/behavioral therapy. In order to devise a more biologically oriented treatment for AVH, our understanding of the anatomical and functional neural architecture underlying AVH should be developed further. We reported on one such attempt. The effect of 1 Hz rTMS to the left or bilateral speech perception cortex on symptom severity was assessed in patients with medication resistant AVH. Moderate changes in AVH severity were observed after a 6 day treatment, particularly in the group receiving stimulation of the left hemisphere, although the bilateral group appeared to benefit from rTMS as well, by showing

reduced emotional responsivity to their AVH. These results are in line with previous clinical trials, and highlight the critical contribution of speech perception areas in AVH. A subsample of patients also underwent resting state fMRI scans before and after treatment, allowing the assessment of alterations in functional connectivity in response to rTMS. This analysis did not reveal changes in the connections previously identified as correlated with AVH severity. Some trends towards alterations in other connections were observed, but clearly the functional consequences of rTMS at the neuronal level deserve further investigation.

2.2. *Towards a comprehensive neurocognitive model ?*

In sum, over recent years significant progress has been made in AVH research. Taken together, the available data appear to suggest that AVH result from alterations in the processing of externally presented and internally generated 'speech' stimuli and the skills involved in discriminating real from imagined events. Evidence furthermore suggests that perceptual discrimination may be more influenced by contextual factors. A bias towards externalized attributions appears to be present as well. Subjects prone to hallucinations may make overconfident and/or hasty decision about the (source of their) perceptions. The link between these aberrant cognitive processes and alterations in their respective neural substrates has been assessed as well. Both in this thesis, and in the literature in general, particularly the network of inner speech processing regions has received a lot of attention. Abnormalities in the production, monitoring and perception of internally generated speech percepts have been observed. However, perhaps due to their inherently subjective character, and the fact that much of the research on AVH relies (at least to some extent) on patient reports in the characterization of the symptom, AVH remain a rather elusive phenomenon, and a comprehensive and empirically validated account of AVH has yet to be defined in detail. Specifically, we would like to suggest that any comprehensive theory of AVH should explain the following aspects, and ideally provide a framework to empirically verify them.

(1) It seems evident that in the case of AVH, an internal event is not recognized as self-generated and thus misattributed to an external source. Inner speech seems a likely candidate to be the raw material of AVH. However, as was Pierre (2009) remarked, the intuitive appeal of the inner speech account notwithstanding, a clear and consistent definition of 'inner speech' is lacking. A further exploration of the phenomenology of inner speech, and how it relates to verbal thought, auditory imagery, verbal memory, and AVH will be vital in accounting for the phenomenology and etiology of AVH.

(2) The suggestion that AVH result from a defective judgment system, and attributional biases, does not imply that these assessments are produced at a conscious level, fitting with the observation that AVH are most often not under the subject's conscious control. But, just what makes certain internally generated events more susceptible to this misattribution? Efforts should be made to identify internal and/or external contextual variables (e.g. psychosocial stress, suggestibility, emotional states, cognitive deficits, …) that may predispose this misattribution.

(3) Given the observation that AVH tend to occur in healthy subjects as well, and the fact that many psychiatric patients present with experiences intermediate between normal images and hallucinations, a theory of AVH should take into account the conception of a continuum between normal perception and hallucinations. The actual form in which hallucinatory experiences present in otherwise healthy individuals and patients with schizophrenia no doubt differ to some extent. For instance, hallucinations in healthy subjects tend to have a more positive message, and are often experienced as helpful or guiding (Sommer et al., 2008a). The underlying processes however must overlap to a certain degree. In any case, given the doubtful pathognomonic status of hallucinations, it seems reasonable to regard them as objects of research in their own right, free from psychiatric classification. The question as to what distinguishes schizophrenic thinking and neural processes from healthy neuro-cognition will thus require elegant and inventive experimental designs that accommodate the possibility of a continuous, rather than dichotomous relationship between "symptoms" and "normal" neurocognitive processes.

(4) AVH are not random discharges of a faulty neural system. They often have a very personal relevance. Presumably the content of an AVH reflects the current situational context, activations of episodic memory, personality characteristics etc. Further research into life events precipitating hallucinations, personality structure, stress levels, and the potential reinforcing consequences of AVH are likely to contribute to a better understanding of psychological determinants the phenomenon. A theory of AVH should explain how these processes interact with the putative neuro-cognitive and/or perceptual deficits observed in hallucinating subjects.

(5) AVH have a distinct emotional component in terms of their precipitating context (stressful life events, social isolation,…), their actual content (abusive and derogatory comments) and in terms of the subject's response (feelings of anxiety and depression). Thus, a particular affective state may influence the occurrence of AVH at different levels. It has been suggested that stress and anxiety may negatively influence self-monitoring systems, resulting in misattributions of internally generated events, and at the same time influence top-down factors, such as perceptual expectations (Aleman & Laroi, 2008). Research paradigms could benefit from the manipulation of the emotional content of presented stimuli, as the cognitive and neural deficits or changes observed in association with AVH may be amplified in response to affectively salient stimuli compared to neutral stimuli.

Finally, the importance of the scientific community's interest in the origin and mechanism of AVH is emphasized by the fact that, especially in the case of medication resistance, AVH represent a significant source of subjective burden (Falloon & Talbot, 1981). In order to devise new and more efficient treatments, it will be necessary to continue to develop a comprehensive and empirically validated account of AVH, and to better our understanding of the phenomenon at different levels of psychological and biological causation and determination.