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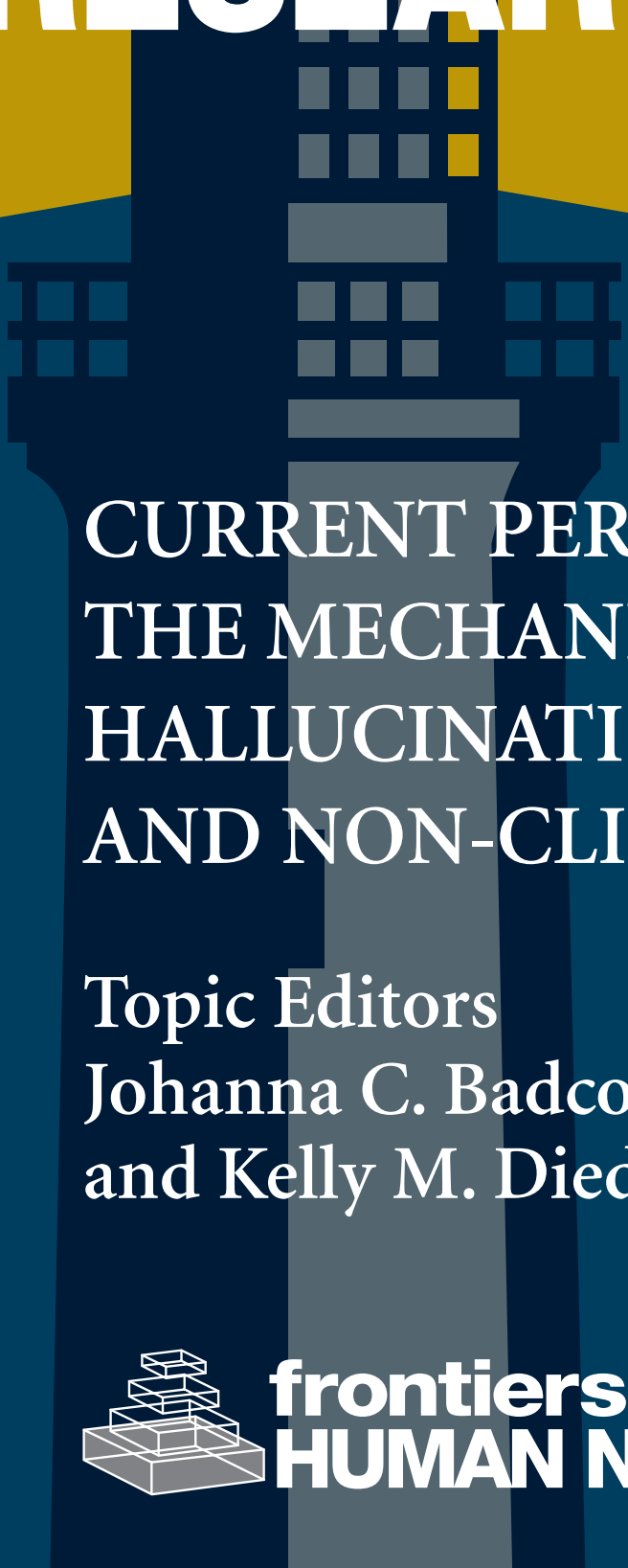

CURRENT PERSPECTIVES ON THE MECHANISMS OF AUDITORY HALLUCINATIONS IN CLINICAL AND NON-CLINICAL POPULATIONS

Topic Editors
Johanna C. Badcock, Frank Larøi, Paul Allen and Kelly M. Diederen

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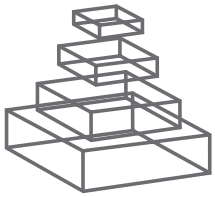

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Topic Editors:
Johanna C. Badcock, University of Western Australia, Australia
Frank Larøi, University of Liege, Belgium
Paul Allen, Insitute of Psychiatry, King's College London, United Kingdom
Kelly M. Diederen, University of Cambridge, United Kingdom

There has been a recent surge of interest in auditory hallucinations (AH) in schizophrenia compared to those experienced by non-clinical (i.e. healthy) individuals. This interest stems in no small part from a keen awareness of the fact that progress in developing more effective treatments for AH in psychosis has been seriously hampered by our limited understanding of the cognitive and biological mechanisms involved. The prevailing notion that AH in clinical and non-clinical populations share the same features and underlying mechanisms - the continuum hypothesis - has been seriously challenged by a growing list of differences, as well as similarities, between these groups. At the phenomenological level this is exemplified in the highly negative content of AH in patients and the markedly earlier age of onset of AH in non-patients. Similarly, several recent studies point to significant differences in cognition, language lateralization and, possibly, dopamine function between these groups. These findings have important implications for the design of future studies, and raise considerable doubt about the adequacy of modelling the functional mechanisms of clinical AH on the basis of non-clinical populations. In short, the time seems ripe to re-evaluate the continuum hypothesis and provide a forum to present alternative perspectives on the functional pathways leading to AH in clinical and non-clinical groups. Such a forum is also timely in view of the renewed interest in AH in other (non-schizophrenic) clinical groups, again examining similarities and differences between such groups. Preliminary studies, for instance, have shown that AH in certain clinical populations (e.g. bipolar disorder, borderline personality disorder, dissociative disorder) share similar phenomenological features with AH in schizophrenia. However, the implications of such findings are not fully understood, and studies have not adequately examined potential differences between AH in these groups.

The goal of this Frontiers Research Topic, therefore, is take the opportunity to bring together research exploring differences and similarities in mechanisms of AH in clinical and non-clinical groups and to stimulate the development of new explanatory models which explicitly link the phenomenological characteristics of AH with underlying mechanisms.

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EDITORIAL
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Current perspectives on the mechanisms of auditory hallucinations: introduction to the special research topic

Johanna C. Badcock[1]*, Frank Larøi[2], Kelly Diederen[3] and Paul Allen[4]

[1] *School of Psychology, University of Western Australia, Crawley, WA, Australia*
[2] *Department of Psychology, Cognition and Behaviour, University of Liège, Liège, Belgium*
[3] *Department of Physiology, Development and Neuroscience, University of Cambridge, Cambridge, UK*
[4] *Institute of Psychiatry, King's College, London, UK*
**Correspondence: Johanna.badcock@uwa.edu.au*

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Hauke R. Heekeren, Freie Universität Berlin, Germany

Keywords: auditory hallucinations, cognition, emotion, hearing voices, non-clinical hallucinations, psychosis, schizophrenia

According to the Oxford English Dictionary (http://www.oed.com) the term "perspective" is derived from the verb *perspicere* (from *per-* "through" + *specere* "to look"), meaning "looked at closely." In keeping with this origin, the contributors to this Frontiers Research Topic have indeed *looked closely* at the experience of auditory hallucinations (AH), providing new insights into the precise nature of hallucinations in clinical and non-clinical groups; the underlying cognitive, emotional and neural processes; and how this evidence might inform the next generation of personalized treatments Connor and Birchwood (2013).

The phenomenology of AH and the mechanisms that underpin them lie at the heart of our research, yet there has been a growing concern that the characteristics of AH prioritized by researchers don't match those considered important to hallucinators themselves. To some degree this disparity reflects the (sometimes) limited scope of popular research assessment tools. However, disregarding the phenomenological diversity of AH may guarantee that we will fail to understand the biopsychosocial processes involved. Consequently, the resurgence of interest in phenomenological research reflected in current contributions is both timely and welcome. McCarthy-Jones et al. (2013) call for more nuanced descriptions of AH that reflect more accurately what the experience is like, and proffer a philosophical phenomenological perspective, which encourages a systematic exploration of (normal and AH) experiences from the first person perspective. Both Badcock and Chhabra (2013) and deLeede-Smith and Barkus (2013) tackle the diverse presentations of AH in clinical and non-clinical groups. deLeede-Smith and Barkus adopt a developmental perspective, charting how the features of AH emerge and persist across the lifespan, and suggest that mechanisms maintaining AH differ across these populations, whilst Badcock and Chhabra (2013) provide an extensive and reflective review of the literature on the perception of voice identity, which points to subtle biases across different levels of voice identity. Rounding out this set of articles, Stephane (2013) emphasizes the heterogeneity of AH from one voice hearer to the next, and persuasively argues that whilst hallucinatory experiences are unique to each individual they are not random collections of features. Instead, Stephane suggests, they arise from a limited number of dimensions of phenomenological AH space—each linked to a separate neural basis.

Continuing the neural processing theme, Kompus et al. (2013) show that while non-clinical voice hearers present with a reduced response to speech sounds in the primary auditory cortex, attentional modulation of this area is intact. In strong contrast, no attentional modulation of this area could be observed in schizophrenia patients with AH. Further similarities as well as differences in mechanisms underlying AH are shown by Dahoun et al. (2013) who compared neural correlates of mentally simulated actions (e.g., "open a window") between hallucination-prone adolescents and a group with a genetic risk for schizophrenia (22q11.2 deletion syndrome). While both groups exhibited decreased activation in regions related to self-other distinction when imagining a close friend performing an action, individuals with a genetic risk for schizophrenia displayed additional decreased activations in areas associated with visual imagery, episodic memory and social cognition when "simply" seeing a cue that said either "you" or "best friend" earlier on in the task.

Another set of articles highlight the role of emotion in AH. Kanemoto et al. (2013) show that university students with high hallucination proneness tended to make more external misattributions of inner thoughts than those with lower hallucinations proneness. Importantly, they also show that emotional valence affected the ability to recall whether a word had been previously heard, or had been imagined, only in the latter group of subjects. Similarly, with the help of an implicit emotional prosody task, Alba-Ferrara et al. (2013) examine how attention is involuntarily captured in patients with schizophrenia and healthy controls, and conclude that patients with AH may be less lateralized in their processing of emotion conveyed in voice. Finally, based on studies that have demonstrated that patients with schizophrenia have difficulty perceiving and discriminating emotions based on affective prosody compared to healthy controls, Tucker et al. (2013) wished to examine whether this may also represent an endophenotype of schizophrenia, i.e., by examining this capacity in non-affected, first-degree relatives. They found that unaffected relatives of AH schizophrenia patients, compared to the matched healthy controls, exhibited some basic impairments in auditory processing, suggesting that auditory processing deficits may be a core feature of AH in schizophrenia, but that the two groups did not differ significantly on a major variable, i.e., number of errors in pitch discrimination. Clearly, more research is needed in

order to examine whether these difficulties represent a potential endophenotype for AH.

Finally, from a neurofunctional perspective, two papers report new findings in patients with schizophrenia and auditory verbal hallucinations (AVH). Homan et al. (2013) used Arterial Spin labeling (ASL)—a Magnetic Resonance technique for measuring cerebral blood flow (CBF)—to show that increased perfusion in the left superior temporal gyrus (STG; a cerebral area known to support language and auditory function) in patients with schizophrenia and AVH, relative to controls and global CBF in patients, was not reduced by treatment with transcranial magnetic stimulation even though AVH symptom scores decreased over the treatment period. These findings are consistent with what has previously been termed a trait marker of AVH in schizophrenia. The second paper by Koeda et al. (2013) used a novel functional MRI favorability judgment task to show that hypo-activation in the left STG may be associated with brain dysfunction in accessing vocal attractiveness in schizophrenia, although right fronto- parietal regions could offset STG dysfunction associated with social communication.

In sum, the variety of perspectives featured in this Research Topic illustrates the vitality of current research on AH across a range of diagnostic groups, and the significant advances that have been made in understanding the mechanisms the underlie them.

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Emotional prosody modulates attention in schizophrenia patients with hallucinations

***L. Alba-Ferrara*[1,2]*, *G. A. de Erausquin*[1], *M. Hirnstein*[2,3], *S. Weis*[2] *and M. Hausmann*[2]**

[1] *Department of Psychiatry and Neurosciences, Roskamp Laboratory of Brain Development, Modulation and Repair, Morsani College of Medicine, University of South Florida, Tampa, FL, USA*
[2] *Department of Psychology, Durham University, Durham, UK*
[3] *Department of Biological and Medical Psychology, University of Bergen, Bergen, Norway*

Edited by:
Johanna C. Badcock, University of Western Australia, Australia

Reviewed by:
David I. Leitman, University of Pennsylvania, USA
Kirstin Daalman, University Medical Center Utrecht, Netherlands

****Correspondence:***
L. Alba-Ferrara, Department of Psychiatry and Neurosciences, Roskamp Laboratory of Brain Development, Modulation and Repair, Morsani College of Medicine, University of South Florida, 3515 E. Fletcher Avenue, Tampa, FL 33613, USA.
e-mail: lalbafer@health.usf.edu

Recent findings have demonstrated that emotional prosody (EP) attracts attention involuntarily (Grandjean et al., 2008). The automat shift of attention toward emotionally salient stimuli can be overcome by attentional control (Hahn et al., 2010). Attentional control is impaired in schizophrenia, especially in schizophrenic patients with hallucinations because the "voices" capture attention increasing the processing load and competing for top-down resources. The present study investigates how involuntary attention is driven by implicit EP in schizophrenia with auditory verbal hallucinations (AVH) and without (NAVH). Fifteen AVH patients, 12 NAVH patients and 16 healthy controls (HC) completed a dual-task dichotic listening paradigm, in which an emotional vocal outburst was paired with a neutral vocalization spoken in male and female voices. Participants were asked to report the speaker's gender while attending to either the left or right ear. NAVH patients and HC revealed shorter response times for stimuli presented to the attended left ear than the attended right ear. This laterality effect was not present in AVH patients. In addition, NAVH patients and HC showed faster responses when the EP stimulus was presented to the unattended ear, probably because of less interference between the attention-controlled gender voice identification task and involuntary EP processing. AVH patients did not benefit from presenting emotional stimuli to the unattended ear. The findings suggest that similar to HC, NAVH patients show a right hemispheric bias for EP processing. AVH patients seem to be less lateralized for EP and therefore might be more susceptible to interfering involuntary EP processing; regardless which ear/hemisphere receives the bottom up input.

Keywords: top-down, bottom-up, emotion, attention, implicit prosody, lateralization, schizophrenia, hallucination

INTRODUCTION

Behavioral studies suggest that schizophrenia patients show deficits in explicit judgments of emotional prosody (EP) (Rossell and Boundy, 2005; Bozikas et al., 2006; Hoekert et al., 2007; Bach et al., 2009). EP is a non-verbal component of language which allows inferring feelings expressed in speech by encoding/decoding variations in pitch amplitude and tempo. EP decoding is usually assessed *explicitly* that is, participants explicitly attend to stimuli they are asked to classify (Buchanan et al., 2000; Kotz et al., 2003). Since in most everyday situations humans are not specifically asked to focus on EP, implicit prosody paradigms (Sander et al., 2005; Aue et al., 2011) are closer to real life settings.

Implicit emotional processing occurs because emotionally enhanced stimuli capture attention regardless of conscious or voluntary engagement (Bradley and Lang, 2000; Vuilleumier, 2005; Lipp and Waters, 2007). Attraction of attention toward certain objects is a typical bottom-up process, involuntary, automatic, and driven by external stimulus (Pessoa et al., 2002). Alternatively, voluntary attention refers to the top-down, effortful direction of attention under control of the individual, such as when participants are instructed to make an explicit judgment of the emotional tone conveyed in prosodic stimuli (Pattyn et al., 2008).

A few prosody studies manipulated involuntary and voluntary attention, to investigate the influence of emotional salience over top-down control (Grandjean et al., 2005; Sander et al., 2005; Aue et al., 2011), assessing implicit processing of EP while participants listened to dichotically presented male or female voices in either angry or neutral tone. Participants were asked to attend to either the left or right ear, and to make judgments about the speaker's sex of the attended ear disregarding the voice emotional tone. The results revealed that angry prosody attracts attention, provoking behavioral and physiological changes (e.g., skin conductance variations) even when not voluntarily attended to (Aue et al., 2011). Moreover, angry (relative to neutral) stimuli, resulted in increased activation in right temporal areas regardless of stimulus laterality and attentional status, suggesting again that EP is a prepotent stimulus (Grandjean et al., 2005). Reaction times (RTs)in the same task show that when the emotional stimuli converge on the side of the attended ear, such a distractor is more difficult to ignore (Sander et al., 2005); perhaps suggesting dominance of the left ear/right hemisphere for processing auditory

emotional stimuli (Grimshaw et al., 2003), such that even if prosody is task-irrelevant, the dominant hemisphere for the task will automatically process the emotional input. Right hemisphere dominance has been repeatedly reported for EP processing in healthy controls (HC) (Ross et al., 1997; Wildgruber et al., 2005).

Implicit perception of EP in schizophrenia has been assessed scantly. A recent study compared schizophrenia patients with controls in two conditions. In the explicit prosody condition, participants attended to semantically neutral words spoken in emotional tones of voice and judged the emotion conveyed by the tone of voice. In the implicit prosody condition participants listened to words with emotional meanings spoken in different prosodic tones and were asked to judge the semantic content of the word ignoring the tone of voice. Importantly, prosodic tone and semantic meaning were either congruent or incongruent (Roux et al., 2010). Schizophrenia patients revealed higher error rates during implicit prosody processing in incongruent trials than HC did, but were not different in response times (which were slower for incongruent trials in both groups). These results suggest that schizophrenia patients are still sensitive to implicit prosody processing (Roux et al., 2010). The increase in error rates may indicate a lack of top-down control (voluntary attention) in the presence of bottom-up salience due to the prosodic features of the stimuli which by capturing attention interfere with the semantic task.

Some studies have found that deficits in EP in schizophrenia patients are linked to basic auditory deficit abnormalities (Leitman et al., 2005, 2011; Jahshan et al., 2012), neurocognitive deficits (Kee et al., 1998), or negative symptoms (Hoekert et al., 2007); whether other did not find an association between emotional perception and negative symptoms (Kee et al., 2003). Instead, Kee and colleagues proposed that emotion processing may be a key mediator between basic neurocognitive abilities and functional outcome (Kee et al., 2003). Most notably to the hypothesis tested in this manuscript, difficulties in EP perception in schizophrenia appear to be strongly associated with the presence and/or history of auditory hallucinations (Rossell and Boundy, 2005; Shea et al., 2007; Kang et al., 2009). Yet, these studies investigated explicit (instead of implicit) EP, limiting their ecological validity. In any case, it has been proposed that the capture of involuntary attention by negative emotional stimuli provides a mechanism for the formation of positive symptoms that is a negative affective bias disturbs contextual processing loosening association of ideas leading to delusions or impeding discrimination between relevant and irrelevant stimuli (Mohanty et al., 2008). A review article on the formation of hallucinations suggests that in auditory verbal hallucination (AVH) patients attention is involuntarily oriented toward certain features of prosody, particularly negative tones, congruent with the emotional valence of most of the AVH that patients suffer from (Alba-Ferrara et al., 2012). If a patient cannot ignore an emotional stimulus even if it is irrelevant or outside the focus of selective attention, such emotional stimulus may gain access to processing in detriment of more relevant external stimuli triggering abnormal perceptions (Alba-Ferrara et al., 2012). There is only one study investigating implicit EP in schizophrenia patients (Roux et al., 2010), which did not, however, differentiate between patients with prominent positive and negative symptoms. The present study therefore investigates implicit EP processing in schizophrenia comparing hallucinators (AVH) with non-hallucinators (NAVH).

The brain representation of EP in normal populations as well as in schizophrenia patients is still a matter of debate. Numerous neuroimaging studies show that emotional prosodic perception involves the interplay between right and left auditory cortical as well as frontal regions (Kotz et al., 2006; Wildgruber et al., 2006; Alba-Ferrara et al., 2011). The right hemisphere is currently thought to predominantly process low frequency modulation signals such as prosody, as well as more articulated tonotopic maps, whereas the left hemisphere has better precision for very fast auditory changes, timing, and lexical properties of speech (Zatorre et al., 1992; Liegeois-Chauvel et al., 2001; Zatorre, 2001; Zatorre and Belin, 2001). However, it should be noted that in a healthy population activation in the left auditory region decreases significantly when the verbal complexity of the prosodic stimulus is reduced, showing that once extract phonetic-segmental information is eliminated, the left hemisphere is not necessary for the prosodic task (Mitchell and Ross, 2008).

Difficulties in implicit EP in hallucinating patients may result from aberrant brain organization. Specifically, AVH patients may display an atypical lateralization of EP, resulting in its impaired processing (Mitchell et al., 2004). EP lateralization in schizophrenia has been extensively debated in the literature (Mitchell et al., 2004; Mitchell and Crow, 2005; Bach et al., 2009), but results remain controversial. Mitchell and colleagues (2004) claim that lateralization is reversed in AVH schizophrenia patients who displayed greater involvement of the left temporal lobe in prosody processing, whereas Bach and colleagues (Bach et al., 2009) found enhanced right lateralization to prosody in these patients. Further clarification is urgently needed.

To investigate the effects that EP exerts on involuntary attention we adopted a dichotic listening paradigm which allows us to investigate EP lateralization (Grandjean et al., 2005; Sander et al., 2005; Aue et al., 2011), to determine whether emotional salience can modulate the allocation of attention. We hypothesized that participants perform generally lower in a gender voice recognition task when prosody stimuli are spoken with a happy or angry voice, especially when emotional stimuli are presented to the attended ear, because both stimuli (i.e., gender prosody and EP) would be processed in the same hemisphere and are thus more likely to interfere. Second, we predict that gender voice recognition in AVH patients is especially susceptible to EP interference compared to NAVH patients and HC. Given that EP lateralization is assumed to be abnormal in schizophrenia, and particularly related to hallucinations, we hypothesized that contrary to the NAVH and HC groups, AVH patients would be distracted by EP even when attending toward the ear opposite to the emotional stimuli.

METHODS

PARTICIPANTS

Twenty seven (21 males) individuals who met the DSM-IV criteria (American Psychiatric Association, 2000) for schizophrenia were recruited from several outpatient clinics from Northumberland, Tyne and Wear NHS foundation trust and

Tees, Esk and Wear Valleys NHS Foundation Trust. The psychiatric diagnosis was confirmed by an independent psychiatrist. All patients were taking antipsychotic drugs (see **Table 1**). An experienced psychiatrist examined the patients to ensure they did not meet any of the following exclusion criteria: current presence and/or history of co-morbidities with axis I disorders of the DSM or existence of neurological condition including head trauma and long periods of loss of consciousness. Additionally, 16 healthy participants (11 males) were recruited via advertisement in the local post office. They were also screened for history of psychiatric and neurological illness and drug use using the Schedules for Clinical Diagnosis in Neuropsychiatry (SCAN, WHO) to exclude psychopathology. Exclusion criteria for controls were the presence (current or history) of any axis I and II disorders of the DSM.

PSYCHOPATHOLOGY ASSESSMENT

Additional interviews in patients were conducted by a qualified clinical psychologist, using the Comprehensive Assessment of Symptoms and History (CASH) (Andreasen et al., 1992). This semi-structured interview includes the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984) and the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1983). Both diagnostic scales require participants to report symptoms during the week prior to the assessment. Twelve patients who were not currently experiencing hallucinations in any modality (as defined by a score of 1 or below in SAPS hallucination global score) were allocated to the NAVH group. The NAVH group consisted of four patients who had never experienced hallucinations, as well as eight patients with a history of hallucinations but currently not experiencing them as measured by the SAPS, as we aimed to study the impact hallucinations exert on the experimental task as a state, not as a trait. Patients reporting hallucinations (scoring at least 3 on the SAPS hallucinations global score) were allocated to the AVH group. None of the patients scored between 1 and 3 in this scale. A cut-off score was chosen based on previous studies (Allen et al., 2004; Shea et al., 2007). The AVH group subsequently completed the auditory hallucination subscale corresponding to the PSYRATS (Haddock et al., 1999). Finally, all subjects were assessed with the National Adult Reading Test (NART) (Nelson and Willison, 1991) to estimate premorbid intellectual performance (IQ) with a high test–retest reliability in schizophrenia (Morrison et al., 2000) (see **Table 2**).

Table 1 | Number of participants for medication type.

Drug	AVH	NAVH
Haloperidol	2	4
Aripiprazole	3	1
Clozapine	3	2
Olanzapine	1	2
Risperidone	4	3

Number of patient taking typical and atypical antipsychotic medication between groups: schizophrenia patients with hallucinations (AVH) and schizophrenia patients without hallucinations (non-AVH).

There were no between-group differences in age [$F_{(2,\ 42)} = 0.72$, ns], education as measured by highest qualification achieved [1 = primary school, 2 = secondary school, 3 = 0 levels, 4 = A levels, 5 = university degree; $F_{(2,\ 42)} = 0.35$, ns], premorbid verbal IQ [$F_{(2,\ 42)} = 0.51$, ns] and handedness measured by the Edinburgh Handedness Questionnaire [$F_{(2,\ 42)} = 1.10$, ns]. AVH patients had significantly higher total scores ($U = 21.00$, $Z = -3.37$, $p < 0.05$), hallucinations global subscale scores ($U = 1.50$, $Z = -4.37$, $p < 0.001$), and delusions global subscale *scores* ($U = 26.50$, $Z = -3.18$, $p < 0.05$) of the SAPS than NAVH patients. None of the other psychopathology measures revealed significant differences between patient groups (all $U < 70.50$, ns).

MATERIALS AND PROCEDURE

Stimuli

The stimuli used in the experimental task were taken from the "Montreal Affective Voices" dataset (Belin et al., 2008). We used 30 non-verbal affect bursts of non-linguistic vocal sounds corresponding to emotions of anger, happiness and neutral

Table 2 | Clinical, neuropsychological and demographic characteristics of the three groups.

Measures	Non-AVH mean (*SD*)	AVH mean (*SD*)	Controls mean (*SD*)
N	12 (2 women)	15 (4 women)	16 (5 women)
Premorbid verbal IQ	110.42 (1.74)	112.14 (1.79)	112.69 (1.24)
Handedness scale	77.50 (16.43)	67.33 (15.96)	93.13 (5.06)
Age	37.83 (2.87)	41.73 (2.62)	42.69 (3.09)
Highest qualification achieved	2.25 (0.37)	2.07 (0.28)	2.44 (0.33)
Duration of illness (years)	15.17 (2.01)	15.33 (2.22)	
SANS total	10.88 (1.51)	10.40 (0.84)	
Affective flattening	1.71 (0.40)	1.53 (0.25)	
Alogia	1.79 (0.47)	1.43 (0.27)	
Avolition	2.29 (0.44)	2.27 (0.27)	
Anhedonia	2.17 (0.42)	2.57 (0.25)	
Attention	2.92 (0.43)	2.60 (0.30)	
SAPS total	4.92 (0.87)	9.90 (0.69)**	
Hallucinations	0.96 (0.23)	3.83 (0.24)**	
Delusions	1.17 (0.31)	2.97 (0.33)*	
Bizarre behavior	1.42 (0.31)	1.47 (0.25)	
Positive formal thought	1.38 (0.33)	1.63 (0.30)	
PSYRATS (hallucination subscale)	–	25.87 (1.73)	

SANS and SAPS: Scale for the Assessment of Negative and Positive Symptoms, respectively. PSYRATS: Scales to measure dimensions of hallucinations and delusions: the psychotic symptom rating scales.

Highest qualification achieved: 1 = compulsory education, 2 = sixth form education, 3 = higher education, 4 = postgraduate education.

$^{**}p < 0.001$; $^{*}p < 0.05$.

expression recorded by 10 actors (five males). Since interaural intensity and length differences are known confounds in dichotic listening tasks (Hugdahl et al., 2008), voice stimuli were edited to equalize them in duration (900 ms) and amplitude (80 DB) using Audacity software (http://audacity.sourceforge.net). Male and female speakers were equally distributed across conditions.

Procedure

Written informed consent was obtained from each participant. The study and procedures were approved by the regional ethics committee from the NHS and Durham University Ethics Advisory Committee. All participants received £30 for their participation. Hearing loss and acuity differences between ears were measured using monaural white-noise bursts (duration 1 s) presented via headphones with various sound-pressure levels (steps of 10 dB). More details about this test can be found in (Hirnstein et al., 2007). Importantly, all participants had normal hearing and none reported hallucinations during testing. A mixed factorial ANOVA was performed with ear acuity (left ear, right ear) as within- and Group as between-subjects factors. In agreement with published data (Kannan and Lipscomb, 1974) the right ear ($M = 30$ dB) was slightly but significantly more sensitive than the left ear ($M = 35$ dB) [$F_{(1, 39)} = 3.65$, $p < 0.05$]. The main effect of Group and the interaction between Ear acuity and Group was not significant (all $F \leq 2.75$, ns).

A pair of male/female voice stimuli (one of which was always neutral) were simultaneously presented, one to each ear, resulting in five possible combinations: Left angry/Right neutral, Left neutral/Right angry, Left happy/Right neutral, Left neutral/Right happy, and Left neutral/Right neutral (this last combination will be referred to as "baseline"). Participants were instructed to selectively attend to the voice presented to either the left or right ear and to decide on the sex of the speaker in the attended ear using a response box. Half of the participants used the left response key to indicate a female voice and the right to indicate a male voice. The response keys were counterbalanced across participants. A total of 144 trials were presented to each participant excluding five practice trials at the beginning of the experiment. In one block (72 trials), participants focused on voices presented to their right ear; in another block (72 trials), they attended to voices presented to their left ear. Block order was counterbalanced across participants. Participants listened to the stimuli and responded during the inter-trial interval of 3000 ms. Accuracy and RTs were analyzed. For the RT analysis, incorrect trials and outliers were excluded.

Degrees of freedom were epsilon-corrected (Greenhouse–Geisser) when sphericity was violated (Mauchly). *Post hoc t*-tests were alpha-adjusted (Bonferroni) for multiple comparisons.

RESULTS

Several previous studies suggest that emotional valence does not affect the relation between attention and implicit EP processing (Grandjean et al., 2008). Angry and happy stimuli were therefore collapsed to increase the trials number per condition and to simplify the experimental design.

ACCURACY (%)

Participants' overall accuracy (across all groups and conditions) in the sex discrimination task was significantly above chance [$M = 73\% \pm SD = 0.05$, $t_{(40)} = 20.1$, $p < 0.001$, one-sample *t*-test, chance level was 50%]. Accuracy scores (%) were subjected to a $2 \times 3 \times 3$ mixed ANOVA with Ear attended (left, right) and Trial-type [neutral binaurally (baseline), emotion on the left ear (LEE), emotion on the right ear (REE)] as within-participants factors and Group (AVH, NAVH, HC) as between-participants factor. The ANOVA revealed a main effect of Trial type [$F_{(2, 76)} = 3.34$, $p < 0.05$]. Alpha adjusted pairwise comparisons indicate that the accuracy during baseline ($75.00\% \pm 0.01$) is higher than during the REE condition ($72.00\% \pm 0.01$, $p < 0.05$). The LEE condition ($73.40\% \pm 0.01$) did not differ from REE and baseline. The main effect of Ear attended did not approach significance [$F_{(1, 38)} = 0.42$, ns]. Moreover, there was a significant interaction between Ear attended and Trial type [$F_{(2, 76)} = 7.94$, $p < 0.05$]. Alpha-adjusted *post hoc t*-tests revealed that in the REE condition, participants obtained lower accuracies when the right ear was attended ($69.40\% \pm 1.27$) than when the left ear was attended [$75.00\% \pm 1.07$, $t_{(41)} = -3.09$, $p < 0.05$], suggesting that if the emotion is presented to the attended ear, there is an increased difficulty to ignore the affective distractor while performing the sex discrimination task (see **Figure 1A**). No other *post hoc* test approached significance (all $t \leq 2.45$, ns). No other main effect or interaction approached significance, (all $F \leq 1.49$, ns).

REACTION TIMES (RTs)

Identical to the accuracy data analysis, a $2 \times 3 \times 3$ ANOVA was calculated for RTs. As predicted, we found a significant main effect of Ear attended [$F_{(1, 38)} = 9.33$, $p < 0.05$] with significantly longer RT when attending to the right (1269 ms ± 39) than the left (1205 ms ± 43) ear, suggesting that, across the whole sample, sex discrimination by voice depends more the right hemisphere. Moreover, in agreement to our hypothesis that emotionally neutral trials are more efficiently processed than emotional trials there was significant main effect of Trial type [$F_{(2, 76)} = 9.23$, $p < 0.001$]; alpha-adjusted pairwise comparisons showed lower RT in the baseline (1187 ms ± 42) than in the LEE (1260 ms ± 38; $p < 0.05$) or REE (1256 ms ± 40; $p < 0.05$) conditions, again suggesting that, across the whole sample, EP interferes with the gender prosody discrimination task. The LEE condition did not differ from REE. Additionally, the main effect of Group was significant [$F_{(1, 38)} = 5.45$, $p < 0.05$]; alpha-adjusted pairwise comparisons revealed only lower RTs for AVH (1354 ms ± 65) than for HC (1062 ms ± 65, $p < 0.05$). Other group differences did not approach significance.

We predicted interference, if both processes that are gender discrimination (explicit task) and EP (implicit) information converge on the same side. The interference between both processes should be even stronger after stimulus presentation to the right ear, corresponding to the left hemisphere (inferior for prosody processing), as the non-specialized hemisphere cannot efficiently deal with both processes simultaneously. Accordingly, there was a significant interaction between Ear attended and Trial type [$F_{(2, 76)} = 8.44$, $p < 0.001$]; alpha-adjusted *post hoc t*-tests revealed a significantly slower RT for the REE condition when

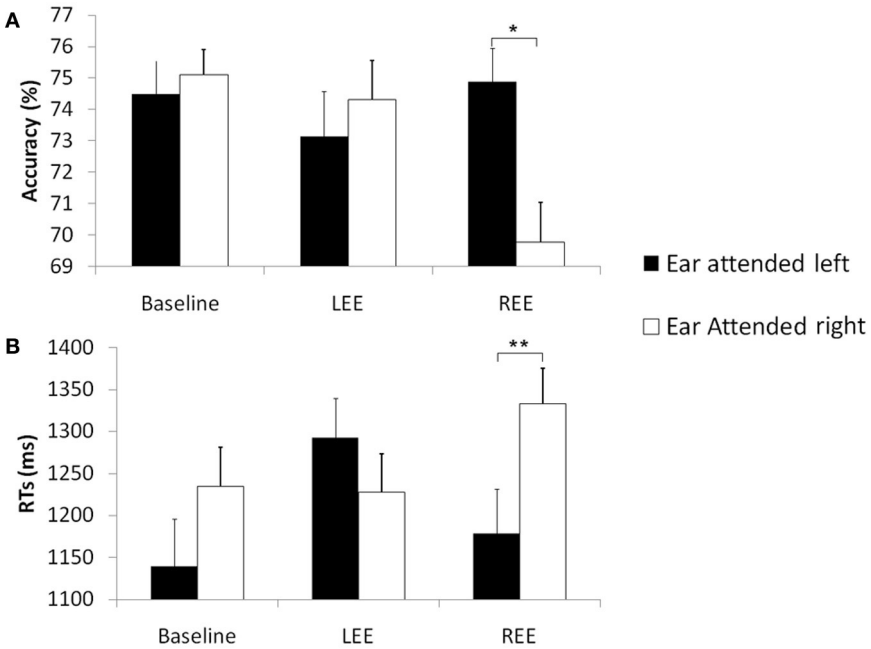

FIGURE 1 | Accuracy and RT in the gender prosody task across groups. Mean accuracies (%) **(A)** and mean reaction times (ms), $^{*}p < 0.05$ **(B)** and standard errors in the sex discrimination task across groups [schizophrenia patients with hallucinations (AVH), without hallucinations (NAVH) and healthy controls] in three different conditions (baseline), trials with emotion presented to the left ear (LEE) and trials with emotions presented to the right ear (REE). Black columns represent trials in which the left ear was attended. White columns represent right ear attended trials, $^{**}p < 0.001$.

the right ear was attended [$t_{(40)} = 4.35$, $p < 0.001$], whereas LEE did not differ from the baseline condition (see **Figure 1B**), suggesting that the left hemisphere (inferior for prosody processing) has difficulties to perform the explicit task when the emotional distractor is simultaneously processed by the same (left) hemisphere.

Finally, there was a significant three-way interaction [$F_{(4, 76)} = 6.74$, $p < 0.001$]. This interaction comprised the factors Ear attended, Trial type and Group. To investigate this effect, three separate ANOVAs (one for each group) were performed. There was no main effect of Ear attended in any of the groups (all $F \leq 3.82$, ns). The main effect of Trial type was only significant in HC [$F_{(2, 28)} = 5.50$, $p < 0.05$], and in the AVH group [$F_{(2, 28)} = 8.74$, $p < 0.001$]. In the control group, alpha-adjusted *post hoc* test showed faster responses in the baseline (1026 ms ± 68) than in the REE condition [1085 ms ± 68, $t_{(14)} = 3.09$, $p < 0.05$] but the baseline condition did not differ from LEE [1076 ms ± 68, $t_{(14)} = 1.36$, ns]. The REE and LEE conditions did also not differ significantly (see **Figure 2**). In the AVH group, the baseline condition (1309 ms ± 73) revealed faster RTs than REE [1395 ms ± 71, $t_{(14)} = 3.01$, $p < 0.05$] and LEE [1384 ms ± 77, $t_{(14)} = 3.52$, $p < 0.05$]. REE did not differ from LEE [$t_{(14)} = 1.62$, ns]. The main effect of Trial type in the NAVH group was not significant [$F_{(2, 20)} = 0.37$, ns]. Most importantly, the interaction between Ear attended and Trial type was significant in HC [$F_{(2, 28)} = 28.07$, $p < 0.001$, $\eta^2 = 0.513$] and NAVH [$F_{(2, 20)} = 15.45$, $p < 0.001$, $\eta^2 = 0.480$] but not in the AVH group [$F_{(2, 28)} = 2.98$, ns, $\eta^2 = 0.131$]. The missing interaction between Ear attended and Trial type in AVH patients indicates that automatic processing of EP interfered with performing the explicit task in this group, regardless which ear was stimulated, probably as a result of aberrant lateralization in processing prosodic information.

To explain the significant interaction between Ear attended and Trial type in HC and NAVH, alpha-adjusted *post hoc t*-tests showed that RTs were slower when the Ear attended and the emotion coincided on the right [healthy controls: $t_{(14)} = 3.70$ $p < 0.05$; NAVH: $t_{(10)} = 3.34$, $p < 0.05$], not when the left ear was attended in the REE condition (all $t \leq 2.55$, ns). The comparison between attended ears was not significant in LEE and the baseline condition (all $t \leq 0.85$, ns). To compare convergent (Ear attended and side of emotion co-occurring at the same hemispace) and divergent condition (Ear attended and the side of emotion occurring at opposite hemispace), additional alpha-adjusted *post hoc t*-tests were performed. The analyses revealed that both control groups showed a significant difference between LEE and REE, when the left ear was attended [healthy controls: $t_{(14)} = 4.88$, $p < 0.001$; NAVH: $t_{(11)} = -2.72$, $p < 0.05$], not when the right ear was attended.

DISCUSSION

We investigated how involuntary attention is modulated by EP in AVH schizophrenia patients. By including a healthy control group and a NAVH patients group, general confounding effects of schizophrenia are controlled for, suggesting that abnormal modulation of involuntary attention by EP is associated specifically with AVH. Specifically, the findings show a right hemispheric bias for EP processing in NAVH and HC. AVH patients seem to be less

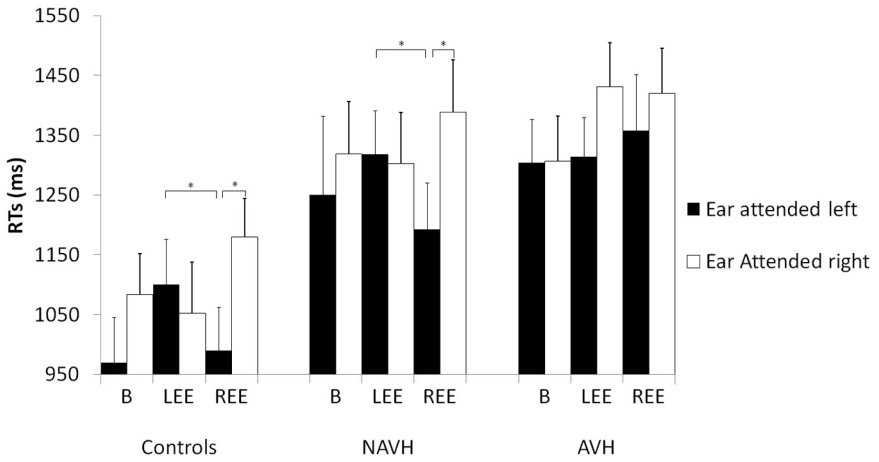

FIGURE 2 | RT in the gender prosody task across groups with three different stimuli pairs and two instructions (attending to either the right or left ear). Mean reaction times (ms) and standard errors (*SE*) in milliseconds in the sex discrimination tasks for the different groups for the different groups [schizophrenia patients with hallucinations (AVH), without hallucinations (NAVH) and healthy controls] in three different conditions (baseline), trials with emotion presented to the left ear (LEE) and trials with emotions presented to the right ear (REE). Black columns represent trials in which the left ear was attended. White columns represent right ear attended trials. *Post hoc* tests are alpha-adjusted for multiple comparisons, $^{*}p < 0.05$.

lateralized for EP and therefore might be more susceptible to the interference caused by implicit EP processing; regardless which ear/hemisphere receives the emotional distractor. Such mechanism could explain why hallucinators focus on irrelevant features of the auditory environment and their attention is captured by the "voices."

INTERFERENCE BETWEEN IMPLICIT EP AND EXPLICIT MALE/FEMALE VOICE DISCRIMINATION

All participants had faster responses in the sex discrimination task when attending to the left (as opposed to the right) ear, in agreement with previous reports (Lattner et al., 2005; Sokhi et al., 2005). Likewise, all participants had faster responses on the emotionally neutral baseline condition than in emotional trials, also in agreement to previous findings (Aue et al., 2011) suggesting that interference with this task by auditory emotional stimuli is due to involuntary capture of attention. Also consistently with others (Grandjean et al., 2008), such interference was independent from emotional valence stimuli. The right hemisphere superiority for sex discrimination (Lattner et al., 2005; Sokhi et al., 2005) and EP (Ross and Mesulam, 1979; Ross et al., 1997; Friederici and Alter, 2004; Ross, 2010) may explain the longer RTs when the right ear was attended to, corresponding to the inferior-for-the-task left hemisphere, as an interhemispheric transfer is required.

We also found lower accuracies and slower responses when emotion was presented to the attended right ear, possibly due to interference caused by the convergence of explicit task and the (implicit) emotion presented in the same hemispace; perhaps because one cerebral hemisphere does not have the capacity to process both tasks in parallel. Interference was less pronounced when the explicit and implicit tasks occurred in opposite sides. Thus, it may be more difficult to allocate voluntary attention when the emotional distractor drives involuntary attention toward irrelevant but salient features of the target stimuli (Grandjean et al., 2005; Sander et al., 2005). Orienting attention away from the task-relevant hemispace probably makes emotional content of the prosody stimulus and its automatic processing less salient, consequently causing less interference.

The convergence of the emotional distractor and the attentional focus on the same side disrupted the performance significantly only when it happened on the right ear side, suggesting that the (inferior-for-the-task) left hemisphere is particularly sensitive to this effect. Sander and colleagues (Sander et al., 2005) observed the same convergence effect, but only in the right hemisphere; however, their sample was much smaller (15 subjects) and did not include patients with schizophrenia, perhaps reducing their ability to identify subtle behavioral change. Indeed, they did not find a significant behavioral asymmetry in the sex-discrimination task (Sander et al., 2005).

Interference differences in AVH patients

Our main finding is that AVH patients are most sensitive to interference effects from EP. Control and NAVH participants' performance decreased when the emotional voice was presented to the attended right ear. By contrast, in AVH patients EP interfered with performance regardless of the ear the distractor was presented to, or of the ear attended, suggesting that (1) AVH patients had difficulties controlling their selective attention during the presence of an emotional distractor and (2) AVH patients are not typically right lateralized for EP.

Firstly, although all groups are affected by emotional salience, both controls and NAVH overcome such difficulty when the salient stimuli are divergent to the ear attended, particularly if the emotional distractor does not converge with the superior-for-the-task attended ear. Conversely, AVH patients cannot benefit from the divergence effect. By contrast we did not find a general top-down deficit in AVH in comparison to NAVH patients, as both groups had comparable overall performance. On the other

hand, our finding is consistent with reports suggesting that voluntary attention in schizophrenia may fail in the presence of salient bottom-up competitors (Hahn et al., 2010). Indeed, since AVH patients had shorter RTs at baseline than in the emotion conditions, even though they were generally slower in the sex discrimination task (including baseline trials), they particularly struggled when EP stimuli were present. Emotional salience of prosodic stimuli captures attention of AVH patients, regardless whether the interfering stimulus is in the focus of attention.

ABNORMAL LATERALIZATION OF EMOTIONAL PROSODY IN THE AVH GROUP

It still remains open whether this abnormal lateralization is a trait or a state in hallucinators. A previous study assessed phonological processing in two groups of schizophrenia patients, one with ongoing AVH and another with history of AVH as well as healthy controls (Løberg et al., 2004). They implemented a dichotic listening paradigm in which participants either focused attention to the left or right ear, or performed a non-forced condition without specific attentional instruction (Løberg et al., 2004). They found that since abnormal dichotic listening asymmetry for language stimuli is a state marker for AVH which is coincident with the perception of AH, the modulation of dichotic listening performance by means of voluntary attention is a trait marker, seen both in patients with ongoing and with only a history of AVH (Løberg et al., 2004). This voluntary attention difficulty in dichotic listening might also relate to schizophrenia in general instead of a AVH trait in particular, however, our data shows that NAVH patients do not present such difficulty suggesting this deficit is an AVH trait.

Importantly, there is vast literature applying lexico-phonological dichotic listening tasks in schizophrenia patients (Green et al., 1994; Bruder et al., 1999; Levitan et al., 1999; Hugdahl et al., 2007; Force et al., 2008). Summarizing the cited studies, we can conclude that schizophrenia patients do not show the normal right ear advantage for lexico-phonological stimulus due to electrophysiological abnormalities in the left temporal lobe (Bruder et al., 1999) and reduced event related potential component of early auditory processing (Force et al., 2008). In relation to hallucinations, AVH patients show lack of ear advantage for linguistic stimulus in comparison to NAVH patient and controls (Green et al., 1994; Hugdahl et al., 2007; Ocklenburg et al., 2013), which are highlighted by gray matter reduction in the left temporal lobe (Hugdahl et al., 2007). Our study complements the literature by suggesting the existence of right hemisphere abnormalities in AVH patients reflected in abnormal lateralization of EP. It has previously been proposed that attentional control on dichotic listening reflects an interaction between frontal executive processing and the left and right temporal lobe speech processing, underlied by frontotemporal connections (Løberg et al., 2006; Hugdahl, 2009), which seems disrupted in AVH patients (Lawrie et al., 2002).

AVH patients could be more symptomatic and thence more cognitively impaired than NAVH patients, but in our sample there were no differences in premorbid verbal IQ. Unfortunately, we cannot fully rule out that a greater general cognitive impairment in the AVH group might have caused top-down difficulties in hallucinators. However, it should be noted that the NAVH and AVH groups did not differ in the baseline condition. Moreover, it is negative, rather than positive, symptoms that are associated with neurocognitive impairment (Lewandowski et al., 2007; Ventura et al., 2009). AVH patients rated higher on the delusion subscale, and therefore we cannot exclude delusions contributing toward the interference of implicit EP. However, impaired performance in dichotic listening in psychotic patients relates to hallucinations particularly (Løberg et al., 2002). We found no differences in hearing thresholds, thus a hearing deficit cannot explain the observed effects. Importantly, we do not disregard the impact that audio perceptual abnormalities such as pitch perception can exert on prosodic processing, which was demonstrated in previous research (Leitman et al., 2005, 2007, 2011). We did not test pitch perception specifically, as it would have exceeded the scope of the study. Both strand of research (pitch perception abnormalities and EP deficits in AVH) do not invalidate each other, but instead they are regarded as complementary. Importantly, in a previous study (Alba-Ferrara et al., 2011) we demonstrated that the brain representation of emotional processing reminds unchanged when statistically controlled for pitch differences.

AVH patients are not typically right-lateralized for EP because they do not benefit from attending to either ear during baseline, and convergent emotion does not deteriorate performance preferentially on either side. In addition, AVH patients' inability to filter emotion trials when the attended ear diverges from the ear in which EP is presented may support lack of hemispheric specialization for implicit EP processing. Although our study included two potentially right lateralized processes (EP and sex discrimination), we believe that the atypical lateralization rather refers to EP because of the significant main effect of ear attended. The left ear advantage for the explicit task was present for all groups. Atypical asymmetries in EP processing in AVH patients might not only help to understand the formation of hallucination and its cognitive impairments. They might also be useful as a diagnostic marker and risk factor for AVH formation in schizophrenic patients.

LIMITATIONS

Several caveats are needed. Since all our patients took antipsychotic medications, we cannot fully ascertain whether the differences between groups are not influenced by them. The ability to ignore irrelevant stimuli, which is compromised in schizophrenia (Leumann et al., 2002), improves with atypical antipsychotics (Green et al., 2001). The three groups did not differ in premorbid IQ, education, years of illness, age, or handedness; thus, these factors are unlikely to explain the findings. Lastly, a mood disorder screening was performed ensuring that our patients were free from such confound. It should, however, be noted that patients had in general longer latencies compared to controls. Slow RT in general have been long recognized as one of the behavioral deficits of schizophrenia (Cromwell and Held, 1969). However, since the NAVH and the control group show the same pattern performance (accuracy and RT across conditions), the AVH group behaves differently in that they do not show the convergence-dependent interference effect.

CLINICAL AND THEORETICAL IMPLICATIONS

The present findings have implications for neuropsychological models of hallucinations. According to Woodruff (Woodruff, 2004), an attentional bias toward emotional stimuli in schizophrenia patients has been previously observed (Green et al., 2001; Waters et al., 2006) and it may underlie AVH. The present results extend the finding of abnormal attentional bias toward prosodic emotional stimuli presented to the non-dominant side regardless of the focus of voluntary attention in AVH patients specifically. Emotional salience of prosodic stimuli may capture attention even when it should be oriented away from the distractor, resulting in emotional inputs accessing processing in detriment of non-emotional competitors. Such attentional bias toward irrelevant EP stimuli might impair the ability to focus on relevant aspects of the acoustical environment (Javitt, 2009). A breakdown in selective attention may cause an overwhelming sensorial influx of irrelevant data resulting in abnormal perceptions (Alba-Ferrara et al., 2012). Hallucinations are aberrant perceptual processes which usually convey emotional salience. Such bottom-up saliency may diminish top-down control as AVH may shift attention toward the perceived voices (Hugdahl et al., 2007).

CONCLUSION

The present study provides evidence that schizophrenia patients can implement top-down control as well as controls. Further, NAVH patients are as good as controls at controlling the effect of bottom-up salience (as manipulated by emotional distractors) on top-down control. Indeed, lower performance can be overcome if emotional distractors are presented to the non-attended ear and to the inferior-for-the-task hemisphere. AVH patients, however, cannot overcome divergent emotional distractors presented to the putative inferior-for-the-task side, suggesting that bottom-up salience may capture attention revealing inefficient top-down control. In AVH patients, a failure of the typical lateralization for EP as the core mechanism underlying abnormal modulation of attention by EP is suggested.

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Stop, look, listen: the need for philosophical phenomenological perspectives on auditory verbal hallucinations

Simon McCarthy-Jones[1,2]*, Joel Krueger[3], Frank Larøi[4], Matthew Broome[5,6] and Charles Fernyhough[2]

[1] Department of Cognitive Science, ARC Centre of Excellence in Cognition and its Disorders, Macquarie University, Sydney, NSW, Australia
[2] Department of Psychology, Durham University, Durham, UK
[3] Department of Philosophy, Durham University, Durham, UK
[4] Department of Psychology, University of Liège, Liège, Belgium
[5] Department of Psychosis Studies, King's College London, Institute of Psychiatry, London, UK
[6] Division of Mental Health and Wellbeing, Warwick Medical School, University of Warwick, Coventry, UK

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Johanna C. Badcock, University of Western Australia, Australia

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Johanna C. Badcock, University of Western Australia, Australia
Paul Allen, King's College London, UK

***Correspondence:**
Simon McCarthy-Jones, Department of Cognitive Science, ARC Centre of Excellence in Cognition and its Disorders, Macquarie University, Balaclava Road, North Ryde, NSW 2109, Australia.
e-mail: s.mccarthyjones@gmail.com

One of the leading cognitive models of auditory verbal hallucinations (AVHs) proposes such experiences result from a disturbance in the process by which inner speech is attributed to the self. Research in this area has, however, proceeded in the absence of thorough cognitive and phenomenological investigations of the nature of inner speech, against which AVHs are implicitly or explicitly defined. In this paper we begin by introducing philosophical phenomenology and highlighting its relevance to AVHs, before briefly examining the evolving literature on the relation between inner experiences and AVHs. We then argue for the need for philosophical phenomenology (*P*henomenology) and the traditional empirical methods of psychology for studying inner experience (*p*henomenology) to mutually inform each other to provide a richer and more nuanced picture of both inner experience and AVHs than either could on its own. A critical examination is undertaken of the leading model of AVHs derived from phenomenological philosophy, the ipseity disturbance model. From this we suggest issues that future work in this vein will need to consider, and examine how interdisciplinary methodologies may contribute to advances in our understanding of AVHs. Detailed suggestions are made for the direction and methodology of future work into AVHs, which we suggest should be undertaken in a context where phenomenology and physiology are both necessary, but neither sufficient.

Keywords: hallucination, phenomenology, psychosis, schizophrenia, interdisciplinary

INTRODUCTION

The experience of hearing a voice in the absence of an appropriate external stimulus, formally termed an auditory verbal hallucination (AVH), is found in people with a range of psychiatric diagnoses, including schizophrenia, bipolar disorder, post-traumatic stress disorder, as well as in non-psychiatric populations (Larøi et al., 2012). In attempting to understand the causes of AVHs, researchers have explored the experience at multiple levels, including the neurological, cognitive, and sociological (McCarthy-Jones, 2012). Yet all these levels of explanation must take into account the findings of phenomenological studies of AVHs. A detailed knowledge of the phenomenology of AVHs is necessary, firstly, in order to ensure that models are explaining what voice-hearers are actually experiencing and, secondly, in order to obtain clues as to what may be underpinning the experience of AVHs (McCarthy-Jones et al., 2012).

Consistent with this proposal, Garcia-Montes et al. (2012) have argued that research should give people diagnosed with psychosis a "turn to speak," i.e., that it should take a phenomenological approach, involving in-depth questioning of people about their subjective experiences, with questions that suspend or "bracket" presuppositions about the phenomena under investigation, including its normality or abnormality, and its causes (Stanghellini and Lysaker, 2007). Garcia-Montes et al. also suggest that giving people "increased importance in defining their experience may assist in fine-tuning concepts used by the cognitive tradition, usually taken from research in basic psychology… and extrapolated without further ado to the field of schizophrenia." They note that this could lead to cognitive psychology "leaving behind its tendency to reduce symptoms or clinical phenomena to premade concepts." Such an approach has the potential to interrogate some unexamined assumptions in the study of AVHs, even if they are eventually found to be innocent. For example, many models in the cognitive psychology paradigm assume that AVHs are altered forms of normal cognitive processes (such as inner speech or memory), and often uncritically recruit such concepts into their explanatory models. However, it is possible that AVHs may be a distinct experience, without roots in these normal cognitive processes, and thus requiring

entirely new mechanisms and processes to explain them. One method by which such assumptions can be examined is through the use of philosophical phenomenology to undertake a detailed phenomenological investigation of AVHs.

Philosophical phenomenology is a systematic investigation of subjectivity, a consideration of experience from the first-person perspective of the "I" (Moran, 2000; Sokolowski, 2000). For phenomenologists, this first-person emphasis involves an analysis of basic structures of consciousness such as intentionality, self-awareness, temporality, embodiment, spatiality, agency, and intersubjectivity. It is through these basic structures that the world becomes manifest within our conscious life. Phenomenology is thus concerned with the constitutive processes that give our experience of the world and ourselves its formal coherence. In light of this first-person orientation, phenomenology might be thought of as the foundational science for psychopathology (Fuchs, 2010; although, as we noted above, there is no necessary link between AVHs and states that could be described as pathological).

Methodologically, phenomenological investigations of consciousness involve a disciplined *seeing* (Gallagher, 2012). This means that phenomenology (literally, the "science of appearances") looks to provide a rigorous description of experiential phenomena as they reveal themselves to consciousness. As Heidegger puts it, this disciplined seeing involves letting "that which shows itself be seen from itself in the very way in which it shows itself from itself" (Heidegger, 1962, 58/34).

The first step of phenomenological seeing begins by suspending taken-for-granted assumptions or judgments about the cause, normality, or reality of what is experienced (Broome et al., 2012). This formal suspension (or *epoché*, as Husserl, 1960, termed it) of metaphysical and scientific judgment is a port of entry into the inner structure of experience. For, rather than focus on external factors or explanations, we instead carefully observe what we experience just as we experience it; our subsequent descriptions are based on this "naïve" presuppositionless seeing. Within the clinical context, this means that the investigator suspends etiological and diagnostic considerations and instead re-focuses on the character and meaning of the patient's experience from their perspective. Questions here include: what is it like for the patient to have a particular experience or be in a particular mental state (e.g., to be depressed or hear voices)? How do salient phenomena within this experience manifest to the patient? What is the meaning of this experience for the patient and how does it relate to their present situation?

In relation to the experience of AVHs, employing a philosophical phenomenological approach and being guided by the experience itself may result in the deprioritization of aspects of their phenomenology which, for a range of good or bad reasons, have previously been deemed salient (although, to be clear, this approach does not set out to depriortize any aspect of the experience stressed by contemporary approaches). For example, as a result of historical factors certain aspects of AVHs have become of a priori concern to the mind sciences, such as the quasi-fetishized property of their location, i.e., whether AVHs are perceived as being internally or externally located to the head. Similarly, widely used AVH assessment tools, such as the Psychotic Rating Scales (PSYRATS-AH: Haddock et al., 1999) have been influential in regard to which aspects of AVHs are deemed important to enquire about (such as loudness, duration, frequency), without any evidence that these are either the aspects research should be focusing on, or those which voice-hearers themselves think are important. We may also consider the very use of the term "voice-hearing" which may not accurately capture what the person is experiencing (McCarthy-Jones, 2012), and instead suspend such ways of seeing to allow the person to report salient aspects of the experience to them, in the phrasing that they prefer.

The second step involves imaginative variation, the eidetic reduction, a process by which we intuit the essence (*eidos*) of the phenomenon under consideration; we use our imagination to alter various aspects of the phenomenon in order to discern the invariant features that define it as the sort of entity that it is. For example, when one sees a particular apple, one can imagine that it might be a different color, texture, size, or weight, or have a different flavor, without it thereby becoming something other than an apple. None of these features are part of its essence. A similar process can be applied to anomalous experiences ranging from affective depersonalization in melancholic depression to disruptions of *ipseity* and embodiment within schizophrenia/AVHs (see below). The payoff of this process is that the phenomenologist gets a clearer picture of the phenomenon's prototypical features, information which is then used to generate more nuanced descriptions of the patient's overall experience. These descriptions are further specified by subjecting them to intersubjective scrutiny within a community of fellow scientists, phenomenologists, and voice-hearers themselves (categories which are, of course, not mutually exclusive). In this way phenomenology can recreate the experiential dimension of psychiatric disorders and in so doing provide acute descriptions of anomalous phenomena (Parnas and Zahavi, 2000).

In relation to the experience of AVH, though, such a process may become problematic due to the heterogeneity of the phenomenology of the experience which makes the boundaries of AVHs hard to define (McCarthy-Jones, 2012). For example, experiences which are traditionally classed under the umbrella term "AVH" may range, phenomenologically, from an experience which is just like hearing another person speak, to an experience that is more thought-like than voice-like, through to an experience of a message being communicated to oneself that takes the form of a soundless, silent "voice" (Moritz and Larøi, 2008; McCarthy-Jones, 2012). Philosophical phenomenology may hence be able to examine whether these are qualitatively distinct experiences (involving distinct neural circuitry) or if they lie on a continuum with each other—e.g., a core experience which may range on dimensions such as its acoustics from clearly heard words to silent messages.

The third step is to return to the experience itself in order to assess the descriptive adequacy of these descriptions and categories. Within psychopathology, this involves a return to the clinical context. Here the phenomenologist can check the appropriateness of her/his findings by the phenomena she/he encounters (Fuchs, 2002). This process of recreating and analyzing the patient's lived experience thus takes the phenomenologist down into the basic structures of consciousness. It provides valuable

insight into how these structures organize non-pathological experiences of self and world and, crucially, how and where these basic structures become compromised or disrupted within anomalous experience.

Whilst philosophical phenomenology is likely to benefit our understandings of a range of experiences, AVHs appear to be an arena where it can be particularly fruitful. This is because there has been both a failure to understand the background of "ordinary" inner experiences that AVHs are (implicitly or explicitly) defined against, as well as a failure to understand exactly what the experience of having AVHs is like. Before continuing though, it is worth being explicit as to what philosophical phenomenology can and cannot offer AVH research. It is not the aim of philosophical phenomenology to offer an explanation of the mechanistic processes underpinning AVHs, which is a task for neurocognitive approaches, but instead to facilitate this indirectly through providing a more accurate description of the experience. This can be of use in a number of ways, some of which we have already discussed. However, two key related benefits are that it can, (1) provide an account of the experience that can be the explanatory target of neurocognitive models of AVHs, and (2) allow the evaluation of existing neurocognitive models against this experience, i.e., if existing models are not explaining the actual experience of AVHs, but rather an incomplete, misleading, or partial portrait of the experience, then they are flawed and in need of revision. Despite this, some argue (e.g., Merleau-Ponty, 1962), that there can be no truly presuppositionless seeing, no "total" epoché, and that, just like cognitive psychology, philosophical phenomenology has its own set of concepts that influence the aspects of AVHs that are attended to, such as the embodiment of the experience or its temporal or spatial character. Such insights have been gained via phenomenological reflection on the nature of experience. However, techniques such as the epoché can at least significantly improve our descriptions of phenomena, bracketing our assumptions re: causation and the "natural attitude" even if they are still viewed through some form of interpretive lens.

INNER EXPERIENCE AND AVHs

Although there are many models of AVHs, such as memory-based models (Waters et al., 2006a), hypervigilance models (Dodgson and Gordon, 2009), and social deafferentation models (Hoffman, 2007), we will focus in this paper on how philosophical phenomenology may be applied to what is currently the dominant model (in terms of being the most empirically investigated, as well as most discussed) model of AVHs, the inner speech model. This model proposes that AVHs result from a disturbance to the process whereby inner speech is attributed to the self (e.g., Frith, 1992; Leudar et al., 1997). However, progress in this area has been hampered by a lack of attention to the phenomenological properties of inner speech and, relatedly, AVHs. In particular, there is a need for improved empirical research on key properties of inner speech that have been proposed to be of value in explaining the relation between inner speech and AVHs (Fernyhough, 2004; Jones and Fernyhough, 2007).

One such factor is *dialogicality*, which refers to the ability of inner speech to incorporate multiple perspectives on reality (Fernyhough, 1996, 2004). Dialogicality has been proposed to result from the development of inner speech through the internalization of structured linguistic exchanges with caregivers and others during the course of development (Vygotsky, 1934/1987; Fernyhough, 1996). This quality of inner speech has been proposed as an explanation for why AVHs often manifest voices of others alongside that of the self (Fernyhough, 2004; Jones and Fernyhough, 2007). A second important quality is *condensation*, the tendency of utterances in inner speech sometimes to appear phenomenally as having a condensed or "note-form" quality. Condensation has been proposed as a further reason why inner speech can take multiple forms, such as in the proposed distinction (Fernyhough, 2004) between "condensed inner speech" (in which the internal utterance is fully stripped-down and abbreviated) and "expanded inner speech" (in which internal utterances retain their full linguistic structure). Transition between forms of inner speech (condensed and expanded) has been put forward, in an extension of the basic inner speech model of AVHs, to explain why voices can suddenly intrude into consciousness (Fernyhough, 2004).

The empirical study of inner speech has of course been hampered by its unobservability. Some support for the dialogicality and condensation dimensions of inner speech was provided by McCarthy-Jones and Fernyhough (2011) who, using a self-report scale (the Varieties of Inner Speech Questionnaire), found the existence of these dimensions in a healthy sample of adults. Other empirical methods proving useful in the study of inner speech are dual-task methods in which the language system is temporarily blocked by, for example, articulatory suppression, and experience sampling methods such as the phenomenological Descriptive Experience Sampling (DES; Hurlburt and Heavey, 2006).

There has been little research on the phenomenological properties of inner speech and AVHs in those who hear voices. In the only study to provide a systematic analysis of inner speech phenomenology alongside AVH phenomenology, Langdon et al. (2009) found no significant differences in inner speech phenomenology between people diagnosed with schizophrenia who heard voices and non voice-hearing healthy controls. For example, there were no differences between the two groups in the form, speed, and pragmatics of their inner speech, and no relations between patients' inner speech and their voices in terms of variables such as frequency and pragmatics. However, there was a trend toward reduced dialogicality of inner speech in the patient group (in the sense of inner speech being less likely to take on an overt dialogic form), potentially suggesting a relation between a reduced normal inner dialogue and the presence of AVHs.

Of course, inner speech only forms a subset of inner experiences (Hurlburt and Heavey, 2006), and a recent study of the phenomenology of AVHs has suggested that a diverse range of inner experiences, such as verbal and non-verbal memories, as well as inner speech, may form the basis of AVHs. McCarthy-Jones et al. (2012) assessed the phenomenology of AHs in 199 psychiatric patients, using an interviewer-led semi-structured interview. In addition to reporting on a comprehensive range of properties of AHs, this study also employed cluster analysis (clustering by variable and hence identifying within-individual differences,

rather than between-individual differences) and found four subtypes of AH, which they termed Constant Commanding and Commenting AVHs, Own Thought AVHs (which did not address the voice-hearer, spoke in the first-person, were experienced as being similar to memories, and possibly being one's own voice/thoughts), Replay AVHs (which were reported as being identical to previously experienced heard speech), and Non-verbal AHs (which were either language which did not make sense, or non-verbal sounds). It appears plausible that each of these subtypes of AH may result from distortions to distinct forms of inner experience, and that a better understanding of normal inner experience is therefore required before this can be mapped onto the phenomenology of AHs.

"*P*HENOMENOLOGY" AND "*p*HENOMENOLOGY"

The empirical methods of psychology for studying inner speech and other forms of inner experience such as AVHs entail clear limitations. Retrospective introspection of the form demanded by self-report studies is likely to be unreliable in certain circumstances, while dual-task methods gain little traction on phenomenology and rely on potentially misplaced assumptions about the recruitment of inner speech in cognitive tasks. Although DES is founded in phenomenological principles and is careful to ensure the bracketing of presuppositions, it can be criticized for its failure to generate generalizable empirical data. Philosophical phenomenology, which we denote here as *P*henomenology (phenomenology with a big "P"), can potentially enrich the methods of self-report, introspection, etc. that psychologists and cognitive scientists have traditionally relied on, which we refer to as *p*henomenology (phenomenology with a small "p").

*P*henomenology can supplement and enrich *p*henomenology because the former works at a distinct but nevertheless complementary level of analysis to the latter. That is, whereas *p*henomenology and its methods of self-report, introspection, etc. yield important data about the specific *contents* of experience (i.e., *what* a subject is experiencing), *P*henomenology is—in addition to this data—also concerned with the formal *structures* of experience (i.e., *how* the subject is experiencing the "what"). This "transcendental" aspiration is essential to *P*henomenological methodology (Husserl, 1989).

Again, this transcendental aspiration is apparent in *P*henomenology's concern with how basic structures inherent in consciousness (e.g., intentionality, self-awareness, temporality, embodiment, spatiality, agency, intersubjectivity, etc.) organize and constitute experience and imbue it with a first-personal character. Data from *p*henomenological reports (e.g., patient vignettes in psychiatry) can lend important clues to how and where these basic structures become compromised or disrupted within anomalous experience. However, *P*henomenology can further contextualize these often fragmentary or isolated reports within a broader transcendental context. This is because *P*henomenology offers a sophisticated framework for describing experience and existence that enables the psychopathologist to address concrete issues of diagnosis and treatment while remaining mindful of how these local concerns relate to overarching issues such as time, space, self, and intersubjectivity (Parnas and Zahavi, 2000). Accordingly, *P*henomenology does not simply consider symptoms in isolation (i.e., as localized manifestations of brain dysfunction); nor does it reduce diagnostic entities to statistically relevant clusters of symptoms (Fuchs, 2010). Rather, these are considered in the broader context of the subject and the whole of consciousness in which they emerge, that is, as typical modes of human experience and existence through which the subject constitutes her experience of self, world, and other.

As Thomas Fuchs (2010) notes, this structural emphasis of *P*henomenology is a search for what he terms "psychopathological organizers" connecting single features (e.g., affective depersonalization in melancholic depression or autism in schizophrenia) within a larger experiential gestalt. This emphasis "helps define mental disorders on the basis of their structural experiential features, linking apparently disconnected phenomena together" (Fuchs, 2010, p. 549). The end result—in light of these complementary levels of analysis—is that *p*henomenology and *P*henomenology can together provide a richer and more nuanced picture of the phenomenon under consideration than can either approach on its own.

PHENOMENOLOGICAL PHILOSOPHY AND AVHs

THE IPSEITY MODEL OF AVHs

One attempt to utilize phenomenological philosophy to help understand AVHs has come from Sass and Parnas (2003). An examination of their resultant account of AVHs is informative of the strengths and limitations of the application of phenomenological philosophy to AVHs. Their model involves a phenomenological analysis of ordinary experience, as well as that experienced by people with AVHs, and then the use of this analysis to propose what processes may be underpinning AVHs. Sass and Parnas's approach is derived from a phenomenological analysis of two facets of the intentional act: (1) a pre-reflective embeddedness in the world, and (2) a tacit or pre-reflective self-awareness or ipseity (literally, "self" or "itself"). The term "ipseity" refers to the experiential sense of being a subject of experience, i.e., one's own first-person perspective on the world. The basic sense of ipseity in normal consciousness, argues Sass (2003), is reflected in someone "whose experiences are unified and owned rather than merely flying about loose" (p. 244).

Sass and Parnas (2003) argue that there are occasions, such as in schizophrenia, where this basic sense of self or ipseity becomes fragmented or otherwise disturbed. In the case of schizophrenia, disturbed ipseity exhibits two main features. The first is hyper-reflexivity, a form of exaggerated self-consciousness in "which something normally tacit becomes focal and explicit" (p. 430). For example, some patients report that normally tacit sensorimotor processes animating everyday behavior (e.g., getting dressed, drinking coffee, interacting with others, etc.) may lose their automaticity. Instead, the background repertoire of proprioceptive and kinaesthetic processes informing this behavior move to the foreground of the patient's focal attention; they become hyper-aware of the effort required to produce each gesture or movement—so much so that their body is eventually experienced as a mechanical object, resulting in an experience of disembodiment or "self-alienation" (p. 429). Alternatively, other patients report that particular details of a scene, or specific qualities of

faces or persons, stand out with a kind of hypersalience; they are dislodged from the gestalt of the situational context and thus appear strange or uncanny (Wiggins and Schwartz, 2007). Even the perceptual act itself may rise to the level of focal awareness (e.g., "I became aware of my eye watching an object," Stanghellini, 2004, p. 113). Hyper-reflexivity thus objectifies normally tacit, pre-reflective processes of agency and perception.

In a later paper (Nelson et al., 2009), the authors make clear that although hyper-reflexivity is a concept that includes an exaggerated intellectual or reflective process, it is not "at its core, an intellectual, volitional, or 'reflective' kind of self-consciousness. It primarily refers to acts of awareness that are automatic (non-volitional) and not intellectual in nature, as in the case of kinaesthetic experiences 'popping' into awareness" (Nelson et al., 2009, p. 809). As hyper-reflexivity makes focal what was once tacit, the experience can hence not be transparently inhabited by the self; hyper-reflexivity introduces a rupture within the basic structure of experience. This leads to the second, complementary component of ipseity disturbance: a diminishment of self-affection, which Sass and Parnas (2003) define as a reduction in the sense of basic self-presence; "the implicit sense of existing as a vital and self-possessed subject of awareness" (p. 429). For example, patients may report feeling an inner distance from their stream of consciousness ("I saw everything I did like a film-cameram" Sass, 1992, p.132), or "an inner void" or "lack of inner nucleus" where the self would normally be (Parnas and Handest, 2003). As ipseity disturbances, hyper-reflexivity and diminished self-affection thus erode the basis sense of self-presence and perspectival coherence that enables us to maintain an experiential grip on the world and on ourselves as embedded in the world.

Sass and Parnas (2003) propose that AVHs (and schizophrenia more generally) result from such an ipseity disturbance. They argue that in texts such as Ey (1973), Tissot (1984), Naudin et al. (2000), an altered state of self-awareness can be seen to occur before AVHs. Specifically, they argue that "the patient experiences his or her own subjectivity as becoming in a certain way ready for something strange to happen… Mental processes and inner speech … are no longer permeated with the sense of selfhood but have become more like introspected objects, with increasingly reified, spatialized, and externalized qualities" (p. 432). Commonly encountered AVHs, such as voices commenting on a hearer's ongoing behavior, are, in Sass and Parnas' view, "emblematic of the self-consciousness that generates this self-alienation." From this they conclude that AVHs "involve a sense of alienation from and a bringing to-explicit-awareness of the processes of consciousness itself." Sass argues that this occurs through "an automatic popping-up or popping-out of phenomena and processes that would usually remain in the tacit background of awareness" (Sass, 2003, p. 156). As such they "do not involve the addition of anything new but only an awareness of what is always present (e.g., of inner speech, the perfectly normal medium of much of our thinking) in the context of diminished self-presence" (Sass and Parnas, 2003, p. 433). In their view, AVHs therefore "represent the perfectly normal phenomena of ordinary human experience—which, however, are radically transformed because of being lived in the abnormal condition of hyper-reflexive awareness and diminished self-affection" (p. 433).

LIMITATIONS OF THE IPSEITY ACCOUNT

Phenomenological fusion

This interesting account has a number of notable limitations. Firstly, and most problematically for an ostensibly phenomenological account, although this model is strong in its analysis of the phenomenology of disturbances to normal experience (e.g., ipseity disturbances) and how this may be applied to AVHs, it lacks a comprehensive understanding of the phenomenology of AVHs to which is it trying to link. It therefore demonstrates what could be termed a lack of "phenomenological fusion," i.e., a failure to link the known phenomenology of inner experience to the known phenomenology of AVHs. This criticism has previously been noted by Leudar and Thomas (2000) who state that Sass' "characterization of voices of schizophrenics [sic] is based on case materials which reflect traditional construals of voices in psychiatry rather than on the ground-floor experiences of individuals with schizophrenia" (p. 95). For example, Sass (1992) states that "the voices schizophrenics [sic] hear tend to emanate not from any particular person or object in external space but from inside the body or from the sky" (p. 233), and that patients with schizophrenia most frequently have voices which "have more of a conceptual or cognitive than a sensory or perceptual taint, as if heard with the mind rather than the ear" (p. 233). Neither of these observations is consistent with the observed phenomenology of the majority of AVHs (Nayani and David, 1996; Moritz and Larøi, 2008; McCarthy-Jones et al., 2012). Indeed, Sass' latter observation above comes from a statement of Bleuer in which Bleuler only says voices "may" take this form. However, Sass, at the time of this theory's development, did not have access to the large systematic studies of AVHs available today (e.g., Nayani and David, 1996; McCarthy-Jones et al., 2012), and hence the recourse to less systematized studies of AVH phenomenology is understandable. The lesson we may take from this is that the philosophical phenomenological approach needs to be applied both to normal experience and to AVHs, and to linking these together.

Specificity to AVHs

A second limitation is that despite the apparent argument made for a causal role of ipseity in AVHs, in a later paper Sass and colleagues (Nelson et al., 2009) argue that "ipseity disturbance seems to be independent of symptom manifestation," still being present in the remitted phase of schizophrenia, hence making it a "trait or underlying marker of vulnerability, independent of the expression of this vulnerability in the form of psychotic symptoms" (p. 809). Similarly, Garcia-Montes et al. (2012) observe that high levels of "self-focused attentions are not exclusive in patients with auditory hallucinations, but that, in general, they characterize all patients with positive psychotic symptoms." This could be interpreted as the proponents of this theory arguing that ipseity disturbances are a necessary, although not sufficient cause of AVHs. However, Sass focusses on AVHs in people diagnosed with schizophrenia, which is not only a contested diagnostic entity (Boyle, 2002) but a diagnosis that only contains around a third of people who hear voices (McCarthy-Jones, 2012). It could therefore potentially be the case that ipseity disturbances are linked to schizophrenia *per se* and have no causal relation with AVHs. It is also possible that

ipseity disturbances are not found in other populations who hear voices, and are therefore not necessary for AVHs, and even if ipseity disturbances were found to be a necessary but not sufficient cause for AVHs, this would still leave the question as to what other additional factors are required for AVHs to ensue. Finally, it is also possible that in some populations or situations ipseity disturbances may be sufficient for AVHs. For example, the presence of AVHs in people undertaking intense introspection, such as the Desert Fathers (Christian monks in the third century who retired to the deserts of Egypt to pray: McCarthy-Jones, 2012) is at least suggestive that self-focus might be a sufficient cause of some AVHs.

Empirical testing and levels of explanation

At present there is very limited empirical evidence supporting Sass's ipseity account of AVHs. Although Sass (2003) was originally explicit that his account was "largely descriptive or interpretative rather than explanatory in nature" (p. 244), a more recent paper by Sass and colleagues (Nelson et al., 2009) has gone on to make some specific hypotheses, such as that the ipseity model predicts "an increase in self-focusing as causing a tendency to experience the object of focus as other-than-self (i.e., externalising or objectifying self-experience)" (p. 813). Linking this to a neurological level of explanation, they further state that this account "would predict that psychotic phenomena should be associated with increased cortical midline system (CMS) activity, to the extent that the disturbances of hyper-reflexivity and diminished self-affection suggest an increase in self-focusing as causing a tendency to experience the object of focus as other-than-self" (p. 813). Although phenomenological work leading to predictions at a neurological level is a promising way forward (see below), unfortunately for this specific hypothesis, activation of such structures during AVHs was not found in a recent meta-analysis (Jardri et al., 2011).

A recent paper by Garcia-Montes et al. (2012) considers the relation between Sass and Parnas's (2003) work and contemporary cognitive psychology. Garcia-Montes et al.'s overall argument is that there are noticeable parallels between "hyper-reflexivity" and some cognitive models of schizophrenia/AVHs that concentrate on attentional processes in such patients. However, it is unclear quite how Sass and Parnas's (2003) concept of hyper-reflexivity maps onto established psychological constructs. One possibility is that it relates to the psychological concept of meta-cognition (Garcia-Montes et al., 2012), which includes a range of items, including cognitive self-consciousness. However, a recent meta-analysis of the association between of meta-cognition and hallucination-proneness found only a weak association (Varese and Bentall, 2011). Nevertheless, what can be seen from this is that phenomenological philosophy needs to engage with (and potentially extend or revise), existing psychological constructs, in order to operationalize and test hypotheses that phenomenological philosophy has generated.

A further empirical limitation of this account is that other theories of AVHs predict the exact opposite to Sass and Parnas (2003). For example, Dodgson and Gordon (2009) argue that hypervigilance AVHs result specifically when attention is externally focussed. There is hence the need for an empirical investigation into the locus of attention of voice-hearers immediately preceding AVHs, which should be a priority for future experience-sampling studies of this phenomenon.

Benefits in terms of informing neurocognitive research

Although there is the need for phenomenological philosophy to engage with the concepts of existing neurocognitive work, it is also worth considering how it may extend these paradigms through critique. For example, Sass and Parnas's (2003) model can be considered in relation to the source-monitoring account of AVHs. Source-monitoring accounts of AVHs argue that a deficit in the skill of being able to distinguish between self-generated internal cognitions and non self-generated external perceptions leads the former to be mistaken for the latter, resulting in AVHs (Bentall, 1990). "Source monitoring" is used as a global term to cover both reality monitoring (the ability to differentiate between internally generated cognitions and external perceptions) and self-monitoring (the ability to differentiate between self- and other-produced stimuli). Although Sass and Parnas (2003) state that their account is "rather different" (p. 432) to the established self-monitoring deficit account of AVHs, they do not clearly set out their points of difference (in a later paper, they state that self-monitoring accounts are "redolent" of their ipseity model; Nelson et al., 2009).

In either case, Nelson et al. (2009) note that source-monitoring studies often require a reflective judgement about the source of a stimulus, making it unclear whether conscious self-reflection or the pre-reflective processes emphasized in their phenomenological accounts of ipseity disturbance in schizophrenia are being assessed. This inconsistency in experimental tasks may be able to account for the limitations in the existing psychological source-monitoring literature, which is somewhat contradictory. For example, whilst a recent meta-analysis has suggested specificity of source-monitoring deficits to AVHs (Waters et al., 2011), other studies have instead suggested that it is delusional ideation, not AVHs, that is linked to source-monitoring deficits (Allen et al., 2006; see McCarthy-Jones, 2012, for a review of the current evidence). There is hence the need for further consideration as to whether source-monitoring tasks involve conscious self-reflection or pre-reflective processes, and to examine these two separate forms of source-monitoring in relation to AVHs specifically, to see if both, neither or just one of these is related to them.

Summary

In summary, accounts of AVHs drawn from phenomenological philosophy may be valuable but need to ensure that: (1) if building from the phenomenology of normal inner experience, that this is then mapped onto the actual phenomenology of AVHs, (2) if descriptions of the experience are developed into a mechanistic account of AVHs, that they offer a mechanism specific to AVHs and not to schizophrenia *per se*, and (3) that their proposals lead to empirically falsifiable predictions at both a neural and cognitive level, clearly operationalizing their concepts in the language of these disciplines through collaboration with colleagues in such areas. For example, if a philosophical phenomenological

approach were to predict that memory disturbances play a causal role in AVHs, then it would need to go on to predict how this may be reflected in neural activation during AVHs, what differences in performance on standard cognitive tests of memory would be expected, and what new memory tasks may potentially be needed in order to detect predicted changes. The resultant benefits of this approach are that it may both offer us a better understanding of the phenomenology of AVHs, and offer valuable critiques of existing psychological constructs, such as source-monitoring.

Once such original first-person data has been collected, it may then be utilized within a wider interdisciplinary research program, to guide the discovery of new objective (third-person) data at the neurophysiological level. Such an approach is already advocated in the methodology of neurophenomenology (Varela, 1996), in which trained introspection leads to first-person data which can then guide investigation at the third-person, neurophysiological level. Neurophenomenological work in non-AVH related fields (Lutz et al., 2002) can be seen to suggest how AVHs may be explored using neurophenomenology. For example, the use of *P*henomenology to detect distinct aspects of the hearing voices experience, such as the claim noted above that an altered state of self-awareness occurs before AVHs, could then be used to lead a search for whether these states have distinct neurological components, and how AVHs result from a cascade of neural activity resulting from an altered state of self-awareness.

Another example of a wider interdisciplinary research program engaging with the phenomenology of hearing voices comes from the work of the "Hearing the Voice" project at Durham University (e.g., Macnaughton, 2011). In this project, work on both the *P*henomenology and *p*henomenology of the hearing voice experience is being undertaken from disciplines including modern and medieval literary studies, theology, philosophy, psychology, and the medical humanities, with each discipline attempting to offer unique insights into the *P*/*p*henomenology of the voice-hearing experience (for example, medieval literary studies providing insights into how hearing voices was experienced and understood in this period of history through analysis of texts and documents from this era). Previous work has already demonstrated how, for example, historical analyses can offer us insights into the hearing voices experience (Jones, 2010). The Hearing the Voice project is further engaging with cognitive neuroscientific perspectives to examine how phenomenology and neuroscience may be mutually informative, leading to better understandings of the voice-hearing experience, and new ways to help people who are distressed by such experiences.

Such methodologies also allow that, in addition to first-person data informing work at the third-person level, this process may also work in reverse (e.g., through the neurophenomenological principle of mutual constraints), with third-person neurological findings informing the study of the first-person phenomenology of the experience (Varela, 1996). An approximation of this process can be drawn from some recent studies. For example, Diederen et al.'s (2010) functional magnetic resonance imaging study of the areas of the brain activated immediately before AVHs showed involvement of the parahippocampal gyrus, a region of the brain implicated in memory processes, suggesting that memory processes may play a role in the aetiology of AVHs. This, in part, motivated a later phenomenological examination of the involvement of memory in AVHs (albeit, using *p*henomenology rather than *P*henomenology) by McCarthy-Jones et al. (2012) who found that a notable subset of people with AVHs (39%) reported that their AVHs were identical and/or similar to "replays" of memories of things people had previously heard. Further work along these lines, in which first-person (phenomenological) and third-person (neurophysiological) perspectives mutually inform each other, is hence to be encouraged.

CONCLUSIONS AND EMPIRICAL PRIORITIES FOR FURTHER PROGRESS IN THIS AREA

Phenomenological philosophy clearly has a role to play in creating a better understanding of AVHs. However, this appears likely to necessitate a multiple stage process. First, there is the need to use phenomenological philosophy to better understand the *P*henomenology of ordinary inner experience, as well as the potential variability in properties of inner experience of specific relevance to AVHs, such as the tendency for inner speech in non voice-hearers to take on a perceptual nature. Second, as we noted above, there is the need to assess whether unusual forms of ordinary inner experience form the raw material of AVHs, or whether AVHs are unrelated to such processes and are qualitatively different, new forms of experiences. *P*henomenological study of both ordinary inner experience and AVHs should contribute to addressing this question.

Third, despite the recent large scale study (McCarthy-Jones et al., 2012) of the *p*henomenology of AHs noted above, there is still the need for *P*henomenological work that explores AHs using the techniques of phenomenological philosophy. For example, McCarthy-Jones et al. found that 12% of patients reported that their AVHs were identical to memories of previous things that had been spoken to them, and that 31% said their AVHs were similar to memories. Yet phenomenological philosophy methods are likely to be needed to probe the *P*henomenology of these experiences, and to establish what exactly participants meant by relating their voices to memories, and the characteristics of these experiences that led them to be labeled AVHs, as opposed to simply intrusive memories (cf. Waters et al., 2006b). Similarly, careful *P*henomenological analysis of the varieties of inner speech and AVHs will benefit our understanding of any relations between these experiences. Such work will need to ensure that it creates what we have termed phenomenological fusion, mapping through the phenomenology of inner experience onto the phenomenology of AVHs.

Fourth, there is the need to use phenomenological philosophy and other methods derived from humanities disciplines to assess the meaning of AVHs for the person hearing them and examine how this relates to their present situation. Such findings are likely to prove of benefit for the development of cognitive behavioral techniques (CBT) aimed at relieving voice-hearers' distress, particularly with regard to being able to create meaningful formulations. Phenomenological philosophy is also likely to provide other benefits to CBT therapists. For example, the greater degree of presuppositionless seeing offered by the technique of epoche, may help limit the degree to which pre-existing

theories of AVHs, whether these be trauma-based, developmental insult-based, or recreational drug triggered-based accounts, are employed in the therapeutic context, allowing the unique personal circumstances of the patient to guide the development of their formulation which is open to multiple explanations at first. Any such studies would benefit from having a longitudinal methodology, in order to create a developmental profile of how individuals move from normal inner experience to AVHs (e.g., Raballo and Larøi, 2011), and whether this is a gradual shift or a sharp change.

Finally, there is the need to build on such studies to map new first-person data onto their underpinning neurophysiological mechanisms (and vice versa), with these approaches reciprocally informing and mutually enriching the other. In this sense, the design of future studies will need to undertake what Gallagher (2003) has termed phenomenological front-loading.

One of the strengths of phenomenological philosophy, its suspension of presuppositions about the causes of the phenomena under investigation, is also a limitation for researchers interested in the causes of AVHs. There is hence the need to explain the results of phenomenological philosophical investigation. If, for example, there is a disturbance of ipseity, what may cause this? It may be important to try to understand why a person enters such a state. This may result from a wide range of situations, such as intense emotion/stress driving the person to turn his/her attentional resources inwards, social isolation resulting in attention turning inwards, or consciously intended meditative introspection, as with mystics throughout the centuries. Similarly, it needs to be established why the "automatic popping-up or popping-out of phenomena …that would usually remain in the tacit background of awareness" (Sass, 2003, p. 156) occurs? Why is there this increased awareness of "what is always present (e.g., inner speech)" (Sass and Parnas, 2003, p. 433)? When does it occur and why? What are the neural correlates of this process? Furthermore, which aspects of the person's inner life are the focus of the person's attention? Does this process account for both increased self-focus on auditory mentation (resulting in AVHs) as well as visual imagery (resulting in visual hallucinations)? It should also be considered that alternative mechanisms may cause different types of AVHs. For example, hyper-reflexivity fits well with AVHs in many healthy individuals who experience them under conditions of intensive introspection. However, it appears less clear how this maps onto AVHs of people who may have their attention externally focused during the AVH (Dodgson and Gordon, 2009).

A final consideration is how *p*henomenology and *P*henomenology may work together to improve our understanding of AVHs. That is, how can philosophical phenomenology potentially enrich the methods of self-report, introspection, etc. that psychologists and cognitive scientists have traditionally relied on? In this sense there needs to be a dialogue between research methods based on the principles of philosophical phenomenology and the standard semi-structured interview which is the mainstay of qualitative research.

In conclusion, phenomenological philosophy is likely to be able to make a significant contribution to our understanding of AVHs, and to be a profitable and necessary partner for neurophysiological research. Phenomenology and physiology are both necessary, but neither are sufficient.

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The role of the primary auditory cortex in the neural mechanism of auditory verbal hallucinations

Kristiina Kompus[1]*, Liv E. Falkenberg[1], Josef J. Bless[1], Erik Johnsen[2,3], Rune A. Kroken[2], Bodil Kråkvik[4], Frank Larøi[5], Else-Marie Løberg[1,2], Einar Vedul-Kjelsås[4,6], René Westerhausen[1,2] and Kenneth Hugdahl[1,2,7]

[1] *Department of Biological and Medical Psychology, University of Bergen, Bergen, Norway*
[2] *Division of Psychiatry, Haukeland University Hospital, Bergen, Norway*
[3] *Department of Clinical Medicine, Section Psychiatry, University of Bergen, Bergen, Norway*
[4] *Division of Psychiatry, Department of Research and Development, St. Olavs University Hospital, Trondheim, Norway*
[5] *Department of Psychology, University of Liège, Liège, Belgium*
[6] *Department of Neuroscience, Faculty of Medicine, NTNU, Trondheim, Norway*
[7] *Department of Radiology, Haukeland University Hospital, Bergen, Norway*

Edited by:
Kelly M. J. Diederen, University of Cambridge, UK

Reviewed by:
Giuliana Lucci, IRCCS Santa Lucia of Rome, Italy
Renaud Jardri, University Medical Centre of Lille, France
Alexander M. Rapp, University of Tuebingen, Germany

***Correspondence:**
Kristiina Kompus, Department of Biological and Medical Psychology, University of Bergen, Jonas Lies vei 91, N-5009 Bergen, Norway.
e-mail: kristiina.kompus@psybp.uib.no

Auditory verbal hallucinations (AVHs) are a subjective experience of "hearing voices" in the absence of corresponding physical stimulation in the environment. The most remarkable feature of AVHs is their perceptual quality, that is, the experience is subjectively often as vivid as hearing an actual voice, as opposed to mental imagery or auditory memories. This has lead to propositions that dysregulation of the primary auditory cortex (PAC) is a crucial component of the neural mechanism of AVHs. One possible mechanism by which the PAC could give rise to the experience of hallucinations is aberrant patterns of neuronal activity whereby the PAC is overly sensitive to activation arising from internal processing, while being less responsive to external stimulation. In this paper, we review recent research relevant to the role of the PAC in the generation of AVHs. We present new data from a functional magnetic resonance imaging (fMRI) study, examining the responsivity of the left and right PAC to parametrical modulation of the intensity of auditory verbal stimulation, and corresponding attentional top-down control in non-clinical participants with AVHs, and non-clinical participants with no AVHs. Non-clinical hallucinators showed reduced activation to speech sounds but intact attentional modulation in the right PAC. Additionally, we present data from a group of schizophrenia patients with AVHs, who do not show attentional modulation of left or right PAC. The context-appropriate modulation of the PAC may be a protective factor in non-clinical hallucinations.

Keywords: auditory verbal hallucinations, primary auditory cortex, non-clinical, schizophrenia, auditory attention

INTRODUCTION

Auditory verbal hallucinations (AVHs) are the subjective experience of hearing voices speaking in the absence of corresponding physical stimulation. The main body of research on AVHs comes from schizophrenia patients, due to the high prevalence of AVHs in this clinical group. However, AVHs as a symptom are not dependent on the schizophrenia syndrome, as is evident by their occurrence in multiple other diagnostic groups (Larøi et al., 2012), and even in isolation in otherwise mentally healthy individuals (Sommer et al., 2010). A particularly interesting feature of AVHs is their perceptual quality: the experience may be indistinguishable from real voices, as it may have characteristics of a personalized human voice and appear to be originating in the external physical space. Due to this, it has been proposed that the brain regions dedicated to auditory processing are relevant to experiencing hallucinations. This idea is supported by so-called "symptom capture" studies, which attempt to measure brain activity while subjects are experiencing AVHs (Woodruff et al., 1997; Dierks et al., 1999; Shergill et al., 2000). There are findings both from functional magnetic resonance imaging (fMRI) as well as electroencephalography (EEG) which are consistent with the idea that auditory processing areas show elevated activation during AVHs compared to silent rest. Of particular interest is the finding that this hallucination-related activation appears to be present in the primary auditory cortex (PAC) (see Kompus et al., 2011), potentially explaining the realistic nature of the experience. Further, Braun et al. (2003) reported consistency of hallucination modalities with brain lesions in corresponding sensory areas. As deficits in auditory processing have been observed in hallucinating patients, it has been suggested that the auditory processing regions, including the PAC, may be dysfunctional, either due to structural or functional aberrations. As speech processing is performed by the language-dominant, usually left, hemisphere, the efforts to associate sensory processing and AVHs concentrate on the structural and functional integrity of the left-sided auditory cortex. While the primary auditory cortices of both hemispheres process speech stimuli, the left PAC may be particularly implicated due to relationship with higher perceptual processing regions within the left hemisphere (see below).

Theoretical approaches to the role of the PAC in the experience of AVHs may be divided broadly into two categories [see also Waters et al. (2012) for discussion]. First, neurons in the PAC may trigger the AVHs, due to, e.g., spontaneous (i.e., stimulus-independent) activity which may be either (1) quantitatively different from spontaneous activity seen in non-hallucinating individuals (see, e.g., Dierks et al., 1999), or (2) quantitatively similar, but due to some other factor, such as lack of inhibition, able to propagate to higher levels of processing (see, e.g., Hunter et al., 2006; Northoff and Qin, 2011). Second, the PAC may be considered a "receptor" of AVHs, activating in response to input from higher processing regions. In such a view, the PAC may be considered as (1) lacking a critical inhibition to prevent such top-down activation (see, e.g., Friston and Frith, 1995; Ford et al., 2001), (2) lacking appropriate feedforward connections with a "monitoring" mechanism which normally identifies the activation as originating from internal source (see, e.g., McGuire et al., 1995), or (3) possessing disproportionate amount of excitatory links with higher processing regions compared to auditory pathways (see, e.g., Ford et al., 2009). It is important to note that in all of these approaches, the PAC is not considered to be the single cause for experiencing AVHs, but rather one constituent region, possibly providing an explanation for the question why AVHs are experienced as perceptual events, rather than intrusive thoughts or imagery.

Multiple approaches to characterizing the PAC properties are represented in the literature, including measurement of structural properties as well as functional responses. There are studies examining qualitative differences between groups (e.g., comparing the volume of the PAC between hallucinating and non-hallucinating subjects), as well as quantitative differences within a hallucinating group (e.g., analyzing whether the PAC volume predicts hallucination severity).

We consider it timely to review the evidence of the PAC functioning in subjects with AVHs, to evaluate the various theoretical propositions of how the PAC is involved in the experience of AVHs. In the first part of this paper, we selectively review studies examining the properties of the PAC in the context of AVHs. In the second part, we present new data where we probe the functional properties of the PAC using a paradigm which integrates the manipulation of bottom-up, perceptual features of stimulation with top-down, attentional manipulation of the auditory processing. We examine the responsiveness of the PAC in a group of non-clinical hallucinators (NCHs) compared to non-clinical non-hallucinators, and compare these groups with a hallucinating schizophrenia group.

AUDITORY VERBAL HALLUCINATIONS AND THE STRUCTURAL FEATURES OF THE PRIMARY AUDITORY CORTEX

The PAC, corresponding to cytoarchitectonically defined Brodmann area 41, is located on the transverse temporal gyrus, or Heschl's gyrus (HG), which runs in mediolateral direction within the Sylvian fissure (see **Figure 1** for schematic illustration). It is surrounded by secondary auditory processing areas on the superior temporal gyrus (STG). To date, studies on the structural correlates of AVHs have mainly been reported from clinical groups, notably schizophrenia. Post-mortem neuropathological studies of schizophrenia patients have been conflicting regarding specific regional alterations in these patients (Harrison, 1999), however, there is a general consensus in the literature of abnormalities in the STG in schizophrenia (Heckers, 1997), e.g., smaller left-sided volume of the planum temporale (Falkai et al., 1995). Sweet and colleagues have provided a thorough series of reports of post-mortem examinations from the left PAC in schizophrenia patients (Sweet et al., 2003, 2007, 2008; Dorph-Petersen et al., 2007). The changes appear to be concentrated within neuronal layer 3, which gives rise to feedforward projections to auditory association cortices (Douglas and Martin, 2004). In this cortical layer of the PAC, schizophrenia patients show a reduced mean volume (but not number) of pyramidal neurons, reduced dendritic spine density, as well as a reduced density of axon terminals (Sweet et al., 2003, 2007, 2008; Dorph-Petersen et al., 2007). Thus, schizophrenia patients demonstrate abnormalities within the excitatory feedforward circuit of the left PAC. Unfortunately, the clinical profile of the patient groups is not considered in these reports, thus it is not known whether these changes are associated with AVHs.

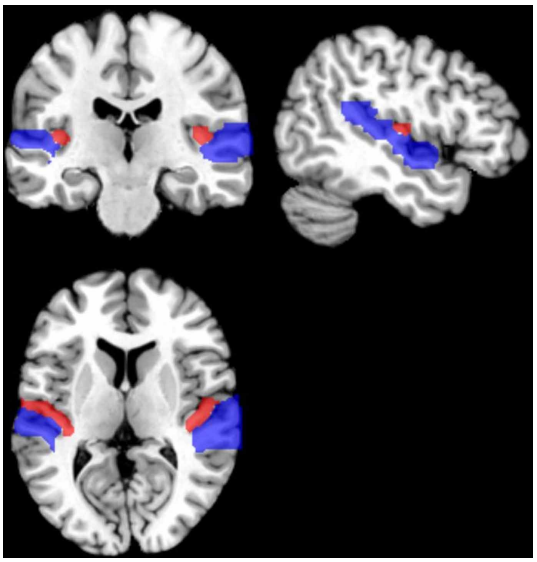

FIGURE 1 | Schematic illustration of the primary auditory cortex (PAC) on a brain template. The PAC occupies most of the Heschl's gyrus (red), which extends mediolaterally within the Sylvian fissure. PAC is surrounded by auditory association areas on the superior temporal gyrus (blue).

With the advent of magnetic resonance imaging (MRI), characterization of brain structures *in vivo* has become possible. Volumetric studies of STG frequently demonstrate reduced volume of STG in schizophrenia patients compared to controls, for instance Sun et al. (2009) report 76% of volumetric studies finding a difference between groups. The data is not entirely unequivocal, for instance while some meta-analyses implicate the superior temporal regions to be reduced in volume (Lawrie and Abukmeil, 1998; Wright et al., 2000), a meta-analysis by Vita et al. (2006) found no difference in the temporal lobe structures in first-episode schizophrenia patients. With respect to the

PAC in particular, Kasai et al. (2003) showed progressive volume reduction of left HG in schizophrenia patients over time. However, this finding was not correlated to the severity of hallucination symptoms. With respect to schizophrenia patients, the effect of other symptoms, such as thought disorder, may also contribute to regional changes in brain volume and structure (see Shenton et al., 1992; Horn et al., 2010), and the effect may be difficult to distinguish from the effect of hallucinations as a specific symptom.

Volumetric studies may differ from each other considerably with respect to definition of the region of interest, thus the studies using voxel-based morphometry (VBM) to examine regional structural variations may give a more coherent picture. Due to considerable amount of literature from group comparisons using VBM, several meta-analyses have been performed. It must be noted that the meta-analyses of whole-brain data differ from the effect size meta-analyses which are commonly used for other research questions. For MR data, commonly used meta-analysis methods, such as "activation likelihood estimation" (Eickhoff et al., 2005) do not include null-findings, only including studies reporting at least one significant difference anywhere in the brain volume. Thus, it is common for meta-analyses of VBM data to represent the spatial convergence across studies which report significant findings anywhere in the brain, not estimation of population effect size as in a traditional meta-analysis. Multiple meta-analyses have been performed, with three recent studies standing out in their scope. Glahn et al. (2008) performed an anatomic likelihood estimation meta-analysis of VBM studies from schizophrenia patients, including in total 1195 schizophrenia patients (first-episode and chronic) and 1262 healthy controls. A left-sided cluster of convergence was found involving insula, inferior frontal gyrus, precentral gyrus, and STG (including BA 22 and 38). From the report, it is not clear whether the cluster does or does not extend to the PAC. Fornito et al. (2009) used the same meta-analytic approach on a partly overlapping and extended sample of studies, and examined differences in both gray matter concentration as well as gray matter volume. The findings largely converge with the findings reported by Glahn et al. (2008), including a cluster on the left insular cortex which, according to the figure included in the report, appears to spread to left anterior STG. It is not clear whether the cluster does or does not extend to the left PAC. However, a group difference in the right PAC was reported. Bora et al. (2011) used a different meta-analysis method ("signed differential mapping") to analyze a partially overlapping and extended set of studies, including 1999 schizophrenia patients and 2180 control subjects. Findings show bilateral clusters centered in insula, and extending to the STG. Again, whether the PAC was particularly involved is not explicitly clear in the report, however, according to the figure presenting the results projected on a brain template, the cluster appears to extend to the HG on the right hemisphere.

While the above meta-analyses on schizophrenia are, by integrating data of multiple reports, certainly statistically powerful, they may be not sensitive with respect to AVHs and the PAC since the included individual studies usually pool data from patients that vary with regard to their hallucinatory status. However, it is reasonable to assume that in each of the meta-analyses the schizophrenia sample had higher likelihood of experiencing auditory hallucinations than the control sample, thus the findings are nevertheless relevant. More specific results are reported in two recent meta-analyses, concentrating particularly on the AVHs in schizophrenia patients (Palaniyappan et al., 2012; Modinos et al., 2013). Both of the meta-analyses report data from studies which test the relationship between AVH severity and gray matter volume in VBM studies. Modinos et al. (2013) report a very selective reduction in gray matter volume with increasing hallucination severity, concentrated in the left STG and PAC (size 210 voxels, STG peak coordinates MNI $x, y, z = -52, -18, 2$, HG peak $-46, -14, 6$). A trend-level reduction is reported in the right STG and PAC. Palaniyappan et al. (2012) report two clusters, one located in the left insula (size 717 voxels, peak at MNI $x, y, z = -42, -4, 2$) extending to inferior frontal gyrus and STG at BA 22, the other in right STG (BA 22), extending to right insula (size 318 voxels, BA 22 peak at MNI $x, y, z = 58, -6, 10$). Thus, although the two analyses broadly agree with bilateral STG being relevant for increased severity of AVHs, they show important divergences in predictors of AVH severity, with Modinos et al. (2013) implicating gray matter loss in bilateral PAC, and Palaniyappan et al. (2012), instead, in bilateral insula as predictors of AVH severity. Consequently, the inferences the authors draw regarding the neural mechanisms of AVHs diverge. Palaniyappan et al. (2012) suggest that insular dysfunction may result in erroneously processing inner speech as external stimulus. Modinos et al. (2013) suggest that "a volumetric abnormality, with the neurons in (STG) being reduced in number and/or spacing or having reduced connectivity [...] would block the normal attribution of internal speech." Considering that the included studies largely overlap, the differences in the results deserve further discussion. While six studies ($n = 268$) are included in both meta-analyses, Modinos et al. (2013) additionally include two further studies (Plaze et al., 2006; van Tol et al., unpublished), resulting in 322 subjects. Palaniyappan et al. (2012) include one further study (Shapleske et al., 2002), resulting in a total of 340 subjects. This study does not report correlational analyses [and is for that reason excluded from Modinos et al. (2013) analysis]. Palaniyappan et al. (2012) report that down-weighting this study did not significantly influence the final results. As the main portion of the subjects overlap, the particular study selection is presumably not the main variable influencing the outcome. The main difference between the two meta-analyses is the analysis method. Palaniyappan et al. (2012) use "signed differential mapping," which consists of calculating mean effect size across the included studies for each voxel in a brain volume (with the reported peaks being smoothed). Modinos et al. (2013) use a method termed "parametric voxel-based meta-analysis," which consists of calculating, for each voxel in a brain volume, the proportion of studies which report a significant peak within 10 mm. In both methods, the significance of a voxel is tested against a random spatial distribution of effects. Thus, the interpretation of the findings is different: whereas in the Modinos et al. (2013) study, a significant finding represents a significant proportion of included studies reporting a peak in the immediate neighborhood; in the Palaniyappan et al. (2012) study a significant finding represents a mean effect size across studies. Consequently, one possible (although admittedly speculative)

interpretation for the divergence is that the finding of gray matter reduction in insula is less consistent across studies, but if present then at a larger effect-size (in turn suggesting that VBM studies may have lower power specifically at insula); whereas the gray matter reduction in the PAC is consistent, albeit at smaller effect size.

In summary, structural studies offer modest support to the idea that AVHs are associated with structural change in the PAC. To date, the available evidence comes from hallucinations in clinical patients, thus it is not clear whether NCHs demonstrate the same pattern. The reduced gray matter volume in the PAC appears to be more consistent in the right compared to the left hemisphere across the entire schizophrenia population. However, the left PAC gray matter volume reduction appears to be more consistently associated to AVH severity (Neckelmann et al., 2006). There is no well-established theoretical model for the mechanisms of association between progressive loss of the PAC gray matter and progressively more severe hallucinations (as opposed to qualitative differences between groups). Attempts to explain the relationship include suggestions that the structural abnormality may lead to a reduced threshold for neuronal triggering, generating spontaneous neuronal activity in the PAC (Neckelmann et al., 2006). Such explanations necessitate a limit point for gray matter loss to which such an assumption is applicable, otherwise a logical paradox arises; the strongest spontaneous neuronal activation would be predicted in situations where all neurons have decayed.

AUDITORY VERBAL HALLUCINATIONS AND THE FUNCTIONAL PROPERTIES OF THE PRIMARY AUDITORY CORTEX

Functional integrity of the PAC may be probed with functional brain imaging methods, including fMRI and EEG, examining the response of the PAC to external stimulation, as well as with behavioral studies assessing the functional integrity of the PAC.

Functional magnetic resonance imaging studies

Recent meta-analyses of fMRI studies examining brain activation to external stimulation in hallucinating subjects indicate that patients with AVHs appear to have reduced fMRI response to external auditory stimuli in the left PAC. Kompus et al. (2011) performed an activation likelihood estimation meta-analysis of 11 studies examining processing of external auditory stimuli, and found convergent reduced activation in the left PAC in schizophrenia compared to control group. Notably, the left PAC was also more activated during "symptom capture" in fMRI studies of ongoing hallucinations (Kompus et al., 2011). A second meta-analysis by Kühn and Gallinat (2012), which did not find convergence in the PAC utilizing a partly overlapping set of studies, is not directly comparable to Kompus et al. (2011) study, as the included contrasts involved a wide variety of conditions (e.g., auditory imagery, speech identity decisions). Ford et al. (2009) reported a region-of-interest (ROI) analysis involving BA 41 responsiveness to auditory stimulation with pure tones in a large sample of patients with schizophrenia and schizoaffective disorder. Hallucinating patients had significantly reduced activation to external sounds in the left BA 41 compared to non-hallucinating patients (with no effect in the right hemisphere). However, this left-sided reduction was not significantly related to the severity of the hallucinations ($r = 0.02$). As the analysis involved a large sample size (66 hallucinating patients) the finding is likely to be reliable.

Considering the relationship between clinical and non-clinical hallucinations, an interesting result was reported by Lewis-Hanna et al. (2011) where individuals prone to sleep-related hallucinations had higher auditory sensitivity, which also co-varied with increased fMRI response to speech stimuli in the left supramarginal gyrus. Further, no differences in the PAC between hallucination-prone and non-prone individuals were reported in tasks examining speech perception and auditory attention. Thus, the functional reduction of the PAC response which is evident in the fMRI studies of schizophrenia patients may not be present in NCHs. This suggestion is supported by Szechtman et al. (1998), who studied a group of subjects susceptible to auditory hallucinations under hypnosis. The hallucination-prone subjects had spatially more extensive activations during auditory stimulation in the superior temporal regions, as measured with positon-emission tomography (PET). However, the individuals described in such studies (sleep-related and hypnosis-related susceptibility to hallucinations) may be a distinct population from NCHs, and thus the relevance of these results to hallucinations in awake state must be interpreted with caution. Compared to persistent non-clinical hallucinations experienced in the awake state, sleep- and hypnosis-related hallucinatory experiences appear to be relatively prevalent in the population and may be predominantly related to sleep disorders (see Ohayon et al., 1996).

To summarize, fMRI response to external auditory stimulation in the left PAC is reduced in hallucinating schizophrenia patients, but the magnitude of reduction does not predict AVH severity. No conclusive data is available for non-clinical hallucinations, but there is a possibility that hallucination-prone healthy individuals do not show reduced activity in the PAC, and may even have more extensive activation to auditory stimulation in other speech-related brain regions. However, the relationship between sleep-related hallucinations and hallucinations in awake state needs to be elucidated further before it can be concluded that such groups are representative of hallucinatory experiences in non-clinical population.

Electroencephalographic studies

With regard to EEG and event-related potential (ERP) studies, there are several electrophysiological components originating in the PAC which have been studied in connection with hallucinations (van Lutterveld et al., 2011; Ford et al., 2012). Here, we concentrate on the mismatch negativity (MMN), N100, and auditory steady-state ERP responses.

Mismatch negativity (MMN). MMN is an ERP component, consisting of a reduction in the measured EEG waveform when an auditory stimulus deviates from a train of preceding stimuli in either frequency or duration [see Näätänen (1995) for an overview]. MMN is hypothesized to depend on synaptic plasticity mediated by glutamatergic *N*-methyl-D-aspartate (NMDA)

receptors in the primary and secondary auditory cortices (Javitt et al., 1996). Thus, an attenuated MMN may indicate inability to adequately modify synaptic plasticity in response to excitatory neurotransmission resulting from external auditory stimulation. MMN attenuation and its possible predictive validity has been studied in multiple pathologic conditions. Shelley et al. (1991) first demonstrated attenuated MMN in schizophrenia patients. Consistent with one subset of cortical generators of MMN residing in the PAC, Salisbury et al. (2007) demonstrated a negative relationship between MMN amplitude and left hemisphere HG gray matter volume in schizophrenia patients. Importantly, the relationship was evident in both cross-sectional as well as longitudinal examinations. This is in good agreement with Wible et al. (2001), who found a wider extent of fMRI response to duration-deviant stimuli in the left HG in controls than schizophrenia patients. Umbricht and Krljes (2005) performed a meta-analysis of MMN studies comparing schizophrenia patients with healthy controls, and found attenuated MMN in schizophrenia patients (at effect size 0.99, indicating a large effect). The difference between groups was particularly pronounced for duration deviants, but also reliably present for frequency deviants. Umbricht and Krljes (2005) also qualitatively reviewed 22 studies which performed a correlation analysis between MMN attenuation and symptom severity, and noted that the majority of studies did not find a significant relationship. Only three of the 22 reviewed studies reported a significant correlation between positive symptom severity and MMN [note that in one of the three studies, Hirayasu et al. (1998), the effect was found only when appropriate correction for multiple tests was not enforced]. Regarding non-clinical hallucinations, van Lutterveld et al. (2010) found no difference in MMN between a group of non-psychotic individuals with AVHs and a control group. Thus, the existing evidence suggests that glutamate-receptor mediated synaptic plasticity in the PAC, as indexed by MMN, is compromised in schizophrenia patients, but may be not specifically related to AVHs.

N100. The N100 (or N1) ERP component is generated in the PAC in response to onset of external auditory stimulus. It is sensitive to bottom-up features of the auditory stimuli as well as top-down modulations, such as attention (Woldorff et al., 1993). Due to this, it can be seen as an index of successfully engaging in context-appropriate modulation of sensory processing. N100 is generally reduced in schizophrenia patients compared to healthy controls (Rosburg et al., 2008). This is in agreement with the fMRI studies which, as reviewed above, show less activation in the PAC to external stimuli in hallucinating groups. However, the reduction appears to depend on the particular characteristics of stimulus presentation, and does not appear to covary with particular clinical symptoms. Rosburg et al. (2008) note that most studies fail to find associations between N100 amplitude and specific symptoms in schizophrenia patients, with N100 reflecting, at best, general psychopathology load. The results regarding N100 sensitivity to attentional modulation in schizophrenia patients are not completely clear, with some studies suggesting considerable variation resulting from other experimental variables (intensity, stimulation rate) (Baribeau-Braun et al., 1983).

Modulation of N100 response by top-down processes has generated some interesting lines of research in the AVHs field. Hubl et al. (2007) reported reduced N100 in hallucinating subjects to pure tones (sinusoidal tones with 1000 Hz frequency and 70 ms duration) during episodes of AVHs compared to silent rest. This finding is typically interpreted as evidence that AVHs engage the PAC, in direct parallel to non-hallucinating subjects showing reduced N100 amplitude when background noise is present. However, considering the attentional modification being at least partially preserved in schizophrenia, it cannot be excluded that the reduction may also be interpreted as subjects attending the hallucinations at the expense of external stimuli, rather than the PAC representing the sensory features of hallucinations as they unfold.

Ford et al. (2001) have used N100 as a tool to test the theory that the dysfunctional "corollary discharge," i.e., specific inhibition of auditory cortex to self-generated sounds (see Paus et al., 1996), is associated to hallucination generation. N100 is reduced to self-produced sounds in healthy adults (Martikainen et al., 2005), presumably due to a feedforward model informing the brain of self-initiated actions (Bäss et al., 2008). In case such inhibition of the PAC is dysfunctional, self-generated sounds or inner speech may be perceived as externally originating sounds (Friston and Frith, 1995). Thus, N100 should be reduced in control subjects during their own speech compared to others' speech, whereas it should be equal in schizophrenia subjects. However, evidence is mixed and predictions complicated. For instance, while Ford et al. (2001) demonstrated reduced N100 due to external speech compared to self-generated speech in schizophrenia group (a result not entirely incompatible with the theory), the control group failed to demonstrate any modulation of N100 response between the two conditions, making the finding in schizophrenia group difficult to interpret.

Auditory steady state response (ASSR). Auditory steady state response is a repetitive evoked potential with constant frequency profile, the frequency corresponding to stimulation rate and/or its higher harmonics. (Spencer et al., 2009) showed that in schizophrenia patients, compared to controls, the gamma-band phase locking and evoked power in response to 40 Hz stimulation were overall decreased. However, within the schizophrenia group, both phase locking and evoked power of gamma-band evoked responses at the left PAC source positively correlated with AVHs. A re-analysis of the same data (Mulert et al., 2011) examined the interaction between left and right PAC sources, and found that the inter-hemispheric phase synchronization was positively correlated with AVH symptom scores. The theoretical explanation of such findings is that the PAC shows aberrant oscillatory synchronization, having increased propensity to enter a stable state of oscillatory synchrony independently of external stimulation (Spencer et al., 2009). Koenig et al. (2012) also report the relevance of gamma band synchronization to steady state stimulation to AVHs.

In summary, ERPs offer a mixed view on the functioning of the PAC with respect to hallucinations. While the steady state responses are interesting as they represent a good candidate for neuronal synchronization with the PAC as crucial in

the emergence of AVHs, more replications would be desirable. Synaptic plasticity in the PAC, as indicated by MMN, appears to be independent of both the likelihood to experience AVHs (as it is not reduced in NCHs) as well as the severity of AVHs. Similarly, neuronal response to onset of auditory stimuli, the N100 response, does not seem to be specifically modified by experiencing AVHs. Finally, it is noteworthy that a study examining ERPs in non-clinical AVHs (van Lutterveld et al., 2010) found that the non-clinical hallucinators had larger amplitude of one ERP component, namely P300. This component is a positive deflection occurring ∼300 ms after the onset of a deviant stimulus, with increased amplitude of P300 reflecting more attentional processing (Picton, 1992). Thus, similarly to fMRI studies, no conclusions can be drawn regarding NCHs; but data suggests that indexes of the PAC function may not differ from non-hallucinating individuals, with some features of auditory processing (localized outside the PAC) showing even enhanced activation.

BEHAVIORAL SIGNS OF IMPAIRED PRIMARY AUDITORY CORTEX FUNCTION

Schizophrenia patients often show lower performance on tasks depending on auditory perception, such as tone matching (Rabinowicz et al., 2000). However, overall reduced acuity does not appear to be predominant, as Mathew et al. (1993) reported that control subjects outperformed patients only at frequencies above 1000 Hz. Additional contribution to the reduced performance in auditory tasks appears to be changed laterality pattern, such as found in dichotic listening tasks. In dichotic listening, different input is provided to different ears simultaneously, and the subjects are to report what they hear (Bryden, 1988; Hugdahl, 2003). Relative proportion of reports from left and right ear may indicate temporal lobe functioning, also including the PAC. In right-handed healthy adults, a right-ear advantage for phonological dichotic listening task is typically found (see Ocklenburg et al., 2013). Løberg et al. (2004) reported that AVHs are associated with a reduction in the right-ear advantage. Thus, the left PAC may be compromised with increasing severity of hallucinations in schizophrenia, in agreement with the VBM studies. This relationship has also been observed in a large, multi-center study (Hugdahl et al., 2012).

SUMMARY

To summarize the literature review, we note that our focus on the PAC in this manuscript does not exclude the importance of higher-order perceptual processing regions, and other brain networks, in the experience of auditory hallucinations. As discussed in the Introduction, the activity of the neurons in the PAC may act as either "triggers" or "receptors" of neural activity related to the experience of hallucinations. In either case, many other brain regions are also implicated in the full experience of hearing a physically non-existing voice speak. This is attested by the wide-spread activation networks observed during the experience of ongoing AVHs, including higher auditory areas in the STG, but also parietal and frontal areas, and subcortical structures (Jardri et al., 2011; Kompus et al., 2011; Allen et al., 2012; see van Lutterveld et al., 2013). The experience of AVHs appears to be initiated as a cascade of activation, spreading along the cortical networks associated with auditory perception, attention and conscious awareness. Interestingly, it has been suggested that the first step in this cascade may be the deactivation of the parahippocampal gyrus (Diederen et al., 2010b), followed by wide-spread activation in temporal, parietal and frontal regions (see also Lennox et al., 1999; Shergill et al., 2004; Hoffman et al., 2008). Due to low temporal resolution of fMRI, the hypotheses of temporal order should be tested with effective connectivity analyses.

EMPIRICAL DATA

As the literature review presented above shows, most of the studies on properties of the PAC in connection to AVHs are confined to schizophrenia patients. Comparatively little is known about the functionality of the PAC in non-clinical hallucinations. Examining non-clinical individuals who experience hallucinations is of considerable interest, as it allows for "isolation" of the AVHs and examining it separately from any confounding variables such as medication or other psychopathological symptoms. Here, we present an analysis of the functional integrity of the PAC in non-clinical auditory hallucinators from an fMRI project on the neural correlates of non-clinical hallucinations. We used a modulated consonant-vowel dichotic listening task allowing for characterization of the PAC sensitivity to bottom-up saliency (intensity) differences and top-down attentional control, as well as the interaction of these factors.

MATERIALS AND METHODS

The group of NCHs consists of eight individuals recruited from the general population. Potential subjects were recruited from among the respondents of a population-based study on hallucinatory experiences (Kråkvik et al., in preparation), distributed to 8000 respondents across Norway, randomly chosen from the nationwide citizen register. Additionally, subjects were recruited via advertisements in the local newspaper, and the laboratory website. Screening for voice-hearing was based on a Norwegian translation of the Launay-Slade Hallucination Questionnaire (Bentall and Slade, 1985) items 1 and 2 (hearing voices when no one is around; or hearing own thoughts as voices). Screening also excluded individuals who had visited a physician or a psychologist due to hearing voices. Potential subjects were interviewed with respect to their hallucinatory experiences on the basis of the PSYRATS interview. All subjects presented here reported hearing voices in an awake state, excluding all individuals who had sleep-related hallucinations. In two subjects, the voices consisted of "mumbling" with no clear verbal content, the others reported hearing clear verbal content. All subjects had hallucinatory experiences at least once a month. In two subjects the onset of the voices was within the last 4 years, all others reported onset in childhood or early teenage years. None of the subjects reported taking any medication due to hearing voices, consistent with the screening criterion excluding any potential subjects who had seen a physician due to voice-hearing. Also, no subject reported taking antipsychotic medication at any point during life. The control group consisted of age-matched non-hallucinating individuals recruited from the community. As presented in **Table 1**,

Table 1 | Demographic characteristics of the non-clinical hallucinator (NCH) and non-hallucinating non-clinical control group.

	NCH	Control
Age, years (SD)*	39.3 (12.7)	36.3 (8.9)
Sex (male/female)	3/5	1/7
Handedness (right/left)	7/1	8/0
Education, years (SD)*	14.7 (2.3)	16.5 (2.7)
Medication[a]	1/8	0/8
Drugs[b]	2/8	0/8

*Note: *No significant difference between groups ($p > 0.05$).*

[a] Self-reported use of psychiatric medication within last 12 months (antidepressants, sedatives, other; excluding antipsychotic medication).

[b] Self-reported use of illicit drugs within last 12 months (cannabinoids, cocaine, LSD, amphetamines, opiates, other).

the groups did not differ in mean age or education. All subjects, except one subject in the NCH group, were right-handed as determined with Edinburgh Handedness Inventory. All subjects were native Norwegian speakers. The subjects' hearing threshold was assessed for frequencies 250, 500, 1000, 2000, and 3000 Hz, using the Hughson–Westlake audiometric test (Oscilla USB-300, Inmedico, Lystrup, Denmark). The study was approved by the Regional Committee for Medical Research Ethics in Western Norway (REK-Vest). The subjects gave informed consent prior to participation.

In order to measure the functioning of the PAC in response to both bottom-up stimulation as well as top-down modulation by attentional demands, we used a consonant-vowel dichotic listening task with attention and inter-aural intensity difference (IID) modification. Detailed description of the task has been provided elsewhere (see Hugdahl et al., 2008; Westerhausen et al., 2010; Falkenberg et al., 2011). In brief, the subjects are presented dichotic pairs of six consonant-vowel pairs (/ba/, /ga/, /da/, /pa/, /ka/, /ta/), spoken by an adult Norwegian male voice with constant intensity and intonation. Only syllables with the same voicing were paired, with stimulus onsets aligned. In each pair, the IID was gradually changed across stimulations to support the perceptual salience of left- and right-ear stimuli. Five levels of IID were used, in steps of 9 dB from strong left-ear preference (18 dB in favor of left ear) to strong right-ear preference (18 dB in favor of right ear). In the condition with 0 IID, the stimuli were delivered at 70 dB sound pressure level; in conditions with variable IID, sound pressure level was kept at 70 dB in the louder ear and reduced in the other ear. To avoid contamination with the MR scanner noise, the stimuli were presented during a silent gap achieved via sparse sampling procedure (see below). Another manipulated factor was attentional instruction. The subjects were instructed to attend and report only from either left- or right-ear stimuli, with the attentional direction alternated between stimulus presentations. The attention instruction appeared 1.5 s before each stimulus. It consisted of a text "attend left/right ear" as well as an arrow pointing in the corresponding direction, and was displayed in goggles mounted to the head coil (NordicNeuroLab, Bergen, Norway). The manipulation with the attention direction, in combination with the IID change, allows this task to be used to flexibly track the neural response to increasingly difficult auditory task (attention and IID favor opposing ears), while keeping constant the type of the of the auditory stimulation (consonant-vowel syllables) (see Hugdahl et al., 2008).

DATA ACQUISITION AND ANALYSIS

The images were acquired on a GE Signa scanner with field strength 3T. Functional scanning was performed using an echo-planar imaging (EPI) sequence ($TE = 30$ ms; flip angle 90 degrees), acquiring 25 axial slices, covering the cerebral hemispheres and most of the cerebellum. A sparse sampling protocol was used, with a TR of 3.5 s and a TA of 1.5 s, leaving "silent gap" of 2 s between each acquisition, during which the auditory stimulus presentation took place (see Van den Noort et al., 2008).

Behavioral data were analyzed using Statistica software (StatSoft Inc., Tulsa, USA). We examined the auditory acuity using an analysis of variance with factors Group (NCH, control) Frequency (250, 500, 1000, 2000, and 3000 Hz) and Ear (left, right). Dichotic listening behavioral performance data were analyzed using an analysis of variance with the factors Attention (FR, FL), IID (5 levels), Ear (left, right), and Group (NCH, controls). Greenhouse-Geisser correction for degrees of freedom was applied. *Post-hoc* tests were performed using Fisher's LSD procedure. The MR images were analyzed using the Statistical Parametric Mapping (SPM8) software (Wellcome Department of Cognitive Neurology, London, UK) running on Matlab R2010b (Mathworks Inc., Natick, MA, USA). Prior to statistical analyses, the data were preprocessed using the following steps. For each subject, the EPI images were realigned to the first image in the time series and unwarped. The corrected images were normalized to a standard EPI normalization template provided by SPM8 representing MNI space. Finally, the images were smoothed using an 8 mm full-width-at-half-maximum Gaussian filter. For statistical analysis, a general linear model was set up, consisting of ten predictors representing each of the experimental conditions (5 IID conditions and 2 attention conditions), convolved with a canonical hemodynamic response function. A temporal high-pass filter (cutoff at 128 s) was applied. The resulting individual beta images from all subjects were entered into a second-order analysis. The second-order model was set up as repeated measures design, including predictors for each of the experimental conditions, and a group factor. A separate model, which did not remove the within-subject variance, was constructed to examine main effect of group differences. All analyses were restricted to the PAC, with left and right hemispheres tested separately. The region of interest was defined using the SPM Anatomy Toolbox (Eickhoff et al., 2005). The PAC was defined as areas Te 1.0, Te 1.1, and Te 1.2 (Morosan et al., 2001), and saved as anatomical masks for left and right hemispheres separately. The areas involved in the mask are based on cytoarchitectonic studies by (Morosan et al., 2001), and cover the HG from medial (Te 1.1) to central (Te 1.0) and lateral (Te 1.2) portions. The central portion, area Te 1.0, is considered the "core" primary auditory area. The correction for familywise error (FWE) in multiple testing within the region of interest was performed using the SPM routines. The results were thresholded at $p < 0.05$ (FWE). An additional extent threshold of 5 voxels was used to prevent spurious voxels.

The MarsBaR toolbox (Brett et al., 2002) was used to extract the parameter estimates from peak voxels to illustrate the direction of results.

RESULTS

AUDITORY ACUITY

In the analysis of auditory acuity, there was a main effect of Group [$F_{(1, 14)} = 9.41$; $p = 0.008$; $\eta^2 = 0.14$], showing lower acuity for the NCH group. This effect was qualified by a significant interaction between Group and Frequency [$F_{(4, 56)} = 3.93$; $p = 0.023$; $\eta^2 = 0.1$]. *Post-hoc* tests showed that the control group had higher acuity at frequencies 2000 and 3000 Hz, with no significant difference at other frequencies. The Group factor did not interact with any other factor. As possible difference between hearing thresholds in left and right ear is of theoretical interest and relevant to the current paradigm, we performed an exploratory *post-hoc* analysis, testing ear acuities at each frequency step for both groups separately. The control group showed no differences between the ear acuities at any frequency. The NCH group showed higher acuity for left ear at 2000 Hz ($p < 0.01$) and a trend for higher acuity for left ear at 500 Hz ($p = 0.059$).

PERFORMANCE OF DL TASK

The results from the three-way analysis of variance are listed in **Table 2**. As can be seen, there was a trend for a main effect of Group [$F_{(1, 14)} = 3.26$; $p = 0.092$; $\eta^2 = 0.06$], reflecting the tendency for lower overall performance for the NCH group. There were no interactions involving the Group variable. Other effects showed the similar pattern as described in earlier reports (cf. Falkenberg et al., 2011), with a weak trend toward interaction of attention, IID and Ear [$F_{(4, 56)} = 2.10$; $p = 0.11$; $\eta^2 = 0.02$] reflecting how both attention as well as IID influenced the verbal reports. Thus, the NCH group showed a trend toward overall lower number of correctly reported syllables, but no difference from the control group in how attention and IID interact in influencing the performance.

IMAGING RESULTS

We first evaluated the planned contrast of Attention × IID, to verify whether the previously described modulation by this interaction in the superior temporal areas was present in the current sample. This was found to be the case: the Attention × IID interaction was significant in the PAC in both the left [MNI (*x*, *y*, *z*,): (−54, −24, 12)] as well as right [MNI (*x*, *y*, *z*): (60, −8, 6)] hemisphere. The direction of the interaction agreed with previous findings (Falkenberg et al., 2011), with increased activation when both attention and IID favored the same stimulus. Next, we examined whether this Attention × IID response interacts with the Group factor. There was no significant Attention × IID × Group interaction in left or right PAC, indicating that the NCH group and control group modulated their PAC similarly.

We performed a qualitative examination of the Attention × IID response in each group separately, to ensure that the response was in fact present in each group. The corresponding results are presented in **Figure 2**. As can be seen, both groups presented the bilateral Attention × IID response. There were subtle differences in the distribution of the activation within the subfields of the PAC, with the NCH group showing spread in more lateral direction. For the control group, over 70% of the activated voxels were situated within area Te 1.0 in both the left and right side, with relatively few voxels spreading in lateral direction to area Te 1.2 (left: 3.7%, right: 12.9%). By contrast, in the NCH group the activation was spread more laterally in both hemispheres. On the left side, the majority of the activated voxels were still within Te 1.0 (56.4%), but a larger proportion of the lateral region Te 1.2 was involved (23.0%). On the right side, most of the cluster was in fact situated within Te 1.2 (78.6%), with only 15.6% of the voxels in Te 1.0. As these differences were not strong enough to give rise to an interaction with the Group factor, this lateral shift in the contextual modulation of the PAC response should be considered as a tentative observation.

Finally, we examined the main effect of Group to see whether activation to the stimulation differed between the groups for the PAC. We found a difference in the right PAC, with the direction showing that the control group activated this area significantly stronger than NCH group (**Figure 3**). The cluster of activation was almost entirely situated within the area TE 1.0, covering a large portion of it (53.3%).

Table 2 | Behavioral data analysis for the dichotic listening task for NCH group and control group.

Effect	*F*	η^2	*p*
Group	3.26	0.06	0.092
Att	2.97	0.00	0.107
Att × Group	0.25	0.00	0.878
IID	**7.76**	**0.04**	**0.001**
IID × Group	0.73	0.00	0.516
Ear	**11.03**	**0.20**	**0.005**
Ear × Group	0.17	0.00	0.683
Att × IID	**12.88**	**0.17**	**0.001**
Att × IID × Group	0.87	0.01	0.395
Att × Ear	**6.23**	**0.05**	**0.026**
Att × Ear × Group	0.49	0.00	0.494
IID × Ear	**7.34**	**0.15**	**0.001**
IID × Ear × Group	1.32	0.03	0.282
Att × IID × Ear	2.10	0.02	0.108
Att × IID × Ear × Group	0.77	0.01	0.527

Note: Significant findings ($p < 0.05$) are marked in bold. F, f-statistic; η^2, effect size; p, significance level.

Results of an analysis of variance, with factors attention instruction (Att), interaural intensity difference (IID), Ear, and Group.

EXPLORATORY COMPARISON WITH CLINICAL HALLUCINATIONS

For the comparison with clinical hallucinations, we re-analyzed a partial sample from a previous study on schizophrenia patients (Falkenberg et al., submitted) with the same task and imaging parameters. We selected 8 subjects (3 males, 5 females), attempting the best possible age-match to the NCH subjects. The mean age of the final sample was 31.1 (standard deviation 9.9), which did not differ significantly from the NCH and control group [$F_{(2, 21)} = 1.1$; $p = 0.34$]. All subjects were right-handed, and the mean illness duration of the group was 6.9

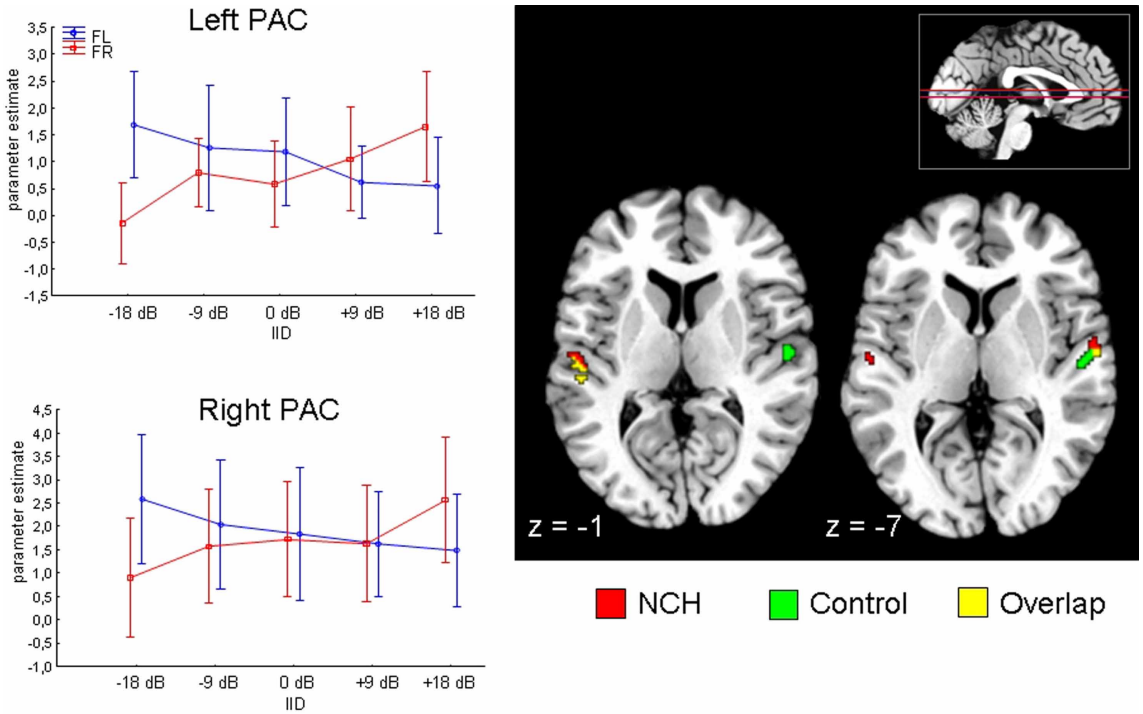

FIGURE 2 | Attention by IID interaction in the primary auditory cortex (PAC) projected on a brain template. Two axial slices are presented, at z-coordinate −1 and −7 (position of slice presented with red horizontal lines on inset in the right corner). Results from NCH (red) and control group (green) are plotted separately for illustrative purposes. Line graphs on the left side show changes in parameter estimates (arbitrary units) in the left and right PAC (peak voxel) to change in interaural intensity difference (IID) and attention (FR, forced-right; FL, forced-left), pooled across groups. Vertical lines represent 95% confidence intervals.

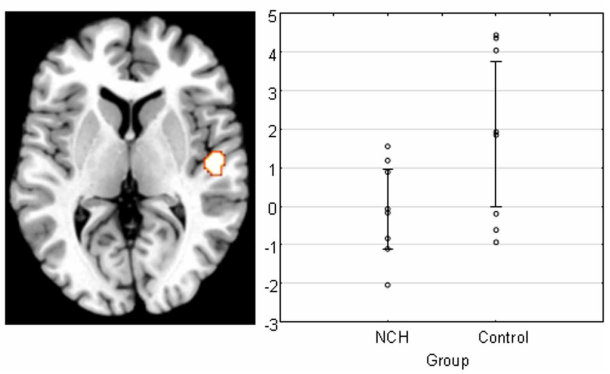

FIGURE 3 | Main effect of group across all levels of attention and IID in the right PAC projected on a brain template. Scatterplot shows the individual subjects' mean parameter estimate at peak voxel, demonstrating that the reduction of activation was consistent within NCH group. Lines represent 95% confidence intervals.

years. These subjects underwent an auditory task where the attentional demands and IID were manipulated identically to the study described above. However, the functional imaging session for these subjects included a "free-report" baseline task immediately preceding the attention and IID manipulation part. Consequently, as the structure of the data set was different from the NCH study described above, we present these data as a qualitative exploration of the Attention × IID interaction effect in the PAC within a schizophrenia group, rather than a direct statistical comparison of group differences with NCH group. We tested whether the schizophrenia sample showed the Attention × IID interaction in the PAC, as demonstrated in both control subjects as well as the NCH group. We could not find a significant interaction in the PAC in either hemisphere. Only when we exploratively used a non-corrected threshold of $p < 0.05$, small clusters of activation were found bilaterally (peak corrected p-value: left 0.18; right: 0.22). Thus, the schizophrenia group showed a qualitative difference in Attention × IID effect in comparison to NCH and control groups.

DISCUSSION

The results of this empirical study show subtle differences for the NCH group in auditory information processing. First, auditory threshold testing showed lower auditory acuity in the NCH group for high frequencies (2000 and 3000 Hz). Exploratory *post-hoc* tests at each frequency step showed that NCH group had significant ear acuity differences at 2000 Hz, with right ear acuity being lower. The energy of the consonant-vowel syllables used in the current study is predominantly represented within 1000 Hz range. Thus the lower acuity at the affected frequencies should not interfere with the current task. In agreement with this, there were no significant differences in the dichotic listening test performance.

While there was a weak trend toward group differences in the overall number of correct reports, the groups did not differ in how the attention and IID influence performance.

In the fMRI data, a significant difference between the NCH and control group was found in the right PAC. This difference was expressed as an overall reduced activation in the right PAC in the NCH group compared to the control group. This difference was confined to area Te 1.0, covering a large proportion of the implicated brain region. This cytoarchitectonically defined area has the widest layer IV of the subfields of the PAC, and receives the majority of the ascending projections from the medial geniculate body in the thalamus (Morosan et al., 2001). Thus, between-group differences in the response of this area to auditory stimulation indicate reduced functionality at the earliest steps of auditory processing. This observation may be interpreted as a parallel to the microstructural alterations in schizophrenia patients, and reduced activation in response to auditory stimulation in hallucinating patients, as discussed above.

In both groups, the bilateral PAC response was sensitive to the interaction between attention and IID. PAC showed increased activation when the attentional direction and IID favored the same ear (i.e., the "stronger" side had to be reported), and decreased activation when the attention and IID were conflicting (i.e., the "weaker" side had to be reported). Such a pattern of combined influences from stimulus features and attention in determining the activation of sensory cortex has been demonstrated in visual attention (Boynton, 2009), and can be interpreted to reflect early attentional modulation effects, e.g., within the biased competition framework (Desimone and Duncan, 1995). As the Attention × IID effect did not interact with the Group factor in either the left or right PAC, and exploratory *post-hoc* tests showed a significant effect for each group, it may be concluded that the NCH group is capable of attentional modulation of the PAC on equal level with the control group. In this, the NCH group shows a qualitative difference from the group of schizophrenia patients who did not show significant Attention × IID modulation in the PAC. A possible interpretation of the data is that a reduction in the PAC activation to external sounds is functionally related to the experience of hallucinations; whereas the preserved ability to modulate the PAC in agreement with the current task set is a protective factor which prevents negative consequences to general functioning. Thus, the current data suggest the possibility that the difference between clinical and non-clinical hallucinations may be expressed as difference in the ability to modulate the brain areas involved in hallucinatory experiences.

An exploratory examination of the spatial features of the Attention × IID effect suggested that there may be slight differences between the groups. In particular, the NCH group showed a lateral spread of the activation into the area TE 1.2, which was particularly pronounced in the right hemisphere. It is possible that the extension of the Attention × IID modulation of the NCH group into the lateral portion of the HG is a consequence of reduced functionality of the central region of the HG. HG demonstrates a "tonotopic" frequency-sensitive gradient, with increasing preference for lower frequencies from medial to lateral direction (Formisano et al., 2003; Humphries et al., 2010; Langers and van Dijk, 2012). Thus, the NCH group may have increased the modulation in the lateral regions to improve sensitivity to the lower-frequency components of the consonant-vowel syllables as a consequence of reduced functionality of the central region.

The main limitation of the current study is the relatively small number of participants. Thus, the negative finding of no difference in attentional modulation of PAC activation should be interpreted with caution due to limited statistical power. The pattern of results from the schizophrenia group, suggests that any dysfunction the NCH may experience in attentional modulation of PAC is not as severe as that observed in schizophrenia population. Due to the small sample size, the present results, albeit consistent with previous literature on the functioning of PAC in subjects with auditory hallucinations, should be considered preliminary, and need to be replicated in larger samples.

Another aspect is the larger number of females among the NCH group (5 subjects), which, considering the overall modest group size, may have influenced the results. We have shown previously that sex differences are not evident in neuronal activation for the type of dichotic listening task used here (Falkenberg et al., 2011; Hirnstein et al., in press), thus we do not consider it likely that the findings presented here are susceptible to sex distribution of the sample. Nevertheless, the trend in the present sample to be female-dominated is similar to other reports of neuroimaging data in NCHs [for example, consider reported male/female ratios such as 3/15 (van Lutterveld et al., 2010), 5/16 (Diederen et al., 2012), 11/24 (Diederen et al., 2010a), 13/22 (De Weijer et al., 2013)], but also in behavioral data. For instance, Sommer et al. (2010) report a sex distribution of 30 men and 73 women in their sample of NCHs. It remains to be examined whether this represents a true sex bias in tendency to experiencing non-clinical hallucinations, or can be explained by other factors, such as willingness to participate in psychiatric studies.

Finally, we note that while the paradigm used here to examine the attentional modulation of PAC has been previously demonstrated to be an effective measure to test the attentional and language networks of the brain (Westerhausen et al., 2010; Falkenberg et al., 2011), it cannot be excluded that it may be relatively less sensitive to subtle changes in the modulation of the PAC by attention. However, as behavioral data from the forced-attention dichotic listening paradigm has shown (Westerhausen and Hugdahl, 2010), a similar type of paradigm is generally sensitive to cognitive dysfunction, including multiple psychiatric conditions, but also, e.g., the effect of sleep deprivation in cognitively healthy young adults.

CONCLUSION

The majority of the studies examining the structural and functional properties of the PAC in relation to AVHs reports data from individuals with a schizophrenia diagnosis. Although AVHs are prevalent in this group, comparison with non-clinical, non-hallucinating control group may be confounded by not only other symptoms of schizophrenia, but also antipsychotic medication. In the schizophrenia group, the structural and functional properties of the PAC tend to show a relationship with AVHs, however, the literature is not entirely consistent. Schizophrenia patients have micro-and macrostructural alterations within the PAC, but a large part of the reports does not consider the hallucinatory status of

the patients, thus there remains the possibility that these findings may be associated with other symptoms of schizophrenia (such as delusions or cognitive decline), and therefore are not specifically associated with the experience of AVHs. There appears to be a relationship between AVH severity and cortical gray matter volume as measured with VBM, but more confirmatory evidence would be desirable before consensus can be reached. Reduced activation of the PAC in response to auditory stimulation, as measured with fMRI, seems to be characteristic of hallucinating subjects compared to non-hallucinating controls. For ERPs, neither MMN nor N100 appear to be specifically related to AVHs, whereas there are a few interesting reports showing that auditory steady-state response to 40 Hz stimulation is affected by AVHs. Behaviorally, AVHs are associated with reduced right-ear advantage in the consonant-vowel dichotic listening task. Relatively little is known about the functioning of PAC in non-clinical hallucinations. Our findings from a group of NCHs show reduction of the right PAC activation for speech sounds, but (in contrast to the group of schizophrenia patients) preserved modulation by interaction of stimulus properties and attention. It is possible that the context-appropriate modulation of the PAC constitutes a protective factor in distinguishing the non-clinical from clinical hallucinations. The precise characteristics of the PAC properties in relation to AVHs should be studied further, including subjects from clinical as well as non-clinical groups with AVHs, with particular emphasis on the functional and structural connectivity of the PAC, higher-order perceptual processing regions and brain areas providing top-down regulation.

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Voices to reckon with: perceptions of voice identity in clinical and non-clinical voice hearers

Johanna C. Badcock*[1,2] *and* ***Saruchi Chhabra*[1]**

[1] *School of Psychology, The University of Western Australia, Perth, WA, Australia*
[2] *Centre for Clinical Research in Neuropsychiatry, School of Psychiatry and Clinical Neurosciences, University of Western Australia, Perth, WA, Australia*

Edited by:
Frank Larøi, University of Liege, Belgium

Reviewed by:
Giuliana Lucci, IRCCS Santa Lucia of Rome, Italy
Emma Barkus, University of Wollongong, Australia

****Correspondence:***
Johanna C. Badcock, School of Psychology, The University of Western Australia, 35 Stirling Highway, Perth, WA 6009, Australia.
e-mail: johanna.badcock@uwa.edu.au

The current review focuses on the perception of voice identity in clinical and non-clinical voice hearers. Identity perception in auditory verbal hallucinations (AVH) is grounded in the mechanisms of human (i.e., real, external) voice perception, and shapes the emotional (distress) and behavioral (help-seeking) response to the experience. Yet, the phenomenological assessment of voice identity is often limited, for example to the gender of the voice, and has failed to take advantage of recent models and evidence on human voice perception. In this paper we aim to synthesize the literature on identity in real and hallucinated voices and begin by providing a comprehensive overview of the features used to judge voice identity in healthy individuals and in people with schizophrenia. The findings suggest some subtle, but possibly systematic biases across different levels of voice identity in clinical hallucinators that are associated with higher levels of distress. Next we provide a critical evaluation of voice processing abilities in clinical and non-clinical voice hearers, including recent data collected in our laboratory. Our studies used diverse methods, assessing recognition and binding of words and voices in memory as well as multidimensional scaling of voice dissimilarity judgments. The findings overall point to significant difficulties recognizing familiar speakers and discriminating between unfamiliar speakers in people with schizophrenia, both with and without AVH. In contrast, these voice processing abilities appear to be generally intact in non-clinical hallucinators. The review highlights some important avenues for future research and treatment of AVH associated with a need for care, and suggests some novel insights into other symptoms of psychosis.

Keywords: hallucination, schizophrenia, voice perception, voice identity, voice recognition

INTRODUCTION

Auditory hallucinations usually involve hearing voices that no-one else can hear (Bentall, 2003). People with schizophrenia hear voices, and people without schizophrenia (or any other form of mental illness) hear voices, though the prevalence rates differ (Romme and Escher, 1989; Beavan et al., 2011; Kelleher et al., 2012). In fact, there is growing recognition of a number of other differences in auditory verbal hallucinations (AVH) in clinical and non-clinical groups (Daalman et al., 2011; Badcock and Hugdahl, 2012a). These differences are of value in distinguishing those who do and do not need professional treatment for their voices, and why, (i.e., in uncovering the different mechanisms involved) (Badcock and Hugdahl, 2012b; Larøi, 2012). A key issue in this regard concerns the emotional response to AVH in these groups.

Hallucinated voices in schizophrenia are usually accompanied by significant distress and disruption to daily life (Nayani and David, 1996; Evensen et al., 2011) which often leads voice hearers to seek help for their experiences. In contrast, voice hearing in individuals without a diagnosis of mental illness is more commonly described as being positive, providing a sense of comfort, support or friendship and involving little or no interference to everyday functioning (Andrew et al., 2008; Daalman et al., 2011; reviewed in Lawrence et al., 2010; Hill and Linden, 2013). The reasons underlying these differences in distress between clinical and non-clinical voice hearers are, therefore, clinically significant and appear to be closely tied to how voices are interpreted or appraised (Chadwick and Birchwood, 1994; Garety et al., 2001; Morrison, 2001). In particular, perceptions and beliefs about the identity (e.g., as sounding like the voice of someone other than the self) and interpersonal attitude (power and intent) of hallucinated voices have been shown to be especially important (Nayani and David, 1996; Birchwood and Chadwick, 1997; Mawson et al., 2010). Within this literature, several important points emerge. First, beliefs about the identity and the content of AVH are clearly separable and sometimes incongruent[1]. This observation is consistent with current models of human voice perception and memory (see **Figure 1**) which show that different types of information (speech, identity, and affect) are processed somewhat independently in the brain (Stevens, 2004; Relander and Rämä, 2009; Belin et al., 2011). Second, beliefs about the identity of hallucinated voices appear to be more decisive in provoking distress than the content of AVH[2] (Peters et al., 2012; Hill and Linden, 2013). Finally, there is a growing body of evidence which suggests

[1]For example, voice hearers might hear positive content in their voices yet perceive the intent of the voice as malevolent and untrustworthy.
[2]We do not mean to imply that the content of AVH is unimportant to distress—it clearly is (Beavan and Read, 2010).

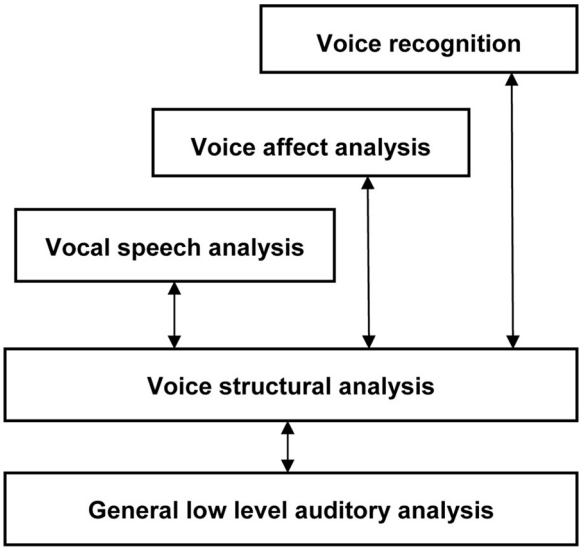

FIGURE 1 | The "auditory face" model of human voice perception, comprising separable functional pathways for processing speech, affect and identity information in voices [adapted from Belin et al. (2011)].

that the voice/voice hearer relationship mirrors "real" social relationships in the voice hearers' daily life (Birchwood et al., 2004; Hayward et al., 2011). Indeed, it has been argued that the defining essence of AVH includes voices with a quality of realness (i.e., distinct from internal dialog) that are assigned a characterized identity (e.g., to a male voice, or a spiritual force), which leads to a relationship with the voice (Beavan, 2011).

These studies highlight the importance of voice identity in distinguishing clinical and non-clinical hallucinations, and raise the possibility that the perception of voice identity in AVH is grounded in the mechanisms of human (i.e., real, external) voice perception. The goal of this review, therefore, is to critically evaluate current evidence on the perception and recognition of voice identity in clinical and non-clinical voice hearers in order to establish any similarities and differences in voice processing ability in these groups. We also aim to expand on the phenomenological description of identity in AVH by drawing on the qualities of real, external voices. The literature in this area is extremely diverse ranging from psychoacoustics to vocal stereotypes but has not previously been integrated with AVH. Here we try to synthesize some of this research to provide a deeper understanding of the features used to judge voice identity in real and hallucinated voices. Whilst we recognize that AVH occur in a range of other disorders, the scope of this review is limited to AVH in people with schizophrenia and in non-clinical (i.e., healthy) comparison groups.

PERCEPTION OF VOICE IDENTITY IN REAL AND HALLUCINATED VOICES

HUMAN VOICE PERCEPTION

Everyday social interactions rely heavily on the information conveyed in voice. In fact, the human voice has often been described as an "auditory face" (see **Figure 1**; Belin et al., 2004, 2011; c.f. Bruce and Young, 1986) since, along with linguistic information, it provides important social information about who you are (speaker identity) and how you feel (emotion). In particular, listeners are generally good at determining the physical characteristics of a speaker from their voice, including their gender (Mullennix et al., 1995; Whiteside, 1998; Sokhi et al., 2005; Pernet and Belin, 2012), approximate age (reviewed in Kreiman and Sidtis, 2011; Zäske and Schweinberger, 2011), size or strength (von Kriegstein et al., 2007; Sell et al., 2010) and attractiveness (Bruckert et al., 2010). For example, Krauss et al. (2002) found that age, height and sex estimated from a two sentence voice sample was only slightly less accurate than that made from a full length photograph. The perception of these physical aspects of identity relies on a variety of low-level acoustic features, including the fundamental frequency (F_0; perceived as voice pitch) and formant frequencies (F_n; related to timbre) of the voice (Hillenbrand, 2005; Ko et al., 2006; Latinus and Belin, 2011) which are correlated with speaker size. Consequently, speakers with either lower F_0 or F_n tend to be rated as larger and more masculine and also more attractive, if male, or less attractive, if female (Pisanski and Rendall, 2011). A common approach to examining the variations perceived in voices is to use multidimensional scaling of voice similarity judgments. Participants in such studies listen to a large number of pairs of voices and rate the degree to which the identity of the voices seem similar or dissimilar. What emerges from this approach is that, in fact, different speaker voices can be mapped as individual points within a common two-dimensional "voice space" (see **Figure 2** for an example, using data obtained from healthy controls and patients with schizophrenia, Chhabra et al., 2012a) defined by such acoustic characteristics (cf. Baumann and Belin, 2010).

In addition to these physical characteristics, we routinely gain an impression of a speaker's psychological and social identity from the voice alone, including their personality, regional origin (e.g., accent), and socio-economic status (Kreiman and Sidtis, 2011; Hu et al., 2012). Importantly, recent evidence suggests that we automatically evaluate voices along two fundamental dimensions of person perception: warmth and competence (Puts et al., 2007; Ko et al., 2009; McAleer et al., 2010; Teshigawara, 2011). Drawing on the Stereotype Content Model (SCM) of social cognition (Fiske et al., 2007; Fiske, 2012) the warmth dimension captures traits related to perceived intent (trustworthiness, friendliness) whilst the competence dimension reflects traits related to perceived ability (dominance, power). Though the evidence is still accumulating, these two dimensions of voice-based person perception (or vocal stereotypes) are clearly related to the physiologically determined acoustic characteristics of voices noted above (Puts et al., 2007; Wolff and Puts, 2010). For example, Puts and colleagues have shown that lower F_0, formants and formant dispersion (D_f) of a voice increases attributions of physical dominance and threat potential among men (Puts et al., 2007, 2012). Social psychologists also argue, however, that warmth and competence judgments are influenced by important social factors, such as perceived cooperativeness and social status cues (Fiske et al., 2007). Thus, individuals high in rank or status are perceived as more competent and powerful than those low in status;

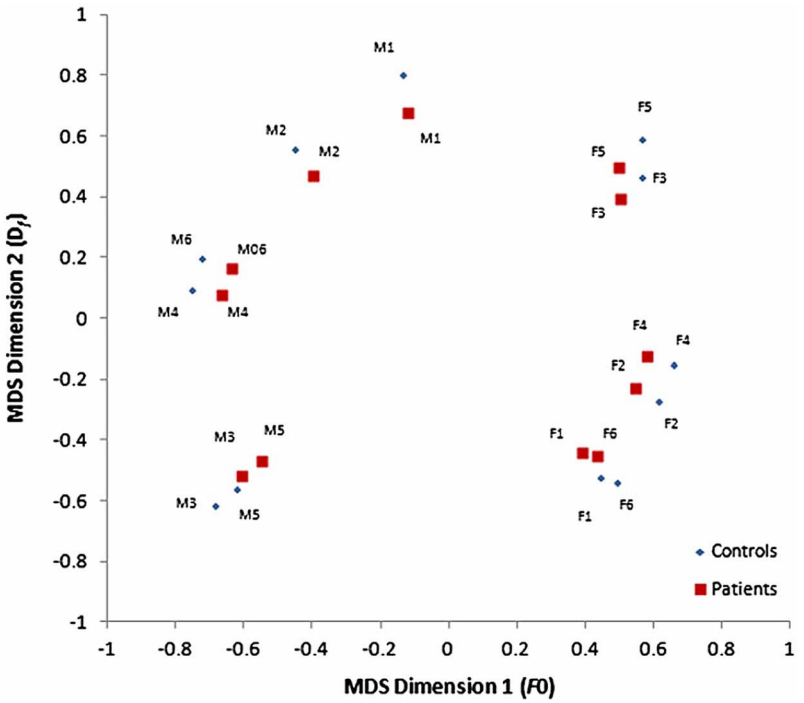

FIGURE 2 | Two-dimensional voice space derived from multidimensional scaling of voice dissimilarity ratings, defined by the fundamental frequency (F_0) and formant dispersion (D_f) of the voice, for healthy individuals and patients with schizophrenia. Voices that appear more widely separated in this voice space are perceived as more different than those closer together. [Reprinted from Chhabra et al. (2012a) with permission from Elsevier]. Note: *M*, male voices; *F*, female voices.

though again the F_0 of a voice may play an important role in communicating relative social status between speakers (Gregory and Webster, 1996; Gregory et al., 2001). Importantly, a number of studies have shown that perceptions of warmth and competence from voice also predict people's emotional and behavioral reactions to others, with important social outcomes (Klofstad et al., 2012; Tigue et al., 2012).

Together this literature suggests a biopsychosocial model of human voice perception in which sensory-acoustic and psychosocial cues are combined to: allow the listener to build a representation of speaker identity; discriminate between unfamiliar voices; and recognize familiar speakers—even when they are not in sight (see Belin et al., 2011; Gainotti, 2011; Latinus and Belin, 2011). This model provides a useful conceptual framework to explore the perception of voice identity in clinical and non-clinical hallucinators. To assist in this process a summary of some of the features used to judge voice identity is provided in **Table 1**. Though not an exhaustive list of features it encourages a detailed comparison (along rows) of identity in real and hallucinated voices, allowing gaps in the phenomenological evidence of AVH to be identified. It also allows a search for any systematic patterns (within columns) of physical and psychosocial features within voice hearing groups that tend to lead to distress.

ABNORMAL VOICE PERCEPTION

Focusing first on the physical characteristics of AVH, phenomenological surveys show that the perception of gender is a salient feature (McCarthy-Jones et al., 2012). Both male and female voices are heard, however, the former appear to be more common in clinical hallucinators, regardless of the gender of the voice hearer, whereas similar proportions of voice gender are reported by non-clinical voice hearers (Nayani and David, 1996; Stephane et al., 2003; Lawrence et al., 2010; McCarthy-Jones et al., 2012). Since the perception of masculinity, both between and within gender categories (Ko et al., 2009), usually arises from lower F_0 and F_n, this difference in gender bias in voice hearers may reflect subtle anomalies in basic sensory processing in clinical hallucinators only (see Badcock, 2010). It must be noted, however, that since this specific proposal has not yet been empirically assessed it is possible that the preponderance of male voices reflects a difference in [cognitive] bias rather than acoustic sensitivity. Nonetheless, subtle shifts toward lower F_0 and F_n would also lead hallucinated voices to sound like an older or stronger speaker. Lending some support to this proposal Nayani and David (1996) observed that hallucinated voices in schizophrenia often sounded "middle-aged" and, more recently, McCarthy-Jones et al. (2012) reported that the majority of clinical hallucinators only heard *adult's* voices. Critically, however, no equivalent data could be found for non-clinical voice hearers, so it is impossible to determine if there are consistent differences across a range of physical characteristics of voice identity between clinical and non-clinical hallucinators. It is important to note, however, that this combination of vocal features (high masculinity, and an older or stronger speaker) would typically be construed as a potential source of threat and could, therefore, contribute to the higher levels of distress associated with clinical

Table 1 | Features of voice identity perceived in real and hallucinated voices.

Healthy (non-patient)	Clinical AH	Non-clinical AH
PHYSICAL CHARACTERISTICS		
Gender	Bias to male voices	No gender bias
Age	Often middle-aged	"–"
Size/strength	"–"	"–"
Attractiveness	"–"	"–"
PSYCHOSOCIAL CHARACTERISTICS		
Competence/ability	Dominant/omnipotent	Less dominant
Intent/trustworthiness	Mostly malevolent	More benevolent, neutral
Personality	"–"	"–"
Accent	Sometimes different from voice hearer	"–"
Social status	Voices often judged of higher social rank	"–"
PERSONIFICATION		
Human	Real/familiar person	Real/familiar person
	Famous/public figure	Family members
Dehumanized	Robots	Voices of the deceased
Spiritual/supernatural	God, the Devil	Angels, spirits

Note: "–" - no information found.

AVH. In sum, despite the importance of characterized identity in AVH (Beavan, 2011), many of the physical characteristics of voice identity are under-investigated in studies of either clinical or non-clinical voice hearers. This state of affairs probably reflects a tradition of assessing only a particular set of features in hallucinated voices, together with a lack of suitably refined assessment tools or agreed terminology (Larøi et al., 2012).

Turning next to the psychosocial identity of AVH, following the influential studies of Chadwick and Birchwood (Chadwick and Birchwood, 1994; Birchwood et al., 2000, 2004; Connor and Birchwood, 2012) it is clear that both patient and non-patient voice hearers judge AVH in terms of their power (omnipotence, dominance) and intent (malevolence/ benevolence) which clearly embodies the fundamental dimensions of competence (ability, dominance) and warmth (intent) respectively, perceived in real, external voices (see **Table 1**). This finding is consistent with the notion that both real and hallucinated voices are constrained by the same underlying mechanisms of interpersonal cognition. Significantly, however, clinical hallucinators are more likely to perceive voices as omnipotent and malevolent compared to non-clinical voice hearers, whose voices are more often judged as neutral or benevolent (Hill and Linden, 2013). The processes underlying this difference are as yet unknown but, drawing from **Table 1**, could be coupled to the physical characteristics of AVH described above. In addition, the differences in behavioral and emotional reaction to hallucinated voices in clinical and non-clinical voice hearers can be readily understood within the warmth × competence person perception framework described above (Fiske et al., 2007). For example, voice hearers who perceive themselves to be of lower social rank (i.e., less competent) than others[3] also feel inferior and less powerful than their AVH, and behave accordingly (Connor and Birchwood, 2012; Paulik, 2012; Hill and Linden, 2013): thus, voices perceived as malevolent and omnipotent (i.e., cold and hostile, yet extremely competent) evoke fear and distress and are actively resisted, whilst those perceived to be benevolent (i.e., warm and trustworthy) are engaged with (Sayer et al., 2000; Peters et al., 2012).

Finally, as with real voices, AVH are often recognized as belonging to a particular person (i.e., personified; Stephane et al., 2003; David, 2004). For example, in one recent survey 70% of clinical hallucinators said their voices were similar to those of people who had spoken to them in the past (McCarthy-Jones et al., 2012), though strictly speaking this response might reflect an increased sense of familiarity with a voice, rather than actual recognition of the identity of the speaker. Conversely, in Lawrence et al. data, 70% of non-clinical voice hearers said the identity of their most dominant voice was unknown (Lawrence et al., 2010). Adding further to this issue, Daalman et al. reported similar rates of attribution of identity to a real or familiar person in clinical and non-clinical hallucinators (Daalman et al., 2011), whilst elsewhere it has been reported that patients often identified their AVH as belonging to public/famous figures, rather than the voices of family or friends as reported by non-clinical hallucinators (Leudar et al., 1997; Larøi, 2012). In sum, therefore, there appears to be both differences and similarities in personification between clinical and non-clinical voice hearers—but there is clearly a shortage of direct comparisons of speaker recognition between these groups. Given this limitation, it should be noted that research on beliefs about the origin of AVH may also be informative on personification, since these beliefs refer to identities perceived as real (i.e., human) or not (i.e., dehumanized or spiritual sources). These studies show that dehumanized (e.g., robots, deceased people) and spiritual (e.g., angels, God, the devil) voices occur in both clinical and non-clinical groups (Daalman et al., 2011), consistent with an enhanced perception of agency (competence) and experience (warmth) (cf. Gray et al., 2011), but again with differences in the valence of intent (harmful

[3]For example, due to individual differences in temperament, or early life experiences, such as trauma and abuse.

demons/devils vs. helpful angels/guardians) in those who seek help for their experiences (see **Table 1**).

What emerges from these comparisons is the extent of the similarity in hearing real and hallucinated voices, as well as some salient differences in the perception of voice identity between patient and non-patient voice hearers. An obvious question therefore arises, namely: do the differences in phenomenology of AVH in clinical and non-clinical voice hearers result from differences in the underlying mechanisms of human voice perception? Consequently, in the following section we provide a summary and critique of several recent studies which have examined the ability to process real, external voices in clinical and non-clinical hallucinators.

VOICE PROCESSING ABILITIES IN CLINICAL AND NON-CLINICAL HALLUCINATORS

Surprisingly few studies have disambiguated the role of voice specifically in AVH, from that of speech and language activation (see Koeda et al., 2006, for a neuroimaging example of how this can be done). Of those that have examined voice, the vast majority have investigated the processing of emotion in voice (emotional prosody) (Hoekert et al., 2007; Shea et al., 2007; Leitman et al., 2010, 2011; Alba-Ferrara et al., 2012a; Gold et al., 2012; Kantrowitz et al., 2013) rather than the recognition or discrimination of speaker identity. Given the partial segregation of emotion and identity in human voice perception (as shown in **Figure 1**), it is possible that processing of emotional prosody could be impaired in schizophrenia (as the literature suggests) with the representation of speaker identity being relatively spared. Evidence of such dissociations has previously been observed, for example, in patients with phonagnosia (Garrido et al., 2009; Hailstone et al., 2010). Nonetheless, recent empirical evidence (described below) suggests that this is not the case in individuals with schizophrenia, since evidence is slowly accumulating for a range of difficulties in voice identity processing that may be relevant to, though not necessarily specific for, the experience of AVH. Conversely, processing of voice identity seems to generally intact in non-clinical hallucinators—though as yet, too few studies have been conducted to be certain of these conclusions.

Two recent studies assessed the ability to recognize familiar voices in patients with schizophrenia, with very different methodologies. Zhang et al. (2008) asked schizophrenia patients with and without AVH to classify spoken voices as familiar (e.g., belonging to friends) or unfamiliar (e.g., those of strangers) as part of a neuroimaging study. The results indicated that voice recognition was impaired in patients with AVH compared to healthy controls, which the authors concluded was related to lower activation in the right superior temporal gyrus. Unfortunately, however, signal detection analysis wasn't used, so it is impossible to determine whether these clinical hallucinators had poorer sensitivity to familiar voices or, alternatively, a different response bias (such as a general tendency to classify voices as unfamiliar) compared to controls. In response to these criticisms, Alba-Ferrara et al. (2012b) adopted a signal detection procedure to examine voice recognition in schizophrenia using an established paradigm from the phonagnosia literature, involving presentation of both famous and non-famous voices. In addition to deciding whether the voices heard were famous or not, participants also had to rate the confidence of their responses (remember, know, or guess) and, where possible, recall the name or other details associated with the voice. The results of this more rigorous investigation showed that patients with schizophrenia, particularly those with AVH, performed poorly on this task: that is, they were less sensitive to famous voices than healthy controls, but did not differ in response bias. Thus, there appears to be a link between impaired voice recognition and AVH in schizophrenia (Alba-Ferrara et al., 2012b) which could contribute to the different phenomenological profile of clinical voice-hearers noted above. As noted by the authors, however, the AVH group in this study also rated higher on delusional thinking, and were not significantly different in sensitivity to famous voices than the non-hallucinating patient control group. It is possible, therefore, that voice recognition difficulties contribute specifically to AVH, or alternatively, they may contribute to symptoms that commonly co-occur with hallucinations (such as delusions) or to a broad range of symptoms (including AVH *and* delusions etc.), meriting further investigation. Another possibility is that abnormalities in voice recognition may be a factor that predisposes individuals to hallucinatory experiences, even in the absence of psychosis. Thus, a significant limitation of these previous studies is that they failed to examine the ability of non-clinical voice hearers to recognize external voices.

Our research group has employed a recognition memory task that overcomes this limitation by assessing the ability of non-clinical, as well as clinical, voice hearers to recognize words and voices and integrate this information in memory (Chhabra et al., 2012b). In this study, participants heard two different words spoken in two different voices in sequence, followed—after a brief delay—by a single spoken word probe. The participants had to judge if the probe was a match to one of the study items: that is, to decide if the *combination* of word and voice identity in the probe was exactly the same as one of the first two stimuli. Using signal detection analyses we showed that patients with schizophrenia—both with and without AVH—were impaired at binding words and voices (i.e., remembering who said what) and markedly less accurate in recognizing individual voices, whilst non-clinical voice hearers had no difficulty either binding information or—importantly—in recognizing new words and voices compared to non-hallucinating controls. Though further work is needed to replicate this finding, it suggests a discontinuity in voice recognition difficulties in clinical and non-clinical hallucinators that could flow through to the different characteristics of hallucinated voices in these groups. However, given the lack of specificity to AVH we cannot exclude the possibility that other symptoms of psychosis also arise from abnormalities in human voice recognition.

Whilst we can recognize the voices of people that we know, we can also distinguish new speakers from the features in their voice (see **Table 1**). Previous literature has shown that this ability to discriminate unfamiliar voices can be dissociated from impairments in voice recognition (Gainotti, 2011); hence clinical and non-clinical hallucinators could share anomalies in voice discrimination even though they differ in vocal recognition. To our knowledge, there have been no direct comparisons of voice

discrimination in clinical and non-clinical voice hearers within a single study. However, our research team used an identical voice discrimination task in two separate studies involving patients with AVH and healthy hallucination prone subjects respectively, and found once again that clinical and non-clinical hallucinators differed in their processing of voices (Chhabra et al., 2012a,c). Both of these studies relied on multidimensional scaling (MDS) of voice similarity judgments, since this technique has previously been used to examine how healthy listeners differentiate separate voice identities (Baumann and Belin, 2010).

In the first of these studies (Chhabra et al., 2012a) we asked patients with schizophrenia, with and without AVH, and healthy age-matched controls to rate the degree of dissimilarity between (same sex and different sex) pairs of unfamiliar voices saying the same three-syllable words. A simple MDS solution for the dissimilarity matrices was found, for both patients and controls, with axes corresponding to the F_0 and formant structure (D_f) of the voice. This two-dimensional voice space is similar to that described previously by Baumann and Belin (2010)[4] and suggests that people with schizophrenia represent external voices in a similar way to healthy controls. However, our analyses also showed that both patients groups (i.e., those with and without hallucinations) made significant less use of resonance cues (i.e., D_f) to discriminate voices compared to controls (see **Figure 2**), pointing to some potentially important differences in voice processing abilities in people with schizophrenia. Since subtle alterations in D_f (described above) have been linked to perceptions of masculinity and dominance (Ko et al., 2006; Puts et al., 2007, 2012) one intriguing possibility that emerges from our findings is that anomalies in vocal resonance shape perceptions of power and dominance in AVH and in other symptoms of psychosis (e.g., persecutory delusions). Another intriguing possibility is that the differences in low level acoustic analysis drive the "otherness" or alien quality of hallucinated voices in clinical groups[5]. Though clearly speculative, these proposals may offer new insights into the pathways to psychosis (Smeets et al., 2012) and deserve further investigation.

In the second of our studies we used the same voice similarity judgment task with a group of young adults (undergraduates) who were either predisposed to hallucinate or not (assessed with the Launay Slade Hallucination Scale-Revised; Bentall and Slade, 1985) but had no current, previous or family history of psychosis (Chhabra et al., 2012c). We found the same two-dimensional MDS voice space, defined by F_0 and D_f, was used to represent voice identities, as in our first study, but there were no significant differences between high and low hallucination-prone groups. Importantly, the difference in outcome of these studies cannot be due to differences in stimuli or method, since the same task and procedure was used across both. Together our findings indicate that voice discrimination is impaired in clinical hallucinators but intact in non-clinical voice hearers. However, given these data have not yet been replicated, or extended to other types of non-clinical hallucinators (Larøi, 2012), further work will be needed to determine the robustness of our conclusions.

SUMMARY AND CONCLUSIONS

The phenomenology of identity in AVH is often scantily assessed, limited to the gender or the age of the voice (Larøi et al., 2012; McCarthy-Jones et al., 2012). By drawing on the literature on human voice perception a more comprehensive understanding of identity in AVH can be gained, ranging from the physical characteristics to the psychosocial identity of hallucinated voices. This multifaceted perspective to the perception of voice identity may also be helpful in the development of refined assessment tools for use in clinical practice, or in therapeutic settings aimed at relationships with voices (Pérez-Álvarez et al., 2008; Hayward et al., 2011).

Studying similarities and differences in voice identity perception between clinical and non-clinical hallucinators is also an important issue, with potential implications for early detection of psychosis and/or distinguishing who does/does not need treatment. Significant differences have been shown to be apparent across different levels of identity between clinical and non-clinical hallucinators. The overall profile of more masculine, dominant, powerful, and negatively personified voices in patients with schizophrenia clearly evokes higher levels of distress and, importantly, may point to systematic (i.e., rather than random) changes in perception that require further investigation. Yet recent data shows that psychotic and non-psychotic voice hearers are not easily differentiated in terms of cortical activation (Diederen et al., 2012). There may be many explanations for this discrepancy, but at least one possibility is that the common areas of activation in clinical and non-clinical hallucinators have different causal drivers (Diederen et al., 2012). Moreover, the limited sensitivity in current neuroimaging approaches means that future studies must adopt more sensitive techniques to elucidate the specific neural mechanisms underlying differences in voice identity in clinical and non-clinical voice hearers (cf. Hill and Linden, 2013). Furthermore, this physiological perspective can also now be coupled with the role of social factors in the experience of AVH, providing some interesting new directions for future research. Taking an embodied cognition perspective (Fay and Maner, 2012) for example, do dysfunctional social interactions involve sensory acoustic signals that promote perceptions of ill-intent in both real and hallucinated voices?

Finally, as a result of recent cognitive studies, a major difference in voice processing abilities in patient and non-patient AVH seems to be emerging, in that significant anomalies recognizing and discriminating human voices have been noted in patients with schizophrenia that do not appear to be present in non-clinical hallucinators. Currently, we can only speculate as to whether the observed impairments in voice cognition are directly relevant to the perception of identity in clinical AVH, since research on the processing of real, external voices has proceeded relatively independently from that on phenomenology of AVH. At the same time it seems that poor voice processing skills may be shared with other symptoms of psychosis since neither voice recognition failures nor differences differentiating between

[4]The stimuli used by Baumann and Belin (2010) were brief vowel sounds, rather than words. Their two-dimensional voice space was defined by the average fundamental frequency (F0) of phonation and the average first formant frequency (F_1).

[5]Thank you to one of the reviewers for this suggestion.

unfamiliar speakers were specifically associated with AVH. How the processing of voice identity contributes to other symptoms is unknown, and will require further consideration, though one likely point of convergence is in the experience of paranoia, given that people with persecutory delusions have a tendency to perceive negative intent in others (Combs et al., 2009). In this context, it would be interesting to examine the developmental trajectories of voice processing abilities, since this may be helpful in revealing if there are different functional pathways in clinical and non-clinical voice hearers.

In conclusion, the current evidence suggests there are many similarities in the physical and psychosocial characteristics of real and hallucinated voices—consistent with the notion that AVH are grounded in the mechanisms of human voice perception (Kompus et al., 2011; Aleman and Vercammen, 2012). Indeed, by harnessing current models of human voice perception (Belin et al., 2011) to AVH we may generate more integrated, testable models of hallucinated voiced which go beyond current models of AVH and auditory perception competing for the same speech and language resources, to encompass the wealth of information conveyed in voice (Badcock, 2010; Allen et al., 2012; Hugdahl et al., 2012).

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Cerebral responses to vocal attractiveness and auditory hallucinations in schizophrenia: a functional MRI study

Michihiko Koeda[1,2]*, Hidehiko Takahashi[3], Masato Matsuura[4], Kunihiko Asai[5] and Yoshiro Okubo[2]

[1] *Voice Neurocognition Laboratory, The Centre for Cognitive Neuroimaging, The Institute of Neuroscience and Psychology, University of Glasgow, Glasgow, UK*
[2] *Department of Neuropsychiatry, Nippon Medical School, Tokyo, Japan*
[3] *Department of Psychiatry, Kyoto University, Kyoto, Japan*
[4] *Department of Biofunctional Informatics, Tokyo Medical and Dental University, Tokyo, Japan*
[5] *Asai Hospital, Chiba, Japan*

Edited by:
Paul Allen, King's College London, UK

Reviewed by:
Thomas P. White, King's College London, UK
Renaud Jardri, University Medical Centre of Lille, France

****Correspondence:***
Michihiko Koeda, Department of Neuropsychiatry, Nippon Medical School, 1-1-5 Sendagi, Bunkyo-ku, Tokyo 113-8603, Japan.
e-mail: mkoeda@nms.ac.jp

Impaired self-monitoring and abnormalities of cognitive bias have been implicated as cognitive mechanisms of hallucination; regions fundamental to these processes including inferior frontal gyrus (IFG) and superior temporal gyrus (STG) are abnormally activated in individuals that hallucinate. A recent study showed activation in IFG-STG to be modulated by auditory attractiveness, but no study has investigated whether these IFG-STG activations are impaired in schizophrenia. We aimed to clarify the cerebral function underlying the perception of auditory attractiveness in schizophrenia patients. Cerebral activation was examined in 18 schizophrenia patients and 18 controls when performing Favorability Judgment Task (FJT) and Gender Differentiation Task (GDT) for pairs of greetings using event-related functional MRI. A full-factorial analysis revealed that the main effect of task was associated with activation of left IFG and STG. The main effect of Group revealed less activation of left STG in schizophrenia compared with controls, whereas significantly greater activation in schizophrenia than in controls was revealed at the left middle frontal gyrus (MFG), right temporo-parietal junction (TPJ), right occipital lobe, and right amygdala ($p < 0.05$, FDR-corrected). A significant positive correlation was observed at the right TPJ and right MFG between cerebral activation under FJT minus GDT contrast and the score of hallucinatory behavior on the Positive and Negative Symptom Scale. Findings of hypo-activation in the left STG could designate brain dysfunction in accessing vocal attractiveness in schizophrenia, whereas hyper-activation in the right TPJ and MFG may reflect the process of mentalizing other person's behavior by auditory hallucination by abnormality of cognitive bias.

Keywords: attractiveness, auditory hallucinations, schizophrenia, greeting, cerebral laterality, social communications, functional MRI

INTRODUCTION

Auditory hallucinations and thought disorder are the main symptoms of schizophrenia, and these symptoms profoundly affect the neural basis of social communications as well as behavior (Brune et al., 2008; Bucci et al., 2008; Wible et al., 2009; Kumari et al., 2010; Granholm et al., 2012; Waters et al., 2012). In order to understand these psychiatric symptoms in schizophrenia, it is important to verify the pathophysiology of cerebral function in auditory communications.

For healthy people, greeting conversations are very essential tools for communicating socially with family, friends, and community. Since favorable greetings strengthen cordial relationships with colleagues, maintaining the skill of socializing with greeting conversations is especially significant (Gronna et al., 1999; Barry et al., 2003). One of the main cognitive models in schizophrenia proposes that hallucinations arise from impaired self-monitoring and abnormality of cognitive bias (Allen et al., 2004). Some studies indicate that schizophrenia patients tend to misapprehend inner speech as external speech by the disturbance of self-monitoring (Morrison and Haddock, 1997; Stein and Richardson, 1999; Ford et al., 2001; Allen et al., 2004). A recent study has suggested that auditory hallucination in schizophrenia may be caused by both impaired brain function in auditory processing and disturbance of attention bias toward internally generated information (Kompus et al., 2011). If patients with schizophrenia mistake unfavorable greetings through their distorted thinking while listening to favorable greetings, social isolation and emotional withdrawal could be produced. In addition, if schizophrenia patients have auditory hallucination, misjudgment of favorable/unfavorable greeting may be induced by abnormality of cognitive bias. However, it is unclear whether schizophrenia patients with auditory hallucinations have impaired abilities to differentiate between favorable and unfavorable greetings.

Functional magnetic resonance imaging (fMRI) studies in schizophrenia have investigated the neural basis of impairment of paralinguistic processing such as emotional prosody and affective vocalizations (Mitchell et al., 2004; Leitman et al., 2007, 2011; Bach et al., 2009; Dickey et al., 2010) as well as language

processing (Woodruff et al., 1997; Kircher et al., 2001; Mitchell et al., 2001; Sommer et al., 2001; Schettino et al., 2010). A previous fMRI study concerning the recognition of emotional speech prosody demonstrated that temporal activation in schizophrenia patients was predominant in the left hemisphere, whereas that in normal control subjects showed right hemispheric dominance (Mitchell et al., 2004). Another fMRI study also found right-lateralized activation in healthy controls in the temporal-parietal region while listening to emotional prosody including meaningless syllables (Bach et al., 2009). In schizophrenia patients, however, this right-lateralized pattern was even more pronounced. These findings indicate that cerebral laterality for emotional prosody in schizophrenia patients could be shifted in comparison to the typical right-lateralized activation in normal control subjects.

We consider that it is important to investigate the relationship between psychiatric symptom and cerebral function in behavior social as well as emotional prosody. Especially, evaluating facial attractiveness is a favorable behavior associated with social communication (Kampe et al., 2001; Winston et al., 2007). Recent studies have demonstrated that facial attractiveness can activate doperminergic regions including amygdala and orbitofrontal cortex that are strongly related to reward prediction (Winston et al., 2007; Cloutier et al., 2008; Chatterjee et al., 2009; Tsukiura and Cabeza, 2011). Clarifying brain mechanisms in these reward systems is very important for understanding the pathophysiology of schizophrenia. A recent study has shown that in schizophrenia, the ratings of attractiveness of unfamiliar faces were significantly reduced compared to healthy subjects (Haut and MacDonald, 2010). Further, this study has demonstrated that when the patient had severe persecutory delusions, attractiveness ratings decreased (Haut and MacDonald, 2010). As well as facial perception, auditory attractiveness in schizophrenia will be a challenging research topic. A recent fMRI study in healthy subjects on auditory attractiveness has demonstrated bilateral superior temporal gyrus (STG) and inferior frontal gyrus (IFG) activates when participants judged whether voices sounded attractive or not. This study suggests that the roles of STG and IFG are essential for perceiving auditory attractiveness (Bestelmeyer et al., 2012). The regions of STG and IFG are heavily implicated in the functional anatomy of auditory hallucination. A recent meta-analysis demonstrated that schizophrenia patients with auditory hallucination had significantly increased activity in fronto-temporal areas involved in speech generation and speech perception (Jardri et al., 2011). A recent fMRI study demonstrated that cerebral activation in fronto-temporal regions is greater than in healthy individuals during AVH but lower during environmental-stimulus processing (Kompus et al., 2011). However, to our knowledge, no study has ever investigated the cerebral response to auditory attractiveness in schizophrenia.

The aim of our research is to clarify cerebral response to auditory attractiveness when patients with schizophrenia are listening to greetings. Greeting conversations are crucial to maintaining social interactions. An fMRI study of social perception indicated that the left prefrontal and left IFG were activated when the subjects judged whether two people were friends or enemies (Farrow et al., 2011). Since the recognition of friendliness and favorability is essential for greeting conversations, the patients with schizophrenia could change cerebral function due to psychiatric symptoms such as auditory hallucinations. To investigate this pathophysiology, using completely the same greetings, we compared cerebral activation when the subjects judged favorability (recognition of auditory attractiveness) and cerebral activation when the subjects judged gender (recognition of non-auditory attractiveness). Prior to the current experiment, we hypothesized that cerebral functions underlying the perception of auditory attractiveness could be impaired in STG and IFG by occurring auditory hallucination.

MATERIALS AND METHODS

SUBJECTS OF fMRI STUDY

Eighteen right-handed controls (9 males and 9 females, mean age 35.5 years, $SD = 8.6$) and 18 schizophrenia patients (10 males and 8 females, mean age 35.7 years, $SD = 8.4$) participated in the present study. As for the subtypes of 18 schizophrenia patients, all patients were diagnosed with paranoid schizophrenia. All 18 patients were receiving neuroleptics (mean risperidone equivalent daily dosage = 4.7 mg, $SD = 2.2$; 9 patients, risperidone; 4 patients, olanzapine; 2 patients, haloperidol; 1 patient, quetiapine; 1 patient, sulpiride; 1 patient, perphenazine). Risperidone equivalents were calculated based on published equivalencies for atypical antipsychotics by Inagaki and Inada (2006). All 36 volunteers were native speakers of Japanese. None of the control subjects was taking alcohol or medication at the time, nor did they have a history of psychiatric disorder, significant physical illness, head injury, neurological disorder, or alcohol or drug dependence. After complete explanation of the study, written informed consent was obtained from all subjects, and the study was approved by the relevant ethics committee. Schizophrenia patients were diagnosed by MK and the attending psychiatrists on the basis of a review of their charts and a conventionally semi-structured interview (First et al., 1995). After the structural interview was performed using PANSS, the patient was synthetically diagnosed according to the diagnostic guidelines of the ICD-10: Classification of Mental and Behavioral Disorders. Exclusion criteria were current or past substance abuse and a history of alcohol-related problems, mood disorder, or organic brain disease. All patients were recruited from the outpatient unit of Asai Hospital. Mean illness duration was 12.3 ($SD = 8.0$) years. Clinical symptoms were assessed by Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). Sum scores for positive and negative symptoms were calculated, with the positive symptom subscale including the following seven items: Delusion, Conceptual disorientation, Hallucinatory behavior, Excitement, Grandiosity, Suspiciousness, and Hostility. The negative symptom subscale also included seven items: Blunted affect, Emotional withdrawal, Poor rapport, Passive/apathetic social withdrawal, Difficulty in abstract thinking, Lack of spontaneity and flow of conversation, and Stereotyped thinking. The mean score of PANSS was 32.4 ($SD = 10.4$). The mean positive symptom score was 15.1 ($SD = 6.4$), mean negative symptom score was 20.7 ($SD = 6.2$), and mean score of general psychopathology was 32.3 ($SD = 7.9$). The candidates were carefully screened and standardized interviews were conducted by a research psychiatrist (MK)

and the attending psychiatrists. They did not meet the criteria for any psychiatric disorders. There was no significant difference in the mean period of education between the controls and patients (mean ± *SD*; patients 13.3 ± 1.3 years, control subjects 13.0 ± 1.0 years; $p > 0.05$, *t*-test). Schizophrenia patients were 14 right-handed and 4 left-handed participants according to the Edinburgh Handedness Inventory (EHI) (Oldfield, 1971). Mean (± *SD*) EHI in right-handed 14 patients was 90.4 ± 13.0. The EHI score of the 4 left-handed patients was −85, −73, −46, −46, respectively. All control subjects were right-handed, and mean (± *SD*) EHI was 96.1 ± 4.7.

RECORDED VOICE

As a sample for clarifying emotional response in voice recognition, Japanese greetings were recorded from 6 native speakers (3 males, 3 females). Ten greetings were recorded: Ohayo (Good Morning), Yah (Hi), Konnichiwa (Good Afternoon), Konbanwa (Good evening), Arigato (Thank you), Domo (Thank you), Irasshai (Welcome), Genki (How are you?), Dozo (Please), and Hisashiburi (Long time no see). These 10 greetings were recorded expressing favorable emotion (positive greeting), unfavorable emotion (negative greeting), or without emotion (neutral greeting), resulting in 180 stimuli in total. The voice was recorded using an IC recorder (Voice-Trek DS-71, Olympus) in a perfectly quiet room. In both the preliminary experiment and the fMRI experiment, all speakers were unknown to all participants.

PRELIMINARY EXAMINATION

Prior to the fMRI study, we asked 32 different control volunteers (16 males and 16 females) to judge the favorability of all 180 greetings (60 favorable, 60 non-favorable, and 60 neutral greetings) using a questionnaire with a 10-point scale. We defined "favorable" if the scale approached 10, whereas "unfavorable" if the scale approached 0. Based on the responses of the 32 subjects, greetings were considered positive if their average score was higher than 6.5. If the average score was less than 3.5, the greetings were considered negative. Neutral greetings were defined as being located within the average score range of 4.5–5.5. Based on these results, each speaker's greeting was evenly selected for the favorable, neutral, and unfavorable greetings.

INSTRUMENTS USED FOR PRESENTATION OF STIMULI

Stimuli were presented by the use of Media Studio Pro (version 6.0 Ulead Systems, Inc., Ulead Systems, Taiwan) running under Windows XP. Subjects listened to the sound stimuli through headphones attached to an air conductance sound delivery system (Commancer X6, MRI Audio System, Resonance Technology Inc., Los Angeles, CA). The average sound pressure of stimulus amplitude was kept at 80 dB.

EXPERIMENT DESIGN

The subjects listened for a total of 10 min and 40 s: 20 s of silence, 5 min of attentive listening (Part A), 20 s of silence, and 5 min of attentive listening (Part B). Part A and Part B each consisted of 60 paired greetings (30: neutral-positive, 30 neutral-negative), with each greeting taking 0.5 s, and pause of 1 s; all together, each of the 10 greetings was spoken 12 times (6 times as a neutral greeting, 3 times as a positive greeting, and 3 times as a negative greeting). In Part A, there were equal numbers of greetings by male pairs and female pairs. The subjects judged which greeting of a pair was more favorable. Using 30 neutral-positive and 30 neutral-negative pairs, we examined the degree of difference in favorability. We named Part A: Favorability Judgment Task (FJT). In Part B, 30 pairs were the same gender and 30 pairs were different gender. The subjects judged whether the speakers in each pair were the same gender or not. We named Part B: Gender Discrimination Task (GDT). The pairings of neutral-positive and neutral-negative appeared in random order (**Figure 1**).

FUNCTIONAL MRI ACQUISITION

The images were acquired with a 1.5 Tesla Signa system (General Electric, Milwaukee, Wisconsin). Functional images of 264 volumes were acquired with T2*-weighted gradient echo planar imaging sequences sensitive to blood oxygenation level dependent (BOLD) contrast. Each volume consisted of 20 transaxial contiguous slices with a slice thickness of 6 mm to cover almost the whole brain (flip angle, 90°; time to echo [TE], 50 ms; repetition time [TR], 2.5 s; matrix, 64 × 64; field of view, 24 × 24).

IMAGE PROCESSING

Data analysis was performed with statistical parametric mapping software SPM8 (Wellcome Department of Cognitive Neurology, London, United Kingdom) running with MATLAB (Mathworks, Natick, Massachusetts). All volumes of functional EPI images were realigned to the first volume of each session to correct for subject motion, and the mean functional EPI image was spatially coregistered with the anatomical T1 images. The anatomical T1 image was segmented into the image of gray matter and white matter. Based on the segmented T1 image of each subject, the anatomical template of diffeomorphic anatomical registration through an exponentiated Lie algebra (DARTEL) was created (Ashburner, 2007). All realigned EPI images were spatially normalized to the standard space defined by the Montreal Neurological Institute (MNI) template with DARTEL template and flow field of each subject. Functional images were spatially smoothed with a 3-D isotropic Gaussian kernel (full width at half maximum of 8 mm). A temporal smoothing function was applied to the fMRI time series to enhance the temporal signal-to-noise ratio. The significance of hemodynamic changes in each condition was examined using the general linear model with boxcar functions convoluted with a hemodynamic response function. The *t*-values were then transformed to unit normal distribution, resulting in z-scores. The models of 4 contrasts were created by event-related design during the fMRI experiments. In FJT task, 2 contrasts [30 pairs of neutral-favorable greetings (FAV) and 30 pairs of neutral-unfavorable greetings (NFV)] were made. In GDT task, 2 contrasts [30 pairs of same gender greetings (SAM) and 30 pairs of different gender greetings (DIF)] were made (**Figure 1**).

STATISTICAL ANALYSIS

Group analysis (2nd-level analysis in spm8) was performed on the data for 18 control subjects and 18 schizophrenia patients using a random effect model on a voxel-by-voxel basis. FMRI data

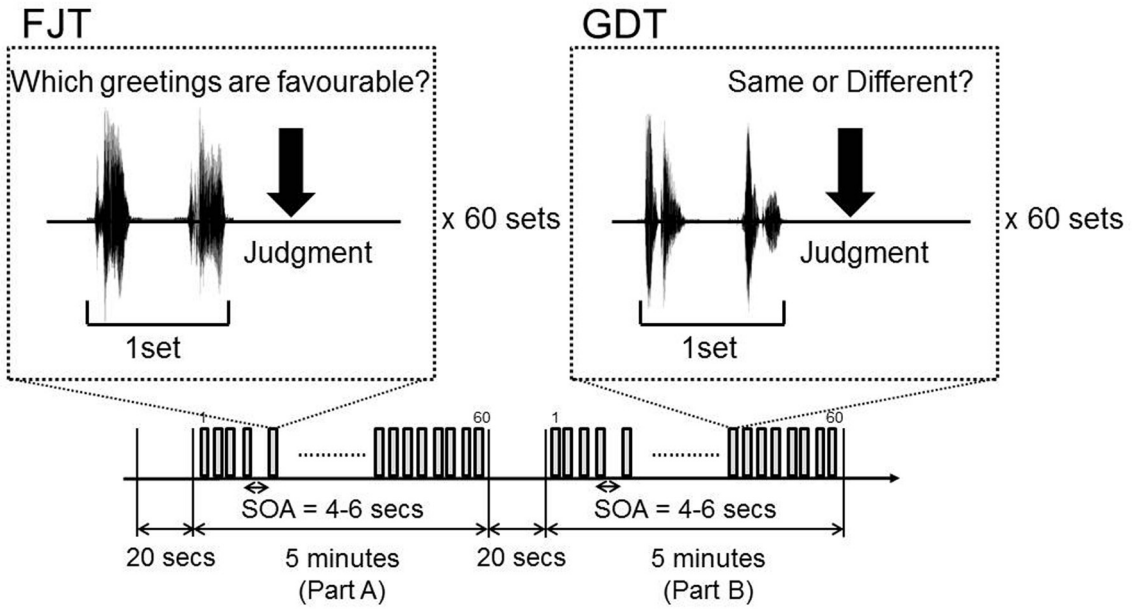

FIGURE 1 | Experimental design of fMRI Part A is Favorability Judgment Task (FJT). Part B is Gender Discrimination Task (GDT).

was analysed based on the 2 × 2 × 2 full factorial model with the factors of Group (control subjects/schizophrenia patients), Task (FJT/GDT) and Within-task (FJT: FAV/NFV, GDT: SAM/DIF) (FDR-corrected voxel-level threshold of $P < 0.05$). By using rfx-plot (Glascher, 2009), cerebral activation at the regions of interests (ROIs) was investigated. In main effect of Group and main effect of Task, ROIs were focused on the coordinates of the peak voxel of activation under FDR-corrected voxel-level threshold of $P < 0.05$. For main effect of Group, cerebral laterality of ROIs was evaluated. In order to investigate cerebral laterality, ROIs were also set on the hemispheric symmetrical region of the MNI coordinates. By using these symmetrical ROIs, the laterality index (LI) was calculated [LI = (L − R)/(L + R) × 100; L = beta estimates of left hemispheric activation, R = beta estimates of right hemispheric activation]. The formula of the LI was calculated based on previous studies (Koeda et al., 2006, 2007; White et al., 2009). In calculation of LI, the beta value of each subject used was either plus or zero, and minus beta values were excluded. In this ROI analysis, correlation between EHI score and beta value was evaluated to investigate the influence of handedness. Correlations between the subscores of PANSS (total scores of positive symptoms, negative symptoms, and general psychopathology) and cerebral activation under FJT vs. GDT contrast were calculated based on simple regression in schizophrenia patients. In linear regression analyses, the three subscores of PANSS were used, each with one predictor, respectively. In the analysis of full factorial design, the statistical threshold used was $p < 0.05$, voxel level, FDR-corrected. In the linear regression analysis, the statistical threshold used was $p < 0.0001$, voxel level, uncorrected (FDR < 0.25, voxel level corrected). Further, the correlation was analysed between the beta value of FJT at the specific ROIs of main effect of Group (**Figure 10**).

RESULTS

PRELIMINARY EXPERIMENTS

Favorability was rated by 32 different control volunteers using a scale of 1–10. **Figure 2** shows the distribution of the rating of favorability. Based on the definition of favorability (Materials and Methods: Preliminary Examination), 30 favorable vocalizations (rating average more than 6.5; 12 males and 9 females), 60 neutral vocalizations (rating average between 4.5 and 5.5; 17 males and 18 females), 30 unfavorable vocalizations (rating average less than 3.5; 7 males and 13 females) were selected. The mean ratings (± *SD*) of favorability were 2.3 ± 0.6 (unfavorable), 4.9 ± 0.3 (neutral), and 7.5 ± 0.6, respectively. Analysis of variance (One-Way ANOVA) was significantly different [$F_{(2,\ 117)} = 1006.9$, $p < 0.001$]. Multiple comparisons were also significant (unfavorable vs. neutral: 2.6 ± 0.1, $p < 0.001$; neutral vs. favorable: 2.6 ± 0.1, $p < 0.001$; unfavorable vs. favorable: 5.2 ± 0.1, $p < 0.001$).

Behavioral data (accuracy)

In the fMRI experiment, the mean percentages (±*SD*) of the accuracy of the control subjects for FJT and GDT were 94.7 ± 6.1% and 97.0 ± 3.1%, and those of schizophrenia patients were 90.9 ± 6.0% and 95.1 ± 4.8%, respectively (**Figure 3**). There was no significant difference between the two groups [FJT: $t_{(34)} = 1.89$, $p > 0.05$; GDT: $t_{(34)} = 1.45$, $p > 0.05$]. Mixed analysis of variance (mixed ANOVA) in the performance did not show a significant main effect of Group (control subjects/schizophrenia patients): $F_{(1,\ 34)} = 2.33$, $p > 0.05$, whereas a significant Task effect (FJT vs. GDT) was observed: $F_{(1,\ 34)} = 11.5$, $p < 0.001$. No interaction effect between Group and Task was observed: $F_{(1,\ 34)} = 0.19$, $p > 0.05$. **Table 1** shows the mean accuracy for judgment of favorable/non-favorable, and judgment of same

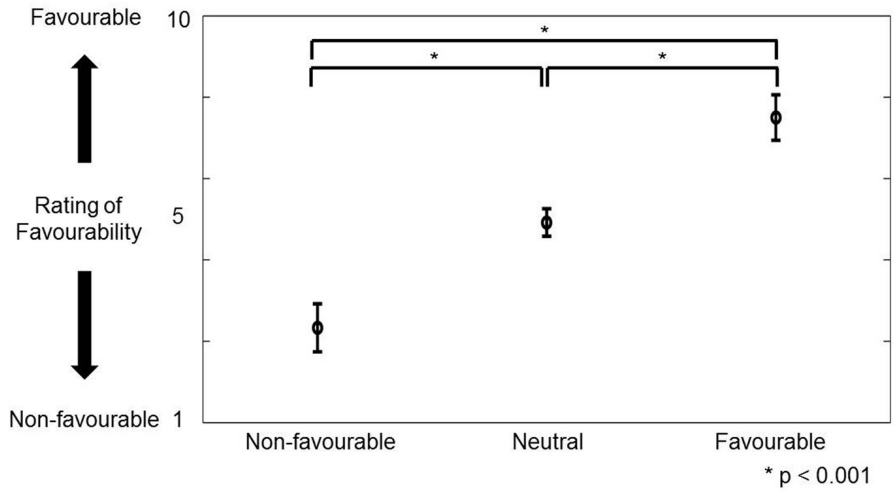

FIGURE 2 | The figure shows the distribution (mean ± *SD*) of rating favorability for portraying favorable, neutral, and unfavorable greetings in preliminary experiment. The vertical axis represents the rating score of favorability (1–10). *Indicates that multiple comparison was significant.

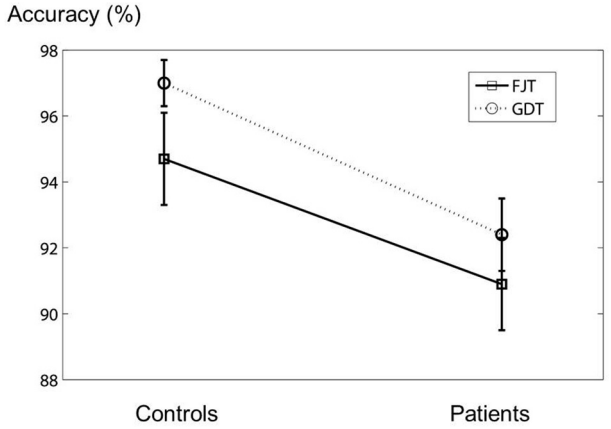

FIGURE 3 | The figure shows the error bar (mean ± *SD*) of the accuracy in the fMRI experiment. The vertical axis represents the accuracy of the experiment.

gender and different gender (FAV controls: 93.5 ± 7.6%; FAV patients: 94.1 ± 6.2%; NFV controls: 94.7 ± 6.1%; NFV patients: 90.0 ± 6.0%; SAM controls: 98.3 ± 2.4%; SAM patients: 95.7 ± 5.6%; DIF controls: 97.2 ± 3.8%; DIF patients: 95.0 ± 4.2%). No significant difference was observed between controls and patients [FAV: $t_{(34)} = -0.24$, $p > 0.05$; NFV: $t_{(34)} = 1.89$, $p > 0.05$; SAM: $t_{(34)} = 1.82$, $p > 0.05$; DIF: $t_{(34)} = 1.67$, $p > 0.05$]. Three-Way ANOVA was calculated for the effect of Group, Task, and Within-task. Task effect was significantly observed [$F_{(1, 34)} = 11.9$, $p = 0.002$], whereas Group effect and Within-task effect were not observed [Group: $F_{(1, 34)} = 2.33$, $p > 0.05$; Within-task: $F_{(1, 34)} = 2.55$, $p > 0.05$]. Interaction effect was not observed in the effect of Group × Task [$F_{(1, 34)} = 0.17$, $p > 0.05$] and the effect of Group × Within-task [$F_{(1, 34)} = 2.80$, $p > 0.05$].

Response time

The mean (± *SD*) response times relative to offset of stimulus (seconds) of control subjects and schizophrenia patients for FJT and GDT were the following: FJT-control: 2.41 ± 0.78 s, FJT-patients: 2.01 ± 0.33 s, GDT-control: 2.15 ± 0.78 s, and GDT-patients 1.99 ± 0.05 s. The response times in FJT were significantly different between control subjects and schizophrenia patients: $t_{(34)} = 2.16$, $p = 0.04 < 0.05$, whereas there was no significant difference in the response times to GDT: $t_{(34)} = 0.84$ $p > 0.05$. Analysis of variance on the response time was performed with the factors of Group (control subjects/schizophrenia patients) and Task (FJT/GDT). There was no significant difference between Groups: $F_{(1, 34)} = 2.29$, $p > 0.05$, whereas there was a significant Task effect: $F_{(1, 34)} = 33.7$, $p < 0.001$. An interaction effect between Group and Task was also observed: $F_{(1, 34)} = 24.4$, $p < 0.001$. **Table 1** (lower part) shows the mean response time for judgment of favorable/non-favorable, and judgment of same gender and different gender [FAV controls: 2.41 ± 0.78 s; FAV patients: 2.17 ± 0.17 s; NFV controls: 2.01 ± 0.13 s; NFV patients: 1.89 ± 0.15 s; SAM controls: 2.15 ± 0.78 s; SAM patients: 1.93 ± 0.14 s; DIF controls: 1.99 ± 0.53 s; DIF patients: 2.07 ± 0.13 s]. Significant difference between controls and patients was observed in NFV and DIF [NFV: $t_{(18.4)} = 3.49$, $p > 0.05$; DIF: $t_{(22.8)} = -2.31$, $p < 0.05$: Welch's *t*-test], whereas no significant difference was observed in FAV and SAM [FAV: $t_{(18.6)} = 1.29$, $p > 0.05$; SAM: $t_{(18.1)} = 1.15$, $p > 0.05$: Welch's *t*-test]. Three-Way ANOVA was calculated for the effect of Group, Task, and Within-task. Task effect was significantly observed [$F_{(1, 34)} = 36.7$, $p < 0.001$], whereas Group effect and Within-task effect were not observed [Group: $F_{(1, 34)} = 1.93$, $p > 0.05$; Within-task: $F_{(1, 34)} = 0.13$, $p > 0.05$]. Interaction effect was significantly observed in the effect of Group × Task [$F_{(1, 34)} = 16.0$, $p < 0.001$], whereas interaction effect was not significantly observed in the effect of Group × Within-task [$F_{(1, 34)} = 1.04$, $p > 0.05$].

Table 1 | Shows the mean ± *SD* of accuracy and response time in fMRI experiments.

		FAV	NFV	SAM	DIF
Accuracy (%)	Controls	93.5 ± 7.6	94.7 ± 6.1	98.3 ± 2.4	97.2 ± 3.8
	Patients	94.1 ± 6.2	90.9 ± 6.0	95.7 ± 5.6	95.0 ± 4.2
Response time (sec)	Controls	2.41 ± 0.78	2.01 ± 0.13	2.15 ± 0.78	1.99 ± 0.53
	Patients	2.17 ± 0.17	1.89 ± 0.15	1.93 ± 0.14	2.07 ± 0.13

FAV, pairs of neutral-favorable greetings; NFV, pairs of neutral-unfavorable greetings; SAM, pairs of same gender greetings; DIF, pairs of different gender greetings.

FUNCTIONAL MRI DATA

Full factorial design analysis

FMRI data was analysed based on the $2 \times 2 \times 2$ full factorial model with the three factors: Group (control subjects/schizophrenia patients), Task (FJT/GDT), and Within-task (FJT: FAV/NFV, GDT: SAM/DIF) (FDR-corrected voxel-level threshold of $P < 0.05$).

Main effect of Group was significantly observed in the bilateral middle frontal gyrus (MFG), left STG, right superior parietal lobe (SPL) temporo-parietal junction (TPJ), right occipital lobe, and right amygdala ($p < 0.05$, FDR-corrected, **Figure 4** and **Table 2**). The upper part (gray bar) of **Figure 4** shows the bar graph for contrast estimates and 90% confidence interval in each activated region (gray bar: controls, the light gray bar: patients). From the results of main effect of Group, ROIs were set on the 5 regions: left MFG [−26, −3, 62], right amygdala [20, −3, 21], left STG [−54, −21, 3], right TPJ [26, −65, 53], and right occipital lobe [8, −77, 2]. In these ROIs, Mann–Whitney test was calculated for beta values between controls and patients. The P-threshold was Bonferroni-corrected based on 5 tests being conducted. Cerebral activation in left STG was significantly greater in control subjects than in schizophrenia patients (L STG: $z = 3.10$, $p = 0.001 < 0.05/5$), whereas cerebral activations in the other regions were significantly greater in schizophrenia patients than in control subjects (L MFG: $z = -3.61$, $p < 0.05/5$; R amygdala: $z = -3.54$, $p < 0.05/5$; R TPJ: $z = -3.61$, $p < 0.05/5$; R occipital: $z = -3.54$, $p < 0.05/5$). In these 5 ROIs and contralateral symmetrical 5 ROIs (right MFG [26, −3, 62], left amygdala [−20, −3, 21], right STG [54, −21, 3], left TPJ [−26, −65, 53], left occipital lobe [−8, −77, 2]), cerebral activation under FAV, NFV, SAM, and DIF conditions was evaluated (middle part of **Figure 4**). Further, the LI was calculated (lower part of **Figure 4**). For each ROI, Two-Way ANOVA was calculated by main effect of Group and Within-task. Regarding Group effect, in the ROIs at the bilateral MFG, bilateral amygdala, bilateral TPJ, and right occipital lobe, the strength of BOLD signal (beta estimates) in patients under the FAV and NFV conditions was significantly greater than that in controls [L MFG: $F_{(1,\ 34)} = 14.1, p < 0.001$; R MFG: $F_{(1,\ 34)} = 21.5$, $p < 0.001$; L amygdala: $F_{(1,\ 34)} = 14.9, p < 0.001$; R amygdala: $F_{(1,\ 34)} = 18.0$, $p < 0.001$; L TPJ: $F_{(1,\ 34)} = 12.7$, $p < 0.001$; R TPJ: $F_{(1,\ 34)} = 4.67$, $p < 0.05$; R occipital: $F_{(1,\ 34)} = 14.4, p < 0.001$], whereas that in bilateral STG was significantly greater in controls than in patients [L STG: $F_{(1,\ 34)} = 12.7$, $p < 0.001$; R STG: $F_{(1,\ 34)} = 4.7$, $p < 0.05$]. In bilateral MFG, right amygdala, and right occipital, BOLD signals of patients under SAM and DIF conditions were significantly greater than in controls [L MFG: $F_{(1,\ 34)} = 14.1$, $p < 0.001$; R MFG: $F_{(1,\ 34)} = 21.5$, $p < 0.001$; R amygdala: $F_{(1,\ 34)} = 7.8$, $p < 0.01$; R occipital: $F_{(1,\ 34)} = 5.9$, $p < 0.05$]. Significant difference of LI was observed in the amygdala and occipital lobe under SAM and DIF conditions [amygdala LI: $F_{(1,\ 34)} = 7.8$, $p < 0.001$; occipital lobe: $F_{(1,\ 34)} = 6.5$, $p < 0.05$], whereas significant difference in the other regions was not observed ($p > 0.05$).

Main effect of Task (FJT/GDT) was significantly observed in the left precentral gyrus (PrCG), left MFG, left IFG, right insula, bilateral STG, left claustrum, and left cerebellum ($p < 0.05$, FDR-corrected, **Figure 5** and **Table 3**). Cerebral activation in the left IFG and bilateral STG was significantly greater in FJT than in GDT [**Figure 5**; L IFG: $t_{(70)} = 3.92$, $p < 0.05/6$; L STG: $t_{(70)} = 4.64$, $p < 0.05/6$; R STG: $t_{(70)} = 2.92$, $p = 0.005 < 0.05/6$]. Interaction effect between Group and Task was not significantly observed at a threshold of $p < 0.05$, FDR-corrected.

CORRELATION BETWEEN PSYCHIATRIC SYMPTOM AND CEREBRAL ACTIVATION

We examined correlations between PANSS and cerebral activation under FJT minus GDT contrast. Significant positive correlations were observed in the right superior frontal gyrus (SFG), right MFG, left IFG, left STG, and right IPL in schizophrenia ($p < 0.25$, FDR-corrected, **Figure 6** and **Table 4**). **Figure 7** demonstrated correlations between the severity of auditory hallucinations and cerebral activation under FJT minus GDT contrast. Significant positive correlations were observed in the right post central gyrus (PsCG), right PrCG, right MFG and right IPL in schizophrenia ($p < 0.25$, FDR-corrected, **Figure 7** and **Table 5**).

CORRELATION BETWEEN HANDEDNESS AND CEREBRAL ACTIVATION

We examined the correlation between handedness and cerebral activation. The beta value of ROI analysis in main effect of Group was used in this analysis. Cerebral activations in most ROIs were not correlated with the handedness score, but activation in STG was significantly negatively correlated with the handedness score (**Figure 8**). In the ROI of STG, differences in LI between 18 controls and 14 patients were analysed after removing 4 left-handed patients. However, significant difference in the LI was not observed.

CORRELATION BETWEEN ACCURACY OF TASK AND CEREBRAL ACTIVATION

In the ROIs of main effect of Group, correlation was analysed between the beta value of FJT at left STG and accuracy.

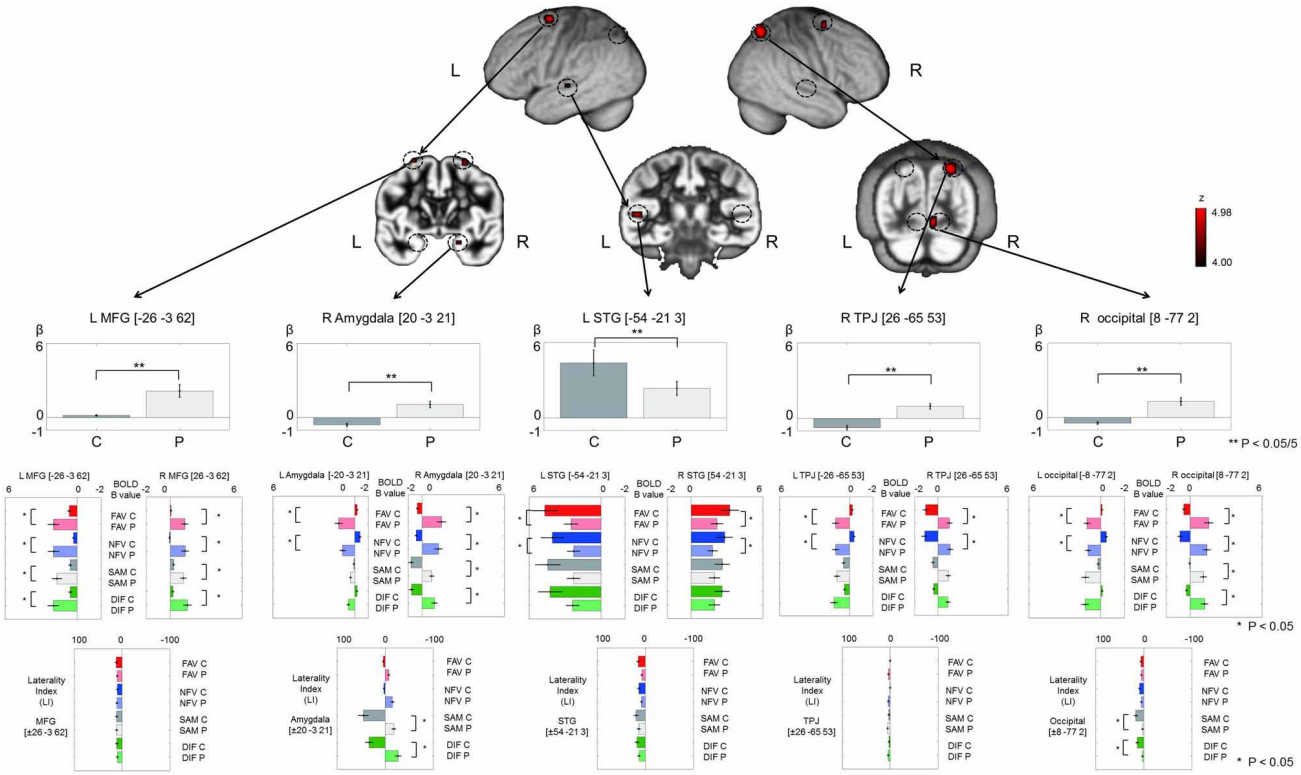

FIGURE 4 | The figure demonstrates the results of main effect of Group (controls/patients) in analysis of 2 × 2 × 2 full factorial design. Upper pictures show cerebral activation on main effect of Group ($p < 0.05$, voxel level, FDR-corrected). Gray bars in the upper row represent the distribution of beta values (mean ± SE) in controls (dark gray color) and patients (light gray color). The vertical axis, beta values; C, controls; P, patients; L, left; R, right. **Indicates $p < 0.05/5$ (Bonferroni correction by 5 ROIs). Color bars in the middle row represent the distribution of beta values (mean ± SE) on 5 ROIs and contralateral symmetrical 5 ROIs under FAV (red), NFV (blue), SAM (gray), and DIF (green) conditions—C, controls (dark gray); P, patients (light gray). Color bars at the bottom represent the distribution of laterality index (mean ± SE) on the 5 ROIs. *Indicates $p < 0.05$. MFG, middle frontal gyrus; STG, superior temporal gyrus; TPJ, temporo-parietal junction; occipital, occipital lobe.

Table 2 | Peak coordinates (*x, y, z*) and their *z*-values of cerebral activation by full factorial design analysis with Group effect (controls and patients).

Brain regions	BA	Coordinate			$F_{(1, 136)}$	*z*-value	*P* (FDR-corrected)
		x	*y*	*z*			
MAIN EFFECT OF GROUP (CONTROLS/SCHIZOPHRENIA)							
Controls > Patients							
L STG	41	−54	−21	3	23.20	4.47	<0.05
Patients > Controls							
L MFG	6	−26	−1	63	23.40	4.49	<0.05
R MFG	6	27	−1	61	19.50	4.10	<0.05
R SPL	7	26	−64	52	29.70	5.04	<0.05
Occipital lobe	18	8	−76	1	21.80	4.34	<0.05
R amygdala		20	−3	−21	18.40	3.99	<0.05

L, left hemisphere; R, right hemisphere; p < 0.05, voxel level, FDR-corrected.

A significantly positive correlation was observed ($r = 0.346$, $p < 0.05$, **Figure 10**). The other areas were not significantly correlated with accuracy. These findings suggest that the less the accuracy is, the less the beta value of FJT at left STG is.

DISCUSSION

To clarify cerebral function underlying the perception of voice attractiveness including greeting conversations in patients with schizophrenia, we investigated the difference of cerebral

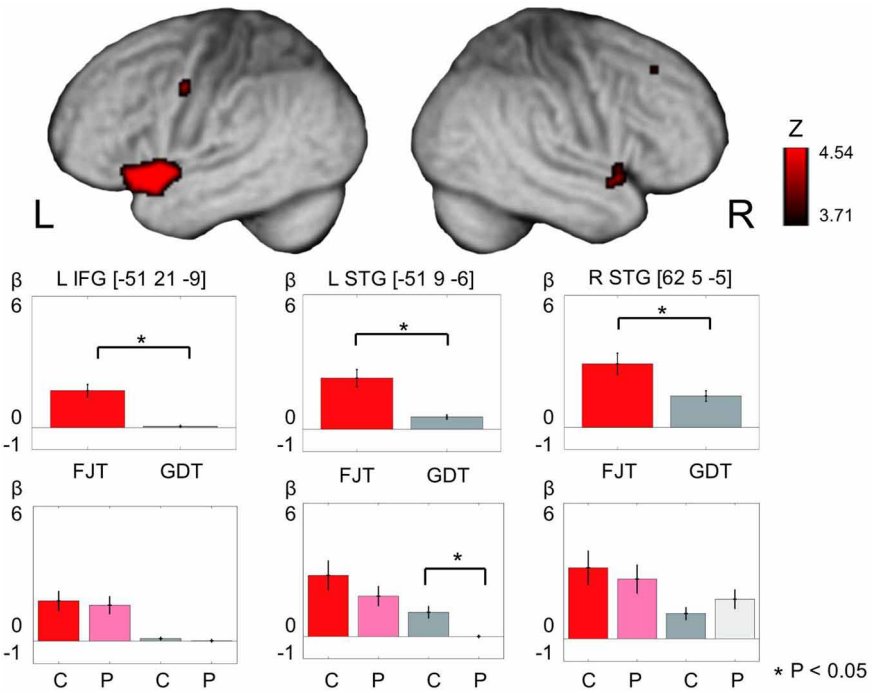

FIGURE 5 | The figure represents cerebral activation on main effect of task [(FJT/GDT): $p < 0.05$, voxel level, FDR-corrected]. Color bars show the distribution of beta values (mean ± *SD*) under FJT (red) and GDT (gray). *Indicates $p < 0.05$—L, left; R, right; dark color, controls; light color, patients.

Table 3 | Peak coordinates (*x, y, z*) and their *z*-values of cerebral activation by full factorial design analysis with task effect (controls and patients).

Brain regions	*BA*	Coordinate			$F_{(1, 136)}$	*z*-value	*P* (FDR-corrected)
		x	*y*	*z*			
MAIN EFFECT OF TASKS (FJT/GDT)							
L PrCG	6	−50	−4	42	18.50	4.00	<0.05
R MFG	8	27	27	43	16.00	3.70	<0.05
L IFG	47	−51	21	−9	23.90	4.54	<0.05
R insula	13	38	5	−3	19.70	4.13	<0.05
L STG	22	−59	9	−2	30.80	5.13	<0.05
R STG	22	62	5	−5	19.00	4.05	<0.05
L Claustrum		−36	−10	−2	22.20	4.39	<0.05
L cerebellum		−12	−43	−21	20.20	4.13	<0.05

L, left hemisphere; R, right hemisphere; p < 0.05, voxel level, FDR-corrected.

activation between control subjects and schizophrenia patients while they were judging favorability or gender of vocalizations. In our present experiment, the left IFG-STG was activated in the processing of favorability judgment in both controls and schizophrenia patients. Although cerebral activation in the left STG was reduced in schizophrenia, cerebral activation in the right MFG, right IPL, and right amygdala was increased. Further, by correlation analysis between psychiatric symptom and cerebral activation of favorability, we confirmed that positive and negative symptoms in schizophrenia are closely related to cerebral dysfunction in the left STG and right MFG-IPL (**Figure 9**).

FRONTOTEMPORAL FUNCTION TO AUDITORY ATTRACTIVENESS AND ITS DYSFUNCTION IN SCHIZOPHRENIA

Our results by full factorial design also exhibited main effect of experimental Task (FJT/GDT) in the left STG and left IFG (**Figure 5**, **Table 3**). Recent auditory fMRI studies demonstrated that the cerebral function of STS is important to grasp auditory social cues (Saarela and Hari, 2008; Scharpf et al., 2010). Further, a recent fMRI study concerning auditory attractiveness demonstrated the importance of the functional connection between STG and IFG (Bestelmeyer et al., 2012). In accord with these findings, our results showed left STG-IFG activation in the recognition of auditory attractiveness including social communications.

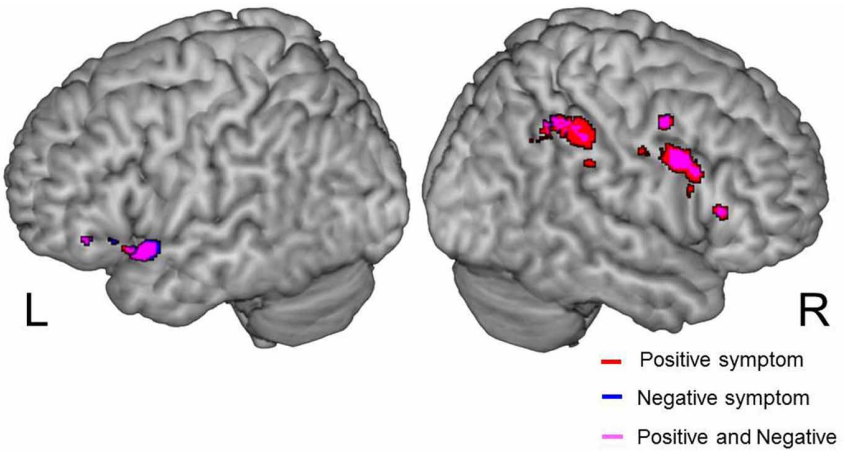

FIGURE 6 | Positive correlation between psychiatric symptom and cerebral activation under FJT > GDT contrast (univariate analysis). Positive symptom is red color, Negative symptom is blue color. Purple color indicates both symptoms. Statistical threshold: $p < 0.25$, FDR-corrected; L, left; R, right side.

Table 4 | Positive correlation between PANSS and cerebral activation under FJT minus GDT, $p < 0.0001$ uncorrected ($p < 0.25$, FDR-corrected), R, right hemisphere.

Brain regions	*BA*	Coordinate			*z*-value	*P* (uncorrected)	*P* (FDR-corrected)
		x	*y*	*z*			
L SFG	6	−6	9	55	3.73	<0.0001	<0.25
R SFG	6	9	8	60	4.04	<0.0001	<0.25
R MFG	9	51	6	36	3.77	<0.0001	<0.25
L STG	38	−50	12	−8	3.72	<0.0001	<0.25
R IPL	40	40	−43	49	4.16	<0.0001	<0.25

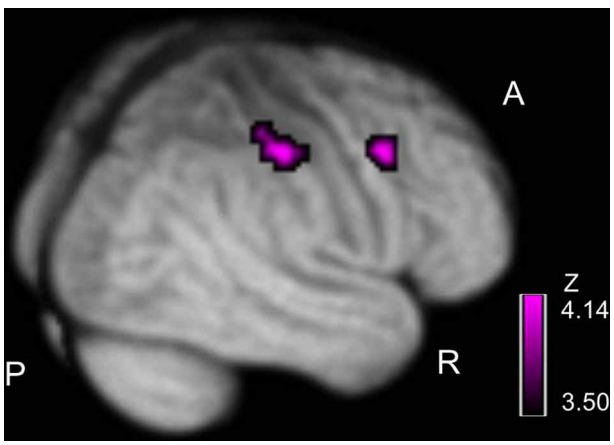

FIGURE 7 | Positive correlation between severity of hallucinatory behavior and cerebral activation under FJT > GDT contrast. Purple color bar shows *z*-value. Statistical threshold: $p < 0.25$, FDR-corrected; R, right; A, anterior; P, posterior.

Before the experiment, we hypothesized that left STG-IFG activation by auditory attractiveness could be impaired in schizophrenia. Predictably, cerebral activation in schizophrenia patients was greater in the bilateral prefrontal regions in comparison with control subjects (**Figure 5**). A recent study indicated that brain activity in the left prefrontal regions reflected the overall perceived attractiveness of the voices (Bestelmeyer et al., 2012). Further, another fMRI study indicated that the left ventrolateral prefrontal cortex, bilateral dorsal IFG, and medial frontal cortex are activated when the subjects judged whether pairs of human individuals were friends or enemies (Farrow et al., 2011). These reports indicate that prefrontal regions are associated with the judgment of favorability and friendliness. In our present study, hyper-frontality and hypo-temporality in schizophrenia patients could designate the dysfunction of left STG-IFG when they judged favorability.

In our study, cerebral activation to favorability judgment was reduced in the left STG, while it was increased in the MFG, amygdala, TPJ, and occipital lobe in the right hemisphere. A recent fMRI study suggested that paradoxical brain activation in schizophrenia patients with auditory hallucination may be caused by both reduced activation due to impaired brain function in auditory processing and increased activation due to disturbance of attention bias toward internally generated information (Jardri et al., 2011; Kompus et al., 2011). In accordance with this recent study, less activation in schizophrenia could represent impairment of favorability judgment in auditory processing, whereas greater activation in schizophrenia may reflect disturbance of attention bias toward

Table 5 | Positive correlation between the severity of hallucinatory behavior and cerebral activation under FJT minus GDT, $p < 0.0001$ uncorrected ($p < 0.25$, FDR-corrected), R, right hemisphere.

Brain regions	*BA*	Coordinate			*z*-value	*P* (uncorrected)	*P* (FDR-corrected)
		x	*y*	*z*			
CORRELATION OF HALLUCINATORY BEHAVIOR							
R PsCG	2	48	−19	30	4.55	<0.0001	<0.25
R PrCG	6	46	−16	30	4.10	<0.0001	<0.25
R MFG	9	48	8	42	3.72	<0.0001	<0.25
R IPL	40	45	−33	46	4.14	<0.0001	<0.25

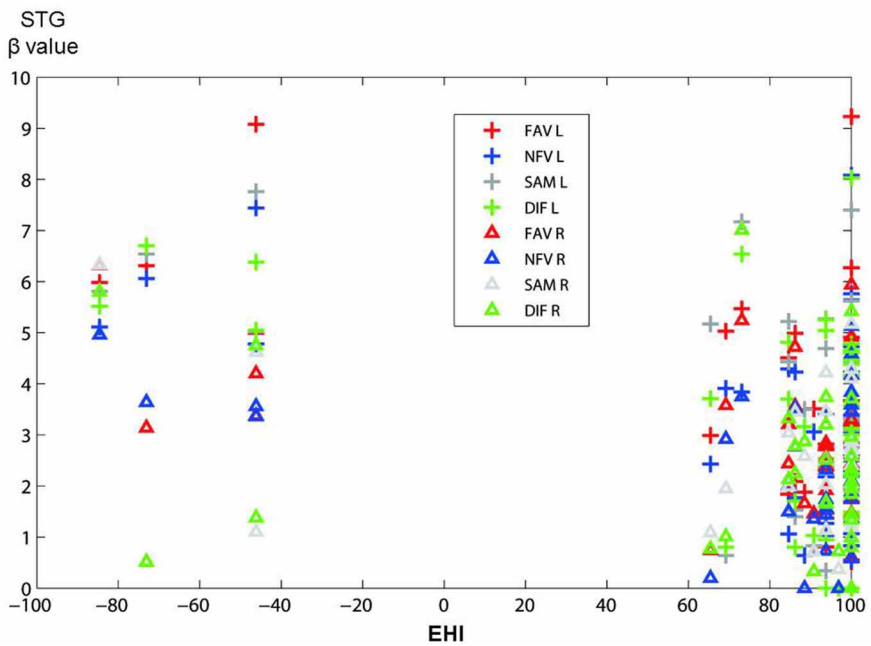

FIGURE 8 | The figure shows the distribution of correlations between activation in STG (in main effect of Group) and handedness score (EHI) in all participants. The vertical axis shows beta value in STG, and the horizontal axis shows EHI score (−100 represents extremely left-handed; 100 represents extremely right-handed). Plus marks, left hemisphere; triangles, right hemisphere; FAV (red), NFV (blue), SAM (gray), DIF (green).

internally generated information by the appearance of auditory hallucination.

CEREBRAL LATERALITY TO AUDITORY ATTRACTIVENESS IN SCHIZOPHRENIA

Interestingly, our results in schizophrenia patients exhibited enhanced right-lateralization to auditory attractiveness mainly in MFG and IPL (**Figure 4**). Previous fMRI studies concerning language processing have demonstrated that schizophrenia patients show either reduced left hemispheric activation (Kiehl and Liddle, 2001; Kircher et al., 2001; Koeda et al., 2006) or reversed language dominance (Woodruff et al., 1997; Menon et al., 2001; Ngan et al., 2003; Bleich-Cohen et al., 2009). Conversely, previous fMRI studies concerning non-linguistic processing in schizophrenia indicated reduced right hemispheric activation (Koeda et al., 2006), reversed right-lateralized activation (Mitchell et al., 2004), or enhanced right-lateralized activation (Bach et al., 2009). In accordance with the latter report, our results showed greater right prefrontal and inferior parietal activation during favorability judgment in schizophrenia (**Figure 4**). In the analysis by full factorial design, main effect of Group (controls/patients) revealed greater activation of schizophrenia in the right hemisphere compared with controls (**Figure 4**). This result also indicates enhanced right hemispheric activation by auditory attractiveness in schizophrenia. It could be speculated that these strong right hemispheric activations compensate the dysfunction of left STG-IFG related to auditory attractiveness (**Figure 4**).

PSYCHIATRIC SYMPTOMS AND AUDITORY ATTRACTIVENESS IN SCHIZOPHRENIA

Our results revealed a positive correlation between psychiatric symptom (total PANSS score, positive and negative symptom) and cerebral activation under FJT vs. GDT contrast at left STG-IFG and right prefrontal and superior/inferior parietal cortex (**Figure 6** and **Table 4**). In both positive and negative symptoms,

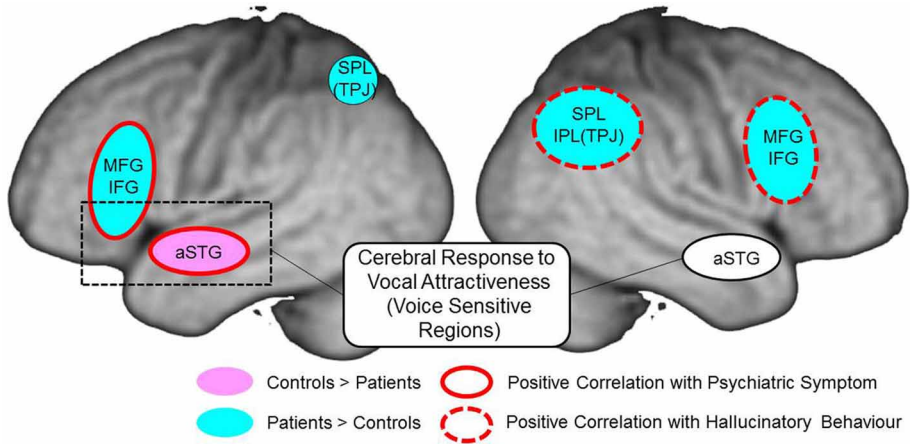

FIGURE 9 | Summary of cerebral response to auditory attractiveness and psychiatric symptom in schizophrenia: red circle shows the area of positive correlation between cerebral activation and total PANSS score; red dashed line shows the area of positive correlation between cerebral activation and hallucinatory behavior; light blue area represents greater activation in patients than in controls; pink area represents less activation in patients than in controls. MFG, middle frontal gyrus; IFG, inferior frontal gyrus; aSTG, anterior superior temporal gyrus; SPL, superior parietal lobe; TPJ, temporo-parietal junction; IPL, inferior parietal lobe.

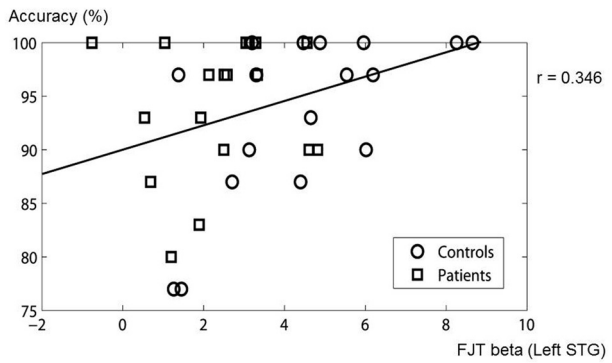

FIGURE 10 | Correlation between beta value of FJT at left STG and accuracy. The circles show control subjects. The rectangles show schizophrenia patients.

almost the same regions were correlated with cerebral activation for auditory attractiveness. Left STG-IFG activation was observed in the favorability judgment (**Figure 5**). These findings could be considered to reflect the dysfunction of the left STG-IFG region in the recognition of auditory attractiveness. Crucially, cerebral activation in the right prefrontal and superior/inferior parietal region was positively correlated with the severity of auditory hallucination (**Figure 7**, **Table 5**). These areas also demonstrated greater activation under FJT vs. GDT contrast in schizophrenia (**Figure 5**, **Table 3**). These findings indicate that greater activation to the favorability judgment in schizophrenia is related to severity of auditory hallucinations. Previous studies indicate that the right MFG/IFG-IPL region is closely related to self-referential processing (Fossati et al., 2003; Canessa et al., 2005; Uddin et al., 2005). Especially, one study demonstrated that right fronto-parietal regions as well as left prefrontal and parietal regions were activated when subjects understood the context related to social communications when two persons exchange goods, i.e., if you give me one, I will give you the other (Canessa et al., 2005). Further, another study exhibited that right dorsal IFG was activated in the processing of social alliance (friendliness) (Farrow et al., 2011). These previous findings support that the right MFG/IFG-IPL region associates with the recognition of social communications such as judgment of favorability. These activations could be attributed to representing the dysfunction of the fronto-parietal region in the processing of social communications by auditory hallucinations.

Recent fMRI studies investigated cerebral function when the subjects mentalize the other person's thoughts and behavior. These reports indicate that the role of the temporal-parietal junction is closely associated with comprehending the mental states of others (Siegal and Varley, 2002; Finger et al., 2006; Shamay-Tsoory et al., 2006; David et al., 2008). A recent study investigated cerebral activation in the processing of self-other distinction. This study demonstrated that the increase in cerebral activation in the right IPL correlated positively with the strength of psychiatric symptoms in schizophrenia (Jardri et al., 2011). Further, recent studies of schizophrenia reported that functional connectivity in the fronto-temporal network was decreased when the subjects comprehended the behavior of the other person (Das et al., 2012), or when the subjects listening to the other person's speech compared it with self-generated speech (Mechelli et al., 2007). Findings of greater right prefrontal-parietal activation (**Figure 4**) in schizophrenia may reflect brain activation due to comprehending other person's mental states through auditory hallucination as well as dysfunction of the fronto-temporal region in perception of vocal attractiveness.

In summary, when cerebral function in auditory attractiveness including social conversations was investigated, cerebral activation was revealed in the left STG and left IFG. Particularly, in schizophrenia, less activation was observed at the left STG

compared with control subjects. In addition, greater activation in schizophrenia was confirmed in the right fronto-parietal region. Further, cerebral response in this region was correlated with the severity of auditory hallucinations. These findings suggest that dysfunction in the left fronto-temporal regions is related to the ability to appropriately assess the attractiveness of vocal communications in schizophrenia. The right fronto-parietal region could offset cerebral dysfunction to auditory attractiveness including social communications.

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A comprehensive review of auditory verbal hallucinations: lifetime prevalence, correlates and mechanisms in healthy and clinical individuals

Saskia de Leede-Smith* and Emma Barkus

Department of Psychology, University of Wollongong, Wollongong, NSW, Australia

Edited by:
Johanna C. Badcock, University of Western Australia, Australia

Reviewed by:
Giuliana Lucci, IRCCS Santa Lucia of Rome, Italy
Agna A. Bartels-Velthuis, University of Groningen; University Medical Center Groningen; University Center for Psychiatry, Netherlands

****Correspondence:***
Saskia de Leede-Smith, Department of Psychology, University of Wollongong, Northfields Ave., Wollongong, NSW 2522, Australia
e-mail: saskia@uow.edu.au

Over the years, the prevalence of auditory verbal hallucinations (AVHs) have been documented across the lifespan in varied contexts, and with a range of potential long-term outcomes. Initially the emphasis focused on whether AVHs conferred risk for psychosis. However, recent research has identified significant differences in the presentation and outcomes of AVH in patients compared to those in non-clinical populations. For this reason, it has been suggested that auditory hallucinations are an entity by themselves and not necessarily indicative of transition along the psychosis continuum. This review will examine the presentation of auditory hallucinations across the life span, as well as in various clinical groups. The stages described include childhood, adolescence, adult non-clinical populations, hypnagogic/hypnopompic experiences, high schizotypal traits, schizophrenia, substance induced AVH, AVH in epilepsy, and AVH in the elderly. In children, need for care depends upon whether the child associates the voice with negative beliefs, appraisals and other symptoms of psychosis. This theme appears to carry right through to healthy voice hearers in adulthood, in which a negative impact of the voice usually only exists if the individual has negative experiences as a result of their voice(s). This includes features of the voices such as the negative content, frequency, and emotional valence as well as anxiety and depression, independently or caused by voices presence. It seems possible that the mechanisms which maintain AVH in non-clinical populations are different from those which are behind AVH presentations in psychotic illness. For example, the existence of maladaptive coping strategies in patient populations is one significant difference between clinical and non-clinical groups which is associated with a need for care. Whether or not these mechanisms start out the same and have differential trajectories is not yet evidenced. Future research needs to focus on the comparison of underlying factors and mechanisms that lead to the onset of AVH in both patient and non-clinical populations.

Keywords: auditory hallucinations, hallucinations, psychosis, schizophrenia, non-clinical, schizotypy, child, adolescent

Auditory verbal hallucinations (AVHs) are a sensory experience that takes place in the absence of any external stimulation whilst in a fully conscious state (Beck and Rector, 2003). AVH occur with a sufficient similarity to the real percept that the individual attributes the event to be out of his/her own control (David, 2004). To date, the mechanism and pathophysiology of AVH, although widely speculated upon, are still largely unknown. The initiation and maintenance of AVH need to be distinguished and both explicated in order to begin to separate clinically relevant from protective factors for a differentiated trajectory of hallucinatory experiences. The current review aims to examine the phenomenology of AVH. We will consider the literature and data available across the lifespan as well as in different clinical and non-clinical groups. Extrapolating differences between clinical and non-clinical hallucinatory experiences provides an understanding of different developmental trajectories, characteristics of the experience and modes of interpretation for the voice hearer. As such, a review is timely which investigates the similarities and differences between the pathological voice hearing experience and AVH which are considered otherwise healthy modes of functioning. By integrating research in this very much evolving field, we can move forward toward a conceptualization of the intricate mechanism(s) responsible for the voice hearing experience.

The framework used in the current review is summarized in **Figure 1**. The biopsychosocial model provides a system where triggers, maintaining and moderating factors can be incorporated informatively. The domains interact with one another on a causal and mechanistic level, demonstrating the etiological complexity of AVH at any point along the lifespan and in both clinical and non-clinical groups. Factors can be conceptualized as background factors which are stable, may be biologically underpinned, and provide a backdrop against which other factors interact. These interacting factors can be mechanisms or triggers,

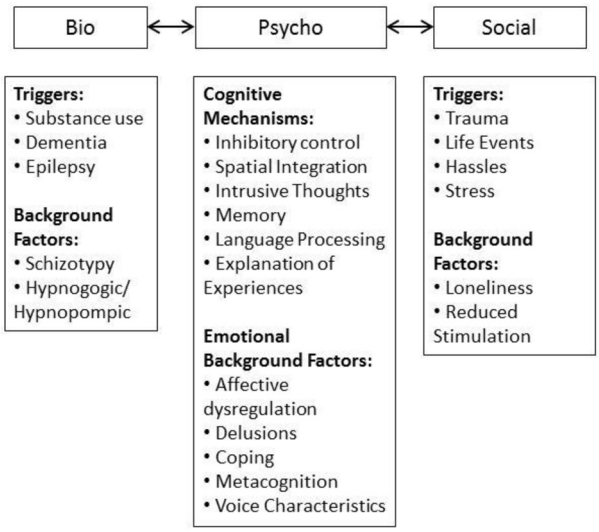

FIGURE 1 | Biopsychosocial framework used in the summary of the AVH literature.

the former contributing to maintenance and the latter initiating onset. However, the relationships between these variables are not discrete, the content of AVH can be informed by social and personal experiences. For example, the triggering environmental stressor can provide information for AVH content. This creates an intricate picture. However, given the complexity of the AVH experience it is not surprising that the factors which both initiate and maintain AVH are multifaceted and not mutually exclusive.

The principles of a systematic review were adopted in completing this literature review. The databases used included PsycInfo, Medline and Science Direct. Only peer reviewed journals were selected and analysed in the review process. However, it must be acknowledged that in all instances the most recent literature was focused upon, given that each of these sections would be deserving of a lengthy systematic review independently from one another. The search terms for each individual sub topic have been listed in brackets at the beginning of the corresponding section.

PREVALENCE OF AVH AND RELATED PHENOMENA

(CHILD, CHILDHOOD, ADOLESCENT, ADOLESCENCE, EARLY ADULTHOOD, ADULT, AUDITORY HALLUCINATIONS, AUDITORY PERCEPTIONS, VOICE HEARING, PSYCHOTIC EXPERIENCES, PSYCHOSIS, CLINICAL, NON-CLINICAL)

AVH are at their most prevalent in diagnosed psychotic disorders such as schizophrenia and schizoaffective disorder (Sartorius et al., 1986) but also occur in other disorders including bipolar disorder, substance intoxication and organic dementias. Recent research has focused on the existence of AVH in general population samples (Moritz and Larøi, 2008; Sommer et al., 2010; Daalman et al., 2011a,b; Temmingh et al., 2011; Larøi et al., 2012; Stanghellini et al., 2012). Epidemiological studies have estimated the prevalence of AVH to be between 5 and 28% in the general population (Tien, 1991; van Os et al., 2000; Johns et al., 2004; Scott et al., 2006). Johns et al. (2002) found 25% of individuals reporting hallucinatory experiences met the diagnostic criteria for a psychotic disorder; however that leaves 75% of people experiencing AVH who are considered otherwise healthy. Possible implications (which are by no means mutually exclusive) for the existence of non-clinical AVH are:

1. Healthy AVH may present as an isolated symptom and may not be related to any sort of predisposition for a psychotic disorder (Daalman et al., 2011a,b).
2. Alternatively, AVH may form part of a genetic predisposition toward psychotic illness. They can co-occur alongside other attenuated psychotic symptoms including paranoid ideation, odd/unusual behavior, delusions and inefficient cognitive processing (Krabbendam et al., 2005).
3. AVH are hypothesized to lie on a continuum of risk ranging from normal experiences to pathological psychotic (Johns and van Os, 2001) suggesting that clinically relevant AVH could be an extension of the processes occurring in otherwise healthy hallucinators.

CHILDHOOD

AVH in children, like adults, are prevalent in both clinical and non-clinical populations (where clinical refers to those children diagnosed with schizophrenia or psychosis, unless stated otherwise). Studying the experience and trajectory of AVH in childhood provides insights into the development of these experiences from a biopsychosocial framework. Since the great majority of children reporting AVH never make the transition to psychotic disorder (Poulton et al., 2000), it seems factors mediate the likelihood of hallucinatory experiences becoming pathological. For example, it is often documented that biological factors such as pre- and peri-natal complications (Clarke et al., 2006; Zammit et al., 2009), along with delayed developmental milestones (Murray et al., 2004; Laurens et al., 2007) are associated with subsequent psychosis development. Examining the prevalence of child AVH in both clinical and non-clinical groups, a recent meta-analysis found rates to be between 5 and 16%, mostly occurring in late childhood or early adolescence (van Os et al., 2009). A prevalence of 8% for AVH has also been found in a cohort of 11-year old children (McGee et al., 2000), whilst Bartels-Velthuis et al. (2010) noted an almost identical prevalence of 9% for 7 and 8 year olds. Children also report musical hallucinations, although these are largely under-investigated and are often related to damage to the ear (Aziz, 2009). In children AVH are documented in conjunction with diagnoses of anxiety (Murase et al., 2000; Escher et al., 2002), migraines (Schreier, 1998) and depression (Ryan et al., 1987; Krabbendam et al., 2005; Scott et al., 2009) as well as conduct disorder (Kim-Cohen et al., 2003; Askenazy et al., 2007). In child clinical outpatients sampled by Askenazy et al. (2007) 100% met the required DSM-IV criteria for conduct disorder. Co-morbid conduct disorder is related to greater persistence and severity of AVH experiences (Kim-Cohen et al., 2003; Askenazy et al., 2007). Thus, the association between AVH and conduct disorders warrants further research. Interestingly, difficulties in metalizing (or theory of mind), particularly the identification of emotions in others, are common to conduct disorder (Sebastian et al., 2012), delusional ideation

(Bartels-Velthuis et al., 2011a) and psychotic symptoms in general (Polanczyk et al., 2010). Potentially this provides a key point of overlap between these clustering of problems (see Bartels-Velthuis et al., 2011a).

It is clear that AVH are detectable in child populations. In most instances childhood AVH spontaneously cease: 76% of children who reported hearing voices aged 7 and 8 years stopped hearing voices by 12 and 13 years (Bartels-Velthuis et al., 2011b). Similarly, 75–90% of child psychotic-like experiences are transitory and regress over time (van Os et al., 2009). These studies imply that hearing voices may not be developmentally disadvantageous; particularly given the consistency with which they are reported to decrease with age (Escher et al., 2004; Askenazy et al., 2007; Bartels-Velthuis et al., 2011b). Further evidence for this can be drawn from the existence of imaginary companions which spontaneously cease, often when children begin school (Fernyhough et al., 2007). It has been reported that 46.2% of children between the ages of 5 and 12 years report the existence of at least one imaginary companion (Pearson et al., 2001). The experience of imaginary companions could be a young child's explanation for hearing voices (Pearson, 1998), although evidence does exist that children are able to distinguish between AVH and imaginary companions (Taylor et al., 1993). Having had or currently having an imaginary companion in childhood is not necessarily associated with negative mental health outcomes (Cohen, 1996; Taylor and Carlson, 1997; Hoff, 2005) and is not restricted in any way to those children with increased levels of creativity and imaginability (Pearson et al., 2001). Thus, the presence of an imaginary companion could be part of the normal development and sociability of the child, however further research in this area is warranted to understand their developmental relevance and long term outcomes.

ADOLESCENCE AND ADULTHOOD

Studies examining the prevalence of non-clinical auditory hallucinations in adolescents are limited compared to child and adult investigations. This is unusual given that the onset for prodromal symptoms for psychosis and other mental health disorders often emerge during mid- to late adolescence. Adolescence is the onset of a series of rapid changes in hormones and brain development. From a biopsychosocial perspective these changes are often cited as a possible explanation for the initiation and presentation of mental health symptoms which can evolve into schizophrenia. The brain's connections are at their greatest during adolescence (Ihara et al., 2009) before pruning and decreasing neuronal connectivity reduces them to adulthood levels (Hoffman and McGlashan, 1997). The stress associated with these changes has previously been cited as a trigger for psychopathology in certain individuals (Corcoran et al., 2003). The range of neurological, emotional and social changes which take place in adolescence may put predisposed individuals in a heightened state of vulnerability to psychopathology.

Estimated prevalence rates for adolescent AVH are similar to that of children, lying between 5 and 16% (van Os et al., 2009). Healthy adult voice hearers report beginning to hear voices at an approximate age of 12 years, which is significantly younger than their clinical counterparts (approximately 21 years; Tien, 1991; Daalman et al., 2011a). Some authors have proposed that aberrant synaptic pruning accounts for the onset of hallucinations (Hoffman and Hampson, 2011). However, given the consistency in the estimates for adolescent AVH and child AVH it is unlikely that this explains all cases. The resolution of childhood AVH coincides with early adolescence (Bartels-Velthuis et al., 2011b). There are a small subset of individuals who begin to re-experience an imaginary companion during adolescence (Barrett and Etheridge, 1992, 1994). However, these individuals have not been investigated to differentiate them from their counterparts or for the persistence of the imaginary friends during adolescence. The existing literature does not yet provide us with sufficient information to determine whether imaginary companions are comparable to AVH. This requires further investigation.

The prevalence of voice hearing in adult non-clinical populations is roughly the same as that in children, ranging from 10 to 15% (Tien, 1991; Sommer et al., 2010). The most common experiences reported by non-clinical adults take place on average every 3 days, for 2–3 min, are controllable for around 60% of the time and cause little to no distress or disruption to daily life (e.g., Daalman et al., 2011a). However, there do seem to be some healthy individuals who experience hearing voices to the same frequency and qualities as clinical patients with schizophrenia (Honig et al., 1998; Faccio et al., 2012). Given that the majority of childhood AVH resolve prior to adolescence, the rates in adulthood suggest that there are a significant group of individuals who develop hallucinations during adolescence and early adulthood which persist onward.

PERSISTENCE OF AVH

Persistence of AVH in childhood is reported to be indicative of a more severe underlying pathology (Bartels-Velthuis et al., 2011b). Under the biopsychosocial framework of AVH development, it is evident that there are certain mechanisms which contribute to the maintenance of hallucinatory experiences past the stage of initial development. A specific factor associated with the persistence of hallucinatory experiences in children is the formation of secondary delusions (Escher et al., 2002; Krabbendam et al., 2004; Freeman et al., 2010). The formation of delusions may be due to aberrant salience, or attributed importance, to AVH (Kapur, 2003). Delusional ideation is more likely to occur under situations of affective dysregulation; affective dysregulation in and of itself has been linked to the formation of psychotic symptoms in adult populations (Smith et al., 2006; Myin-Germeys and van Os, 2007; Bentall et al., 2009), warranting the need for investigation in children and adolescents. When states of anxiety, depression and stress interact with pre-existing hallucinatory phenomena affective disturbances can culminate to create delusional pathology (Krabbendam et al., 2005). Some authors have suggested that the combination of secondary delusions and emotional factors provides the mechanism for healthy AVH to become pathological experiences (Bartels-Velthuis et al., 2012). The need to find an explanation for the, often, unusual nature of AVH seems a logical necessity for human behavior. However, given that children are not necessarily bound by conventions of thought and social desirability (Osório et al., 2012) it is less clear why the ideas formed become unusual, fixed and associated with distress (delusional ideation). In 9–11 year olds, delusional-like ideas identified in children have been associated with more severe symptomatology

(Laurens et al., 2012). It suggests that the distress associated with AVH is not necessarily socially bound and may be inextricably linked within the nature of the experiences.

In childhood the incidence of AVH has been reported to be a risk for a later transition to schizophrenia (Fenning et al., 1997; Poulton et al., 2000; Dhossche et al., 2002; although see Garralda, 1984). Besides psychosis, the presence of childhood AVH are concurrently associated with depression and anxiety (Murase et al., 2000; Escher et al., 2002; Krabbendam et al., 2005; Smith et al., 2006; Best and Mertin, 2007). They are also predictive for the later onset of depression, anxiety, paranoia, and bipolar disorder as well as psychosis (Bentall et al., 2012; Goghari et al., 2012; Goldstone et al., 2012; Smeets et al., 2012). Similarly, the presence of AVH during early or mid-adolescence has been associated with a substantially increased risk for a diagnosis of schizophrenia-spectrum disorders in their early twenties (Poulton et al., 2000; Welham et al., 2009).

Rates of discontinuation of AVH in adolescence have been reported to be between 3 and 40% each year (Rubio et al., 2012). Therefore, the significant minority for whom AVH persist during adolescence represent a distinct group (e.g., De Loore et al., 2011; Rubio et al., 2012). The persistence of AVH may be more likely to precipitate the need to generate explanations of the experiences as outlined above. The persistence-impairment model (van Os et al., 2009), suggests that the progression to increased impairment from psychotic-like experiences occurs at a point where the individual is exposed to sufficient environment stressors. The increasing independence required to navigate adolescence successfully would present many opportunities for increasing environmental stressors of a social (e.g., peer interactions, increased academic expectations) and biological (substance use) nature. Persistence of AVH in adolescence has been associated with increasing depression, general psychopathology, delusional ideation and need for care (Escher et al., 2004; Hanssen et al., 2005; De Loore et al., 2011; Dominguez et al., 2011; Mackie et al., 2011).

Often the investigation of AVH in adolescents coincides with the progression through to the prodrome for psychosis, bipolar disorder and other adult mental health difficulties. The development of the Clinical Staging Model (Wood et al., 2011) distinguishes residual symptoms or early signs in order for them to be detected more readily before progression to full psychopathology. The key factors implicated would be the persistence of the AVH, the presence of distress, other mental health symptoms and any type of help seeking behavior (Yung and McGorry, 1996). Since the majority of documented AVH in adolescence are considered to be non-pathological, there must be certain factors that impinge on the individual at some stage of their development to convert normal AVH to pathological problems requiring a need for care. Perhaps tracking these experiences over time, as well as the way in which they are interpreted, their qualities and the associated distress will help to highlight which child and adolescent AVH should be of concern to clinicians.

When examining the phenomenology of AVH in adolescents compared to healthy adult voice hearers, population based studies seem to illustrate a shared experience. Pearson et al. (2008) documented adolescent AVH which mirror those of adults, with these parallels being suggestive of a continuum of non-pathological hallucinatory experiences. The existence of such a continuum for healthy hallucinators progressing into adulthood could have functional benefits in relation to clinical staging assessments. Adolescence makes up a pivotal time of development where hallucinatory and other symptoms can progress to a prodromal stage requiring the first steps in a need for care. Clinical staging characterize disorders according to their seriousness, development and features. Such a conceptualization would be considerably useful if for example the individual's hallucinatory experiences were to progress past the initial stage to a more ingrained chronic impairment.

The consideration of prevalence and persistence of AVH leads to some consideration of the possible implications of AVH in the general population. That such symptoms exist within the general population now seems to be widely accepted within the literature. Additionally, the similarity in the levels in children, adolescence and adulthood implies that they do not necessarily confer developmental disadvantage. From the evidence considered so far, it appears that non-clinical AVH become pathological when they persist, lead to the development of other symptoms and cause distress and functional impairment. Accordingly, it could be argued that they do lie on a continuum of risk, ranging from normal healthy experiences, through to pathological psychotic (Johns and van Os, 2001). However, it cannot be determined whether the mechanisms which underpin non-clinical AVH are the same as those demonstrated in clinical AVH. Even though they may lie on a gradient of risk, this does not imply that the features present at the functioning end of such a spectrum mirror those at the extreme end of the spectrum. As has been presented, AVH are only associated with other attenuated psychotic symptoms when they require care. Therefore, non-clinical AVH in and of themselves do not seem to be indicative of the progression to mental health disorders. Additional clues to the developmental trajectories which differentiate clinical from healthy AVH can be derived from consideration of the phenomenology, cognitive mechanisms, and emotional regulation differences between the two populations.

COMPARISON OF CLINICAL AND NON-CLINICAL HALLUCINATIONS IN ADULT POPULATIONS

(EARLY ADULTHOOD, ADULT, AUDITORY HALLUCINATIONS, AUDITORY PERCEPTIONS, VOICE HEARING, PSYCHOTIC EXPERIENCES, PSYCHOSIS, CLINICAL, NON-CLINICAL, PHENOMENOLOGY, SCHIZOPHRENIA)

In a comparison of the phenomenological features of child and adult voice hearers (**Table 1**), it is evident that components such as the localization, number of voices, and loudness of the voice hearing experience are largely consistent between clinical and non-clinical groups. Therefore, meaningful information can be derived by examining which features distinguish voice hearing in clinical groups from healthy voice hearers. Compared to AVH in schizophrenia (referred to as a "clinical" population in this section and including those with psychosis), non-clinical AVH have been found to occur much less frequently, and usually occur after specific conditions such as high stress or sleep deprivation (Larøi et al., 2012). The most commonly reported difference between

Table 1 | Phenomenological characteristics of AVH in clinical and non-clinical groups.

Adult AVH		Clinical (confirmed psychotic disorder) AVH	Non-clinical AVH	Able to distinguish between clinical and non-clinical groups?
	Localization	Inside head (near ears) (Daalman et al., 2011a) Heard via the ears (78%) (Romme and Escher, 2000)	Inside head (further from body) (Daalman et al., 2011a) Heard via the ears (57%) (Romme and Escher, 2000)	No
	Explanation of origin	50% External (Nayani and David, 1996; Daalman et al., 2011a) Either inside or outside the head (hard to distinguish) (Nayani and David, 1996; Stephane et al., 2003; Copolov et al., 2004)	60% external, 40% internal (Daalman et al., 2011a) External source-mostly benevolent spirits (Sommer et al., 2010)	No
	Loudness	Little softer than own voice (Daalman et al., 2011a)	Little softer than own voice (Daalman et al., 2011a) 36% rated their voices as "normal" in loudness (Lawrence et al., 2010)	No
	Voices speaking in third person	50% (Daalman et al., 2011a) 39% (Romme and Escher, 2000)	25% (Daalman et al., 2011a) 27% (Romme and Escher, 2000)	Yes
	Controllability	20% of the time (Daalman et al., 2011a) 17% of the time (Romme and Escher, 2000)	60% of the time (Daalman et al., 2011a) 87% of the time (Romme and Escher, 2000)	Yes
	Number of different voices	11.44 (Daalman et al., 2011a)	7.62 (Daalman et al., 2011a) 51% heard only one voice (Lawrence et al., 2010)	Yes
	Frequency	One every hour (Honig et al., 1999; Daalman et al., 2011a)	One every 3 days (Honig et al., 1999; Daalman et al., 2011a) 25% heard their voices several times a day, 37% had not heard it lately (Lawrence et al., 2010)	Yes
	Duration	40 min (Daalman et al., 2011a) Continuous (Honig et al., 1999)	2–3 min (Daalman et al., 2011a)	Yes
	Types of voices experienced	Commenting voices (72%) (Romme and Escher, 2000)	Commenting voices (18%), voices speaking with each other (11%) (Sommer et al., 2010) Commenting voices (47%) (Romme and Escher, 2000)	Yes
	Mean age at first experiencing voices	21 years (Daalman et al., 2011a) 11% onset before 12 years (Honig et al., 1999)	14 years (Sommer et al., 2010) 12 years (Daalman et al., 2011a) 40% onset before 12 years (Honig et al., 1999)	Yes
	Disturbance to daily functioning	Moderate to severe distress, disruption (Daalman et al., 2011a) Significant disturbances to daily functioning (Honig et al., 1999) Disrupting daily life in 100% of voice hearers (Romme and Escher, 2000) Significant distress and disruption to the person (Evensen et al., 2011)	Disrupting daily life in 9% of voice hearers (Sommer et al., 2010) Almost no discomfort, disruption to daily life (Daalman et al., 2011a) Disrupting daily life in 20% of voice hearers (Romme and Escher, 2000)	Yes
	Emotional valence of voice	Majority of voices are unpleasant/annoying (Daalman et al., 2011a) 100% of voice hearers experience negative voices (Honig et al., 1999) (Romme and Escher, 2000)	4% of voice hearers experience negative content only (Sommer et al., 2010) Seldom unpleasant voices/content (Daalman et al., 2011a) 53% of voice hearers experience negative voices (Honig et al., 1999; Romme and Escher, 2000) Are evaluative of others but have mundane content (Leudar et al., 1997)	Yes

(Continued)

Table 1 | Continued

Adult AVH		Clinical (confirmed psychotic disorder) AVH	Non-clinical AVH	Able to distinguish between clinical and non-clinical groups?
	Effect on individual	Frightening effect (78%); upsetting effect (89%) (Romme and Escher, 2000) Feelings of anxiety or depression (Freeman and Garety, 2003; Hoffman et al., 2008) 75% had moderate-severe anxiety ratings, 81% had moderate-severe depression ratings (Chadwick et al., 2000)	Frightening effect (none); upsetting effect (27%) (Romme and Escher, 2000) Over 50% fell within the normal range for anxiety and depression measures (Lawrence et al., 2010)	Yes
	Childhood trauma	33% Childhood sexual abuse (Honig et al., 1999) 53% childhood sexual abuse (Read and Argyle, 1999) 38% childhood sexual abuse (Offen et al., 2003) Experience of early trauma (Fowler et al., 2006) 75% experienced some sort of traumatic event (Escher et al., 2004)	Significantly more prevalent than healthy controls (Sommer et al., 2010)	No
	Family history axis I disorders	Increased risk of AVH in those who have biological relatives with the disorder (Erlenmeyer-Kimling et al., 1997; Aukes et al., 2008; Goldman et al., 2009)	Sig more prevalent than healthy controls (Sommer et al., 2010)	No
Child AVH	Localization	Similar to those in adults although not explicitly documented.	Inside their head (Best and Mertin, 2007) Attribution to an external source (Bartels-Velthuis et al., 2010)	No
	Number of voices	43.6% between 2 and 5, and 26% over 10 (Escher et al., 2004)	60% heard between 1 and 5 (Escher et al., 2004)	Partial overlap
	Frequency of voice hearing	20% hourly, 35% daily (Escher et al., 2004)	32% daily, 22% weekly (Escher et al., 2004)	Partial overlap
	Emotional valence	75% mainly negative (Escher et al., 2004)	33%+ heard unpleasant/threatening comments (Garralda, 1984) 47% mainly negative (Escher et al., 2004)	Yes
	Effect on the individual	10% associated anxiety/depressive symptoms (Escher et al., 2004)	Male voice: critical or threatening; female voice: helpful or supportive (Best and Mertin, 2007) 6% associated anxiety/depressive symptoms (Escher et al., 2004) 66% reported no/mild subjective burden (Bartels-Velthuis et al., 2010)	No
	Childhood trauma	Significantly more sexual and emotional abuse compared to healthy controls (Daalman et al., 2012)	100% from families with parents separated and domestic violence being a factor in many incidences (Best and Mertin, 2007) 1% reported sexual approach or abuse (Bartels-Velthuis et al., 2012) Sig more sexual and emotional abuse compared to healthy controls (Daalman et al., 2012)	No
	Family history axis I disorder	Heritability of schizophrenia, with certain abnormalities being trait markers for psychosis development (Weinberger and McClure, 2002; Cannon et al., 2003; Gilbert et al., 2003; Yucel et al., 2003)	50% family history of affective disorders (Garralda, 1984) Positive family histories for psychosis and depression (Burke et al., 1985)	No

This table provides a comparison of the characteristics of child and adult clinical and non-clinical voice hearers. It also outlines whether each phenomenological characteristic is able to distinguish between those with clinical and non-clinical AVH.

healthy and clinical voice hearers is the emotional valence of the voice (Honig et al., 1998; Choong et al., 2007; Sommer et al., 2010), with a negative emotional appraisal of the voice having a predictive value of 88% for the presence of a psychotic disorder (Daalman et al., 2011a). Other phenomenological differences between the groups include a reduction in perceived control for psychotic AVH, as well as a higher frequency of AVH, and later age of onset (average of 21 years) when compared to healthy voice hearers (average of 12 years) (Daalman et al., 2011a). On the other hand, factors such as the loudness of the voice, attribution of source and perceived location all remain largely consistent between the groups, which is suggestive possibly of AVH differing primarily in terms of severity, rather than them being separate phenomena. Some authors have gone as far as to say that voice hearing may be adaptive for some healthy individuals (Faccio et al., 2012).

Apart from differences in those factors which may predispose individuals to experience AVH, there are a number of cognitive capacities which also distinguish clinical and non-clinical voice hearers, both of whom are distinguishable from healthy volunteers. These differences in cognitive capacities lend weight toward the view that there may only be a partial overlap in the healthy and clinical AVH experiences. Whilst the cognitive mechanisms may be detectable in the general healthy population, the degree to which they become "hard wired" responses used to process information from the environment may determine the development of other symptoms. The features which differentiate clinical and non-clinical groups, (namely those specific phenomenological characteristics and certain cognitive capacities) may be the key to understanding how AVH develop into a pathology requiring a need for care. For instance, the metacognitive component of low cognitive confidence was found to significantly predict auditory hallucinations (Morrison et al., 2007; Barkus et al., 2010). It is believed that difficulties in memory lead to fragmented retrieval, which in turn creates confusion and a lack of confidence for the individual (Morrison and Wells, 2003). AVH have been hypothesized to come about from a breakdown in the processes monitoring memory retrieval and the source of those memories (Seal et al., 2004). The link between hallucinations and memories (e.g., Bentall, 1990) and the possibility that hallucinations and intrusive thoughts share some commonality (Morrison, 2001, 2005) have been investigated in clinical and non-clinical AVH (e.g., Brébion et al., 1998, 2005; Moritz et al., 2001). Patients with schizophrenia who hallucinate have higher rates of intrusive thoughts than both non-clinical voice hearers and healthy volunteers (Morrison and Baker, 2000), whilst hallucination prone healthy volunteers reported more intrusive thoughts than low scoring counterparts (Jones and Fernyhough, 2006). The degree to which AVH impacts on the individual in terms of pathology is related in part to the individual's ability to understand, interpret and cope with intrusive thoughts (Lobban et al., 2002).

A cognitive factor that has been found to distinguish clinical from non-clinical AVH is inhibitory control. Inhibitory control and intentional cognitive inhibition specifically, is a reduction in the ability to inhibit the intrusive memories and thoughts discussed previously. Intentional cognitive inhibition has been specifically related to AVH above and beyond any other negative or positive psychotic symptoms (Waters et al., 2003). This poor inhibitory control has been replicated and extended in subsequent studies concerned with the prevalence and frequency of AVH in schizophrenia (Badcock et al., 2005; Soriano et al., 2009) and healthy individuals with high hallucinatory predisposition (Paulik et al., 2007). The relationship between AVH and intentional cognitive inhibition may be associated with executive resources in the prefrontal cortex (Badcock and Hugdahl, 2012). Whilst it seems that both clinical and healthy AVH groups have problems in inhibitory control along a gradient of severity (Waters et al., 2003; Paulik et al., 2007), Paulik et al. (2008) suggests the source of intrusions may be related to emotional dysregulation in non-clinical groups, whereas for clinical populations the source may relate more to impaired memory processes. This would account for the greater frequency of intrusions in clinical compared to non-clinical groups (Badcock et al., 2008; Daalman et al., 2011b).

The main feature which has been said to distinguish a person's normal thoughts from that of another voice (as in the voice hearing phenomenon) is the content of that thought. Most individuals with AVH hear sentences or words which they do not recognize as their own (Hoffman et al., 2008). The normal workings of inner speech for an individual usually change according to the pervasive mood of the person at the time, and also the situations which surround them (Langdon et al., 2009). Contrastingly, the content of AVH in diagnosed psychotic disorders usually reflects a more derogatory pattern of communication; characterized by a low linguistic complexity (i.e., the repetition of single words or phrases), usually through the form of accusation, command, or abuse (Nayani and David, 1996). The difference of their own thought patterns from those of AVH is one of the main reasons patients believe their thoughts stem from another source or location (Hoffman et al., 2008), with this process termed "alienation." It is this non-self aspect which leads patients to believing such thoughts arise from external agents, such as; spirits, ghosts, deceased relatives or demons (Daalman et al., 2011a). However, the specific derogatory content of AVH in psychotic disorders has not been mirrored in studies involving the phenomenology of AVH in non-clinical populations. In such studies, the content of hallucinatory phenomena represents a more regular profile; either commenting on events taking place during the day, providing an evaluation of those around the individual or giving mundane utterances (Leudar et al., 1997; Romme and Escher, 2000; Sommer et al., 2010). In hardly any cases do non-clinical voice hearers report that the content of those experiences cause distress or dysfunction to their daily functioning (Sommer et al., 2010; Daalman et al., 2011a). When evaluating the voice hearing experience therapeutically, the content of voices is quite often ignored, with pharmacological interventions being the preferred method of treatment, rather than psychological. However, given the differences in the content of clinical vs. non-clinical hallucinatory phenomena, perhaps the content of voice hearing requires a greater degree of consideration in that which differentiates healthy experiences from pathological. It may be that the content of the voice is what drives the emotional appraisal of that voice, and as such represents an important

phenomenological characteristic to be explicated upon in future research.

Compared to healthy non-voice hearers, higher levels of negative affect are common to AVH in schizophrenia (Delespaul et al., 2002) and otherwise healthy voice hearers (van't Wout et al., 2004; Allen et al., 2005) both during hallucinations and also when hallucinations are not present [for review see Freeman and Garety (2003)]. This is suggestive of emotional arousal possibly premeditating hallucination onset, or being a factor involved in the occurrence of these perceptual experiences (Slade and Bentall, 1988). Anxiety has the most predictive power for the predisposition to hallucinate in non-clinical groups (Paulik et al., 2006), over and above depression and stress ratings. Anxious non-clinical individuals have been shown to have a greater number of hallucinatory experiences (Allen et al., 2005), whilst in clinical voice hearers, there is a significant relationship between positive symptoms (hallucinations) and anxiety, rather than depression (Norman et al., 1998). Depression in clinical groups however, has been specifically associated with AVH of greater severity compared to their non-depressed counter parts (Smith et al., 2006). This points to a dynamic whereby higher depression ratings may be indicative of greater severity of the AVH to the individual, whilst higher anxiety is more strongly related to the level of distress those AVH illicit (Hartley et al., 2012).

Temporal contextual integration is one area dissimilar findings have been documented for healthy compared to clinical hallucinators. Performance on voice and location binding tasks is impaired in AVH with schizophrenia (Brébion et al., 2002; Chhabra et al., 2011) but not in hallucination prone healthy participants (Ruiz-Vargas et al., 1999; Badcock et al., 2008; Chhabra et al., 2011). This is indicative of differences in the ability to integrate spatial location cues for clinical vs. non-clinical groups, and suggests that a deficit in contextual integration does exist in psychosis specifically. Interestingly, the intact binding of memories for hallucination prone participants occurs specifically for the content and context (speaker identity) aspect of speech (Chhabra et al., 2012). This is suggestive of a dysfunction in the contextual integration of clinical hallucinators that has some sort of relation to the content or personal aspects of the memory itself. In related research, Bendall et al. (2011) were unable to demonstrate a deficit in the contextual binding of memories for individuals with first episode psychosis. This could be suggestive of memory binding dysfunctions only occurring when psychosis is completely developed, which may co-occur with the already demonstrated deterioration in memory function for these individuals (Frommann et al., 2011). As a result, deficits in contextual integration may be representative of a general vulnerability for psychosis, instead of specific to hallucination predisposition.

Another area of dissimilarity between clinical and non-clinical AVH groups concerns lateralization of language functions during verbal fluency tasks (Diederen et al., 2010). Decreased lateralization of language function has been well documented in schizophrenia literature [for review see Li et al. (2009)]. In healthy participants, verbal fluency tasks typically activate the prefrontal cortex in the left hemisphere, which has also been reported in healthy voice hearers (Diederen et al., 2010). This implies that the failure to establish left hemisphere dominance for language is not a specific mechanism that underlies AVH. However, it does not rule out the possibility that decreased language lateralization may be related to the pathological nature of AVH specifically, such as the frequency or negative emotional content which differentiates them from healthy hallucinatory experiences.

The type of functional coping strategy used to manage hallucinatory experiences is emerging as an important determinant of the risk of progression to pathological AVH. A tendency to suppress unwanted hallucinatory stimuli is associated with persistent and pathological hallucinations (Goldstone et al., 2012). Clinical voice hearers have been found to adopt passive strategies that do not allow control over their experiences (Larøi, 2012). In comparison, healthy voice hearers have been found to possess a feeling of control over their experiences through the use of problem solving, distraction and other active coping strategies (Larøi, 2012). This is just one of many vulnerability factors identified which may impact on the progression to pathological AVH and which require further research.

A comparison of the previously discussed phenomenological characteristics of AVH in adults and children, and across clinical and non-clinical groups has been provided in **Table 1**. When comparing information regarding the perceptual quality of the voice hearing experience in both child and adult populations, it can be seen that features such as the localization, number of voices, and loudness of the voice hearing experience are largely consistent between clinical and non-clinical voice hearers. Antecedent features which may be associated with the onset of the voice hearing experience also seem similar between clinical and non-clinical groups, regardless of age. This could point to common developmental trajectories for AVH in both groups, with similar environmental and biological factors associated with the onset of AVH. As a result it can be asserted that it is not the experience of voice hearing *per se*, or features predisposing AVH onset that are associated with psychological dysfunction. Why the developmental trajectories are "triggered" in some during childhood rather than adolescence has not been investigated. Given that younger age of onset of AVH seems to be associated with healthy voice hearing suggests this is worthy of investigation.

The most notable differences between healthy and clinical voice hearers seem to be the emotional valence of the voice and the distress voice hearing elicits. This seems to be particularly in regard to the controllability and the increased frequency of the experience for clinical voice hearers. These differences may stem from an interaction between:

1. Cognitive mechanisms: appraisal of the content; coping; thoughts/delusions related to the experience; and, inhibitory control;
2. Emotional regulation: appraisal of the emotional tone of the experience; metacognitive processes underpinning emotions and general metacognitive capacity. These dictate the emotional tone and loading of thoughts, specifically through experiential avoidance (Goldstone et al., 2012) or metacognitive beliefs in general (e.g., Varese et al., 2011).

One of the major cognitive mechanisms suggested as a component cause in the generation of AVH experiences is a lack of

inhibitory control. Instinctively appealing, such a conceptualization satisfies the notion reported in many phenomenological studies of a reported lack of personal control over the generation and subsequent experience of voice hearing in both clinical and non-clinical groups. Impairments in intentional cognitive inhibition (the conscious active suppression of mental processes/thoughts) specifically have been put forward as factors linked to AVH experiences. This relationship is independent of any association to other positive, negative and disorganized symptoms of schizophrenia (Waters et al., 2003), demonstrating its specific association to AVH as a symptom unto itself. Intentional cognitive inhibition deficits follow a gradient of severity whereby non-clinical hallucinators demonstrate an impairment intermediate to clinical hallucinators (at the extreme) and healthy members of the general population (where little/no deficit exists) (Waters et al., 2003; Paulik et al., 2007). This relationship mirrors our observations of the phenomenology of clinical and non-clinical AVH experiences, lending to its significance in the generation of hallucinatory phenomena.

If deficits in intentional cognitive inhibition are implicated in the experience of AVH for all individuals, what component must interact with this dysfunction to create clinically significant AVH experiences in some people, but not in others? This difference is believed to lie in the way in which emotions are regulated, appraised and controlled for clinical vs. non-clinical groups. High levels of negative affect, primarily anxiety, depression and stress, have been documented both prior to and at AVH onset for clinical voice hearers [for review see Freeman and Garety (2003)]. Such emotional states are suggested to be involved in the development of the AVH rather than a consequence of it, as levels of negative affect have been found to fall (rather than rise) at the end of a hallucinatory episode, and increase immediately prior to an episode (Delespaul et al., 2002). So how is it that this dysregulation of emotion acts to create differences in the appraisal of AVH for clinical and non-clinical voice hearers? It has been put forward that high states of anxiety act to exacerbate deficits in intentional cognitive inhibition by increasing intensity above a critical threshold (Slade and Bentall, 1988) which act to create distressing intrusive thoughts (Paulik et al., 2006). Under this hypothesis, the individuals control over intrusive cognitive events is compromised even further by a heightened state of arousal which impairs that person's ability to function rationally and with clarity. It is also hypothesized that under this increased state of arousal, the individual's control regarding the feasibility of their metacognitive beliefs is compromised. Patients with AVH score higher on metacognitive beliefs in relation to uncontrollability and worry (Baker and Morrison, 1998). When these metacognitive beliefs occur in the context of AVH, they may act to exacerbate the negative emotional states which are already present as a result of AVH onset. The interplay between these beliefs and an already heightened mood state may dictate the appraisal of a negative emotional tone for the individual, and place emphasis on ways of thinking associated with paranoia, anxiety and distress. Although feasible, this line of reasoning requires further research before claims to its plausibility can be made.

An alternative line of research has suggested that the effectiveness of inhibitory control is dependent on limited, finite self-control resources (Baumeister et al., 2007; Goldin et al., 2008). In schizophrenia, suppression is used as an (ineffective) resource to deal with unwanted emotional expression (Henry et al., 2007, 2008). It has been put forward that the tendency to over use suppression to control unwanted emotions acts to deplete executive resources, the same of which control inhibition and are already reduced in schizophrenia (Gyurak et al., 2009). As a result, exacerbations in cognitive inhibition occur, which act to increase the severity and duration of AVH in clinical voice hearers (Waters et al., 2003). Thus, it could be argued that the reliance on emotional suppression to reduce unwanted emotions in clinical patients may result in a reduction of executive resources dedicated to inhibitory control. As cognitive inhibitory mechanisms have already been demonstrated as depleted in voice hearers, a subsequent reduction may act to increase the duration, frequency, and overall distress associated with AVH for clinical groups (Badcock et al., 2011). As this is only speculation at this point further research is warranted.

What seems to be pertinent to present research is the identification of features which allow these experiences to be dealt with in a beneficial manner. What strategies do non-clinical voice hearers adopt which allow them to regulate their experiences in an emotionally beneficial manner? It seems that they may possess coping strategies which allow them to deal with their experiences in the face of highly stressful or traumatic events. Research concerning the adaptive strategies of non-clinical voice hearers has suggested that an increased use of adaptive emotional regulation strategies (such as reappraisal) may allow the individual to adequately cope with the distressing nature of their experiences (Larøi, 2012). In contrast, clinical voice hearers have been found to use a greater number of maladaptive emotional regulation strategies (such as suppression) (van der Meer et al., 2009; Badcock et al., 2011). As a result, this leaves them in a position where they are unable to appropriately cope with their experiences, resulting in higher levels of distress and a negative emotional appraisal of the voice hearing experience. However, the precise mechanisms and processes which are involved in regulating the emotional appraisal associated with hallucinatory experiences has not yet been disseminated. As such, an understanding of these mechanisms is pertinent to the conceptualization of the differing developmental pathways leading to either: (a) clinically relevant AVH which cause distress and impairment, or; (b) healthy AVH experiences which allow the individual to function adaptively in society.

TRAUMA AND HALLUCINATIONS

(CHILD, CHILDHOOD, ADOLESCENT, ADOLESCENCE, EARLY ADULTHOOD, ADULT, AUDITORY HALLUCINATIONS, AUDITORY PERCEPTIONS, PSYCHOTIC EXPERIENCES, VOICE HEARING, PSYCHOSIS, CLINICAL, NON-CLINICAL, TRAUMA, SEXUAL ABUSE, ABUSE, INTRUSIVE THOUGHTS, RE-EXPERIENCING TRAUMA, PTSD)

One of the most well researched triggers implicated in the pathway to AVH development is that of traumatic life experiences. Romme and Escher (1989) found that 70% of voice hearers sampled first began to hear their voices following a traumatic or significant emotional event. The traumas focused on in the existing literature can include severe trauma such as abuse, neglect, the loss of a parent or more commonly experienced traumas of

childhood such as bullying and parental separation. Traumatic events which occur early on in development during childhood or adolescence are primarily cited. Perhaps traumatic events as environmental stressors during critical periods of development establishes voice hearing as a coping style or contributes to the development of cognitive mechanisms which may lead to voice hearing in adult life. Under this assumption, voice hearing becomes an adaptive process, yet the mechanism that makes this process pathological in some and functional in others is still unknown.

Trauma is implicated in the initiation and clinical relevance of child AVH (Escher et al., 2002; Morrison et al., 2003; Whitfield et al., 2005; Kelleher et al., 2008; Freeman and Fowler, 2009; McAloney et al., 2009; Elklit and Shevlin, 2011; Mackie et al., 2011). One of the largest areas of trauma associated with AVH is child sexual abuse (e.g., Janssen et al., 2004; Read et al., 2005). Although controversial, one group of researchers go so far as to claim causality (Read et al., 2005). McCarthy-Jones (2011) noted that 36% of clinical (which, as previously refers to those diagnosed with schizophrenia or psychosis) patients with AVH reported child sexual abuse, as well as 22% of healthy voice-hearers. Similarly, 56% of clinical patients who reported child sexual abuse also experienced AVH. The content and qualities of the voices heard has been linked to the identity of the abuser and verbalizations during the abuse (Read and Argyle, 1999; Read et al., 2003).

The emotional appraisal and nature of the abuse have been put forward as significant contributing factors. Associations of AVH in childhood have also highlighted the involvement of stressful life events (Bartels-Velthuis et al., 2012), daily stress (Myin-Germeys et al., 2005) and delusional ideation (Bartels-Velthuis et al., 2012) as other impacting factors. Traumatic experiences have been found to reflect the content of AVH indirectly in 58% of cases and directly in 13% of cases (Hardy et al., 2005). Therefore, it is possible that the relationship between AVH and child trauma operates through memory (see Bentall, 1990). However, it may be through a subjective interpretation of the trauma rather than directly through relived intrusive thoughts [(Morrison, 2001; Waters et al., 2006), and for a meta-analysis see Waters et al. (2012)]. Emotional distress associated with trauma may contribute to decreasing reality monitoring and increase the likelihood that memories and/or thoughts are attributed to an external source (Mertin and O'Brien, 2012).

Bullying is an emerging concern for contributing to the development of AVHs (e.g., Arseneault et al., 2010). Bullying in childhood leads to an approximately 2-fold increased risk for the presence of psychotic symptoms (Lataster et al., 2006; Schreier et al., 2009). This relationship existed for both subjective and independent reports (Schreier et al., 2009). Females reporting bullying at aged 8 years were associated with need for care and antipsychotic treatment in adulthood (Sourander et al., 2009). The emotional appraisal of the bullying and the development of secondary beliefs surrounding paranoia (which may be protective albeit maladaptive), have been implicated in reporting psychotic-like experiences following bullying (Campbell and Morrison, 2007). The capacity to experience AVHs in childhood and adolescence may co-occur with the expression of other symptomatology such as depression, anxiety or unusual personality traits such as schizotypy. These may mark a child or young person as "different" from their peers and therefore more likely to experience victimization (Turner et al., 2010). The factors which lead to the bullying, and indeed other traumatic events, need to be established since they may be indicative of psychopathology and potential confounds in the relationship between traumatic experiences and AVHs. This is particularly important when considering that experiencing one traumatic event as a child seems to increase the likelihood other traumatic events will occur (e.g., Finkelhor et al., 2007; Cuevas et al., 2010).

Like the aforementioned deleterious effects of trauma experienced during childhood, traumatic experience occurring and/or being re-experienced in adulthood can have similar psychological consequences. In one of the first epidemiological studies examining this relationship (Read et al., 2005), there were significantly more associations found between childhood maltreatment and voice hearing in adulthood, compared to any other symptom dimension (delusions, negative symptoms, thought disorder). This finding has been replicated in many subsequent investigations: the experience of AVH is significantly more likely to occur after psychological trauma in clinical (Read et al., 2003; Hardy et al., 2005; Romme and Escher, 2006, 2010; Reiff et al., 2012) and non-clinical (Honig et al., 1998; Shevlin et al., 2007; Kelleher et al., 2008; Sommer et al., 2010) groups. Therefore, the experience of trauma in and of itself does not constitute a good distinguishing factor between clinical and non-clinical groups. However, in an exploratory study, clinical and non-clinical voice hearers were compared in terms of the nature and frequency of their experienced trauma (Andrew et al., 2008). Clinical voice hearers reported significantly more incidences of childhood sexual abuse than non-clinical. Seventy-eight percent of clinical voice hearers also demonstrated symptoms indicative of DSM-IV post-traumatic stress disorder (PTSD). This suggests that perhaps severity of abuse and the emotional response may be distinguishing factors predicting clinical status. Subsequent research has suggested a dose-dependent relationship, with the greater the amount of trauma (severity and/or new events) associated with an escalation in risk of voice hearing (Bentall et al., 2012). For example, Whitfield et al. (2005) reported a 5-fold increased risk for AVH in adulthood for those who have experienced over seven adverse childhood experiences, compared to those who have experienced none at all. Similarly, Shevlin et al. (2011) reported that respondents who had experienced three different types of trauma (sexual and physical assault, rape) were eleven-times more likely to develop AVH compared to their trauma-free counterparts.

The experience of trauma as a vulnerability factor leading to hallucinatory experiences has been illustrated from child populations through to adulthood. Combining several risk factors from enduring vulnerabilities, proximal life stressors and dysfunctional psychological coping strategies, Goldstone et al. (2012) showed that childhood emotional trauma, metacognitions and life hassles all predicted the presence of auditory hallucinations in a non-clinical sample. Past research has found sexual trauma to be explicitly predictive of hallucinatory experiences (Kilcommons and Morrison, 2005; Kilcommons et al., 2008), yet this model was

only able to account for 20% of the variance in vulnerability to AVH specifically. Being one of the strongest predictors of AVH, emotional trauma cannot be discounted. However, the experience of trauma *per se* has also been shown to increase sensitivity of an individual to other life stressors (Read et al., 2001), which mirrors the previously mentioned findings of increased trauma leading to greater susceptibility to AVH (Whitfield et al., 2005; Shevlin et al., 2011). This increased sensitivity in and of itself could enhance the likelihood of clinical symptom development in an already at risk population, with the interaction of traumatic effects predisposing individuals to a heightened risk of AVH development.

One way in which trauma may act on the individual to result in AVH experiences is via intrusive thoughts and the re-experiencing of traumatic memories. The association between AVH and PTSD is well documented (e.g., Braakman et al., 2009; Anketell et al., 2010; Soosay et al., 2012). Characteristic of DSM-IV PTSD, these AVH experiences have many phenomenological similarities with "flashback" symptoms: uncontrolled revisiting of the traumatic experience (Morrison et al., 2003). A specific diagnosis of PTSD has been argued to depend on the individual's level of awareness of the intrusive thoughts and its link to previous trauma (Steel et al., 2005). There have been instances in which the intrusive memories relate directly back to the trauma (Hardy et al., 2005). However, this only occurred in a minority of cases analysed, which suggests that the relationship between trauma and AVH is not usually so clear-cut. The role of dissociation in mediating this relationship has been extensively investigated (e.g., Perona-Garcelán et al., 2012; Varese et al., 2012) and may help to account for the "separateness" or "otherness" which leads to experiences being subjectively appraised as hallucinations and not thoughts or memories (Perona-Garcelán et al., 2011; Longden et al., 2012). Other factors, such as high levels of unusual and schizotypal beliefs have also been shown to impact on the experience of intrusive thoughts resulting from trauma (Berenbaum, 1999).

Another factor identified as impacting on the existence of AVH after trauma is negative schematic beliefs that exist about the individual and others around them (Gracie et al., 2007). Negative schemas come about via the social and emotional learning of an individual (Birchwood, 2003). In voice hearers who have experienced trauma from an early age, these schemas can become ingrained over a long period of time. As these beliefs feed into and encourage the development of delusions (Freeman et al., 2002) it seems likely that they may also predispose certain people to develop AVH. Although this is one avenue which still requires more thorough research, the relation of negative schemas to the re-experiencing trauma-related AVH seems to be one facet which may be preventable through a targeted intervention.

The examination of childhood trauma predisposing AVH is often assessed through retrospective recall. This invites the possibility of factors that may impinge on the reliability of traumatic memories. Bias in recall can occur through: repression (Colangelo, 2009), suggestibility of the individual reinforced through practices such as leading questions and hypnosis (Andrews et al., 1999), the need to rationalize the presence of AVH (Schacter, 2001); and, for clinical patients: delusions (Young et al., 2001) and cognitive deteriorations (Driesen et al., 2008). Although these should be kept in mind when examining the veracity of self-reported trauma and AVH, it should also be noted that research indicates a strong tendency to under- instead of over-report abuse in psychiatric patients (Spataro et al., 2004; Fisher et al., 2011). The reliability of retrospective reports of childhood abuse has been tested, with high levels of concurrent validity and test-retest reliability for adult retrospective abuse accounts compared with clinical case notes (Fisher et al., 2011). Similar findings have been gained for female clinical patients (Meyer et al., 1996) and the retrospective accounts of child abuse in patients diagnosed with schizophrenia or bipolar disorder (Goodman et al., 1999). Additionally, the prospective epidemiological research tends to support those data collected through subjective rating scales. Corroborating documentation from independent parties can also be used to increase the confidence in data collected.

SIGNIFICANCE OF THE SCHIZOTYPAL PERSONALITY TRAIT (CHILD, CHILDHOOD, ADOLESCENT, ADOLESCENCE, EARLY ADULTHOOD, ADULT, AUDITORY HALLUCINATIONS, AUDITORY PERCEPTIONS, VOICE HEARING, PSYCHOTIC EXPERIENCES, PSYCHOSIS, CLINICAL, NON-CLINICAL, SCHIZOTYPY, SCHIZOTYPAL, CONTINUUM)

Under a continuum model of psychosis, schizotypy is believed to represent a trait-like marker of schizophrenia personality which is evident in the general population (Johns et al., 2004). Although the continuum model is not regarded in the current review as a dominant framework of causation for AVH, schizotypy is readily regarded as a biological precursor for hallucinatory experiences, with a common etiologic component being identified between hallucinatory symptoms and schizotypy in non-clinical (Mata et al., 2000, 2003) and clinical (Grove et al., 1991; Kwapil, 1998; Gooding et al., 2005) groups. Accordingly, an increase in this personality trait has been conceptualized as part of the at-risk mental health criteria (ARMS; e.g., Wood et al., 2011). Individuals who score highly on schizotypy are more likely to display a propensity for anomalous experiences including AVH (e.g., Barkus et al., 2007). It involves qualities such as odd behavior, unusual perceptual experiences, aloofness, introversion, and cognitive disorganization (Raine, 2006). The personality trait is reported to decrease with age (Rössler et al., 2007), being at its peak in adolescence (Fossati et al., 2007), although there are limited investigations of its base rate in children. The most robust difference of healthy voice hearers compared to the general population is a significantly increased level of overall schizotypy (Sommer et al., 2010). Since AVH are a positive symptom of psychotic illness voice hearers would be expected to display a significant increase in positive schizotypy only, as it is a trait vulnerability for the experience of hallucinatory phenomena (Tsakanikos and Reed, 2005). However, the difference between healthy voice hearers and controls reflects a general increase in all schizotypal dimensions. This could be indicative of the presence of AVH being associated with subclinical levels of all schizotypal phenomena. In combination with an increased family loading for psychosis (Sommer et al., 2010), these findings may be suggestive of a genetic predisposition for psychosis for those experiencing AVH who have increased schizotypal levels and a genetic labiality. Evidence for an etiologic

component linking hallucinatory predisposition and schizotypy has also been illustrated by Mata et al. (2003) through the identification of relatives of psychotic patients who display significantly elevated schizotypy levels compared to controls. In adolescents, positive schizotypy and anxiety have been reported to have a reciprocal relationship, both of which increase the likelihood maladaptive metacognitions will be present (Debbané et al., 2012). With the exception of controllability of thought, many of the maladaptive metacognitions are common to both ARMS patients and high schizotypes who hallucinate (Barkus et al., 2010).

Healthy individuals high on the schizotypal dimension have also been found to share a degree of liability toward AVH under experimental conditions. In these studies, under ambiguous conditions, healthy individuals high on the schizotypal personality dimension are shown to be significantly more likely to report the existence of some sort of auditory perceptual experience in the absence of any such corresponding stimuli (Tsakanikos and Reed, 2005; Barkus et al., 2007, 2010; Galdos et al., 2011). Although these individuals do not actually experience AVH, their pattern of responding is consistent with that of those healthy individuals who do experience AVH (Haddock et al., 1995). It seems then, that some shared cognitive component (for example, the externality hypothesis; Garety et al., 2001) may be responsible for the biased attributional process present in both schizotypal and AVH populations.

NEUROIMAGING STUDIES

(EARLY ADULTHOOD, ADULT, AUDITORY HALLUCINATIONS, AUDITORY PERCEPTIONS, VOICE HEARING, PSYCHOTIC EXPERIENCES, PSYCHOSIS, CLINICAL, NON-CLINICAL, NEUROIMAGING, fMRI)

Recently, studies examining the distribution of brain regions recruited during AVH have flourished. The development of functional imaging techniques have allowed the capture of the brain activation related to AVH. As these techniques become more refined, we are able to pinpoint activation patterns as the hallucinatory symptom is being experienced. This allows activation patterns to be documented and studied in order to gain a better understanding of the biological mechanisms underpinning AVH. By studying these biological mechanisms we are able to gain a more precise understanding of the neurological changes that occur leading up to, during and in the cessation of hallucinatory phenomena. In a recent meta-analysis Jardri et al. (2011) noted several brain networks to be activated (fMRI, PET) during AVH, including fronto-temporal brain regions, and hippocampal/parrahippocampal regions. Allen et al. (2008) also noted the involvement of the prefrontal premotor cingulate, secondary auditory cortex, Heschl's gyrus (primary sensory cortex), anterior cingulate, middle and superior temporal gyri, cerebellar areas, and aberrant activation from emotional attention centers such as the rostral/ventral anterior cingulate. In another meta-analysis, Kompus et al. (2011) compared neuroimaging (fMRI, PET) findings for patients with schizophrenia while they process external auditory stimuli, to studies of patients experiencing AVH in the absence of any external auditory stimuli. A paradoxical brain activation in relation to AVH was noted, such that there exists an overlap in the activation of the left primary auditory cortex and right rostral prefrontal cortex. These areas display increased activation in the absence of external stimuli (AVH) and decreased activation when an external stimulus is actually present. The authors deduced that an attentional bias may exist in patients who experience AVH so much so that attention is focused predominantly on internally generated information. This is significant in that the mechanism underpinning AVH occur could be explained by a bias in the cognitive processing of auditory stimuli. As this mechanism deserves a level of detail which is beyond the scope of this paper, a comprehensive review of the area has been conducted by Badcock and Hugdahl (2012).

There has been less of an emphasis on the investigation of non-clinical AVH using imaging techniques. Barkus et al. (2007) revealed that non-clinical experimentally elicited hallucinations broadly activate the same regions associated with AVH in patients with schizophrenia. This study requires replication in a larger sample size. Diederen et al. (2012) is the only neuroimaging study to date which compares AVH across clinical and non-clinical groups. Using fMRI, several areas were found to be significantly activated for both groups while experiencing AVH, including: superior temporal gyri, insula, bilateral inferior frontal gyri, inferior parietal lobule, left precentral gyrus, right cerebellum, and superior temporal pole. Significantly, no differences were found between non-clinical and clinical groups, suggesting the same brain regions are involved for all AVH. Also, the brain regions activated during AVH are the same as those which have been documented for AVH in schizophrenia and other previous research [for review see Allen et al. (2008)].

The focus in many imaging studies to-date has been on AVH in patients with schizophrenia or the investigation of non-clinical correlates such as imagining speech. One study has investigated the differences between patients with Parkinson's disease who do and do not experience AVH (Matsui et al., 2006). In contrast to many of the fMRI studies in patients with schizophrenia they reported hypoperfusion of the bilateral prefrontal cortex and right superior temporal gyrus in those with AVH. These are similar areas to those seen in patients with schizophrenia who experience AVH, however the mechanism appears to be about reduced rather than increased activation.

Given that AVH occur in other disorders besides psychosis consideration of these needs to be included in a comprehensive review. Some reference has been made to other disorders in the previous text; below we will give consideration of disorders which could be seen as providing an altered state of consciousness leading to ripe conditions for AVH to occur.

EPILEPSY

(ADULT, AUDITORY HALLUCINATIONS, AUDITORY PERCEPTIONS, VOICE HEARING, PSYCHOTIC EXPERIENCES, PSYCHOSIS, CLINICAL, NON-CLINICAL, EPILEPSY, NEUROLOGICAL ABNORMALITY)

Apart from AVH in healthy and psychological clinical groups, AVH have also been reported to occur in temporal lobe epilepsy (Brasic and Perry, 1997; Hug et al., 2011; Hauf et al., 2012). As a neurological disorder, epilepsy can create the biological threshold under which hallucinatory symptoms develop due to neurological abnormalities [such as hyperfusion of the primary auditory cortex (Hauf et al., 2012)]. The manifestation of AVH in epilepsy form part of a unique trajectory that is believed to

be separate again from that of psychotic AVH or non-clinical AVH. Evidence supporting this model is seen in studies comparing AVH in psychosis to those experienced in temporal lobe epilepsy. Through such a comparison, it can be seen that auditory phenomena are usually perceptually lateralized to the left side in epilepsy patients, with this relationship not evident in psychotic groups (Clarke et al., 2003; Florindo et al., 2006; Hug et al., 2011). As such, a clinical differentiation between AVH experiences in epilepsy and psychotic groups seems likely. Prevalence rates of hallucinatory experiences range from 3.3% in epilepsy generally, to 14% in temporal lobe epilepsy specifically (Torta and Keller, 1999). Phenomenologically, these occurrences mirror those documented in clinical (schizophrenia/psychosis) groups, with hallucinations ranging in complexity from ringing and tonal sensations, right through to more complex phenomena including musical and melody perceptions and AVH of human voices (Hug et al., 2011). Patients with epilepsy also demonstrate similar results on behavioral and neuroimaging analyses when compared to patients with schizophrenia, providing further evidence for AVH existing trans-diagnostically, that is, a symptom independent of diagnostic categorization. That the neuropsychological and neuroimaging indices of AVH in epilepsy are similar to those found in schizophrenia (Korsnes et al., 2010) lends weight once more to AVH being orthogonal of any one diagnosis.

One factor that is specific to temporal lobe disturbances is the high frequency of religious and mystical experiences reported (Ozkara et al., 2004). In the context of AVH experienced during temporal lobe epilepsy, this means that patients reporting such experiences can often attribute them to some sort of religious sensation or clarity of experience relating to God or spirits (Åsheim Hansen and Brodtkorb, 2003). This may include hearing a voice telling the individual to kneel and worship God (Ogata and Miyakawa, 1998), hearing hallucinations of God's voice (Åsheim Hansen and Brodtkorb, 2003), hearing the repetition of a religious expression (Ozkara et al., 2004) or the AVH may be regarded as a prophecy or deeper message being conveyed to the individual (Åsheim Hansen and Brodtkorb, 2003). The experience of these religious AVH for individuals with temporal lobe epilepsy does not usually result in distress or discomfort. Rather, they appear to mimic AVH in healthy voice hearers, so much so that any dysfunction that may occur is usually associated with other phenomena taking place in that individuals life (for instance the epileptic seizures or reduced quality of life associated with severe temporal lobe epilepsy). What differentiates these AVH from those experienced in healthy voice hearers is the intense religious experience which occurs. This seems to be inextricably linked to the right temporal lobe seizures which take place during and after these spiritual events (Devinsky and Lai, 2008).

SUBSTANCE-INDUCED AUDITORY VERBAL HALLUCINATIONS

(ADULT, AUDITORY HALLUCINATIONS, AUDITORY PERCEPTIONS, VOICE HEARING, PSYCHOTIC EXPERIENCES, PSYCHOSIS, CLINICAL, NON-CLINICAL, SUBSTANCE INDUCED, CANNABIS, COCAINE, AMPHETAMINES, OPIATES, ILLICIT DRUG USE, DRUGS)

AVH are also frequently documented under substance-induced states. Under the biopsychosocial model of AVH development, whilst illicit substance use is conceptualized as being an environmental and psychologically motivated facet (via substance abuse and addiction models; Cavaiola, 2009), the causes are on a biological level. The ingestion of illicit substances into the body acts by altering neurotransmission and, with persistent and pernicious use, may lead to structural and functional changes in the brain. The subjective effects of substances such as cannabis are subject to individual variability which may be accounted for by biologically meaningful phenotypes such as schizotypy (e.g., Stirling et al., 2008). Even considering the well-documented relationship between cannabis and psychosis, cannabis is considered a component cause which operates against a background of other risk factors (Castle, 2013). Hallucinations experienced in these states can be acute and transitory, passing once the substance ceases activation in the body, or they can be more chronic and ingrained-possibly leading to the development of later psychoses (Barkus and Murray, 2010). It is not known however what features differentiate individuals who do experience AVH in these states compared to those that do not. Several studies concerned with different classes of illicit drug have found that use of these substances, specifically: amphetamines (e.g., Ujike and Sato, 2004; Akiyama, 2006), cannabis (e.g., Arseneault et al., 2002; Semple et al., 2005) and cocaine (e.g., Karila et al., 2010) predate the onset of psychotic symptomatology, including AVH. The experience of psychotic symptoms (delusions and auditory hallucinations) has been reported in over half of a sample of cannabis and cocaine substance abusers, either during the use or withdrawal of those substances (Smith et al., 2009). Dependent users of cocaine (Mahoney et al., 2008), opiates (Smith et al., 2009), methamphetamine (Srisurapanont et al., 2003; Auten et al., 2012) and cannabis (Arendt et al., 2005) also experience delusions and AVH (Smith et al., 2009), usually in over 50% of responses for each study. The severity of the psychotic symptoms are almost always significantly related to the rate of substance use, such that severity of psychotic symptomatology increased with increasing rate of dependence. This association mimics a dose-dependent relationship (Thirthalli and Benegal, 2006) between the rate of substance use and the severity of psychotic symptom presentation.

In those using cocaine specifically, the AVH experienced are usually always quite vivid, isolated, and associated with the thought content at the time (Roncero et al., 2012). More often than not this is a state of paranoia, such that the person believes they hear footsteps and are being followed by spies, as an example. AVH have also been documented in cocaine users after the high has subsided (i.e., during abstinence), with this condition significantly more likely to occur in women compared to men (Mahoney et al., 2010). The reason for this difference between the sexes is still yet to be investigated. Interestingly, not all studies report an association between illicit substance use and AVH, with Ohayon (2000) reporting a significant association with the use of drugs (opiates, cocaine, amphetamines) and all hallucinatory phenomena (visual, tactile, gustatory, haptic) except auditory. Given the magnitude of this population based study (12,500 + participants), such results are surprising and warrant further investigation. It may be that other variables related to schizophrenia, such as schizotypy scores, are involved in increasing the

likelihood that AVH will occur after illicit substances (e.g., Barkus et al., 2006; Barkus and Lewis, 2008).

HYPNAGOGIC AND HYPNOPOMPIC EXPERIENCES

(ADULT, AUDITORY HALLUCINATIONS, AUDITORY PERCEPTIONS, SLEEP RELATED, PERCEPTUAL EXPERIENCES, SLEEP, HYPNAGOGIC, HYPNOPOMPIC, PHENOMENOLOGY, SLEEP EXPERIENCES)

One of the most common instances in which healthy individuals experience AVH is during the reduced level of consciousness associated with falling asleep (hypnagogic) and waking up (hypnopompic) (henceforth H/H experiences). Both these experiences are believed to represent the same group of phenomena (Mavromatis, 1988). In a relatively recent review, Ohayon (2000) found that 25% of people from the general population reported having a hypnagogic experience, whilst 18% reported a hypnopompic experience. Although significantly more common in the general population than conscious AVH, the fact that these experiences only occur in certain individuals lends to the idea that some biological factor may be mediating this relationship. Recent research has identified significant associations between dissociative personality traits and H/H experiences, which may be able to account for the predisposition to such experiences (Koffel and Watson, 2009). Disruptions to the sleep-wake cycle have been found to intensify dissociative symptoms (Giesbrecht et al., 2007), and interestingly, increased levels of dissociation and schizotypy have been found to be common in those with H/H experiences (Watson, 2001; Koffel and Watson, 2009). In student populations prevalence rates of H/H experiences have been documented to be as high as 85% (Jones et al., 2009). Similarly, rates of dissociative tendencies have also been found to decline with age in adulthood (Torem et al., 1992), which provides further support for the biological link between dissociative personality traits and H/H experiences. These experiences usually include any one of the following phenomenological characteristics; a person's name being called, reference to a past conversation, meaningless words, quotes and remarks directed at the individual (Mavromatis, 1988). When compared to the AVH experienced during wakefulness, there are some common features present. Just like AVH, they are more likely to be the voice of someone known to the person, speak directly to the person, and are more likely to be affect neutral (like those of healthy voice hearers) (Jones et al., 2010). Different to those of AVH in wakefulness however, are findings of unclear voices, contrary to the usual clearly audible voices heard in AVH, and unlike voice hearing in the general population, command AVH are only reported around 4% of the time (Jones et al., 2010). The link between H/H experiences and AVH in wakefulness, however, is still unclear. Recent research has uncovered intrusive auditory imagery as a significant predictor in the onset of H/H experiences (McCarthy-Jones et al., 2011). This is reflective of cognitive models of clinical AVH, whereby intrusive thoughts and source monitoring errors have been implicated in the onset of hallucinatory experiences (Morrison and Baker, 2000). Could it be that the two share underlying biological mechanisms such as a lack of cognitive inhibitory control, or a possible loss of the agency of self vs. other in relation to cognitions? Likewise, it is not known whether H/H experiences could represent a precursor or vulnerability marker for the subsequent development of more pathological hallucinatory experiences. As this area is still in such early stages of understanding, further research aimed at elucidating the significance of H/H experiences is warranted.

HALLUCINATORY EXPERIENCES IN THE ELDERLY

(ADULT, LATE ADULTHOOD, ELDERLY, SENIOR, AUDITORY HALLUCINATIONS, AUDITORY PERCEPTIONS, PSYCHOTIC EXPERIENCES, VOICE HEARING, PSYCHOSIS, CLINICAL, NON-CLINICAL, MUSIC HALLUCINATIONS, ALZHEIMER'S, DEMENTIA, NEURAL DEGENERATION, BEREAVEMENT)

Interestingly, prevalence rates of hallucinatory experiences have been shown to increase when adults reach an age of 60 and over (Tien, 1991; Turvey et al., 2001), with factors such as the loss of a spouse, neurocognitive degeneration and sensory deficits being implicated as risk factors for the elderly (Grimby, 1993, 1998). The types of hallucinations found to occur in the elderly are often slightly different to those in the general population, with visual hallucinations more frequently reported, as well as musical hallucinations, where the hearer experiences tunes or harmonies instead of voices (Berrios, 1990). The development of brain disease, hearing loss and advanced age are shown to be significantly related to the experience of musical hallucinations (Stephane and Hsu, 1996; Tanriverdi et al., 2001; Cole et al., 2002).

Whilst visual hallucinations are more commonly reported in dementia there are also studies which speak to the prevalence of auditory hallucinations. Auditory hallucinations occur at a rate of 6.8% in elderly populations diagnosed with Parkinson's disease; with depression and sleep difficulties being predictive of those psychotic symptoms, over and above motor or cognitive symptoms (Lee and Weintraub, 2012; Mack et al., 2012). The experiencing of auditory hallucinations in Parkinson's disease is believed to be related to the pathophysiology of the disease, not merely a side effect of medication (Fénelon, 2008). Auditory hallucinations are also found in Alzheimer's and Lewy body dementia (Ballard et al., 2001). In Alzheimer's the presence of hallucinations may be indicative of a more rapid progression of symptoms (Förstl et al., 1993). Within an institutional setting the reports of hallucinations may be related to environmental factors such as lack of entertainment or perceptual stimulation (e.g., Cohen-Mansfield and Golander, 2012). That AVH are present in dementias, where marked neural degeneration is occurring, points to the neurologically driven nature of these experiences. It seems that environmental factors or the co-occurrence of other psychiatric symptoms increases the likelihood they will occur, suggesting other symptoms share common underpinnings or that one may exacerbate the other.

Although there is still a major deficit in knowledge concerning the experience of hallucinations in the elderly, it has been shown that musical hallucinations can progress into AVH over time (Cole et al., 2002; Fischer et al., 2004). Such a transition is indicative of a decline in psychological functioning, and is found to be associated with a decline in treatment response as well as degree of insight of the affected individual (Fischer et al., 2004). It seems then, that the hallucinatory experiences

in the elderly may be more attributable to sensory loss and decline in cognitive functions, rather than those factors and traits discussed previous which predispose those of a younger age (see Tanriverdi et al., 2001; Evers and Ellger, 2004; Sanchez et al., 2011). Thus, the etiology of AVH in the elderly compared to the young may differ; further evidence for this is demonstrated in the effective treatments of elderly patients which are anti-convulsant and anti-depressive rather than antipsychotic in nature (Evers and Ellger, 2004; Larøi et al., 2005; Cope and Baguley, 2009).

For those elderly individuals who have experienced the loss of a spouse however, AVH are much more common, occurring in up to one third of the bereaved (Grimby, 1993). The hallucinations occur in the clear conscious state, and are often reported as being comforting and positive to the individual, rarely causing distress. As these hallucinatory experiences occur during times of excessive emotion, confusion can come about, often resulting in reports of the person believing their spouse is actually present (Grimby, 1993). Hallucinations occurring out of bereavement have not been found to ascribe to any definitions of pseudo-hallucinations (Baethge, 2002). Similarly, they do not meet any diagnostic criteria for psychological disorders. As a result, the existence of this type of hallucinatory experience seems to be in line with those of healthy voice-hearers, in that they do not cause any sort of distress, and thus, do not warrant any sort of clinical intervention (Pierre, 2010).

METHODOLOGICAL CAVEATS

(CHILD, CHILDHOOD, ADOLESCENT, ADOLESCENCE, EARLY ADULTHOOD, AUDITORY HALLUCINATIONS, AUDITORY PERCEPTIONS, VOICE HEARING, PSYCHOTIC EXPERIENCES, PSYCHOSIS, CLINICAL, NON-CLINICAL, HEP SEEKING)

As with many areas within psychiatry, the studies investigating auditory hallucinations in both psychiatric and healthy volunteers have their limitations. Some are attributable to the subjective nature of the experiences, whilst others can be considered directly related to the methodologies used.

In relation to studies assessing outcomes for those voice hearers who experienced childhood trauma and significant distress, there exist a number of issues limiting research findings. First, the reliance on cross-sectional methodology, although providing a wealth of current information, fails to provide reliable information on antecedents to psychological dysfunction without the probable interference from retrospective bias. Furthermore, this methodology limits the conclusions that can be drawn relating to precursors of voice hearing, prevalence of AVH at different time points and the differential patterns of clinical outcome for voice hearers. Studies in children who have been abused are often from a retrospective standpoint which ensures they are focused on one illness outcome such as psychosis. Given the multiple exposures to adverse psychopathology associated with abusive childhood environments (ambiguous communications, substance abuse, parental psychopathology and neglect to name but a few) there are many factors which need to be taken into account, and are often ignored, in the current literature. Retrospective studies, as discussed early on, come up against similar pitfalls, specifically concerning retrospective recall and bias in recall, especially when memories are sought over a decade later.

Another issue that needs to be considered across studies is the specificity of what is considered an auditory hallucination. Psychiatrically, an auditory hallucination is a sensory experience which: 1. occurs in the absence of any external stimulation; 2. takes place with sufficient conviction such that it is considered reality; and 3. occurs outside of conscious control (David, 2004). Yet it is unclear then, whether auditory events such as hearing tones, or "noises" (Shevlin et al., 2007) other than voices should be classified as AVH. It is possible that different definitions of AVH may bias results, and prevent replication across studies. Inclusion of more lax criteria under the perception of an auditory hallucination may result in an inflated prevalence of voice hearing for some studies and could limit the reliability of those results, particularly when generalizing from healthy voice hearers to clinical voice hearers. Given that we use many of the findings from healthy voice hearers to understand the mechanisms occurring in clinical samples, this raises concerns about the relevance and validity of some of the cognitive models proposed. Perhaps the time has come to form a consensus on what is understood to comprise an AVH so as to minimize any further discrepancies across studies. This may include determining under what circumstances non-clinical AVH provide useful information for clinical samples both in terms of underlying mechanisms and protective factors from help seeking behaviors.

Another factor particularly pertinent in comparing clinical voice hearers to those who do not have a psychiatric diagnosis is the separation of voice hearers into their respective research groups. For instance, it is unknown whether "healthy" voice hearers are in fact just that, or whether they are reflective of the prodrome period before psychosis onset. Similarly, categorizing people as healthy voice hearers simply because they do not experience any distress or have any other psychotic symptomatology associated with their AVH is inherently simplistic; especially considering the large variations in frequency, duration and number of voices each individual presents with. Is it so that someone who hears voices once a week can be understood to be categorically the same as someone who hears voices four times a day, simply because there is no other associated distress or dysfunction? Further research aimed at understanding the implications of these phenomenological differences is required before categorization of voice hearers as simply "clinical" or "healthy" is unduly accepted. This limitation is partly driven by the diagnostic categories emphasis on help seeking and reduced capacity to function in day-to-day life as defining whether someone meets the criteria for being a patient. The requirement of functioning in a day-to-day manner is highly subjective in and of itself. For example; many of the components of schizotypal personality disorder are likely to coincide with "healthy voice hearing," yet one is classified as a disorder whilst the other is not. Perhaps the conceptualization of diagnostic manuals with a greater emphasis on the continuum approach will assist this to some degree. However, it is recognized that the prime mechanism for people receiving treatment will always be whether they are help seeking themselves or put in a position where they are compelled to seek help.

Finally, as this review has delved into the multitude of AVH presentations across the lifespan and in different modalities of dysfunction, we want to drive home the importance of considering these hallucinatory experiences as a symptom in isolation of any specific psychiatric diagnosis. As is evident by the research presented, AVH are very similar in many respects in clinical and non-clinical groups, however they also differ on considerable key areas. The importance of this phenomenological diversity cannot be overlooked, and should be understood in terms of a symptom that is heterogeneous and may depend upon the population it occurs in. The implications for this in terms of conceptualizing a model of AVH comes back to a question of whether AVH should be recognized as an independent symptom in and of itself, or whether it should be classified as part of specific disorders diagnostic criteria. Although research findings delving into phenomenological comparisons of AVH across psychiatric and non-clinical populations are valuable, further research concerned with the changing dynamics of AVH presentation, as well as its association with other symptoms such as delusions and dissociation (outside of just schizophrenia research) is necessary.

CLINICAL IMPLICATIONS

Before drawing any firm conclusions about the mechanisms which underlie AVH, and how these mechanisms can be targeted in future clinical research it is important to consider that AVH take many forms. Some (and often the most severe) are associated with psychotic illnesses, others are understood to be manifestations of neurological disorders or substance induced, whilst others again are conceptualized as a type of healthy coping mechanism which comes about as a result of traumatic and distressing event(s). The very distinct nature of each of these manifestations of AVH implies that we should not consider them as a single category, and the heterogeneity of AVH should not be ignored. It appears that it is this heterogeneity in the presentation of AVH across different groups of the population which may make them diagnostic specific. What we see emerging as a common pattern in clinical groups is that distress is a defining factor determining need for care. The presence of voice hearing in and of itself is not sufficient for deteriorating functioning. As is evident in the review of non-clinical research, AVH usually do not cause distress or impair functioning in these voice hearers. Thus, is it not the experience of voice hearing in and of itself that leads to a decline in functioning, but the associated distress. The implications of this are two fold. First, we need to stop referring to AVH and psychotic disorders as interchangeable features. The fact that AVH occur in a multitude of different psychological, neurological and substance-induced disorders, as well as the general healthy population, means that AVH should no longer be recognized as a diagnostic indicator. Secondly, we need to start conceptualizing AVH as a symptom unto itself, and not intrinsically related to the outcome of the patient or individual. As AVH should not be understood as a diagnostic marker, it then follows that AVH have no bearing on the functional outcome of the individual. The presence of AVH in an individual by no means indicates poor functioning, but the level of functioning is one of the most pivotal markers of whether their experience of AVH is associated with pathology. Functioning is connected intricately with the level of distress experienced by the voice hearer but also is reflected in the emotional regulation of the individual. As has been suggested previously, this has an important impact on how different cognitive mechanisms interact in the voice hearing experience, to either function as a healthy coping mechanism for the individual, or create dissonance and associated distress, requiring clinical intervention.

Moving forward from these implications toward suggestions for the clinical utility of these findings first requires a focus on distress as a central component in dysfunction associated with AVH. As such, cognitive-behavioral therapy centered around reducing the distress caused by voice hearing should become a priority, over and above current models which instead place emphasis on the perceptual phenomena of voice hearing (Fowler et al., 1995; Thomas et al., 2011). The persistence of AVH was also found to be associated with the cognitive and emotional interpretations of the voice, specifically through the formation of delusions, and associated anxiety, paranoia and depression. Targeting and challenging negative schemas which exist in combination with AVH may aid in reducing the associated distress elicited by AVH in clinical groups. Finally, cognitive-behavioral therapy whereby both the client and therapist collectively dispute irrational delusions associated with AVH may also help to alleviate distress and associated dysfunctional cognitive components.

However, it needs to be acknowledged that distress is not the only component which determines a need for care in people who experience AVH. For instance, PTSD is a psychological disorder associated with significant rates of distress when compared to associated pathologies. Yet AVH are only experienced by a subgroup of patients (Anketell et al., 2010). Therefore, distress cannot be the sole predictor of clinical dysfunction. It may be that the period of AVH onset is a defining feature of whether or not that experience becomes pathological. For instance, we have seen that those AVH which follow onwards from trauma may be more likely to be followed by some sort of psychosis. Contrastingly, those voice hearing experiences which occur in childhood quiet often abate once the child enters adolescence, suggesting that the experience of voice hearing is not an indicator of problematic development. It may be that AVH are used by the human brain as some sort of coping mechanism in response to change, distress, or stress. That is, it is not the perceptual experience of voice hearing *per se* that leads to pathology-it is the associated features, or other dysfunctional mechanisms in the individual (the factors labeled background features in our framework provided in **Figure 1**). If the individual is not able to regulate and respond to their challenges and stress in an emotionally cohesive way this creates dissonance, which may result in the progression to pathology. Such a conceptualization is purely theoretical, and further clinical research is necessary to disentangle our understanding of clinical voice hearing from that which occurs in the healthy, functioning individual. Longitudinal research on a large population scale would be optimal to unravel the connection which exists between stressful life events and subsequent voice hearing. Additionally, research focused on the coping mechanisms of these individuals,

whether it be cognitive, behavioral or emotional, would also benefit our understanding of the clinical consequence of voice hearing perception in the manifestation and maintenance of AVH.

Finally, it seems clear that an understanding of the phenomenology of clinical voice hearing as a symptomatic component of psychosis has reached a stage of competent understanding. Perhaps the time has come for psychosis research to begin focusing on stable risk components such as schizotypy, rather than symptoms like AVH. It has become clear that AVH are a transdiagnostic symptom which cannot give us an indication of outcome, especially one specific to psychosis. In clinical staging models (Wood et al., 2011) early phases must focus on stable rather than transitory features of pathology which are able to separate high risk individuals from their counterparts. Clinical features such as AVH seem no longer able to provide us with such a distinction. As a result, a move toward early indicators of risk, such as neurological soft signs and schizotypy appear to be a much more feasible line of enquiry.

CONCLUSIONS

The phenomenology of AVH reveals individual differences in the experiences which are unsurprising given their subjective nature. The clarity and authenticity of AVH ensures that they have some impact on the lives of those who experience them; a differential factor is whether this influence is positive or negative. Even when considering short lived transient phenomena such as hypnogogic and hypnopompic experiences, the often frightening and alarming nature of the experiences can reduce affect in the proceeding hours. The clinical relevance of AVH under conditions of reduced consciousness needs further investigation. From considering the factors which precipitate AVH in childhood, adolescence and adulthood two points become evident. First, there is a consistency in environmental and social factors thought to trigger AVH across all ages. This suggests that these phenomena are comparable across the lifespan which has diagnostic and therapeutic implications in itself. Additionally, it may point to the underlying biological and cognitive mechanisms underpinning AVH being consistent regardless of age. Second, there is a paucity of research considering adolescence as a separate vulnerability group. Despite the field acknowledging the rapid social, psychological and neurobiological changes associated with adolescence, there are few papers considering them a group of unique interest. These studies are of particular importance given the need to identify factors which lead to the persistence of AVH from childhood into adulthood and elucidating which factors cluster to differentiate clinically at risk samples from those who will remain psychologically intact. These questions require investigation and addressing to facilitate prevention and early intervention in those at risk for serious mental health disorders.

Returning to **Figure 1** to reconsider the biopsychosocial framework used to outline this literature review. Many of the AVH attributable to biological causes such as epilepsy or dementia are treated as symptoms to be managed and/or eliminated from what is a complex neurological picture. The content of voices is often ignored and not engaged in a therapeutic manner; given the biological nature of the cause, interventions are frequently pharmacological in nature. Additionally, substance induced and sleep related phenomena are equally dismissed given the altered states involved. Individual differences in the experiences reported after using substances such as cannabis may in fact be informative. Given the pharmacologically "dirty" nature of many drugs of abuse, any pre-existing dysregulation in neurobiology will be further exacerbated by substance use and could account for the variation in experiences reported. Similarly sleep disturbances may be indicative of other vulnerabilities particularly when the associations between sleep problems and psychiatric conditions are kept in mind.

The cognitive mechanism and factors associated with AVH are clustered to provide attempts to explicate the processes underpinning AVH which may be ameliorated by psychological therapies such as cognitive behavioral therapy. The difference between clinical and non-clinical groups lies in the heterogeneous way in which each respective group processes their experiences. Consequently the identification of common mechanisms underpinning both clinical and non-clinical AVH may highlight protective factors. The most notable psychological factor which differentiates clinical from non-clinical experiences of AVH is affect regulation and subsequent negative interactions with the voices heard. Degree of preoccupation and distress associated with voice hearing is consistently associated with help seeking behaviors regardless of age or origin of the AVH. Interestingly, distress attributable to AVH is still found in those underpinned by neurological disorders despite the origins being concrete in nature. This suggests that the distress and preoccupation may be attributable to other accompanying factors and may interact with the cognitive mechanisms underpinning AVH. An alternative explanation may be that the experience of voice hearing is the end point of a number of causal pathways. Given its lack of specificity as a diagnostic symptom this may be the case. Perhaps the focus of future research should therefore be in trying to reduce the heterogeneity of the experiences by more closely defining the phenomena under consideration. Once experiences are more closely defined the multiple and complex etiological factors of AVH could be subclassed according to type of experience. For instance the causes of persisting imaginary friends in adolescents could be different to the first presentation of a voice in early adulthood. Do AVH cognitive mechanisms in individuals exposed to trauma differ from those without traumatic experiences who have high schizotypy scores? The competing cognitive explanations of AVH may be focusing in on different sub-classes of experiences. This requires further refinement and investigation.

It is likely that social and environmental factors interact with more stable vulnerability factors to lead to need for care in those who experience AVH. The key point with these factors is that they are malleable. They lack the hidden unknown qualities associated with genetic, biological and cognitive risks for AVH. As a simple example, providing sensory stimulation to elderly residential care settings would reduce the likelihood of AVH occurring. Developing targeted interventions to improve coping and stress responses to life events and even trauma may help vulnerable individuals interact with their voices in a less distressing manner.

Interventions targeting stress and affect regulation can often be delivered in a group setting without the stigmatization associated with "therapy" in the formal sense.

With the aim to improve the outcomes for young people who are at risk for developing serious mental health disorders further research is needed to determine the factors which predict persistence and need for care. Identifying the cluster of factors which produce differential developmental trajectories from childhood through to adulthood will be essential to assist earlier identification of those at risk. A move away from the consideration of triggers for AVH in isolation needs to happen for this to be achieved. Additionally research needs to become focused on the mechanisms underpinning relationships between variables. For example, the relationship between AVH and trauma is well documented; research now needs to move to determine why this relationship exists and what other factors co-occur which may be relevant to determining need for care. Recognition that AVH are not exclusive to schizophrenia-spectrum disorders needs to pervade the literature. Researchers interested in this as an end point need to now begin to refine their phenotyping to ensure that they are examining a non-clinical "psychosis-enriched" healthy volunteer sample or relevant clinical samples.

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Through the looking glass: self-reassuring meta-cognitive capacity and its relationship with the thematic content of voices

Charlotte Connor* and Max Birchwood

Birmingham and Solihull Mental Health Foundation Trust, University of Birmingham, Birmingham, UK

Edited by:
Johanna C. Badcock, University of Western Australia, Australia

Reviewed by:
Johanna C. Badcock, University of Western Australia, Australia
Adolfo J. Cangas, University of Almería, Spain
Filippo Varese, University of Manchester, UK

****Correspondence:***
Charlotte Connor, Senior Research Fellow and Honorary Fellow, Birmingham and Solihull Mental Health Foundation Trust, University of Birmingham, 66-68, Hagley Road, Birmingham, B16 8PF, UK.
e-mail: c.s.connor@bham.ac.uk

Aims: To examine the self-critical thoughts and self-reassuring meta-cognitive capacity of those who hear voices and explore whether they are associated with the theme of voice content and appraisals of voice power and voice expressed emotion.

Method: A cross-sectional design was used, combining semi-structured interviews and self-report measures. Data on symptomatology, self-critical thoughts and self-reassuring meta-cognitive capacity, thematic voice content, and appraisals of voice power and expressed emotion were collected from 74 voice-hearers in Birmingham, UK.

Results: Common themes of voice content reflected issues of shame, control, and affiliation. Controlling content was the most prevalent theme, however, no significant predictor of this theme was found; shaming thematic voice content linked with reduced capacity to self-reassure following self-critical thoughts. Voice-hearers with the greatest level of self-critical thoughts appraised their voices as powerful and high in voice expressed emotion.

Conclusions: Findings suggest that voice-hearers self-critical thoughts are reflected in the *type* of relationship they have with their voice. However, access to self-reassuring meta-cognitive capacity may serve as a protective factor for those who hear voices, resulting in more benign voice content. These findings highlight the importance of this specific meta-cognitive capacity and will inform future therapeutic interventions for the management of voices in this vulnerable group.

Keywords: voice-hearers, voice content, self-critical thoughts, self-reassuring meta-cognition, auditory hallucinations, voice power, voice expressed emotion

INTRODUCTION

The "thoughts we have about our thoughts," or our meta-cognitive capacity, helps us manage and control the flow of our cognition (Flavell, 1979). Inability to manage intrusive and unwanted cognitions, such as self-critical thoughts, intrinsic to the concept of shame, are commonly seen in those with depression (Gilbert and Miles, 2000; Gilbert et al., 2001; Connor and Birchwood, 2011a,b), who seem unable to access self-reassuring "thoughts about these thoughts" with which to alleviate the distress caused by them (Purdon and Clark, 2001).

Greater *frequency* of unwanted and intrusive thoughts and failure to cope with them has been associated with auditory hallucination proneness and are thought to underpin the phenomenon; a greater need to control their own "thoughts" associated with severity of hallucinations (Morrison and Baker, 2000; Varese and Bentall, 2011; Perona-Garcelan et al., 2012). The cognitive model of auditory hallucinations argues that voices arise due to misattribution of such unwanted intrusive thoughts to an *external* source in an unsuccessful attempt to dissipate the negative arousal that occurs on hearing them (Morrison et al., 1995). *Unwanted* and *intrusive* thoughts may be extremely distressing and voice-hearers may be particularly keen to dispel and attribute them to someone else, however, a recent study exploring the relationship between voice-hearers thoughts and voices has established that voice-hearers are able to distinguish voices from their everyday thoughts, reporting much less control over them in comparison to their own thoughts, the words heard seeming to reflect another "personality" (Hoffman et al., 2008).

The interpersonal nature of the voice/voice-hearer relationship is well documented, in about 40% of cases voices are described as "known" to the voice-hearer and voice-hearers in contact with mental health services commonly report hearing hostile and critical content which causes them much distress, including high levels of depression (Nayani and David, 1996; Leuder and Thomas, 2000). Such voice content can be likened to that heard in "real-world" high expressed emotion relationships which have been associated with increased rates of relapse in both psychosis and depression (van der Gaag et al., 2003), and linked with high levels of anxiety and low self-esteem (Bebbington and Kuipers, 1994; Barrowclough et al., 2003).

Parallels between general relationships and the voice/voice-hearer relationship have been observed by Birchwood et al., whose cognitive model of voices (Birchwood et al., 2000) revealed that voice-hearers appraisals of powerful and omnipotent voices were

reflections of their own subordination and low status in general relationships; self-evaluative appraisals of low social rank identified as the primary predictors of depression in voice-hearers, independent of voice activity (Soppitt and Birchwood, 1997). Our recent work explored how these appraisals of voice power and expressed emotion might impact on the affective response to voices and revealed that those who appraised their voices as both powerful *and* high expressed emotion had the most severe depression and suicidal ideation (Connor and Birchwood, 2011a,b).

A disparity between voice content and the affective response to voices, however, has been observed, some voice-hearers, despite hearing powerful, critical and hostile voices, remaining emotionally unaffected by them, happy to maintain contact with their voices and feeling in control of the experience (Romme and Escher, 2000; Sanjuan et al., 2004; Jenner et al., 2008). This suggests that affective response to voices may be dependent on voice-hearers *mood* and *self-evaluation*.

Ability to self-reassure (vs. self-attack) intrusive and negative thoughts about ourselves and the capacity to disengage from the flow of thought is a distinct meta-cognitive capacity (Teasdale, 1999); this is the foundation for the therapeutic concept of mindfulness which has been shown to prevent relapse of depression (Gilbert, 2004). Access to such capacity may help to explain how some voice-hearers are happy to maintain contact with their voices, despite their hostile and critical nature; helping them dissipate the negative arousal that would otherwise be caused by being confronted by such negative content and enabling them to remain in control of the experience.

This paper focuses on the self-critical thoughts and self-reassuring capacity of voice-hearers in relation to thematic content of voices and their appraisals of their voice power and voice expressed emotion.

HYPOTHESES

1. Voice-hearers' self-critical thoughts and self-reassuring meta-cognitive capacity will be associated with thematic content of voices.
2. Voice-hearers-hearers' self-critical thoughts and self-reassuring meta-cognitive capacity will be associated with appraisals of voice power and voice expressed emotion.

METHODS

DESIGN

A cross-sectional design was used. Data were collected from individual sessions with 74 participants, including structured and semi-structured interviews and self-report measures.

Individual examples of thematic voice content were examined using Framework Analysis, a deductive qualitative methodology designed for research which is applied or policy driven, highly appropriate for studies which have pre-set aims and objectives (Pope et al., 2000). Emergent categories of the themes were first indexed and then organized into thematic charts. All themes were rated independently by two qualitatively trained researchers. Individual ratings were then discussed and agreed upon to ensure concurrence.

INCLUSION/EXCLUSION CRITERIA

Eligibility criteria for participation in the study were a current diagnosis of schizophrenia or related disorder (WHO, 1992), in addition to the presence of auditory hallucinations for a minimum of the past 3 months. No exclusion criteria were used.

SAMPLING

Participants were recruited from 15 Community Mental Health Teams based in urban National Health Service Trusts in Birmingham and Derby, UK. Interviews were conducted at a day care center, clinic, or in clients own home.

MEASURES

SYMPTOMATOLOGY

Structured clinical interview for positive and negative syndrome scale

This widely used clinical measure assesses severity of positive and negative symptoms and general psychopathology (Opler and Lindenmayer, 1988). It is a 30-item interview rating severity of Positive symptoms (7 items; range, 7–49), Negative symptoms (7 items; range, 7–49), and General Psychopathology (16 items; range, 16–112). Regularly used in psychosis research, it takes approximately 30–45 min to complete and has good reliability and construct validity (Cronbach's alpha = 0.86). Reliability in the present sample = 0.68.

Calgary depression scale for schizophrenia

This structured interview is specifically designed to assess depression in schizophrenia *free of contamination by negative symptoms* (Addington et al., 1993). Consisting of eight scales reflecting the main symptoms of depression, each item is rated on a four-point rating scale; a higher overall score indicating a greater level of depression. Scores are classified into none, mild, moderate, or severe depression, using cut-off scores of 0–2 (no depression), 3–4 (mild depression), 5–6 (moderate depression), and 7+ (severe depression). It has excellent psychometric properties, and correlates highly with the Beck Depression Inventory ($r = 0.87$) (Beck et al., 1961), is easy to administer, discriminates well between those with and without major depression and has good internal consistency (coefficients of between 0.71 and 0.79). Reliability in the present sample = 0.75.

AUDITORY HALLUCINATIONS

Voice power differential scale (VPD)

This is a measure of the power differential between voice and voice hearer, and consists of 7 items rating participants perceived power, confidence, knowledge, strength, respect, ability to inflict harm, and superiority in relation to their voice (Birchwood et al., 2004). Using a 5-point Likert scale, it yields an overall total score; the greater the score, the greater the perceived power differential. Used frequently with voice hearers, it has good construct validity and reliability, a 1-week retest reliability of 0.8, and is internally reliable (Cronbach's alpha = 0.85). Reliability in the present sample = 0.82.

Level of expressed emotion scale (38 items, patient version) (LEE)

Although derived directly from EE theory (Hooley and Parker, 2006), this is not an alternative to the Camberwell Family

Interview (the usual measure associated with rating *observed* EE), but functions as an easily administered, preferred self-report measure of *perceived* EE. It consists of 38 items and 4 scales: emotional support (19 items), intrusiveness (8 items), irritation (6 items), and criticism (5 items). It uses a 4-point Likert scale, yielding total scores for each constituent item and an overall score (range, 38–152), with a higher score reflecting a greater level of EE. The standardized cut-off for high EE was 80.45, and has high internal reliability (Cronbach's alpha = 0.91) (Cole and Kazarian, 1988). For the purposes of this study, the LEE was partially modified, in order to refer to voices rather than actual people, and instructed participants: "…the following statements describe the ways in which your voice may act toward you. Please indicate whether your voice has acted in these ways during the past 3 months." All amendments were independently rated and agreed by both authors prior to implementation. Reliability in the present sample = 0.63.

SELF-CRITICAL THOUGHTS AND SELF-REASSURING CAPACITY

The other as shamer scale (OAS)—external shame

This measure was adapted from Internalized Shame Scale (Cook, 1993) and specifically measures "external shame" (Goss et al., 1994). It consists of 18 items rated on a 5-point scale according to the frequency of evaluations about how one thinks other people judge the self (0 = Never; 4 = Almost always), including statements such as: "I feel other people see me as not good enough," "I think that other people look down on me" and "Other people put me down a lot." It has high internal consistency (Cronbach's alpha = 0.92). Reliability in present sample = 0.77.

The function of self-criticizing scale (FSCS)—internal shame

Developed from clinical work focusing on self-critical thoughts and the ability to access self-reassuring meta-cognitions (Allan et al., 1994), this measure consists of 22 items rated on a 5-point scale according to how one feels the statements apply to the self (0 = Not at all like me; 4 = Extremely like me). It is made up of three factors: "inadequate self" (feeling internally put-down and inadequate following failure); "hated self" (a sense of self-dislike and aggressive/persecutory desire to hurt the self-following failure); and "reassured self" (a sense of encouragement and concern for the self when things go wrong) and includes statements such as: "I am easily disappointed with myself," "I am able to remind myself about positive things about myself" and "I have a sense of disgust with myself." It has high internal consistency (Cronbach's alpha = 0.86). Reliability in present sample = 0.69.

The forms of self-criticizing scale (FSCRS)—internal shame

This measure explores the *reasons* why people are self-critical. It consists of two factors: "self-correction" (wanting to improve performance and keep up standards), and, "self-persecution" (dislike and contempt for the self) (Allan et al., 1994). The measure begins with the statement "I get critical and angry with myself…" and is followed by 21 possible reasons for self-attacking, including statements such as: "to make sure I keep up my standards," "to stop myself being happy" and "to show I care about my mistakes," It is rated on a 5-point scale (0 = not at all like me; 4 = extremely like me) and has good internal consistency (Cronbach's alpha = 0.92). Reliability in present sample = 0.67.

Analysis

Statistical Package for Social Sciences (SPSSW) for Windows, version 20 was used to analyse data. After testing to ensure data did not violate assumptions of normality, a correlational analysis was conducted to examine associations between symptom severity, self-critical thoughts, capacity to self-reassure, and appraisals of voice power and expressed emotion. This was followed by a series of logistic regression analyses analysis exploring the relative contribution of self-critical thoughts and self-reassuring meta-cognitive capacity in the prediction of voice power, voice expressed emotion, and thematic content of control, affiliation and shame. The latter were coded as "present" = 1 or "absent" = 0 for the purpose of the analysis.

RESULTS

One hundred and two clients were approached to participate in the study; 28 did not participate: 7 (6.8%) refused; 5(4.9%) were unable to participate due to relapse; 3 (2.9%) cancelled appointments; 3 (2.9%) denied hearing voices; 2 (1.9%) did not attend their appointments and were subsequently unable to be contacted. There was no feedback for 8 (7.8%) clients failed to respond to the initial request to participate. This resulted in a response rate of 73%, with 74 clients remaining in the final cohort.

Participants were predominantly male (59.5%), with a mean age of 43 years. 64.9% of them were white European, 20.3% Afro-Caribbean, 6.8% Indian-Asian, 4.1% mixed heritage, 2.7% British Pakistani, and 1.4% African. 55.4% of participants were single, and 86.5% were unemployed. 66.2% had been diagnozed with schizophrenia, 13.5% with depressive psychosis, 9.5% schizoaffective disorder, 2.7% affective disorder and 2.7% paranoid psychosis, 1.4% bi-polar disorder, 1.4% drug induced psychosis, 1.4% borderline personality disorder and 1.4% other. 71.6% had experienced their mental health problems for more than 10 years. Over half of the participants (58.1%) heard 5+ voices; for the purposes of this study only the dominant voice experienced was considered.

Symptomatology was assessed at entry into the study using the Structured Clinical Interview for Positive and Negative Syndrome Scale (SCI-PANSS). Mean scores revealed high levels of moderate hallucinatory behavior (**Table 1**). Forty-one (55.4%) participants were at least moderately depressed, with a mean CDSS score of 6.14 (*SD* = 4.64) (**Table 2**).

THEMATIC CONTENT OF VOICES

Seventy-three (99%) voice-hearers gave typical examples of what their voice said to them (see Appendix **Table A1**). Identification of thematic content of voices was based on the number of times each theme occurred, and corrected for overall output of themes. Eight overarching themes emerged all based on the spoken message reported by voice-hearers: controlling (45%), affiliative (38%), shaming (35%), threatening (22%), killing (16%), prosaic (12%), deceiving (5%), and obscene (3%). The three most frequent themes (controlling, affiliative, and shaming) appeared together

Table 1 | Mean scores for Positive symptoms (SCI-PANSS).

	Mean score (SD)
Positive symptoms ($n = 74$)*	**16.43 (4.30)**
Conceptual disorganization**	1.78 (0.99)
Hallucinations**	4.80 (0.77)
Excitement**	1.57 (0.77)
Grandiosity**	1.73 (1.15)
Suspiciousness/persecution**	2.66 (1.42)
Hostility**	1.08 (0.27)
Delusions**	2.76 (1.47)

Potential range of scores = 7–49.

***Potential range of scores = 1–7; 1 (absent), 2 (minimal), 3 (mild), 4 (moderate), 5 (moderate/severe), 6 (severe), 7 (extreme).*

Table 2 | Depression, suicidal thinking, and hopelessness (Calgary depression scale).

Depression score	Mean (SD) 6.14 (4.64)
	Number (%)
DEPRESSION[1]	
No depression	15 (20.3)
Mild depression	18 (24.3)
Moderate depression	11 (14.9)
Severe depression	30 (40.5)
SUICIDAL THOUGHT[2]	
No suicidal thought	53 (71.6)
Suicidal thoughts	21 (28.4)
HOPELESSNESS[3]	
No hopelessness	40 (54.1)
Mild hopelessness	20 (27)
Moderate/severe hopelessness	14 (18.9)

[1] *cut-scores: 0–2, none; 3–4, mild; 5–6, moderate; 7, severe.*

[2] *cut-off scores: 0, none; 1–3, suicidal thoughts.*

[3] *cut-off scores: 0, none; 1, mild; 2/3, severe.*

on only one occasion, whereby a female voice-hearer heard the voices of her husband and father-in-law (affiliative) advising her on everyday things (controlling) and criticizing her for wanting a divorce (shaming). However, themes of control and shame often appeared alongside those which were affiliative; 28% of the time in both cases.

Hypothesis 1: voice-hearers' self-critical thoughts and self-reassuring meta-cognitive capacity will be associated with thematic content of voices

Correlational analysis found significant positive correlations between CDSS and OAS (external shame) (0.50; $p = 0.01$); FSCRS (self-persecution) (0.49; $p = 0.01$); FSCS (inadequate self) (0.60; $p = 0.01$) and (hated self) (0.54; $p = 0.01$). A negative correlation was also found with FSCS (self-reassuring capacity) (0.47; $p = 0.01$). This was followed by a regression analysis to examine the relative contribution of self-critical thinking and self-reassuring capacity in relation to thematic content of voices, controlling for CDSS, which was first force entered followed by OAS, FSCS, and FSCRS (**Table 3**). The best predictors of the thematic content of affiliation were OAS (external shame) (standardized Beta, −0.510; $p = 0.001$) and FSCS (self-persecution) (standardized Beta, −0.308; $p = 0.028$) (adjusted R-square = model 1: 0.090, significant F change = 0.005; model 2: 0.138, significant F change = 0.028). The only predictor of thematic content of shame was FSCRS (self-reassuring) (standardized Beta: −0.273; $p = 0.019$) (adjusted R square = 0.062). No significant predictor of the thematic content of control was found.

Table 3 | Results of logistic regression analysis examining voice power, expressed emotion, and thematic content of voices and their association with self-critical thinking and self-reassuring capacity.

	VPD	LEE	Controlling theme	Affiliative theme	Shaming theme
CDSS	0.529	0.636	0.334	0.854	0.409
OAS	**0.047**	0.211	0.791	**0.001**	0.935
Self-correction	0.153	0.596	0.204	0.981	0.605
Self-persecution	0.099	0.420	0.544	**0.028**	0.408
Inadequate self	0.357	**0.008**	0.882	0.226	0.500
Hated self	**0.004**	0.342	0.433	0.249	0.976
Reassuring self	0.100	0.068	0.037	0.389	**0.019**

Hypothesis 2: voice-hearers hearers' self-critical thoughts and self-reassuring meta-cognitive capacity will be associated with appraisals of voice power and voice expressed emotion

Significant positive correlations were found between CDSS and VPD (0.35; $p = 0.01$) and LEE (0.37; $p = 0.01$). This was followed by a regression analysis to examine the relative contribution of self-critical thinking and self-reassuring meta-cognitive capacity in the appraisal of VPD and perceived LEE (**Table 3**). After force entering CDSS, followed by OAS, FSCS, and FSCRS this revealed that VPD was significantly predicted by OAS (standardized beta, 0.255; $p = 0.047$) and FSCRS "hated self" (standardized beta, 0.380; $p = 0.004$) (adjusted R square = model 1: 0.281, significant F change = 0.000; model 2: 0.312, significant F change = 0.047). The only predictor of LEE was FSCRS "inadequate self" (standardized Beta, 0.478; $p = 0.008$) (adjusted R square = 0.281).

DISCUSSION

This paper has examined the self-critical thoughts and self-reassuring meta-cognitive capacity of those who hear voices in order to understand their relationship with the thematic content of voices and appraisals of voice power and voice expressed emotion.

Our findings have revealed that, overall, the most common thematic content heard by our voice-hearers was controlling, whereby voices dominated the voice-hearer, often with orders, and instructions on how to live their life. This was, however, closely followed by shaming content, with voices commenting

on the voice-hearers personal flaws and/or dishonorable behavior and affiliative content, whereby voices had some affiliative connection with the voice-hearer (either real-life or implied). These themes are indicative of voice omnipotence and the interpersonal nature of the experience, commonly reported by voice-hearer (Nayani and David, 1996; Leuder and Thomas, 2000; Gilbert et al., 2001; Connor and Birchwood, 2011a,b).

THE RELATIONSHIP BETWEEN SELF-CRITICAL THINKING, SELF-REASSURING META-COGNITIVE CAPACITY, AND THEMATIC CONTENT OF VOICES

Whilst the majority of self-critical thoughts were not associated with thematic content of voices, affiliative thematic content (content regarding an interpersonal connection of some sort) was found to be heard by voice-hearers with the least self-critical thoughts, in particular, *external shame* (fear of negative evaluation by others) and *self-persecutory* thoughts. This suggests that voice-hearers who are not fearful of the negative evaluation of others in the real-world, and whose self-critical thinking doesn't serve a self- persecutory function, may be more likely to hear thematic content relating to interpersonal connection.

In addition, we revealed that the capacity to self-reassure, following self-critical thoughts, exerted an impact on the level of shaming content heard. We interpret these findings as preliminary evidence that voice-hearers self-critical thoughts and their capacity to self-reassure those thoughts determine the *theme* of what is heard.

THE RELATIONSHIP BETWEEN SELF-CRITICAL THINKING, SELF-REASSURING META-COGNITIVE CAPACITY, AND APPRAISALS OF VOICE POWER AND EXPRESSED EMOTION

Appraisals of voice power and high expressed emotion were most frequently reported by voice-hearers who expressed self-critical thoughts of self-hatred and inadequacy. Interestingly, no other self-critical thoughts were associated with these appraisals, suggesting that feelings of self-hatred and inadequacy may be particularly relevant in determining the *type* of interpersonal relationship voice-hearers have with their voice, particularly in relation to their social status and perceived level of emotional support; two dimensions of the voice/voice-hearer relationship found to be important predictors of depression and suicidal ideation in voice-hearers, in recent work (Connor and Birchwood, 2011a,b).

METHODOLOGICAL ISSUES

We acknowledge that the present findings are a merely a snapshot of a specific group of voice-hearers with high levels of depression and long-term mental health issues, therefore, any conclusions made will apply to this population only, who occupy the most distressed end of the voice hearing spectrum. Future research will be informed by a much wider cohort of voice-hearers, including those new to hearing voices, those of a younger age and include a non-clinical sample.

One of the main methodological issues with this study was the relatively small sample size ($n = 74$) which limited the power of the analyses and any sub-group comparisons.

Another issue was choice of cross-sectional design, which, whilst allowing us to collect the data swiftly and easily, may have been less effective than a longitudinal design through which we may have been able to establish whether our findings were supported over time.

Whilst our findings are encouraging, we were surprised at the absence of any association between *controlling* thematic content and self-critical thinking. One explanation for this finding could be that controlling thematic content (powerful, dominant, and often involving orders or instructions) is not a direct translation of self-critical thoughts of personal inadequacies and flaws but rather a reflection of voice-hearers subordination and low social rank in relation to others. In this context, and for future studies, it may be more useful to differentiate between several dimensions of self-critical thinking.

We must not, however, dismiss the possibility that our failure to find a greater number of associations between thematic content and self-critical thinking is evidence of no *direct* relationship between the two. Future research should consider whether voice-hearers self-critical thinking might serve a more indirect purpose, not in *determining* thematic content or appraisals of power and EE, but serving to *maintain* the type of relationship they have with their voices. However, our earlier work exploring abuse and dysfunctional relationships in childhood found that voice-hearers who had experienced emotional abuse in childhood had the greatest levels of present-day shame cognitions (Connor and Birchwood, 2011a,b). Unsupportive early relationships are well-known to predispose individuals to later interpersonal difficulties (Collins and Read, 1990; Bretherton and Munholland, 2008). Such dysfunctional relationships in childhood determine how we regard ourselves and, how we believe others will respond to us. Self-reassuring meta-cognitive skills are theorized to originate through positive and reaffirming interpersonal early attachments with caregivers (Bowlby, 1982) who become increasingly recognized as reliable sources of affiliative support, equipping individuals with the skills to successfully negotiate future interpersonal relationships. These findings suggest that self-critical thoughts and self-reassuring capacity may be present *prior to* the development of auditory hallucinations and whilst they may serve a role in maintaining the relationship with voices, may also be implicated in their inception.

A recent review of the meta-cognitive beliefs account of auditory hallucinations by Varese and Bentall (2011), concluded that there was insufficient robust evidence to suggest a direct association between meta-cognitive beliefs and auditory hallucinations, and argue that meta-cognitive beliefs may have more in common with co-morbid symptoms; for example, thought insertion or delusions (Morrison, 2001; Linney and Peters, 2007). We should treat our findings, therefore, as a proof-of-principle study in order to provide preliminary testing of the hypotheses which will need to be confirmed in further work. Our initial findings are, however, promising and our application of strict and careful procedures to ensure concordance and inter-rater reliability we hope will help us build on these initial foundations.

THERAPEUTIC IMPLICATIONS

Auditory hallucinations have been suggested to arise due to misattribution of unwanted and intrusive thoughts, emerging in an attempt to negate their impact (Morrison et al., 1995); the metacognitive beliefs voice-hearers hold about their intrusive thoughts suggested to be associated with the *distress* caused by the experience (van der Gaag et al., 2003; Brett et al., 2009; Hill et al., 2012). The present findings support and add to this literature, revealing that in a cohort of voice-hearers with long-term mental health issues, self-critical thoughts and *incapacity* to self-reassure has an impact on the *type* of interpersonal relationship they have with their voice.

"Compassionate Mind Training" (CMT) is aimed at reducing self-critical thoughts and has been extremely successful in *increasing* feelings of self-reassurance and acceptance in non-psychotic patients with depression, resulting in *significant reductions* in shame and self-critical thoughts (Gilbert and Procter, 2006). We hope this study will inform the design of similar therapeutic interventions for depression and suicidal ideation in this vulnerable group.

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APPENDIX

Table A1 | Examples of voice themes.

Examples				
Husband and father-in-law advising her on everyday things; criticizing her for wanting a divorce	Shame	Control	Affiliation	Bullying
Woman she used to work with asking how she is	Affiliation			
Very distressed woman asking for their help	Affiliation			
Male and female strangers telling her to kill her family	Control			Bullying
Male and female strangers swearing and saying, he's by the car and I'm going to kill you	Threat			Bullying
Brother and sister-in-law telling he to come to new Delhi on holiday	Affiliation			
Ex-boyfriend and nephew asking her where she's going and discussing her appearance	Shame	Control	Affiliation	Bullying
People calling out her name and cats crying	Affiliation	Prosaic		
Friends and family saying you are going to hell, people don't love you, people don't like you	Shame		Affiliation	Bullying
Woman he knew saying come and save me and look for me; handful of male and female strangers pretending to be woman and saying I'm alright now, it's okay, trying to make out that they are her and to prevent him from rescuing her	Affiliation	Deception	Control	

Definitions of thematic content:
Affiliation – content regarding an interpersonal association, relationship or connection with someone known or suggestion of desired affiliation.
Shame – content regarding dishonor or ignominy; this could include appearance, sexuality, or other behavior.
Control – content regarding power or domination; this could include orders and instructions.
Killing – content regarding killing of self or others.
Deception – content regarding voice pretending to be someone else.
Threat – content regarding violent and/or threatening behavior (not killing).
Prosaic – mundane content.
Obscene – content of a sexual nature.

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External misattribution of internal thoughts and proneness to auditory hallucinations: the effect of emotional valence in the Deese–Roediger–McDermott paradigm

Mari Kanemoto[1]*, Tomohisa Asai[2], Eriko Sugimori[3] and Yoshihiko Tanno[1]

[1] *Department of Cognitive and Behavioral Science, Graduate School of Arts and Science, The University of Tokyo, Tokyo, Japan*
[2] *Department of Psychology, Chiba University, Chiba, Japan*
[3] *Department of Psychology, Yale University, New Haven, CT, USA*

Edited by:
Kelly Maria Johanna Diederen, University of Cambridge, UK

Reviewed by:
Simon McCarthy-Jones, Macquarie University, Australia
Ben Alderson-Day, Durham University, UK

****Correspondence:***
Mari Kanemoto, Department of Cognitive and Behavioral Science, Graduate School of Arts and Science, The University of Tokyo, 3-8-1 Komaba, Meguro, Tokyo 153-8902, Japan
e-mail: mkanemoto@beck.c.u-tokyo.ac.jp

Previous studies have suggested that a tendency to externalize internal thought is related to auditory hallucinations or even proneness to auditory hallucinations (AHp) in the general population. However, although auditory hallucinations are related to emotional phenomena, few studies have investigated the effect of emotional valence on the aforementioned relationship. In addition, we do not know what component of psychotic phenomena relate to externalizing bias. The current study replicated our previous research, which suggested that individual differences in auditory hallucination-like experiences are strongly correlated with the external misattribution of internal thoughts, conceptualized in terms of false memory, using the Deese–Roediger–McDermott (DRM) paradigm. We found a significant relationship between experimental performance and total scores on the Launay–Slade Hallucination Scale (LSHS). Among the LSHS factors, only vivid mental image, which is said to be a predictor of auditory hallucinations, was significantly related to experimental performance.We then investigated the potential effect of emotional valence using the DRM paradigm. The results indicate that participants with low scores on the LSHS (the low-AHp group in the current study) showed an increased discriminability index (d') for positive words and a decreased d' for negative words. However, no effects of emotional valence were found for participants with high LSHS scores (high-AHp group). This study indicated that external misattribution of internal thoughts predicts AHp, and that the high-AHp group showed a smaller emotional valence effect in the DRM paradigm compared with the low-AHp group. We discuss this outcome from the perspective of the dual-process activation-monitoring framework in the DRM paradigm in regard to emotion-driven automatic thought in false memory.

Keywords: auditory hallucination-like experience, DRM paradigm, emotional valence, source monitoring, schizophrenia, thought insertion

INTRODUCTION

Schizophrenia is a severe psychiatric disorder characterized by positive (e.g., auditory hallucinations and delusional beliefs) and negative symptoms (e.g., anhedonia). Auditory hallucinations are one of the most common symptoms of schizophrenia, occurring in approximately 60–80% of affected individuals (Wing et al., 1974; Slade and Bentall, 1988; Ditman and Kuperberg, 2005), and is used as a diagnostic criterion for the illness (APA, 1994) (Waters et al., 2012). Beavan and Read (2010) observed that studies employing strict definitions of hearing a voice that has no corresponding external stimulus while in a conscious, wakeful state reported that 2–4% of the general population has experienced auditory hallucinations (Read et al., 2006; Beavan and Read, 2010). However, if the definition of voices is broadened to include those experienced while in an altered state of consciousness, such as hypnogogic and hypnopompic hallucinations or drug-induced states (or banal misinterpretations of ambiguous noises, such as hearing one's name called in a public place), then up to 84% of the general population have experienced hearing voices (Millham and Easton, 1998). Auditory hallucinations within the general population have been found to be associated with the same risk factors that predict psychotic disorders (Van Os et al., 2009), which is consistent with the hypothesis of a symptom continuum from nonclinical through clinical populations (Van Os et al., 2000). It might then be expected that auditory hallucinations within the general population are driven by cognitive mechanisms that are similar to those underlying auditory hallucinations in psychotic patients. Therefore, studies investigating the cognitive mechanisms underpinning the proneness to auditory hallucinations (AHp) in nonclinical samples are likely to be relevant to the early detection of psychosis (Johns and Van Os, 2001).

SELF-MONITORING APPROACH TO AUDITORY HALLUCINATIONS

Among the positive symptoms of schizophrenia, auditory hallucinations, thought insertion, and delusions of control are called passive phenomena because the patient perceives his/her actions and thoughts as originating from external stimuli (Asai et al.,

2008). Frith (1987) first suggested that passive phenomena may be attributable to a self-monitoring disorder (self-monitoring theory). Self-monitoring theory predicts that, by nature, normal people may be able to monitor their own actions or thoughts, whereas those who suffer from passive phenomena may lack this ability and thereby misattribute their own actions or thoughts to external stimuli. Many experimental methods have been proposed to investigate self-monitoring theory. For example, experiments using the "on-line self-monitoring task" revealed that people experiencing hallucinations were more likely than normal healthy people to regard their own voices as belonging to someone else when feedback of their own voices was altered on-line (e.g., Johns et al., 2006). "Source-monitoring tasks" revealed that people experiencing hallucinations were more likely than normal healthy people to misattribute the source of words uttered by themselves to the experimenter (e.g., Brébion et al., 2000). Similar results have been found in non-clinical populations using the on-line self-monitoring task (Asai and Tanno, 2012) and the source-monitoring task (Sugimori et al., 2011a).

THE DRM PARADIGM AND MISATTRIBUTIONS OF INTERNAL THOUGHTS

Auditory hallucinations may occur without any actual audible output (McGuire et al., 1996a,b; Jones and Fernyhough, 2007), suggesting that auditory hallucinations could be one form of thought insertion (Morrison et al., 1995). Sommer et al. (2010) proposed a theoretical framework in which verbal auditory hallucinations have two essential components: audibility, including verbal imagery or thoughts, and alienation, and that the latter component might lead to the symptom of thought insertion. Moreover, neuroimaging studies have already suggested that patients with schizophrenia demonstrate not only impaired verbal self-monitoring, but also failure to activate cortical areas underlying normal monitoring of inner speech and verbal imagery (McGuire et al., 1996a,b).

Although it is important to investigate the external misattribution of internal thoughts to understand the mechanisms underpinning auditory hallucinations, the factor of "thought" was overlooked in previous behavioral studies of speech because it is difficult to directly investigate it via an on-line self-monitoring task. Memory tasks should be useful for investigating the external misattribution over thought. That is, the memory "I was thinking about that at that time" can serve as a potential indicator of on-line self-monitoring (e.g., the sense of agency) of thought ("I am thinking about that now") because contemporaneous judgments about the origins of thoughts are difficult to measure. Daprati et al. (2003) proposed a link between memory and the sense of agency on the basis of experiments investigating the effect of agency on both explicit and implicit memory traces (Franck et al., 2000; Daprati et al., 2005). Furthermore, in order to directly demonstrate the relationship between sense of agency (on-line-sense of enactment) and recalled judgment about enactment (the judgment of "I did it"), we previously focused on speech (Sugimori et al., 2011a). Through these experiments, the probability has been suggested that memory judgment of enactment might be based on the on-line sense of enactment.

The Deese–Roediger–McDermott, or DRM, paradigm (Roediger and McDermott, 1995) has also been used to investigate the external misattribution of "internal thoughts" or "inner speech" (Sugimori et al., 2011b).

The DRM paradigm was originally proposed to measure false memories (Roediger and McDermott, 1995). In this paradigm, participants are presented with a series of words (e.g., *door, glass, pane, shade, ledge, sill, house, open, curtain, frame, view, breeze, sash, screen*, and *shutter*) that are strongly associated with an unidentified target item, referred to as the critical lure (in this case, *window*; Howe et al., 2010). Roediger and McDermott (1995) and others (e.g., Deese, 1959) have found that normal healthy controls often falsely recall or recognize the critical lure in subsequent testing, and that such false memories are often associated with high levels of confidence.

The dual-process activation-monitoring framework was developed to explain how semantic related false memories occur in the DRM paradigm (McDermott and Watson, 2001). According to this framework, when we hear list items during encoding or retrieval, we think about the critical non-presented associate (critical lure) and made it more easily accessible through spreading activation in the semantic network. In this sense, the DRM paradigm, in which the critical lures falsely recalled by subjects are their externalized inner associations, is also the measure of self-monitoring error (e.g., externalizing) of inner thought or inner speech.

When considering the dual-process nature of the DRM paradigm, however, we speculate that false memories of critical lure were caused by a self-monitoring error only when the semantic network activation is similar for each participant. Indeed, as patients with schizophrenia generally experience the particular symptom of a thought disorder known as loose associations, some studies have suggested that they may not be able to activate the semantic network for the critical lure, resulting in findings of no difference in the false-alarm rates of patients and controls (Elvevag et al., 2004; Moritz et al., 2004; Lee et al., 2007). On the other hand, in a sample of recruited non-clinical individuals, Sugimori et al. (2011b) did not find the semantic activation deficit in participants who were highly prone to auditory hallucinations (high-AHp) and could extract only the effect of external misattribution. Sugimori et al. (2011b) therefore concluded that the higher false-alarm rates found for the high-AHp group represent a tendency towards the external misattribution of one's own automatic internal thoughts.

EMOTIONAL VALENCE IN AUDITORY HALLUCINATIONS

A classical perspective in the assessment of schizophrenia emphasizes derogatory content in auditory hallucinations (Fish, 1967). Others have maintained that auditory hallucinations incorporate affirmative and/or benevolent content (Miller et al., 1993; Chadwick et al., 2000). Previous studies have investigated external misattribution bias in schizophrenic and AHp subjects as modulated by the affective components of hallucination-related content (Johns et al., 2001; Larøi et al., 2004; Costafreda et al., 2008). These studies suggested that, compared with controls, schizophrenia and AHp groups were significantly more likely to produce external misattributions under the negative-word

than under the neutral-word condition. Given that previous research with schizophrenic subjects viewed external attribution as a mechanism for reducing anxiety, it was not surprising that hallucination-negative content was externalized, whereas hallucination-neutral content was not (Costafreda et al., 2008). However, the effects of the emotional valence of hallucination-positive content remain unknown. Moreover, as these previous studies used either the on-line self-monitoring task or the source-monitoring task (Johns et al., 2001; Larøi et al., 2004; Costafreda et al., 2008), the negative emotional valence effect on the external misattribution of internally generated thoughts remains unclear. In this study, we used the DRM paradigm to investigate the effects of both positive and negative emotional valence on the external misattribution of internally generated thoughts.

One potential result might reflect a higher rate of false memories of the critical lure in the high-AHp group than in the low-AHp group in the negative word condition because of their increased source-monitoring errors. This result is consistent with the results of previous studies using source-monitoring and on-line self-monitoring tasks (Johns et al., 2001; Larøi et al., 2004; Costafreda et al., 2008). However, we could have expected the opposite result by using the DRM paradigm with regard to the negative emotional valence effect, because the DRM paradigm includes another complicating factor; namely, semantic network activation processing.

In healthy people, emotional valence strengthens similarity between words and increases activation of the semantic network (Kensinger, 2004). Yet it is thought that both the negative and positive symptoms of patients with schizophrenia reflect emotional deficits (Alba-Ferrara et al., 2012). For example, previous findings indicate that patients with schizophrenia are more likely to delay the processing of emotion-laden material, when compared with controls (Rockstroh et al., 2006; Seok et al., 2006). It has also been reported that schizotypal individuals were less affected by emotional priming, suggesting that this population produces fewer emotion-driven associations (Kerns, 2005). Additionally, schizophrenic patients tend to avoid negative emotional stimuli, possibly, at least in part, because this patient population presents as emotionally overwhelmed when encountering such perceived negatively associated stimuli (Aleman and Kahn, 2005; Kerns, 2005; Seok et al., 2006). Because of such emotional deficits, emotion-driven semantic activation may not occur in the high-AHp group, which can lead them not to think about the critical lure and, consequently, reduce false recollection. Therefore, we hypothesized that the false memory of critical lures, under the negative condition, occurs more frequently in the low-AHp group than in the high-AHp group. Results in support of this hypothesis suggest that the emotional DRM paradigm has utility for investigating the effect of emotional valence, not only on the external misattribution of internal thoughts, but also on the activation of the semantic network in auditory hallucination prone subjects.

THE CURRENT STUDY

We initially hypothesized that this study would find a positive correlation between scores on auditory hallucination scales and rates of external misattribution of internal thoughts in the DRM task. Additionally, we examined potential emotional valence effects on the DRM task in terms of individual differences in AHp. We evaluated study outcomes regarding the auditory hallucination process from the perspective of self-monitoring theory, as well as from the perspective of the dual-process activation-monitoring framework for associative and/or automatic thought.

MATERIALS AND METHODS

PARTICIPANTS

Fifty Japanese university students were recruited. But one female was excluded due to obtaining outlying scores on the AHES-17 and the Launay–Slade Hallucination Scale (LSHS) (see next section) that would have biased the results, particularly in the correlation analyses. Thus, data from 49 participants were analyzed (mean age = 19.53; age range = 18–25 years; sex = 34 males, 15 females). Participants were tested individually and provided written informed consent before the experiments were conducted.

EXPERIMENTAL TASK

Materials

We used Japanese emotional word lists that were highly likely to induce false memories of critical non-presented words within the context of the DRM paradigm (Roediger and McDermott, 1995; Takahashi, 2001; Kobayashi and Tanno, 2012). Included for use were four negative lists (e.g., *pressure, pain, suicide, war*), four positive lists (e.g., *wish, sun, nature, courtesy*), and four neutral lists (e.g., *opinion, stamp, important, clock*) taken from Kobayashi and Tanno (2012) and Takahashi (2001). Each list consisted of 15 Japanese words, whose emotional valences were investigated by Kobayashi and Tanno (2012). We added 5 unrelated neutral words to each list, and each complete list included 15 associated words and 5 non-associated words. Ten of the 15 associated words of each list were designated as to-be-learned items in the learning phase and used as targets in the test phase; the remaining 5 associated words (critical lures) and the 5 non-associated words (non-critical lures) were used as distractors in the test phase only. Free auditory-editing software was used to pre-record the 10 to-be-learned items; these items were recorded as a female voice.

We selected 5 critical lures, with their emotional valence to be consistent with that of the list, as not all 15 words had an emotional valence (Kobayashi and Tanno, 2012). Non-associated words (5 words per list, 60 words in total) were selected from the other 4 neutral lists not used in the learning phase. Their listed words were not semantically associated with the listed words used in the learning phase. As a result, 10 to-be-learned words, five critical lures, and five neutral non-critical lures were used in each trial.

Procedure

In the experiment, participants completed 12 trials (four positive-, four neutral-, and four negative-emotion lists), in random order, following one practice trial. Each trial included a learning phase (auditory presentation of 10 words), a filler task (simple math calculations), and a test phase (visual presentation of 20 words for old–new recognition). Participants completed

the computer-based experiment (Windows XP, E-prime 2.0) in a dark, semi-soundproof booth.

In the learning phase, after participants pushed the space key, 10 words were presented in random order over headphones. The duration of each word was approximately 1200 ms, and the interval between words was 300 ms. Participants were instructed to "just carefully listen to these words." During the filler phase, participants were instructed to complete computational math questions that were presented on computer for 1.0 min. They received feedback on the correctness of each answer and were instructed to solve as many problems as possible. During the test phase, including the old–new recognition test, 20 words were presented in random order and participants were instructed to indicate whether each word presented had been presented during the learning phase. After all questions were answered, the learning phase for the next trial was ready to start. If participants felt tired, they could rest before the learning phase of the next trial.

QUESTIONNAIRE BATTERY

Participants were given two booklets of questionnaires and completed all questions. One booklet, administered before the experimental task, included the Beck Depression Inventory–Second Edition (BDI-II; Beck et al., 1996) to control for the influence of mood on performance of the DRM task. The remaining booklet was administered following the experimental task and included the AHES-17, the LSHS, and the Schizotypal Personality Questionnaire–Brief Form (SPQ-B; Raine and Benishay, 1995). Participants could take as much time as they needed to complete the questionnaires.

Auditory hallucination experience scale–brief version (AHES-17)

The AHES-17 is a 17-item self-report questionnaire scored on a five-point (1–5) Likert scale (e.g., "I heard someone's voice, but nobody was actually around"). Test–retest reliability ($r = 0.78$, $p < 0.0001$) and internal reliability ($\alpha = 0.84$) were adequate, and investigation of criterion-related validity showed that the AHES-17 was strongly correlated with scales measuring the positive symptoms of schizophrenia including auditory hallucinations. Furthermore, we initially reconfirmed the reliability and factor structure of these instruments in a large sample (379 men, 234 women; mean age of 19.23, $SD = 0.98$). The AHES-17 has two factors. One is auditory hallucination-like experiences about internal speech, music, and others. The other factor is delusions or thought insertions related to auditory hallucinations (Asai et al., 2011).

Launay–slade hallucination scale (LSHS)

The LSHS (Bentall et al., 1989; Launay and Slade, 1981) is a 12-item self-report questionnaire scored on a five-point (1–5) Likert scale (e.g., "I often hear a voice speaking my thoughts aloud"). The LSHS measures hallucination-like experiences, including auditory hallucinations. This scale is frequently used to measure hallucinatory experiences in both clinical and nonclinical populations. According to recent research, the LSHS has two factors: one is hallucinatory experience and the other is vivid mental events (Fonseca-Pedrero et al., 2010).

Schizotypal personality questionnaire-brief form (SPQ-B)

The SPQ-B is a 22-item, true/false self-report questionnaire consisting of items selected from the SPQ, a 74-item self-report scale based on the diagnostic criteria for schizotypal personality disorder in the Diagnostic and Statistical Manual, Third Edition, Revised (DSM-III-R; APA, 1987). The SPQ-B has the same three-factor structure as does the SPQ and includes items such as, "Have you ever noticed a common event or object that seemed to be a special sign for you?" "Have you found that it is best not to let other people know too much about you?" and "I find it hard to communicate clearly what I want to say to people." These test items measure cognitive, interpersonal, and disorganized factors, respectively.

Beck depression inventory–second edition (BDI-II)

The BDI-II, a 21-item self-report questionnaire that is one of the most widely used instruments for measuring the severity of depression, was developed based on the diagnostic criteria for depression included in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV). The fourth edition of the DSM incorporated several significant changes to the diagnostic criteria for Major Depressive Disorder. For this study, participants were asked to rate how they have been feeling for the past 2 weeks, on a four-point scale (0–3). The Japanese version of the BDI-II has been confirmed as equivalent to the original edition.

On the basis of results of our previous study (Sugimori et al., 2011b) we expected that scores on the LSHS and AHES-17 would be correlated with performance on the experimental task. We used the BDI-II to control for the influence of mood and used the SPQ-B to control for other schizophrenic-like personality traits.

ANALYSIS

We assessed the external misattribution of automatic and/or associative thought with the discriminability index (d') based on signal detection theory (Macmillan and Creelman, 1990). This index was calculated for each participant for critical lures as follows:

$$d' = z\,(\text{hits}) - z\,(\text{false alarms})$$

When the rate of false alarms was zero, a correction was applied such that the zero count was replaced by a count of $1/2N$, where N = total hits + misses. When the rate of hits was one, a correction was applied such that the one count was replaced by a count of $1 - 1/2N$, where N = total correct rejections + false alarms (Macmillan and Creelman, 1990). The d' varies from zero, where 0 = chance performance, to 4.64, where 4.64 = perfect performance.

First, we conducted an analysis of variance (ANOVA) for each emotional condition in the experimental performance in order to investigate an emotional valence effect in the DRM paradigm regardless of individual differences. Second, to determine individual differences in the DRM paradigm, we conducted a simple correlation and multiple regression analysis between questionnaire-based traits and the d'-values for the critical lure. We also analyzed correlations between questionnaire-based traits

and false alarms for non-critical lures to confirm that subjects had no semantic activation deficit. Semantic activation deficit was measured as a decrease in false memories of the critical lure and an increase in those of the non-critical lure as memories of items semantically associated with learned items may not be activated, whereas memories of items not semantically associated with learned items may be activated (Huron and Danion, 2002). We did not use d' for non-critical lures because the false-alarm rate for non-critical lures was zero for many subjects. If external misattribution of internal thought were highly related to the factor of auditory hallucination, no other questionnaire score, such as SPQ-B or BDI-II, would predict the d' of critical lures. Furthermore, we conducted a group comparison (high-AHp group vs. low-AHp group) to examine the relationship between the negative and positive emotional valence effects and auditory hallucination proneness in terms of the interaction model of the ANOVA (emotional valence effects on $d' \times$ AHp groups).

RESULTS

GENERAL PERFORMANCE IN THE EMOTIONAL DRM PARADIGM

Table 1 presents the demographic data for the current and normative samples. Compared with results of our previous study (Sugimori et al., 2011b), the scores for hallucination-related traits (LSHS, AHES-17, and Cog in SPQ-B) were slightly lower in the current sample, although the distributions in each study were almost equivalent.

Regardless of emotional valence, the mean hit rate (i.e., the rate at which learned items were correctly identified as learned) was.84 ($SD = 0.08$), whereas the mean rate of false alarms (i.e., the rate at which unlearned words were incorrectly identified as learned) was 0.31 ($SD = 0.13$) in response to critical non-presented words and 0.03 ($SD = 0.03$) in response to non-critical non-presented words. Because these results meant that critical non-presented words were associated with more false alarms than were non-critical non-presented words, we confirmed that critical lures caused enough false alarms for this procedure and for the select lists used in this experiment (e.g. Dehon et al., 2010; Sugimori et al., 2011b). The calculated mean d'-value from these hit-and-false-alarm ratios was 1.56 ($SD = 0.40$).

When we examined the effect of emotional valence on d', the averaged d' was 1.44 ($SD = 0.43$) under the negative condition, 1.64 ($SD = 0.56$) under the neutral condition, and 1.82 ($SD = 0.70$) under the positive condition (**Figure 1**). A one-way ANOVA (three emotional conditions) with repeated measures was performed. The main effect of emotional conditions was significant [$F_{(2,\ 96)} = 8.37$, $p < 0.001$]. The *post hoc* comparison using Ryan's method revealed significant differences between negative and neutral ($p = 0.01$) and negative and positive ($p < 0.001$) conditions, indicating the presence of emotional valence effects; that is, the discriminability index, d', for negative words was lower and the d' for positive words was higher. In this study, the former is referred to as the "negative emotional valence" effect and the latter as the "positive emotional valence" effect. Although the emotional valence effects on false memory have not been observed in a consistent way in previous studies, the results of the current study are consistent with those of two earlier studies (see Discussion for details) with regard to the negative emotional valence effect.

CORRELATION AND MULTIPLE REGRESSION ANALYSIS BETWEEN QUESTIONNAIRE SCORES AND EXPERIMENTAL PERFORMANCE

Pearson's correlation analysis revealed a significant correlation between the total d' for critical non-presented words and scores on the LSHS ($r = -0.29$, $p = 0.045$) (**Table 2**, **Figure 2**). This correlation remained significant while controlling for the emotional state (i.e., scores on the BDI-II) during the experimental task (partial correlation $r = -0.30$, $p < 0.042$). Correlations between d' and AHES-17 ($r = -0.05$, $p = 0.72$), and d' and SPQ-B scores ($r = -0.12$, $p = 0.43$), were not significant. These results indicate that participants with higher LSHS scores showed lower discriminability for the critical lures on the old–new recognition task. When we applied multiple regression analysis to control for the possibility of making a type I error, our model showed significant amount of variance in d' scores [$R^2 = 0.20$, $F_{(6,\ 41)} = 2.93$,

Table 1 | Demographic data of the current and normative samples.

Measure	Sample means (*SD*)	Norms means (*SD*)
Launay-slade hallucination scale (LSHS)	23.7 (7.1)	26.7 (7.8)
Auditory hallucination experience scale (AHES-17)	48.5 (10.9)	51.6 (11.5)
Schizotypal personality questionnaire-Brief (SPQ-B)	8.9 (4.4)	10.2 (5.0)
Cognitive (Cog)	1.6 (2.2)	2.2 (1.9)
Interpersonal (Int)	4.3 (1.4)	4.7 (2.0)
Disorganization (Dis)	3.0 (2.0)	3.3 (3.4)
Beck depression inventory (BDI-II)	9.0 (7.1)	N.A.

Note: Norms based on the data of our previous study, Sugimori et al. (2011b) (N = 172, for each).

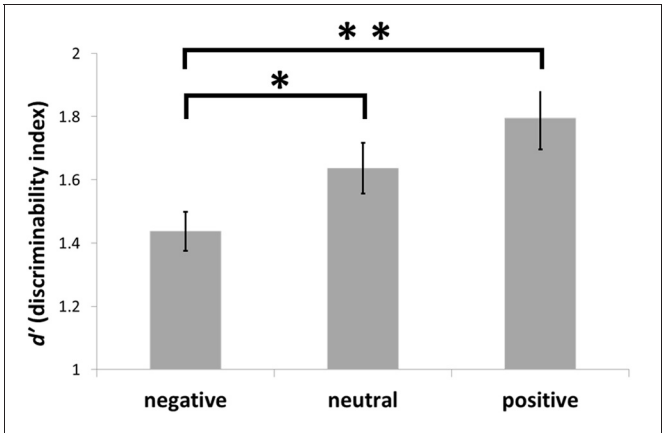

FIGURE 1 | The d' under each emotional condition in the DRM paradigm. Note: error bars mean ± 1 S.E. * < 0.05, ** < 0.01.

Table 2 | Correlation between the experimental performances and questionnaire measures.

	d′ for critical lure				FA for non-critical lure			
	Total	**Negative**	**Neutral**	**Positive**	**Total**	**Negative**	**Neutral**	**Positive**
LSHS	−0.29*	−0.05	−0.29*	−0.29*	0.19	0.31*	0.02	0.11
AHES-17	−0.05	0.12	−0.11	−0.08	0.24	0.29*	0.01	0.26
SPQB	−0.12	0.12	−0.19	−0.16	0.12	0.14	0.01	0.15
Cog	0.08	0.26	−0.01	−0.05	−0.02	0.06	−0.13	0.02
Int	−0.13	0.08	−0.23	−0.13	0.11	0.10	0.12	0.02
Dis	−0.17	−0.02	0.15	−0.18	0.16	0.15	−0.02	0.29
BDI-II	0.09	0.26	−0.01	−0.01	0.20	0.18	0.25	0.03

* *< 0.05.*

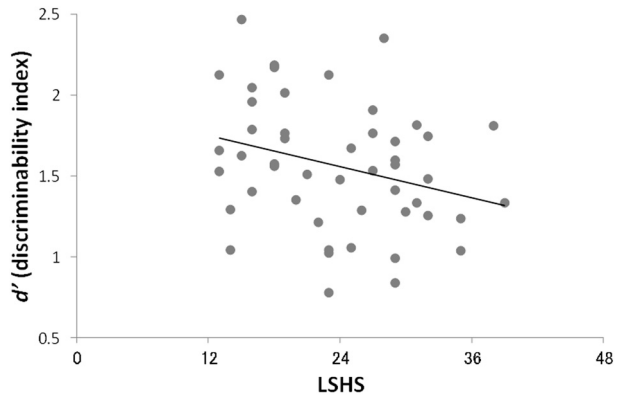

FIGURE 2 | Scatter plot between LSHS scores and total *d′*.

Table 3 | Simultaneous regression analysis of d′ for critical lures in relation to the AHES-17, LSHS, SPQ-B, and BDI-II.

		Total *d′*				
Variable		***B***	**S EB**	**ß**	***t***	***P***
LSHS		−0.033	0.011	−0.59	−3.12	0.00*
AHES-17		0.014	0.008	0.38	1.82	0.08
SPQ-B	Int	−0.021	0.027	−0.11	−0.77	0.45
	Cog	0.107	0.046	0.38	2.31	0.03*
	Dis	−0.101	0.037	−0.50	−2.72	0.01*
BDI-II		0.014	0.009	0.26	1.63	0.11

* *<0.05.*

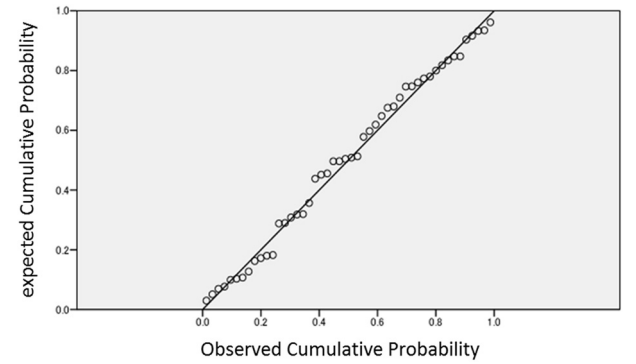

FIGURE 3 | The Normal P-P plot of Regression Standardized Residual.

$p = 0.02$], and the LSHS, nevertheless, made a significant contribution to the explanation of the total d'-values ($p = 0.003$) (**Table 3**). We confirmed normality of residuals in order to verify whether the assumption that the residuals or error terms were normally distributed has been met (see **Figure 3**). The plot of residuals fits the expected pattern well enough to support a conclusion that the residuals were normally distributed.

Our result was different from that of Sugimori et al. (2011b), who indicated that both the LSHS and AHES-17 were significantly correlated with performance of the DRM task and only the AHES-17 contributes significantly to the explanation of performance on the neutral DRM task. In order to further investigate which factor of the auditory hallucination-related scales could predict the performance of the DRM task, we conducted a multiple regression analysis again considering each of the 2 factors of the AHES-17 and LSHS (Fonseca-Pedrero et al., 2010; Asai et al., 2011) (**Table 4**). Our model showed significant amount of variance in d' scores [$R^2 = 0.17, F_{(8,\ 39)} = 2.23, p = 0.046$], and only one factor of the LSHS, Vivid Mental Events, made a significant contribution to the explanation of the total d'-values ($p = 0.01$). Vivid Mental Events is a factor composed of six questions (e.g., "Sometimes my thoughts seem as real as actual events in my life") and measures individual differences in participants' vividness of mental image. Although Sugimori et al. (2011b) did not discuss the factors of the AHES-17 or the LSHS, the current finding suggests that the present emotional DRM paradigm might be related to vividness of mental image rather than being directly related to auditory hallucinations itself in the non-clinical sample.

Table 2 also presents the correlations under each emotional condition or correlations between the false-alarm rates for non-critical lures and the scores on questionnaires. Regarding emotional valence, the correlation between LSHS and d' was significant under the neutral ($r = -0.29, p = 0.046$) and positive ($r = -0.29,\ p = 0.047$) conditions, but not under the negative condition ($r = -0.05,\ p = 0.74$) (see the next section for the detailed analysis of emotional valence effect).

Table 4 | Simultaneous regression analysis of *d′* for critical lures in relation to the each factor of AHES-17 and LSHS, and SPQ-B, BDI-II.

		Total d′				
Variable		***B***	**S EB**	**ß**	***t***	***P***
LSHS-I (vivid mental events)		−0.043	0.016	−0.532	−2.61	0.01*
LSHS-II (hallucinatory experience)		−0.021	0.024	−0.162	−0.91	0.37
AHES-17-I (auditory hallucinations)		0.016	0.009	0.379	1.85	0.07
AHES-17-II (delusions or thought insertion)		0.006	0.021	0.049	0.27	0.79
SPQ-B	Int	−0.016	0.029	−0.086	−0.55	0.59
	Cog	0.119	0.050	0.423	2.38	0.02*
	Dis	−0.107	0.038	−0.536	−2.78	0.01*
BDI-II		0.016	0.009	0.279	1.72	0.09

* *<0.05.*

On the other hand, correlations between the total rate of false alarms for non-critical lures (regardless of emotional valence) and scores were not significant, which confirmed that even individuals in the current sample who were relatively high in terms of schizotypal traits had no semantic activation deficit. However, we found a significant correlation between LSHS (as well as AHES-17) scores and the rate of false alarms for non-critical lures under the negative condition ($r = 0.31$, $p = 0.03$). This result indicates that high-AHp subjects showed higher false-alarm rates for non-associated words under the negative condition (see the Discussion for a detailed interpretation). As the LSHS is used to measure auditory hallucination proneness in nonclinical samples (Larøi, 2012), and the LSHS was the strongest predictor of *d′* in the current result, we focused on LSHS scores in the further detailed analyses.

PRONENESS TO AUDITORY HALLUCINATIONS AND THE EFFECT OF EMOTIONAL VALENCE

To directly investigate the relationship between the positive and negative emotional valence effect on the DRM task and AHp, we first divided participants into a low-AHp group and a high-AHp group based on LSHS scores (**Table 5**). Subjects who scored in the bottom 25th percentile comprised the low-AHp group ($N = 13$), and those who scored in the upper 25th percentile comprised the high-AHp group ($N = 12$) (see **Table 5**). Our cut-off point for bottom 25th percentile was 18 (20 in Sugimori et al., 2011b) and the point of upper 25th percentile was 29 (32 in Sugimori et al., 2011b). Our points for grouping are slightly lower than previous studies, but each group has nearly ten points gap between two groups. Furthermore, the following statistical results were identical when we divided participants using the criteria of +1 *SD* ($N = 9$) and −1 *SD* ($N = 11$).

Figure 4 shows the negative and positive emotional effects in the low-AHp and high-AHp groups. The negative effect was the difference between the negative and neutral conditions: negative-*d′* - neutral-*d′*. The positive effect was the difference between the positive and neutral conditions: positive-*d′* - neutral-*d′*. These calculations were necessary because the neutral-*d′* was correlated with LSHS scores (**Table 2**), indicating that the neutral-*d′* should be the baseline for the emotion effects. Whereas the low-AHp group showed similar emotion effects as found for the general population (**Figure 1**), the high-AHp group did not show these effects. A two-way ANOVA (two groups × two emotional valence effects) with repeated measures showed that the interaction between group and emotional valence effects [$F_{(1, 23)} = 7.74$, $p = 0.01$] and the main effect of emotional valence were significant [$F_{(1, 23)} = 11.52$, $p = 0.002$]. The simple main effect of emotional valence was also significant for the low-AHp group ($p < 0.001$), whereas the effect of emotional valence was not significant for the high-AHp group (**Figure 4**). These findings indicated that low-AHp participants showed positive and negative emotional valence effects in the DRM paradigm, whereas the high-AHp group did not show effects for either valence.

Table 5 | Characteristics of low-and high-AHp groups.

	low-AHp	**high-AHp**	**Significance**
Age	19.85 (1.95)	19.08 (0.67)	$p = 0.21$
Sex ratio (M/F)	12/1	8/4	
LSHS total score	15.15 (1.73)	32.75 (3.31)	$p < 0.01$**
AHES-17	37.54 (8.75)	57.42 (6.22)	$p < 0.01$**
SPQ-B	6.92 (4.91)	11.46 (3.05)	$p = 0.01$*
Cog	1.00 (1.08)	2.46 (1.57)	$p = 0.01$*
Int	3.77 (2.49)	5.27 (0.97)	$p = 0.09$
Dis	2.15 (2.15)	3.73 (1.74)	$p = 0.07$
BDI-II	9.31 (8.48)	11.58 (7.94)	$p = 0.50$

* *<0.05,* ** *<0.01.*

DISCUSSION

This study investigated the external misattribution of internally generated thoughts and emotional valence effects on it in high-AHp people. We used the LSHS and the AHES to measure auditory hallucination proneness, and a memory task, the DRM paradigm (Roediger and McDermott, 1995), to measure externalizing bias of internal thought. The DRM paradigm induces spontaneous thought of words semantically associated with presented words, and these thought of words are externalized with a high probability. If the self-monitoring hypothesis is true, then high-AHp people will make this error more often than low-AHp people. The present results showed that the LSHS score (measure of AHp in this study) was positively correlated with the

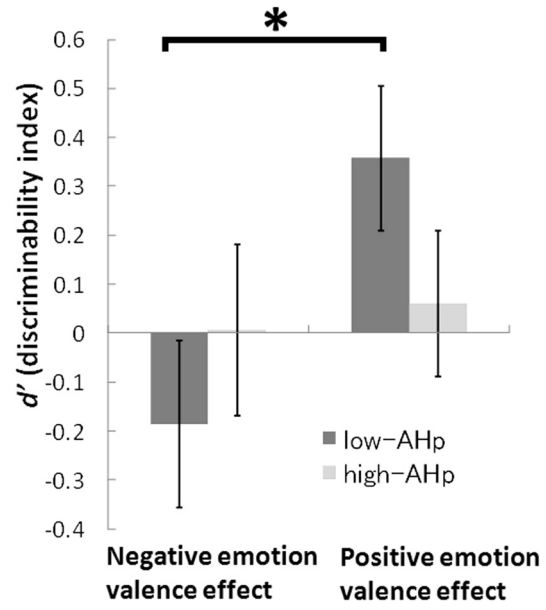

FIGURE 4 | Negative and positive emotional valence effect in AHp groups. Note: negative emotion valence effect = negative − neutral condition. Positive emotion valence effect = positive − neutral condition. Error bars mean ± 1 S.E. * < 0.05.

overall *d*' results for critical lures (the total of negative, positive, and neutral lures). Additionally, we found no emotional valence effects among high-AHp subjects, even though these effects were observed in the low-AHp group. We discuss these results from the perspectives of both the self-monitoring theory for auditory hallucinations and the dual-process activation-monitoring framework in the DRM paradigm (McDermott and Watson, 2001).

GENERAL PERFORMANCE OF THE EMOTIONAL DRM PARADIGM

According to **Figure 1**, the emotional valence effect was reflected in data showing that the discriminability of negative words was lower than that for positive words. Previous studies have not observed the emotional valence effects in false memory in a consistent way (Dehon et al., 2010). However, recent studies have reported a higher frequency of false memories under the negative condition compared with the neutral condition when vigilance, word length, semantic similarities, and familiarity were controlled (Brainerd et al., 2008; Dehon et al., 2010). The results of the present study suggest that negative emotional valence increased false memories, which supports the results reported by Dehon et al. (2010) and Brainerd et al. (2008).

Brainerd et al. (2008) explained that the reason that the emotional valence effect increased false memories under the negative condition and decreased them under the positive condition was that similarities between false and true items increased under the negative condition whereas they decreased under the positive condition, thereby rendering confusion of true and false memories more likely under the negative than the positive condition. On the other hand, Dehon et al. (2010) suggested that the Paradoxical Negative Emotion (PNE) hypothesis was relevant to these results. The PNE hypothesis, recently put forward by Porter and colleagues (e.g., Porter et al., 2008, 2010) suggests that evolution has changed the brain such that negative information, compared with neutral or positive information, is more likely to be recalled over time and is also more vulnerable to memory distortions. According to the PNE hypothesis, there is adaptive value in having access to information from various sources regarding potential future dangers (Schacter and Addis, 2007); this increases the likelihood that people will misattribute internal negative content to actual external events. In summary, we not only increase semantic network activation by increasing semantic similarity, but also make more source-monitoring errors leading to experiencing more false memories in the DRM paradigm under the negative condition.

PRONENESS TO AUDITORY HALLUCINATIONS AND EXTERNAL MISATTRIBUTION

As predicted, we replicated the positive correlation between AHp and the external misattribution of critical lures in the DRM task (Sugimori et al., 2011b). The same result was confirmed by multiple regression analysis. We conclude that this overall result (the total of the negative, positive, and neutral lures) indicates that high-AHp people tend to make more external misattributions of their internal thoughts given that no semantic activation deficits were found for participants in the present study. Moreover, this correlation persisted even when we controlled for the influence of negative mood (using the BDI-II). Apart from negative mood, which is commonly seen in people experiencing hallucinations, AHp relates to the external misattribution of internal thoughts. These results are important to future explorations of the mechanisms underlying auditory hallucinations, particularly in view of the fact that external misattribution of internal thoughts is said to be one form of thought insertion (Morrison et al., 1995). Many previous studies found a relationship between AHp and the external misattribution of actions and speech (e.g., Sugimori et al., 2011a; Asai and Tanno, 2012), but a relationship involving internally generated thoughts has not been reported until recently (Brébion et al., 2010; Sugimori et al., 2011b).

In this study, correlation and multiple regression analysis revealed that only the LSHS has a significant relationship with the performance of the DRM task. Interestingly, Sugimori et al. (2011b) reported a significant correlation between the performance of the DRM task and the AHES-17 and LSHS, and significant contribution of the AHES-17. To explore this issue further, we conducted a linear multiple regression analysis considering each of the two factors of the AHES-17 and the LSHS (Fonseca-Pedrero et al., 2010; Asai et al., 2011). We found that only the factor of vivid mental events in the LSHS made a significant contribution to experimental performance (**Table 4**). Many previous studies have reported that vividness of mental image and auditory hallucinations have a strong relationship (e.g., Van de Ven and Merckelbach, 2003). The present result suggests that vividness of mental image might have a stronger relationship with performance than auditory hallucination itself in the emotional DRM paradigm. It is still uncertain which components of psychotic phenomena are related to an externalizing bias. For example,

Brookwell et al. (2013) reported that extant studies have found that an externalizing bias is related to hallucinatory predisposition only. However, delusional ideation has also been related to an externalizing bias (Dehon et al., 2008). Further research is needed to clarify this issue.

Regarding emotional valence, LSHS scores were significantly ($p < 0.05$) correlated with d' under the neutral and positive conditions but not under the negative condition. Moreover, LSHS scores were significantly correlated with the false alarm-rates for non-critical lures under the negative condition (discuss in the next session). We have to note that these correlation results are exploratory and could be subject to Type I error. Because the lack of correlation under the negative condition cannot be understood within the context of source-monitoring theory, we examine this finding in the context of the dual-process considerations of the DRM paradigm in the section below.

PRONENESS TO AUDITORY HALLUCINATIONS AND EMOTIONAL DEFICITS

We conducted a group comparison of high-AHp and low-AHp individuals to examine the potential effects of negative and positive emotional valence on the d' for critical lures. We predicted two opposite results for the high-AHp group in terms of the effect of negative emotional valence on false memory in the DRM task. One prediction was that the external misattributions of critical lures would increase more in the high-AHp than in the low-AHp group under the negative emotional condition, possibly as a result of source-monitoring errors, which would be consistent with findings of earlier studies (Johns et al., 2001; Larøi et al., 2004; Costafreda et al., 2008). The second prediction was for minimal external misattributions of critical lures by the high-AHp group under the negative condition as participants in this group may not rely as heavily as those in the low-AHp group on emotion-driven associations for the activation of the semantic network in the DRM task. Our findings support the second prediction and, in terms of performance on the DRM task, the high-AHp group did not show negative or positive emotional valence effects. However, the low-AHp group revealed significant emotional valence effects such that the d' under the negative condition was low and that under the positive condition was high under the neutral condition when compared with the comparable figures for the low-AHp group (**Figure 4**).

In healthy people, emotional valence strengthens associations between words because of emotional similarities (Kensinger, 2004). The high-AHp group, however, may not have made these emotion-driven semantic associations, perhaps because they might be not good at processing emotional components in a situation in which the auditory stimuli are presented very fast. Indeed, research has indicated that patients with schizophrenia experience delayed processing of emotional components compared with control subjects (Rockstroh et al., 2006; Seok et al., 2006). It has also been reported that schizotypal individuals are less affected by emotional priming, which implies they make fewer emotion-driven associations (Kerns, 2005). It is possible that the high-AHp group was unable to successfully make emotion-driven associations because of these deficits, given that the interval between words was very short in this study (about 300 ms). Moreover, studies have found that patients with schizophrenia experiencing positive symptoms tend to avoid directing attention at negative emotional stimuli because they are easily overwhelmed by the negative emotional components of these phenomena (Aleman and Kahn, 2005; Kerns, 2005; Seok et al., 2006). Thus, they may make fewer associations and retain verbatim memories by avoiding attending to negative images. This may also explain the correlation between LSHS scores and false-alarm rates for non-critical lures under the negative condition. That is, high-AHp subjects made more task-irrelevant mistakes as a result of being overwhelmed by negative words. Although the high-AHp group may have demonstrated more external misattribution of internal thoughts under the negative condition than did the low-AHp group, this effect may be offset by fewer emotion-driven associations.

The positive emotional valence effect in the low-AHp group (higher d') may be attributable to decreased external misattribution and decreased semantic similarity. The PNE hypothesis holds that positive emotional valence decreases memory distortion (Porter et al., 2008). The high-AHp group may not have experienced this effect because of their tendency toward external misattribution and their deficits related to processing emotional components. However, further research into the positive emotional valence effect on external misattributions is needed.

LIMITS OF THE PRESENT STUDY AND FUTURE ISSUES

The present study has three limitations. First, it is still unclear which factor of the auditory hallucination experiences could be related to the externalizing bias. Despite the strong correlation between scores on the AHES-17 and those on the LSHS ($r = 0.69$) found in the present study, scores on the AHES-17 revealed no significant correlation with the performance of the DRM paradigm. Moreover, our analysis of each of the two factors of the LSHS and AHES-17 revealed that only the factor of vivid mental events made a significant contribution to the externalizing bias index. Future studies need to selectively use questions about auditory hallucination, delusional ideation, and vivid mental events. Second, the DRM lists used in the present study were not controlled in terms of vigilance or degree of semantic associations between emotional conditions. Thus, the results of this study related to emotional valence are related to the specific lists used. Previous studies that controlled for vigilance (e.g., Brainerd et al., 2008), degree of associations, familiarity, and word length (e.g., Dehon et al., 2010) also reported that false-alarm rates under the negative condition were higher than those under other conditions. In this context, the results of the present study may nonetheless suggest an emotional valence effect in the DRM paradigm and individual differences in AHp. Third, our sample size (i.e., 49) was smaller than that in other studies comparing high and low hallucination proneness (Badcock et al., 2008; Paulik et al., 2008). For example, Paulik et al. (2008) initially recruited over 500 participants to be assigned to either a high or a low LSHS group (final group size was 28 and 25 for each). Our sample data, however, has a distribution that is similar to that of the previous studies that utilized a large sample (172 in Sugimori et al., 2011b; 589 in Paulik et al., 2006). Further, our cut-off points for the high and low groups have a scoring

gap between the two groups that is similar to the one found in Sugimori et al. (2011b). These data suggest that our high or low groups are directly comparable to those of previous studies.

This study found that high-AHp individuals showed a less pronounced emotional valence effect on false memories in the DRM paradigm than did low-AHp individuals. Moreover, when it comes to its responsible factor, the component of vividness of mental image in auditory hallucination proneness was most related to externalizing bias measured by the emotional DRM paradigm. In the future, we need only to develop a paradigm to enable separate examinations of the emotional valence effect on external misattributions and on semantic network activation in high-AHp individuals, and to further explore what component of psychotic symptoms is related to externalizing bias.

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An examination of auditory processing and affective prosody in relatives of patients with auditory hallucinations

Rachel Tucker[1], John Farhall[1], Neil Thomas[2,3], Christopher Groot[4] and Susan L. Rossell[2,3]*

[1] School of Psychological Sciences, La Trobe University, Melbourne, VIC, Australia
[2] Brain and Psychological Sciences Research Centre, Swinburne University, Melbourne, VIC, Australia
[3] Monash Alfred Psychiatry Research Centre, The Alfred, Melbourne, VIC, Australia
[4] School of Psychological Science, University of Melbourne, Melbourne, VIC, Australia

Edited by:
Frank Larøi, University of Liege, Belgium

Reviewed by:
Frank Larøi, University of Liege, Belgium
Katharina S. Goerlich-Dobre, RWTH Aachen University Hospital, Germany

***Correspondence:**
Susan L. Rossell, Monash Alfred Psychiatry Research Centre, The Alfred, Level 4, 607 St. Kilda Road, Melbourne, VIC 3004, Australia
e-mail: srossell@swin.edu.au

Research on auditory verbal hallucinations (AVHs) indicates that AVH schizophrenia patients show greater abnormalities on tasks requiring recognition of affective prosody (AP) than non-AVH patients. Detecting AP requires accurate perception of manipulations in pitch, amplitude and duration. Schizophrenia patients with AVHs also experience difficulty detecting these acoustic manipulations; with a number of theorists speculating that difficulties in pitch, amplitude and duration discrimination underlie AP abnormalities. This study examined whether both AP and these aspects of auditory processing are also impaired in first degree relatives of persons with AVHs. It also examined whether pitch, amplitude and duration discrimination were related to AP, and to hallucination proneness. Unaffected relatives of AVH schizophrenia patients ($N = 19$) and matched healthy controls ($N = 33$) were compared using tone discrimination tasks, an AP task, and clinical measures. Relatives were slower at identifying emotions on the AP task ($p = 0.002$), with secondary analysis showing this was especially so for happy ($p = 0.014$) and neutral ($p = 0.001$) sentences. There was a significant interaction effect for pitch between tone deviation level and group ($p = 0.019$), and relatives performed worse than controls on amplitude discrimination and duration discrimination. AP performance for happy and neutral sentences was significantly correlated with amplitude perception. Lastly, AVH proneness in the entire sample was significantly correlated with pitch discrimination ($r = 0.44$) and pitch perception was shown to predict AVH proneness in the sample ($p = 0.005$). These results suggest basic impairments in auditory processing are present in relatives of AVH patients; they potentially underlie processing speed in AP tasks, and predict AVH proneness. This indicates auditory processing deficits may be a core feature of AVHs in schizophrenia, and are worthy of further study as a potential endophenotype for AVHs.

Keywords: auditory hallucinations, schizophrenia, auditory perception, affect recognition, first-degree relatives

INTRODUCTION

Auditory verbal hallucinations (AVHs) are a phenomenon in which people experience hearing speech in the absence of appropriate sensory stimulation and with the full sense of reality of a true perception. Although occurring in a range of populations, AVHs are most frequently associated with schizophrenia, affecting approximately 75% of the schizophrenia population during a 1-year period (Bauer et al., 2011). This paper examines the role of auditory processing in AVHs, and examines whether difficulties with auditory processing are a core difficulty also observable in the relatives of persons with AVHs.

Auditory deficits have frequently been found in persons with schizophrenia (Cooper, 1976; Rabinowicz et al., 2000; Veuillet et al., 2001; Iliadou and Iakovides, 2003); with some studies establishing these deficits are more profound in patients with a history of AVH (Mckay et al., 2000). Neurophysiological literature has also established auditory deficits in schizophrenia. Mismatch negativity (MMN) is a negative polarity element of an event-related potential (ERP) that typically occurs from 100 to 200 ms after stimulus onset, when a deviant sound is perceived among a homogenous set (Näätänen et al., 1978). MMN is said to represent pre-attentive acoustic processing (Shinozaki et al., 2002). Impaired MMN (attenuated amplitude) in response to duration-deviant stimuli has been found in both schizophrenia patients (Baldeweg et al., 2002; Umbricht and Krljes, 2005) and unaffected relatives (Michie et al., 2002; Sevik et al., 2011). Further, attenuated MMN amplitude in response to pitch-deviant stimuli have also been observed in patients (Umbricht and Krljes, 2005) and relatives (Jessen et al., 2001). A number of recent studies have suggested that presence of AVH contribute to the pattern of MMN deficits (attenuated duration MMN amplitudes) in schizophrenia (Fisher et al., 2011, 2012).

It has been suggested that behavioral tasks that require participants to discriminate between two tones that differ in pitch are

behavioral representations of neurophysiological deficits of pitch-deviant MMN (Javitt et al., 2000). Such pitch perception deficits have been found in schizophrenia patients (Leitman et al., 2005); a finding that has been consistently replicated (Leitman et al., 2006, 2010a; Matsumoto et al., 2006; Kantrowitz et al., 2013). This finding appears robust, regardless of the stage of illness, with deficits found in chronic inpatients, outpatients, and first episode schizophrenia patients (Rabinowicz et al., 2000). Further, pitch has been shown to be a key element that is manipulated to convey various emotions, along with amplitude and duration (Leitman et al., 2010b).

A number of studies have demonstrated that schizophrenia patients have difficulty perceiving and discriminating emotions based on affective prosody (AP) cues, compared with controls (Murphy and Cutting, 1990; Kerr and Neale, 1993; Rabinowicz et al., 2000; Edwards et al., 2001; Rossell and Boundy, 2005; Bozikas et al., 2006; Leitman et al., 2007, 2010a; Shea et al., 2007; Kantrowitz et al., 2013). Further, there is increasing evidence to suggest that AVH status is associated with schizophrenia patients' performance in AP detection and discrimination: AVH patients have been found to perform worse on AP tasks than non-AVH schizophrenia patients (Rossell and Boundy, 2005; Shea et al., 2007; Rossell et al., in press).

Some authors have theorized that AVHs could be the result of these developmental deficits in auditory sensory processing (Woodruff et al., 1997; Rossell and Boundy, 2005). It is further argued that these bottom-up sensory processes affect higher order cognitive processes, such as AP, required to comprehend emotion content of speech (Leitman et al., 2005). For example, recognition of AP requires accurate detection of variability in basic elements of auditory perception such as pitch, duration, and amplitude and deficits in these basic abilities would affect the ability to decode emotions based on AP.

An endophenotype is a characteristic associated with a particular illness, that occurs in non-affected family members at a higher rate than in members of the general population, and is not directly observable (Gottesman and Gould, 2003). Studying endophenotypes for schizophrenia is useful, as predisposing factors for the illness can be examined whilst confounding effects associated with psychosis, such as interactions with treatment and medication, long term unemployment, and hospitalization among other factors, can be controlled. Potential endophenotypes in schizophrenia have been found in cognition, including verbal memory, attention, and executive function (Sitskoorn et al., 2004). The most robust findings appear to be in impaired attention, as measured by the continuous performance task (Erlenmeyer-Kimling and Cornblatt, 1978; Nuechterlein, 1983; Appels et al., 2003; Birkett et al., 2007). However, potential emotion recognition endophenotypes have also been identified. Relatives of schizophrenia patients display similar impairments to patients in facial emotion recognition (Leppanen et al., 2008; Erol et al.) and on social cognition tasks (Anselmetti et al., 2009; de Achaval et al., 2010). Although, to date, these impairments have not been related to AVH proneness in the relatives; or examined for differences between relatives with a family member with a positive history of AVH vs. a negative history.

Whilst endophenotypes have been studied in relation to schizophrenia, there is no research examining potential endophenotypes specific to AVHs. Given observations of broader emotion perception deficits in relatives of people with a schizophrenia diagnosis, and specific auditory AP and associated basic auditory perception difficulties in patients with AVH compared to those without AVH; AP and associated auditory perception abilities are promising potential endophenotypes specific to AVHs worth investigation.

This study compared first degree relatives of schizophrenia patients with AVHs and controls in pitch, amplitude, duration, and AP perception. Based upon the strong findings of pitch perception deficits in schizophrenia (Leitman et al., 2005, 2006, 2010b; Kantrowitz et al., 2013), and preliminary evidence of similar reduced pitch MMN in relatives similar to that found in patients (Jessen et al., 2001), we first predicted that relatives would be less accurate than controls in pitch discrimination. In addition, exploratory comparisons were conducted between controls and relatives for amplitude and duration discrimination prompted by the absence of published studies examining these processes in relatives.

Given AVH schizophrenia patients exhibit deficits in AP (Rossell and Boundy, 2005), relatives were expected to perform less accurately in emotion identification based on AP. Given that difficulties with AP may be less pronounced in relatives, we additionally predicted that relatives would exhibit significantly slower reaction times (RTs) than controls when required to identify emotions based on AP. RT has been used as an important variable when investigating social cognitive processes, including AP perception (Green et al., 2008). Further, previous research has linked schizophrenia patients and their relatives to slower reaction time (RT) on tasks that require sustained attention (Birkett et al., 2007). If perceiving AP is difficult for an individual, one could assume their RT would be slower than for individuals who find the task easy. Therefore, RT is likely to function as an objective indicator of difficulty in perceiving AP, and was measured in addition to accuracy. Given prior findings of impaired attention in relatives, we examined whether RT on the AP task was independent of performance on attention and vigilance tasks.

We further wanted to explore whether acoustic processing deficits are related to psychosis proneness in general, or whether they are specific to AVHs. We hypothesized that within the overall sample, acoustic processing deficits would predict AVH proneness specifically, using an AVH-specific sub-factor derived from the Launay-Slade Hallucination scale—LSHS (Laroi and Van der Linden, 2005), but would not predict overall psychosis proneness with the AVH proneness items removed, which was examined using a broader measure of schizotypy.

MATERIALS AND METHODS

PARTICIPANTS

Thirty-three non-clinical controls (14 males and 19 females) and 19 first-degree relatives (4 males and 15 females) of schizophrenia patients who experience AVHs were recruited for this study, with an age range of 18–65 years. Relatives comprised parents, siblings, and offspring of schizophrenia patients who had experienced AVHs during the course of their illness. That is, had frequent AVH

(almost all the time) and were classified as persons with chronic schizophrenia (illness durations of 5 years plus). Participants were recruited using the Monash Alfred Psychiatry Research Center (MAPrc) participant registry, advertisements, and convenience sampling.

Participants from both groups were excluded if they reported significant hearing impairment such as tinnitus, or failed a basic auditory threshold testing frequencies of 500, 1000, 1500, 2000, 3000, 4000, and 6000 Hz, with 25 dB used as the threshold of normal hearing for inclusion in the study. Controls were excluded if they currently suffered from an Axis I disorder, or if they had a first-degree relative with a psychotic disorder. Relatives were excluded if they had a history of a psychotic disorder, met criteria for schizophrenia, were taking antipsychotic medication, or if their relative with schizophrenia had never experienced AVHs in the course of their illness. Participants were paid a gratuity of $30 for their time and travel expenses.

MEASURES

Mini international neuropsychiatric interview

To screen for Axis I disorders, as classified by the DSM-IV TR, a Mini International Neuropsychiatric Interview (MINI) screen and if necessary, MINI interview 5.0.0 (Sheehan et al., 1998) were administered to all participants. The MINI has been shown to have good inter-rater and test-retest reliability and has good concordance with DSM-IV diagnoses (Sheehan et al., 1998).

Oxford-liverpool inventory of feelings and experiences (O-LIFE)

The O-LIFE (Mason et al., 1995) was utilized to assess group differences in psychosis proneness. The four main scales of the O-LIFE are: unusual experiences (UnEx: this scale is thought to represent hallucination-proneness), cognitive disorganization (CogDis), introvertive anhedonia (IntAn), and impulsive nonconformity (ImpNon). Each of these scales are said to represent an element of schizotypy (Mason et al., 1995). A sub-factor of the O-LIFE comprising IntAn, CogDis, and ImpNon was created to measure psychosis proneness in the absence of hallucinatory elements (UnEx). This new sub-factor achieved a Cronbach alpha of 0.92, indicating it is a reliable measure for psychosis proneness; and is the measure used in the analysis.

Launay-slade hallucination scale (LSHS)—modified version

The modified version of the LSHS (Bentall and Slade, 1985) was used to measure hallucination proneness in the sample. However, this version of the LSHS contains some items that are not relevant for AVHs. Several factor structures were considered, but their hallucinatory components contained items relating to visual as well as auditory hallucinations (Aleman et al., 2001; Waters et al., 2003; Fonseca-Pedrero et al., 2010). Laroi and Van der Linden (2005) identified an auditory hallucination factor in their principal components analysis, with an Eigenvalue of 1.61. The LSHS hallucination factor (LSHS-HF) includes three items ("I have been troubled by hearing voices in my head"; "In the past, I have had the experience of hearing a person's voice and then found that no one was there"; and "I often hear a voice speaking my thoughts aloud") with loadings of 0.73, 0.68, and 0.63, respectively. The maximum score for the sub-factor is 12. This factor was found to be reliable, with a Cronbach alpha of 0.76, and was used in the analysis as it appeared to be the most reliable sub-factor that isolated AVH symptoms from other hallucinatory items.

Wechsler test of adult reading (WTAR)

The WTAR (The Psychological Corporation, 2001) is a vocabulary measure, developed to estimate overall intellectual functioning. The number of correct pronunciations is calculated and using the provided norms, a scaled score and predicted full scale intelligence quotient (PFSIQ) are generated. The PSFIQ was utilized in this study as a way of determining whether the two groups were similar in intellectual functioning.

Auditory tasks

For all the auditory tasks used in this study, Presentation® software (Neurobehavioral Systems) was utilized via laptop computer, using headphones. Three tone discrimination tasks (TDTs) were created to assess individuals' ability to perceive differences in pitch (TDT-P), amplitude (TDT-A), and duration (TDT-D). They were closely modeled on TDTs from earlier studies (Strous et al., 1995; Leitman et al., 2005). There were 144 pairs of tones presented in both the TDT-A and TDT-D tasks, and 143 pairs of tones presented in the TDT-P.

For each of the TDTs, the initial tone in each pair was always set at 70 dB, 150 ms in duration, and had a frequency of 1500 Hz. The second tone within each pair was presented 500 ms after the initial tone. The second tone was either identical to the first, or increased or decreased by 2, 5, 10, 25, and 50% for that acoustic element (e.g., duration). Based on this information, the range of amplitude for the differing tones in the TDT-A varied from 35 to 105 dB. For the TDT-D, duration of differing tones ranged from 75 to 225 ms in length. The pitch of differing tones in the TDT-P varied from 750 to 2250 Hz. The variables used for analysis was accuracy (measured as a percentage correct) for the same condition and each of the abovementioned levels of deviation, leaving six variables for each TDT. Participants were required to identify whether they believed each pair of tones were the same or different, using allocated keys on the laptop keyboard.

Affective identification task (AIT)

The AIT was developed to assess participants' ability to identify emotion based on AP. It consisted of 24 semantically neutral sentences (e.g., "The window is made of glass") which were spoken by both male and female actors (12 sentences per gender) in one of the following emotions: happy, sad, fearful, and neutral. Each sentence is approximately 3 s long. Sentences were presented in a randomized order. During the AIT, participants were required to indicate which emotion they believed the sentence was spoken in from the above options by pressing the corresponding key on the keyboard. Participants were measured on accuracy (percentage of correct guesses) and RT (ms) for each of the four emotions.

Continuous performance tasks—identical pairs version (CPT-IP)

Attention was measured using CPT-IP (Marder and Fenton, 2004) which was administered via laptop. The CPT-IP was divided into 3 s, where participants were asked to look for identical pairs in numbers that were two, three, and four digits long,

with 150 trials per condition (30 hits, 30 false alarms, and 90 random numbers). The "on" time for each stimulus was 50 ms, with a dark time between stimuli of 950 ms. During the CPT-IP, participants were required to respond by clicking the mouse whenever they saw two identical numbers flash on the screen consecutively. An age and gender corrected *T*-score was generated for this task and was the variable used in the analyses.

PROCEDURE

Once screening was complete (MINI), participants completed a demographics questionnaire measuring participants' gender, age, date of birth, whether they had a relative with a psychiatric disorder, educational and employment information. Auditory tasks were alternated with the other questionnaires and the CPT to avoid participant fatigue. All of the activities undertaken to complete this paper was approved by the La Trobe University Faculty of Science, Technology and Engineering Human Ethics Committee, Approval Number FHEC09/R71, and the University of Melbourne Human Research Ethics Committee, Approval Number 0714996.1.

DATA ANALYSIS

Data screening and normality

Each of the variables was screened for normality using *z*-scores of the skewness and kurtosis levels. A single outlier, in years of education, was reduced to the maximum score of three interquartile ranges from the mean. LSHS-HF violated assumptions of normality and was transformed using log transformation. Untransformed means are presented in tables for ease of interpretation.

For the TDTs, scores were derived for the degree of difference between tones, (collapsing data from increased and decreased deviation levels), expressed as 6% level differences for each TDT. Each of the TDTs had a violation of normality for at least one of the percentage levels. The data were converted to error scores, and log-transformation of these scores successfully normalized the data to meet the assumptions required for the analyses.

The AIT overall accuracy variables for happy, sad and fear all violated normality and were log-transformed. No transformation normalized neutral sentences, and untransformed variables were used.

Analysis

Demographic variables were compared across groups using analysis of variance (ANOVA) or Chi squared, as appropriate. For each TDT, there were a total of 6% levels of difference (same, 2, 5, 10, 25, and 50%), with 2 and 5% representing the most difficult conditions. To explore group-based differences across the whole task, and to examine for interactions with different levels, each of the TDTs were analyzed using a 2 × 6 mixed design ANCOVA with group as the between subjects factor and degree of difference between tones as the within subjects factor. Given that age was shown to be significantly different across the groups, age was included as a covariate. Further, significant differences reported on the ANCOVAs were followed up with *post-hoc* One-Way analyses of variance. These ANCOVAs were conducted at each percentage level to determine where differences were occurring, with age being again used as a covariate. Similarly, to examine for group differences across the different emotional categories on the AIT, for the accuracy data, a 2 × 3 mixed design ANCOVA was conducted for happy, sad, and fear, with group being a between subjects factor and emotion being a within subjects factor, with age again being used as a covariate. An independent samples *t*-test was used to explore group differences for the neutral condition of the AIT for accuracy (due to the violated normality as noted above). For RTs, a 2 × 4 mixed design ANCOVA was used. Bonferroni corrections were not adopted to account for multiple comparisons for the TDT and AIT data, due to the small sample sizes. Mean effect sizes and observed power were calculated to aid interpretation of results. As noted in the introduction, group differences when examining RT data, could be due to poor attention. Therefore, a One Way ANCOVA was conducted to examine for group differences on the CPT task, which was followed up with a correlation between CPT RT and the overall RT on the AIT.

To explore the relationship between acoustic processing and AP, a correlation was conducted on the entire sample using deviation levels for the three TDTs (same, 2, 5, 10, 25, and 50%) and accuracy on the four emotions of the AIT. To further confirm whether relationships between variables were related to AVH or psychosis proneness, LSHS-HF and O-LIFE-NH were included. These correlations are reported in **Table 4**; they are presented to allow description of possible relationships and it is acknowledged that they have not been corrected for multiple comparisons.

The variable that was most highly correlated with LSHS-HF in the abovementioned correlational analysis was then entered into a hierarchical regression for the whole sample. Age and group were entered at the first step, and appropriate TDT variable was entered at the second step to assess whether acoustic processing predicted AVH proneness. An identical hierarchical regression was conducted using O-LIFE-NH instead of LSHS-HF to further establish whether acoustic processing deficits also predict psychosis proneness, or are specific to AVH proneness.

RESULTS

DEMOGRAPHICS

The proportion of males and females did not differ between the groups, χ^2 (1, $N = 52$) = 2.43, $p = 0.12$, but age was found to differ significantly between the groups, $t_{(50)}$ = -2.20, $p = 0.033$, so age was entered as a covariate for subsequent analyses. Demographic variables are presented in **Table 1** below; they reveal that the groups were matched according to the number of years in education and PSFIQ.

AUDITORY PROCESSING

Table 2 displays the mean error rates across the three TDT tasks.

Pitch discrimination

There was a main effect for degree of difference between tones $F_{(5, 44)} = 17.42$, $p < 0.001$, but no main effects were observed for age [$F_{(1, 48)} = 1.72$, $p = 0.196$] or group [$F_{(1, 48)} = 0.53$, $p = 0.470$]. There was an interaction between degree of difference between tones and group, $F_{(5, 44)} = 3.05$, $p = 0.019$, with relatives making more errors than controls for the more difficult deviation levels and fewer errors than controls for the

easier deviation levels. An interaction between degree of difference between tones and age $F_{(5,\ 44)} = 2.54$, $p = 0.042$, was also observed. *Post-hoc* analyses established a trend difference at 2%, where relatives appear to make more errors than controls (see **Table 2**).

Amplitude discrimination

Results from the mixed design ANCOVA reveal that there was a within subjects main effect for the degree of difference in tone amplitude, $F_{(5,\ 40)} = 16.91$, $p < 0.001$, but no overall main effect for group or age were observed, nor were any interaction effects observed.

However, *post-hoc* follow-up One Way analyses of variance indicated that controls and relatives differed when discriminating between tones that differed by 2, 5, and 10%, with group differences approaching significance at 25%.

Duration discrimination

The mixed design ANCOVA for the TDT-D revealed a within subjects main effect for degree of difference in duration $F_{(5,\ 40)} = 8.52$, $p < 0.001$, but no between subjects main effects for group or age. Trends for interactions between degree of difference between tones and both group [$F_{(5,\ 40)} = 2.27$, $p = 0.065$] and age [$F_{(5,\ 40)} = 2.16$, $p = 0.078$] were observed. **Table 2** illustrates relatives made more errors from 2 to 25%, although this was only significant at 25%, with a trend toward significance at 5%.

AFFECTIVE PROSODY

Accuracy of emotion identification

The hypothesized effect of group fell outside statistical significance, $F_{(1,\ 46)} = 2.71$, $p = 0.106$, as did the effect for emotion, $F_{(2,\ 45)} = 2.85$, $p = 0.068$. No interactions were found between emotion and age [$F_{(2,\ 45)} = 1.52$, $p = 0.230$] or emotion and group [$F_{(2,\ 45)} = 0.50$, $p = 0.612$]. The *t*-test performed on the neutral emotion on the AIT revealed no group differences in the ability to detect neutral sentences, $t_{(47)} = -1.36$, $p = 0.18$. Group performances on the AIT, measured by accuracy, can be found in **Figure 1** below.

Table 1 | Mean (standard deviation) of demographic characteristics for controls and relatives.

	Controls		Relatives			
	n	*M*(*SD*)	*n*	*M*(*SD*)	*F*	*p*
Age	33	36.79 (13.72)	19	46.05 (16.12)	−4.84	0.033
EdYears	32	17.06 (3.18)	19	17.05 (3.08)	0.00	0.953
PSFIQ	33	109.21 (5.69)	19	107.11 (6.75)	2.93	0.093
LSHS-HF (max 12)	33	0.52 (1.18)	18	1.00 (1.64)[#]	3.59	0.064
UnEx	32	3.5 (4.34)	18	3.33 (2.43)[#]	1.53	0.222
CogDis	32	6.66 (6.1)	18	8.78 (6.92)	2.82	0.100
IntAn	32	3.94 (2.46)	18	7.17 (5.11)[†]	−6.35	0.020
ImpNon	32	6.19 (3.44)	18	6.11 (4.07)	0.04	0.851
STA	32	7.97 (6.51)	18	9.11 (5.65)[#]	2.34	0.133

The LSHS score is the hallucination sub-factor discussed previously.

[#] One-Way ANCOVAs for these variables were conducted using log transformed scores due to violation of normality. Non-transformed scores are presented for ease of interpretation.

[†] Analysis was performed using independent samples t-test. The statistic was squared to aid interpretation.

UnEx, Unusual Experiences; CogDis, Cognitive Disorganisation; IntAn, Introvertive Anhedonia; ImpNon, Impulsive Non-conformity; STA, Schizotypy.

Table 2 | Error rates for controls and relatives across each percentage level difference in pitch, amplitude, and duration on the tone discrimination task.

Percentage level (%)	Controls		Relatives					
	M	*SD*	*M*	*SD*	*F*	*p*	*D*	*OP*
PITCH								
Same	4.75	4.12	6.53	8.56	2.54	0.118	−0.26	0.26
2	15.36	17.63	19.96	13.51	3.21	0.080	−0.29	0.27
5	9.58	15.85	10.15	12.91	0.09	0.768	−0.04	0.07
10	7.94	14.25	8.77	13.17	0.00	0.972	−0.06	0.08
25	1.04	2.59	0.44	1.31	1.30	0.261	0.29	0.27
50	0.14	0.80	0.00	0.00	1.02	0.318	0.25	0.22
AMPLITUDE								
Same	8.79	10.41	6.88	7.20	1.21	0.276	0.21	0.22
2	50.30	18.35	62.30	17.84	4.56	**0.038**	−0.66	0.75
5	38.33	17.80	49.78	16.13	5.00	**0.030**	−0.67	0.77
10	28.33	18.65	41.89	20.95	5.49	**0.024**	−0.68	0.78
25	12.04	12.93	24.06	26.21	3.96	0.053	−0.58	0.66
50	2.53	3.98	5.7	12.05	0.12	0.733	−0.35	0.34
DURATION								
Same	8.18	7.65	3.51	6.10	2.79	0.102	0.67	0.77
2	47.10	19.14	56.58	17.25	1.86	0.180	−0.52	0.58
5	50.22	15.05	60.53	12.53	3.92	0.054	−0.74	0.84
10	56.32	18.72	66.88	19.62	1.21	0.278	−0.55	0.62
25	17.26	16.89	27.85	20.51	4.33	**0.043**	−0.56	0.63
50	5.51	10.46	5.70	10.96	0.29	0.595	−0.02	0.06

The analyses for this data were performed on log-transformed error-rates and controlled for age. The figures presented here are the untransformed error-rates to aid in interpretation. Bold numbers indicate that relatives made significantly more errors in identification of different tones than controls.

OP, observed power.

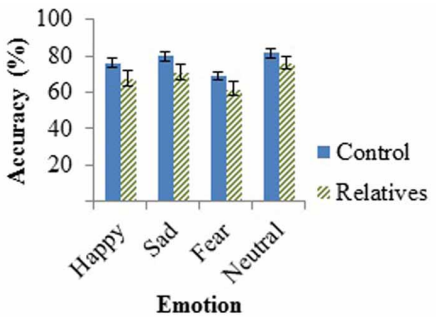

FIGURE 1 | Mean accuracy of controls and relatives for each emotion tested in the AIT, with standard error of the mean (SEM) bars.

Reaction time for emotion identification

For emotion identification RT, there was a significant main effect of group, $F_{(1, 46)} = 10.77$, $p = 0.002$, as well as a main effect of age, $F_{(1, 46)} = 11.39$, $p = 0.002$. There was no main effect for emotion, $F_{(3, 44)} = 1.31$, $p = 0.282$, although there were trends for an interaction between emotion and group, $F_{(3, 44)} = 2.25$, $p = 0.095$, and an interaction between emotion and age, $F_{(3, 44)} = 2.38$, $p = 0.082$. Group mean RTs for each emotion on the AIT are in **Table 3**. In a secondary analysis, a series of follow up One-Way ANCOVAs were conducted on RT for each of the four emotions. The relatives performed slower than controls in the happy [$F_{(1, 49)} = 6.53$, $p = 0.014$] and neutral [$F_{(1, 49)} = 11.80$, $p = 0.001$] conditions.

Attention

A univariate ANCOVA revealed that group differences in attention approached significance, $F_{(1, 31)} = 3.99$, $p = 0.056$, with relatives exhibiting lower T-scores ($M = 42.24$) than controls ($M = 48.86$). A correlation analysis was conducted between attention and RT on the AIT to determine whether slower RT was associated with impaired attention on the CPT; no correlations were significant.

Relationship between the variables

A further correlation analysis was conducted to examine the relationships between acoustic processing and AP, and the relationships between acoustic processing and AVH and psychosis proneness (**Table 4**). The correlation was conducted on the entire sample.

This analysis indicates that recognition accuracy for happy and neutral sentences was moderately correlated with accuracy in amplitude discrimination (2, 5, 10, and 25%). Recognition accuracy for happy sentences was also correlated with pitch discrimination at the 2% level. Affective identification appeared unrelated to duration discrimination. Variables measuring AVH and psychosis proneness are also presented in **Table 4**. Pitch discrimination was specifically predictive of AVH proneness (LSHS-HF), whilst the 2% condition of the TDT-D was correlated with both AVH and psychosis proneness (O-LIFE-NH).

As AVH proneness was most significantly correlated with the TDT-P at 2%, this variable was chosen as the best predictor to enter into the regression analyses. The regression analysis conducted for AVH proneness is found in **Table 5** below. This analysis reveals that both age and group, and TDT-P 2% significantly predict AVH proneness, with the model found to be significant, $F_{(3, 46)} = 5.74$, $p = 0.002$ and accounting for 23% of the total variance. A similar regression was performed using the same predictor variables and the O-LIFE-NH. This model was not significant.

Table 3 | Mean, standard deviation and effect sizes of RT (ms) for controls and relatives for each of the four emotions of the AIT.

	Controls		Relatives					
	M	*SD*	*M*	*SD*	*F*	*p*	*d*	*OP*
Happy	874.25	254.84	1143.90	331.37	6.53	**0.014**	−0.91	0.80
Sad	831.78	172.40	970.87	261.94	2.39	0.129	−0.63	0.87
Fear	1051.27	283.18	1212.74	299.10	1.14	0.291	−0.55	0.93
Neutral	783.05	205.97	1038.41	280.36	11.80	**0.001**	−1.04	0.90

Age controlled for as a covariate in each analysis. Bold numbers indicate that relatives made significantly more errors in identification of different tones than controls.

DISCUSSION

The aim of the current study was to empirically investigate acoustic processing and AP in a sample of controls and relatives. Further, this study aimed to determine whether pitch perception was related to AP, and whether pitch perception predicted AVH proneness. We present preliminary data addressing these aims.

In examining acoustic processing, our main hypothesis was that relatives would make significantly more errors in pitch discrimination on the TDT-P. This hypothesis was not supported. The literature regarding amplitude and duration discrimination is more limited, therefore, no predictions were made with regards to differences between controls and relatives on both the TDT-D and TDT-A. However, groups were shown to differ on the TDT-A at 2, 5, and 10%, whilst they differed on the TDT-D at 25%.

Pitch perception is the element of acoustic processing most consistently found to be impaired in schizophrenia patients

Table 4 | Descriptive correlations between error rates for variables in the TDT-A, TDT-D, TDT-P, the four emotions of the AIT, hallucination proneness, and psychosis proneness.

	Amplitude						Duration						Pitch					
	0%	2%	5%	10%	25%	50%	0%	2%	5%	10%	25%	50%	0%	2%	5%	10%	25%	50%
Happy	−0.11	0.35*	0.37*	0.49***	0.38**	0.20	−0.03	0.14	0.06	0.09	0.23	0.08	−0.00	0.33*	0.28	0.24	0.12	0.08
Sad	0.10	0.00	−0.01	0.02	0.10	0.22	0.23	−0.02	0.04	0.03	0.04	−0.06	0.15	0.05	0.02	0.06	−0.08	−0.07
Fear	0.19	0.05	−0.10	0.00	0.05	0.20	−0.11	−0.08	−0.14	0.03	0.27	0.16	0.20	0.07	0.24	0.15	0.07	0.17
Neutral	−0.05	0.11	0.37*	0.49***	0.38**	0.20	−0.03	0.14	0.01	0.25	0.22	0.16	0.23	0.20	−0.02	0.05	0.05	−0.01
LSHS-HF	0.22	0.15	0.17	0.20	0.21	0.06	−0.03	0.32*	0.26	0.19	0.28	0.17	−0.06	0.44***	0.29*	0.32*	0.34*	−0.06
O-LIFE-NH	0.03	−0.07	0.17	0.20	0.21	0.06	−0.03	0.32*	0.10	0.18	0.20	0.08	−0.11	0.25	0.22	0.10	0.08	−0.11

The correlation analysis was conducted on error rates for the four emotions and for each variable from the three TDTs.
$^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$.

Table 5 | Hierarchical multiple regression analysis predicting hallucination proneness from acoustic processing.

	Hallucination proneness				
Predictor	**B**	**Adjusted R^2**	**ΔR^2**	**ΔF**	**Δp**
Step 1		0.10	0.13	3.57	0.036*
Age	−0.33				
Group	0.28				
Step 2		0.23	0.14	8.87	0.005**
Age	−0.43				
Group	0.18				
TDT-P 2%	0.41				

The dependent variable measuring hallucination proneness was the LSHS hallucination factor extracted in accordance with Laroi and Van der Linden (2005).
$^*p < 0.05$; $^{**}p < 0.01$.

(Rabinowicz et al., 2000; Leitman et al., 2005, 2007, 2010b; Matsumoto et al., 2006; Phillips, 2009; Kantrowitz et al., 2013), so it was unexpected that it was on this task that there was least evidence for differences in relatives. However, there may be differences in difficulty between the tasks of pitch, duration and amplitude discrimination. Indeed, first episode and chronic schizophrenia patients only tend to show difficulties in pitch discrimination below 3–5% differences in pitch (Rabinowicz et al., 2000). Given that the extent of deficits may be smaller still in relatives, it may have been that the pitch discrimination task used was insufficiently sensitive to pick up difficulties.

The current TDT-P was closely based on that by Leitman et al. (2005) and Strous et al. (1995). Leitman et al. used three sets of base frequencies of 500, 1000, and 2000 Hz to help avoid learning effects; an approach that has since been replicated (Rabinowicz et al., 2000; Leitman et al., 2006, 2010a; Kantrowitz et al., 2013). The current study utilized a base frequency of 1500 Hz, which is halfway between Leitman's middle and upper base tones. Further, other studies utilized a base frequency of 1000 Hz for their standard tone (Strous et al., 1995; Javitt et al., 2000). It may be that subtle differences are much easier for participants to detect at a higher frequency of 1500 Hz, rather than 500 or 1000 Hz.

Nonetheless, we found a statistically significant effect for duration. Group differences were found between controls and relatives when required to discriminate between tones altered in duration where the tones differed by 25%. Effect sizes were either moderate or moderate-to-large for every condition except for 50%. Duration is one of the key acoustic processes involved in AP (Leitman et al., 2010a) and, based on these findings, duration may be important to explore in schizophrenia patients and relatives. The finding of group differences for tone discrimination based on duration is consistent with the literature showing that schizophrenia patients have reduced amplitude MMN in response to duration deviant stimuli (Baldeweg et al., 2002; Umbricht and Krljes). There is also some evidence to suggest that reduced amplitude duration MMN can also be found in those at high risk for schizophrenia (Shin et al., 2009) and relatives of schizophrenia patients (Michie et al., 2002; Sevik et al., 2011). More research needs to be conducted to determine the role of impaired duration discrimination in predisposition to AVHs.

The current results also showed that relatives differed from controls in their ability to detect subtle differences in amplitude between two tones at 2, 5, and 10%. To our knowledge, no one has investigated amplitude discrimination in schizophrenia patients before, let alone relatives with either behavioral or neurophysiological methods. The findings from this study suggest that this area warrants further investigation to ascertain the role of amplitude perception in schizophrenia patients and possibly specifically in AVHs.

Pitch perception, as previously described, is involved in the contextual encoding of auditory information when perceiving or re-experiencing verbalizations, and is particularly relevant to decoding the affective meaning of speech. Duration and amplitude also play a role in these mechanisms. Leitman et al. (2010b) have previously outlined how combinations of these aspects of sound contribute to each emotion. The effect sizes observed in this study suggest each of these processes warrant further investigation in both schizophrenia patients and their relatives. Perhaps deficits in all three areas are underlying patients' difficulty in perceiving information accurately during encoding, as well as assigning the appropriate source to inner thought or re-experienced events.

Relatives were expected to have greater difficulty in emotion perception on the AIT, which was expected to be reflected in lower accuracy scores. Although relatives appeared to have higher error rates than controls on the AIT, there were no significant effects for group or emotion. This is inconsistent with schizophrenia research which has found patients to perform worse than controls on happy, fear, and neutral sentences (Leitman et al., 2010b). Relatives' slower RT on the AIT for happy and neutral sentences suggests that RT may be a more sensitive variable. Further research with a greater number of participants needs to be conducted to ascertain whether AP perception deficits are confined to schizophrenia patients or whether they are also present in relatives.

One criticism of AP tasks is that simulated portrayals of emotion are stereotypic with exaggerated differences between various emotions (Edwards et al., 2002). In everyday situations, natural emotions are conveyed by context, the content of utterances, and the speaker (Edwards et al.). Therefore, difficulties in recognizing specific emotions may not be identified in AP tasks due to the exaggerated nature of the emotions presented, making them easier to detect. Naturally recorded emotions may be a more effective way at assessing individuals' abilities to recognize and distinguish between various emotions. Furthermore, in our study, participants appeared to be performing at close to ceiling on the AIT, with both groups displaying mean error rates of between 2 and 4%. This suggests that perhaps the artificial nature of the task made it easy for participants to identify the emotion, and thus the task was not sensitive enough to distinguish the two groups.

Whilst relatives did not differ significantly from controls in their ability to accurately identify emotions, they did take

significantly longer to do so. Results from the AIT indicated that relatives were slower at identifying happy and neutral sentences, with effect sizes supporting this finding. Decreased performance for sad sentences approached significance. This supports previous findings linking AP deficits in schizophrenia to impaired recognition of sadness (Murphy and Cutting, 1990; Edwards et al., 2001; Rossell and Boundy, 2005; Bozikas et al., 2006; Leitman et al., 2010a), happiness and neutral sentences (Leitman et al., 2010a), thus suggesting that relatives display some impairment in their ability to perceive AP cues. Interestingly, happiness is associated with high levels and variability of pitch and amplitude, whilst sadness is associated with low levels and variability in amplitude and low levels of pitch (Leitman et al., 2010a), and neutral sentences can often be the most difficult to detect as they use medium levels of pitch and amplitude variability and can be very person specific. Thus, happy sentences should have been the easiest to identify, even in the presence of amplitude and pitch difficulties in the relatives. Therefore, it is unclear, based on the current data, why such "emotion" specific reaction time differences are present. Further work is needed confirming these deficits.

Impaired attention has previously been theoretically linked with impaired RT (Nuechterlein, 1977) and thus it was important to ascertain whether relatives' RTs on the AIT were related to impaired attention (lower *T*-scores), or whether RT reflected task difficulty for relatives. Results showed that attention was not significantly correlated with RT for any of the emotions, indicating no systematic relationship between these factors. This is consistent with Kee et al. (1998) who found no relationship between attention/vigilance measured by the CPT and AP. The direction of our findings and Kee et al.'s findings, suggest that RTs on AP measures for patients and relatives are less related to impaired attention, and likely mediated by their difficulty in emotion discrimination. Additionally, future research may benefit from investigating auditory attention, specifically as the CPT is a visual attention task. It maybe the lack of relationship between attention scores and the RT on the AP task were due to modality differences.

TDT-P at 2% and a number of levels of the TDT-A were found to be positively correlated with happy sentences, and the 5, 10, and 25% conditions of the TDT-A were also correlated with neutral sentences. Interestingly, happy and neutral sentences were the two conditions of the AIT where relatives displayed slower reaction times. Therefore, higher error rates on the TDT-A and TDT-P appear to be associated with increased error rates for happy and neutral sentences of the AIT. This suggests that acoustic processing deficits underlie deficits in AP perception, and supports the link between pitch perception and AP previously highlighted by Leitman et al. (2005).

Hallucination proneness was predicted to be positively correlated with error rates on the TDT-A, TDT-D and the TDT-P. Results showed that the TDT-D at 2% was weakly positively correlated with AVH proneness in the entire sample. Further, the TDT-P was positively correlated with AVH proneness at 4% levels, with the strongest positive correlation (moderate in strength) at 2%. Therefore, pitch perception appears to be closely related to AVH proneness.

In the current study, pitch perception was shown to be linked with AP perception, with AP perception previously found to be more impaired in AVH schizophrenia patients than non-AVH patients (Rossell and Boundy, 2005; Shea et al., 2007). Further analysis revealed that performance on pitch discrimination when tones differ by 2% appears to predict AVH proneness in the current sample. Further, pitch discrimination did not significantly predict psychosis proneness when hallucinatory factors have been removed from the proneness measure. This provides support for basic acoustic processing deficits, particularly with pitch perception, predicting higher order processes such as AP perception, leading to the experience of AVHs. This supports previous findings where pitch alterations of auditory stimuli increased the likelihood of schizophrenia patients attributing their recorded voice to an external source (Johns and McGuire, 1999; Johns et al., 2001, 2006). Patients appear to have difficulty extracting sufficient auditory cues of speech, which may contribute to their difficulty recognizing their own voice, or misattributing the sources of auditory verbal stimuli.

The most obvious limitations of the current investigation are those of a small sample size, and unequal group sizes. Thus, our data can only be classified as preliminary. For example, the small sample size prevented us from running separate regressions for controls and relatives when exploring the link between pitch perception and hallucination proneness. It is likely that if this analysis was re-run separately for each group, with an increased sample size, the model predicting hallucination proneness would likely have explained more of the variance for relatives than for controls. Furthermore, no corrections were made for the number of secondary analyses conducted for the TDTs or AIT, increasing the likelihood of a Type II error. Nonetheless, a number of promising results were recorded and effect sizes were calculated to support effects that were detected. Furthermore, the description of endophenotypes for schizophrenia outlined by the Consortium on the Genetics of Schizophrenia (Gur et al., 2007) suggests that endophenotypes for schizophrenia yield small to moderate effect sizes between relatives and controls, which were indeed observed here. Thus, it is highly likely that increased sample sizes in future studies would provide further evidence for the auditory deficits observed here, and perhaps would increase the likelihood of observing group differences for other neurocognitive domains such as processing speed. In addition, it is recommended that future work complete a detailed clinical interview with the patients of the relatives being studied. This will allow for a detailed history of the exact phenomenology of AVH experienced by the patients, including frequency and types of voices experienced.

The current investigation decided to utilize parents, siblings and offspring of schizophrenia patients with AVHs in the first-degree relatives group, which is consistent with each of these groups being used in the previous literature [siblings (Condray and Steinhauer, 1992; Leppanen et al., 2008; Erol et al., 2010), offspring (Erlenmeyer-Kimling and Cornblatt, 1978; Nuechterlein, 1983), and parents (Appels et al., 2003; Anselmetti et al., 2009)].

Erol et al. (2010) have critiqued the use of mixed relatives samples used in previous research (Toomey et al., 1999) but stopped short of explaining why. The use of siblings and offspring appears acceptable given strong research of genetic predisposition to schizophrenia (Matthysse and Kidd, 1976; Cannon et al., 1998; Allen et al., 2008). However, the use of parents in samples of relatives could be considered risky. When recruiting parents, one cannot be certain that the parent with the genetic predisposition to schizophrenia has been chosen. Therefore, it can be proposed that the results of the current investigation may have been strengthened if the relatives sample comprised only siblings and offspring.

We suggest possible endophenotypes in relatives of schizophrenia patients with AVHs compared with controls. However, these skills need to be investigated in first degree relatives of schizophrenia patients who have never experienced AVHs. If no evidence of these deficits is found in the second schizophrenia relative cohort, then it is reasonable to suggest that the endophenotypes that this investigation has potentially uncovered are indeed related to AVHs specifically, and are not endophenotypes for schizophrenia in general.

CONCLUSION

The results from the current investigation contribute to the literature regarding endophenotypes in schizophrenia. Impaired pitch perception was related to slower performance on the AIT and predicted AVH proneness in relatives, suggesting it may be a potential endophenotype for AVHs in schizophrenia and strengthens the argument that auditory processing is a fruitful area to investigate in endophenotype research. The endophenotypes identified are, as far as we are aware, the first to be investigated in relation to AVHs specifically. More research needs to be conducted to determine whether these endophenotypes are limited to relatives of patients with AVHs, or whether they are present in all schizophrenia relatives. To further confirm that pitch perception deficits are related to predisposition to AVHs specifically, it would be prudent to conduct a similar study that includes AVH and non-AVH patients, relatives of AVH and non-AVH patients, and controls. Confirmation of an endophenotype for AVHs centered on acoustic processing could lead to the establishment of assessment and pre-screening of individuals, to identify those who are at increased risk of developing AVHs, thus adding to the prevention and early intervention approach already shown to be successful in the treatment of schizophrenia.

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Action simulation in hallucination-prone adolescents

Tarik Dahoun[1]*, Stephan Eliez[1,2], Fei Chen[1], Deborah Badoud[1,3], Maude Schneider[1,3], Frank Larøi[4] and Martin Debbane[1,3]

[1] Office Médico-Pédagogique Research Unit, Department of Psychiatry, University of Geneva School of Medicine, Geneva, Switzerland
[2] Department of Genetic Medicine and Development, University of Geneva School of Medicine, Geneva, Switzerland
[3] Adolescence Clinical Psychology Research Unit, Faculty of Psychology and Educational Sciences, University of Geneva, Geneva, Switzerland
[4] Department of Psychology, University of Liège, Liège, Belgium

Edited by:
Kelly M. J. Diederen, University of Cambridge, UK

Reviewed by:
Carrie E. Bearden, UCLA School of Medicine, USA
Emma Barkus, University of Wollongong, Australia

***Correspondence:**
Tarik Dahoun, Office Médico-Pédagogique Research Unit, Department of Psychiatry, University of Geneva School of Medicine, 1 David Dufour, CP 50, 1211, Geneva 8, Switzerland
e-mail: tarik.dahoun@unige.ch

Theoretical and empirical accounts suggest that impairments in self-other discrimination processes are likely to promote the expression of hallucinations. Studies using a variety of paradigms involving self-performed actions argue in favor of perspective taking confusion in hallucination-prone subjects. However, our understanding of such processes during adolescence is still at an early stage. The present study thus aims (1) to delineate the neural correlates sustaining mental simulation of actions involving self-performed actions (first-person perspective; 1PP) and other-performed actions (third-person perspective; 3PP) during adolescence (2) to identify atypical activation patterns during 1PP/3PP mental simulation of actions in hallucination-prone adolescents (3) to examine whether differential risk for schizophrenia (clinical vs. genetic) is also associated with differential impairments in the 1PP/3PP mental simulation of actions during adolescence. Twenty-two typically developing controls (Control group; 6 females), 12 hallucination-prone adolescents [auditory hallucination (AH) group; 7 females] and 13 adolescents with 22q11.2 Deletion Syndrome (22q11.2DS group; 4 females) were included in the study. During the fMRI task, subjects were presented with a cue (self-other priming cues) indicating to perform the task using either a first person perspective ("you"-1PP) or a third person perspective ("best friend"-3PP) and then they were asked to mentally simulate actions based on the type of cue. Hallucination-proneness was assessed using a self-report questionnaire [Cardiff Anomalous Perception Scale (CAPS)]. Our results indicated that atypical patterns of cerebral activation, particularly in the key areas of self-other distinction, were found in both groups at risk for auditory hallucinations (AHs and 22q11.2DS). More precisely, adolescents in the AH group presented decreased activations in the right middle occipital gyrus BA19, left cingulate gyrus BA31, and right precuneus BA31 for the 3PP > 1PP contrast. Adolescents in the 22q11.2DS group presented decreased activations in the right superior occipital gyrus BA19, left caudate tail and left precuneus BA7 for the 3PP > 1PP contrast. In comparison to the Control group, only the 22q11.2DS adolescents showed a decreased activation for other-related cues (prime other > prime self contrast) in areas of visual imagery, episodic memory and social cognition. This study characterizes the neural correlates of mental imagery for actions during adolescence, and suggests that a differential risk for hallucination-proneness (clinical vs. genetic) is associated to similar patterns of atypical activations in key areas sustaining self-other discrimination processes. These observations may provide relevant information for future research and prevention strategies with regards to hallucination-proneness during adolescence.

Keywords: auditory hallucinations, 22q11.2, action simulation, perspective-taking

INTRODUCTION

Auditory hallucinations (AHs) have been conceptualized as a neurodevelopmental phenomenon (Bentall et al., 2007) with a prevalence varying from 6 to 33% in adolescence (see review Larøi et al., 2006). A number of cognitive processes are thought to sustain the expression of AH, such as attention shift/enhancement, executive and inhibitory deficits, and source monitoring (SM) (Hugdahl, 2009; Jones, 2010; Badcock and Hugdahl, 2012; Waters et al., 2012). The developmental course of these cognitive processes during childhood and adolescence suggests that investigating hallucination-proneness during these key developmental windows may help better understand the onset of early AH.

SM is a processes associated with the development of AH. Impairments in SM are thought to lead to the misattribution of self-generated mental contents such as thoughts, memories or action to external sources in hallucination-prone adults (Bentall and Slade, 1985; Rankin and O'Carroll, 1995; Larøi et al., 2004, 2005), in adults with schizophrenia (Bentall et al., 1991; Rankin and O'Carroll, 1995; Blakemore et al., 2000; Brebion et al., 2000;

Brunelin et al., 2006) and in adolescents at high genetic risk for psychosis (22q11.2 Deletion Syndrome; Debbane et al., 2010).

Most of these studies used a verbal SM paradigm. However Larøi and collaborators used a SM task for actions and found evidence for misattribution of imagined actions in hallucinations-prone adults (Larøi et al., 2005). In this study, subjects were asked to (1) imagine themselves or (2) the experimenter performing an action (3) repeat the action statement without imaging the action or (4) simply observe the experimenter carrying out the action. The results revealed that hallucination-prone subjects more often remembered self-performed imagined actions as being imagined actions performed by the experimenter.

A subsequent study employed a similar action-monitoring paradigm with adolescents affected by a 22q11.2 deletion syndrome (22q11.2DS) (Debbane et al., 2008). 22q11.2DS is a neurogenetic disorder with an ultra-high risk for developing schizophrenia (Murphy et al., 1999; Karayiorgou et al., 2010). Transient psychotic experiences are characteristic of more than half of the adolescents with this syndrome (Baker and Skuse, 2005). Furthermore, AHs are the most commonly reported symptoms in the sample of 22q11.2DS children and adolescents investigated by our group (Debbane et al., 2006). The assessment of 22q11.2DS adolescents with a SM task adapted from Larøi et al. (2005), showed that adolescents with 22q11.2DS committed more source confusions by recalling imagined-experimenter actions as actions they had mentally repeated (and vice versa), suggesting potential impairments in third person perspective (3PP) taking.

These two studies (Larøi et al., 2005; Debbane et al., 2008) highlight the impairments in *offline* SM for actions in two populations with hallucination-proneness. Their results might come from disturbances in how information is encoded between first-person perspective (1PP) and 3PP. Theoretical explanations suggest that encoding processes during *online* representation of actions may promote subsequent confusion between self and other by two complementary aspects (1) increased salience of internal representations leading to exaggerated self-focused orientation (Ingram, 1990; Ensum and Morrison, 2003; Kapur, 2003; Perona-Garcelan et al., 2011) (2) impairments in the sense of agency, i.e., the ability to experience oneself as the agent of one's own actions (Gallagher, 2000), as evoked by several authors (Schneider, 1959; Seal et al., 2004; Jones and Fernyhough, 2007; Asai and Tanno, 2012). Among the multiple neurocognitive models of the sense of agency (David et al., 2008; Sperduti et al., 2011; Gallagher, 2012), Jeannerod and colleagues propose to differentiate between actions overtly executed and those that remain covert, i.e., internally represented (Jeannerod, 1994; Georgieff and Jeannerod, 1998). Self-other attribution of covert actions might be sustained by the activity of brain areas specifically devoted to self-other representations (Georgieff and Jeannerod, 1998; Jeannerod and Pacherie, 2004; Jeannerod, 2006).

In order to identify the specific regions involved in the discrimination of self-other action simulation, Ruby and Decety (2001) employed positron emission tomography (PET) to compare the neural correlates of action simulation in a 1PP and a 3PP. Their results showed that both 1PP and 3PP involve overlapping areas of neural processing, in accordance with the shared neural representations theory (Georgieff and Jeannerod, 1998; Grezes and Decety, 2001; Decety and Chaminade, 2003; Decety and Sommerville, 2003). However, specific regions were identified in the right inferior parietal, precuneus, posterior cingulate and frontopolar cortices for 3PP, and in the left inferior parietal and somatosensory cortices for 1PP. The authors concluded that the right inferior parietal, precuneus and somatosensory cortices are key areas involved in self/others action discrimination. The inferior parietal lobule is thought to be involved in body image, self-recognition and integration of information coming from sensory modalities and proprioceptive signals (Jeannerod and Pacherie, 2004; Torrey, 2007). Interestingly, increased activation in the inferior parietal lobule has been observed during conflict between a self-produced action and its consequences (Farrer et al., 2003). The anterior region of the precuneus is related to self-centered imagery and the posterior part to successful episodic memory retrieval (Cavanna and Trimble, 2006). According to the authors, the somatosensory cortex could play a role in self-representation (Ruby and Decety, 2001, 2003, 2004).

Another study focused more specifically on the visuo-spatial aspects of perspective taking during action imagery (Jeannerod and Anquetil, 2008). The authors compared brain activity with PET while subjects imagined the same action (reaching and grasping a cylinder) from a 1PP and 3PP. This paradigm revealed increased activation in the parieto-occipital junction (BA19) specifically for the 3PP. The authors conclude that the right BA 19 is a key area for self-other differentiation by evaluating the difference in spatial localization between oneself and an other's perspective.

In summary key areas of self/other distinction for covert actions are thought to essentially engage the parietal cortex region for multi-modal integration and the parietal-temporal-occipital region, which underpins the shift to another location in space during perspective taking (Ruby and Decety, 2001, 2003, 2004; Vogeley and Fink, 2003; Jeannerod, 2004; David et al., 2007).

In order to investigate the neural correlates underlying both self- and other-focused orientation and self-other perspective taking during action imagery, we used a functional magnetic resonance imagery paradigm adapted from Larøi et al. (2005). During this task subjects were first primed with a self-other priming cues (namely "you" or "best friend") and secondly were asked to mentally simulate actions with either from a first-person (1PP) or a third-person (best friend) perspective (3PP) in accordance with the priming cue. Typically developing adolescents and adolescents clinically prone to hallucinate (AH group) as well as with a 22q11.2 deletion syndrome (22q11.2DS group) underwent this task.

This study has three aims: (1) delineate the neural correlates of action simulation in specific 1PP and 3PP during adolescence (2) identify potential impairments at a neurofunctional level in hallucination-prone adolescents (3) examine whether a differential risk for schizophrenia (clinical vs. genetic) is also associated with differential impairments in the mental simulation of action during adolescence.

We hypothesized that: (1) typically developing adolescents would activate specific regions devoted to 1PP and 3PP already observed in adult subjects (Ruby and Decety, 2001; Jeannerod

and Anquetil, 2008) (2) the AH group and the 22q11.2DS group would present atypical patterns of brain activation in regions sustaining self-other action simulation, along with confusion in self-other remembered actions. (3) Subjects with 22q11.2DS would present atypical patterns of activation in the parietal cortices due to functional and structural impairments (Simon et al., 2005b; Dufour et al., 2008; Bearden et al., 2009; Schaer et al., 2010; Debbane et al., 2012) whereas the AH group would exhibit atypical activations in the prefrontal cortex, as suggested by previous SM studies (Vinogradov et al., 2008; Lagioia et al., 2011; Wang et al., 2011).

MATERIALS AND METHODS

PARTICIPANTS

Eighty adolescents aged from 12 to 20 years participated in the study. Exclusion criteria included age, the presence of any neurological problem or a diagnosis of schizophrenia or schizoaffective disorder according to DSM-IV-TR criteria. Thirty-two subjects were excluded for head movement exceeding 4.7 mm in any of the 6 directions during the scan sessions (Control group: $N = 9$, AH group: $N = 6$, 22q11.2DS group: $N = 17$). In the Control group, we excluded subjects with maladaptive functioning above the clinical cut-off of the Internalizing and Externalizing scales (t-score >64) in the Youth Self-Report and Adult Behavior Checklist (Achenbach, 1991, 1997) ($N = 1$). After excluding these 33 subjects, the 47 remaining youths were distributed in the following three groups: typically developing adolescents (Control group: $N = 22$), adolescents with transient AHs (AH group: $N = 12$) and adolescents with a 22q11.2 Deletion Syndrome (22q11.2DS group: $N = 13$).

Out of the 22 subjects in the Control group (mean age: 16.00, $SD = 2.04$, 16 males), 6 were recruited within the siblings of 22q11.2DS participants and 16 from the Geneva state school system.

In the AH group, 12 subjects with subclinical AHs (mean age: 15.97, $SD = 2.12$, 5 males) were recruited through patient associations, by word of mouth or through the Child and Adolescents Outpatient Public Service (Office Médico-Pédagogique). Subjects were selected on the basis of a positive answer (yes or no) on the Cardiff Anomalous Perceptions Scale (CAPS) items describing AH items [i.e., items 3, 7, 11, 13, 28, or 32; (Bell et al., 2006; Debbané et al., 2011); see **Table 1**]. If they answered positively to an item, they were asked to rate their distress, the intrusiveness and the frequency of the experience by circling a number between 1 (not at all) and 5 (very).

In the 22q11.2DS group, all adolescents (mean age: 16.14, $SD = 2.55$, 9 males) were recruited through parent associations in France, Belgium and Switzerland. The 22q11.2 deletion was confirmed using DNA polymorphism analysis based on short sequence repeats or by fluorescence in situ hybridization performed on metaphase spreads spanning the deleted region.

Written informed consent was accepted by all parents and/or subjects under protocols approved by the Institutional Review Board of the Geneva University School of Medicine. The three groups (Control, AH and 22q11.2DS) did not significantly differ according to age and gender ($p > 0.05$). At the time of testing, no participants were receiving psychotropic medication (data for this was missing for one subjects in the 22q11.2DS group). All participants underwent the Block Design subtest (Kohs, 1920) in order to assess intellectual scores.

DESIGN AND PROCEDURE

Before the scan session, the experimenter described the task to the participants (see **Figure 1**). The paradigm was adapted from Larøi et al. (2005) and included 60 actions to be mentally simulated (imagined) either from a 1PP or 3PP. Simple, universal and gender-neutral actions were chosen. All actions implied a movement and an object (for example *take a picture, open a bottle, open a window, play the violin, brush your hair*). 30 actions were tested with a 1PP and 30 with a 3PP, in the same randomized order for each participant.

At the start of each session, the task's instructions appeared on the screen as a reminder. Then, a cross appeared on the screen for 665 ms. Immediately after the self-other priming cue appeared for 1 s stating either "You" written in red or "Best friend" in blue. Then, the photo of an object accompanied by a written instruction specifying the action to be imagined (i.e., play the violin, open a bottle, knock on a door) appeared for 1487 ms. Then the participants were reminded to either "Imagine yourself doing the action" or "Imagine your best friend doing the action" in accordance with the self-other priming cue. This instruction remained on the screen for a total of 4 s. An instruction in the center of the screen asked participants were asked to evaluate the difficulty of imagining the previous action, by pressing 1 (very easy) to 4 (very

Table 1 | CAPS selected items for auditory hallucinations (Bell et al., 2006; Debbané et al., 2011).

Item 3: "Do you ever hear your own thoughts repeated or echoed?"
Item 7: "Do you ever hear your own thoughts spoken aloud in your head, so that someone near might be able to hear them?"
Item 11: "Do you ever hear voices commenting on what you are thinking or doing?"
Item 13: "Do you ever hear voices saying words or sentences when there is no one around that might account for it?"
Item 28: "Have you ever heard 2 or more unexplained voices talking with each other?"
Item 32: "Do you ever hear sounds or music that people near you don't hear?"

	CAPS mean sum selected items	CAPS mean selected items distress	CAPS mean selected items frequency	CAPS mean selected items intrusiveness
Control group	0	N/A	N/A	N/A
AH group	2.25 (1.91)	2.66 (1.25)	1.77 (0.66)	2.78 1.10
22q11.2DS group	0.54 (0.47)	2.71 (1.89)	2.79 (1.81)	2.38 (1.60)

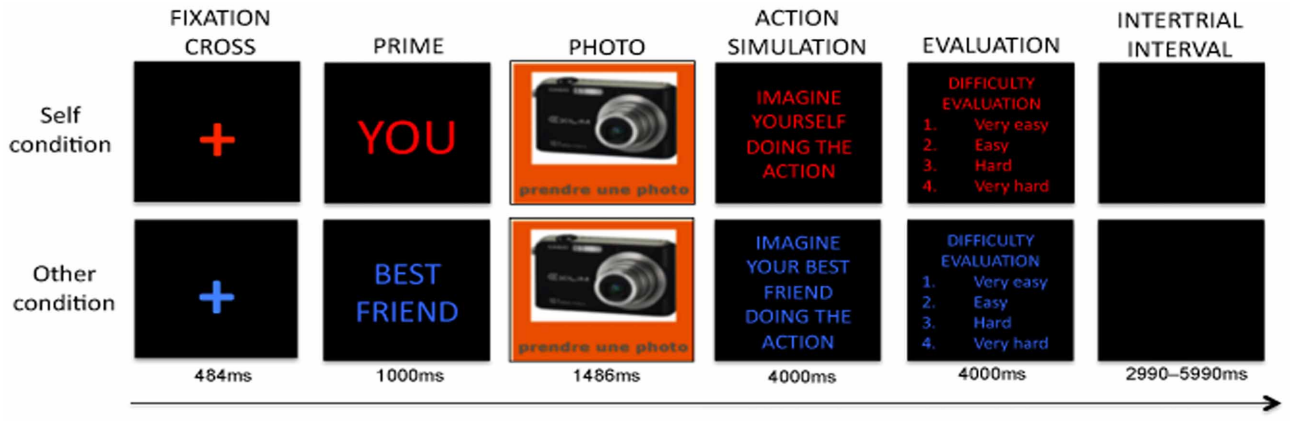

FIGURE 1 | Action simulation task adapted from Larøi et al. (2005).

hard) on a set of buttons on a console. This last step was used to make sure that the subjects performed the task. When a button was pressed, a blank screen appeared followed by the inter-trial interval (ITI) period, which lasted from 2990 to 5990 ms.

fMRI DATA ACQUISITION

A 3T Siemens TIM Trio system was used to acquire anatomical and functional images [*TR* (inter-trial between scan acquisition) = 2400 ms, Echo time (*TE*) = 30 ms, Slice thickness = 3.20 mm, Flip angle = 85°, FOV 235 mm]. The functional scan session consisted of 380 volumes that comprised 38 slices oriented parallel to the AC-PC lines and collected in a descending sequence. High-resolution three-dimensional anatomical images were also obtained [*TR* (inter-trial between scan acquisition) = 2400 ms, *TE* = 30 ms, Slice thickness = 1.1 mm, Flip angle = 8°, 192 coronal slices, FOV 220 mm].

fMRI DATA ANALYSIS

We used Statistical Parametric Mapping (SPM) 8, (Welcome Department of Neuroscience, London, UK) to analyse the data. First of all images had to be spatially transformed during the pre-processing step in order to reduce movement effects or shape differences among a series of scans. We realigned every image with respect to the first one. Then, slice timing correction was performed using the middle slice as a reference. We co-registered structural images of each participant to the mean of the realigned functional images. Gray matter separation was established by segmentation of the anatomical image. Thereafter, the normalization produced images that were warped to fit to a standard Template brain. We normalized the realigned and slice-timed images into the Montreal Neurological Institute (MNI) template using $3 \times 3 \times 3$ mm isotropic voxels. The images were spatially smoothed with an isotropic Gaussian smoothing Kernel of 6 mm full width half maximum (FWHM) to conform to inter-individual brain size variability.

After pre-processing, the brain responses of each subject were estimated at every voxel using a general linear mode. We defined two main conditions namely "self" and "other." The "self" condition corresponds to the trials starting with the word "you" in the priming period and when imagining an action performed by oneself (action stimulation period). The "other" condition refers to the trials starting with the word "best friend" in the priming period and when imagining an action performed by the best friend (action stimulation period). The return to baseline periods were set in the ITIs during which subjects saw a blank screen for 2990 ms to 5990 ms between each trial. In order to compare the specific areas devoted to the two different periods of the task (prime period and action simulation period) voxel value maps of t statistics were obtained for 4 contrasts: (1) prime self > prime other (2) prime other > prime self (3) 1PP > 3PP (4) 3PP > 1PP. These contrasts were performed for the following reasons. First, the prime self > prime other contrast will shield information on the neural correlates related to attention oriented to the self. In relation to our knowledge about overlapping activated brain regions for 1PP and 3PP-taking, some authors have suggested that 3PP requires "additional" areas in contrast to 1PP and vice-versa (Jeannerod, 2004, 2006; Jeannerod and Pacherie, 2004; Jeannerod and Anquetil, 2008). As such, it may be that hallucination-prone subjects fail to properly engage these areas, thereby increasing possible confusions between self and other. The two other contrasts (1PP > 3PP, 3PP > 1PP) follow the same logic, but when considering actual action imagery. T-maps were produced to identify atypical activation of the neural correlates sustaining self-other orientation and perspective taking for actions.

We first performed a one-sample *t*-test to characterize typical activations in control adolescents, and then proceeded to group comparison analyses. Using a two-sample *t*-test (comparison between groups), we compared Control and AH groups, Control and 22q11.2DS groups, and finally 22q11.2DS and AH groups. S{T} maps were obtained with a threshold of $p < 0.05$ and an extend threshold k of 20 voxels. Cluster level peak functional activity at $p < 0.05$ (Family-Wise corrected) was then localized on a mean structural scan with approximate Brodmann areas estimated from the Talairach and Tournoux (1988) atlas after having

converted coordinates from MNI to Talairach templates (http://www.bioimagesuite.org/Mni2Tal/index.html). Age was entered as a covariate in each analysis without any significant effects on the results obtained.

For *post-hoc* examination of potential associations between hallucination-proneness scores and activations resulting from group comparisons, we planned to extract local brain activity of regions of interest (ROIs) using SPM8 toolbox Marsbar (http://marsbar.sourceforge.net/). The ROIs were delimited around the peak of significant activations in prime self > prime other, prime other > prime self, 1PP > 3PP, 3PP > 1PP contrasts for the group comparisons. A 5 mm radius sphere was defined around the center of mass for each subject to extract Beta Values. We performed Pearson correlations between Beta Values obtained for different ROIs and CAPS components for each subjects (AHs distress, intrusiveness, frequency, total scores, as well as subscale scores) (Bell et al., 2006; Debbané et al., 2011).

RESULTS

BEHAVIORAL RESULTS

Differences regarding evaluation results between the three groups and the two different conditions were analysed using a repeated-measures ANOVA 3(groups) × 2(conditions) with *post-hoc* Tukey analyses.

With regard to the evaluation of difficulty ratings (see **Table 2**), our 3 × 2 ANOVA yielded a non-significant effect of diagnosis [$F_{(2,\ 44)} = 1.875$, $p = 0.165$], a significant effect of condition [$F_{(1,\ 44)} = 13.315$, $p = 0.001^{***}$] (mean evaluation for self condition = 1.6820, $SD = 0.40360$), (mean evaluation for other condition = 1.8504, $SD = 0.47230$) and a non-significant interaction between diagnosis and conditions [$F_{(2,\ 44)} = 0.752$, $p = 0.477$].

With regard to response time (see **Table 2**), results yielded a non-significant effect of diagnosis [$F_{(2,\ 44)} = 0.319$, $p = 0.729$], a non-significant effect of condition [$F_{(1,\ 44)} = 2.054$, $p = 0.159$] and a non-significant interaction between diagnosis and condition [$F_{(2,\ 44)} = 0.593$, $p = 0.557$].

NEUROIMAGING RESULTS

Control group

Prime period. The prime other > prime self contrast was associated with activations in a first cluster (2623 voxels, $p = 0.001$), including significant activations in the right cuneus BA18, right posterior cingulate BA30 and left cuneus BA17 (see **Table 3**). A second cluster (2272 voxels, $p = 0.004$) included significant activations in the right superior frontal gyrus BA6, left middle frontal gyrus BA46 and right superior frontal gyrus BA6 (see **Table 3**). No significant results were obtained in the prime self > prime other contrast.

Action simulation period. The 3PP > 1PP contrast was associated with activations in a first cluster (4098 voxels, $p = 0.000$)

Table 2 | Evaluation, response time, and Block DESD in each group.

	Control group (*N* = 22)	AH group (*N* = 12)	22q11.2DS group (*N* = 13)
Evaluation other	1.72 (0.38)	2.06 (0.45)	1.87 (0.57)
Evaluation self	1.59 (0.33)	1.79 (0.34)	1.74 (0.53)
Evaluation total	1.67 (0.32)	1.92 (0.37)	1.79 (0.53)
Answer time other	1142.24 (446.29)	1082.13 (294.93)	1118.20 (351.85)
Answer time self	1135.46 (425.56)	992.64 (266.31)	1076.48 (306.47)
Answer time total	1138.93 (425.45)	1037.40 (261.78)	1097.20 (303.49)
Block DESD	11.5 (3.25)	11.75 (2.53)	4.86 (2.73)

Table 3 | Regions of peak activations in the Control group.

Contrast	Cluster level - *p* -FEW-corr	Cluster level - Ke - voxels	Side	Brain regions activation	Brodmann area	*T*-value	*X, Y, Z* (MNI)
Prime other > Prime self	0.001	2623	Right	Occipital lobe, cuneus	BA18	5.10	3, −76, 19
	0.001		Right	Limbic lobe, posterior cingulate	BA30	5.06	9, −67, 10
	0.001		Left	Occipital lobe, cuneus	BA17	4.72	−21, −82, 13
	0.004	2272	Right	Frontal lobe, superior frontal gyrus	BA6	5.04	6, 32, 64
	0.004		Left	Frontal lobe, middle frontal gyrus	BA46	4.07	−51, 29, 19
	0.004		Right	Frontal lobe, superior frontal gyrus	BA6	3.90	21, 26, 64
3PP > 1PP	0.000	4098	Right	Limbic lobe, cingulate gyrus	BA23	4.90	3, −31, 28
	0.000		Right	Occipital lobe, cuneus	BA18	4.55	6, −73, 16
	0.000		Left	Occipital lobe, middle occipital gyrus	BA18	4.52	−21, −85, 16
	0.025	1692	Left	Frontal lobe, precentral gyrus	BA6	3.69	−39, 2, 40
	0.025		Left	Frontal lobe, superior frontal gyrus	BA6	3.68	−3, 17, 67
	0.025		Left	Frontal lobe, superior frontal gyrus	BA9	3.57	−18, 41, 43

including activations in the right cingulate gyrus BA23, right cuneus BA18 and left middle occipital gyrus BA18. A second cluster (1692 voxels, $p = 0.025$) included significant activations in the left precentral gyrus BA6, left superior frontal gyrus BA6 and left superior frontal gyrus BA9. No significant results were obtained in the 1PP > 3PP contrast.

NEUROIMAGING RESULTS: GROUP COMPARISONS

Comparisons between control and AH groups

Action simulation period. We observed significant results for the Control > AH comparison in the action simulation period (see **Table 4**). Specifically, the 3PP > 1PP contrast was associated with activations in a single cluster (5569 voxels, $p = 0.000$) including significant activations in the left middle occipital gyrus BA19, left cingulate gyrus BA31 and in the right precuneus BA31.

Comparisons between control and 22q11.2DS groups

Prime period. We observed significant results for the Control > 22q11.2DS comparison (see **Table 5**). The prime other > prime self contrast was associated with activations in a single cluster (2716 voxel, $p = 0.001$) with significant activations in the left cuneus BA18, left precuneus BA31, right middle temporal gyrus BA39.

Action simulation period. The 3PP > 1PP contrast was associated with activations in a single cluster (7020 voxels, $p = 0.000$) with significant activations in the right superior occipital gyrus BA19, left caudate tail and left precuneus BA7 (see **Table 5**).

Comparisons between 22q11.2DS and AH

Prime period. We observed significant results for the AH > 22q11.2DS comparison (see **Table 6**). The prime self > prime other contrast was associated with activations in a single cluster (1468 voxels, $p = 0.041$) with significant activations in the left caudate body, right anterior cingulate gyrus BA32 and right superior frontal gyrus BA 10. The prime other > prime self contrast was associated with activations in a single cluster (1696 voxels, $p = 0.020$) with significant activations in the right postcentral gyrus BA3, left superior frontal gyrus BA10 and right superior frontal gyrus BA8. No significant clusters were detected in the action simulation period.

ROIs analyses

No significant results were obtained for Pearson correlations between *T*-values activations in Control > AH, Control > 22q11.2DS and AH > 22q11.2DS group comparisons and CAPS subscales scores for each subjects.

Table 4 | Regions of peak activations for group comparisons Control > AH.

Contrast	Cluster level - *P* FEW-corr	Cluster level - Ke - voxels	Side	Brain regions activation	Brodmann area	*T*-value	*X, Y, Z* (MNI)
3PP > 1PP	0.000	5569	Right	Occipital lobe, middle occipital gyrus	19	4.42	33, −76, 19
	0.000		Left	Limbic lobe, cingulate gyrus	31	4.17	0, −37, 31
	0.000		Right	Occipital lobe, precuneus	31	4.09	24, −79, 31

Table 5 | Regions of peak activations for group comparisons Control > 22q11.2DS.

Contrast	Cluster level - *P* FEW-corr	Cluster level - Ke - voxels	Side	Brain regions activation	Brodmann area	*T*-value	*X, Y, Z* (MNI)
Prime other > Prime self	0.001	2716	Left	Occipital lobe, cuneus	BA18	4.52	−6, −82, 19
	0.001		Left	Parietal lobe, precuneus	BA31	4.13	−18, −73, 25
	0.001		Right	Temporal lobe, middle temporal gyrus	BA39	3.98	30, −67, 22
3PP > 1PP	0.000	7020	Right	Occipital lobe, superior occipital gyrus	BA19	5.37	36, −76, 25
	0.000		Left	Sub-lobar, caudate, caudate tail		4.93	−18, −25, 19
	0.000		Left	Parietal lobe, precuneus	BA7	4.92	−21, −73, 31

Table 6 | Regions of peak activations for group comparisons AH > 22q11.2DS.

Contrast	Cluster level - *P* FEW-corr	Cluster level - Ke - voxels	Side	Brain regions activation	Brodmann area	*T*-value	*X, Y, Z* (MNI)
Prime self > Prime other	0.041	1468	Left	Sub-lobar, caudate, caudate body		3.79	−12, 26, 16
	0.041		Right	Limbic lobe, anterior cingulate	BA32	3.67	15, 32, −8
	0.041		Right	Frontal lobe, superior frontal gyrus	BA10	3.24	24, 59, 10
Prime other > Prime self	0.020	1696	Right	Parietal lobe, postcentral gyrus	BA3	3.22	66, −19, 37
	0.020		Left	Frontal lobe, superior frontal gyrus	BA10	2.88	−12, 71, 16
	0.020		Right	Frontal lobe, superior frontal gyrus	BA8	2.84	6, 38, 52

DISCUSSION

This study is the first to compare neural correlates in self-other priming cues and action simulation using a 1PP or 3PP in typically developing adolescents (Control group), adolescents with transient AHs (AH group) and adolescents at genetic risk for schizophrenia (22q11.2DS group). The three objectives of this study were (1) to delineate the neural correlates sustaining mental simulation of actions involving 1PP and 3PP during adolescence; (2) to identify potential atypical neural activations during self-other priming and/or action simulation in hallucination-prone adolescents; (3) to examine whether differential risk for hallucination-proneness (clinical vs. genetic) is also associated with differential impairments in self-related cues and in action simulation. Our findings showed that (1) the Control group activated the key areas involved in *other* related cues when primed for their best friend compared to themselves, and in action simulation performed by others; (2) in the 3PP condition both hallucination-prone groups exhibited decreased activation in the parieto-occipital region, which has been related to self-other distinction of imagined actions (Jeannerod and Anquetil, 2008); (3) the priming period for both self and other related cues showed decreased activations in subjects with 22q11.2DS compared to those at clinical risk.

Control group activation patterns during prime and action simulation periods will first be discussed. Then, the unique activations in the AH group and the 22q11.2DS group will be brought into consideration, followed by a discussion concerning the differences between the two hallucination-prone groups.

CONTROL GROUP

Typically developing adolescents showed significant increased activations for the "other" condition compared to the "self" condition in both the prime and the action simulation periods.

For the 3PP, we found increased activations in the PCC and the parieto-occipital regions (see **Figure 2**). These regions may underlie the influence of visuo-spatial components and episodic memory when adolescents imagine actions performed by their best friend. PCC is involved in the processing of familiar stimuli (Qin and Northoff, 2011; Qin et al., 2012), and it has been shown that it plays an important role in memory tasks such as remembering familiar people (Maddock et al., 2001), remembering familiar objects and places (Sugiura et al., 2005) and autobiographical memory (Summerfield et al., 2009; Van Der Meer et al., 2010). The mental simulation of actions may involve the retrieval of memorized visual representations (Farah, 1984; Annett, 1995) of the imaginary action.

Areas in the parieto-occipital region lobe are activated when processing visuo-spatial information in the context of action representation (Kilintari et al., 2011), object-distance representation (Berryhill and Olson, 2009), including position and prediction of moving objects (Maus et al., 2010), coherent moving visual motion (McKeefry et al., 1997; Braddick et al., 2001), and motor imagery of hand action (Willems et al., 2009). The 3PP contrast might engage supplementary areas devoted to motion and visuo-spatial information, as an other's perspective implies a shift in visual-spatial perspective (Vogeley et al., 2004).

Activations in the frontal lobe could reflect the self-relevance evaluation of the prime period and the motor cognition aspect of action simulation. For the prime other > prime self contrast, we found significant increased activations in the right superior frontal part of the medial prefrontal cortex and the left dorsolateral prefrontal cortex DLPFC (Mayka et al., 2006; Northoff et al., 2006; Murray et al., 2012). These results are consistent with recent findings on self-other related processes in healthy adults. According to a recent meta-analysis, the dorsomedial prefrontal cortex DMPFC, DLPFC, and PCC act together in the evaluation and decision-making processes of self versus other relevant information (Van Der Meer et al., 2010).

For the action simulation period, we obtained significant results in the ventral part of the dorsal premotor cortex (Grezes and Decety, 2001; Mayka et al., 2006), the left pre-supplementary motor area (pre-SMA) (Mayka et al., 2006) and the DLPFC. These regions could be recruited by the task's motor aspects. It has been shown that the ventral part of the dorsal premotor cortex plays a role in motor preparation (Hoshi and Tanji, 2007), the pre-SMA in maintaining an action representation (Stadler et al., 2011) and the DLPFC in the cognitive control of motor behavior (Passingham, 1993; Hoshi, 2006; Cieslik et al., 2012).

In summary, our results showed that the mental simulation of actions performed by others engage increased activations in the posterior midline structure including PCC and the parieto-occipital region. Our results may reflect the visuo-spatial

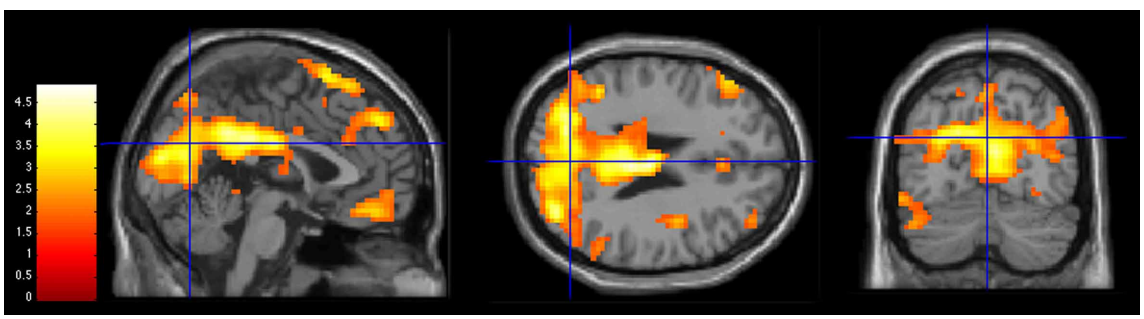

FIGURE 2 | Activations during 3PP > 1PP contrast in Control group at a statistical threshold of $p < 0.05$. Slice views at MNI coordinates ($x = 0$, $y = -70$, $z = 25$). The bar on the left shows the range of T-values.

and episodic memory components of self-other discrimination for imagined actions.

SIMILARITIES AND DIFFERENCES FOR THE AH GROUP AND THE 22q11.2DS GROUP COMPARED TO CONTROL GROUP

Both hallucination-prone groups showed significant decreased activations for the 3PP > 1PP contrast compared to the control group. The AH group and the 22q11.2DS group presented an atypical pattern of activations in the parieto-occipital region with significant decreased activations in the occipital gyrus BA19 and the precuneus.

As reviewed above, it has been shown that the right superior occipital BA19 is specifically devoted to 3PP in an action imagery task focusing on a visuo-spatial perspective switch (Jeannerod and Anquetil, 2008). According to the authors, the mental simulation of actions performed by others first occurs through a shift in space in order to mentally represent the other's place, and is then followed by the action simulation per se. In this framework, BA 19 would be a key area for self-other distinction by evaluating the difference in spatial localization between oneself and someone else. This interpretation is supported by data demonstrating the role of BA19 in the manipulation of spatial relationships between objects (Haxby et al., 1991; Kosslyn et al., 1998) and further confirmed by a meta-analysis (Zacks, 2008). Clinical studies have also shown that posterior parietal lesions provoke visuo-spatial dysfunction (Mendez, 2001; Harvey and Rossit, 2012) or disturbances in the capacity to represent relative location of objects with respect to the subject (Aguirre and D'Esposito, 1999). Recent evidence shows that the parieto-occipital junction responds to both gaze- and body-centered representation when reaching a target visually presented (Bernier and Grafton, 2010). This could be an argument in favor of a gaze and body reference computed by parieto-occipital junction during shift in 3PP.

Concerning the 22q11.2DS, Bearden et al. (2009) interestingly detected an decreased cortical thickness in the right parieto-occipital cortex, while to our knowledge, no clear structural alterations have been identified in this region in hallucination-prone subjects (Allen et al., 2008). Moreover, it has been shown that children with 22q11.2DS tend to present significant decreased activation in the parietal and occipital lobe during a visuo-spatial working memory task (Azuma et al., 2009). From a clinical point of view, visuo-spatial impairments have been extensively reported in the syndrome (Wang et al., 2000, 2011; Simon et al., 2005a; Jacobson et al., 2010). Together, these findings argue in favor of an atypical neuro-development of the parieto-occipital region in 22q11.2DS, which could lead to deficits in visuo-spatial perspective shifting in actions with objects.

The second region showing decreased activation during 3PP > 1PP contrast for both hallucination-prone groups was located in the right precuneus BA 31 (AH group) and the left precuneus BA7 (22q11.2DS group). In the PET study previously mentioned, Ruby and Decety (2001) found stronger activation bilaterally in the precuneus for 3PP > 1PP, and thus considered the region as specifically involved in distinguishing self and other action imagery. According to their view, the precuneus would play a role in the self's representation with an overactivation during 3PP. The precuneus responds to a wide range of cognitive processes including internal self-representation, episodic memory retrieval, visuo-spatial imagery, 1PP and agency processes (Cavanna and Trimble, 2006). The anatomical and connectivity data reviewed by them converges toward a functional subdivision between the anterior (y closer to −60 mm) and posterior (y closer to −70 mm) precuneus (Cavanna and Trimble, 2006). Our results for both the AH group and the 22q11.2DS group correspond to a decreased activation in the posterior region. Importantly when considering left and right disparity between the AH and 22q11.2DS groups no evidence of inter-hemispheric specialization emerged. Whereas the anterior region responds to self-centered mental imagery strategies, the posterior region is involved in successful episodic memory retrieval (Cabeza and Nyberg, 2000; Cavanna and Trimble, 2006). Episodic memory relies on the ability to remember past experiences (Tulving, 1972) with autobiographical references (Tulving, 1983) and plays a role in mental imagery (Tulving, 1983; Cabeza and Nyberg, 2000; Rubin et al., 2003; Daselaar et al., 2008). Clinical data have pointed out to a link between impaired episodic memory and auditory verbal hallucinations (Seal et al., 2004; Badcock et al., 2005; Berenbaum et al., 2008; Daselaar et al., 2008).

From a structural point of view, a significant volume reduction of the parietal lobe has been described in 22q11.2DS (Schaer et al., 2010). Results from functional connectivity also show atypical connectivity involving the left precuneus and PCC regions during resting state (Debbane et al., 2012). Concerning patients with hallucinations however, no clear alterations of the precuneus have been identified as far as we know (Allen et al., 2008).

In addition to the BA 19 and posterior parietal similarities, the at-risk groups showed unique differences in comparison to the controls. Compared to the control group decreased activation in the left parieto-occipital junction and the right posterior temporal BA39 was found in the 22q11.2DS group, but not in the AH group. This finding might correspond to a diminished salience for other related cues in 22q11.2DS. As mentioned in the last section, posterior parietal cortex, especially the posterior part of the precuneus, is particularly involved in successful retrieval of episodic memory (Wagner et al., 2005; Cavanna and Trimble, 2006; Elman et al., 2013) and in remembering familiar people (Maddock et al., 2001). The right temporo-occipital region (BA39) has been implicated in face processing (Puce et al., 1995; Dichter et al., 2009) and in the increased attention to salient social information because of its interactive processing with emotional information (Norris et al., 2004). Interestingly, it has recently been shown that the right temporo-occipital region presents decreased activation in response to affective social versus affective non-social images in schizophrenia (Bjorkquist and Herbener, 2013). Clinical data indicates that the 22q11.2DS syndrome exposes to an increased risk of social withdrawal, poor social functioning and emotion recognition deficits (Baker and Skuse, 2005; Debbane et al., 2006; Campbell et al., 2009).

In summary, our results show that both groups at risk (clinical and genetic) for hallucinations exhibited decreased activation in the parieto-occipital region during 3PP compared to the Control group (see **Figures 3** and **4**), which has been related to

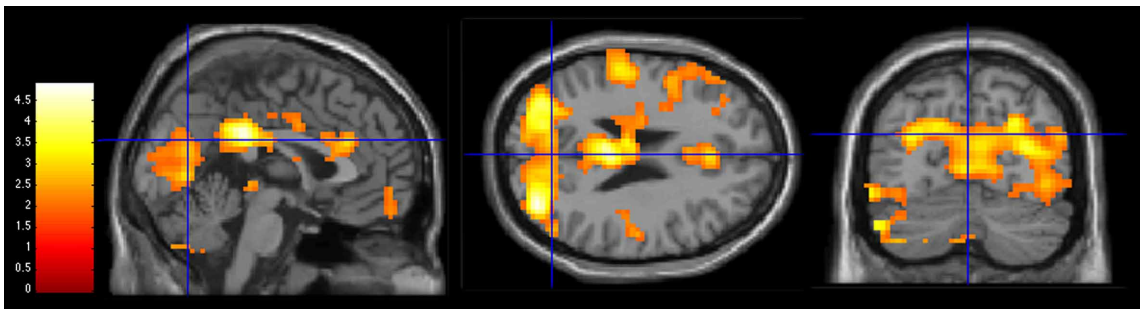

FIGURE 3 | Activations during 3PP > 1PP contrast in group comparisons (Control group > AH group) at a statistical threshold of $p<0.05$. Slice views at MNI coordinates ($x = 0$, $y = -70$, $z = 25$). The bar on the left shows the range of *T*-values.

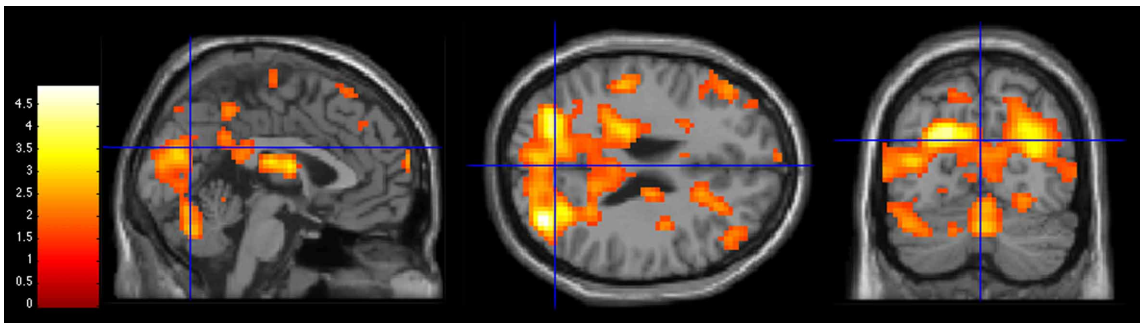

FIGURE 4 | Activations during 3PP > 1PP contrast in group comparisons (Control group > 22q11.2DS group) at MNI coordinates ($x = 0$, $y = -70$, $z = 25$). Statistical threshold of $p<0.05$. The bar on the left shows the range of *T*-values.

self-other distinction of imagined actions. We suggest that an impaired shift perspective and/or episodic memory dysfunctions might alter self-other distinction in hallucination-prone subjects. Consequently, the lack of reliable representations of the actions performed by others could account for SM action impairments previously observed by Larøi et al. (2005) and Debbane et al. (2008). Our results also argue in favor of a decreased salience toward others in the 22q11.2DS, as illustrated by the decreased activations in regions sustaining social cognition and episodic memory.

AT-RISK GROUPS: DIFFERENCES BETWEEN THE AH GROUP AND THE 22q11.2DS GROUP

We only obtained results for the prime condition when comparing the AH group and the 22q11.2DS group. This comparison indicated that the salience of self-other priming cues was different between the two groups at-risk for hallucinations, whereas no significant findings emerged for the 1PP and 3PP contrasts.

Compared to the AH group, adolescents with 22q11.2DS exhibited decreased activations of the caudate body, anterior cingulate BA32 and right superior frontal BA 10 for the prime self > prime other contrast. In line with our results, a significant lower level of activation was found in the caudate nucleus and the anterior cingulate cortex during self-reflective processing in adolescents with 22q11.2DS (Schneider et al., 2012). Several meta-analyses have highlighted the role of the anterior cortical midline structure and especially the anterior cingulate cortex in self-specific stimuli processing (Van Der Meer et al., 2010; Murray et al., 2012; Qin et al., 2012). It has also been shown that the caudate nucleus and the anterior cingulate cortex are engaged in reward and personal relevance, i.e., valuing external and internal stimuli with regard to their meaning for the subject (Enzi et al., 2009).

Our results might therefore reflect a decreased salience toward self-related cues in the 22q11.2DS compared to the AH group. The differences between the two groups could be related to neuro-structural alterations in the 22q11.2DS. Indeed reduced volume grey matter and cortical thickness have been described in the anterior cingulate cortex (Dufour et al., 2008; Bearden et al., 2009) and several studies have shown an increased volume of the caudate nucleus (Eliez et al., 2002; Kates et al., 2004; Gothelf et al., 2007). However according to several studies these regions are relatively spared in adolescents and adults with schizotypal traits (Spencer et al., 2007; Moorhead et al., 2009; Ettinger et al., 2012).

Compared to the AH group, adolescents with 22q11.2DS exhibited decreased activations in the right postcentral gyrus BA3 (somatosensory cortex S1) and anterior prefrontal cortex BA10 for prime other > prime self-contrast. The decreased activation of the somatosensory cortex in the 22q11.2DS group for the prime other > prime self contrast is in contradiction with previous work indicating that this region responds specifically to 1PP

(Ruby and Decety, 2001, 2003, 2004). In our task however the role of the right somatosensory cortex and the anterior prefrontal cortex BA10 might be related respectively to emotion processing (Adolphs et al., 2000; Pourtois et al., 2004; Hooker et al., 2008; Saxbe et al., 2012) and mental states attribution (Gilbert et al., 2006; Burgess et al., 2007; Benoit et al., 2010). The reduced activations in these regions are in line with clinical evidence showing impairments in cognitive theory of mind tasks in 22q11.2DS (Chow et al., 2006; Campbell et al., 2011; Ho et al., 2012).

In summary, in comparison to subjects at clinical risk, adolescents with 22q11.2DS showed atypical patterns of activations when primed for themselves and their best friend. More precisely, decreased activations were found in regions involved in self-relevance, emotion processing and attribution.

LIMITATIONS

The present study must be considered with limitations. First, the restricted sample sizes make it difficult to completely exclude the absence of significant results for the 1PP > 3PP contrasts. Future studies with increased statistical power could address this issue. Concerning the group selection, the 22q11.2DS group had lower IQ scores compared to the Control group. However, the behavioral results showed that response times and difficulty ratings did not significantly differ between groups. This suggests that 22q11.2DS subjects were not put in a more difficult position due to the intellectual deficits they might present.

The functional imaging paradigm did not include a cognitive control for the prime and action simulation period other than the perspective-taking variants, which could be included in a future version of this paradigm.

Future studies should address the neurodevelopmental issues of action simulation during adolescence by also comparing children and adults data or data with longitudinal follow-up. More research exploring shift perspective and agency processes may further contribute to a better understanding of action misattribution biases in hallucination-prone subjects.

CONCLUSION

This study constitutes the preliminary step of a neuroscientific examination targeting the neural correlates of self-other discrimination in mental imagery for hallucination-prone adolescents. We suggest that impairment in the capacity to shift perspective and/or episodic memory dysfunction may alter self-other distinction in hallucination-prone subjects.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: http://www.frontiersin.org/HumanNeuroscience/10.3389/fnhum.2013.00329/abstract

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Repeated measurements of cerebral blood flow in the left superior temporal gyrus reveal tonic hyperactivity in patients with auditory verbal hallucinations: a possible trait marker

Philipp Homan[1], Jochen Kindler[1], Martinus Hauf[2], Sebastian Walther[1], Daniela Hubl[1] and Thomas Dierks[1]*

[1] *Department of Psychiatric Neurophysiology, University Hospital of Psychiatry, University of Bern, Bern, Switzerland*
[2] *Support Center for Advanced Neuroimaging, Institute of Diagnostic and Interventional Neuroradiology, Inselspital, University of Bern, Bern, Switzerland*

Edited by:
Paul Allen, Insitute of Psychiatry, UK

Reviewed by:
Giuliana Lucci, IRCCS Santa Lucia of Rome, Italy
Matthijs G. Bossong, Institute of Psychiatry, UK

***Correspondence:**
Thomas Dierks, Department of Psychiatric Neurophysiology, University Hospital of Psychiatry, University of Bern, Bolligenstrasse 111, CH-3000 Bern 60, Switzerland
e-mail: dierks@puk.unibe.ch

Background: The left superior temporal gyrus (STG) has been suggested to play a key role in auditory verbal hallucinations (AVH) in patients with schizophrenia.

Methods: Eleven medicated subjects with schizophrenia and medication-resistant AVH and 19 healthy controls underwent perfusion magnetic resonance (MR) imaging with arterial spin labeling (ASL). Three additional repeated measurements were conducted in the patients. Patients underwent a treatment with transcranial magnetic stimulation (TMS) between the first 2 measurements. The main outcome measure was the pooled cerebral blood flow (CBF), which consisted of the regional CBF measurement in the left STG and the global CBF measurement in the whole brain.

Results: Regional CBF in the left STG in patients was significantly higher compared to controls ($p < 0.0001$) and to the global CBF in patients ($p < 0.004$) at baseline. Regional CBF in the left STG remained significantly increased compared to the global CBF in patients across time ($p < 0.0007$), and it remained increased in patients after TMS compared to the baseline CBF in controls ($p < 0.0001$). After TMS, PANSS ($p = 0.003$) and PSYRATS ($p = 0.01$) scores decreased significantly in patients.

Conclusions: This study demonstrated tonically increased regional CBF in the left STG in patients with schizophrenia and auditory hallucinations despite a decrease in symptoms after TMS. These findings were consistent with what has previously been termed a trait marker of AVH in schizophrenia.

Keywords: schizophrenia, auditory verbal hallucinations, cerebral blood flow, arterial spin labeling, superior temporal gyrus, longitudinal study

INTRODUCTION

In schizophrenia, auditory verbal hallucinations (AVH) comprise a critical domain. The 1-month prevalence of these hallucinations exceeds 70% (Sartorius et al., 1986), and, in 25–30% of patients, these perceptions are resistant to medication, resulting in functional disability and a low quality of life (Shergill et al., 1998; Copolov et al., 2004). The development of new therapeutic strategies (Homan et al., 2011) is urgent and would benefit from a better understanding of the neurophysiology of AVH.

The results of resting perfusion and functional imaging studies have implied that AVH are associated with altered neuronal activity in cerebral areas that are responsible for language production and perception (Allen et al., 2008; Strik and Dierks, 2008). AVH have been shown to be positively correlated with resting-state perfusion (regional cerebral blood flow, CBF) in the medial temporal lobe (Liddle et al., 1992), the superior temporal lobe (Gur et al., 1995), and the anterior cingulate cortex (Lahti et al., 2006) and negatively correlated with perfusion in the hippocampus/parahippocampus (Lahti et al., 2006). In addition, when CBF has been measured before and after interventions with transcranial magnetic stimulation (TMS), it has been found to be decreased at the stimulation site, which is the left superior temporal gyrus (STG), and in interconnected regions and increased in the contralateral cortex and the frontal lobes after 10 days of TMS treatment (Horacek et al., 2007). In a previous study, we found an association of favorable TMS treatment effects and decreased neuronal activity in the primary auditory cortex, Broca's area, and the cingulate gyrus (Kindler et al., 2013), suggesting that CBF might be a biological marker for the effectiveness of TMS. Furthermore, the CBF in the left STG before treatment predicted the response to TMS, indicating that resting perfusion measurements before treatment might be appropriate for differentiating possible responders and non-responders to TMS (Homan et al., 2012). However, those CBF measurements were limited to only one time point, which was before treatment, and the time courses of the CBF and the psychopathological symptoms were not assessed with repeated measurements. Several studies have investigated the clinical severity of hallucinations longitudinally

(Arndt et al., 1995; Marengo et al., 2000; Mancevski et al., 2007; Chang et al., 2009; Schneider et al., 2011). Until now, it has been unclear in which way the neuronal activity followed the clinical course of AVH longitudinally in individual patients. Regions with neuronal activity that follow the clinical course may be regarded as state-dependent, whereas areas that demonstrate continuous aberrant activity compared to those in non-hallucinators and healthy subjects may be regarded as trait-specific.

In this study, we repeatedly measured CBF in a region of interest (ROI) that has been previously identified (left STG, **Figure 1**) to exhibit predictive CBF before TMS treatment in patients with medication-resistant AVH (Homan et al., 2012). Patients were treated with TMS according to a 10-day-treatment protocol between the first and the second measurement (Kindler et al., 2013). Our aim was to gain insights into the fluctuations of CBF and symptoms. In order to measure CBF, we used magnetic resonance (MR) arterial spin labeling (ASL), which is a MR technique that provides a direct quantitative measure of CBF (Horn et al., 2009; Jann et al., 2010; Viviani et al., 2010; Walther et al., 2012). ASL is a non-invasive technique that has been shown to provide converging results with those that have been obtained by invasive positron emission tomography perfusion imaging (Xu et al., 2010). It thus can more easily and less invasively be applied in situations that require repeated examinations.

In this study, we were interested in whether the proposed responsiveness of regional CBF in the left STG to TMS (Homan et al., 2012) was a stable (trait-like) feature over time or whether there were fluctuations in neuronal activity across time. Additionally, we compared the initial measurements of the series with measurements in 19 healthy controls. Based on the results of a recent meta-analysis that have suggested that the neuronal activity in the left STG might be a trait-like feature in AVH (Kuhn and Gallinat, 2012), we hypothesized that the CBF in the left STG would be increased compared to healthy controls and would not change across time.

METHODS

PATIENTS AND CLINICAL INVESTIGATION

The same patient population as that described in Homan et al. (2012) was used. However, only 11 patients were willing to undergo repeated measurements after TMS treatment. The patients who were included in the study had a diagnosis of schizophrenia or schizoaffective disorder according to the International Statistical Classification of Diseases and Related Health Problems (ICD)-10, medication-resistant AVH, and ages of 18–65 years, and they were right-handed. The right-handed healthy control subjects had no history of any psychiatric disorders and no major psychiatric conditions in their first-degree relatives ($n = 19$). The exclusion criteria were MR contraindications and any medical disorders other than schizophrenia or schizoaffective disorder in the patients. None of the subjects reported substance misuse in the 4 weeks before or during the study. All patients underwent identical diagnostic procedures, including the MR protocol. The diagnostic procedures were conducted based on the clinical interviews and psychiatric histories. The psychopathology assessment, which consisted of the Positive And Negative Syndrome Scale (PANSS) (Kay et al., 1988) and the Psychotic Symptom Rating Scale (PSYRATS) (Haddock et al., 1999), was performed on the same occasion as the ASL. In order to ensure that all subjects were right-handed, the Edinburgh Handedness Scale (Oldfield, 1971) was assessed. The investigation was conducted in accordance with the Declaration of Helsinki and was approved by the local ethics committee. All subjects provided informed written consents to participate in the study.

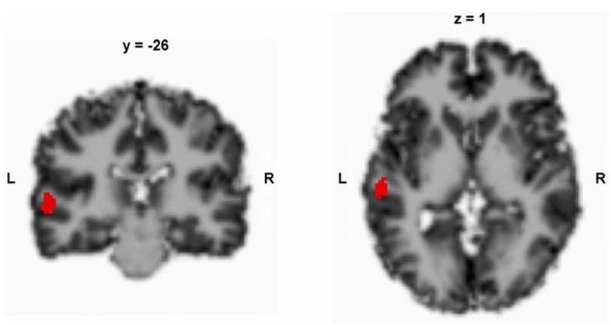

FIGURE 1 | Predefined region of interest in the left superior temporal gyrus. The local maximum peak values were retrieved from a previous study (Homan et al., 2012); according to SPM 8, $x, y, z = -58, -26, 4$; x, y, z coordinates in Talairach space.

STUDY PROCEDURE

Patients and controls were measured with ASL at baseline. The psychopathology in the patients was assessed. Patients then underwent 10 days of TMS treatment. Within 36 h after the TMS treatment, the patients' psychopathology and CBF with ASL were assessed again. Patients underwent two follow-up examinations of perfusion MRI and psychopathology 4 weeks and 8 weeks post-TMS.

TMS PROTOCOL

The TMS protocol has been described elsewhere (Homan et al., 2012; Kindler et al., 2013). Briefly, the target region for TMS was the sensorimotor speech region, which is called the Sylvian parietotemporal (Spt) area and which is located in the Sylvian fissure at the parietotemporal boundary. We applied a modified version of the language processing task that was developed by Hickok et al. (2009) to localize the Spt area for TMS treatment in a functional MR imaging (fMRI) scan of each patient in the first MR measurement. This fMRI measurement was conducted immediately after the ASL measurement. The individual's fMRI activation map was superimposed on reconstructed anatomical mesh, and the target point of the Spt area was marked for TMS. We used a custom TMS stimulator (MagPro R 100, Medtronic Functional Diagnostics A/S, Skovlunde, Denmark) to generate repetitive biphasic magnetic pulses with a figure-8 coil (Magnetic Coil Transducer MC-B70, Medtronic Functional Diagnostics A/S). The individual resting motor threshold was identified by stimulation of the motor cortex with single TMS pulses until a movement of the contralateral thumb was detected (Schutter and Van Honk, 2006). TMS pulse intensity was then adjusted to 90% of the resting motor threshold. Patients were randomly assigned to receive 1 Hz ($n = 7$) or theta burst ($n = 4$)

TMS. The target area was stimulated for 10 consecutive days in both groups. Common TMS safety protocols were applied according to international safety standards (Rossi et al., 2009). A frameless, ultrasound-based, stereotactic system was used for neuronavigation (Brainvoyager™ TMS Neuronavigator System, Brain Innovation B.V., Maastricht, Netherlands) (Sack et al., 2009).

MRI DATA ANALYSIS: ASL

MRI was conducted on a 3.0-Tesla whole-body MRI system (Magnetom Trio, Siemens Medical Systems, Erlangen, Germany) with a standard 12-channel radiofrequency head coil. High-resolution three-dimensional (3D) structural MRI and ASL were acquired in each session. T1-weighted 3D magnetization prepared-rapid gradient echo (MP-RAGE) scans were recorded (number of slices, 176; matrix, 256 × 256; slice thickness, 1 mm; voxel size, $1 \times 1 \times 1\,mm^3$), and they served as high-resolution 3D anatomical templates for coregistration with the functional data. A pseudocontinuous ASL (pCASL) technique was used to measure CBF (Wang et al., 2005). In this gradient-echo echo-planar imaging sequence, interleaved images with and without labeling were acquired. A delay of 1250 ms was applied between the end of the labeling pulse (label time, 1600 ms) and image acquisition (slice acquisition time, 45 ms) in order to reduce transit artifact (field of view, $220\,mm^2$; matrix, 64 × 64; repetition time/echo time, 4000/18 ms; flip angle, 90°; and labeling efficiency a, 0.95). A total of 14 slices (voxel size, $3.4 \times 3.4 \times 6\,mm^3$; slice gap, 1.5 mm) was acquired in the anterior and posterior commissure line from inferior to superior in sequential order. The pCASL scan comprised 80 acquisitions. The ASL data analysis was performed in a manner that was similar to that described by Homan et al. (2012). Briefly, we used aslm (Homan et al., 2012) (downloadable at http://aslm.sourceforge.net), which is based on MATLAB® (MATLAB version 8, release 14; The MathWorks, Inc., Natick, MA, USA) and statistical parametric mapping (SPM 8, Wellcome Department of Imaging Neuroscience, London, England; www.fil.ion.ucl.ac.uk/spm8). All ASL time series were first realigned to correct for motion artifacts. We calculated a flow-time series by subtracting the labeling images from the control images and subsequently computed mean CBF images for each subject (Federspiel et al., 2006). Each individual subjects' T1 anatomy was segmented into gray matter (GM) and white matter (WM). The mean ASL images were then coregistered to the GM-segmented T1 images. T1, GM, WM, and ASL images were normalized to the SPM MNI T1 template. ASL images were spatially smoothed with a 3D 8-mm full-width at half-maximum Gaussian kernel. Data were *z*-transformed [$z = (\text{voxel CBF} - \text{global GM CBF})/\text{SD}$] in order to remove sources of variance that were caused by differences in the global mean CBF between acquisitions and corrected for GM by using GM segments as inclusive masks.

STATISTICAL ANALYSIS: CBF

A global and assumption-free investigation of the whole-brain CBF was computed. CBF values were then extracted from the a priori-defined ROI in the left STG that corresponded to the finding described in Homan et al. (2012) with aslm. Therefore, the ROI was used as an inclusive mask of each subject's ASL measurement. The mean regional blood flow of the ROI was calculated by taking the mean of all voxels inside the mask. A full-factorial linear mixed model with a restricted maximum likelihood estimation was then computed with the pooled global and regional CBF values of the baseline measurements as outcome measures and diagnosis, localization (global, regional), and the diagnosis-by-localization interaction as fixed effects. The longitudinal patient data were then examined separately in full-factorial mixed models with restricted maximum likelihood estimation in order to examine the effects of localization, time, and medication (chlorpromazine dose equivalent, CPZE) on the CBF outcome measures. In order to additionally assess the effect of psychopathology on CBF, PSYRATS, and PANSS were included as additional fixed effects in these models. For the outcome measures of psychopathology (PSYRATS, PANSS), the effects of time, TMS protocol, and medication were assessed for the first 2 observations (pre- and post-TMS treatment). For the additional observations (at $t = 2$, 3, and 4), the effects of time and medication were assessed on the outcome measures of the PSYRATS and PANSS. In order to account for the different intervals between the measurements after TMS treatment, interval was also included as a fixed effect in these longitudinal models. Furthermore, these models included a subject effect in order to account for the repeated measurements. The Schwarz Bayesian criteria were used to determine the best fitting covariance structure for each set of measures in cases where the typical compound symmetry approach that was used by ANOVA did not provide the optimal structure for the extant data. A heterogeneous variance first-order autoregressive covariance structure proved to be appropriate for all mixed models. The *post-hoc t*-tests involved a Tukey correction for multiple comparisons. SAS 9.2 (SAS Institute, Inc., Cary, NC, USA) was used for all analyses. The means are reported with their associated standard deviations (SDs). Statistical significance was set at $p < 0.05$.

RESULTS

CLINICAL DATA

Eleven patients and 19 healthy controls were measured at baseline. Three additional repeated measurements were conducted on the patients. The intervals between measurements differed across the patient group (mean ± SD, 28.2 ± 32.9 days). Altogether, 44 measurements were conducted in the patients. The clinical and demographic characteristics of the subject sample are detailed in **Table 1**. The mean CPZE at baseline was 714.5 ± 475.5 mg and remained stable during the study. Between the first and second measurement, which was after the TMS treatment, the PANSS [$F_{(1,\ 10)} = 14.88, p = 0.003$; **Figure 2A**] and PSYRATS [$F_{(1,\ 10)} = 9.97$, $p = 0.01$; **Figure 2B**] scores were decreased significantly in the patients. No effect of TMS stimulation mode (1 Hz vs. theta burst) was found on the PANSS [$F_{(1,\ 10)} = 0.18, p = 0.7$] and PSYRATS [$F_{(1,\ 10)} = 1.19$, $p = 0.3$] scores, and no effect of medication was evident. The PSYRATS score remained stable after TMS treatment across all further measurements, which included observations at $t = 2$, 3, and 4 [$F_{(2,\ 19)} = 1.04$, $p = 0.37$; **Figure 2B**]. The PANSS scores displayed a trend toward a time effect after TMS, which included observations at $t = 2$, 3, and 4, [$F_{(2,\ 19)} = 3.18, p = 0.06$; **Figure 2A**].

Table 1 | Subject characteristics of the patients ($n = 11$) and healthy controls ($n = 19$).

Characteristic	Patients ($n = 11$)	Healthy controls ($n = 19$)	Test statistic	p-value
Sex, F/M	8/3	11/8	Fisher's exact	0.5
Diagnosis	11 Sz	n.a.	n.a.	n.a.
Age, mean (SD), y	37.1 (8.8)	38.5 (12.2)	t-test	0.7
Age at onset, mean (SD), y	23.3 (4.4)	n.a.	n.a.	n.a.
Chlorpromazine equivalent dose at study entry, mean (SD)	714.5 (475.5)	n.a.	n.a.	n.a.
Global mean cerebral blood flow corrected for gray matter at study entry, mean (SD)	65.7 (7.7)	67.1 (6.2)	*t*-test	0.6
PANSS score at study entry, mean (SD)	67.1 (18.9)	n.a.	n.a.	n.a.
PSYRATS score at study entry, mean (SD)	35.4 (2.0)	n.a.	n.a.	n.a.

Values are presented as means ± SD. Abbreviations: F, female; M, male; Sz, schizophrenia (according to ICD-10); n.a., not available; PANSS, Positive and Negative Syndrome Scale; SD, standard deviation; PSYRATS, Psychotic Symptoms Rating Scale; CBF, cerebral blood flow.

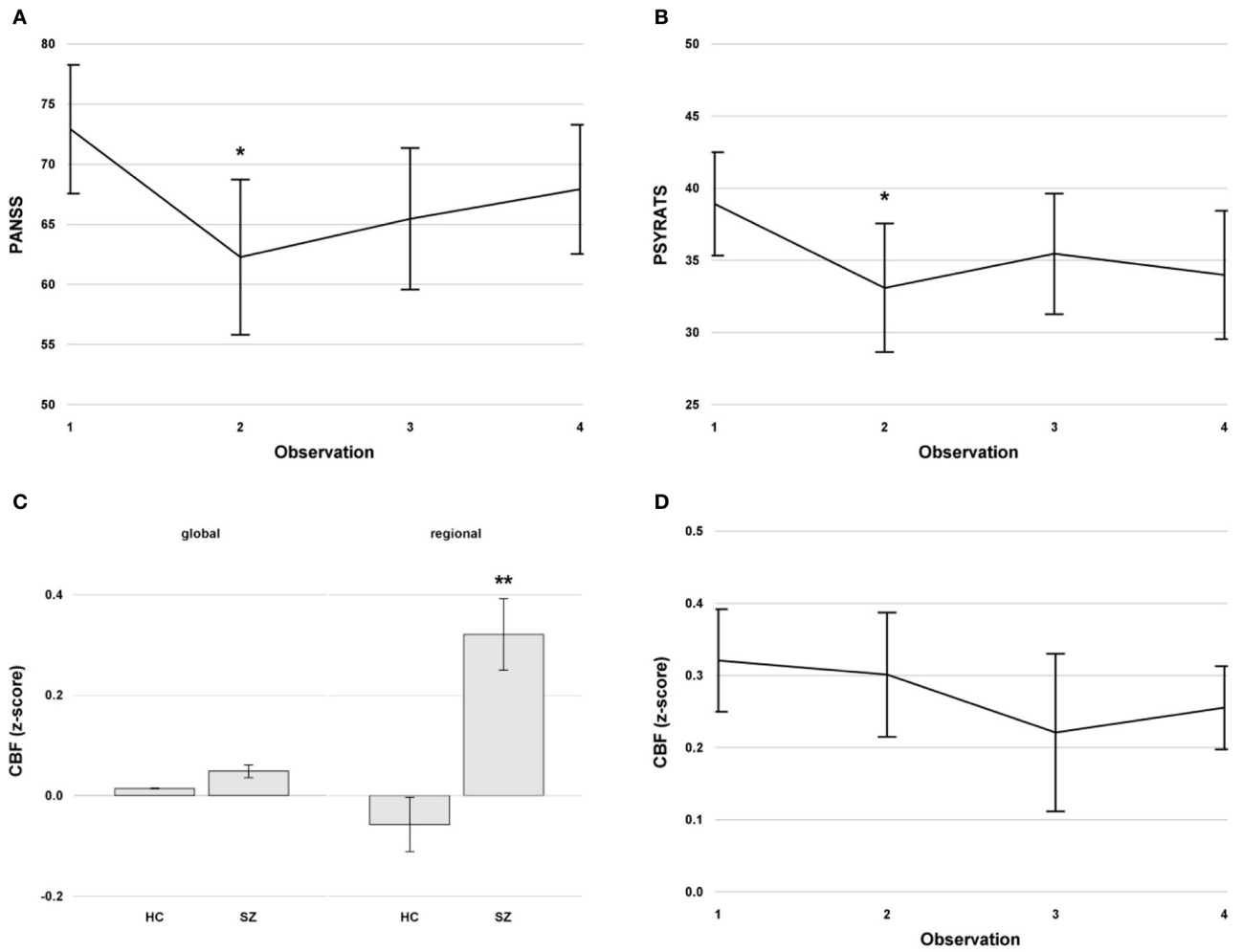

FIGURE 2 | (A) Mean PANSS scores with standard errors across time in the patients. **(B)** Mean PSYRATS scores with standard errors across time in the patients. **(C)** Mean global and regional cerebral blood flow (CBF) in the left superior temporal gyrus with standard error at baseline in healthy controls and patients with schizophrenia with persistent auditory verbal hallucinations. **(D)** Mean regional CBF with standard errors in the left superior temporal gyrus across time in the patients. The CBF values were z-transformed. **indicates a significant difference at $p < 0.01$, *indicates a significant difference at $p < 0.05$. Abbreviations: PANSS, Positive and Negative Syndrome Scale; PSYRATS, Psychotic Symptoms Rating Scale; CBF, cerebral blood flow. HC, Healthy Controls; SZ, Schizophrenia.

GLOBAL AND REGIONAL CBF AT BASELINE

The pooled CBF (global and regional) was significantly higher in patients with schizophrenia compared to healthy controls [$F_{(1,\ 28)} = 21.19$, $p < 0.0001$], and the regional CBF in the left STG was significantly higher in the entire sample [$F_{(1,\ 28)} = 5.02$, $p < 0.04$]. The localization-by-diagnosis interaction was also significant [$F_{(1,\ 28)} = 14.74$, $p < 0.0007$]. The *post-hoc* tests revealed a significantly higher regional CBF in patients compared to controls [$t_{(1,\ 28)} = 5.97, p < 0.0001$, **Figure 2C**]. Furthermore, regional CBF in the left STG in patients was significantly higher compared to global CBF [$t_{(1,\ 28)} = 3.82$, $p < 0.004$, **Figure 2C**], an effect that was not found in healthy controls [$t_{(1,\ 28)} = 1.32$, $p = 0.6$].

LONGITUDINAL CHANGES OF GLOBAL AND REGIONAL CBF

The regional CBF in the left STG was significantly higher compared to the global CBF in patients across time [$F_{(1,\ 10)} = 24.67$, $p < 0.0007$]. There was no time effect [$F_{(3,\ 30)} = 0.98$, $p = 0.4$], no effect of interval [$F_{(1,\ 69)} = 0.01$, $p = 0.9$], and no time-by-localization interaction [$F_{(3,\ 30)} = 0.23$, $p = 0.9$] in the longitudinal patient data (**Figure 2D**). In addition, no TMS effect was evident in the left STG CBF for the first 2 measurements [$F_{(1,\ 10)} = 0.1, p = 0.75$]. After TMS with $t = 2$, 3, and 4, CBF in the left STG of patients was still increased compared to the baseline CBF of healthy controls [at $t = 2$: $t_{(1,\ 28)} = 5.27, p < 0.0001$; at $t = 3$: $t_{(1,\ 28)} = 3.62$, $p = 0.001$; at $t = 4$: $t_{(1,\ 28)} = 5.3$, $p < 0.0001$]. Furthermore, no medication effect of CPZE was evident [$F_{(1,\ 9)} = 0.15, p = 0.7$].

CORRELATION OF REGIONAL CBF AND PSYCHOPATHOLOGY

The regional CBF in the left STG was negatively associated with the PSYRATS scores across time [$F_{(1,\ 28)} = 9.93$, $p = 0.004$]. No such association was found between CBF and the PANSS scores [$F_{(1,\ 28)} = 1.7, p = 0.2$].

DISCUSSION

Until now, longitudinal studies of global and regional CBF in patients suffering from schizophrenia and AVH have not been conducted. In this study, we were able to investigate patients who were suffering from AVH several times during the course of their disease, and we were able to demonstrate that the patients had significantly higher CBF in a predefined region, the left STG, compared to healthy controls and compared to global CBF. Furthermore, the increase in regional CBF was a stable feature across time that was unaffected by treatment with TMS.

The aim of the current study was to gain further insight into the involvement of the left STG in AVH. Indeed, this region is thought to play a key role in AVH interventions. Previous studies have suggested that the left STG might be an appropriate target region in TMS in patients with schizophrenia and AVH. Ten days of TMS treatment to the left STG resulted in a clinically relevant improvement of symptoms as measured by the PSYRATS, and this has been shown to be correlated with decreases in the CBF in primary language and auditory regions (Kindler et al., 2013) but not with CBF changes in the STG. Furthermore, responders and non-responders to TMS were identified by the CBF in the left STG before treatment. One aim of the current study therefore was to search for fluctuations in the regional CBF in the left STG that would be consistent with the proposed responsiveness to TMS (Homan et al., 2012). However, we did not find fluctuations in the regional CBF but a persistent hyperperfusion in the left STG during all 4 measurements compared to the baseline CBF of healthy controls and the global CBF, suggesting that increased regional CBF in the left STG is a trait and not a state marker in patients with schizophrenia and AVH. This was further supported by the fact that treatment with TMS between the first and second measurements did not alter CBF in the left STG, which was in contrast to previous findings of decreased regional glucose metabolism at the stimulation site in the left STG after 10 days of TMS (Horacek et al., 2007). However, the finding of the latter study was located more anteriorly and more inferiorly (at the temporal pole) than the ROI in the current study. Thus, the current finding might indicate that patients who have regional CBF values below the previously proposed cutoff value (Homan et al., 2012) are unlikely to change to a responsive state across time.

In addition, the findings of continuously increased left STG CBF in patients with AVH provided further evidence of the involvement of the left STG in AVH, which has also been shown for patients with AVH of epileptic etiology (Hauf et al., 2013). It has been suggested that AVH arise from a disorder of inner verbal experiences, particularly from a disorder of the monitoring of inner speech (David, 1994; McGuire et al., 1995). A bottom–up model has been proposed that includes alterations in secondary and sometimes even primary sensory cortices, speech production and reception areas (inferior frontal gyrus, left STG) and in the coupling with monitoring areas (anterior cingulate) (Allen et al., 2008). Specifically, alterations in the connectivity of the STG, the inferior frontal gyrus, and the anterior cingulate cortex might be the precondition for altered activity in language processing areas (Allen et al., 2008). Thus, in the aforementioned model, AVH are thought to be associated with decreased top–down control by the ventral anterior cingulate, prefrontal, premotor, and cerebellar cortices and failure in monitoring and volitional assignment. Together, these alterations might be the neuronal basis of the experience of perceptions without sensory stimuli (Allen et al., 2008). This is in line with previous research that has focused on the possible therapies of AVH. With regard to therapy, it is known that low-frequency repetitive TMS that is delivered to the left temporoparietal cortex, which is a brain area that is critical to speech perception, reduces AVH (Hoffman et al., 2000, 2003; Aleman et al., 2007). Recently, the first case report was published of a patient with schizophrenia and medication-resistant AVH who was successfully stimulated at the same region with transcranial direct current stimulation (Homan et al., 2011), and this finding has been confirmed by a larger study that used a slightly different stimulation paradigm (Brunelin et al., 2012).

The present study conducted repeated measurements of psychopathology and CBF. Our finding of persistent regional hyperperfusion in the left STG in AVH was consistent with a recent meta-analysis that has suggested that neuronal activity in the left STG is a trait marker in AVH (Kuhn and Gallinat, 2012). That study classified neuroimaging studies that explored AVH in state and trait studies. Symptom-catching state studies compare periods of the presence of hallucinations with periods of the

absence of hallucinations within subject, whereas trait studies compare the brain activity between hallucinating subjects with that of non-hallucinating patients with schizophrenia or healthy controls. The findings in the meta-analysis have supported the idea that AVH are caused by a permanent defective monitoring of inner speech (trait) and a temporary misattribution of internally generated speech (state). State-like brain regions have been consistently found in frontal speech-generating regions, whereas the left temporal brain regions (left STG, left middle temporal gyrus) have been found in trait studies. The alteration that was found in these left temporal regions was less activation during tasks involving verbal material-like inner speech generation or prerecorded listening. However, the direction of this alteration has been somewhat difficult to interpret because brain activity is first compared on a within-subject basis, and this difference is then contrasted between participants. This raised the question of whether hallucinating patients could have tonically high activity or tonically low activity that is independent of state (the degree of subjectively experienced AVH) in the temporal lobe, which would then contribute to the small differences that were observed in the within-subject comparison between conditions and to the seemingly decreased activation in hallucinating subjects compared to non-hallucinating subjects (Kuhn and Gallinat, 2012). Thus, our findings of persistently increased CBF in the left STG was in line with the suggestion of tonically high activity in hallucinating patients and extends the proposed trait marker to the confirmation of the increased hyperperfusion, at least for our 4 measurement time points.

Some limitations of our study design merit comment. No direct relationship between brain activity and the occurrence of hallucinations during scanning was investigated because, in ASL, the mean cerebral perfusion was calculated over the scanning time. Therefore, the temporal resolution was low. In addition, the variance of the intervals between the measurements was certainly a weakness of the present study. However, we took this variance into account by including the intervals between measurements as a fixed effect in the general linear mixed models that we computed, and no effect was evident. In addition, ASL measured a baseline CBF increase, which can be interpreted as a trait for AVH. However, because we did not exactly know when during the measurements that the patients were hallucinating, one cannot exclude that this region also can show state-dependent behavior like that previously described for the primary auditory cortex (Dierks et al., 1999; Jardri et al., 2011; Kompus et al., 2011). As long as a ceiling for neural activity for a certain region has not been reached, a region with a higher baseline CBF can generate additional neuronal activation. Finally, the small sample size has to be considered. The study might thus have been underpowered for detecting significant differences in the left STG CBF across time.

In conclusion, this study showed that the regional CBF in the left STG was tonically increased in patients with schizophrenia and AVH, and this was consistent with what has previously been termed a trait marker of AVH in schizophrenia.

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Auditory verbal hallucinations result from combinatoric associations of multiple neural events

Massoud Stephane*

Department of Psychiatry, Oregon Health and Science University, Portland, OR, USA

Edited by:
Johanna C. Badcock, University of Western Australia, Australia

Reviewed by:
Johanna C. Badcock, University of Western Australia, Australia
Kenneth Hugdahl, University of Bergen, Norway

****Correspondence:***
Massoud Stephane, Department of Psychiatry, Oregon Health and Science University, mail code: UHN 80, 3181 SW Sam Jackson Park Road, Portland, OR 97239, USA
e-mail: stephane@ohsu.edu

While Auditory Verbal Hallucinations (AVH) refer to specific experiences shared by all subjects who have AVH—the perception of auditory speech without corresponding external stimuli, the characteristics of these experiences differ from one subject to another. These characteristics include aspects such as the location of AVH (inside or outside the head), the linguistic complexity of AVH (hearing words, sentences, or conversations), the range of content of AVH (repetitive or systematized content), and many other variables. In another word, AVH are phenomenologically heterogeneous experiences. After decades of research focused on a few explanatory mechanisms for AVH, it is apparent that none of these mechanisms alone explains the wide phenomenological range of AVH experiences. To date, our phenomenological understanding of AVH remains largely disjointed from our understanding of the mechanisms of AVH. For a cohesive understanding of AVH, I review the phenomenology and the cognitive and neural basis of AVH. This review indicates that the phenomenology of AVH is not a pointless curiosity. How a subject describes his AVH experiences could inform about the neural events that resulted in AVH. I suggest that a subject-specific combinatoric associations of different neural events result in AVH experiences phenomenologically diverse across subjects.

Keywords: AVH, schizophrenia, cognition, inner speech, language

Decades of neuroscience research demonstrate that mental disorders are heterogeneous at the levels of neural circuits and genes (Insel, 2009), and that any specific defective neural circuit and any specific gene exists across diagnostic categories (Cross-Disorder Group of the Psychiatric Genomics Consortium et al., 2013). One could think that individual mental experiences/symptoms such as Auditory Verbal hallucinations (AVH) could offer better chance than mental disorders for corresponding to a neural specificity. However, like mental disorders, AVH are heterogeneous.

AVH are encountered in multiple psychiatric and neurological diseases and in non-clinical populations and are phenomenologically diverse. While all subjects with AVH necessarily share a common experience [the perception of speech in the auditory modality without corresponding external stimuli (Stephane et al., 2001a)], they differ from each other with respect to the characteristics of these experiences. For example, some subjects experience AVH inside their heads while others experience them outside their heads, and some subjects experience AVH with limited repetitive content while others experience AVH with variable rich content. A careful examination of these characteristics indicates that at least some of them correspond to neural specificities.

For years, research of AVH mechanisms has been largely based on the hypothesis that AVH result from a unitary deficit. However, emerging evidence suggest that a single deficit model does not explain the phenomenology of AVH and that multiple deficits are needed to adequately account for AVH experiences (Larøi and Woodward, 2007; Jones, 2010). To date, there are multiple models for the mechanisms of AVH; however, many of the existing models remain largely disjointed from AVH phenomenology and as such our understanding of AVH remains limited (Laroi et al., 2010).

For a cohesive phenomenological-neural understanding of AVH, here, I review the literature from the patient experience (phenomenology) to the brain (cognitive and neural basis). Based on current phenomenological and neural knowledge of AVH, I suggest an integrated phenomenological-neural framework.

THE PHENOMENOLOGY OF AVH

Phenomenology as a philosophical discipline is a method for the study of first person (subjective) experiences for the purpose of identifying invariant inter-subjective (shared) phenomena "essences" (Zahavi, 2003). In a later development of philosophical phenomenology, heterophenomenology (Dennett, 1991), it was pointed out that shared first person subjective experiences are not infallible. It is commonplace for people, in certain situations, to experience movement and to see lines and color changes in the absence of movement, lines, or changing colors, respectively. In the tradition of heterophenomenology, first person subjective experiences are valid only as far as they are validated by natural science methodologies. Phenomenological research of AVH has proven to be in the latter tradition.

Phenomenological research of AVH shows that while all subjects with AVH share a common experience—hearing auditory speech without corresponding external stimuli, they differ from each other with respect to a number of characteristics of this common experience. For example, AVH differ across-subject in

respect to space location (inside or outside the head), clarity (similarity to external speech or verbal thoughts), content (systematized or repetitive; new or previously experienced), linguistic complexity (hearing individual words, individual sentences, or conversations), concomitancy to normal external speech (hearing voices when alone in silence or while talking to other people), insight, or nosognosia [defined as awareness or not of the perceptions/object dissociation (Copolov et al., 2004)], gender (male or female voices), familiarity (familiar or unfamiliar voices), frequency, and loudness, and a number of other characteristics (Claude and Ey, 1932a,b; Jaspers, 1959; Sedman, 1966; Nayani and David, 1996; Stephane et al., 2003). In another word, AVH are phenomenologically heterogeneous experiences, which is to be distinguished from the heterphenomenological philosophical approach mentioned above (AVH phenomenological heterogeneity refers to experiences of AVH that differ across subject while philosophical heterophenomenology refers to the possibility of having erroneous first person subjective experiences and the need for validation of these experiences by natural science methods).

Phenomenological research of AVH has not been about marveling about the curiosity of AVH characteristics but, rather about the implications of these characteristics. For over a century, psychiatrists, psychologists, and philosophers considered that phenomenological variables point to qualitative (categorical) differences in hallucinatory experiences—that is, for example, AVH associated with AVH-anosognosia are qualitatively different from AVH with preserved nosognosia. As any given phenomenological variable is invariant only in a subset of subjects with AVH, they divided AVH, although inconsistently, into multiple sub-categories. For example, Claude and Ey (1932b) identified a "hallucinosis" subgroup when insight was present and a pseudohallucinations subgroup when the content was repetitive "etats obssessionels parasites" (Claude and Ey, 1932a). Jaspers, on the other hand used the term pseudohallucinations to refer to AVH that are concomitant to normal external stimuli, located in inner space, and lacked clarity of external perceptions (Jaspers, 1959). While Sedman considered pseudohallucinations to reflect AVH when insight into the unreality of the perception was present (lack of AVH-anosognosia) (Sedman, 1966). Jaspers also identified "sense-memory" subgroup when the content of AVH was previously experienced (Jaspers, 1959), a phenomenon also referred to as experiential hallucinations. Studies also examined AVH phenomenology for cues to discriminate between different categories of mental illness, and found that some AVH phenomenological variables differentiate between psychotic illnesses categories in use in that era (Lowe, 1973).

The above sub-categorization of AVH was considered as a premature closer; (Dening and Berrios, 1996) and, indeed, none of the above categories of AVH, beside experiential hallucinations, which could be produced by stimulation of the superior temporal gyrus (Penfield and Perot, 1963), were validated by neuroscience methods.

Motivated by numerous indirect evidence that the phenomenological variables of AVH reflect specific neural dysfunctions (see next section), our research group carried out a study to investigate the phenomenological space of AVH as a means to investigate the neural circuitry of AVH (Stephane et al., 2003). We used multidimensional scaling, a method that create an n-dimension maps based on distance or similarity data (here, the jacquard coefficient, which is the ratio of co-occurrence of two phenomenological variables to the sum of the occurrence of either), and found a three-dimension solution, linguistic complexity (hearing words, hearing sentences, hearing conversations), inner space-outer space locations, and self-other attribution of AVH. Based on evidence that language levels (lexical, sentence, discourse) are related to specialized neural resources (Caplan, 1992), that the neural correlates for sounds perceived in inner space differ from the neural correlates of sounds perceived in outer space (Hunter et al., 2003), and that of neural mechanisms for agency (self or other) (Feinberg, 1978), we suggested that the above dimensional structure mirrors the neural dysfunctions that result in AVH, such that AVH consisting of single words, sentences, or conversations result from dysfunction in lexical, sentence, and discourse neural resources, respectively. Similar arguments are made with respect to AVH experienced inside/outside the head and attributed to other/self in relation to neural resources for sound localization, and self-other distinction. Recently McCarthy-Jones et al. (2012) carried out cluster analysis using a wider subset of phenomenological variables than the one used in our previous study (Stephane et al., 2003) and found four clusters with main features that include repetitive content and running commentary, memory-like, replay of memories and nonverbal hallucinations. Both studies illustrate the useful information that could be derived from AVH phenomenology.

Furthermore, AVH phenomenology does not only provide a basis for the identification of categories of AVH that could be validated from neuroscience standpoint, it could also inform the experimental design in AVH research, (Larøi and Woodward, 2007; Laroi et al., 2010) an approach that has been proven fruitful (see last section).

The potential relevance of AVH phenomenology to the neural basis and treatment of AVH lead to another line of phenomenological research, the evaluation of the reliability of the patient report about hallucinations characteristics. Three decades ago, Junginger and Frame (1985) examined how consistent patients were in their report about a small subset of the phenomenological variables of AVH (such as frequency, loudness, location, and clarity). They asked patients to rate these variables on analog scales. Each variable was rated twice with question differently worded, and the consistency between the ensemble of questions pairs was computed. In our group, we undertook two approaches to examine the reliability of the report about AVH, the consistency of report and the frequency of endorsement of items. Both approaches are implemented in the computerized binary Scale of Auditory Speech Hallucinations (cbSASH) (Stephane et al., 2006a) The consistency approach is similar to that of Junginger and Frame however it examines the mismatches of binary variables of AVH. The frequency approach is based on standard techniques for detection of deception, where the endorsement of high numbers of infrequently endorsed statements indicates deception (Butcher et al., 1989).

The above considerations indicate that AVH phenomenology might not be an arbitrary collection of patients' first person subjective experiences; phenomenological research indicates the

neural basis of AVH could be phenomenology-dependent. While indirect evidence in support of this thesis could be found in the literature for decades, it is not until recently that direct evidence of neural basis for AVH phenomenology was demonstrated.

THE NEURAL BASIS OF AVH PHENOMENOLOGY

INDIRECT EVIDENCE OF THE NEURAL BASIS OF AVH PHENOMENOLOGY

The literature provides multiple indirect evidence of a neural basis for a number of phenomenological variables of AVH, including: AVH-anosognosia (unawareness of the perception-object dissociation), content (systematized or repetitive), space location (inner or outer space), and familiarity and the gender of the "voices." Anosognosia of neurological symptoms (e.g., cortical blindness, and left side hemiparesis) is associated with symptom-specific neural correlates—lesions of the visual associative cortex (Magitot and Hartmann, 1926) or frontal lobes (McDaniel and McDaniel, 1991) in the case of cortical blindness, and lesions in the non-dominant motor cortex in the case of left side hemiplegia (Babinski, 1914). As AVH in the clinical population are symptoms of brain disease just like blindness or hemiplegia, AVH-anosognosia could be associated with specific neural substrates (Stephane et al., 2003).

It has also been shown that the neural correlates for speech perception differ according to whether the verbal stimuli are repetitive or variable (Cottraux et al., 1996), whether they are perceived to be inside or outside the head (Hunter et al., 2003), according to the familiarity of the speech sounds (Nakamura et al., 2001), and according to the gender of the perceived speech (Sokhi et al., 2005). While the difference in neural circuitry between the perception of actual feminine and masculine voices (for example) could result from different factors associated with these perceptions, it is plausible that similar differences in neural circuitry exist with the perception of hallucinated feminine and masculine voices. Consequently, it could be argued that the neural basis of AVH differs according to the content (repetitive or systematized), space location (inside or outside the head), and the gender and familiarity of perceived voices.

DIRECT EVIDENCE OF NEURAL BASIS OF AVH PHENOMENOLOGY

Recently, numerous studies have investigated the neural correlates associated with a number of the phenomenological variables of AVH and confirmed that the neural correlates of AVH are phenomenology-dependent (with respect to the investigated variables). One study has shown that, in patients with AVH, abnormalities in the right temporoparietal junction, a key area in the "where" auditory system, depend on the spatial location of the experience of AVH (inner or outer space) (Plaze et al., 2011). In another study, the loudness of AVH was associated with decreased activity in the bilateral angular gyrus, anterior cingulated gyrus, left inferior frontal gyri, and left temporal cortex (Vercammen et al., 2010). Furthermore, one fMRI study has shown that the acoustic clarity of AVH (similarity of AVH to speech or to thoughts), which was referred to as "sense of reality" in the study at hand, was associated with reduced language lateralization (Vercammen et al., 2010). However, another methodologically different fMRI study has shown that acoustic clarity was associated with activity in the inferior frontal gyri (Raij et al., 2009). The different findings could be related to differences in the methodology between the two studies (for example, in the first study, subjects were scanned while they performed a metrical stress evaluation task to activate inner speech, in the second study, patients were scanned during hallucinations). Therefore, while the exact neural correlates of the acoustic clarity of hallucinations remain unknown, these two studies provide evidence of a neural basis of acoustic clarity of AVH. Additionally, in drug naïve patients experiencing high linguistic complexity AVH (conversations), an FDG PET study showed higher metabolic rates in the left superior and middle temporal cortices, bilateral superior medial frontal cortex relative to psychotic patients without AVH (Horga et al., 2011). Furthermore, patients with AVH, compared to healthy controls, showed different patterns of speech related activation depending on the familiarity of speech (Zhang et al., 2008). While this does not indicate that patients with AVH consisting of familiar "voices" are different from patient with AVH consisting of unfamiliar voices, it emphasizes that dysfunction of neural processes for speech familiarity might play a role in the pathogenesis of AVH. Furthermore, preliminary evidence indicates that AVH with repetitive content respond to treatment by an antiobsessionalagent (Stephane et al., 2001b).

The studies outlined above, therefore, bring third person (objective) validation to the patients' first person subjective experiences of AVH. Whether such validation would extend to the other phenomenological variables is possible but remains to be proven.

COGNITIVE MODELS OF BRAIN ACTIVITY ASSOCIATED WITH AVH

Three categories of cognitive models could be identified, including: inner speech, bottom-up and top-down processing of perceptions, and intrusions of thoughts and memories.

INNER SPEECH

Inner speech was a natural place to start in AVH research as this type of hallucinations refers to the perception of speech. In the mid twentieth century, based on observations that AVH are associated with lip movements without audible speech (Forrer, 1960), subvocal speech (SVS) that could be amplified and recorded (Gould, 1950), and Electromyographic speech muscle activity (Roberts et al., 1952), it was suggested that hallucinating patients are virtually hearing their self-generated faint SVS (Gould, 1948, 1950). This theory was short lived since maneuvers blocking SVS did not alleviate AVH (Stephane et al., 2001a). Given that both inner speech and AVH are associated with both motor and perceptual components (Sokolov, 1972; MacKay, 1992), We suggested, instead, that a disorder of generation of inner speech would result in a perceptual component (AVH) and a motor component (SVS) as an un-bothersome byproduct (Stephane et al., 2001a).

The vast majority of studies on this line of research focused on explaining the attribution to other of a self-generated inner speech. In the literature, inner speech theory is sometimes equated with a particular model (the forward model) (Frith and Done, 1988); here I discuss the ensemble of models that implicated inner speech in the pathogenesis of AVH.

The corollary discharge deficit or forward model is one of the most widely studied models of AVH mechanisms, and received empirical support from many studies (Ford et al., 2001; Stephane et al., 2006b). It was based on Feinberg theory that, "*motor commands in the nervous system are associated with neuronal discharges that alter activity in both sensory and motor pathways. They may act to inform sensory systems that the stimulation produced by movement is self-generated rather than environmentally produced. In this way these discharges are, at least in an abstract sense, crucial for the distinction of self and non-self and that could apply to higher functions*" (Feinberg, 1978). The forward model postulates that a disconnection between speech generation and speech perception results in a failure to compute the expected sensory experience of self-generated inner speech, and would lead to experiencing self-generated inner speech as alien.

Another model for self-other misattribution is that of altered preconscious planning of discourse, where a speaker generates a discourse that is incongruent with the goals or intentions of the speaker (Hoffman, 1986). While unintended tick (for example) is not attributed to other, Hoffman considered that the complexity of unintended inner speech, relative to unintended motor tick, suffices for the other-misattribution of the former (Hoffman, 1991).

Bentall (1990) argued that cognitive deficits such as the above do not explain the cultural, historical and emotional aspects of hallucinations "*hallucinators don't hallucinate random events,*" he suggested that self-other misattribution (defective reality monitoring) could result from a variety of deficits in metacognition (knowing that we know) as conceptualized by the American psychologist John H. Flavell (1979).

Fernyhough (2004), motivated by the infinite regress objection to the above theories, brilliantly examined the work of Vygotsky on inner speech development (Vygotsky, 1978) for clues about self-other misattribution. He suggested that alteration of the transformation that social speech undergoes to become inner speech (disruption of the internalization or re-expansion) could result in inner speech attributed to other (AVH), as inner speech is dialogical by nature.

Finally, in an imaging study carried out by our group (Stephane et al., 2006b), right handed hallucinating schizophrenia patient (but not matched non-hallucinating schizophrenia patients and healthy controls), showed abnormal laterality of the Supplementary Motor Area (SMA) activation during a speech generation task. As the SMA has been implicated in attributing self-generated actions to self, we suggested that the abnormal laterality of the SMA during the action of inner speech generation could result in occasional failure in attributing to self a self-generated speech (just like a right handed individual could fail carrying out actions with his/her left hand).

Unlike AVH, which could be experienced in outer space, inner speech is experienced in inner space. However, this apparent disorder in the spatial localization of inner speech received much less attention than self-other misattribution of inner speech. Nonetheless, The literature shows that three studies have examined this aspect of inner speech and all reported tendency of schizophrenia patients to confuse speech experienced in inner space with speech experienced in outer space (Harvey, 1985; Franck et al., 2000; Badcock, 2010; Stephane et al., 2010a).

BOTTOM UP AND TOP DOWN MODELS

That perceptions depend on both external sensory stimuli and on representation of past perceptual experiences is an age-old idea. For example, Taylor (1979) observes that, in dim lighting, a rhomboid table could be perceived as rectangular table. Another example is that misspelled words in a text are often correctly read without noticing misspelling (Jaspers, 1959). Current AVH research implicates both the sensory pathway (bottom up) and past perceptual experiences and expectation (top down) in hallucinations pathogenesis.

Bottom-up factors point to unconstrained activity in the sensory and perceptual brain resources due to scarce external sensory stimuli. Auditory hallucinations have been often reported in patients with acquired deafness (Thewissen et al., 2005), in survivors of long solitary ordeals (Logan, 1993), and, to a lesser extent, during sensory deprivation experiments (Slade and Bentall, 1988). Furthermore, in psychotic patients, a dramatic social withdrawal preceding the onset of hallucinations has been reported (Hoffman, 2008).

Top down role in the pathogenesis of hallucinations has been also proposed for about half a century. French philosopher, Maurice Merleau-Ponty, considered hallucinations to reflect the "intentionality" of the hallucinator who creates a world according to his intentions and expectations (Merleau-Ponty, 2002), and Italian psychiatrist Silvano Arieti considered hallucinations to result from moments of heightened auditory attention "listening attitude" (Arieti, 1974). Recent studies bring support to these perspectives. Hallucinations scores were correlated with imagery-perception facilitation with pure tones (Aleman et al., 2003), and with the effect of semantic expectation on the perception of sentences (Vercammen and Aleman, 2010). Furthermore, increased incidence of auditory hallucinations is reported with high auditory attentional demands in healthy populations (Baraldi Knobel and Ganz Sanchez, 2009). It was suggested that an imbalance between top-down and bottom-up processing of stimuli could result in erroneous percepts that, when repetitive, would train the network to perceive hallucinations (Aleman et al., 2003). It was also suggested that a cognitive control deficit results in a failure of top-down inhibition of bottom-up erroneous percept (Hugdahl et al., 2009).

INTRUSIONS OF THOUGHTS AND MEMORIES

Many studies in the past decade implicated intrusions of memories and thoughts in the pathogenesis of hallucinations. Based on findings indicating deficits in intentional inhibition in hallucinating patients, it was suggested that failure of suppression of irrelevant memories and other mental associations could result in intrusive memories experienced as hallucinations (Badcock et al., 2005; Waters et al., 2006). The theory finds support in many studies showing intrusions errors and false recognition with free recall and Sternberg paradigms (Brébion et al., 2007; Brebion et al., 2010), and that ruminations were related to hallucinations indirectly through the mediating factor intrusive thoughts (Jones and Fernyhough, 2009). Additionally, two

fMRI studies showing deactivation of the parahippocampal gyrus prior to hallucinations (Hoffman et al., 2008; Diederen et al., 2010), and one magentoencephalography (MEG) study a decrease in theta-band power in the right hippocampus at the onset of AVH (van Lutterveld et al., 2012) bring further support to this theory. Studies also implicated intrusive thoughts in hallucinations through association with cognitive dissonance, the evidence, however, is not conclusive (van de Ven, 2012).

OTHER ASPECT OF BRAIN ACTIVITY ASSOCIATED WITH AVH

Some basic aspects of brain function affect all cognitive operations. These include, laterality, connectivity and the default modes system; all of which were implicated with AVH and schizophrenia in general. For example, studies have shown lack of right ear advantage in dichotic listening task (Hugdahl, 2009), and abnormal SMA laterality with a speech generation task in hallucinating schizophrenia patients (Stephane et al., 2006b). The above-mentioned forward model is a special case of dysconnectivity. Moreover, evidence of dysconncectivity implicates many other systems such as dorsolaterofrontal/superior temporal gyrus (Lawrie et al., 2002) and between the anterior cingulated gyrus and superior temporal gyrus (Mechelli et al., 2007), as well as dysconnectivity within the default mode network (van de Ven, 2012).

MATCHES AND MISMATCHES BETWEEN AVH PHENOMENOLOGY AND AVH MODELS

Here we take a close look on how the above models for AVH could explain some phenomenological variables but fail to explain others. This look is theoretical and based on current knowledge of AVH phenomenology and models. Direct empirical support is lacking as research designs did not generally take in consideration AVH phenomenology. It should be also mentioned that an exhaustive look on matches and mismatches may not serve much purpose and the account below is meant to be illustrative.

First, while any of the models of self-other misattribution could explain AVH attributed to other, they don't explain AVH attributed to self as encountered sometimes in schizophrenia (Stephane et al., 2003) and in survivors of long solitary ordeals who at some point during the ordeal undergo a transition from talking to themselves to experiencing their own voice as coming from outside (Logan, 1993). Furthermore, each of the self-other misattribution models may explain the self-other misattribution in certain phenomenological categories of AVH but not in others. For example, the forward model, presumes one speaker only "the hallucinator." Therefore, it would account for self-other misattribution in AVH consisting of one, but not multiple "voices." Altered discourse planning could produce unintended words and/or sentences (verbal messages) that result in a fragmented discourse. This model presumes that the unintended verbal messages are experienced as hallucinations and as such this model would explain self-other misattribution when AVH consist of words and sentences but not conversations. Finally Fernyhough's model presumes internal dialog between the hallucinator and other(s). Therefore, it could account for self-other misattribution when AVH consist of one or more "voices," but not when AVH consist of multiple "voices" talking to each other. These arguments favor the visionary suggestion of Bentall, that self-other misattribution could result from a number of different deficits in the metacognitive domain *"It should be noted that many different types of cues are likely to be important in reality discrimination and that many different traits and deficits are therefore likely to be associated with hallucinatory experiences. The failure of reality discrimination in hallucinating patients might therefore be considered a final common pathway underlying their experiences, rather than the ultimate cause of their hallucinations. Moreover, it is probable that different kinds of cognitive deficits will be associated with different types of hallucinations"* (Bentall, 1990).

Additionally, as many times pointed out (Badcock, 2010; Jones, 2010; Laroi et al., 2010) self-other misattribution models do not account for aspect of AVH such as why AVH are repetitive in some and systematized in others, or why some subjects are aware of the lack of object for AVH while others are not (anosognosia). AVH *"are more than just words; it involves the perception of information about speaker identity and vocal affect. . . ,"* Badcock notes (Badcock, 2010).

Similar reasoning could apply to Bottom up/top down and intrusions models. For example, heightened semantic expectation and listening attitude (top down) model could explain AVH consisting of words or sentences, but not conversations. Intrusive memories and intrusive thoughts could account for AVH with certain characteristics but not with others. Intrusions usually refer to singular events (the event, here, being a hallucination). When the hallucinations are repetitive words or sentences, it could be easily conceived that the hallucinations result from intrusions. However, when the hallucinations consist of complex multi-element auditory objects such as familiar voices issuing tirades of abuse untypical of the speaker (to whom the voices are attributed), or conversations with variable rich content (systematized), intrusions may not explains these hallucinatory experiences as well. Furthermore, metacognitive beliefs related cognitive dissonance does not account for AVH with positive content. Finally, inner speech, intrusive memories and intrusive thoughts are all experienced in inner space, and, as such, don't account for the outer space location of AVH. Of the above models, only models involving deficits in the inner space-outer space distinction, the "where" and "what" pathways, and top-down/bottom-up interaction could explain the outer space location of AVH.

COMBINATORICS: RESOLVING THE PHENOMENOLOGICAL PUZZLE

Thus far it appears that AVH experiences are associated with rather complex patterns of commonality and differences across subjects, and that combinatoric association of AVH phenomenological variables accounts nicely for the observed phenomenological heterogeneity. Taking in considerations that at least some of the phenomenological variables appear to point to specific deficits in brain function, and that any given single deficit model does not adequately account for AVH, it could be concluded that the diverse AVH phenomenology results from combinatoric association of neural deficits. I suggest that AVH experiences require necessarily activity in Wernicke's area, which constitute a final common pathway (Stephane et al., 2000) for a widely distributed

network that underlies emotions and aspects of cognition such as language, attention, memory. AVH arise from dysfunction (e.g., abnormal laterality or dysconnectivity) at combinations of nodes in the network that are subject specific, which determine the phenomenology of AVH in the subject at hand.

Concerning normal and abnormal brain function, combinatorics is not a novel idea. A century-old visionary theory of Korbinian Brodmann suggested that higher brain functions depend on a set of elementary neural resources combined in temporospatial patterns specific to each function (Brodmann, 1909); and this view is currently readily accepted in the neuroscience community (Stephane et al., 2010b). More importantly, emerging evidence about a small subset of AVH phenomenological variables supports this approach. For example, Waters and colleagues have shown that AVH could result from a combined deficits in intentional inhibition and context memory (Waters et al., 2006). The first would result in intrusions of memories into consciousness and the second would explain the other-misattribution of these memories. Additionally, based on imaging findings in our research group, we previously suggested that combined abnormal activity of Wernicke's area and of the SMA results in AVH; the former would explain the perceptual experience "Hearing" and the latter the other-misattribution of what is heard (Stephane et al., 2006b).

To date, the most substantiated combinatoric of deficits is that between self-other, and inner space-outer space confusions. Based on the phenomenological structure of AVH (Stephane et al., 2003), Larøi and Woodward have suggested that AVH could result from combinatoric abnormalities in inner space-outer space and self-other distinctions, where either can be present or absent (Larøi and Woodward, 2007). We have investigated these capacities in the same subjects and with similar experimental designs and found, as has been previously reported, that hallucinating schizophrenia patients showed other- and outer space-misattributions (Stephane et al., 2010a,c). More importantly, we found that inner space-outer space and self-other distinction capacities are independent (Stephane et al., in preparation), which mirrors nicely the different "where" and "what" pathways for speech processing (Badcock, 2010). Recently, Waters et al. (2012), presented the most elaborate model yet, which combines multiple deficits/abnormal activity including the auditory cortex, signal detection, intentional inhibition, and top-down factors. According to my proposal above, all deficits need not be present in all subjects. Any given deficit can be present or absent in any given subject, which makes hallucinating subjects different from each other as is commonly observed.

Finally, the current proposal is meant as a framework for resolving the puzzle of AVH and not a resolution for the puzzle itself. It has two main practical implications for future research.

First, taking in consideration AVH phenomenology (i.e., studying subgroups phenomenologically defined) could improve the signal/noise ratio. If indeed the neural basis of AVH differs in specific aspects according to AVH subtypes (e.g., inside or outside the head location of AVH), an experimental design that include both subtypes in one group would add noise to the signal generated by the aspect that differentiate the two subtypes. Thus, this approach could maximize the chance of understanding of the cognitive and neural basis of AVH. Better understanding of the cognitive basis could also facilitate treatment efforts for AVH through cognitive remediation.

Second, the phenomenological subgroups could also inform the experimental design. Any given AVH characteristic could provide clues about the malfunctioning cognitive and neural processes that resulted in AVH with that particular characteristic. For example AVH with lexical, sentencial, and discourse linguistic complexity could point to dysfunction in lexical, sentential, and discourse processes, respectively. Therefore, the appropriate cognitive task could be designed for the appropriate phenomenological type.

Finally, the success of phenomenological research depends in no small measures on the reliable identification of the phenomenological subtypes.

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