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Auditory Hallucinations and the Mismatch Negativity:
Processing Speech and Non-Speech Sounds in Schizophrenia

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Thesis submitted to the
Faculty of Graduate Studies and Research
in partial fulfillment of
the requirements for the degree of
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ABSTRACT

In line with current research strategies focusing on specific symptoms rather than global syndromes in psychiatric disorders, this study examined the functional neural correlates of auditory verbal hallucinations (AHs) in schizophrenia. Based on neuroimaging and behavioural evidence suggesting a reciprocal relationship between auditory cortex response to external sounds versus that induced by AHs, the preconscious auditory change detector mismatch negativity (MMN), a well established event-related potential (ERP) index of auditory cortex function, was assessed in 12 hallucinating patients (HP), 12 non-hallucinating patients (NP) and 12 healthy controls (HC). The primary endpoints, MMNs and latencies recorded from anterior and posterior scalp regions, were measured in response to non-phonetic and phonetic sounds (experiment 1), the latter being presented in silence and background noise conditions (experiment 2). No significant between group differences were observed but, compared to NPs and HCs, whose MMN amplitudes were greatest in response to across phoneme change at frontal but not temporal sites, temporal but not frontal MMNs of HPs were maximally sensitive to phonetic change. MMNs in HPs were selectively attenuated by white noise (vs. traffic noise), and across phoneme change-elicited frontal MMN amplitude and latency (during white noise) were associated with self-ratings of hallucinatory activity. These findings demonstrate that auditory verbal hallucinations are associated with impaired preattentive processing of speech in fronto-temporal networks, which may involve defective attribution significance that is sensitive to resource limitations. Overall, this research suggests that MMN may be a useful non-invasive tool for probing relationships between hallucinatory and neural states within schizophrenia and the manner in which auditory processing is altered in these afflicted patients.

AUTHOR'S NOTE

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Auditory Hallucinations and the Mismatch Negativity

1. Introduction

1.1 Schizophrenia: An overview of symptomatology

Within the realm of mental illness, schizophrenia is unique in the sheer heterogeneity of the symptoms and syndromes it encompasses. Patients may be assigned this diagnosis based on a wide range of symptoms associated with the disorder, not least of which include disturbances of thought, behaviour, emotion and perception. These perceptual disturbances within schizophrenic individuals may include, but are certainly not limited to, distorted beliefs about themselves, others or the world in general (i.e. delusions) or the perception of phenomena that do not exist (i.e. hallucinations), often resulting in a marked impairment in the individual's cognitive ability to function within society if left untreated. The associated symptoms manifested within each affected person are so individual that the resulting cluster may be seen as a psychiatric fingerprint, unique to each patient.

The heterogeneous nature of schizophrenia has been noted in both the clinical and research realms (Carpenter and Kirkpatrick, 1988). It has been part of the described nature of schizophrenia since the inception of the term; both Kraepelin (1919) and Bleuler (1950) asserted that the heterogeneity of the disease was a fundamental part of its nature. It is with this heterogeneity in mind that efforts have been made to establish sub-patterns, sub-types or syndromes (defined by the presence of a particular cluster of symptoms and clinical characteristics) in an attempt to bring diagnostic order to the chaos of the associated symptoms. One of the more recent, successful and frequently used sub-type

systems within the umbrella diagnosis of schizophrenia is that of the positive (Type I) and negative (Type II) syndromes (Crow, 1980; Andreasen and Olsen, 1982), which has since been incorporated into the American Psychiatric Association's (APA) Diagnostic and Statistical Manual (DSM) of Mental Disorders (DSM-IV TR; 2000).

The positive syndrome of schizophrenia consists of florid symptoms, such as delusions, hallucinations, disordered thinking and disordered behaviour (ranging from inappropriate agitation and aggression to catatonic stupor), which actively interfere with mental functioning, and may be seen as an amplification or excess of normal functions. The negative syndrome, in contrast, may be seen as a poverty or diminished capacity of normal cognitive, affective and social functions, including blunted or flat affect, poverty of speech, and loss of drive (avolition). Neuropharmacological research has pointed to dopamine as the main neurotransmitter involved in each of these syndromes. The original dopamine hypothesis states that it is an excess of sub-cortical dopamine acting on the D2 receptor that is responsible for the positive symptoms of schizophrenia. A later update (Davis et al., 1991) expanded this theory, adding that it is a deficit of dopamine in the pre-frontal cortex that contributes to the negative symptoms and that a sub-cortical excess of dopamine can co-exist with a cortical deficit.

Certainly, within each grouping of syndromes there have been attempts to further sub-classify patients with schizophrenia. The DSM (APA, 2000) lists five clinical subtypes of schizophrenia; paranoid type, disorganized type, catatonic type, undifferentiated type, and residual type. The paranoid type of schizophrenia is marked by prominent delusions or auditory hallucinations, with relative preservation of cognitive functioning and affect. Patients diagnosed with the disorganized type display

disorganized speech, disorganized behaviour, flat or inappropriate affect, and neurocognitive deficits, but in the absence of catatonia. The catatonic type is applied to patients exhibiting motor immobility, excessive motor activity, pathological parrot-like repetition of a word or phrase just spoken by another person (echolalia), repetitive imitation of another person's movements (echopraxia), and maintenance of a rigid posture despite attempts to be moved or resistance to instructions (extreme negativism). The essential feature of undifferentiated type is a diagnosis of schizophrenia, but without meeting criteria for catatonic, disorganized or paranoid type. Finally, patients diagnosed as residual type are those who have had at least one episode of schizophrenia, but do not currently exhibit positive psychotic symptoms, yet still show some negative symptoms (e.g. flat affect, poverty of speech) or attenuated positive symptoms such as eccentric behaviour or odd beliefs. Within these sub-categories, the paranoid type tends to be the least severe while disorganized type is the most severe. There has been considerable research interest in establishing even more homogeneous symptom clusters in the hope that these will lead to better treatments of afflicted patients (Blanchard, Horan, and Collins, 2005; Weiser, Van Os, and Davidson, 2005).

1.2 Auditory Hallucinations in Schizophrenia

Although a great deal of clinical and research efforts in schizophrenia have chosen to focus on global syndromes, this approach has been considered by some to be too broad, and it has been suggested that a more focused attempt to characterize the individual symptoms of schizophrenia will help reveal important insights into the disease as a whole (Shapleske et al., 2002) and its underlying psychological processes (Persons,

1986; Bentall et al., 1988). One of the most prevalent symptoms of schizophrenia is the presence of hallucinations, which, like schizophrenia itself, can be extremely heterogeneous in nature. With that in mind, it is important to have a solid construct of hallucinations to work from; this investigation takes the view of a hallucination as “a sensory experience which occurs in the absence of corresponding external stimulation of the relevant sensory organ, has a sufficient sense of reality to resemble a veridical perception, over which the subject does not feel s/he has direct and voluntary control, and which occurs in the awake state” (David, 2004, p. 110). Hallucinations can occur in any of the five senses; auditory, visual, tactile, olfactory, and gustatory hallucinations have all been reported in schizophrenic patients (Weiss & Heckers, 1999), however the most commonly occurring hallucination is that of hearing ‘voices’. Auditory hallucinations (AHs) are one of the hallmark symptoms of patients with schizophrenia (David, 1999); within schizophrenic patients, auditory hallucinations have a reported prevalence of 50-80% (Andreasen & Flaum, 1991). These hallucinations tend to occur in patients diagnosed with the paranoid sub-type, which, according to the DSM (APA, 2000), tends to be associated with the least neurocognitive decline. It is thought that these hallucinations are the result of a dysfunction of the metacognitive processes that discriminate between self-generated and external sources of information (Bentall & Slade, 1985; Morrison & Haddock, 1997), in addition to other deficits of information processing (Hoffman, 1987). There are a number of good structured instruments designed to quantify the different dimensions of the AH experience, such as the Psychotic Symptom Rating Scales (PSYRATS; Haddock et al., 1999), the Structured Interview for Assessing Perceptual Anomalies (SIAPA, Bunney et al., 1999), and the Mental Health

Research Institute Unusual Perceptions Schedule (MUPS; Carter et al., 1995), as well as the auditory hallucination scale within the Positive and Negative Syndrome Scale (PANSS; Kay, Opler & Lindenmayer, 1989). The PSYRATS is a particularly promising scale for quantifying hallucinations as it is relatively brief, rates AHs over a number of domains, and has shown excellent psychometric properties.

1.3 Phenomenology of Auditory Hallucinations

Auditory hallucinations, much like schizophrenia itself, show considerable heterogeneity in their presentation and form, a fact that has simultaneously interested and frustrated researchers who have attempted to categorize AHs. One of the earliest attempts to categorize abnormal experiences used the groupings of ‘hallucinations’ and ‘hallucinoses’, whereby the latter implied insight into the bizarreness of the experience (Claude & Ey, 1932). This idea was updated by Sedman (1966), who used the terms ‘imagery’, ‘pseudo-hallucinations’ and ‘true hallucinations’ to describe experiences that were lacking in perceptual reality, mimicked perceptual reality but with insight into the abnormal experience, and clear perceptions without insight, respectively.

Much of this early research did not focus on hallucinations within schizophrenia exclusively, as hallucinations are known to occur in other psychiatric conditions, such as post-traumatic stress disorder (Asaad, 1990), in response to certain drugs, such as psilocybin (Hyde et al., 1978), and even among those in the general population with no psychiatric diagnosis nor under the influence of psychedelic drugs (van Os et al., 2000).

More recent work has focused on hallucinations within schizophrenia, especially AHs, and with that has come better attempts to characterize and describe the

hallucinatory experience. Lowe (1973) began this trend by examining several variables of AHs in greater detail, detailing that these characteristics can be used as “discriminatory indicators for differential diagnosis among psychotics.” The characteristics this research focused on included frequency, location (internal or external), similarity to external speech, loudness, constancy, effect on behaviour, source attribution, affective response, and content of AHs. This work was expanded to include personification (accent, gender, familiarity of voice), coping mechanisms and degree of control, number of voices, linguistic complexity, and insight into the experience (Nayani and David, 1996). It is along these lines that research has moved, despite the idiosyncratic nature of individual AHs.

There have been many reported features of the AH experience. Some recent work has used statistical methods such as hierarchical cluster (HC) and multidimensional scaling analysis (MDS) to investigate relationships between phenomenological variables of AHs (Stephane et al., 2003). This approach started by identifying twenty variables of AH (e.g. location, time course, linguistic complexity) based on the relevant literature and clinical experience of the investigators, and then used the above statistical methods to determine the statistical significance of these within a patient population. The hierarchical cluster analysis revealed two main clusters of AHs. The first included AHs with low linguistic complexity (single word), repetitive content, self-attribution, located in outer space (i.e. ‘outside the head’), and association with many different control strategies. The second cluster encompassed AHs with high linguistic complexity (conversations), systematized content (non-repetitive), multiple voices, attributed to others, and located in inner space (i.e. ‘inside the head’). These clusters make intuitive sense on many levels;

AHs of a single word will often result in repetition of that word, while linguistically complex AHs will have systematized content, and may include multiple voices. In addition, when multiple voices are present, it seems logical that they will be attributed to others. These findings (Stephane et al., 2003) are echoed in the MDS analysis, which identified three prominent dimensions of AHs; linguistic complexity, attribution, and location. Identification of linguistic complexity as a dimension indicates that hallucinating patients experience AHs as either having low complexity (single words), medium complexity (single sentences) or high complexity (conversation), and rarely hear combinations of the three. Stephane and colleagues (2003) suggest that this could represent different levels of language abnormalities in patients. The second identified dimension of AHs, attribution, is also of importance as it lends empirical support to the idea that some patients experience AHs as being their own voice (self-attribution), while others experience them as the voice of another (other attribution). Finally, a third dimension showed that AHs will occur either in inner space (perceived as being inside the head) or in outer space (outside the head), but rarely a combination of the two. This dimension is supported by a functional magnetic resonance (fMRI) study showing different neural substrates for auditory stimuli perceived outside the head versus those perceived inside the head (Hunter et al., 2003).

One of the most complete surveys of AH phenomenology in schizophrenia was performed by Nayani and David (1996), who described several key characteristics of AHs. Most participants (73%) described voices as being at normal conversational volume, as opposed to whispers (14%) or shouting (13%), and nearly all noted that angry voices were experienced as being louder. The members of their sample mostly

experienced hallucinations from several times a day to most of the day; only a small percentage experienced continual, non-stop hallucinations throughout the day. Almost half the participants (42%) experienced their AHs for more than an hour at a time, and those who experienced AHs more often heard a greater variety of hallucinated words. With regards to location, nearly half the sample (49%) heard the voices as external stimuli, as though through their ears, while 38% experienced the voices as being internal and 12% experienced AHs as both internal and external AH percepts. Interestingly, over time AHs were more likely to move to internal space and become more complex. The study participants experienced a range of one to fourteen voices (mean ~ 3), which were sometimes described as arguing or conversing about the patient. All subjects, regardless of gender, were more likely to hear a male hallucinated voice. Overall, patients were more likely to hear a middle-aged voice, except for those under 30, who most commonly heard a young voice. Nearly three-quarters of the sample described the accent of the voice to be different from their own, either by region or by class; the most common description was of an upper-class radio-announcer 'BBC voice'. Most patients admitted to knowing the identity of one or more of their voices, commonly thought to be one of: God, the Devil, a relative, a neighbour or a doctor. Patients experienced an average of 5 different types of voices, with the most common being a command, criticism, verbal abuse, frightening content, and third-person/neutral commentary.

Despite the fact that these results (Nayani & David, 1996) reflect some degree of cultural specificity (e.g.. that of a 'BBC voice'), most of the findings can be applied to AHs within schizophrenia regardless of cultural background. To demonstrate this, the findings were followed up by an American study (Miller, 1996), which replicated many

of Nayani and David's findings, while adding the observation that most patients believe that they are the only ones who can perceive the hallucinatory experience.

While there is evidence of prevalent experience of abusive/critical AHs, this is not always the case. There is significant evidence that many patients do experience some positive or pleasant voices (Nayani & David, 1996), while in one study, nearly 10% of patients experienced pleasurable AHs as the norm, with one patient stating: "If I did not have them, what a boring old age I would have! Some day they will give me a mission," (Sanjuan et al., 2004, p. 275). While there does not appear to be any association between pleasurable auditory hallucinations and age or sex, research has shown a correlation between pleasurable AHs and chronicity of hallucinations (Sanjuan et al., 2004). Despite this select population who experience pleasurable AHs, the majority of those afflicted simply wish that the voices would go away, with 98% of patients in one study noting adverse effects of AHs and 68% wishing their AHs would stop (Miller, O'Connor, & DiPasquale, 1993). In this same study, one patient stated that "...sometimes the voices say they're going to kill me or I'll die tonight; I feel threatened," while another said "I've never been able to have a job because of this," (p. 587). It has yet to be established why AHs are so frequently abusive/critical. However, research into thought suppression has shown that attempts to suppress critical thoughts will often result in the opposite effect (Wegner & Erber, 1992), thus an agitated patient may actually increase the number of abusive AHs by attempting to quell them.

Many patients with AHs must use coping techniques to function in society (Nayani & David, 1996), including separating the voices from other thoughts and actions, using a portable music device for distraction, and simply ignoring the voices. As one

sufferer explains, “For me, the voices are externalized and real... Far better is to accept that the voices will be there and try to deal with them.” (Cockshutt, 2004).

1.4 Variables Affecting Auditory Hallucinations

The occurrence of AHs appears to be influenced by several factors, including emotion and stress (Bentall, 1990b). Many authors have noted stress-induced arousal to have a significant role in psychosis, a point emphasized by Birley and Brown (1970) in their work showing stressful life events to be significantly associated with schizophrenic episodes. Subsequent research has linked hallucinatory experiences with stressful events such as losing a spouse (Alroe & McIntyre, 1983; Wells, 1983), and terrorist attacks (Siegel, 1984). Clinical data also indicates that AHs are more likely to follow periods of stress (Slade, 1972) or anxiety (Delespaul, de Vries, & van Os, 2002). This is mirrored by work showing a direct relation between AH onset and increases in skin conductance level, an index of autonomic nervous system arousal, in schizophrenia (Cooklin, Sturgeon & Leff, 1983). In addition, sadness may also be a precipitant of AHs, with half the subjects of one study reporting the experience of sadness encouraging hallucinations (Nayani & David, 1996).

It has also been suggested that AH occurrence may be in part determined by predisposing factors, such as genes. Much of the genetic research into this question, however, has been undermined by questions of validity due to their anecdotal nature or poor control of extraneous variables (Bentall, 1990b). Some of the more convincing evidence pointing to a role for predisposing factors in AH occurrence comes from studies examining the cognitive processes of hallucinators and non-hallucinators. This work

examined the position that AHs reflect misattribution of sensory information and postulated that those with AHs should be poorer at recognizing their own thoughts compared to non-hallucinators (Heilbrun, 1980). Indeed, hallucinating patients did perform more poorly when asked to identify their own verbatim statements of opinion from a selection of similar statements. A subsequent study also identified hallucinating patients as being particularly poor at detecting the spatial location of sounds (Heilbrun, Blum & Haas, 1983), further implicating predisposing factors as being important in influencing the occurrence of AHs.

While environmental conditions (i.e. being in a specific room or place) do not control the occurrence, intensity, or nature of AHs, social context can influence the course of an episode, especially when combined with other variables, like arousal level. There appears to be an interaction between environment and arousal, as relative isolation combined with stress appears to precipitate hallucinations (Comer, Madow, & Dixon, 1967; Siegel, 1984). Even isolation on its own has been shown to worsen hallucinations (Nayani & David, 1996). It also appears that passive leisure activities (e.g. watching television) and doing nothing increase the intensity of hallucinations, AH intensity is negatively correlated with activity level in a pseudo-linear fashion. (Delespaul, de Vries, & van Os, 2002). Comparatively, engaging in work activities (e.g. job-related or domestic tasks) has been found to decrease hallucinatory intensity over time (Delespaul, de Vries, & van Os, 2002), as has attention to meaningful stimuli. A study of patients with AHs exposed to various levels of auditory stimulation found that as the attended stimuli became more meaningful, the rate of AHs significantly decreased and that during

periods of non-meaningful stimulation (i.e. white noise) or during sensory deprivation, AHs increased (Margo, Helmsley, & Slade, 1981).

These diverse findings relating to variables affecting AHs appear to support, at least in part, Slade's four-factor model of hallucinations (1976b). In this working model, Slade proposes that: (1) 'stress events' produce an internal arousal that results in mood state disturbances; (2) these mood state disturbances raise hallucinatory tendency above a critical threshold whereby AHs may be triggered; (3) whether or not an AH occurs is dependent on whether there are sufficient attentional resources for the production and processing of such an event; (4) the result of a hallucinatory experience is a resolution of the mood state disturbances, thereby reinforcing the occurrence of AHs, and lowering the threshold needed to be obtained for future occurrence. Particular emphasis has been placed on the third factor of this model; the conceptualization of attention as a limited-capacity resource means that increasing processing demands reduce the amount of attention available for the hallucinatory experience. Or, as Slade himself puts it: 'sources of external stimulation can only be consciously responded to at the expense of those emanating from within, and vice-versa' (1976b, pp.416). This model is based on three intensive case-studies of AHs in schizophrenia (Slade, 1972, 1973, 1975), as well as two studies investigating the effects of manipulating external stimulation (Slade, 1974) and the psychological factors contributing to AHs (Slade, 1976a) in schizophrenic patients.

Slade's four-factor model of AHs is supported by the fact that work activities and passive leisure activities have attenuating and enhancing effects on AH intensity, respectively (Delespaul, de Vries, & van Os, 2002). This corroboration, when combined with Slade's own research, seems to support the theory of a limited-capacity attention

system having a modulating effect on the appearance, frequency and intensity of AHs in schizophrenia. However, while illustrating the factors that can exert an influence on the form and occurrence of hallucinations, this work does not satisfactorily illuminate the mechanisms behind AH.

1.5. Neurocognitive Models of Auditory Hallucinations

Despite being recognized as a characteristic symptom of schizophrenia, researchers have yet to come to a firm conclusion regarding the neural mechanisms that mediate auditory hallucinations. While it is clear that there are some cognitive biases (maladaptive sets of thinking), it is important to consider several neurocognitive models in attempting to understand exactly what these cognitive deficits are and how they generate AHs (Seal, Aleman, & McGuire, 2004). Among the many theories, there are three that stand out for their coherence and empirical support; these three theories attribute AHs to abnormal auditory verbal imagery, dysfunction in verbal self-monitoring, and dysfunction of episodic memory processes.

Some of the earliest attempts to explain AHs used a model of abnormal auditory verbal imagery, beginning with Galton's (1943) assertion that those who experience particularly vivid and realistic mental imagery are more prone to hallucinations. This was then applied to the idea that hallucinating schizophrenic patients experience particularly vivid imagery, resulting in AHs. Over the years, however, this explanation received little in the way of experimental support. Many studies found either no difference between schizophrenic patients and normal controls with regards to experience of auditory imagery (Brett & Starker, 1977; Chandiramani & Varma, 1987; Bocker et al., 2000;

Evans et al., 2000). In fact, there is only one study that shows a relationship between auditory imagery vividness and propensity to hallucinate auditorily (Mintz & Alpert, 1972). In this oft-cited study, dubbed the “White Christmas” investigation, participants were asked to close their eyes and listen to a recording of the song “White Christmas”, despite the fact that the record was not actually playing. The results of this study showed that participants with a predisposition to hallucination were more likely to hear the song, and more likely to believe that a record had indeed been playing. While this study displays some evidence of imagery vividness in schizophrenic patients who experience AHs, it can also be interpreted as showing the influence of ‘top-down’ processing in schizophrenia, an idea that requires further empirical support before one can properly surmise the role of expectation in these patients (Frith & Dolan, 1997). What one can be reasonably sure of, however, is that, as Seal and colleagues (2004) pointed out in their review of cognition and auditory hallucinations, there is no compelling evidence that abnormal auditory imagery is related to AHs in schizophrenia. This conclusion is consistent with a body of research that predisposition to hallucinations has no relationship to aberrant auditory imagery in the general population (Merckelbach & van de Ven, 2001; Aleman, Bocker & de Haan, 2000).

The most common explanation of AHs is that they are a type of inner speech that is mistakenly attributed to an external or alien source; that is to say there is some dysfunction in verbal self-monitoring. This idea is supported by the finding that manipulations which block subvocalization (e.g. speaking out loud, keeping the mouth open), also attenuate the presence of AHs (Gallagher et al., 1994). Further evidence of misattribution of inner speech can be elucidated from a study of corollary discharge. It

has been suggested that motor actions are accompanied by a corollary discharge to the sensory cortex, which signals that the incoming sensory input is self-generated (Sperry, 1950). In healthy controls there is a corollary discharge, indicating communication between the frontal lobes where speech is generated and temporal lobes where it is heard, during talking and during inner speech. It has been suggested that this mechanism is behind our ability to distinguish between our own and others' speech by aiding in the monitoring of our own speech, thoughts and behaviours (Ford et al., 2002).

Schizophrenic patients, especially those with prominent hallucinations, showed significant corollary discharge dysfunction (Ford et al., 2001; Ford et al., 2002; Ford and Mathalon, 2004). One notable study has demonstrated this dysfunction using a model of EEG coherence (Ford et al., 2002); if there is communication between two cortical regions, there should be coherence (i.e. frequency dependent matching of EEG) between these regions seen in the EEG. In patients with schizophrenia, there is reduced coherence, especially in the delta and theta bands, between frontal and temporal areas of the brain, indicating a disconnection of these regions and corollary discharge dysfunction.

Furthermore, impaired coherence of the theta band is even more marked in hallucinating schizophrenics, and it is thought that the failure of this mechanism could lead to the misattribution of self-generated thoughts to external sources. This work has since been replicated, lending further support to the idea of corollary discharge dysfunction in schizophrenia, particularly in the presence of AHs (Ford & Mathalon, 2004). It is unknown whether this is the result of pathway or receptor deficits, however these results do suggest that there is a failure to alert the brain that incoming auditory input is self-generated, and this lack of signaled intention leads to the mistaken attribution of inner

speech to alien sources, producing the experience of auditory hallucinations (Ford and Mathalon, 2004).

One study that attempted to objectively measure this dysfunction in self-monitoring had participants make judgements about the origin of perceived speech while talking, with another person's speech and their own distorted speech mixed in with the subject's responses (Johns et al., 2001). In this case, speech was to be attributed to 'self', 'other' or 'unsure'. While schizophrenic patients as a group made more errors than healthy volunteers, hallucinating subjects, in particular, were more likely to misattribute their own distorted speech to an external speaker. This result has since been replicated in a functional neuroimaging study of verbal self-monitoring (Fu et al., 2001), where acutely psychotic schizophrenic patients were unable to identify their own distorted voice, identifying it as originating from an 'other'. Online scanning using fMRI showed this was associated with dysfunction of the neural areas implicated in verbal self-monitoring.

However, despite the compelling evidence that defective self-monitoring may contribute to the experience of AHs, there is further evidence that this theory alone cannot completely explain this phenomenon. In one study, hallucinating and non-hallucinating schizophrenic patients and healthy controls had their voices recorded and, after a delay, were asked to identify the source (self vs. other) of the pre-recorded speech that was either distorted or undistorted (Allen et al., 2003). While this study did not measure immediate verbal self-monitoring, as subjects were not generating speech during the task, hallucinators were still more likely to identify their own speech as originating

from another. These results suggest that abnormal verbal self-monitoring is not the only component involved in auditory hallucinations.

A third influential neurocognitive theory of AHs revolves around dysfunctional episodic memory processes. Episodic memories are those that include sensory and semantic/conceptual features of an event, as well as concurrent affective response, motor action and cognitive processes. Given this, it has been hypothesized that hallucinations result from deficient memory encoding, resulting in altered memories that may include improper attribution of speech. This is thought to be due to some verbal information being stored in long-term memory in a pathological way, resulting in an interference of language production processes, and sometimes overtaking these processes by creating inner speech that is experienced as unintended, external auditory input (Hoffman et al., 1995). Investigations into the dysfunction of episodic memory have attempted to manipulate the conditions under which sensory information is encoded. This approach allows memory to be parsed into item memory (content of memory), source memory (context of memory) and response bias (Murnane & Bayen, 1998). Research into item memory found that when tasks are difficult, schizophrenic patients perform more poorly than healthy controls (Brebion et al., 1997; Seal et al., 1997; Franck et al., 2000), indicating poor memory encoding under these conditions. It is of note, however, that under relatively easy task conditions the difference between schizophrenic and control groups disappears (Vinogradov et al., 1997). For the most part, investigations of source memory, have found that schizophrenic patients with hallucinations show marked deficiencies in discriminating between memories of their own speech and that of another (Brebion et al., 2000; Keefe et al., 2002). Studies in this area, however, have been far

from conclusive as deficits in source memory were seen in conjunction with deficits in item memory, indicating that perhaps hallucinating participants are unable to correctly identify speech source as they are unable to remember the event properly in the first place. Curiously, given this context, schizophrenic patients with AHs are still more likely to attribute self-generated speech to an external source. This suggests that there is a general response bias, a tendency to misattribute words they have said or thought to another speaker, associated with those who experience AHs.

Bentall (1990a, b) argues that the tendency to misattribute event source reflects a bias in the sensory attribution system. This bias is thought to be influenced by ‘top-down’ processes (the patient’s expectations about the kinds of events likely to occur); any sudden intrusive thoughts falling outside of these expectations are attributed to an external source. It has been demonstrated that auditory hallucinators have a bias towards attributing internal experiences to external sources under conditions of uncertainty (Bentall & Slade, 1985). Furthermore, hallucinating schizophrenics have been shown to be more likely to misattribute self-generated words to an external source (e.g. an experimenter) compared to deluded subjects (Bentall et al., 1991). This is consistent with Keefe’s (1998) suggestion that the positive symptoms of schizophrenia are associated with ‘autonoetic agnosia’, a deficit in identification of self-generated events.

Bentall’s model also argues that the misattribution of internal speech may be subject to reinforcement processes through the reduction of anxiety; it has been suggested that AHs act to reduce cognitive dissonance created by increased anxiety (Delespaul, DeVries, & Van Os, 2002). Similar findings have shown that when intrusive thoughts are inconsistent with global beliefs and values, this leads to the misattribution of these

intrusive thoughts as AHs, a mechanism that also serves to reinforce the subject through the reduction of cognitive dissonance (Morrison et al., 1997). This reinforcement may also be obtained for some patients through the experience of ‘pleasurable’ AHs, a phenomenon found to occur in 26% of patients in one sample (Sanjuan et al., 2004). This same study found pleasurable AHs to be positively associated with chronicity of hallucinations, also suggesting there is some type of reinforcement mechanism at work.

Thus, it appears that there is more than one type of cognitive mechanism driving the phenomenon of AHs; certainly, deficits of verbal self-monitoring, impaired episodic memory, abnormal top-down processing, and a response bias of attributing speech to another during forgetfulness or lack of certainty all play a role. As Seal and colleagues (2004) point out, this conclusion makes intuitive sense as it is “unlikely that any unidimensional model of cognitive dysfunction could account for the diverse and striking experiences reported by hallucinating individuals.” (p. 60)

1.6 Structural and Functional Anatomy of Auditory Hallucinations

Nearly 170 years ago, psychiatrist Jean-Etienne-Dominique Esquirol (1838) put forward the view that hallucinations are brain-based, instead of due to outside forces such as demonic possession, and that they arise from aberrant brain functioning. Although it is obvious that Esquirol was right in his prediction that hallucinations originate from the brain, the specific brain regions and mechanisms regulating the appearance and intensity of AHs are still unknown.

It has been suggested that the diversity with AH phenomenology could reflect the diversity of responsible neural mechanisms (Stephane et al., 2003). It is not unreasonable

to assume that a phenomenon such as auditory hallucinations would be associated with neuroanatomical abnormalities, and while this appears to be true, there is certainly no definitive consensus as to which specific brain structures are implicated in AH. Structural neuroimaging techniques such as computerized axial tomography (CT) and magnetic resonance imaging (MRI), as well as post-mortem analysis of afflicted patients, have shown regional abnormalities associated with hallucinations. Several studies of schizophrenic patients have shown increased ventricular volume, and reduced volume of temporal lobe structures, particularly in the left hemisphere (McLure et al., 1998; Andreasen et al., 1990). A further study specifically examining the correlation between structural abnormalities and AHs showed a significant inverse relationship between hallucination severity and volume of the left superior temporal gyrus (incorporating the auditory association cortex), this in conjunction with the overall smaller superior temporal gyri (bilaterally), left amygdala, and larger third ventricle volume found across schizophrenic patients (hallucinators and non-hallucinators) in general (Barta et al., 1990).

More recent studies using similar techniques have demonstrated a bilateral reduction of auditory association cortex volume in hallucinating patients (Weiss and Heckers, 1999). This finding is paralleled in part by the observation that the severity of AHs appears to be negatively correlated with the volume of the left anterior portion of the superior temporal gyrus (Rajarethinam et al., 2000). Reductions of cerebral volume have also been reported in schizophrenic with respect to hallucinators vs non-hallucinators, where a deficit of the left hemisphere grey matter, including the insula (which is critical in speech production; Dronkers, 1996) extending to the uncus and medial part of the

superior temporal gyrus, has been seen (Shapleske et al., 2002). In addition, this study showed a combination of grey-matter deficit with white matter excess. This suggests that excessive connection, due to a failure of neuronal pruning, to aberrant grey-matter may lead to hallucinatory symptoms due to ‘cross-talk’ between the inner speech and auditory processing modules.

Where the static neuroimaging of these so called ‘structural trait’ studies comparing hallucinators and non-hallucinators have lacked for volume of research and regional specificity in AHs, functional neuroimaging studies have improved on both of these points. Characterized as ‘functional trait’ studies when comparing regional cerebral functioning in schizophrenic hallucinators and non-hallucinators, or ‘functional state’ studies when recording cerebral activity captured during hallucinations, this research has done much to expand our knowledge of brain functioning underlying AHs, as well as their particular neural signature.

Early functional trait studies employing fMRI or cerebral blood flow methodologies pointed to a number of different areas of activation in hallucinators. Among the most consistent results were decreased activity of the temporal lobes in schizophrenic patients experiencing AHs as compared to controls (Musalek et al., 1989; Cleghorn et al., 1992), however there have also been, in AH patients compared to controls, reports of increased hippocampal activity (Musalek et al., 1988; Musalek et al., 1989), decreased frontal lobe activity (Musalek et al., 1988; Walter et al., 1990), and decreased striatal activity (Walter et al., 1990; Cleghorn et al., 1990). The results of these studies must be interpreted cautiously due to the low resolution of the imaging equipment used, as well as a lack of experimental control in the patients’ neuroleptic use. It is also

important to consider the intrinsic nature of these studies when reviewing their results; namely that these studies looked at the global cortical functioning of schizophrenic patients who do, at some times, experience AHs, but who were almost certainly not experiencing hallucinations the entire time they were being scanned, and may not have experienced them at all during testing.

As Weiss and Heckers (1999) have stated: “Functional trait studies... give us an estimate of the function of the brain prone to hallucinations, but cannot give us specific data regarding cerebral activity specifically during the hallucinatory state (‘functional state’)”. It is with this in mind that the first so-called ‘symptom capture’ protocols were put into place, recording participants while they were hallucinating. McGuire et al. (1993) reported increased blood flow to Broca’s area, the left anterior cingulate gyrus, and the left temporal lobe during hallucinations, while Suzuki et al.’s (1993) results found that the hallucinatory state was associated with a significant increase of activity in the left superior temporal cortex and anterior cingulate gyrus, closely mirroring the McGuire group’s findings. Silbersweig et al. (1995) then introduced a breakthrough method of tracking the neural signature of the auditory hallucination; scanning patients continually using positron emission tomography (PET) and having them press a button to indicate the start of an AH, then press a second button to indicate the end of the AH. By eliminating confounding factors associated with testing in different sessions, the Silbersweig group (1995) was able to obtain relatively state-specific data showing AHs to be associated with increased bilateral activity of the hippocampus, parahippocampal gyrus, and thalamus, as well as the right ventral striatum and right anterior cingulate gyrus.

Dierks and colleagues (1999) expanded these findings by showing evidence that the primary auditory cortex is involved in the experience of auditory hallucinations. A similar methodology of having patients indicate hallucinating and quiescent states showed activation of the left inferior parietal and left middle frontal gyrus, the temporal lobes and the frontal lobes, in addition to bilateral activation of the superior temporal gyri (Lennox et al., 2000). However, this latter study also examined the unique activation pattern of each subject, and saw that the anterior cingulate, thalamus, cerebellum, and parahippocampal gyrus were differentially activated among the subjects, never showing the same activation pattern, and possibly reflecting the unique nature of the experience for each individual. These studies, as well as others (Woodruff et al., 1995), show that AHs activate the same temporal cortical area activated by verbal auditory speech and inner speech (Shergill et al., 2000), suggesting that hallucinations may compete with exogenous and endogenous sound input for temporal cortical activation.

Auditory verbal imagery has been used as an easily accessible model for AHs, albeit with mixed results. During auditory verbal imagery, prominent frontal lobe activation has been noted (Silbersweig & Stern, 1998), a finding not replicated in functional imaging studies of AHs. However, it is thought that this frontal activation indicates voluntary conjuring of auditory verbal imagery as compared to the automatic, uncontrolled nature of AHs (Silbersweig & Stern, 1998). Conversely, activation of the primary sensory cortex (thought to be a key event in the experience of AHs as 'real') has been observed in AHs, whereas it has not been observed in consciously controlled auditory verbal imagery studies (McGuire et al., 1996). There are also some key areas of overlapping activation between these two conditions (McGuire et al., 1996); PET

imaging has shown both AHs and auditory verbal imagery to activate the anterior cingulate and posterior superior temporal gyrus (STG).

It has been shown that there are alterations of the auditory cortical response to speech in schizophrenic patients with AHs (Woodruff, 1997). In patients scanned both during and after AH occurrence, activation of the temporal cortex, specifically the right medial temporal gyrus, was attenuated during AH occurrence when external speech was presented. This result was echoed in a case study involving a patient with chronic AHs; this patient showed elevated activity of the right medial temporal and left superior temporal gyri during the absence of external speech (and, hence, presence of AHs) which disappeared in the presence of real external speech (Bentaleb et al., 2002). Thus it can be seen that AHs activate the auditory cortex, and even compete with external speech for attentional resources. This model of competition within the auditory cortex has been dubbed the 'saturation hypothesis' (Woodruff, 1997) and is demonstrated in Figure 1 (Woodruff, 2004, pg. 82). Accordingly, temporal lobe activation is represented by the vertical arrow in the centre of the figure, with this activation arising from both external speech and auditory hallucinations (as indicated by arrows). The circle between external speech and AH activation indicates a reciprocal relationship between these stimuli, as is indicated by the saturation hypothesis. Finally, temporal lobe activation is modulated by attention, which alters the general responsiveness of the temporal cortex whereby the more attention is allocated to external speech or auditory hallucinations, the greater the temporal lobe activation.

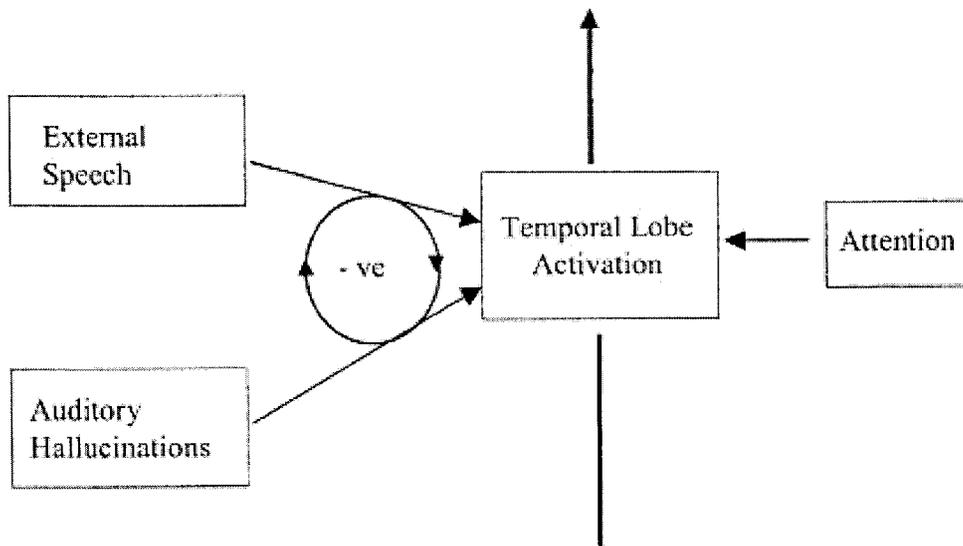


Figure 1. Model of the Saturation Hypothesis

It has also been suggested that increased sensitivity to specific speech characteristics increase the chance of experiencing AHs (Woodruff, 2004). Certainly, schizophrenic patients with AHs showed increased auditory cortex responsivity compared to those patients without AHs (Woodruff et al., 1998). It has been shown in some studies that there is a right lateralized response of the auditory cortex (Woodruff et al., 1997), that prosodic processing is also mainly lateralized to the right (Buchanon et al., 2000), and that passive listening to happy-sounding vs. happy-meaning speech amplifies this right cortical response in normal controls (Mitchell et al., 2003). However, this latter effect was reversed in schizophrenic patients, with happy-sounding (vs. happy-meaning) sentences enhancing temporal activity on the left side rather than the right (Mitchell & Woodruff, 2001), suggesting that the areas responsible for prosody processing are reversed in schizophrenia. This could result in altered sensitivity to emotional content and problematic semantic processing, which generally occurs in the left temporal cortex.

1.7 Attention, and Attentional Deficits in Schizophrenia

Early theories of attention posited that attention selected certain incoming sensory attention for conscious awareness and processing, while filtering out the remaining sensory information. The first of these theories, entitled the early-filter theory (Broadbent, 1958), stated that attention worked in an all-or-nothing fashion, much like a light switch, selecting and filtering sensory information before the sensory signals attain meaning. The result of this being that the filtered sensory information is cast aside forever. This theory was quickly disproved by the work of Cherry (1953), who used a

dichotic listening task in which participants shadowed the message in one ear while ignoring stimuli presented in the other. According to the early-filter theory, there should be no meaningful processing of the unattended message under these conditions. Yet, when performing this task, if half of a sentence is presented in one ear and then switches to the other, if the meaning of the shadowed sentence switches to the unshadowed ear, shadowing is disrupted with the participant experiencing confusion and switching to the unshadowed ear (Treisman, 1960). This led Treisman (1964) to propose a modified theory of attentional filter whereby attention works more like an attenuator, allowing gradation in the amount of sensory information being processed, while still maintaining Broadbent's idea that filtering occurs at the sensory memory level.

Concurrent to the early-selection models, theorists were proposing late-selection filter models, hypothesizing that all input to the sensory receptors activate representations in long-term memory (Deutsch & Deutsch, 1963; Norman, 1968). Each of these long-term memory representations differ in pertinence (how well the representation fits into the context of the situation), with the input that creates the best combination of activation and pertinence being selected to enter awareness. However, it is very difficult to design an experiment that would allow for a response to two different pieces of sensory information. In light of this, the filter model was abandoned, but not before its limitations spawned a new question: why can't we respond to two different pieces of sensory information at once. With that, the capacity model of attention was brought into the theoretical world.

The capacity model of attention (Kahneman, 1973) assumes that our attentional resources are finite; we have only a certain amount of cognitive capacity that can be

allocated to various tasks. Seeing as tasks differ in the amount of capacity they require, the number of tasks that can be performed at any one time depend on the attentional demands of each. Following on from that, the attentional resources required by one task will come at the expense of capacity available to other tasks. Knowing this, it is possible to measure the capacity demands of a task.

Within a capacity model of attention, there are capacity limitations. Research in this field has shown that there is an inverse relationship between difficulty of the primary task and performance on a secondary task (Johnston et al., 1970; Britton & Tesser, 1982; Tyler et al., 1979). The most extreme case of capacity limitations would involve serial processing, whereby only one stimulus can be processed at a time, therefore perceptual analysis of one stimulus must be completed before another can begin. The other extreme case is one of parallel processing, whereby multiple stimuli can be processed at the same time, however in a limited capacity model, individual cognitive operations would be slower when processing more than one task at once. The results of the dichotic listening task presented earlier (Treisman, 1960) seem to point to parallel processing, as two different stimuli can be processed at once. However, the resulting confusion from the semantic switch of ears indicates that such an action causes the finite resource of attention to reach its limit. In a groundbreaking study by Lindsay, Taylor, and Forbes (1968), participants were presented a brief tone and a spot, followed by another tone and spot after an inter-stimulus interval of 500ms. This comprised one trial. Each trial could involve any of four judgement tasks: deciding which of the tones was higher in pitch or intensity, and deciding which of the two spots was higher or leftward of the other. Within a block of trials, subjects performed one, two or four of the tasks. The more judgements

that had to be made, the worse the performance. This seems to suggest that processing occurred in a parallel manner when demands were lower and in a serial manner (resulting in lower accuracy due to sensory memory decay) when task demands were high.

The literature of divided attention appears to present a hybrid model: capacity limits are certainly present beyond a certain point and at a certain difficulty level, task processing appears to operate in a serial manner. While stimulus load is below the capacity limit, however, processing appears to be parallel. Thus, one can expect that a demanding task will monopolize a significant portion of the attentional resources available, causing performance in any other tasks to suffer. Certainly, deficits of attention are well documented in schizophrenia (Laurens et al., 2005; Braff, 1993). It has been noted that patients exhibiting positive symptoms have difficulty directing their attention appropriately (Posner et al., 1988; Maruff et al., 1995) and it has been suggested that attentional deficits in schizophrenia may arise from dysregulation of executive attention control processes (Frith, 1992; Early et al., 1989). Subsequently, patients with schizophrenia often experience an increased vulnerability to distraction by task-irrelevant stimuli (Braff, 1993), which may include AHs. Applying a capacity model theory to auditory hallucinations in schizophrenia, it is not difficult to imagine that the invasive, and often distressing, nature of AHs would usurp attentional resources which may be more appropriately directed to relevant goal-direct behaviours. Thus, even when performing one task visible to an observer, the patient experiencing hallucinations would have divided attention and an already drained capacity of attention. What remains to be seen is how much attention hallucinations demand and how this affects cognitive performance.

1.8 Event-Related Potentials

Within the fields of attention and information processing, the electroencephalographically (EEG)-derived event-related potentials (ERPs) provide an exquisitely sensitive method of indexing cognition that can both complement and clarify behavioural observations. The ERP waveform is elicited in response to a specific stimulus, such as tones or light flashes, or cognitive events, such as recognition, decision making or response to specific stimuli events. Specifically, ERPs represent an average of the neural activity that follows the onset of a stimulus. They are extracted from recorded brain activity by averaging an EEG window (called an epoch) that is time-locked to a specific stimulus or behavioural event, causing the random background noise of the EEG to cancel to zero, leaving behind a constant and invariant waveform. When recorded concurrently with behavioural measures of task performance, ERPs provide a fuller picture of the cognitive features underlying different arousal, mood and psychiatric states.

The averaged ERP plots voltage (microvolts: μV) as a function of time (milliseconds: ms); the resultant waveform appears as a series of deflections or peaks. Conventionally, these components are described in terms of polarity (positive peaks labeled P; negative peaks labeled N), and sequence (ordinal position of peak) or peak latency of where the ERP typically occurs. In this manner, the third positive peak in the waveform may be labeled the P3 or the P300, as it is expected to occur approximately 300 ms after stimulus onset.

Classification of ERPs is generally divided into two types: the early-occurring exogenous components, and the later endogenous components. The exogenous ERPs are

generally those occurring within 100 ms of stimulus onset and are so named because their respective amplitudes and latencies are primarily determined by the properties of the eliciting stimulus, such as intensity and rate. (Friedman & Squires-Wheeler, 1994). As such, they are relatively insensitive to psychological variables such as mood and attention (Roth, 1977). These ERPs are mainly generated in the primary sensory cortex and association areas of the brain (Chiappa, 1990). By contrast, the endogenous ERP components (latency > 100ms) are highly influenced by cognitive and psychological variables manifest upon the subject and are relatively independent of eliciting stimulus' physical characteristics (Pritchard et al., 1986).

The primary advantage of ERPs resides in the fact that one can probe aspects of information processing without requiring any active, overt response on the part of the subject, thus making them ideal in the cognitive study of psychiatric populations, which may be unable to perform behavioural tasks due to cognitive and/or motor deficits. Furthermore, ERPs provide a temporal resolution far superior to some of the more sophisticated imaging techniques (i.e. PET, fMRI), making this methodology far more suitable for capturing instantaneous changes in information processes. The auditory mismatch negativity (MMN) waveform, in particular, can be especially useful as it does not require any behavioural response, and does not even require the subject's attention to the stimuli due to its intrinsic nature as an index of automatic sensory perception (Näätänen, 2003). In addition, the MMN is an inexpensive and easy to use tool which has been shown to objectively index general brain deterioration in clinical populations (Näätänen, 2000).

1.8.1 Mismatch Negativity

The mismatch negativity is an event-related potential that is elicited by any discriminable change in auditory stimulation; the resulting waveform is a negative peak with a frontal-topography maximum amplitude and an expected peak latency of 90-250ms. Generally, the MMN is generated by randomly inserting low-probability (i.e. rare) deviant auditory stimuli into a train of repetitive (i.e. standard) sounds. These auditory stimuli may deviate in any number of ways from the standard, with deviations in frequency, duration, intensity and location eliciting an MMN (Näätänen & Ahlo, 1997). Notable is the fact that the MMN occurs irrespective of whether or not one is consciously aware of, or attending to, such a change (Näätänen, 1982; Näätänen, 1992). The automaticity of the MMN generator processes is provided by findings of MMN being recorded, albeit with smaller amplitudes, in anesthetized animals (Ruusuvirta, Penttonen, & Korhonen, 1998), coma patients (Kane, Butler & Simpson, 2000), as well as during Stage-2 and Rapid Eye Movement (REM) sleep (Sabri, DeLugt & Campbell, 2000; Saalinen, Kaartinen, & Lyytinen, 1996). It is thought that the MMN is generated in response to a comparison of the novel stimulus with a well-formed sensory or 'echoic' memory trace of the standard auditory stimulus. When the incoming auditory stimulus differs from the existing memory trace, the MMN is generated.

Given the MMN's association with auditory sensory information processing, it makes sense that MMN generators are located bilaterally in the left and right supratemporal lobes, specifically in the auditory cortex (Rinne et al., 1999). Furthermore, different areas of the auditory cortex are associated with MMN generation in response to different deviances of auditory information. MMNs to linguistic information (i.e.

phonemes) on the other hand are generated in the left auditory cortex, specifically in the region of Wernicke's area (Rinne et al., 1999). In addition to the MMN generators in the temporal lobes, which are responsible for detection of sensory auditory deviance, there are also right-hemisphere dominant MMN generators in the frontal lobes. These generators are associated with involuntary attention switching to relevant stimuli (Giard et al., 1990), and it is thought that activation of the frontal MMN generators is triggered by the auditory cortex following detection of salient information. This is supported by data demonstrating a slight delay in frontal activation following auditory cortex activation (Rinne et al., 2000).

Within Näätänen's model (1992), automatic detection and processing of auditory stimuli, irrespective of focused attention on the stimuli, has two main functions: extraction of sensory information from the environment and switching of attention to novel, and potentially relevant, changes in the auditory environment. These occur during the short phase of sensory memory, lasting 150-200ms from stimulus onset, while the sensory features of the incoming information is integrated with those of the preceding stimulation. Within this model, the result of the completed sensory analysis is a stimulus representation as opposed to a fixed memory. Past auditory stimuli are then held in a pure-memory long phase auditory store, sometimes called echoic memory (Neisser, 1967), which fades after 10-20 seconds unless new representations are added. An essential part of this model is that stimulus processing is automatic, and, therefore, does not require or imply conscious sound perception. When a discrepancy is detected in the short memory phase between the incoming stimulus and past stimuli representation, a mismatch signal is generated to indicate the detection of acoustic change and an interrupt

signal is sent to the executive mechanisms (Näätänen, 1986). This signal may lead to conscious perception of the deviant acoustic stimuli if the signal is strong enough, and whether or not attention is strongly focused elsewhere.

The strength and speed (i.e. latency) of the MMN signal produced is related to both the size of the deviance (i.e. how different the novel stimuli is from the defined memory trace) and the probability of the deviance occurring and is independent of the requirements of the task. When attention is directed to the auditory stimuli in an anticipatory way, even weak stimuli may be perceived consciously. By contrast, if attention is strongly focused elsewhere, such as a primary task, it would require a very intrusive or salient stimulus to penetrate into consciousness. Should this happen, the stimulus is then evaluated to determine whether it is significant or not; insignificant stimuli are quickly discarded and attention is re-directed back to the original task without conscious perception of the intrusive sound, whereas significant stimuli, such as a threat or the sound of one's own name, will likely result in conscious perception of the stimulus and attention being switched to its source (Näätänen, 1992).

Paying attention to the MMN-eliciting stimuli can cause other deviant-related ERP components, such as the later occurring negativity at 200ms (N2b), which may overlap temporally and spatially with the MMN. The confounding influence of N2b-related processes in MMN studies can be controlled for by varying the nature/difficulty of a diversion task (e.g. reading a book, watching a movie, performing a visual task) during MMN elicitation, thus reducing the possibility of N2b contamination as attention is not actively directed to the auditory channel in which the MMN-eliciting stimuli are presented (Muller-Gass et al., 2005).

While the MMN is generally elicited in a laboratory using pure tones as both standard and deviant stimuli, this ERP component has proved sensitive to a wide range of simple and complex sounds, including speech. Used as an index of discrimination of linguistic stimuli, such as phonemes and consonant-vowel (CV) syllables, MMN amplitudes generally increase with easier discriminations and diminish, or are not elicited, if two phonemes or syllables are not discriminated by subjects (Näätänen, 2001). Using a dense electrode array to examine regionalized hemispheric specialization of early auditory processing of non-phonetic (tones) and phonetic (vowels) sounds, Rinne and colleagues (1999) reported left-hemisphere (over the superior temporal gyrus) maximum MMN amplitudes in response to phonemes and stronger right hemisphere activation in response to tone like sounds. This early, pre-attentive, left-hemisphere predominant MMN indexing of auditory analysis of phonetic features is not evident with MMNs elicited by complex tones or foreign language phonemes (Näätänen et al., 1997). These observations support the classic view that the left hemisphere processes phonetic or semantic aspects of stimuli and is reinforced by the finding that magnetic MMNs elicited by duration changes in speech sounds are left hemisphere maximum while duration changes evoked by non-speech sounds are right hemisphere dominant (Takegatu et al., 2004). MMN has also been used as an index of voice discriminability, as shown in one study where subjects were presented with a repetitive vowel sound spoken by a female which was interspersed with four 'deviant' stimuli consisting of the same vowel sound pronounced by a male speaker or one of three different female speakers (Titova & Näätänen, 2001). Here, an MMN was elicited by all deviant voices; the more dissimilar the deviant voice was (as rated by the subjects), the larger the amplitude of the MMN. It

has also been demonstrated that native speakers exhibit a larger MMN to similar vowel sounds in their own language, as opposed to non-native speakers, to whom the discernable difference between the vowel sounds is presumably smaller (Peltola et al., 2003; Winkler et al., 1998; Näätänen et al., 1997). Subsequent magnetic measurements of this mother-tongue MMN (MMNm) enhancement in a Finnish population showed the left auditory cortex, specifically Wernicke's area, to be the focus of this effect (Rinne et al., 1999).

The mismatch negativity, despite being predominantly moderated by 'bottom-up' processes, also appears to some degree, under specific conditions, sensitive to 'top-down' processes including the availability of attentional resources. High demand processing tasks result in a significant decrease in MMN amplitude; as more resources are required for processing of a primary task, there is a corresponding drop-off in resources available to the MMN generator (Kramer et al., 1995). The lowered effectiveness of the generator is seen in the reduction of MMN amplitude.

MMN amplitude also seems to be sensitive to the nature of the diversion task used. The MMN elicited by to-be ignored intensity deviants was attenuated when subjects were counting targets presented to the opposite ear, as opposed to when reading (Näätänen et al., 1993). This difference has been attributed to the greater attentional focus required by the counting task. A similar result of dampened MMN during a dichotic listening task as compared to reading as a diversion has been since replicated (Alain & Woods, 1997), indicating that MMN is indeed modulated with the diversion task, again implicating processing resource capacity as an important modulator of the mismatch negativity. However, a recent study reported that a diversionary task may, via increased

cortical excitability, actually increase MMN amplitude (Muller-Gass, Stelmack, Campbell, 2005). Related to the issue of the effects of diversionary tasks on the MMN-indexed early auditory processes are studies focusing on the effects of sound context on hemispheric processing of speech stimuli. The finding that CV syllable deviants elicit a stronger MMNm in the right hemisphere when embedded in either a speech-sound or non-speech sound context than when presented alone (where the left-hemisphere MMNm is stronger than the right) has been interpreted to reflect a general right-hemisphere specialization for the analysis of contextual acoustic information (Kujala et al., 2002). A number of behavioural studies have also suggested that the basic functional asymmetry of central speech processing is affected by acoustical disturbances, including background noise. For example, inactivation of the right hemisphere, but not of the left hemisphere by electroconvulsive therapy has worsened word perception in noisy backgrounds (Balonov & Degler, 1970). As well, during dichotic listening tasks, perception of words presented to the right ear, but not the left ear, decreased in the context of noise as compared with silence (Galoonov, Korolyova, & Shourgaya, 1988; Koroleva & Shurgaya, 1997). In an investigation of background noise influence on magnetic brain responses to spoken sentences, noise was found to affect syntactical processes in both hemispheres but altered early auditory processes only in the right hemisphere (Herrmann et al., 2000). With respect to MMNs, CV-syllable deviants presented against a white noise background (vs. silence), while not affecting behavioural discriminability, diminished MMNm in the left hemisphere, increased MMN amplitude in the right hemisphere (Shtyrov et al., 1998), and increased activation of additional right auditory cortical structures not evidenced in silence (Shtyrov et al., 1999). Thus it seems that the addition of noise competitors at

intensities which reduce speech/sound discriminability results in diminished MMNs (Salo et al., 1994; Martin et al., 1997; Martin et al., 1999) and displaces MMN-related activity to the right hemisphere during speech discrimination (Muller-Gass et al., 2001), presumably due to effects on peripheral auditory mechanisms (i.e. by shifting thresholds or reducing audibility). However, the findings by Shtyrov and colleagues suggest that these noise competitors also impact on central auditory processing in a manner that decreases involvement of the left hemisphere, while involvement of the right hemisphere increases. That there is more to hearing in noise competition than just the audibility of the signal at the peripheral auditory level is supported by the observations that various background conditions result in different effects on speech recognition performance compared to silent conditions. Speech recognition performance is more deleteriously affected by speech competitors than non-speech competitors (Garstecki & Mulac, 1974; Van Tasell & Yanz, 1987), and is more affected by meaningful speech competitors than non-meaningful speech competitors (Sperry et al., 1997). MMN indexing of the effect of different types of real-life noises on central auditory processing of speech (CV-syllables) has shown MMNs to speech stimuli to be affected by noises more than non-speech stimuli. As well, whereas industrial noises and babble noises reduced MMNs to both stimulus types, only speech elicited MMNs were diminished by traffic noise (Kozou et al., 2005).

Considering the apparent involvement of a dysfunctional left hemisphere auditory cortex in hallucinatory experiences of schizophrenic patients, the modulating role of auditory competitors on hallucinations, and the sensitivity of MMN in indexing hemispheric asymmetric shifts in early central auditory processing, MMN may be a

particularly suitable tool for probing brain mechanisms underlying hallucinations in schizophrenia.

1.8.2 MMN and Schizophrenia

Given the cognitive deficits associated with schizophrenia, research into the mismatch negativity in affected patients has been a major point of interest since the first study linking the two was published (Shelley et al., 1991). In general, chronic schizophrenic patients exhibit robust MMN deficits (Javitt et al., 1993; Umbricht et al., 2003; Youn et al., 2002). This deficit in MMN generation appears to be somewhat specific to schizophrenia, as there have been no reported MMN alterations in any of the other major psychiatric disorders such as depression or bipolar disorder (Catts et al., 1995; Umbricht et al., 2003). This suggests that, within chronic schizophrenia, there is impairment of auditory sensory memory and context-dependent information processing at the level of the primary and secondary auditory cortices (Umbricht & Krljes, 2005).

MMN deficits have been shown to be associated with faulty NMDA receptor function in both animals (Javitt et al., 1996) and humans (Umbricht et al., 2000, 2004). These receptor deficiencies could be due to a loss of dendritic spines, a primary location of NMDA receptors (Nimchinsky et al., 2002). Dendritic abnormalities, including loss of spines, have been previously noted in schizophrenia (Glantz & Lewis, 2000).

In addition, MMN deficits appear to become more prominent as the probability of the deviant stimulus decreases (Umbricht & Krljes, 2005). The effect of deviant probability is thought to reflect efficiency of standard stimulus encoding. Therefore, these findings could support a view of deficient stimulus encoding in schizophrenia, a

previously reported phenomena in this patient population (Fleming et al., 1997; Keefe et al., 1997).

It is of note that the majority of studies examining MMN in schizophrenia make little or no effort to examine the effects of the associated syndromes or symptoms, a troubling finding given the heterogeneous nature of the disease. One study that did examine the correlation between MMN and auditory hallucinations, as measured by the Positive and Negative Syndromes Scale (Kay et al., 1987), found an initial correlation that disappeared upon follow-up analysis using a Bonferroni procedure. Of the two other studies that looked for a correlation between MMN and auditory hallucinations, one found no significant effect; however, it used a vague measure of hallucinations (Schall et al., 1999). The other study found a significant negative correlation between a measure of hallucinatory behaviour and left MMN equivalent current dipole power (Youn et al., 2002). As yet, there has been no systematic study examining whether auditory hallucinations make a unique contribution to the overall deficit in mismatch negativity generation. This is surprising, given how well suited the MMN is to index AHs, especially in the context of previous work by Kozou et al (2005), whereby background noise (in this case as a sort of cocktail party effect) attenuates MMN amplitude. Pursuant to this, one could imagine that further distraction would attenuate the MMN further if AHs do indeed monopolize cognitive attentional resources.

While there are no studies examining MMNs in relation to AHs per se, Kasai and colleagues' (2002) work examining preattentive perception of speech sounds in schizophrenia has some interesting implications regarding this issue. In this study, subjects were exposed to three different tasks designed to elicit MMN in response to

changes in pure tone duration, changes in duration of a spoken vowel (Japanese vowel /a/) and across-phoneme (Japanese vowel /a/ vs. Japanese vowel /o/) changes. The results of this study showed no difference in ERP amplitudes between schizophrenic patients and a matched sample of healthy controls for either the pure tone or vowel duration tasks. However, the schizophrenic patients (vs. controls) did exhibit abnormal lateralization during the phoneme duration task, as well as lower MMN amplitudes in both hemispheres in the across phoneme condition. That MMN amplitude was only affected within the across-phoneme condition suggests that schizophrenia is associated with dysfunction of the comparative processes of stimulus encoding, while formation and maintenance of sensory memory remains intact. Although not specifically examined in relation to hallucinatory symptomatology in these patients, the abnormal lateralization of the MMN during the phoneme duration condition in the absence of altered MMN amplitudes could be indicative of AH-modulated altered speech processing within schizophrenia.

1.9 Summary, Objectives and Hypotheses

Despite the phenomenological thoroughness resulting from over 2000 years of observations, the cause and mechanism of auditory verbal hallucinations in schizophrenia remain unclear. Although no comprehensive neurocognitive theory has satisfactorily explained why AHs are *perceived* in the absence of an external stimulus, brain-based approaches employing functional neuroimaging to study these mental phenomena *in vivo* have progressed our understanding of the neural basis of hallucinations. Reports of abnormal activation of the left primary auditory cortex by the experience of AHs and its

inhibition by external speech suggests, as several studies have indicated (Barta et al., 1990; Barta et al. 1997), that experiencing AHs and listening to external speech might be subserved by some common neurological substrates. If the final common path to AH experiences lies within the auditory cortex itself, it is reasonable to ask whether the temporal cortex of hallucinating patients processes speech normally; whether it is predisposed to aberrantly respond to contextual aspects of speech which may influence AH hallucinatory experience. Insights into the predisposition of the temporal cortex to respond to specific aspects of auditory signals preferentially is provided with positron emission tomography (PET), which has demonstrated that human brain regions involving the superior temporal gyrus (including the left planum temporale) respond specifically to voices as opposed to environmental sounds (Belin et al., 2000).

The degree to which this differential responsivity may reflect early pre-attentive processes, which may be uniquely dysfunctional in hallucinating patients, is yet to be explored. However, the MMN, used to probe auditory central processing on a millisecond basis with no attentional task requirements, has consistently reported discrimination of speech sounds (vs. non-speech sounds) to occur predominantly in the left hemisphere (Rinne et al., 1999; Shtyrov et al., 2000; Takegata et al., 2004). In the limited research examining differences between the discrimination of speech and non-speech sounds in schizophrenia, patients have shown greater MMN amplitude deficits (compared to healthy volunteers) in the detection of phoneme (vowel) changes than in the detection of non-phoneme (tone) changes (Kasai et al., 2002). As yet these effects have not been assessed with respect to the presence or absence of AHs.

One objective of this proposal, using MMN recorded from multiple scalp sites, is to compare hallucinating (HP) and non-hallucinating (NP) patients with respect to differences in left and right hemisphere response discrimination of speech and non-speech stimuli. Employing the stimulus paradigms used by Kasai and colleagues (2002), it is hypothesized that MMN amplitudes elicited by phoneme (vowel) and non-phoneme (tone duration) changes will be smaller in patients than in non-patient healthy controls (HC). Furthermore, it is expected that patient differences will be most evident in the discrimination of phonetic stimuli, with HPs exhibiting smaller MMNs, particularly in the left hemisphere at the temporal recording sites.

The suggestion that AHs may drive the normal hearing apparatus (temporal cortex) and compete with external speech for attentional/processing resources allocated to that apparatus (Woodruff, 2004; Woodruff et al., 1997) is supported by the finding that AHs are reduced when listening to external speech (Slade, 1974; Margo, Helmsley, & Slade, 1981). Furthermore, compared to healthy controls, who exhibit fMRI-indexed bilateral temporal activation during external speech perception (Bentaleb et al., 2002), schizophrenic patients experiencing severe hallucinations evidenced marked right temporal cortical hypo-responsivity to auditory perception of speech (Woodruff et al., 1997). Given that the responsivity of the auditory cortex varies according to 'host-specific' and contextual qualities of auditory signals (Belin et al., 2000), examining the influence of factors modulating central response to speech stimuli may provide a unique approach for understanding pathophysiological brain mechanisms underlying AHs. Central processing (of external speech) beyond the peripheral auditory mechanism is affected by speech competitors such as background noise and is reflected at the pre-

attentive level by reductions in MMN and regional displacement of maximal amplitudes from left to right hemisphere (Shtyrov et al., 1998; Shtyrov et al., 1999; Muller-Gass et al., 2001; Kujala et al., 2002).

A second objective of this proposal, using MMN recorded from multiple scalp sites, is to compare HP and NP patients with respect to the altered cerebral functional asymmetry of speech perception resulting from background noise. As more structured and meaningful auditory input is associated with greater reductions in AHs (Margo, Hemsley & Slade, 1981), and as MMN-indexed pre-attentive speech discrimination is differentially affected by noise types (Kozou et al., 2005), MMN responses to CV syllable changes will be assessed in silence, during background broadband white noise and 'real-life' (traffic) noise. As sound competitors can in turn influence AHs, the effects of noise on subjective ratings of AHs will also be assessed. As some, but not all, studies have found schizophrenic patients to exhibit increased sensitivity to noise (Woodruff, 2004), and for white and traffic noise to increase AH intensity (Alpert, 1985; Bentall, 1990; Fonagy & Slade, 1982; Margo, Hemsley & Slade, 1981; Tarrier, 1987), it is hypothesized that, compared to HCs, both patient groups will exhibit reduced left (temporal) hemisphere MMNs during silence, this effect being more evident in HPs who will, along with increased subjective ratings of AHs (i.e. intensity, clarity and duration), exhibit greater overall noise-induced reductions in left and right temporal hemisphere MMNs, but with the effect being greater with traffic noise than with white noise.

2. Method

2.1 Study Participants

2.1.1 Experimental Participants

Twenty-four experimental volunteers, all presenting with a primary diagnosis of schizophrenia, were recruited from the Outpatient Schizophrenia Clinic of the Royal Ottawa Hospital. During an initial clinical interview (with the primary care physician) in which volunteers were assessed with respect to inclusion and exclusion criteria, both clinical history and ratings on the Positive and Negative Syndrome Scale (PANSS) for schizophrenia were used for allocation of volunteers to HP and NP groupings. HPs (n=12) were patients reporting a definite, consistent history of AHs over the course of their illness, exhibiting a score ≥ 3 (mild or greater hallucinatory experiences) on the hallucination item of the PANSS positive symptom scale (based on self-reported symptoms over the past month), and NPs (n=12) were patients exhibiting a score of 1 on this item (hallucinatory experiences absent) and no previous consistent history of AHs.

The presence and/or absence of AHs were subsequently confirmed by the experimenter, who rated the patients on the AH subscale of the Psychotic Symptom Rating Scale (PSYRATS). This 11-item, 5-point (0-4) rating scale assesses hallucinations with respect to frequency, duration, severity and intensity of distress and also symptom specific dimensions of controllability, loudness, location, negative content, degree of negative content, beliefs about origin of voices, and disruption. HP and NP groups were matched as closely as possible with respect to age, gender, PANSS scores

(Positive Scale, Negative Scale and General Psychopathology Scale) and medication dosage (clinical equivalence in schizophrenia rating; Bezchlibnyk-Butler & Jeffries, 2005). In addition to the PANSS and PSYRATS, assessments included a general medical/health questionnaire, a handedness (right vs. left) scale (Edinburgh Handedness Inventory; Oldfield, 1971), the National Adult Reading Test (NART; Nelson and Willison, 1991) which is designed to give a score of Full-Scale I.Q., questionnaires on substance use including the Drug Abuse Screening Test (DAST; Skinner, 1982), the Alcohol Use Disorders Identification Test (AUDIT; Saunders et al., 1993), and the Fagerstrom Test for Nicotine Dependence (FTND; Heatherton et al., 1991). A summary of participant demographics is given in table 1.

The study was conducted following approval of both the Royal Ottawa Hospital (ROH) and Carleton University (CU) Research Ethics Boards.

2.1.1.1 Inclusion Criteria

All patient participants were to be between the ages of 18-65. Patients were to be judged as clinically stable for the four weeks prior to testing (as indicated by no significant changes in symptoms or medications) and their primary medication was to be limited to one of the atypical anti-psychotics. All participants were required to understand spoken and written English, though participants were allowed to have a first language other than English. Due to the auditory requirements of the study, all participants had to demonstrate normal hearing according to an audiometric assessment, conducted by the primary investigator in the research laboratory, requiring thresholds of 25 dB (SPL) or

less (using a 'descending method of limits' procedure) to pure tones of 500 Hz, 1000 Hz, and 2000 Hz.

2.1.1.2 Exclusion Criteria

Participants were excluded if they meet any of the following criteria: co-morbid DSM-IV TR Axis I disorder; total PANSS score >65, reflecting an acute psychotic episode; current history of drug abuse or dependence; history of head injury resulting in loss of consciousness; diagnosis of epilepsy or any other neurologic disorder; electro-convulsive therapy (ECT) treatment within the previous year; significant cardiac illness; extrapyramidal symptoms (EPS) resulting in movement disorders which could affect ERP recordings; or abnormal audiometric assessment.

2.1.2 Control Participants

Normal participants (HC) were twelve healthy volunteers, who, for exclusion/inclusion purposes, were required to self-report negative psychiatric, medical, neurological and alcohol/drug abuse histories, to report non-use of medications, and display normal hearing. Experimental and control groups were matched as closely as possible with respect to age, gender and scores on the NART.

Table 1. Summary of participant demographics (mean \pm SE). * = significant difference between groups ($p < .05$)

	HP	NP	HC
Age	44.25 (3.16)	45.67 (3.16)	39.75 (3.16)
FTND*	4.33 (0.97)	3.58 (0.97)	0.83 (0.97)
AUDIT	2.33 (1.18)	3.25 (1.18)	5.50 (1.18)
DAST*	1.25 (1.04)	7.25 (1.04)	0.50 (1.04)
Handedness	64.24 (12.06)	63.92 (12.06)	83.68 (12.06)
NART*	103.39 (1.95)	108.98 (1.95)	114.54 (1.95)
NART (corrected)	107.13 (3.04)	111.89 (2.02)	115.96 (1.83)
Rx Clinical Equivalent in SCZ	5.00 (0.67)	3.17 (1.58)	-
PANSS Positive	16.45 (0.98)	11.00 (1.20)	-
PANSS Negative	14.45 (1.22)	13.75 (1.51)	-
PANSS General	27.73 (1.84)	21.25 (4.31)	-
PANSS Hallucination Item	3.64 (0.19)	-	-
PSYRATS	28.67 (0.69)	-	-

2.1.3 Group Differences

There were several differences between groups. Firstly, there was a significant difference on FTND scores, $F(2, 33) = 8.172, p < .04$, with the HC group exhibiting a smaller score than both the HP group ($p < .02$) and the NP group ($p < .05$). This difference is to be expected given that schizophrenic patients as a group have a tendency to smoke more than the normal population (Kalman et al., 2005). In order to neutralize this difference, smokers were permitted to have a cigarette immediately before testing, so that withdrawal effects would be reduced or completely negated.

The higher score for the NP group on the DAST questionnaire, $F(2, 33) = 12.561, p < .01$, is well below the average score of 15.2 reported in drug and alcohol abusers (Skinner, 1982). Furthermore, given that all participants included are non-abusers of drugs, this score would not be indicative of current illicit drug use.

There initially appeared to be a significant difference between the groups on their respective NART scores, $F(2, 33) = 8.172, p < .01$, indicating an overall difference of I.Q. This would be significant, given that I.Q. has been shown to have a significant effect on MMNs (Beauchamp & Stelmack, in press). However, each of the groups, and the HP group in particular, encompassed several participants whose first language was not English (with mother tongue ranging from French to Arabic to Mandarin-Chinese), thereby invalidating the test. When these participants were removed from the analysis, there was no significant difference between the groups (in the corrected analysis) with regards to NART-derived Full-Scale I.Q.

2.2 Study Design

Following the signing of an informed consent, volunteers attended the laboratory for one test session in which they underwent two experiments, in the following order: (a) MMNs elicited by speech (phoneme) and non- speech (pure tone) sound ‘duration’ deviants and across-phoneme deviants, and (b) MMNs elicited by CV syllable change presented in silence and during two background noise conditions: wideband white noise and traffic noise.

2.3 Study Procedure

Testing was conducted around midday (11:00am-2:00pm) with participants being required to abstain from drugs, medications (except for anti-psychotics and adjunct drugs), and alcohol beginning at midnight of the previous day. Upon arrival at the laboratory, following informed consent, participants completed demographic

questionnaires and underwent audiometric assessment. Following this, EEG electrodes were applied and volunteers were assessed with respect to the two experiments, during which they were instructed to view a silent, neutral emotive video and to ignore the presented auditory stimuli.

2.4 Task Stimuli

2.4.1 Experiment 1: Speech vs. Non-Speech Deviants

Replicating Kasai et al's (2002) methodology, volunteers were presented with auditory stimulus sequences (binaurally, through headphones) consisting of 1,080 standard stimuli and 120 deviant stimuli delivered in a pseudo-randomized order, with a minimum of three standard stimuli being presented between each deviant stimulus. Standard and deviant probabilities were 90% and 10% respectively, with inter-stimulus intervals (ISI) varying between 550-600 ms.

The stimulus sequences were presented in three separate conditions in a counterbalanced order using a Latin Square design. One condition was designed to elicit MMNs to pure tone (1000 Hz) duration deviants (standard: 100 ms, deviant: 50 ms). The second and third conditions used phonemes as stimuli, with one condition aiming to elicit MMNs in response to vowel duration (standard vowel: 'a' with 150 ms duration, deviant vowel: 'a' with 100 ms duration) while the other condition elicited MMNs in response to across-phoneme (vowel) change (standard vowel: 'a', 150 ms duration, deviant vowel: 'o', 150 ms duration). As with Kasai et al. (2002), the vowel stimuli were created by having a male speak the vowels into a studio microphone and then having them digitized,

according to Muller-Gass et al. (2001), using the Audacity program (22 kHz sampling rate, 11 kHz anti-aliasing filter, 12 dB/octave), and edited for duration effects. All stimuli were presented at an intensity of 70 dB sound pressure level (SPL), with 10 ms rise-decay times. Phonemes were delivered using a digital-to-analog sampling rate of 16 kHz. Spectral analysis of the phonemes showed them to display most of their power in the 100-3000 Hz range, with very little power above 4000 Hz. This was confirmed by Fast Fourier Transform (FFT) analysis, which showed most of the auditory energy to exist in the 100-3000 Hz range.

2.4.2 Experiment 2: Speech Deviants in Noise

MMN assessments were carried out in three background conditions: no noise (SL), wide-band white noise (WN) and traffic noise (TN). The CV stimuli used for eliciting MMNs was identical to those employed by Muller-Gass et al (2001). For each of the conditions, the stimuli 'ba' (standard) and 'da' (deviant) were presented in one block of 600 stimuli: 510 standards ($p = 0.85$) and 90 deviants ($p = 0.15$), with the blocks being presented in a counter-balanced order using a Latin Square design. Stimuli were presented with an ISI of 550-600 ms in a pseudo-randomized order such that a minimum of three standard stimuli were presented between each deviant stimulus. The CV stimuli were created by having a male speak into a studio microphone and then having the stimuli digitized using the Audacity program (22 kHz sampling rate, 11 kHz anti-aliasing filter, 12 dB/octave), and edited to 150 ms duration. Spectral analysis of the CV stimuli showed them to display most of their power in the 100-2000 Hz range, with very little power above 4000 Hz. This was confirmed by Fast Fourier Transform (FFT) analysis

which showed most of the auditory energy to exist in the 100-2000 Hz range in both CVs.

The WN and TN backgrounds were created within the hospital Audio-Visual department by digitizing from a pre-recorded sound effects audio tape and transferring ~12 min segments of each noise type to (CD) disc for subsequent playing in a CD player. Background noise was presented through external speakers and computer-presented CV stimuli (delivered using a digital-to-audio sampling rate of 16 kHz) were delivered binaurally through headphones, with the peak intensity of the CV signals being 10 dB (SPL) than the background noise intensity of 60dB (SPL). Therefore the signal-to-noise ratio (SNR) was +10 dB in the combined conditions.

2.5 Hallucination Ratings

Hallucination ratings in patients were assessed after both tone and vowel recordings in Experiment 1, and after each of the three noise-related readings in Experiment 2. Subjective ratings were carried out in a manner similar to that used by Margo et al (1981), requiring volunteers to assess hallucinations experienced during the recordings on 3 dimensions: 1) duration (0 = no AHs; 7 = continuous AHs); 2) loudness (0 = not audible; 7 = extremely loud); and 3) clarity (0 = unintelligible; 7 = very clear)

2.6 Behavioural Discrimination

Following MMN assessments, behavioural evaluation of perceptual discriminability of sound changes were carried out by presenting the same non-speech (tones) and speech (vowels, CVs) stimuli (with identical stimulus probabilities) used in

the ERP recordings, but in shorter auditory sequences (300 stimuli). Behavioural discrimination of tones and vowels were carried out in silent background conditions, and CV discrimination was carried out during silence and both noise (WN, TN) conditions in a randomized order. The behavioural discrimination task required volunteers to press a button each time they heard the deviant stimulus. Button presses occurring within 200-1000ms from deviant stimulus onsets were regarded as correct 'hits', and all other button presses were categorized as false positives (FP). Both hits and FPs were expressed as % values and subjected to analysis.

2.7 ERP Recording

MMNs (see Figure 2 for an example in a single participant) were extracted from EEG activity recorded with an electrode cap with $\text{Ag}^+/\text{Ag}^+-\text{Cl}^-$ ring electrodes at thirty-two scalp sites according to the 10-20 system of electrode placement, including three midline sites (frontal [F_z], central [C_z], parietal [P_z]), as well as four left hemisphere (frontal [F_3], fronto-central [FC_5], temporal [T_7], central-parietal [CP_5]) and four right hemisphere (frontal [F_4], fronto-central [FC_6], temporal [T_8], central-parietal [CP_6]) scalp sites (see appendix). Electrodes were also used to record left (LM) and right (RM) mastoid activity and electrodes were placed on the mid-forehead and nose to serve as ground and reference, respectively. Bipolar recordings of horizontal (HEOG) and vertical (VEOG) electro-oculogram activity were taken from supra-/sub-orbital and external canthi sites, respectively. All electrode impedances were kept below 5k Ω . Electrical activity was recorded using BrainVision Recorder software with an amplifier bandpass of

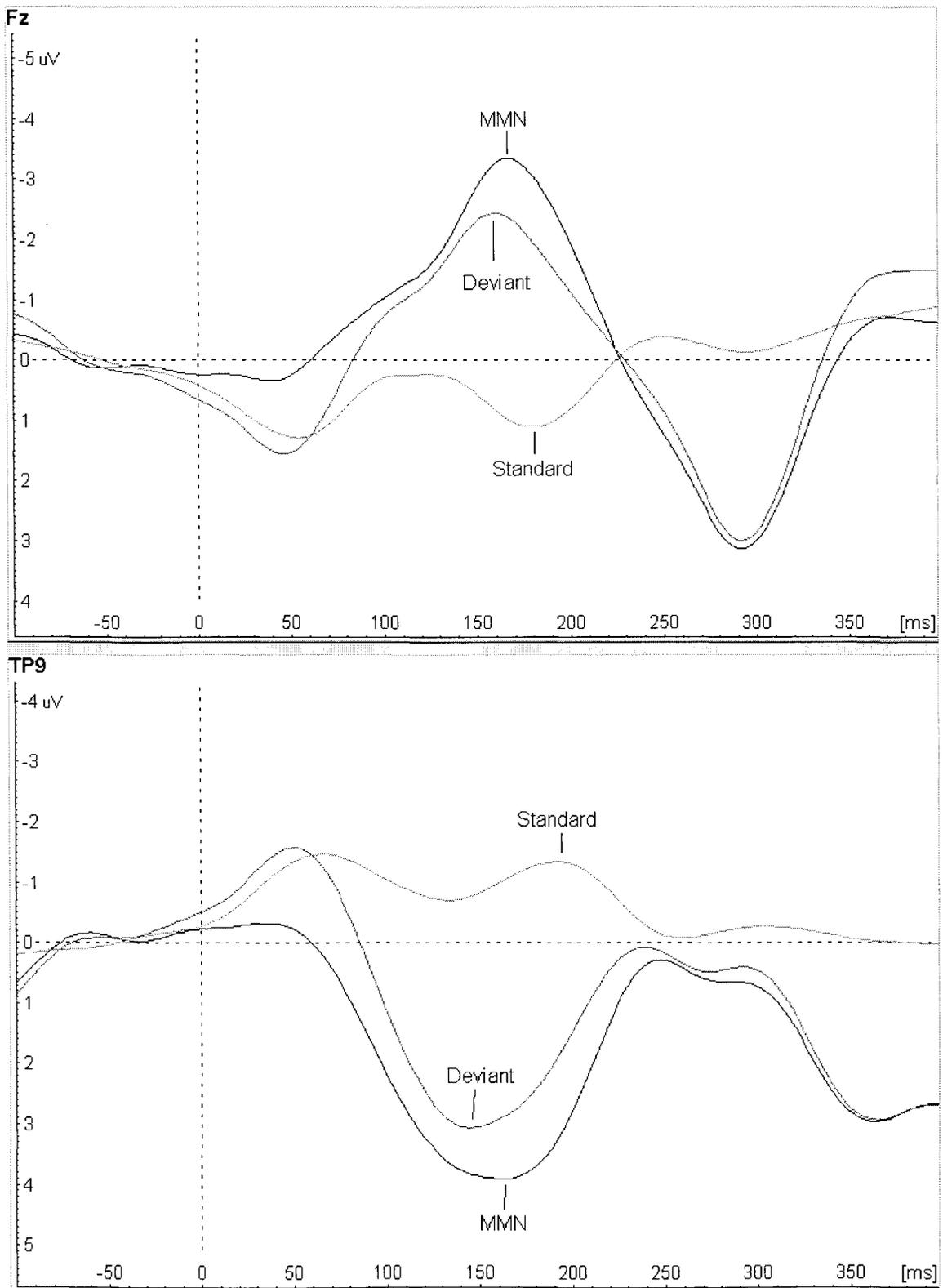


Figure 2. Example of MMN (with standard and deviant waveforms) in a single subject at frontal (F_z) and left mastoid (TP₉) sites.

0.1 and 30 Hz, digitized at 500 Hz, and stored on hard-disk for later off-line analysis using BrainVision Analyzer software.

Electrical epochs (500 ms duration, beginning 100 ms pre-stimulus) were corrected for residual eye movement and eye blink activity using the Gratton & Coles algorithm which operates in the time and frequency domain (Gratton, Coles & Donchin, 1983), and any corrected epochs with EEG voltages exceeding $\pm 100 \mu\text{V}$ were excluded from further analysis.

Within each of the MMN test paradigm conditions of the two experiments, epochs were separately averaged for each standard and deviant stimulus type and then digitally filtered using band pass 0.15-8 Hz (Leung et al., 2006) and a slope of 24 db/octave. For each site and condition, MMN difference waveforms were derived by point-by-point subtraction of the standard stimulus values from those elicited by the deviant stimulus, and MMNs were assessed by quantifying peak negative amplitudes within a window tailored for each individual paradigm, which was obtained by examining grand average waveforms. For Experiment 1, the windows used were: Pure Tone, 90-260ms; Phoneme Duration, 90-310ms; Across Phoneme, 80-250ms. Experiment 2 employed the same analysis window (80-310ms) across all three noise conditions. MMN peaks were then picked as the most negative point within each condition's respective analysis window and output was the average within five voltage points (2ms) to the left and right of the peak amplitude. MMN latency measurements were only measured at F_z , the site of maximum amplitude, and at the left mastoid site.

2.8 Data Analysis

Separate analyses were carried out for each of the two experiments using the Statistical Package for the Social Sciences (SPSS; SPSS Inc., Chicago, IL). For the first experiment (non-speech vs. speech deviants), MMN amplitudes were subjected to mixed univariate analysis of variance (ANOVA) procedures with one between group (3 levels: HC, HP, NP) and three within group factors (hemisphere [right and left], region [limited to the frontal (F), fronto-central (FC), temporal (T) and central-parietal (CP) regions] and stimulus condition [x3]). However, due to the orientation of the mismatch generator dipole, waveforms in regions anterior to the generator (F and FC) show a negative peak, while those posterior to the generator (T and CP) show a positive peak. To reduce confusion associated with the mixing of positive and negative values, analysis of MMN amplitudes were divided into three separate analyses: one with the anterior sites (F₃, FC₅, F₄, FC₆), one with the posterior sites (T₇, CP₅, T₈, CP₆) and one involving the two mastoids. For the second paradigm, (deviants in noise), MMN amplitudes were subjected to the same ANOVA procedures. Analysis of MMN latency and each behavioural (% hits, % FPs) and hallucination rating scale (duration, intensity, clarity) score were similar, but ANOVAs did not contain a site factor.

Where appropriate, Greenhouse-Geisser epsilon correction factors were applied to the degrees of freedom and the adjusted degrees of freedom have been reported. Regardless of the presence or absence of significant main or interaction effects planned comparisons involving between- and within-group comparisons with respect to deviant type, hemisphere, region and noise condition were carried out for hypothesis testing. Significant effects were followed-up with Bonferroni-adjusted pairwise comparisons.

Relationships of MMNs to hallucination ratings (PSYRATS scores) were examined with correlational (Pearson's r) statistics.

3. Results

3.1 Experiment 1

3.1.1 Hallucination Ratings

Table 2 shows the mean (\pm SE) hallucination ratings taken following each stimulus paradigm. Analysis showed that there were no group, condition or interaction effects with respect to the duration, loudness or clarity of the hallucinations experienced during stimuli presentation.

Table 2.

Mean (\pm SE) hallucination ratings across stimulus conditions in experiment 1.

AH Rating	Tasks		
	Pure Tone	Phoneme Duration	Across Phoneme
Duration	3.25 (0.64)	3.75 (0.71)	3.08 (0.67)
Loudness	2.17 (0.39)	2.58 (0.54)	1.83 (0.34)
Clarity	2.75 (0.76)	2.33 (0.59)	1.58 (0.40)

3.1.2 ERPs

The analysis of ERP amplitudes was divided into three separate analyses: one analysis involving MMN negative voltage amplitudes in the anterior (frontal [F₃, F₄] and fronto-central [FC₅, FC₆]) sites, one analysis involving inverse MMN positive voltage

amplitudes in the posterior (temporal [T₇, T₈] and central-parietal [CP₅, CP₆]) sites, and an analysis of MMNs at left and right mastoid sites.

3.1.2.1 Anterior MMNs

There was a main effect of stimulus condition, $F(1.9, 61.8) = 5.88, p < .01$, which, when followed up, showed MMN elicited by the across phoneme deviants ($M = -1.51 \mu\text{V}$, $SE = 0.14$) to be significantly larger (see Figure 3) than MMNs elicited by phoneme duration deviants ($M = -0.95 \mu\text{V}$, $SE = 0.10; p < .01$). A main effect of hemisphere, $F(1,33) = 7.71, p < .01$, showed MMN to be larger on the right ($M = -1.33 \mu\text{V}$, $SE = 0.11$) compared to the left hemisphere ($M = -1.08 \mu\text{V}$, $SE = 0.09$). There was a further main effect of cerebral region, $F(1, 33) = 59.86, p < .01$, with MMN amplitude at the frontal sites ($M = -1.51 \mu\text{V}$, $SE = 0.11$) being greater than at the fronto-central sites ($M = -0.90 \mu\text{V}$, $SE = 0.08$).

There were no significant group differences or interaction effects in the original analyses, but planned comparisons examining between and within group effects with respect to the three stimulus conditions revealed, as shown in Figure 4, that the HC group exhibited significantly ($p < .02$) greater MMN amplitudes resulting from the across-phoneme deviants ($M = -1.72 \mu\text{V}$, $SE = 0.24$) compared to the phoneme duration deviants ($M = -1.04 \mu\text{V}$, $SE = 0.18$) but not to the pure tone deviants ($M = -1.49 \mu\text{V}$, $SE = 0.24$). This finding was mirrored ($p < .05$) in the NP group, where MMN amplitudes to across-phoneme deviants were significantly larger ($M = -1.44 \mu\text{V}$, $SE = 0.24$) compared to those elicited by the phoneme duration deviants ($M = -0.89 \mu\text{V}$, $SE = 0.18$), but not to the pure tone deviants ($M = -0.90 \mu\text{V}$, $SE = 0.24$). No

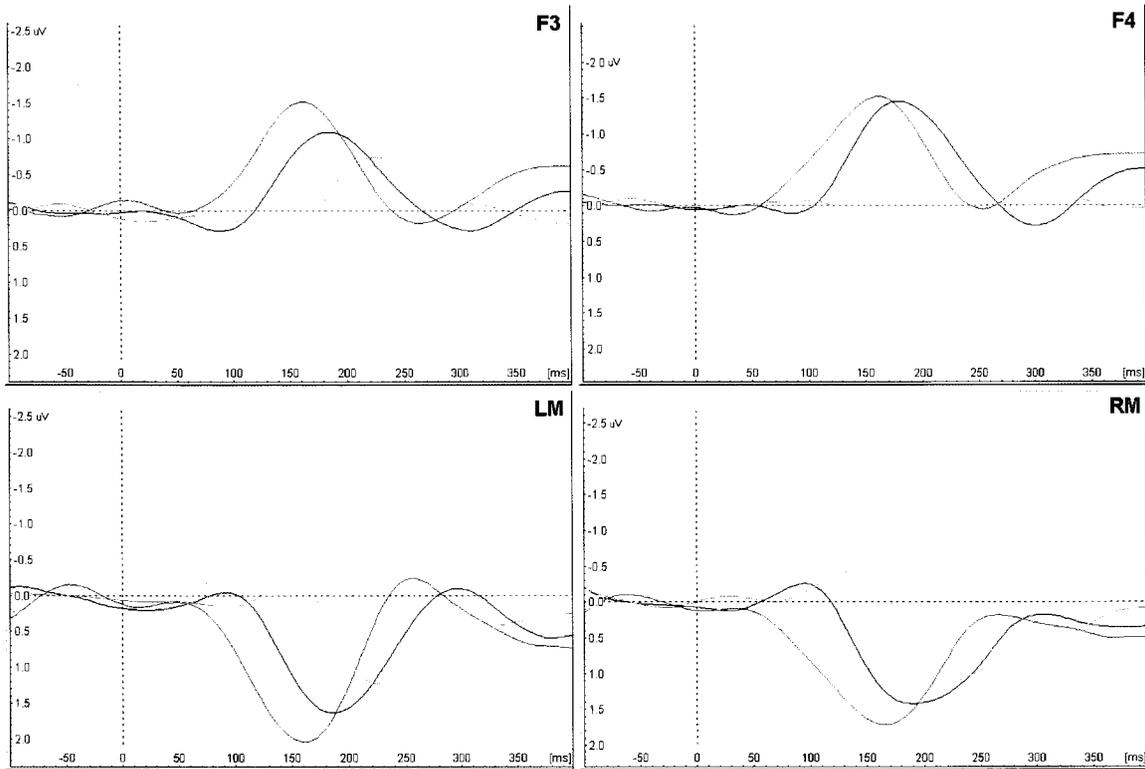


Figure 3. MMNs to across phoneme (red), pure tone (black) and phoneme duration (green) deviants at frontal (F₃, F₄) as well as right (RM) and left (LM) mastoids.

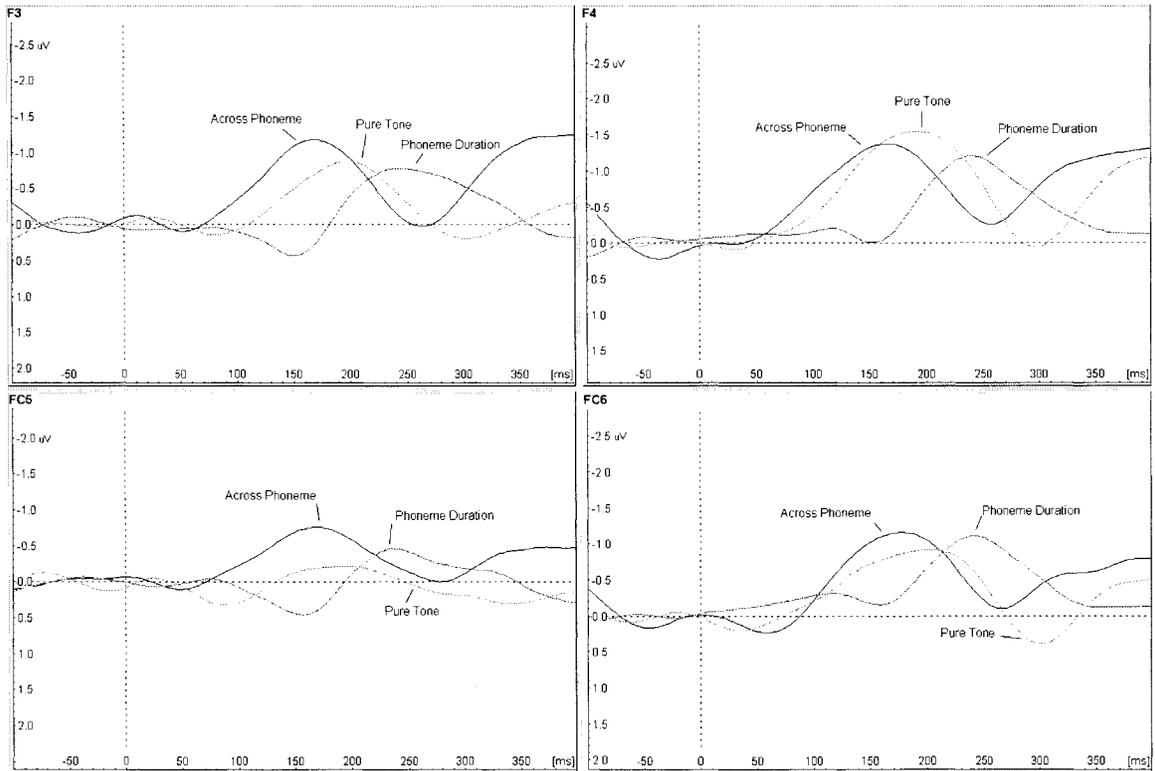


Figure 4a. Anterior MMNs to all stimulus conditions in hallucinating patients.

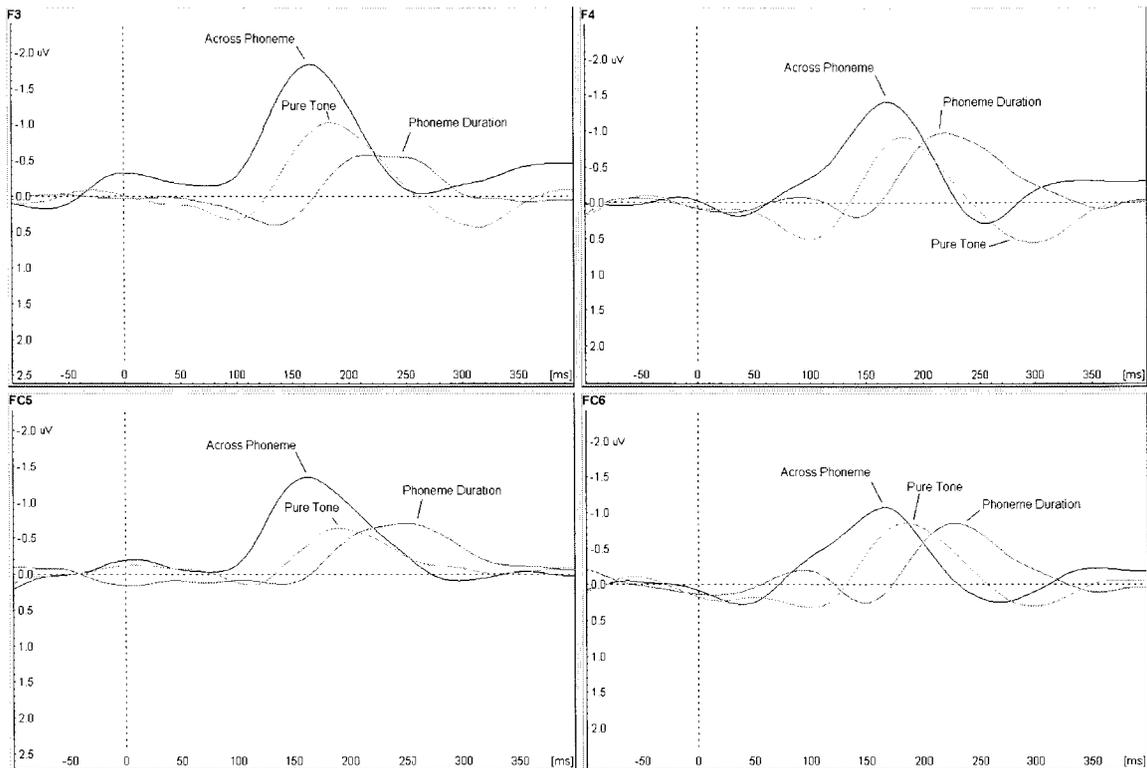


Figure 4b. Anterior MMNs to all stimulus conditions in non-hallucinating patients.

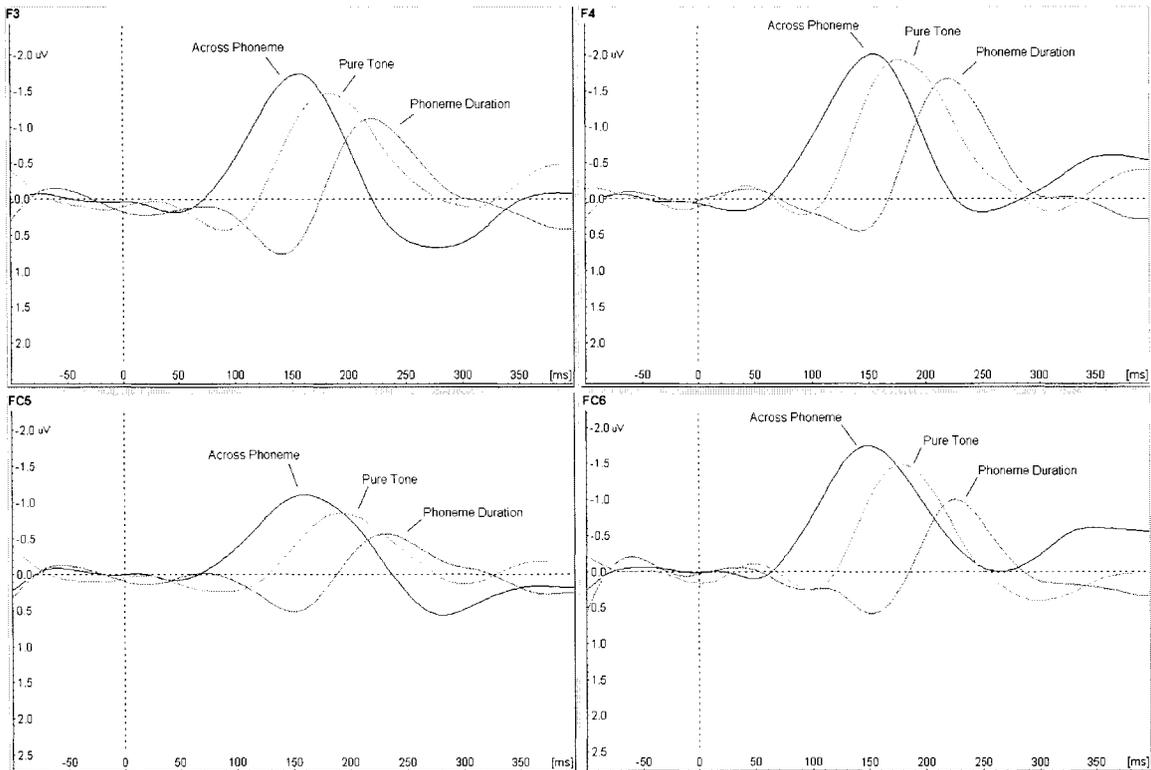


Figure 4c. Anterior MMNs to all stimulus conditions in healthy controls.

significant difference in MMN amplitude was observed across the three different stimulus conditions in the HP group.

Planned comparisons attempting to localize the across-phoneme effect found, as shown in Figure 5, larger across-phoneme deviants (vs. phoneme duration deviants) to be lateralized to the left frontal (F_3) region in HC and NP groups and to be bilateral at fronto-central regions in the HC group. No hemispheric asymmetries were evident in the HP group.

3.1.2.2 Posterior MMNs

Analysis revealed a main effect of group, $F(2,33) = 4.58, p < .02$, which, when followed up, showed that amplitudes in HCs ($M = 0.70 \mu\text{V}$, $SE = .09$) were larger than those in NPs ($M = 0.32 \mu\text{V}$, $SE = .09$). Also shown was a hemisphere effect, $F(1, 33) = 4.02, p < .05$, resulting from significantly larger positive amplitudes on the left hemisphere ($M = 0.63 \mu\text{V}$, $SE = .08$) than the right hemisphere ($M = .413$, $SE = .071$) and a main effect of region, $F(1,33) = 9.90, p < .01$, due to larger overall amplitudes in the temporal region ($M = 0.70 \mu\text{V}$, $SE = 0.08$) compared to the central-parietal region ($M = 0.35 \mu\text{V}$, $SE = 0.07$).

Follow-up analysis of a significant region-by-group interaction, $F(2, 33) = 3.31, p < .05$, showed that the HC group exhibited a significant difference between MMN amplitudes at temporal ($M = 1.06 \mu\text{V}$, $SE = .14$) and central-parietal ($M = 0.34 \mu\text{V}$, $SE = 0.12; p < .01$) regions, which was not observed in either of the patient groups. This

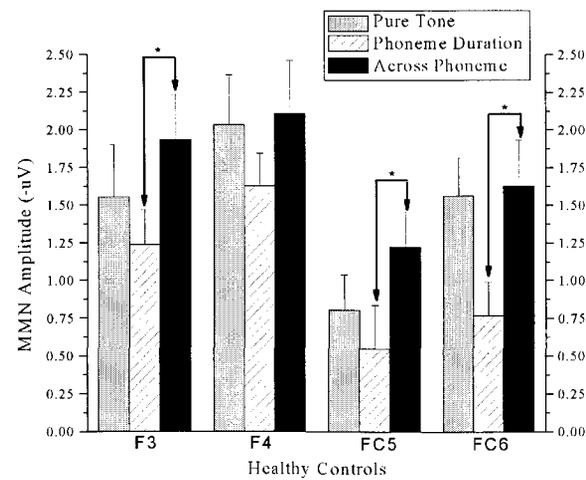
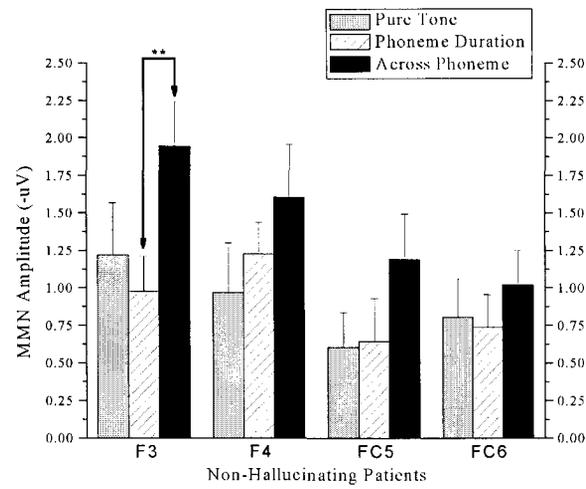
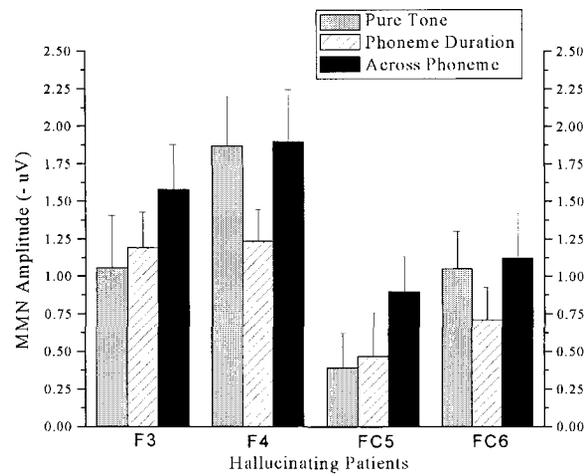


Figure 5. Effect of stimulus condition (\pm SE) across groups at all anterior recording sites.
 * $p < .05$, ** $p < .01$

effect is bilateral in the HC group, with significant differences being observed between the left ($p < .01$) temporal ($M = 1.29 \mu\text{V}$, $SE = 0.20$) and central-parietal ($M = 0.49 \mu\text{V}$, $SE = .14$) regions as well as between the right ($p < .02$) temporal ($M = 0.83 \mu\text{V}$, $SE = 0.18$) and central-parietal ($M = 0.19 \mu\text{V}$, $SE = 0.16$) regions.

Planned comparison of the interaction between the stimulus conditions and groups showed that the HC group ($M = 0.89 \mu\text{V}$, $SE = 0.13$) was significantly different ($p < .02$) than the HP group ($M = 0.48 \mu\text{V}$, $SE = 0.16$) as well as significantly different ($p < .01$) than the NP group ($M = 0.25 \mu\text{V}$, $SE = 0.13$) in their response to the phoneme duration stimuli. Furthermore, with the phoneme duration deviants, the HC group exhibited significantly larger amplitudes ($M = 1.26 \mu\text{V}$, $SE = .23$) than both the HP ($M = 0.59 \mu\text{V}$, $SE = 0.23$; $p < .05$) and NP ($M = 0.13 \mu\text{V}$, $SE = 0.23$; $p < .01$) groups at the temporal region, bilaterally.

Planned within-group comparisons showed HPs to exhibit larger amplitudes to the across phoneme deviants ($M = 0.74 \mu\text{V}$, $SE = 0.15$) than to the phoneme duration deviants ($M = 0.41 \mu\text{V}$, $SE = 0.13$; $p < .05$). Conversely, the HC group had larger amplitudes in response to the phoneme duration deviants ($M = 0.89 \mu\text{V}$, $SE = 0.13$) than in response to the across phoneme deviants ($M = 0.56 \mu\text{V}$, $SE = 0.15$; $p < .05$). Further analysis, as shown in Figure 6, showed that in the HP group, the finding of larger amplitudes to the across phoneme deviants versus the phoneme duration deviants was limited to the left hemisphere ($p < .02$) and, more specifically, the left temporal region (T_7 ; $p < .04$). This same analysis found the HC group exhibited larger amplitudes to the phoneme duration deviants than to the pure tone ($p < .03$) or across phoneme deviants ($p < .027$) in the right hemisphere, and, when limited to the right temporal region, displayed

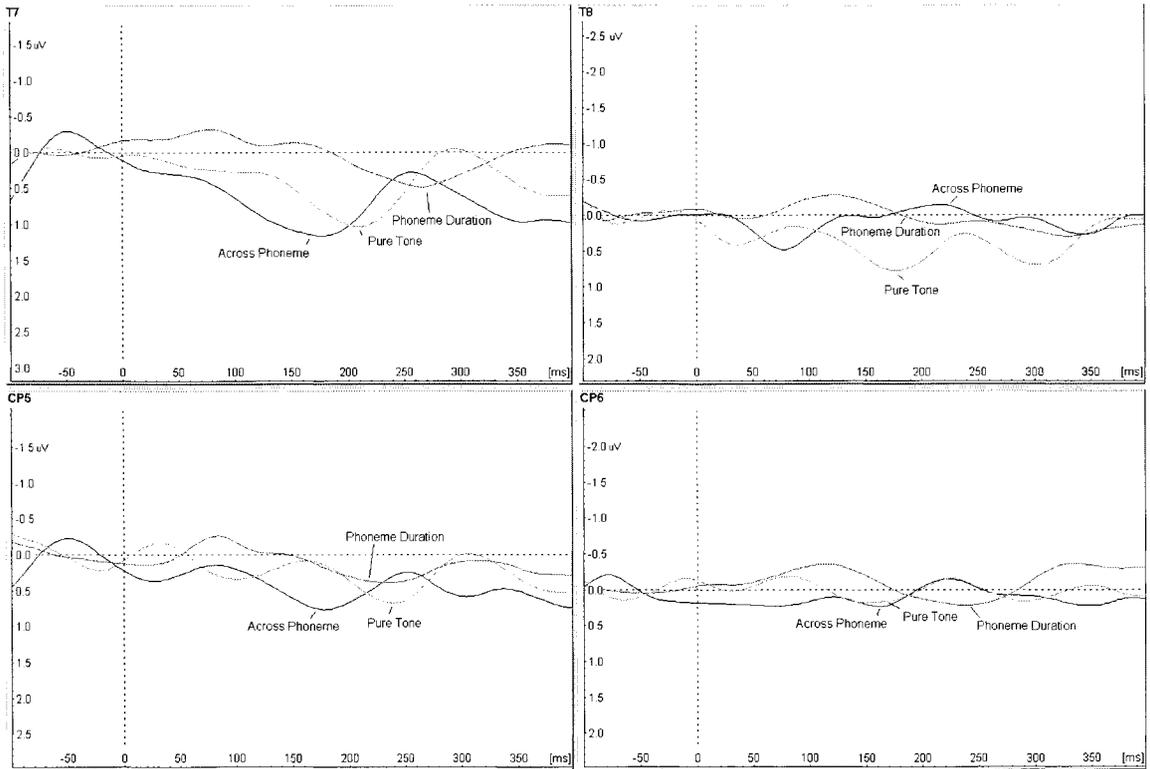


Figure 6a. Posterior MMNs to all stimulus conditions in hallucinating patients.

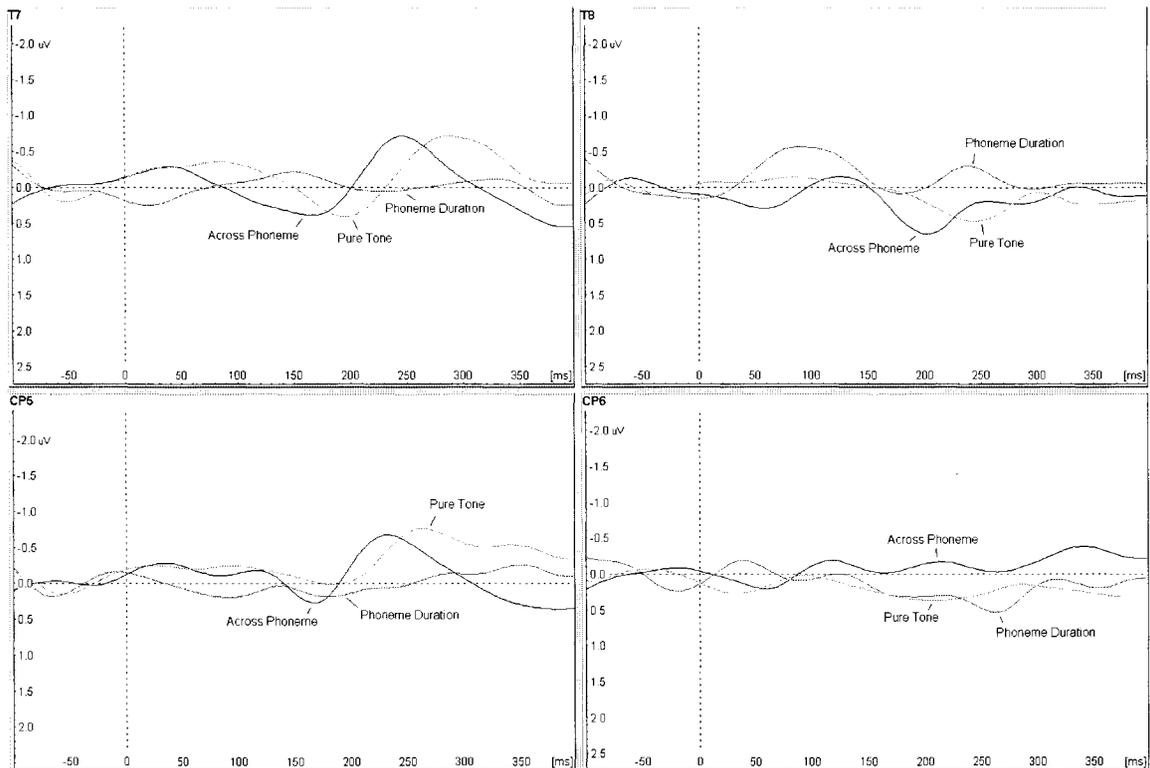


Figure 6b. Posterior MMNs to all stimulus conditions in non-hallucinating patients.

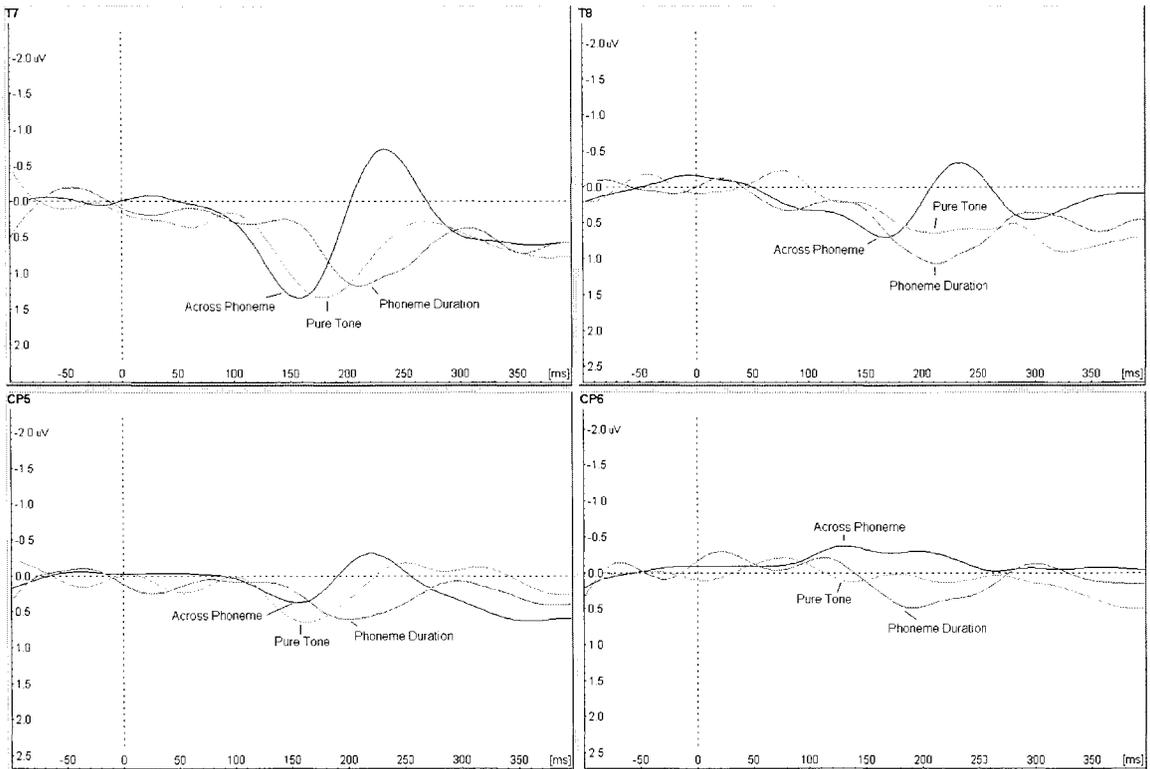


Figure 6c. Posterior MMNs to all stimulus conditions in healthy controls.

larger amplitudes to phoneme duration deviants than to pure tone deviants ($p < .02$).

3.1.2.3 Mastoid MMNs

Main effects of stimulus condition, $F(1.856, 61.261) = 5.76, p < .01$, and hemisphere, $F(1, 33) = 9.07, p < .01$, were observed in the analysis of mastoid MMNs, the latter showing that amplitudes at the left mastoid ($M = 2.00 \mu\text{V}, SE = 0.15$) were significantly larger than those at the right mastoid ($M = 1.59 \mu\text{V}, SE = 0.15$). The former shows that the amplitudes of across-phoneme deviants ($M = 2.28 \mu\text{V}, SE = 0.24$) are significantly larger than those of pure tone deviants ($M = 1.62 \mu\text{V}, SE = 0.20; p < .03$) and phoneme duration deviants ($M = 1.48 \mu\text{V}, SE = 0.15; p < .01$). No additional effects were observed with planned comparisons.

3.1.2.4 F_z Latency

MMN latency, taken at site F_z, differed significantly across the three stimulus conditions, $F(1.83, 60.43) = 62.78, p < .01$. Follow-up analysis revealed that each of the individual latencies, shown in Figure 6, differed significantly from one another ($p < .01$) with across-phoneme deviants producing the shortest latencies and phoneme duration deviants resulting in the longest latencies.

3.1.2.5 Mastoid Latency

Mastoid MMN latency also differed significantly across the three stimulus conditions, $F(1.46, 43.04) = 53.61, p < .01$, in a manner similar to that seen with F_z latencies (Figure 7).

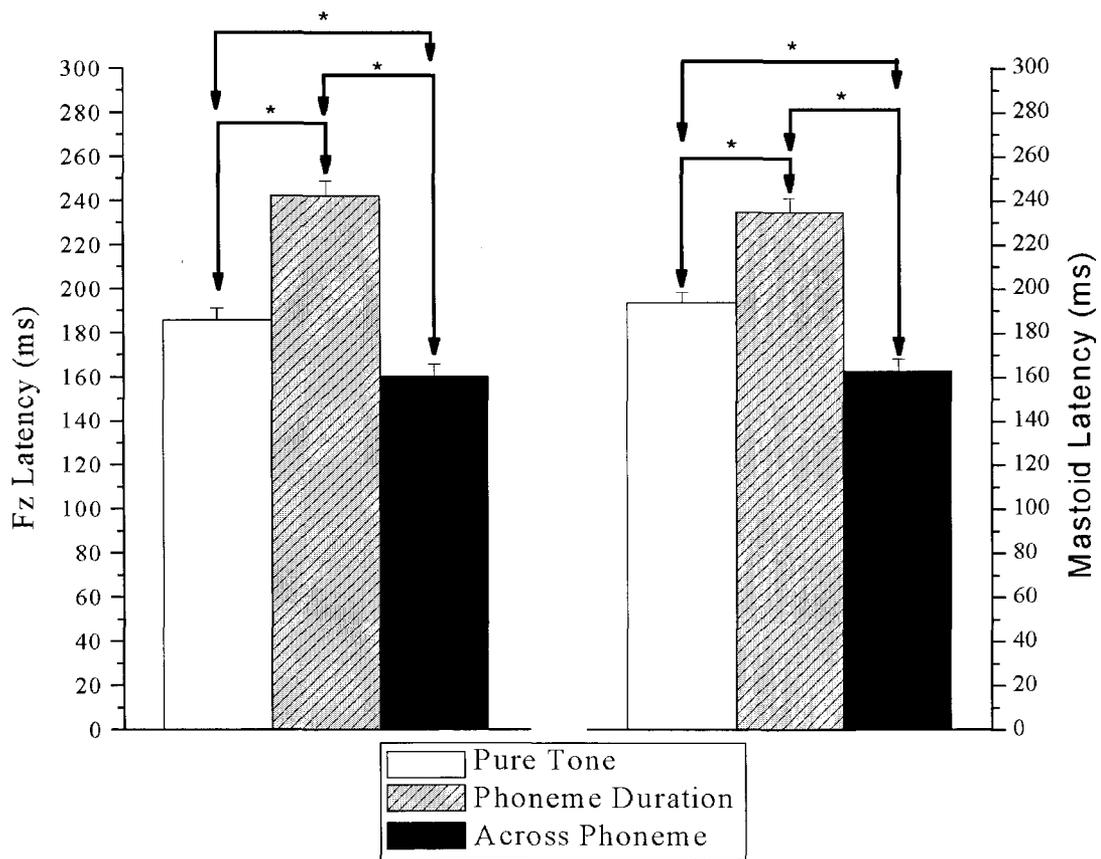


Figure 7. F_z and mastoid MMN latencies (\pm SE) to stimulus conditions collapsed across groups. * $p < .05$

3.1.3 Correlations

Bivariate correlations (Pearson's r) examining MMN and hallucination rating relationships were restricted to MMNs derived from frontal (F_3, F_z, F_4) sites, the region of maximal MMN amplitude. One-tailed significance levels were employed due to the unidirectional nature of our hypothesis regarding these relationships: increases in the ratings will be associated with decreases of MMN amplitude. The results of this analysis showed the perceived clarity of AHs, but not the duration or loudness of AHs, to be negatively correlated with phoneme duration ($r = -.64, p < .02$) and across-phoneme deviant ($r = -.56, p < .03$) MMN amplitudes at F_z .

3.1.4 Behavioural Discrimination

In general, discrimination accuracy of deviants vs. standards was relatively high, ranging between 82-99% correct (Table 3). Analysis of the percentage of correct responses showed significant effects of stimulus condition, $F(1.58, 52.14) = 37.05, p < .01$, group, $F(2, 33) = 4.94, p < .02$, and a significant stimulus-by-group interaction $F(3.16, 52.14) = 5.84, p < .01$. A follow-up of the main stimulus effect revealed that the percent of correct detections in the pure tone condition was significantly different than in the phoneme duration ($p < .03$) and the across phoneme condition ($p < .01$). Furthermore, the across phoneme condition had a significantly higher percentage of correct responses than the phoneme duration condition ($p < .01$).

Table 3.

Mean (\pm SE) behavioural discrimination percentages across stimulus conditions in experiment 1.

Group	Tasks		
	Pure Tone	Phoneme Duration	Across Phoneme
	% Correct		
HP	91.10 (2.10)	82.70 (2.70)	99.40 (0.40)
NP	86.10 (2.10)	87.40 (2.70)	98.40 (0.40)
HC	95.50 (2.10)	95.40 (2.70)	99.40 (0.40)
	% False Positives		
HP	2.65 (0.65)	1.11 (0.94)	0.62 (0.13)
NP	1.14 (0.65)	2.25 (0.94)	0.68 (0.13)
HC	0.43 (0.65)	0.31 (0.94)	0.09 (0.13)

Further inspection of the difference between groups found the HCs to exhibit significantly more correct responses than either the HP group ($p < .02$) or the NP group ($p < .01$). There was no difference between the two patient groups. Within the stimulus-by-group interaction, in the pure tone condition, the HC group had a significantly higher percentage of correct detections ($p < .01$) than the NP group. Within the phoneme duration condition, the HC group showed a higher percent correct than both the HP ($p < .01$) and the NP group ($p < .05$). Furthermore, while the HP group showed significant differences between the pure tone, phoneme duration and across phoneme conditions (all $p < .01$), and the NP group exhibited differences between the across phoneme and both the pure tone ($p < .01$) and phoneme duration ($p < .01$) conditions, the HC group showed no significant differences in correct detections across any of the conditions.

Analysis of false positive responses (Table 3) revealed no significant effects of either stimulus type or group, nor did it show a significant stimulus-by-group effect.

3.2 Experiment 2

Initial analysis of experiment 2 included all participants, despite the fact that not all participants within each group exhibited recognizable MMN components.

3.2.1 Hallucination Ratings

Group means (\pm SE) for the hallucination ratings (duration, loudness, clarity) taken following each stimulus condition are shown in Table 4. There were no differences between the 3 noise conditions with regards to the duration, loudness, or clarity of the hallucinations.

Table 4.

Mean (\pm SE) hallucination ratings across noise conditions in experiment 2.

AH Rating	Noise		
	Silence	Traffic Noise	White Noise
Duration	2.08 (0.57)	2.83 (0.61)	2.50 (0.57)
Loudness	1.50 (0.29)	1.75 (0.30)	1.91 (0.45)
Clarity	1.75 (0.54)	1.83 (0.40)	2.08 (0.54)

3.2.2 ERPs

Similar to the analysis of ERPs for experiment 1, the analysis of ERPs for this experiment (silence vs. noise conditions) was divided into three separate analyses: one analysis involving MMN amplitudes in the anterior (frontal [F₃, F₄] and fronto-central [FC₅, FC₆]) sites, one analysis involving inverse positive MMN amplitudes (positive deflections) in the posterior (temporal [T₇, T₈] and central-parietal [CP₅, CP₆]) sites, and an analysis of MMN amplitude in the left and right mastoids.

3.2.2.1 Anterior MMNs

Analysis revealed a main effect of region, $F(1, 33) = 73.14, p < .01$, whereby the frontal region exhibited larger amplitudes ($M = -0.91 \mu\text{V}, SE = 0.13$) than the fronto-central region ($M = -0.35 \mu\text{V}, SE = 0.11$). None of the other main effects or interactions achieved significance, however the group-by-hemisphere-by-region interaction did approach significance, $F(2, 33) = 3.14, p < .06$. Follow-up of this interaction again showed that for all three groups, the MMN amplitude in the frontal region was larger than that in the fronto-central region, bilaterally.

Planned comparisons did not evidence any significant between- or within-group effects with respect to condition or hemisphere. Only expected regional differences (frontal > fronto-central) were consistently observed.

3.2.2.2 Posterior MMNs

No significant main or interaction effects were observed with ANOVAs. There were no other main or interaction effects and, with the exception of regional differences

(temporal > central-parietal), no significant findings were observed with any of the planned comparisons.

3.2.2.3 Mastoid MMNs

Analysis of the mastoid data revealed a significant effect of hemisphere, $F(1, 33) = 51.80, p < .01$, with amplitudes in the left hemisphere ($M = 1.49 \mu\text{V}$, $SE = 0.12$) being greater than those in the right ($M = 0.87 \mu\text{V}$, $SE = 0.13$).

3.2.2.4 F_z Latency

MMN latency, taken at site F_z , differed significantly across the three noise conditions, $F(2, 66) = 4.99, p < .01$. Follow-up analysis revealed longer latencies during the traffic noise condition ($M = 231.22$ ms, $SE = 10.98$) compared to the silence condition ($M = 187.28$ ms, $SE = 12.26; p < .01$) and the white noise condition ($M = 193.61$ ms, $SE = 10.95; p < .02$).

As illustrated in Figure 8, planned comparisons showed HPs to have significantly prolonged latencies to the traffic noise condition ($M = 235.50$ ms, $SE = 19.03$) compared to the silence condition ($M = 166.83$ ms, $SE = 21.24; p < .02$) and the white noise condition ($M = 176.67$ ms, $SE = 18.97; p < .04$). Neither the HC nor the NP group showed any significant differences in latencies across the three background noise conditions.

3.2.2.5 Mastoid Latency

There were no significant main or interaction effects, nor were there any significant findings with planned comparisons.

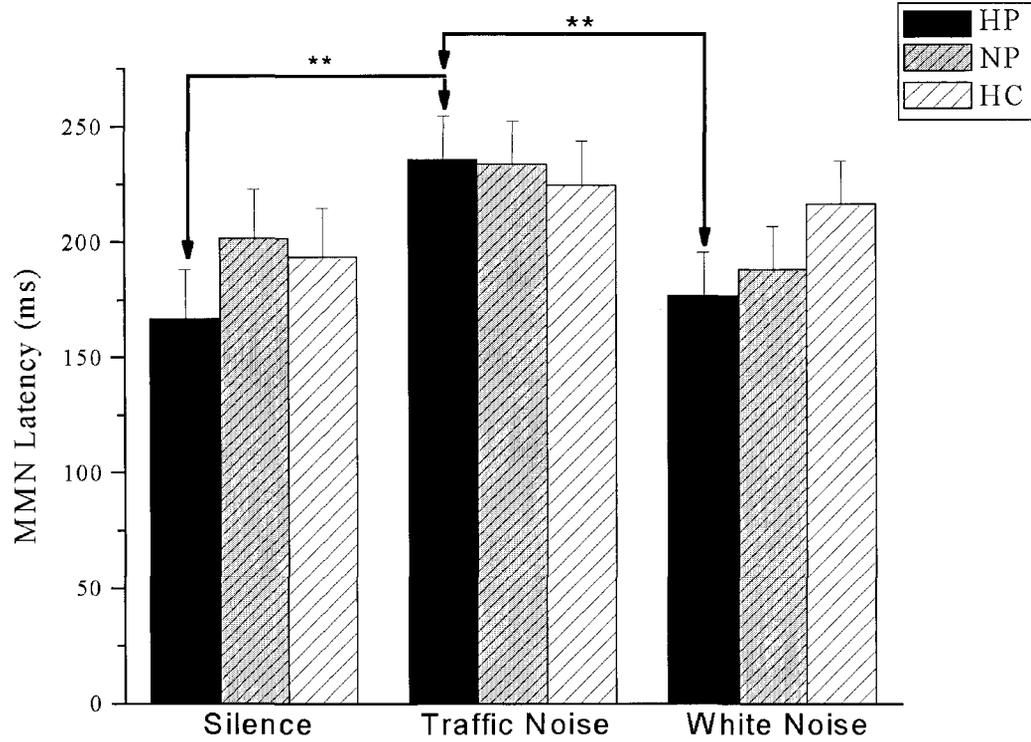


Figure 8. F_z MMN latencies (\pm SE) in noise conditions collapsed across groups. ** $p < .01$

3.2.3 Correlations

There were no significant correlations observed between frontal MMN amplitude or latency and any of the three auditory hallucination ratings associated with the three noise conditions.

3.2.4 Behavioural Discrimination

Table 5 displays the mean (\pm SE) correct detections for the groups in the different noise conditions. There was no difference between the groups or noise conditions with regards to either percentage of correct detections, $F(2, 66) = 1.10, p < .34$, or false positives, $F(2, 66) = 0.42, p < .57$.

Table 5.

Mean (\pm SE) behavioural discrimination percentages across noise conditions in experiment 2.

Group	Noise		
	Silence	Traffic Noise	White Noise
	% Correct		
HP	88.60 (3.70)	90.40 (2.40)	95.00 (2.70)
NP	92.80 (3.70)	88.40 (2.40)	92.10 (2.70)
HC	99.10 (3.70)	96.40 (2.40)	96.60 (2.70)
	% False Positives		
HP	0.52 (3.88)	1.67 (2.20)	0.95 (4.21)
NP	9.25 (3.88)	1.31 (2.20)	8.99 (4.21)
HC	0.49 (3.88)	4.31 (2.20)	3.53 (4.21)

3.3 Experiment 2 Post-Hoc Analysis

Due to the fact that some participants in each group did not appear to exhibit a clear MMN (i.e. MMN was less than zero μV at F_z , failed to invert at mastoids, and/or its peak latency extended beyond 250 ms, even within the silence condition, see Figure 9) it was decided to perform a post-hoc analysis of the data while only including those exhibiting a clear MMN in the silence condition. Only participants with a peak F_z negative voltage of at least $-0.25 \mu\text{V}$ between 80-250 ms in the silence condition (and which showed inversion at mastoids) were included. Each waveform was visually inspected to ensure that a clear MMN at F_z (and mastoids) was present and met revised criteria. Under these conservative criteria, ERP analysis proceeded with the data from 7 HC participants, 8 HP participants and 8 NP participants. Analyses of MMNs proceeded identically to those used for the full ($n=12$) groups.

3.3.1 Anterior MMNs

Analysis revealed a significant effect of region, $F(1, 20) = 45.18, p < .01$) where the frontal region ($M = -1.10 \mu\text{V}$, $SE = 0.17$) exhibited larger amplitudes than the fronto-central region ($M = -0.52 \mu\text{V}$, $SE = 0.13$). As shown in Figure 10, planned comparisons of the relationship between noise condition and group showed HPs to have significantly ($p < .01$) smaller MMNs during the white noise condition ($M = -0.56 \mu\text{V}$, $SE = 0.33$) compared to the silent condition ($M = -1.44 \mu\text{V}$, $SE = 0.23$). Neither of the other two groups exhibited a significant difference between any of the noise conditions. When followed-up with respect to hemisphere, it was shown that this effect in HPs was bilateral as hallucinating patients had smaller amplitudes to the white noise condition

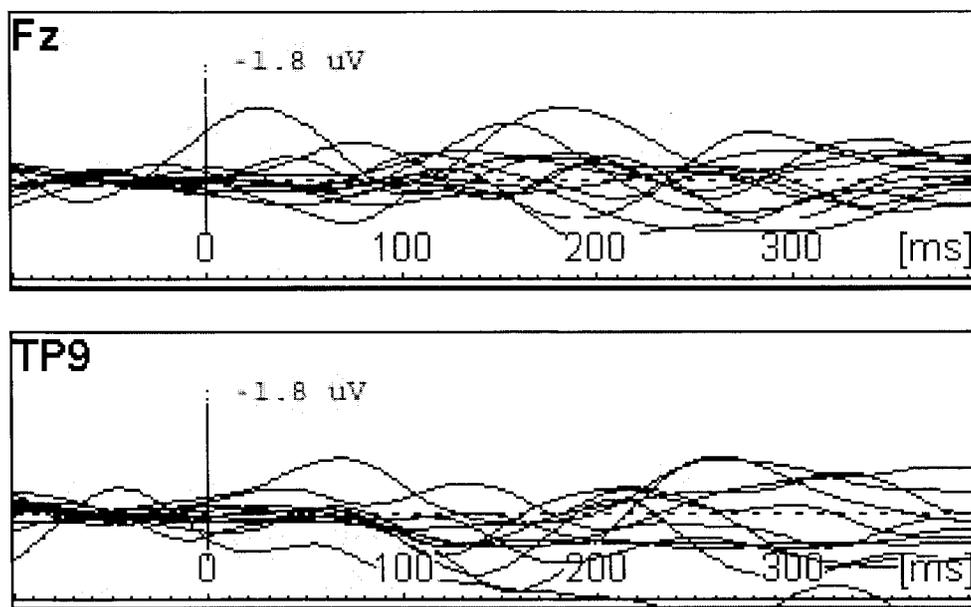


Figure 9. Frontal (F_z) and left mastoid (TP₉) MMN waveforms for each of the 12 participants in the HC group during the silent noise condition.

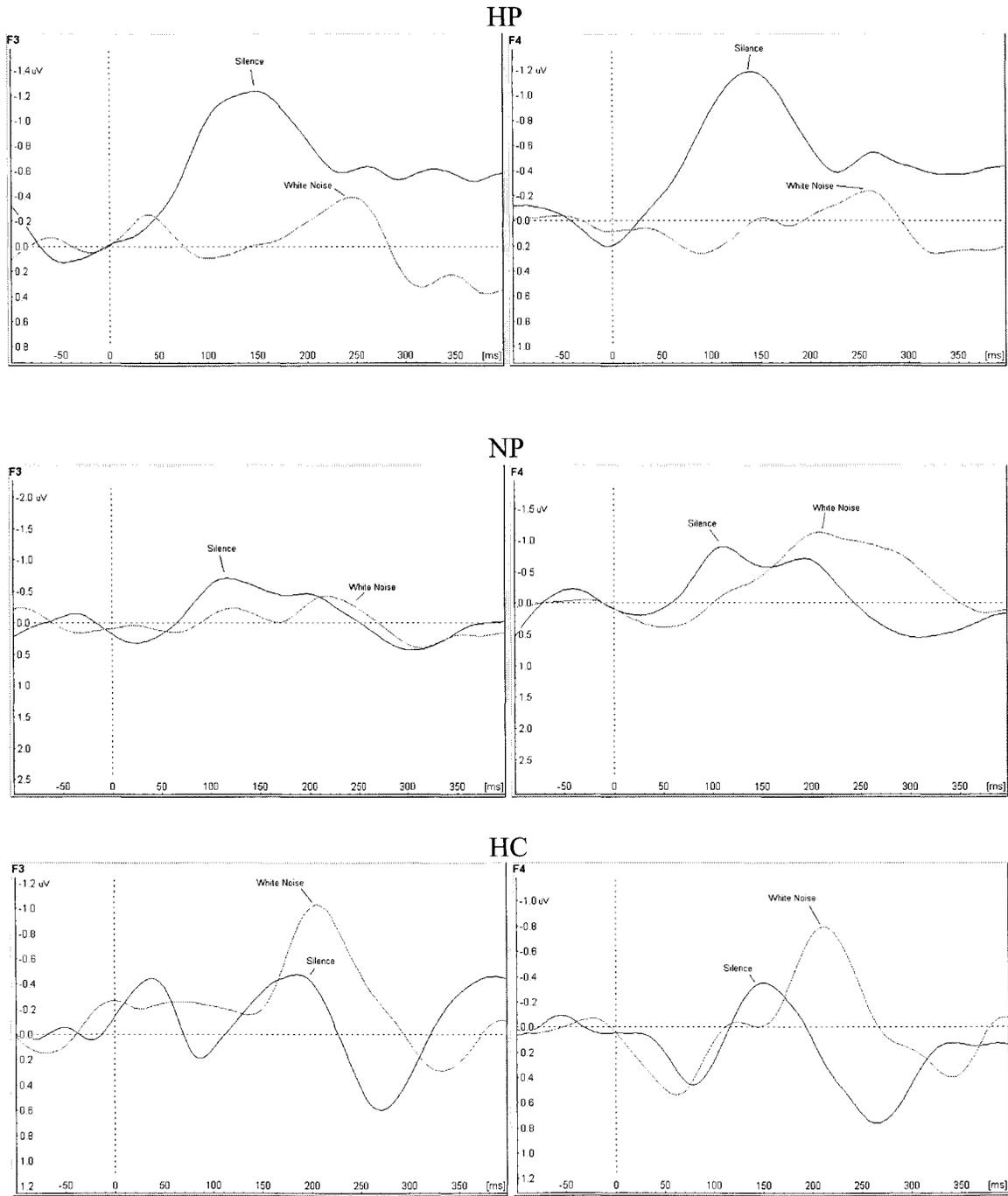


Figure 10. MMN waveforms to silence and white noise conditions in each group.

($M = -0.51 \mu\text{V}$, $SE = 0.34$) than to the silence condition ($M = -1.49 \mu\text{V}$, $SE = 0.23$) in the left hemisphere ($p < .02$), and smaller amplitudes to the white noise condition ($M = -0.60 \mu\text{V}$, $SE = 0.40$) than to the silence condition ($M = -1.39 \mu\text{V}$, $SE = 0.29$) in the right hemisphere ($p < .04$). With respect to hemispheric region, HP amplitudes at site F_3 were shown to be smaller ($p < .01$) during the white noise condition ($M = -0.70 \mu\text{V}$, $SE = 0.37$) than during the silence condition ($M = -1.81 \mu\text{V}$, $SE = 0.27$); this is also seen at site F_4 within the HP group, where amplitudes within the white noise condition ($M = -0.69 \mu\text{V}$, $SE = 0.48$) were smaller ($p < .04$) than those in the silence condition ($M = -1.71 \mu\text{V}$, $SE = 0.37$). In contrast, the NP group showed larger ($p < .04$) amplitudes during the white noise condition ($M = -0.74 \mu\text{V}$, $SE = 0.36$) than during the silence condition ($M = 0.01 \mu\text{V}$, $SE = 0.26$), and only at the FC_6 site.

3.3.2 Posterior MMNs

There were no main effects of noise type, $F(1.86, 37.22) = 0.14$, $p < .88$, or group, $F(2, 20) = 0.61$, $p < .56$. Overall, there were no significant main or interaction effects, nor were there any significant findings with planned comparisons.

3.3.3 Mastoid MMNs

There was a main effect of hemisphere, $F(1, 20) = 27.34$, $p < .01$, due to overall larger amplitudes in the left hemisphere ($M = 1.54 \mu\text{V}$, $SE = 0.15$) than in the right hemisphere ($M = 0.95 \mu\text{V}$, $SE = 0.13$).

3.3.4 F_z Latency

MMN latency showed a main effect of noise type, $F(2, 40) = 14.09, p < .01$.

Follow-up analysis revealed shorter latencies during the silence condition ($M = 154.04$ ms, $SE = 9.73$) compared to the traffic noise condition ($M = 230.24$ ms, $SE = 12.37; p < .01$) and the white noise condition ($M = 197.45$ ms, $SE = 12.34; p < .01$).

Figure 11 shows the MMN latencies in each group within each noise condition. Planned comparisons showed HPs to have significantly prolonged latencies to the traffic noise condition ($M = 240.50$ ms, $SE = 20.94$) compared to the silence condition ($M = 139.50$ ms, $SE = 16.46; p < .01$) and the white noise condition ($M = 176.25$ ms, $SE = 20.88; p < .03$). The NP group had longer latencies for the traffic noise condition ($M = 242.50$ ms, $SE = 20.94$) than for the silence condition ($M = 163.75$ ms, $SE = 16.46; p < .01$). HC participants exhibited larger latencies to the white noise condition ($M = 214.86$ ms, $SE = 22.32$) than to the silence condition ($M = 158.86$ ms, $SE = 17.60; p < .04$).

3.3.5 Mastoid Latency

There were no main effects with mastoid latency. Planned comparisons of noise type and group showed that within the white noise condition, the HP group ($M = 245.25$ ms, $SE = 19.83$) exhibited a longer latency ($p < .02$) than the NP group ($M = 169.50$ ms, $SE = 19.83$).

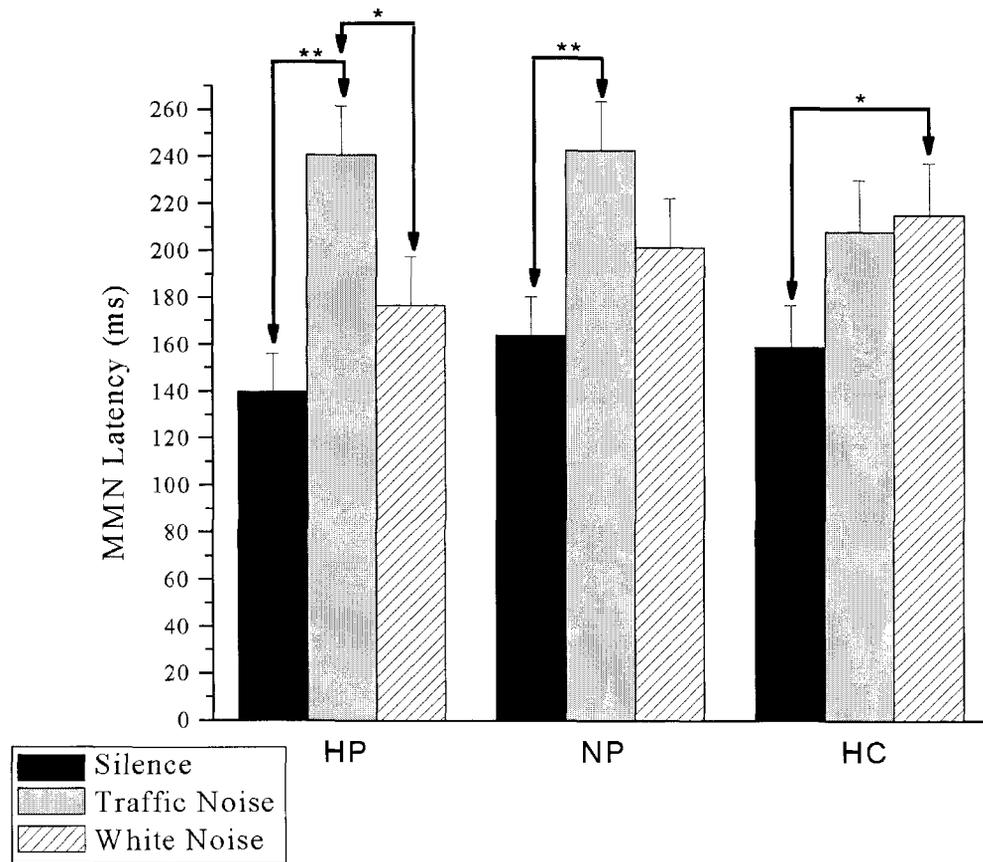


Figure 11. MMN latencies at $F_z (\pm SE)$ for in all three noise conditions. * $p < .05$; ** $p < .01$

3.3.6 Correlations

There was a significant correlation between MMN latency and hallucinatory duration in the white noise condition ($r = .725, p < .03$), indicating that MMN latency increases are associated with increases in the duration of hallucinations.

4. Discussion

Given prior neuroimaging research of schizophrenic patients with AHs showing dysfunctional processing of external speech in the auditory centers, presumably related to usurpation of resources directed at the processing of internal speech, this current study furthered the probing of auditory cortex involvement in AHs by utilizing MMN to assess the pre-attentive neural response to speech and non-speech stimuli and the moderating effects of speech competitors. Although no differences of between group MMNs were observed, differential responding to speech and non-speech stimuli and to noise manipulations by hallucinating patients offered important insight into the mechanisms underlying AHs in schizophrenia.

4.1 Experiment 1

The fact that no significant between-group differences were observed with regards to the different stimulus conditions may suggest that the presence or absence of auditory hallucinations has no effect on the brain's overall ability to pre-consciously detect auditory change in the environment. However, correlational analyses between MMNs and AH ratings, indicating that reductions in frontal MMN amplitude are associated with increases in clarity of AHs, suggest that this is not the case and that there is indeed some relationship between AHs and preconscious auditory stimulus detection. Indeed, these latter relationships buttress findings of two previous reports showing an association between pre-attentive processing and AHs, with MMNs in left frontal/temporal sites being negatively correlated with AH ratings (Hirayasu et al., 1998; Youn et al., 2002). While lack of statistical power related to relatively small group samples may contribute

to the negative findings, it is also possible that the AHs of the HP group were not of sufficient intensity or consistency to saturate the auditory cortex to the point of significantly reducing auditory processing resources. While there were no significant between-group findings, within-group analysis resulted in several interesting observations.

In general, anterior scalp recordings showed across phoneme deviants to be processed more intensely and quicker than phoneme duration and pure tone deviants as evidenced by larger MMN amplitudes and shorter MMN latencies, respectively. These observations, which parallel our behavioural findings of increased across phoneme detections, may be related to the fact that both the English language (spoken by all participants) and the French language (mother tongue of 8 participants) relies more on phoneme changes than duration changes, unlike some languages such as Thai, Finnish or Japanese. Thus, this form of MMN deviant would be particularly phonologically relevant in English and French speakers, just as duration changes in speech are phonologically relevant in Finnish and Japanese speakers (Takegata et al., 2004). However, the preferential pre-attentive processing of across phoneme deviants was differentially expressed within the three study groups, with the HC group exhibiting significantly larger left frontal and bilateral fronto-central amplitudes to across phoneme deviants than to phoneme duration deviants. This finding, contrasting with that of Kasai et al. (2002), was mirrored in the NP group in the left frontal region, but not in the HP group who exhibited similar frontal MMN amplitudes to all three deviant types. In contrast to these anterior findings, inverted positive MMNs at posterior temporal, but not mastoid, sites showed a reverse pattern in HCs, with across phoneme deviants eliciting smaller right temporal

amplitudes (vs. phoneme duration deviants), while across phoneme deviants elicited greater left temporal amplitudes (vs. phoneme duration deviants) in HPs.

Originally, the frontal negative and temporal positive MMN subcomponent scalp topography (see with nose reference recordings) was explained by tangentially-oriented bilateral dipolar generator sources in the superior plane of the auditory cortices, oriented so that the negative voltage maximum of the resulting electrical field is located at the fronto-central scalp areas and the positive maximum at the at the sub-temporal areas. Subsequent evidence from source modeling, scalp current density distribution maps, intracranial recordings and imaging have shown MMN to result from at least two generators, one in the temporal lobe and one in the frontal lobe (Giard et al., 1990; Schröger, 2005). Whereas activation of the former (and earlier) has been associated with auditory feature analysis and deviance detection to unattended sounds, activation of the latter (and later) has been linked to involuntary attentional switching to sound changes initiated by the deviance-detection mechanism in the auditory cortex (Optiz et al., 2002; Paavilainen et al., 2003; Rinne et al., 2000). The independence of the frontal negative and temporal positive scalp MMNs is reflected by differential sensitivity to standard/deviant probabilities (Baldeweg et al., 1999), contextual (Sussman & Winkler, 2001) and dichotic features (Deouell et al., 1998). Whereas unilateral prefrontal lesions reduce overall MMN amplitude, unilateral temporal cortex lesions only diminish scalp MMNs contralateral to the ear stimulated (Alain et al., 1998).

While the preponderance of MMN studies in schizophrenia have focused on anterior brain regions and have consistently reported attenuated frontal amplitudes, recent studies have found the temporal component to be of normal magnitude (Baldeweg et al.,

2002; Sato et al., 2003). Although appearing normal in patients, the output of the temporal (deviance-detection) mismatch process may, due to cortico-cortical disconnection, fail to activate subsequent frontal lobe generators subserving attention switching (Baldeweg et al., 2002), a suggestion which is supported by functional neuroimaging showing reduced connectivity between the superior temporal gyrus and dorsolateral prefrontal cortex in HPs (Lawrie et al., 2002). Although not specifically referring to hallucinatory phenomena, Oades and colleagues (1997) suggest that hypofrontal MMN activation may result in a compensatory processing strategy being allocated to temporal lobes, a strategy which may account for the contrasting differential MMN sensitivity to across phoneme and phoneme duration comparisons seen in HPs at frontal and temporal sites.

The absence of differential sensitivity of the anterior MMNs to different deviants suggests that each was processed in a similar manner by the HP group, perhaps due to some level of frontal lobe dysfunction. In fact, this infers that, in hallucinating patients, the across phoneme changes were not given enough “weight” (i.e. not allocated proper significance by the frontal lobes). This improper “weighting” of incoming stimuli could illuminate the mechanism underlying the presence of AHs: perhaps hallucinating patients’ own inner speech is not properly weighted to indicate its significance, therefore one’s own speech is processed similarly to the speech of another. If both incoming and self-generated speech are processed the same way, with no discrimination between them, it is reasonable to expect that they are experienced as being the same, thereby causing the belief that one’s own speech is alien in origin. This idea of improper weighting/discrimination appears to support the theory of impaired corollary discharge in

HPs. Corollary discharge indicates there is communication between the frontal lobes where speech is generated and temporal lobes where it is heard during talking and during inner speech, which appears to be behind our ability to distinguish between our own and others' speech by aiding in the monitoring of our own speech, thoughts and behaviours (Ford et al., 2002). Patients with schizophrenia have shown significant corollary discharge dysfunction (Ford et al., 2001; Ford et al., 2002; Ford and Mathalon, 2004), as noted by reduced coherence, especially of the delta and theta bands, between frontal and temporal areas of the brain, indicating a disconnection of these regions. Furthermore, impaired coherence of the theta band is even more marked in hallucinating schizophrenic patients, and it is thought that the failure of this mechanism could lead to the misattribution of self-generated thoughts to external sources (Ford & Mathalon, 2004). This suggests that there is a failure to alert the brain that incoming auditory input is self-generated, and this lack of signaled intention could lead to schizophrenic patients with AHs misattributing their own inner speech to an "other", producing the experience of auditory hallucinations (Ford and Mathalon, 2004). However, this could arise from a failure to attach proper significance to auditory stimuli in the first place, thereby inhibiting production of the corollary discharge, and resulting in misattribution of inner speech.

The finding of dysfunctional weighting of auditory stimuli could also be seen as corroborating the idea of AHs arising from an impairment in reality monitoring. Patients with schizophrenia who experience AHs have been shown to exhibit a primary reality-monitoring abnormality (Ditman & Kuperberg, 2005); they misattribute the source of emotionally valenced stimuli to an "other", especially in an immediate or real-time

setting whereby patients are asked to assign attribution their own (distorted or undistorted) voice during word production (Johns et al., 2001). In this way, it could be argued that patients are failing to attach proper “weight” to their own speech due to frontal lobe dysfunction, causing this misattribution process.

Of interest to schizophrenia in general is the finding that NP and HP groups exhibited smaller temporal amplitudes to the phoneme duration deviants than the HC group. Although no significant group differences were observed with pure tone duration deviants, duration MMN deficits (vs. frequency MMNs) have been a relatively robust finding in schizophrenia but have tended to be more apparent with short (vs. long) duration deviants (Shelley et al., 1991). The phoneme duration condition appeared to be the most difficult in which to discern the deviant stimuli, as seen by the overall longer MMN latencies and reduced percentage of correct detections in the behavioural task. This suggests that, especially for complex auditory stimuli with subtle differences in auditory features, schizophrenic patients show a cerebral dysfunction in auditory processing. This finding is consistent with the overall view of compromised auditory cortex function in schizophrenia (Bramon et al., 2004), as well as evidence of structural abnormalities, such as reduced temporal lobe structure volume, in patients with schizophrenia (McLure et al., 1998; Andreasen et al., 1990; Barta et al., 1990).

4.2 Experiment 2

The initial analysis of results from Experiment 2 was hampered by the absence of any identifiable MMN component at frontal or mastoid sites in a number of subjects. Interpretation of the absence of MMNs in silence is complicated, particularly as MMNs

have been frequently elicited by similar speech sounds in healthy controls (Muller-Gass et al., 2001) and the sounds were clearly discriminated at the behavioural level by all subjects in noise and non-noise conditions. Although unlikely, especially in the healthy controls, absent MMNs may reflect a deficit in one or more processes of the MMN eliciting mechanism (e.g. encoding, trace formation, or comparative processes) or the presence of other temporally and spatially overlapping neural processes that obscure MMN (Schröger, 2005). Although diminished MMNs were expected with noise manipulations, the absence of visible MMNs in the silence condition is problematic when assessing noise conditions due to floor effects. Nevertheless, for reasons of experimental validity, not to mention clarity of findings, post-hoc analyses were performed using only participants who demonstrated a clear MMN at F_z (and mastoids) during silence. This acted to ensure that any reductions of MMN amplitude (as hypothesized) were due to noise-related interference rather than non-response to the CV stimuli.

4.2.1 Experiment 2 – Post-Hoc Analysis

Although no between group differences were observed with MMN amplitudes, and despite that noise failed to alter CV discriminability, AH ratings in HPs, or MMN lateralization, HPs showed overall smaller frontal, but not posterior or mastoid, MMNs during the white noise condition compared to the silence condition, a finding not seen in either of the other two groups. This finding appears to give credence to the study hypothesis and to the saturation hypothesis in particular (Woodruff, 2004). It is possible that the mere presence of hallucinations in this group was not enough to surpass the limit of auditory cortex resources sufficiently to affect preconscious processing of sound; in

fact, the relatively low level of self-reported hallucinatory activity seen during the tasks leads one to believe that AHs were not occupying significant levels of auditory attentional resources. However, these results suggest that the modest AH activity reported, in combination with the input of the wide-band white noise, was enough to surpass the saturation threshold sufficiently to alter auditory processing, as indexed by the MMN. This is supported by findings that in the white noise condition, MMN latency was positively correlated with AH duration, showing a slowing of MMN processes occurring conjointly with increasing hallucinatory duration. It seems reasonable that this effect would be seen during the constant, consistent white noise condition compared to the traffic noise condition, which showed variations in intensity of auditory activity. This wax-and-wane effect in the traffic condition may mean that the auditory resource threshold was not consistently exceeded, resulting in it appearing to be effectively no different than the silent condition.

The constant nature of the white noise condition could also possibly explain finding of larger right fronto-central MMN amplitudes during the presentation of white noise than during the silence condition in NPs. Specifically, this noise condition could relate to previous findings that environmental conditions during the diversionary task could actually increase MMN amplitude via increased cortical excitability (Muller-Gass et al., 2005). If this is indeed the case, this could be related to deficits of sensory gating often seen in schizophrenia (Adler et al., 1982), as in this case background noise would not dampen responsivity, or at least leave auditory responsivity unaltered, but would rather increase the amount of auditory information being processed at any one time. This would also suggest that the basal excitability of the auditory cortex is different across the

two schizophrenia groups, a suggestion which is supported by functional neuroimaging evidence of increased activation in HPs (vs. NPs and HCs) in auditory cortices during passives states (Weiss & Heckers, 1999; Woodruff, 2004).

Analysis of MMN latency at F_z showed a main effect of noise, with longer latencies being recorded in the noise conditions vs the silence condition. However, the specific noise effect varied within each group, with both NPs and HPs exhibiting slowing with traffic noise, while the HC group exhibited slowing with white noise. This initially appears at odds with findings of reduced MMN amplitude during white noise in HPs, with no effect of traffic noise. However, these two findings together appear to paint a picture of compromised auditory processing which is differentially sensitive to speech processing competitors: in the white noise condition, the degree of preattentive processing is reduced due to insufficient resources, and with less resources available, the process is left somewhat incomplete, though appears to occur within a time frame comparable to that of silence. However, within the traffic noise condition, there are sufficient resources for full processing of the incoming auditory stimuli, yet due to the interference of the background noise, this process occurs at a slower rate. The susceptibility of processing speed in HPs to noise interference is further supported by the observation that MMN latencies were slower in HPs than in NPs during white noise exposure. These combined findings in white noise, with MMN amplitudes being selectively attenuated and MMN latencies being slowed, and with the degree of slowing being associated with noise-induced increased hallucinatory activity, suggest that early auditory processing of external speech and hallucinatory behaviours may share common neural substrates.

4.3 Summary

Given the study limitations, including small samples and the medicated status of the patients, the study observations need to be treated with caution. Notwithstanding these restrictions, the neural probing of speech processing in the auditory cortex with MMN found preattentive processing in hallucinating patients to be insensitive to stimulus relevance and hypersensitive to speech competitors. As AHs are frequently interpreted to arise of misinterpretation of internal speech, and as HPs often misattribute their own voices and words to external sources, future experiments may further explore the MMN-relevancy relationship by comparing MMNs to one's own and other's speech sounds. Combining this exploration with noise and attentional manipulations, the latter being shown to moderate attentional bias (Ensum and Morrison, 2003), would provide useful information regarding the neuronal basis of bottom-up and top-down cognitive processes involved in auditory hallucinatory phenomena.

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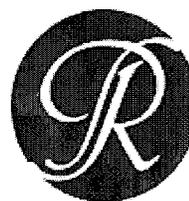
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APPENDICES

6.1 APPENDIX A: INFORMATION SHEET AND CONSENT FORM
(PATIENT VERSION)



Carleton
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INFORMATION SHEET (Patient Version)

(Version 26/5/2006)

Title of Proposal: Auditory Hallucinations and the Mismatch
Negativity: Processing Speech and Non-Speech
Sounds in Schizophrenia

Principal Investigator: Derek Fisher, B.Sc.

Research Supervisors: Verner Knott, D.Phil., C.Psych;
Hymie Anisman, Ph.D.

INTRODUCTION

Please take time to read carefully and consider the following information before you give your consent to be a research volunteer in this study. This information describes the purpose and procedures and the possible risks and benefits of the proposed research. You are encouraged to discuss any questions with the study investigators and other members of the research laboratory. You will receive a copy of this information sheet to keep for your records if you consent to participate. This study will be conducted in English only.

BACKGROUND

Schizophrenia is a psychiatric illness that results in the brain functioning in ways that are different than the general population. This can lead to some patients with schizophrenia experiencing auditory hallucinations, which are sounds that the patient hears even though there is nothing in the outside world causing these sounds.

It has also been shown that the way the brain responds to real sound, especially speech, is altered in patients with schizophrenia. However, we do not know exactly why the brain responds to external sound differently and what effect auditory hallucinations may have on this.

PURPOSE

Attempts to understand how the brain processes sounds can involve the monitoring of brain electrical activity from the surface of the scalp; this provides us with an objective non-invasive means of measuring brain function during the processing of sounds and during auditory hallucinations. The primary purpose of this study is to examine the effect of auditory hallucinations on the processing of speech and non-speech sounds using brain electrical monitoring together with self-reports and performance tasks.

In order to best understand the unique effect of auditory hallucinations on brain function, this study will assess persons diagnosed with schizophrenia who experience auditory hallucinations, persons diagnosed with schizophrenia who do not experience auditory hallucinations, and healthy controls with no psychiatric diagnosis.

PROCEDURES

You will participate in one, 3-hour test session. You will be asked to abstain alcohol and drugs (except for psychiatric medications) beginning at midnight prior morning test session, which will take place between 8:00 - 11:00 a.m. In the test session, sensors will be placed on your scalp and around your eyes to monitor electrical activity of the brain. Once the sensors are in place, you will be given practice time on the computerized performance tasks to be used in the assessments. You will be assessed under two different conditions: 1) while you are watching a silent, neutral video and ignoring sounds presented through headphones; and 2) while you are taking part in a computer task requiring the detection and response to auditory stimuli, such as tones and speech-like sounds. The assessments for each will involve the recording of brain electrical activity, and the completion of questionnaires regarding the presence/absence of auditory hallucinations. Some tasks will require responding (by the pressing of a computer mouse key) to pure tones. Questionnaires regarding your auditory hallucinations, cigarette/drug/alcohol behaviour and personality style will also be completed at the beginning of the study. You have a right to skip any questions you do not wish to answer.

RISKS

The electrode sensors may result in temporary redness and irritation of the skin that will disappear in a few hours.

BENEFITS

There are no immediate benefits for participating in this study but you will be paid an amount of \$25.00 for your time and effort.

PARTICIPATION

Your participation is voluntary and you may withdraw from the study at any time without penalty and without jeopardizing your continued care at the Royal Ottawa Hospital.

CONFIDENTIALITY

Information will be coded and your privacy will be protected. Any scientific publication or presentation resulting from this work will be presented so that your anonymity is preserved. Data collected from the study will be stored on computer discs (computer tasks) and in bankers boxes (study questionnaires) in a locked storage room and kept for a period of 10 years post-publication, after which point it will be destroyed. At all times, only the principal investigator (DF) and associated investigators (VK, HA) will have access to this information.

INFORMATION

If you have any specific questions about this study, you should contact the principal investigator, Derek Fisher (613-722-6521 ext. 6757), or immediate research supervisor, Dr. Verner Knott (613-722-6521 ext. 6843).

If you have any general questions regarding the ethics of this study, you may contact the Chairman of the Royal Ottawa Hospital Research Ethics Board, Dr. Douglass (613-722-6521 ext 6226) or the Chair of the Carleton University Ethics Committee for Psychological Research, Dr. Janet Mantler, (613-520-2600 ext. 4173, email: janet_mantler@carleton.ca).



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UNIVERSITY



CONSENT FORM

Title of Proposal: Auditory Hallucinations and the Mismatch Negativity: Processing Speech and Non-Speech Sounds in Schizophrenia

Principal Investigator: Derek Fisher, B.Sc.

Research Supervisors: Verner Knott, D.Phil., C.Psych;
Hymie Anisman, Ph.D.

Statement: I, _____, agree to participate in the above described research project, the nature and possible complications of which have been explained to me as outlined in the attached Information Letter of which I have received a copy.

I agree not to drink alcohol or take drugs (except for psychiatric medications) beginning at midnight prior to the morning test session.

I understand the risks and benefits of the study that have been explained to me.

I will not be identified in any scientific presentation or publication.

I may keep a copy of this consent form (with one copy being kept by the study investigators) and I may withdraw from participation at any time without influence on my current or future treatment.

Name of Volunteer (printed)

Signature of Volunteer

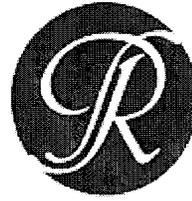
Date

Name of Investigator (printed)

Signature of Investigator

Date

6.2 APPENDIX B: INFORMATION SHEET AND CONSENT FORM
(HEALTHY CONTROL VERSION)



INFORMATION SHEET (Healthy Volunteer Version)
(Version 31/3/2006)

Title of Proposal: Auditory Hallucinations and the Mismatch
Negativity: Processing Speech and Non-Speech
Sounds in Schizophrenia

Principal Investigator: Derek Fisher, B.Sc.

Research Supervisors: Verner Knott, D.Phil., C.Psych;
Hymie Anisman, Ph.D.

INTRODUCTION

Please take time to read carefully and consider the following information before you give your consent to be a research volunteer in this study. This information describes the purpose and procedures and the possible risks and benefits of the proposed research. You are encouraged to discuss any questions with the study investigators and other members of the research laboratory. You will receive a copy of this information sheet to keep for your records if you consent to participate. This study will be conducted in English only.

BACKGROUND

Schizophrenia is a psychiatric illness that results in the brain functioning in ways that are different than the general population. This can lead to some patients with schizophrenia experiencing auditory hallucinations, which are sounds that the patient hears even though there is nothing in the outside world causing these sounds. It has also been shown that the way the brain responds to real sound, especially speech, is altered in patients with schizophrenia. However, we do not know exactly why the brain responds to external sound differently and what effect auditory hallucinations may have on this.

PURPOSE

Attempts to understand how the brain processes sounds can involve the monitoring of brain electrical activity from the surface of the scalp; this provides us with an objective non-invasive means of measuring brain function during the processing of sounds and during auditory hallucinations. The primary purpose of this study is to examine the effect of auditory hallucinations on the processing of speech and non-speech sounds using brain electrical monitoring together with self-reports and performance tasks.

In order to best understand the unique effect of auditory hallucinations on brain function, this study will assess persons diagnosed with schizophrenia who experience auditory hallucinations, persons diagnosed with schizophrenia who do not experience auditory hallucinations, and healthy controls with no psychiatric diagnosis.

PROCEDURES

You will participate in one, 3-hour test session. You will be asked to abstain from alcohol and drugs (except for psychiatric medications) beginning at midnight prior morning test session, which will take place between 8:00 - 11:00 a.m. In the test session, sensors will be placed on your scalp and around your eyes to monitor electrical activity of the brain. Once the sensors are in place, you will be given practice time on the computerized performance tasks to be used in the assessments. You will be assessed under two different conditions: 1) while you are watching a silent, neutral video and ignoring sounds presented through headphones; and 2) while you are taking part in a computer task requiring the detection and response to auditory stimuli, such as tones and speech-like sounds. The assessments for each will involve the recording of brain electrical activity, and the completion of questionnaires regarding the presence/absence of auditory hallucinations. Some tasks will require responding (by the pressing of a computer mouse key) to pure tones. Questionnaires regarding your auditory hallucinations, cigarette/drug/alcohol behaviour and personality style will also be completed at the beginning of the study. You have a right to skip any questions you do not wish to answer.

RISKS

The electrode sensors may result in temporary redness and irritation of the skin that will disappear in a few hours.

BENEFITS

There are no immediate benefits for participating in this study but you will be paid an amount of \$25.00 for your time and effort.

PARTICIPATION

Your participation is voluntary and you may withdraw from the study at any time without penalty.

CONFIDENTIALITY

Information will be coded and your privacy will be protected. Any scientific publication or presentation resulting from this work will be presented so that your anonymity is preserved. Data collected from the study will be stored on computer discs (computer tasks) and in bankers boxes (study questionnaires) in a locked storage room and kept for a period of 10 years post-publication, after which point it will be destroyed. At all times, only the principal investigator (DF) and associated investigators (VK, HA) will have access to this information.

INFORMATION

If you have any specific questions about this study, you should contact the principal investigator, Derek Fisher (613-722-6521 ext. 6757), or immediate research supervisor, Dr. Verner Knott (613-722-6521 ext. 6843).

If you have any general questions regarding the ethics of this study, you may contact the Chairman of the Royal Ottawa Hospital Research Ethics Board, Dr. Douglass (613-722-6521 ext 6226) or the Chair of the Carleton University Ethics Committee for Psychological Research, Dr. Janet Mantler, (613-520-2600 ext. 4173, email: janet_mantler@carleton.ca).

6.3 APPENDIX C: PSYRATS

Subject Code: _____

Date: _____

1. Frequency
 - Voices not present or present less than once a week 0
 - Voices occur at least once a week 1
 - Voices occur at least once a day 2
 - Voices occur at least once an hour 3
 - Voices occur continuously or almost continuously 4

2. Duration
 - Voices not present 0
 - Voices last for a few seconds, fleeting voices 1
 - Voices last for several minutes 2
 - Voices last for at least one hour 3
 - Voices last for hours at a time 4

3. Location
 - No voices present 0
 - Voices sound like they are inside head only 1
 - Voices outside the head, but close to ears or head 2
 - Voices inside head may also be present
 - Voices sound like they are inside or close to ears 3
 - and outside head away from ears
 - Voices sound like they are outside the head only 4

4. Loudness
 - Voices not present 0
 - Quieter than own voice, whispers 1
 - About the same loudness as own voice 2
 - Louder than own voice 3
 - Extremely loud, shouting 4

5. Beliefs re: origin of voices
 - Voices not present 0
 - Believes voices to be solely internally 1
 - generated and related to self
 - Holds <50% conviction that voices originate from 2
 - external causes
 - Holds >50% (but <100%) conviction that voices 3
 - originate from external causes
 - Believes voices are solely due to external causes 4

6.	Amount of negative content of voices	
	No unpleasant content	0
	Occasional unpleasant content (<10%)	1
	Minority of voice content is unpleasant or Negative (<50%)	2
	Majority of voice content is unpleasant or Negative (>50%)	3
	All of the voice content is unpleasant or negative	4
7.	Degree of negative control	
	Not unpleasant or negative	0
	Some degree or negative content, but not personal comments relating to self or family	1
	Personal verbal abuse, comments on behaviour	2
	Personal verbal abuse relating to self-concept	3
	Personal threats to self (threats to harm self or family, extreme instructions, commands to harm self or others)	4
8.	Amount of distress	
	Voices not distressing at all	0
	Voices occasionally distressing, majority not distressing (<10%)	1
	Minority of voices distressing (<50%)	2
	Majority of voices distressing, minority not distressing (>50%)	3
	Voices always distressing	4
9.	Intensity of distress	
	Voices not distressing at all	0
	Voices slightly distressing	1
	Voices are distressing to a moderate degree	2
	Voices are very distressing, although subject could feel worse	3
	Voices are extremely distressing, feel the worst he/she could possibly feel	4

10. Disruption to life caused by voices
- | | |
|--------------------------------------------------------------------------------------------------------------------------------------------|---|
| No disruption to life, able to maintain social/
family relationships (if present) | 0 |
| Voices cause minimal amount of disruption to life | 1 |
| Voices cause moderate amount of disruption to
life causing some disturbance to daytime
activity and/or family and social activities. | 2 |
| Voices cause severe disruption to life so that
hospitalization is usually necessary. | 3 |
| Voices cause complete disruption of daily life
requiring hospitalization. | 4 |
11. Controllability of voices
- | | |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---|
| Subject believes they can have control over the
voices and can always bring on or dismiss
the voices at will. | 0 |
| Subject believes they can have some control over
the voices on the majority of occasions | 1 |
| Subject believes they can have some control over
the voices approximately half the time | 2 |
| Subject believes they can have some control over
the voices, but only occasionally. The
majority of the time the subject experiences
voices that are uncontrollable. | 3 |
| Subject has no control over when the voices occur
and cannot dismiss or bring them on at all. | 4 |

6.4 APPENDIX D : AUDIT

AUDIT

Date: _____ ID#: _____

Please circle the answer that is correct for you

1. How often do you have a drink containing alcohol?
Never Monthly Two to four Two to three Four or more
 or less times a month times a week times a week
2. How many drinks containing alcohol do you have on a typical day when you are drinking?
1 or 2 3 or 4 5 or 6 7 or 9 10 or more
3. How often do you have six or more drinks on one occasion?
Never Less than monthly Monthly Weekly Daily or almost daily
4. How often during the last year have you found that you were not able to stop drinking once you had started?
Never Less than monthly Monthly Weekly Daily or almost daily
5. How often during the last year have you failed to do what was normally expected from you because of drinking?
Never Less than monthly Monthly Weekly Daily or almost daily
6. How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session?
Never Less than monthly Monthly Weekly Daily or almost daily
7. How often during the last year have you had a feeling of guilt or remorse after drinking?
Never Less than monthly Monthly Weekly Daily or almost daily
8. How often during the last year have you been unable to remember what happened the night before because you had been drinking?
Never Less than monthly Monthly Weekly Daily or almost daily
9. Have you or someone else been injured as a result of your drinking?
No Yes, but not in the last year Yes, during the last year
10. Has a relative or friend, or doctor or other health worker been concerned about your drinking or suggested you cut down?
No Yes, but not in the last year Yes, during the last year

6.5 APPENDIX E: DAST

DAST Questionnaire

The following questions concern information about your involvement and abuse of drugs. Drug abuse refers to (1) the use of prescribed or “over the counter” drugs in excess of the directions or (2) any non-medical use of drugs. Carefully read each statement and decide whether your answer is yes or no. Then circle the appropriate response.

1 Have you used drugs other than those required for medical reasons?	Yes	No
2 Have you abused prescription drugs?	Yes	No
3 Do you abuse more than one drug at a time?	Yes	No
4 Can you get through the week without using drugs? (other than those required for medical reasons)	Yes	No
5 Are you always able to stop using drugs when you want to?	Yes	No
6 Do you abuse drugs on a continuous basis?	Yes	No
7 Do you try to limit your drug use to certain situations?	Yes	No
8 Have you ever had "blackouts" or "flashbacks" as a result of drug use?	Yes	No
9 Do you ever feel bad about your drug use?	Yes	No
10 Does your spouse (or parents) ever complain about your involvement with drugs?	Yes	No
11 Do your friends or relatives know or suspect you abuse drugs?	Yes	No
12 Has drug abuse ever created problems between you and your spouse?	Yes	No
13 Has any family member ever sought help for your problems related to drug use?	Yes	No
14 Have you ever lost friends because of your use of drugs?	Yes	No
15 Have you ever neglected your family or missed work because of your use of drugs?	Yes	No
16 Have you ever been in trouble at work because of drug abuse?	Yes	No
17 Have you ever lost a job because of drug abuse?	Yes	No
18 Have you gotten into fights when under the influence of drugs?	Yes	No
19 Have you ever been arrested because of unusual behaviour while under the influence of drugs?	Yes	No
20 Have you ever been arrested for driving while under the influence of drugs?	Yes	No
21 Have you engaged in illegal activities in order to obtain drugs?	Yes	No
22 Have you ever been arrested for possession of illegal drugs?	Yes	No
23 Have you ever experienced withdrawal symptoms as a result of heavy drug intake?	Yes	No
24 Have you had medical problems as a result of your drug use? (e.g. memory loss, hepatitis, convulsions, bleeding, etc...)	Yes	No
25 Have you ever gone to anyone for help for a drug problem?	Yes	No
26 Have you ever been in a hospital for medical problems related to your drug use?	Yes	No
27 Have you ever been involved in a treatment program specifically related to drug use?	Yes	No
28 Have you been treated as an out-patient for problems related to drug abuse?	Yes	No

Score: _____

6.6 APPENDIX F: Smoker History and FTND

Smoker History Questionnaire

Date: _____

ID#: _____

1. Presently, how many cigarettes do you smoke on average per day? _____
2. At what age did you start smoking on a daily basis? _____
3. What type of cigarettes do you usually smoke? _____
4. Do you smoke more during the: morning ___ / afternoon ___ / evening ___
5. How soon after you wake do you smoke your first cigarette? _____
6. How many nights per week do you wake up and smoke a cigarette during the night? _____

Fagerstrom Questionnaire

Write the number of the answer that is most applicable on the line to the left of the question.

- _____ 1. How soon after you awake do you smoke your first cigarette?
 0. After 30 minutes
 1. Within 30 minutes
- _____ 2. Do you find it difficult to refrain from smoking in places where it is forbidden, such as the library, theater, or doctors' office?
 0. No
 1. Yes
- _____ 3. Which of all the cigarettes you smoke in a day is the most satisfying?
 0. Any other than the first one in the morning
 1. The first one in the morning
- _____ 4. How many cigarettes a day do you smoke?
 0. 1-15
 1. 16-25
 2. More than 26
- _____ 5. Do you smoke more during the morning than during the rest of the day?
 0. No
 1. Yes
- _____ 6. Do you smoke when you are so ill that you are in bed most of the day?
 0. No
 1. Yes
- _____ 7. Does the brand you smoke have a low, medium, or high nicotine content?
 0. Low
 1. Medium
 2. High
- _____ 8. How often do you inhale the smoke from your cigarette?
 0. Never
 1. Sometimes
 2. Always

6.7 APPENDIX G: Handedness Inventory

Please indicate your preferences in the use of hands in the following activities by putting + in the appropriate column. Where the preference is so strong that you would never try to use the other hand unless absolutely forced to, put ++. In any case you are really indifferent put + in both columns.

Some of the activities require both hands. In these cases the part of the task or object for which hand preference is wanted is indicated in brackets.

Please try to answer all the questions and only leave a blank if you have no experience at all of the object or task.

Task	Left	Right
Writing		
Drawing		
Throwing		
Scissors		
Toothbrush		
Knife (without fork)		
Spoon		
Broom (upper hand)		
Striking match (match)		
Opening box (lid)		
Which foot do you prefer to kick with?		
Which eye do you use when using only one? (E.g. taking picture with a camera.)		

L.Q. _____ (Leave this space blank)

6.8 APPENDIX H: Hallucination Ratings

Hallucination Ratings

Task: _____

Please rate your auditory hallucinations (“voices”) based on how they appeared during the previous task

Duration

No Hallucinations 1 2 3 4 5 6 7 Continuous

Loudness

Not audible 1 2 3 4 5 6 7 Extremely
loud

Clarity

Unintelligible 1 2 3 4 5 6 7 Very clear

6.9 APPENDIX I: 10-20 System of EEG Electrode Placement

