Using the conditional inference paradigm to explore the basis for reduced mismatch negativity (MMN) size in individuals with schizophrenia.

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Abstract

Scope: The scope of this thesis includes a review of existing literature on various theories put forward to explain the reduction of event-related potential component, mismatch negativity (MMN) in the mental illness schizophrenia. Evaluation of existing literature builds the argument for purpose and experimental design of this thesis. Purpose: The purpose of this thesis was to explore the integrity of the inferential process and basis for reduced MMN in schizophrenia. Methodology: The thesis features the application of a novel MMN paradigm to explore what is impaired and what is intact in the inferential process underlying MMN generation in schizophrenia. Sixty-five participants (35 individuals diagnosed with schizophrenia or schizoaffective disorder and 30 matched controls) completed the MMN paradigm together with cognitive testing and clinical assessment. Results: The data indicate that although MMN is smaller in size in this sample (replicating prior research), the ability persons with schizophrenia to reduce MMN size to a deviant sound when the timing of its occurrence can be inferred from predictive cues is equivalent to that of healthy controls. Conclusions and Implications: The paradigm was designed on the assumption that the reduced size of MMN to a predictable deviation reflects a dynamic shift in a perceptual inference model. This process is intact within schizophrenia. However, our data reveal other group differences within the paradigm that have methodological implications for research in this field.
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Critical Literature Review

This thesis explores the ERP component known as mismatch negativity and its reduction in the mental illness schizophrenia. The purpose of this literature review is to present multiple perspectives as to why mismatch negativity is reduced in this group building an argument for the objectives and experimental design of this thesis.

Mismatch Negativity

Mismatch negativity (MMN) is an event-related potential (ERP), component evoked automatically to any deviation in a repeating sequence of sounds (Näättänen & Winkler, 1999). MMN in its simplest form is measured by subtracting the response waveform to a regularly repeating ‘standard’ sound from that to a ‘deviant’ sound, which violates the regular pattern in some way. The difference between these two waveforms (the MMN) is dependent upon the degree to which the representation of the deviant sound varies from that of the standard with larger physical differences and more rare deviant presentation being associated with larger MMN responses (Näättänen, 2008; Picton, Alain, Otten, Ritter, & Achim, 2000). MMN has been interpreted as a prediction error signal indicating when there is a discrepancy between the perceptual inference based on a memory representation dependent upon recency and probability of sound characteristics encountered, and the actual event experienced (Näättänen, Jacobsen, & Winkler, 2005; Todd, Michie, Schall, Ward, & Catts, 2012). As well as alerting to potentially salient environmental changes, the MMN also represents the brain’s attempt to modify the inference regarding the state of the environment to incorporate the change in experience in order to minimise future errors or ‘surprises’ (Friston, 2005; Winkler, Karmos, & Näättänen, 1996).

Auditory and frontal cortical areas have been proposed as contributing to MMN generation, specifically, bilateral dipolar sources in the auditory cortex along the supratemporal plane and predominantly right-hemispheric frontal areas (Näättänen, Paavilainen, Rinne, & Alho, 2007). The dominant contribution to MMN is believed to derive from neural activity in the auditory
cortices coding the deviant feature (Alho, 1995), however studies have implicated an additional contribution from frontal regions (Deouell & Bentin, 1998; Deouell, Bentin, & Giard, 1998), and particularly the right fronto-opercular cortex (Opitz, Rinne, Mecklinger, Von Cramon, & Schröger, 2002) to MMN generation. The temporal generator is believed to reflect perceptual detection of stimulus change, while the frontal generator has been associated with involuntary attention switch directed by auditory change ( Näätänen et al., 2007). Interestingly, a study conducted by Sato and colleagues (2002) revealed that the amplitudes of the MMN component recorded at FZ, assumed to reflect frontal contribution, increased as probability of the standard stimuli increased but the amplitude at the temporal generator was not. These results suggest that the frontal generator has a greater contribution as the probability difference between the standard and deviant increases (Sato et al., 2003).

The mechanism underlying MMN is commonly described as a hierarchical neural system. That is, a multi-level cortical representation based on reciprocal exchanges between top-down expectation from the frontal region based on the memory trace of previous sounds and bottom-up sensory input from the auditory cortex (Garrido, Kilner, Stephan, & Friston, 2009). This notion of MMN as a hierarchical neural system is supported by a functional magnetic resonance imaging study of deviance. This study reported that although the auditory cortical source increased over three incremental frequency changes, the frontal source was smallest at the middle deviation compared to when frequency deviation was smallest and largest (Doeller et al., 2003). The authors postulated that the right inferior frontal gyrus engaged with the auditory cortex to produce a contrast enhancing effect that facilitated the detection of the smaller frequency resulting in a larger frontal source for the smaller compared to the mid-range deviation. The frontal region has been identified for having greater sensitivity, or response to musicality. The largest deviation utilized within this study was exactly one octave above the standard. This ‘musical’ relationship has been suggested as an explanation for the increased frontal source involvement to this deviant (Doeller et al., 2003).
Reduced MMN and Pathology of Schizophrenia

Reduced MMN is a robust finding in those with schizophrenia (Michie et al., 2000; Todd, Michie, & Jabletky, 2001; Todd et al., 2012). Evidence indicates that reduced MMN size is present in individuals at the very early stages of schizophrenia (Salisbury, Kuroki, Kasai, Shenton, & McCarrey, 2007), and in those who are at ultrahigh risk of developing schizophrenia (Atkinson, Michie, & Schall, 2012; Baker, Baldeweg, Sivagnanasundaram, Scambler, & Skuse, 2005). MMN reduction has also demonstrated predictive value in identifying who will transition into psychosis among those identified to be at ultra-high risk (Bodatsch et al., 2011).

Magnetic resonance imaging studies by Salisbury and colleagues (2007) found that reduced MMN corresponded with smaller grey matter volume in auditory regions in those with schizophrenia but not in healthy controls. As the pathology of schizophrenia progresses multiple affected brain regions exhibit changes in the density, number, size and organization of neurons which leads to disruption to local microcircuits (Iritani, 2007). Progressive decline in MMN amplitude has been shown to be strongly associated with progressive loss of auditory cortical matter over the early course of schizophrenia (Ho et al., 2003; Salisbury et al., 2007). Salisbury and colleagues found that frequency MMN in schizophrenia patients at the time of first hospitalisation did not differ from patients diagnosed with bipolar dipolar or healthy controls. At 18 month follow-up only the schizophrenia patients exhibited both reduced MMN amplitude and diminished grey matter volume of the left-hemisphere Heschl’s gyrus. Furthermore, reduced frequency MMN was significantly correlated with decrease in Heschl’s gyrus matter volume at the time of follow-up. This relationship between MMN amplitude and grey-matter volume within those with schizophrenia has not been identified in healthy controls (Rasser et al., 2011). It is important to note that while correlations between MMN and grey matter loss in multiple brain regions may indicate a functional link, it is also possible that this relationship reflects the concurrent developing consequences of pathology (Todd et al., 2012). However, the results of Salisbury and colleagues suggest that there is an interrelated
progressive reduction of functional and structural measures and may indicate a progressive pathological process that can be monitored via MMN (Näätänen & Kähkönen, 2009).

Additionally, study by Todd and colleagues (2008) has identified that those considered in the early stages of the illness (mean of 2.6 years since diagnosis) demonstrated clear reduction in MMN to duration and intensity but not frequency deviants. Those with longer length of illness (mean = 18.9 years) demonstrated reduction in MMN to frequency and duration deviants as well as intensity deviants to a lesser degree. The authors conclude that the differing pattern across the progression of the illness indicate a pronounced age-related decline in addition to any illness-related progression of MMN reduction, although also note that this information provides potentially complementary information on the onset and progression of neuropathological changes that underlie the reduction in MMN in schizophrenia.

Impaired N-Methyl-D-aspartate (NMDA) receptor mediated plasticity has been suggested as contributing to reduced MMN in schizophrenia. NMDA receptors mediate excitatory synaptic transmission (Liu et al., 2004), specifically glutamatergic neurotransmission, which is critical to the processing of the relationship between sounds. The experience dependent alteration in neuron firing is reliant on the interaction between excitatory and inhibitory processes mediated by NMDA and Gamma-Amino Butyric Acid-A (GABA\textsubscript{A}) receptors (Javitt, Steinschneider, Schroeder, & Arezzo, 1996). This explanation is consistent with the view of schizophrenia as a neurodevelopmental disorder. The genes proposed to confer susceptibility to schizophrenia either directly or indirectly relate to this NMDA mediated glutamatergic transmission process, implicating glutamatergic synapses as a common site of action (Harrison & Owen, 2003).

A role for impaired NMDA receptors in the mechanism underlying MMN is supported by pharmacological studies. When NMDA receptor channels are blocked in primates, the brain responds normally to the individual sounds in a sequence, without registering any violation to the homogenous stream of sound. As there is no effect on ERP components of the standard
repetitive sound, this indicates that NMDA receptors are essential to representing the contextual memory of sound repetition (Javitt et al., 1996). Additionally, the administration of the NMDA receptor antagonists known as ketamine has been demonstrated to induce psychotic symptom development (Corlett, Honey, & Fletcher, 2007; Honey et al., 2008) and healthy participants who produced small MMN amplitudes at baseline exhibit the most pronounced psychotic-like symptoms (Schmidt et al., 2011; Umbricht, Koller, Vollenweider, & Schmid, 2002). Ketamine administration has also been demonstrated to cause a dose-dependent reduction in MMN amplitude in both primates (Kantrowitz & Javitt, 2010) and humans (Umbricht et al., 2002). These studies provide indirect evidence linking vulnerability in the NMDA receptor system, and aberrant prediction-error coding to the propensity for psychotic symptom development (Umbricht et al., 2002). Coyle (2006) proposes hypofunction of the NMDA receptor system as ‘a final common pathway that accounts for the neurophysiological dysfunction in the several affected brain regions that result in the symptoms of schizophrenia’ (p 366, Coyle, 2006). Although links between NMDA receptor function and MMN are commonly accepted (Näätänen et al., 2012) it should be recognised that some NMDA antagonists can indirectly affect dopamine levels also (Lindfors, Barati & O'Connor, 1997). However, given the links, MMN reduction in schizophrenia has been proposed to index dysfunction in NMDA receptor mediated plasticity.

Reduced MMN and Symptoms of Schizophrenia

Theories implicating aberrant prediction-error coding in schizophrenia symptomatology suggest a relationship with positive symptoms including the development of delusions and possibly hallucinations (Corlett et al., 2007; Coyle, 2006). Given the proposed use of prediction error to prioritize which events should receive attention, aberrations in this process could lead to irrelevant experiences reaching the focus of awareness. Delusion formation is thought to arise, in part, from the individual’s imposed explanation for the aberrant salience coding in an effort to make sense of why events reached their awareness as significant (Kapur,
In fact, in their review, Corlett and colleagues acknowledge the relevance of MMN reduction in schizophrenia to their theory but note that the impact of the reduced MMN on subsequent behaviour is unknown. A consistent relationship to delusions has not been demonstrated and reduced MMN is considered a stable feature rather than fluctuating with the illness.

Perhaps one exception to this is a study by Fisher and colleagues (2008) that suggests MMN may probe pathology specifically associated with auditory hallucinations. The finding of this study demonstrated an association between auditory verbal hallucinations and impaired pre-attentive processing of speech in front-temporal networks as measured by MMN. MMN amplitude was measured to non-phonemic and phonemic sounds at anterior and posterior scalp sites for schizophrenia patients reporting a definite, consistent history of auditory hallucinations, schizophrenia patients denying history of auditory hallucinations and healthy controls. The study revealed that where healthy controls and schizophrenia patients without hallucinations, elicited greatest MMN amplitude to across phoneme change at the frontal sites, MMN elicited by those patients with hallucinations at the frontal sites were not significantly differ across stimuli. Instead, sensitivity to phonemic change was maximal at the temporal sites as measured by MMN. The authors conclude that these results provide evidence for the use of MMN to explore the potential relationship between hallucinations and cortical processes within schizophrenia (Fisher, Labelle, & Knott, 2008).

Despite reduced MMN being a robust finding in schizophrenia, and with the exception of the Fisher study, the phenomenon has yet to be found to fluctuate with the illness. However the literature does appear consistent in the implication of aberrant prediction-error coding as a contributing mechanism for the symptomology of schizophrenia.

**Tone Discrimination Acuity**

Difficulty in accurately discriminating between the standard and deviant sounds has been proposed as a key mechanism underlying reduced MMN in schizophrenia (Javitt, Shelley,
Silipo, & Lieberman, 2000; Javitt, Strous, Grochowski, Ritter, & Cowan, 1997; Todd, Michie, Budd, Rock, & Jablensky, 2000). The size of the MMN elicited is impacted by the size of the variance between the standard and deviant sounds. This relationship is supported by a correlation between performance on behavioural discrimination tasks and MMN size (Nätänen & Alho, 1997). A reduced capacity to quantify the difference between the deviant and the standard may therefore lead to a smaller MMN as the deviant is perceived as less distinct.

A study completed by Leitman and colleagues (2010) provides some supportive evidence for this theory. The authors presented participants with two sequences of sound, one where the deviant was set at a fixed frequency difference from the standard; the second sequence used the same standard however the deviant was individualized for each participant. This was done by presenting the deviant at a frequency difference that the participant was able to detect with 79.4% accuracy on a behavioural task. Leitman and colleagues found that MMN was significantly reduced in those with schizophrenia at the fixed frequency difference but not in the individualized deviant presentation. These results suggest that MMN amplitude is dependent on the acuity of the individual’s tone discrimination.

There have however been some criticisms of the theory of impaired discrimination accuracy. Todd and colleagues (2012) highlighted that if impaired discrimination does underlie reduced MMN in schizophrenia, group differences should be most pronounced when discrimination is most difficult; when the deviant is less distinct. However, Javitt and colleagues (1998) found that in fact reduced MMN in schizophrenia is most pronounced when the deviant is more different to the standard. Group differences only emerged when the deviant differed from the standard by more than 20%. This may explain why Leitman and colleagues found no group difference, where the average difference between the deviant and standard was 3% and 14% for schizophrenia and controls respectively. A significant difference in MMN amplitude between schizophrenia and matched control groups has also been found to exist despite the groups having equivalent discrimination thresholds as measured by psycho-physical
tasks (Todd, Michie, & Jablensky, 2003). Based on the available literature it seems likely that problems in discrimination acuity may contribute to reduced MMN size in schizophrenia. However given that reduced MMN in schizophrenia is not most pronounced when discrimination is more difficult and that the phenomenon remains in those with no evidence for impaired discrimination acuity, the theory of impaired sound discrimination does not adequately explain reduced MMN in schizophrenia.

**What Can Alternative Paradigms Teach Us?**

The size of MMN increases to more distinct deviants in schizophrenia as it does in matched controls, however MMN amplitude in those with schizophrenia appears to plateau earlier (Javitt, Grochowski, Shelley, & Ritter, 1998; Shelley, Silipo, & Javitt, 1999). Resultantly, those with schizophrenia demonstrate restriction in accurate representation of the environment as equivalent MMN amplitude is generated for both small and larger violations of the inferred sound properties. This has also been demonstrated using deviants occurring at different degrees of probability. For example, Javitt and colleagues (1998) demonstrated that for those with schizophrenia, the MMN generated to a sound occurring at 20% probability was not significantly different from that generated to a sound with 5% likelihood of occurring (Javitt et al., 1998). One possibility prompting experimental design in this thesis was that perhaps the inferential process underlying MMN is indeed intact within schizophrenia, but the MMN size simply cannot increase to the same level as controls, resulting in restricted dynamic range in MMN amplitude (Todd et al., 2012). One way to examine this is to assess the integrity of inferential processes under conditions where ‘intact’ inference should produce a smaller MMN.

Research exploring MMN within schizophrenia has primarily used what is known as the ‘oddball paradigm’. This paradigm involves presentation of a relatively simple sound sequence whereby highly probable standard sounds are interspersed with randomized presentation of rare deviants. In this paradigm the prediction model is based on the probability of sound features
learned from a repetitive sequence, and updating the brain about violations to one or more sound features. The encoded inference is that the next sound will hold the same characteristics of the standard. However there is a large body of evidence suggesting that the brain can infer and develop predictive models based on more complex sound relationships. For example there is evidence that the brain is able to encode patterns that emerge over times such as repeating melody (Tervaniemi, Schroger, & Naatanen, 1997) and simultaneously reflect both local and global rules governing a sound sequence (Horvath, Czigler, Sussman, & Winkler, 2001). It is believed that in both simple and complex cases the repeated exposure is used to infer what the properties of the proceeding sound and that MMN is elicited when the inference is incorrect (Winkler, 2007).

Auditory sensory memory ability has been strongly associated with the ability to track simple sequence rules (Näätänen & Winkler, 1999) and this impact is likely to be increased for more complex sequence rules (Todd, Myers, Pirillo, & Drysdale, 2010). However as sequences increase in complexity, other cognitive abilities have been found to play a role in the capacity to extract predictive rules. One such cognitive process suggested as influencing MMN beyond sensory memory trace is contextual relevance imposed by higher levels within the hierarchical neuron system that underlies MMN. In a recent study (Winkler, Schröger, & Cowan, 2001) MMN was elicited using unattended deviants within a string of homogenous standards repeating at a 0.5s interval. The deviants were presented at either a 0.5, 2, 5, 7 or 10s delay. The participant’s results fell into either a ‘long’ or ‘short’ context processing group dependent on their ability to elicit MMN at the 7s delay. When the same sound sequence was presented at a regular 7s interval both the short and long context processing groups elicited an equivalent MMN. These results suggest that something beyond degraded memory trace caused the ‘short’ contextual processing group to not produce an MMN to the deviant at the 7s delay in the first 0.5s interval sequence. The authors explained these results by suggesting that the influence of
contextual factors on automatic interpretation of sound relevance differed between the groups (Winkler et al., 2001).

A more complex paradigm has been introduced to explore the process that underlies MMN. The ‘Conditional Inference’ paradigm proposes to place greater demand on the inferential learning process (Todd et al., 2010). This paradigm includes a comparison between MMNs elicited for deviants when they occur randomly in a sequence versus when they occur in pairs. The pairing of deviants in the linked sequence provides additional information for anticipating the most probable characteristics of the next sound. Specifically, the first deviant in the pair acts as a cue used to predict the characteristics of the respective second deviant of the pair. It is believed that through repeated pairing of the deviants the brain learns the association between the two sounds and to expect the occurrence of the cued deviant. Smaller MMN elicited to the second, cued deviant in the linked sequence compared to that in the random sequence is proposed by the authors to reflect the capacity of the auditory system to use current input to switch between inference models in memory (Todd et al., 2010). This reduction in MMN size has been termed a ‘conditional inference effect’. This term reflects the presumption that the cue sound enables the brain to make a context-dependent change in its inference about the most likely properties of the next sound (Todd et al., 2010; Todd & Robinson, 2010).

There have been several studies that provide empirical support that the MMN to a cued deviant can be significantly smaller than the MMN to the same sounds presented as a random deviant (Nousak, Deacon, Ritter, & Vaughan, 1996; Sussman & Winkler, 2001; Todd & Mullens, 2011). Importantly this conditional inference effect is not demonstrated to a second of two deviants in chance pairings of deviant events (Nousak et al., 1996; Todd & Mullens, 2011), which indicates that the link must be learnt. A repetition of the dominant rule (that most sounds will have the properties of the repeating standard) is encountered, on average, every 400 ms. In contrast, the paired deviants only repeat every 6-13 seconds on average. This makes the cue-link repetition much less frequent in time and also in the total number of repetitions. In
order for this suppression of MMN to occur the brain is required to use the first cue deviant as the context to override the dominant prediction model (i.e. that the next sound will have the same properties as the standard), and switch the bias in auditory cortex response to instead expect the respective second deviant. It is assumed that this process places a higher demand on the memory system underlying MMN. Therefore if reduced MMN size in schizophrenia is related to impaired neuroplasticity, then this new paradigm may provide a more sensitive index of the deficits involved in schizophrenia (Todd et al., 2010).

Several advantages for using the Conditional Inference paradigm have been identified. Firstly, as noted above, learning the cue-link deviant pairing should place a higher demand on memory and therefore neuroplasticity. Furthermore, using the occurrence of the cue to adjust predictions about sound properties is a highly dynamic application of learning.

The conditional inference paradigm provides a second advantage over traditional MMN sequences, in that it can account for any influence of discrimination ability. In traditional sequences, the size of the MMN will reflect the capacity to discriminate between the representation of the standard and deviant sounds. Better behavioural discrimination performance has been found to correlate with larger and earlier MMN to detect sound deviations (Näätänen & Alho, 1997). Therefore any impairment in discrimination should lead to smaller MMN as the deviant event will be perceived as less distinct from the repeating pattern. Impairment in encoding sound properties may impact the capacity to quantify the difference between deviant and standard events and is one factor that has been postulated to contribute to the reduced MMN in schizophrenia (Javitt et al., 1997). If true, the error between expected and actual events would not be registered if the representations of both events are largely overlapping, leading to a problem with prediction error estimation. Application of the new paradigm allows the subtraction of MMN elicited in linked sequence, from that elicited in the random sequence. Doing so statistically removes any between group differences that may
exist in discrimination, “purifying” the paradigm as a measure of the influence of learned association on perceptual inference (Todd et al., 2012).

The third advantage of the new paradigm includes the presentation of a sequence in which all deviants are presented as a repetitive standard. The averaged ERP to these deviant-as-standards can then be used as a partial control for exogenous effects on the ERP when computing the MMN (Jacobsen & Schroger, 2003; Todd & Mullens, 2011).

Reduced MMN in schizophrenia is a well-established phenomenon, with links to the pathology of the illness and potentially, to symptomology. Yet the comparative responsiveness of MMN to experimental manipulation between those with schizophrenia and healthy controls suggests that certain aspects of the MMN system are intact within schizophrenia. Using the conditional inference paradigm we impose a condition where greater inference accuracy is demonstrated by production of smaller MMN amplitude thus allowing the integrity of the inferential process to be explored within schizophrenia compared to healthy controls.
Using the conditional inference paradigm to explore the basis for reduced mismatch negativity (MMN) size in individuals with schizophrenia.

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Abstract

Objective: To examine the integrity of inferential processes underlying the generation of mismatch negativity (MMN) within schizophrenia using a “conditional inference” paradigm. Methods: Sixty-five participants (35 diagnosed with schizophrenia or schizoaffective disorder and 30 matched controls) were presented two sequences of sound featuring an oddball MMN paradigm and novel MMN paradigm counterbalanced across participants as well as cognitive testing and clinical assessment. In each sequence, four rare deviants (duration, frequency, glide, loud) were presented amongst a sequence of regularly repeating identical standard tones. In one (Random sequence) deviants were presented pseudo-randomly distributed. In the other (Linked sequence) there was a conditional linkage created by consistently pairing the deviants. MMN was computed traditionally using deviant minus within-sequence standards and using a controlled method where deviant-as-standard ERPs were subtracted from deviant ERPs. Group differences in sequence effects and method of MMN computation were explored using mixed ANOVAs. Results: The schizophrenia group demonstrated a significant reduction in ‘traditional’ MMN compared to matched controls. This group difference was abolished using the ‘controlled’ method of computing MMN. The morphology of ERP to standard repetitive sounds was more differentiated in matched controls compared to those with schizophrenia. However, sequence by deviant effects were comparable between the two groups with both groups demonstrating reduced MMNs to duration and glide deviants in the linked versus random sequence. Conclusions and significance: The findings of this study are consistent with intact inferential processing within schizophrenia under conditions in which the inference can be used to reduce MMN size. Group differences to repetitive standards after 200ms had an impact on group differences in MMN size and highlight the need for more information on how early auditory processing deficits generally relate to smaller MMN in this group.
Introduction

Mismatch negativity (MMN) is a component of the auditory event-related potential (ERP), that presents as a negative deflection in response to a sound that deviates in some way from an otherwise homogenous sequence of auditory stimuli (1). MMN has been proposed to be a form of prediction error signal that indicates when an event does not conform to the expected. When exposed to a repetitious sequence of homogenous or ‘standard’ sounds the brain forms a memory of the sound characteristics and extrapolates a probabilistic-based inference of the likely properties of the next sound (2, 3). This perceptual inference is encoded as altered neural responsiveness to sound. Repeated exposure results in a diminished responsiveness to sounds that match anticipated properties, such as an identical repetitious standard. However MMN is elicited when the inference is incorrect, that is, when a sound is presented that deviates in some way from the homogenous sequence such as physical properties or timing etc. (‘deviant’ sound). The MMN therefore acts as a signal indicating that a memory-based expectation has been violated. The perceptual inference is then adjusted in response to the error to incorporate this new information in order to reduce the likelihood of future prediction errors (Winkler, Karmos & Näätänen, 1996). The size of the MMN elicited is dependent upon the degree to which the representation of the deviant sound varies from that of the standard sound properties, where greater differences are associated with larger MMN responses (4, 5).

Reduced MMN amplitude has been consistently demonstrated in those with schizophrenia (6). Smaller MMN size in schizophrenia has been identified amongst medicated (7) and non-medicated patients (8) and at very early stages of the illness (9). There is also evidence suggesting that reduced MMN size is present in those who are at elevated risk of developing schizophrenia (10) and has demonstrated predictive value in identifying who will transition into psychosis among those classified as being at ultra-high risk (11, 12).

There have been a number of hypotheses generated in an attempt to explain why MMN is reduced in schizophrenia. One hypothesis is that those with schizophrenia are less able to quantify the difference between deviant and standard events which contributes to reduced
MMN size due to imprecision in sound representation (13). Better performance on behavioural discrimination tasks has been found to correlate with larger and earlier MMN to sound deviations (14). Therefore any impairment in discrimination should lead to smaller MMN as the deviant event will be perceived as less distinct from the repeating pattern. If discrimination is indeed impaired in those with schizophrenia, the error between expected and actual events would not be registered if the representations of both events are largely overlapping, leading to a problem with prediction error estimation. This notion is supported by a number of studies revealing concurrent deficits in behavioural measures of tone discrimination and reduced MMN to changes in the same property of sound in persons with schizophrenia (15, 16). One recent study demonstrated that group differences in MMN size were abolished when the frequency difference between the deviant and the standard was individualised such that each participant could detect the difference with 79.4% accuracy on a behavioural detection task (17). Todd and colleagues (2012) however highlight that in the process of equating discriminability, Leitman and colleague’s study also results in the use of very small differences between standard and deviant sounds which earlier research suggests is not optimal for studying group differences and is not where group differences are most pronounced. An earlier study that found when a 1000Hz standard was used (as in Leitman et al) significant group differences in frequency MMN were only found when deviants differed by more than 20% from the standard (18). Reduced MMN generation in schizophrenia was found to be most pronounced when there is a large difference between the deviant and standard (i.e. under conditions in which discrimination is easier). This should be taken into consideration when viewing the result of Leitman and colleagues where the deviant sound used in the individualised condition differed on average by 3% and 14.4% for the control and schizophrenia groups respectively.

MMN size is affected by experimental manipulation the same way in schizophrenia as in healthy controls where increased amplitude reflects increasingly rare or larger physical deviation (18, 19). However, the MMN size in schizophrenia has been demonstrated to plateau
earlier where impairment in MMN generation is most pronounced where differences between the deviant and the standard are very large or where deviants are very rare (18, 20). As a result of this earlier plateau, equivalent MMN amplitude can occur to both small and larger violations of the expected sound properties. Similar results have been demonstrated using deviants occurring at different degrees of probability. For example, Javitt and colleagues (1998) demonstrated that for those with schizophrenia, the MMN generated to a sound occurring at 20% probability was not significantly different from that generated to a sound with 5% likelihood of occurring (18). As highlighted in a review by Todd and colleagues (2012), little is known about the functional consequences of what appears to be a reduced dynamic range for MMN size in schizophrenia.

Reduced neural plasticity mediated by N-Methyl-D-Aspartate glutamate (NMDA) receptor channels has been suggested to explain the earlier plateau in MMN amplitude in schizophrenia. NMDA receptors mediate excitatory synaptic transmission (21), specifically glutamatergic neurotransmission, which is critical to the processing of relationships between sounds in an MMN sequence. The experience-dependent alteration in neuron firing is reliant on the interaction between excitatory and inhibitory processes mediated by NMDA and Gamma-aminobutyric Acid (GABA_A) receptors (22). Pharmacological studies have demonstrated that the memory-based inference process underlying MMN is critically dependent upon the activity of the NMDA receptors (Javitt et al., 1996). When NMDA receptor channels are blocked in primates, the brain responds normally to the individual sounds in a sequence, while showing a dose-dependent decrease in response to violation in the pattern in sound. As there is no effect on ERP components of the standard repetitive sound, authors conclude that NMDA receptors are essential to representing the contextual memory of sound repetition (22). That is, NMDA receptor activity is believed to play a pivotal role in the integration of top-down biases with bottom-up confirmations of the predictions.
Additionally, MMN studies have provided indirect evidence linking vulnerability in the NMDA receptor system, and aberrant prediction-error coding to the propensity for psychotic symptom development (23, 24). Healthy participants who produce small MMN amplitudes at baseline have been found to exhibit the most pronounced psychotic-like symptom development following administration of the NMDA receptor antagonist ketamine. Ketamine administration has also been shown to cause a dose-dependent reduction in MMN amplitude in both primates (25) and humans (23). Given the demonstrated links, MMN reduction in schizophrenia has been proposed to index dysfunction in NMDA receptor mediated plasticity. The earlier plateau in MMN amplitude in schizophrenia may therefore indicate a reduced capacity to make context-sensitive predictions about the environment, or a core limitation in perceptual learning.

Hypofunction of glutamatergic neurotransmission has been identified as central in the neurochemistry of schizophrenia and has also been implicated in an observed reduction in cortical grey matter volume in schizophrenia (26). Coyle proposes hypofunction of the NMDA receptor system as 'a final common pathway that accounts for the neurophysiological dysfunction in the several affected brain regions that result in the symptoms of schizophrenia' (p 366, Coyle, 2006). As the pathology of schizophrenia progresses multiple affected brain regions exhibit changes in the density, number, size and organization of neurons which leads to disruption to local microcircuits (27). In a prospective study, progressive decline in frequency MMN has been shown to be significantly correlated with progressive loss of auditory cortical matter over the early course of schizophrenia (9). Smaller MMN amplitude to frequency and duration deviants been found to correlate with smaller grey matter volume in the auditory and frontal brain regions within those with schizophrenia but not in healthy controls (28). In sum, the reliable deficit in MMN size in schizophrenia appears early in the illness, is progressive and correlates with quantifiable structural brain pathology. Current theories include a possible tie to dysfunction in NMDA-receptor based plasticity – a proposition that finds additional support in one study that demonstrated that MMN amplitude in persons with schizophrenia (but not in
healthy controls) could be augmented by treatment with an indirect NMDA-receptor agonist(29). The present study features a new measure designed to be a potentially more sensitive index of this deficit while concurrently clarifying which aspects of the MMN system are intact and which are impaired in schizophrenia.

The paradigm was developed to be more taxing on perceptual learning and hence explore the notion of a core deficit in perceptual inference underlying reduced MMN in schizophrenia. MMN studies have traditionally used an ‘oddball’ paradigm where highly probable standard sounds are presented with interspersed pseudo-randomized presentation of rare deviants. The new paradigm features the same design with the addition of a second ‘linked’ sequence where two deviants are presented in pairs so that the first deviant (cue) predicts the occurrence of the second (cued) deviant with 100% accuracy (30). The linked sequence therefore introduces a second ‘contingency’ rule where the occurrence of the second deviant is contingent upon the presentation of the respective paired cue deviant.

Studies using stimulus linked sequences have demonstrated that the MMN to the second of the paired deviants is reduced (31-33) and importantly that this reduction in MMN to the second of the paired deviants occurs only after repeated pairing, i.e., the link must be learned (Nousak et al., 1995). The presentation of a cue deviant provides additional information to predict the likely properties of the next sound. The reduced MMN to the cued deviant has been termed “conditional inference” reflecting the presumption that the cue deviant sound enables the brain to make a context-dependent change in inference about the most likely properties of the next sound. Todd and colleagues suggest that learning the cue-link deviant pairing places a higher demand on memory and that using the occurrence of the cue to adjust predictions about sound properties is a highly dynamic application of learning (30, 31, 34).

The ‘Conditional Inference’ paradigm also has an advantage over traditional MMN sequences, in that it can control for the influence of discrimination ability on the MMN and therefore arguably refine the measurement of perceptual inference. In traditional sequences, the
size of the MMN will reflect the capacity to discriminate between the representation of the standard and deviant sounds. This will be true of MMN in both the random and linked sequences within the conditional inference paradigm. The key variable in the paradigm is the degree of change in MMN elicited to the deviant when it is cued versus randomly presented. Since the discriminability of the sounds is a constant in this comparison of the two methods of analysis, between group differences that may exist in discrimination are removed leaving the change in MMN size as a refined measure of the influence of learned association on perceptual inference (6).

The current study was designed to further explore the inference process and the basis for reduced MMN in schizophrenia. The conditional inference paradigm adopted in previous studies (30, 31, 34) was administered here to both a clinical sample of individuals diagnosed with schizophrenia as well as matched controls.
Method

Participants
Sixty-five volunteers participated in this study. The details of the sample can be seen in Table 1. The sample included 35 individuals within the schizophrenia group recruited either via the Australian Schizophrenia Research Bank (ASRB) or had previously participated in a prior study and had indicated that they would like to be contacted for future research as well as 30 age-matched controls recruited via the ASRB and from the community. The age range for the entire sample was 27-61; the mean age for the schizophrenia and matched control groups are presented in Table 1. There were 24 males within the schizophrenia group and 12 in the matched control group. All participants completed the Diagnostic Interview for Psychosis (35). In the schizophrenia group the DIP was used to confirm DSM-IV and ICD-10 diagnosis for Schizophrenia (n= 28) or Schizoaffective Disorder (n= 6). The average age of illness onset amongst the schizophrenia group was 19.23 years of age and the average illness duration of 19.73 years. All except one of the participants within the schizophrenia group were medicated at the time of assessment; 2 with typical, 31 with atypical and 1 with both typical and atypical antipsychotic medication. Chlorpromazine (CPZ) dose equivalents were calculated using published equivalencies for atypical antipsychotics (36) and ranged from 4.5 to 300mg/day. Of those medicated 12 were also taking a form of antidepressant or mood stabilizer. All volunteers were excluded from participating if they were under 18 or over 65 years of age, had any known neurological conditions, significant hearing impairments, serious head injury, used recreational drugs or were a heavy drinker of alcohol. Matched controls were also excluded if they were currently diagnosed or being treated for a mental illness or had a personal history or first degree relative with history of a psychotic disorder (ascertained using the DIP). Each participant provided written informed consent and was reimbursed $30 per appointment attended.

Clinical and Cognitive Assessment
All participants completed a cognitive assessment component of the study. This included completion of the Vocabulary and Matrix Reasoning subtests of the Wechsler Abbreviated
Scale of Intelligence (37) as well as Letter-Number sequencing and Digit Span (forward and backward) subtests of the Wechsler Adult Intelligence Scale- Fourth Edition (Wechsler, 2001) to obtain Full Scale IQ and Working Memory index scores for cognitive functioning. The Wechsler Test of Adult Reading (38) was also administered as an estimate of premorbid intelligence.

Individuals within the schizophrenia group also completed the Scale for Assessment of Positive Symptoms (39) and the Scale for Assessment of Negative Symptoms (40) to rate the severity of symptoms within the past six weeks. Level of functioning was also measured for those within the schizophrenia group using the self-report version of the Independent Living Skills Survey (41) and Global Assessment of Functioning Scale (42) based on the client’s responses to the Living Skills Survey and observations throughout the clinical interview and testing appointments.

**Stimuli and Sequences**

Two sound sequences (Random and Linked) were presented binaurally over headphones at a constant 400ms stimulus asynchrony. Both sequences contained 2200 pure tone sounds with 5ms rise/fall time. Although identical in composition, the discriminating feature between the two sequences was the degree to which the occurrence of the deviant could be predicted based on the preceding sound (31). As illustrated in Figure 1 both of the sequences contained a dominant identical standard repeated every 400ms with four low probability \((p =0.06\) each) deviants. The physical properties of the standard included presentation at 1000Hz, 756DB SPL, spanning 60ms duration. In the Random sequence, sounds were presented according to the traditional oddball paradigm where the highly probable standard sounds were interspersed with pseudo-randomized presentation of the rare deviants. In the Linked sequence the deviants were presented in pairs so that all duration deviants followed a randomly occurring frequency deviant and all glide deviants followed a randomly occurring loud deviant. All deviants in the
Random sequence and all deviant pairs in the Linked sequence were separated by a minimum of two standard sounds.

The sequence order was counterbalanced across participants. Sequences were divided into two shorter blocks of equal length to allow participants to have short breaks from sitting still. Each of the four sound sequences was preceded by 300 consecutive presentations of one of the deviants to obtain a ‘deviant-as-standard’ measure. The advantage of presenting a stream in which the cued deviant is presented as a repetitive sound is that the averaged ERP to these deviant-as-standards can then be used as a partial control for exogenous effects on the ERP when computing the MMN (31, 43).

Procedure
Participants completed a screening interview via telephone, if exclusion criteria did not apply the participants attended two appointments approximately two hours in duration. The cognitive and clinical assessments were completed first followed by the ERP in the second. Most participants selected to complete these two appointments on the same day with a lunch break between the appointments.

At the start of the first appointment an audiometric test for hearing thresholds across 750Hz to 4000Hz was conducted to screen for adequate hearing (thresholds below 25 dB SPL) before completing the DIP and SAPS and SANS as appropriate. Measures of cognitive function included those listed above and also two versions of the Continuous Performance Task; Identical Pairs (CPT-IP; (44) and the AX version (CPT-AX; (45)). The Continuous Performance Tasks were included as part of a broader research focus and are not included within this report.

For MMN measures, continuous EEG was recorded on a Synamps2 Neuroscan system using a Neuroscan Quickcap with tin electrodes at 1000Hz sampling rate (high-pass 0.1 Hz, low-pass 50Hz, and a fixed gain of 2010). EEG data was gathered from 12 electrode locations (FZ, FCZ, CZ, PZ, F3, FC3, C3, F4, FC4 and C4) in accordance with the 10/20 system and two electrodes for vertical and horizontal electro-oculogram recordings and electrodes placed over
the left and right mastoids all referenced to the nose. Participants were asked to remain as still as possible while recording, to ignore the sounds played over the headphones and to focus their attention on the closed captioned DVD movie presented with subtitles and sound muted.

**Data Processing and Analysis**

**ERP.** Eye blink artefacts were corrected using procedures implemented in Neuroscan (46). Movement artifacts contaminating the continuous recording were identified and manually deleted. Data were epoched from 50ms pre-stimulus to 400ms post-stimulus. Epochs were baseline corrected, averaged with respect to stimulus type, low-pass filtered (30 Hz for standards and deviants and 18 Hz for MMN) then baseline corrected to the pre-stimulus period.

Eight MMNs were calculated (one for each deviant in the Random and Linked sequence). For the purposes of this study, MMN that was computed by subtracting the ERP to the within-sequence repetitive standard from the ERP to the deviant (e.g. Random sequence standard from Random sequence deviants) will be termed ‘Traditional’ MMN. MMN that was computed by what has been termed the ‘controlled method’ (subtracting the average response to each deviant-as-standard from the respective deviants) was termed ‘Controlled’ MMN.

ERP data were analysed in a mixed model ANOVA. Group differences were visible in the response to deviant-as-standard ERPs over 225-335ms. The mean amplitude over this period was extracted over the frontal sites and analysed in a mixed model ANOVA with a between subjects factor of Group (Matched Control, Schizophrenia) and within-subjects factors of Type (Duration, Frequency, Loudness, Glide) and Site (FZ, F4, F3). Peak MMN amplitude was computed within 100 – 250 ms post stimulus for each of the eight MMN measures across fronto-central sites where MMN is maximal (FZ, F4 and F3). Group differences in traditional measures of Random Sequence MMN were explored in a mixed model ANOVA with a between subjects factor of Group (Matched Control, Schizophrenia) and within-subjects factor of Deviant (Duration, Frequency, Loudness and Glide), and Site (FZ, F3 and F4).
A mixed model ANOVA with between subjects factor of group (Matched Control, Schizophrenia) and between subjects factors of method of calculation (Traditional, Controlled), Deviant (Duration, Frequency, Loudness and Glide), and Site (FZ, F3 and F4) was then used to explore the effect of method of calculating MMN. Method was also explored within each group separately with a repeated-measures ANOVA using within subject factors of method of calculation (Traditional, Controlled), Deviant (Duration, Frequency, Loudness and Glide), and Site (FZ, F3 and F4).

The effect of sequence type was first assessed using a mixed model ANOVA with a between subjects factor of Group (Matched Control, Schizophrenia) and within-subjects factors of Sequence (Random, Linked), Type (Duration, Frequency, Loudness, Glide) and Site (FZ, F4, F3). This effect was then also assessed separately for both schizophrenia and matched controls MMNs within a repeated measures ANOVA using within-subjects factors of Sequence (Random, Linked), Deviant (Duration, Frequency, Loudness and Glide), and Site (F3, FZ and F4).

**Clinical and Cognitive Measures.** Raw scores were calculated for the WASI and WAIS subtests administered and converted into scaled scores using the United Kingdom norms. The scaled scores were then utilized to obtain a Full Scale IQ score from the Vocabulary and Matrix Reasoning subtests of the WASI and a Working Memory Index score was obtained using the scaled scores of the Letter-Number Sequencing and Digit Span subtests. Group differences on all clinical and cognitive measures were explored using independent sample t-tests. In addition to these measures, SAPS and SANS total scale and sub-scale scores, a GAF rating and Living Skills Survey subscale scores were calculated for the Schizophrenia group. Two-tailed Spearman Rank correlations were used to examine covariance between the clinical and cognitive measures.
Results

The means and standard deviations of each group for the demographic, clinical and cognitive measures are summarised in Table 1. Independent sample t-tests revealed a significant difference between the groups the WASI IQ estimate ($t_{(59)} = 2.76, p < .01$), but not the WTAR estimate of premorbid intelligence. There was also a significant group difference between Letter Number Sequencing ($t_{(52)} = 2.84, p < .01$) and Digit Span Total Scores ($t_{(62)} = 2.76, p < .01$). Within the schizophrenia group scores on the SAPS and SANS were highly varied with scores ranging from 0 – 93 and 0 – 60, respectively. The schizophrenia sample was also varied on level of functioning as measured by the Living Survey and GAF, where scores ranged from 6.20 – 9.52 and 35 - 80 respectively.

Spearman’s rank correlations were completed to explore any relationships between the clinical and/or cognitive measures. Lower WTAR scores significantly correlated with higher rating on the total SANS score ($r_{(34)} = -.29, p < .05$). Higher WASI scores were significantly related to higher level of functioning on the GAF ($r_{(34)} = .34, p < .05$). Lower levels of functioning, as measured by the GAF, was also significantly related higher rating both the total SAPS and total SANS ($r_{(34)} = -.48, p < .01$ and $r_{(34)} = -.65, p < .01$ respectively).

Deviant as Standard

The group averaged ERPs to each of the six repetitious tone sequences (Duration, Frequency, Loudness, Glide, Random Standard and Cued Standard) are presented in Figure 2. As evident in the figure there is a clear difference in morphology of ERPs generated by the schizophrenia group compared to the matched controls. This difference is confirmed by analysis of the mean amplitudes of repetitive sounds revealing a main effect of group ($F_{(1,62)} = 7.73, p < .01$) consistent with larger negativity over 225-335ms in the matched control group.

Group Differences in MMN to Traditional Random Sequence Deviants

Group averaged ERPs to each deviant type presented within the random sequence at FZ are presented in Figure 3. The first column contains MMN calculated via the Traditional method (subtracting the within sequence standard from the deviant waveform). A consistent
group difference can be seen across all deviants with the MMN elicited by the schizophrenia group being visibly smaller than that elicited by the matched controls. Analysis of the peak MMN amplitudes confirms this revealing a significant between-group difference in traditional MMN elicited to randomly presented deviants \((F_{1,62} = 4.63, p < .05)\). Although it appears in Figure 3 that the difference between the groups is most pronounced for MMN produced to the duration deviant, there was no significant interaction found between group and deviant. However a significant main effect of deviant was identified \((\varepsilon = .89, F_{3,186} = 11.21, p < .01)\) with MMN generally smaller to frequency deviants. A significant main effect of site \((\varepsilon = .91, F_{2,124} = 7.35, p < .001)\) was also found, which reflected the tendency for the MMN size to be smaller at F3 compared to FZ and F4.

**Method of MMN Calculation**

The right column of Figure 3 features MMN to each of the four deviants in the Random sequence when calculated using the respective deviant-as-standard ERPs (controlled method). Statistical analysis revealed significant main effects of method of calculation \((F_{1,62} = 6.19, p < .05)\), deviant \((\varepsilon = .94, F_{3,186} = 9.50, p < .01)\) and site \((\varepsilon = .93, F_{2,124} = 7.10, p < .01)\). That is MMN was less negative (smaller) when calculated using the controlled method. Again MMN tended to be smaller to the frequency deviants and MMN at F3 was generally smaller compared to FZ and F4. The method of calculation was further modified by a trend-level group by method interaction \((F_{1,62} = 3.00, p = .09)\). The effect of group was explored within the two methods of calculation separately. A significant group difference was found for the traditional method \((F_{1,62} = 4.63, p = .035)\), but not for the controlled method \((F_{1,62} = 2.55, p = .12)\).

Due to group differences in the response to standards, the effect of the method of calculation within the two groups were also explored separately within groups. Method of calculation had a significant impact on MMN size for the matched control group (MMN was smaller when the deviant-as-standard (controlled method) was used to calculate the MMN, \(F_{1,29} = 11.51, p < .01)\), but not for the schizophrenia group \((F_{1,29} = .25, p = .62)\).
Effect of Sequence Type

The MMN generated to the four deviant sounds in both the Random and Linked sequences at FZ, F4 and F3 are presented for both groups in Figure 4 (controlled method MMNs)\(^1\). As expected there are clear sequence effects on MMN amplitude for cued deviants (duration and glide) but not to the cue deviants (loud and frequency). This is evident in the graph where there is a notable change in plotted MMN amplitude across the Random and Linked sequences for the cued deviants only. The MMN elicited to cue deviants (Frequency and Loud) however are not significantly different between the linked and random sequences. Analysis confirmed a deviant by sequence interaction ($\epsilon = .93$, $F(3,186) = 18.54, p < .001$). This interaction was found to also be modified by site and group ($\epsilon = .80$, $F(6,372) = 2.42, p = .03$). To explore this interaction further, effects were analysed separately for each group and each sequence.

Analysis of the data from the schizophrenia group alone revealed a significant sequence by deviant interaction only ($\epsilon = .89$, $F(3,99) = 9.5, p < .001$). This is evidenced in Figure 4 where MMN amplitude for the schizophrenia group to duration and glide deviants but not the cue deviants were clearly smaller in the linked relative to the random sequence.

Within the matched control group the significant sequence by deviant interaction is also modified by site ($\epsilon = .73$, $F(6,174) = 3.53, p < .01$). MMN to each deviant was then analysed individually within this group, which revealed a main effect of sequence for the duration deviant ($F(1,33) = 58.71, p < .01$). This is clearly visible in Figure 4 where the MMN elicited to the duration deviant within the matched control group is significantly reduced when presented within the context of the linked sequence compared to that in the random sequence at all sites. A significant site by sequence interaction was found for the glide deviant ($\epsilon = .98$, $F(3,58) = 6.21, p < .01$). This is also clearly depicted in Figure 4 where the MMN amplitude within the matched control group to the glide deviant in the linked sequence is significantly reduced at FZ.

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\(^1\) Analyses are presented for controlled method MMNs only for compatibility with prior publications on the conditional inference effect. The results are equivalent for traditional method MMN.
and F3 but not at F4. As with the schizophrenia group, there was no significant effect of
sequence on MMN elicited to the Frequency and Loud deviants.
Discussion

The aim of the present study was to determine whether impaired inferential processes contribute to reduced MMN within schizophrenia. The inclusion of a ‘linked’ sound sequence (containing repeated deviant pairings) was presumed to enable the brain to make a context-dependent change in inference about the most likely properties of the next sound. The capacity for the schizophrenia and matched control groups to form this ‘conditional inference’ was examined by comparing the change in MMN elicited to the deviants in the random sequence vs. when cued in linked sequences. The results obtained suggest that sequence structure influences MMN amplitude similarly in those with schizophrenia compared to matched controls. The schizophrenia and matched control groups both demonstrated reduced MMN to the cued deviants (duration and glide) but not the cue deviants (frequency and loud) in the linked sequence. The smaller MMN to cued deviants in the linked sequence suggests that both groups demonstrated the ability to adjust their prediction about the properties of the next sound based on the learned association between the respective deviant pairs. The deviant by sequence interaction was found to be comparable between the two groups, consistent with there being no deficit in this measure of perceptual inference amongst those with schizophrenia. Despite this, there were several significant group differences found in the data.

A significant reduction in Traditional MMN in schizophrenia was identified compared to the matched controls. This finding is consistent with previous research (6, 30, 31, 47, 48), and the replication of this well-established phenomenon indicates that the schizophrenia sample who participated in this study were comparable to others in previous research.

The groups also differed significantly in ERP in response to the repetitious sound sequences, with matched controls eliciting a more negative response over 225 – 325ms. There is a paucity of data with which to compare this finding. Most MMN research examining the standard ERP waveforms explore any group difference over the period where MMN is maximal; between 100-300ms (19). This is a generally accepted form of analysis as it explores whether any difference in MMN may be a result of a difference in response to the standard over
that period. Unlike previous studies, the focus here was not only on the within-sequence standard, but also inclusion of ERP to each sound within the sequence as a repetitive tone. The period over which the group differences occur is not where MMN is maximal suggesting that group differences in MMN are not a direct result of differences in the response to the standard. The period where the group differences to the repetitious sound occur is consistent with an auditory N200. The N200 is a negative potential that peaks between 200-350ms post stimulus and is generally examined in response to target tones or sounds to which one must inhibit a proponent response (49). Neither situation was present in the unattended presentations of a sequence of irrelevant sound adopted by this study. It is therefore difficult to know what this component reflects in the present data.

The morphology of ERPs to the repetitious sequence of sound to different tones is more differentiated in the matched controls than in schizophrenia (Figure 2). It is tempting to suggest that this might reflect greater precision in encoding or more perceptual discriminability within matched controls. However, a group difference occurring at this long latency is more consistent with endogenous effects on the ERP (those reflecting psychological demands) rather than exogenous effects (those reflecting properties of the sensory stimuli) (50). ERP components occurring after approximately 100ms are considered to be largely independent of the physical features of the stimulus (50). There are certainly small differences over the N1/P2 in some cases (e.g. frequency and loud tones (51) however the area of greatest group difference is evident after 200ms, an area not generally associated with stimulus characteristics (Rugg & Coles, 1995). It is noteworthy that there are pronounced age-related declines in this ‘component’ of the waveform to repetitive tones observed both in our lab (Todd et al., manuscript in preparation), and visible in published data (Figure 5, (52), Figure 3 (53). It is possible that the schizophrenia related decline in amplitude seen here is an exacerbation of whatever causes this age-related decline. The relevance of this finding remains open.
When using the controlled method of compute MMN, the group difference, while visible in *Figure 4*, is no longer significant. Method of calculating the MMN therefore had an impact on the size of the group difference in MMN. The purpose of including this method of calculation was to obtain a more ‘pure’ measure of the memory-based component of MMN. The elimination of the group difference in controlled MMN could suggest that processes other than memory-based processes play a major role in generating the group difference identified in the uncontrolled (Traditional) MMN.

The site dependent reduction in MMN elicited to the glide deviant in matched controls but not schizophrenia is also perplexing. MMN elicited by matched controls at F4 to the glide deviant does not significantly differ between the linked and random sequences. This result is not consistent with previous findings of Todd and Mullens (2011) where a MMN reduction to glide deviant in the linked sequence was not site dependent for young controls. There is however a notable, 14 year difference in the mean ages of the samples in the present study and that of Todd and Mullens, which may explain the inconsistency between the two findings. For example, perhaps it is possible that older adults can use predictive information to adjust the main supratemporal MMN generators but not the contribution from prefrontal cortex (typically localised to right inferior frontal gyrus (54)) leading to no significant change in linked glide MMN at the F4 site. This is certainly consistent with a posthoc observation of data referenced to the nose. Using this reference the mastoid electrode sites represent a more direct index of supratemporal generators and frontal sites represent a combination of the two (55). The matched controls show very clear reduction in cued glide MMN over mastoid sites but not frontal sites (see Supplementary Figure 1). This is not true of young controls where MMN is reduced at both mastoid and frontal sites (see Figure 2, Todd & Mullens, 2011). It is not clear why this true of the glide but not duration MMN nor why this pattern is absent in schizophrenia. However, schizophrenia is thought to be associated with a particularly pronounced reduction in frontal generators of MMN. If this is the case, there would be less
frontal contribution to the random MMN which could then explain why any age-related impairment in reducing this component in the linked sequence has limited impact on the data. These possibilities are of course speculative and the answers require data with a higher montage suitable for source analysis.

The findings of the present study have provided further insight into what is intact, and what is not in the system underlying MMN generation in schizophrenia. In the present study, persons with schizophrenia are equally able to reduce MMN to a rare deviation from a commonly occurring standard when provided with information about when the sounds will occur. What these results highlight is that if the reduced size of MMN to cued deviants in the linked sequence reflects a dynamic shift in the prediction model, then this process is intact within schizophrenia. Despite this, MMN size overall remains smaller in this group. Our results indicate that there are group differences in responding to repetitive trains of physically distinct sounds. It is certainly possible that the factors contributing to these group differences are also contributing to smaller MMN size. Illuminating the causes of group difference in response to tones in this “n200” timeframe may be a useful path forwards in understanding the early auditory processing deficits giving rise to smaller MMN size.
References

40. Andreasen NC. Scale for the Assessment of Negative Symptoms (SANS). Iowa City: University of Iowa; 1983.
### Tables and Figures

#### Table 1

*Demographic and Clinical Group Means and Standard Deviations in Parentheses*

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#### Figure 1

*Diagram of the Random and Linked sequence structure presented to participants.*
Figure 2. MMN to Standard ERP for Matched Control and Schizophrenia groups.
Figure 3. MMN elicited at FZ to deviant sounds calculated by Traditional and Controlled methods for Matched Control and Schizophrenia groups.
Figure 4. MMN elicited by schizophrenia and matched control groups to cue and cued deviants within Random and Linked sequences across F3, FZ and F4.
Supplementary Figure 1. MMN elicited by matched controls to cue and cued glide deviants within Random and Linked sequences – Nose-referenced data.
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Appendix A

Clinical Neurophysiology Guide for Authors

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Eigenfactor Score Clinical Neurophysiology ranks 36th out of 230 in the Neurosciences category and 15th out of 167 in the category Clinical Neurology.
Appendix B

HUMAN RESEARCH ETHICS COMMITTEE

Notification of Expedited Approval

To Chief Investigator or Project Supervisor: Dr. Juanita Todd
Cc Co-Investigators / Research Students: Professor Patricia Michie
                                      Associate Professor Ulrich Schall
Re Protocol: Primitive intelligence in the brain: Tracking sound patterns to predict future events
Date: 29-Jun-2009
Reference No.: H-2009-0164
Date of Initial Approval: 25-Jun-2009
Approved To: 24-Jun-2012

Thank you for your Response to Conditional Approval submission to the Human Research Ethics Committee (HREC) seeking approval in relation to the above protocol.

Your submission was considered under Expedited review by the Chair/Deputy Chair.

I am pleased to advise that the decision on your submission is Approved effective 25-Jun-2009.

Approval is granted to the date indicated above or until the project is completed, whichever occurs first. If the approval of an External HREC has been ‘noted’ the approval period is as determined by that HREC.

The full Committee will be asked to ratify this decision at its next scheduled meeting. A formal Certificate of Approval will be available upon request. Your approval number is H-2009-0164.

If the research requires the use of an Information Statement, ensure this number is inserted at the relevant point in the Complaints paragraph prior to distribution to potential participants. You may then proceed with the research.

Conditions of Approval

This approval has been granted subject to you complying with the requirements for Monitoring of Progress, Reporting of Adverse Events, and Variations to the Approved Protocol as detailed below.

PLEASE NOTE:
In the case where the HREC has ‘noted’ the approval of an External HREC, progress reports and reports of adverse events are to be submitted to the External HREC only. In the case of Variations to the approved protocol, or a Renewal of approval, you will apply to the External HREC for approval in the first instance and then Register that approval with the University’s HREC.

* Monitoring of Progress

Other than above, the University is obliged to monitor the progress of research projects involving human participants to ensure that they are conducted according to the protocol as approved by the HREC. A progress report is required on an annual basis. You will be advised when a report is due.
Reporting of Adverse Events

1. It is the responsibility of the person first named on this Approval Advice to report adverse events.

2. Adverse events, however minor, must be recorded by the investigator as observed by the investigator or as volunteered by a participant in the research. Full details are to be documented, whether or not the investigator, or his/her deputies, consider the event to be related to the research substance or procedure.

3. Serious or unforeseen adverse events that occur during the research or within six (6) months of completion of the research, must be reported by the person first named on the Approval Advice to the (HREC) by way of the Adverse Event Report form within 72 hours of the occurrence of the event or the investigator receiving advice of the event.

4. Serious adverse events are defined as:
   - Causing death, life threatening or serious disability.
   - Causing or prolonging hospitalisation.
   - Overdoses, cancers, congenital abnormalities, tissue damage, whether or not they are judged to be caused by the investigational agent or procedure.
   - Causing psycho-social and/or financial harm. This covers everything from perceived invasion of privacy, breach of confidentiality, or the diminution of social reputation, to the creation of psychological fears and trauma.
   - Any other event which might affect the continued ethical acceptability of the project.

5. Reports of adverse events must include:
   - Participant's study identification number;
   - Date of birth;
   - Date of entry into the study;
   - Treatment arm (if applicable);
   - Date of event;
   - Details of event;
   - The investigator's opinion as to whether the event is related to the research procedures; and
   - Action taken in response to the event.

6. Adverse events which do not fall within the definition of serious, including those reported from other sites involved in the research, are to be reported in detail at the time of the annual progress report to the HREC.

Variations to approved protocol

If you wish to change, or deviate from, the approved protocol, you will need to submit an Application for Variation to Approved Human Research. Variations may include, but are not limited to, changes or additions to investigators, study design, study population, number of participants, methods of recruitment, or participant information/consent documentation. Variations must be approved by the (HREC) before they are implemented except when registering an approval of a variation from an external HREC which has been designated the lead HREC, in which case you may proceed as soon as you receive an acknowledgement of your Registration.

Linkage of ethics approval to a new Grant

HREC approvals cannot be assigned to a new grant or award (ie those that were not identified on the application for ethics approval) without confirmation of the approval from the Human Research Ethics Officer on behalf of the HREC.

Best wishes for a successful project.

Associate Professor Alison Ferguson
Chair, Human Research Ethics Committee