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## Abnormal Pitch Mismatch Negativity in Individuals with Schizotypal Personality Disorder

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### Abstract

**Background**—The goal of the study was to examine mismatch negativity (MMN) in schizotypal personality disorder (SPD) individuals. Abnormal MMN has been a consistent finding in chronic schizophrenia and there are also have been reports of reduced duration MMN in first episode schizophrenia patients (Umbricht & Krljes, 2005), with some studies finding no pitch MMN amplitude differences (Salisbury et al., 2002) while others reporting a modest reduction (Umbricht et al., 2006) in recent onset schizophrenia patients. To our knowledge no reports exist of MMN in SPD individuals.

**Methods**—Twenty six normal (14 females) control and 23 SPD (12 females) individuals were tested using the pitch MMN paradigm. Normal control (NC) and SPD individuals were recruited

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C.C. Dickey reviewed the manuscript and collaborated on the design of the experiment. M.Voglmaier supervised neuropsychological testing and conducted clinical assessments of the participants.

L.J. Seidman contributed to that grant that supports this work, participated in diagnostic reliability studies, and contributed to the manuscript writing.

M.E. Shenton reviewed drafts of the manuscript and provided important feedback on various aspects of the research.

R.W. McCarley contributed funding that supports this work, helped develop the protocol, helped with data analysis, and manuscript writing.

All authors approved the final manuscript.

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from the general population and assessed using DSM-IV. SPD individuals were included if they met 5 or more criteria for SPD disorder. The subjects listened to 2000 frequent 1 kHz pure tones and 100 rare 1.2 kHz pure tones while reading a magazine article. MMN was measured from a difference waveform within the latency window of 175–276 msec.

**Results**—Reduced MMN amplitude was found in SPD relative to NC subjects ( $p < 0.045$ ).

**Conclusions**—These results point to potential differences between SPD and schizophrenia, where no reduction in MMN was found in most studies of first episode patients.

### Keywords

MMN; SPD; schizophrenia; auditory processing; auditory cortex

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### Introduction

Schizotypal personality disorder (SPD) has been proposed to belong to schizophrenia spectrum disorders with several lines of evidence documenting similarities between SPD and schizophrenia in clinical, neuropsychological, electrophysiological and brain structure domains. The study of SPD is important for several reasons. It allows studying both commonalities and differences between SPD and schizophrenia without the confounding effects of chronicity and medication. The study of SPD also provides a different perspective than the study of family members of schizophrenia patients in that symptoms are present in the SPD albeit in a milder form. SPD is different from the study of first episode patients because SPD does not progress to frank psychosis. Therefore, studying SPD individuals makes possible identification of neurobiological mechanisms that may be associated with heritable traits and may help identify protective mechanisms that prevent progression. A measure of the interest in SPD because of these features is the 501 papers devoted to SPD in the last 5 years (PubMed search 6/03/08).

One of the better documented findings in chronic schizophrenia is a dysfunction in the auditory system, specifically in the sensory pre-attentive processing as measured by mismatch negativity (MMN). MMN is an event related potential generated when a feature of the stimulus presented on a given trial deviates from features of preceding stimuli, e.g., in terms of duration, frequency or intensity. It is believed that repeatedly presented auditory stimuli generate a template in short-term auditory (echoic) memory. Provided that this template is available for comparison, any stimulus that does not match it elicits MMN (Näätänen et al., 2001). Thus, MMN can be used as an index of the integrity of echoic memory. However, modulatory contributions from attention have been also observed (e.g., Sabri et al., 2006).

Mismatch negativity is thought to be generated primarily in auditory cortex with contributions from secondary auditory cortex (e.g., Javitt et al., 1994; Oknina et al., 2005; Oades et al., 2006; Saint-Amour et al., 2007) and frontal sources (e.g., Näätänen, 1995; Oknina et al., 2005; Oades et al., 2006). The available evidence suggests an involvement of the N-methyl-D-aspartate receptor (NMDAR) in the generation of MMN (Javitt et al., 1994; Javitt et al., 1996; Umbricht et al., 2000; Pang & Fowler, 1999). However, MMN reductions

after treatment with ketamine have not been found (Oranje et al., 2000). In addition, modulating influences of GABA-ergic (Rosburg et al., 2004) and nicotinic receptors (Inami et al., 2005; Baldeweg et al., 2006) have also been noted. Finally, it has been reported (Baker et al., 2005) that COMT Val<sup>108/158</sup> Met polymorphism modifies MMN amplitude in individuals with 22q11 deletion syndrome, suggesting the involvement of catecholamines in the generation of MMN and in mediating aspects of schizophrenia symptoms.

The original finding of abnormal MMN in chronic schizophrenia (Shelley et al., 1991) has been well replicated (see Umbricht & Krljes, 2005; Niznikiewicz et al., 2004) but it is unclear if it is present by the time of the first episode. The critical differences between studies in terms of reported results seem to be related to how soon after the illness onset the patients were assessed and to their clinical status, since there is now evidence for a progression of pitch MMN abnormalities in the 1.5 years following first hospitalization (Salisbury et al., 2007). For example, normal MMN has been reported in first episode schizophrenia (Salisbury, et al., 2002; Valkonen-Korhonen et al., 2003; Salisbury et al., 2007; Javitt et al., 2000), unaffected twins (Ahveninen et al., 2006) and unaffected first degree relatives of schizophrenia patients (Bramon et al., 2004).

Reduced MMN that correlated with Heschl gyrus has also been reported in first episode patients re-tested 1.5 years later (Salisbury et al., 2007). Also, reduced MMN was found in patients 3.5 years into their illness (Javitt et al., 2000), in recent onset schizophrenia (Umbricht et al., 2006) and those first episode patients who presented with low pre-morbid educational achievement (Umbricht et al., 2006). Also, reduced MMN has been reported in adolescents at the onset of illness (Oknina et al., 2005; Oades et al., 2006), adolescent individuals with 22q11 deletion syndrome who did not manifest schizophrenia (Baker et al., 2005), and in children at high risk for schizophrenia (Schreiber et al., 1992), and socially withdrawn children (Bar-Haim et al., 2003). Reduced duration MMN has also been reported in relatives of schizophrenia patients (Michie et al., 2002), and in prodromal subjects relative to normal controls (but not significantly) (Brokhaus-Dumke et al., 2005).

Given that most studies, especially those using pitch MMN paradigms, did not find reduced MMN in first episode schizophrenia patients, a simple model of increasing severity from SPD to first episode to chronic schizophrenia would suggest that no MMN abnormality should be found in SPD. However, if the constellation of symptoms in each of these groups do not conform to a linear model of increasing severity, MMN abnormality may be present in SPD even if it is absent in first episode schizophrenia. In addition, we need to consider that, as mentioned above, in spite of genetic similarities, SPD is not a milder form of schizophrenia and it may instead be associated with a unique presentation in terms of biological and neurophysiological manifestations.

To date, there are no existing studies of MMN ERP in SPD. Thus, the current study sought to examine pre-attentive auditory processing in individuals diagnosed with SPD in order to add to our understanding of auditory pre-attentive functioning in schizophrenia spectrum disorders. We have used a MMN paradigm with pitch deviants in a community recruited sample of SPD meeting full diagnostic DSM-IV criteria.

## Methods

### Subjects

Twenty six normal comparison subjects (14 females) and 23 SPD individuals (12 females) were tested. The two groups did not differ in age, IQ, years of education, socioeconomic status (SES) or parental SES (see table 1). There were also no differences between SPD men and women in clinical variables derived from a SCID interview (see Table 2).

SPD subjects lived in the local community, were recruited into the study with newspaper ads, and had never been exposed to psychotropic medications. They were diagnosed based on a SCID-II interview and accepted into the study if they fulfilled 5 out of 9 DSM-IV SPD criteria. The diagnostic criteria include: 1) ideas of reference (excluding delusions of reference), 2) odd beliefs or magical thinking that influences behavior and is inconsistent with sub-cultural norms, 3) unusual perceptual experiences including bodily illusions, 4) odd thinking and speech, 5) suspiciousness or paranoid ideation, 6) inappropriate or constricted affect, 7) behavior or appearance that is odd, eccentric or peculiar, 8) lack of close friends or confidants other than first-degree relatives and 9) excessive social anxiety that does not diminish with familiarity. Normal control subjects (NC) were recruited via newspaper ads and were screened for psychopathology using a SCID interview. To be included in the study the participants could not suffer from neurological illness that would affect central nervous function, abuse drugs or alcohol for the last 6 months, they should be right-handed and speak English as their first language, and normal comparison subjects could not have a first degree relative with Axis I or Axis II disorder. The SPD individuals could not carry the diagnosis of schizophrenia, and none of the SPD participants had a relative with a history of schizophrenia.

Before participating in the study, all participants had the procedures fully explained to them and read and signed an informed consent form to confirm their willingness to be in the study. The consent form has been approved by the local Institutional Review Board committee for the protection of human subjects.

### EEG recording and experimental paradigm

EEG was recorded using a 64-channel electrode cap and a Neuroscan Synamp system. There were 2000 tones which included 95% frequent tones and 5% rare tones, delivered binaurally at 1 kHz for frequent tones and 1.2 kHz for the rare tone, at 75 dB loudness, 100 ms in duration and 10 ms rise/fall times, over Sony Dynamic stereo headphones. The ISI was 300 msec. The subjects listened to the tones while reading a magazine article. The left ear electrode was used as a reference and the EEG was re-referenced to average ears off-line. The impedances across all electrodes were held below 5 kOhms. The EEG data were corrected for artifacts and averaged off-line. Eye movements were mathematically corrected, and the EEG was low-pass filtered at 24 Hz. The EEG was epoched into 300 ms segments with a 100 ms baseline. Trials exceeding  $\pm 100$  microvolts were excluded from further analysis. The average number of trials accepted for analysis was 887.8 in normal comparison and 887.8 in SPD individuals for the frequent stimulus and 98.9 in normal comparison and 98.7 in the SPD group for the deviant stimulus, and these numbers were not

statistically different. Separate individual waveforms were computed to rare and frequent tones and individual difference waveforms were constructed. The MMN was measured at Fz and Cz as a mean amplitude under the curve between 125–226 ms post-stimulus onset in a difference waveform.

### **Clinical and Neuropsychological Measures**

IQ was measured using the Vocabulary and Block Design subscales of the WAIS-R (Brooker and Cyr, 1986). Clinical data were derived from a SCID for DSM-IV Personality Disorders, the SES was computed from the Hollingshead Index of Social Position, and handedness from the Edinburgh Index of Handedness.

### **Statistical analyses and results**

MMN amplitude was analyzed using a MANOVA model with group (SPD and NC) as a between subject factor and electrode as a within subject factor. A reduced MMN was found in SPD subjects relative to NC subjects ( $F(1,47) = 4.23, p < 0.045$ ) (see Figure 1; effect size of .72). There was also a main effect of electrode ( $F(1,47) = 20.9, p < 0.0001$ ) with a larger MMN recorded at Fz than at Cz. We also correlated the number of SPD symptoms with MMN amplitude at Fz and Cz. There was no association between symptom severity and MMN.

### **Discussion**

In this study, a reduced pitch MMN was found in the SPD group relative to NC individuals. To our knowledge, this is the first study of MMN in SPD and the first one to report reduced MMN in this population. A medium effect size of .72 was associated with this finding. Given the very stringent inclusion criteria, and the fact that the MMN reduction was observed in SPD individuals who did not have 1<sup>st</sup>-degree relatives with schizophrenia, and thus in whom the expected effect size would be modest, we believe that we are reporting a novel and reliable finding, albeit in need of replication. Given the lack of other studies on MMN in SPD, the comparisons can be made only with studies of first episode schizophrenia and persons in the putative prodrome to psychosis to provide some context for this finding.

The reduced MMN in SPD found in this study is in contrast with several studies of first episode schizophrenia and one study of the prodrome where either normal pitch MMN or non-significantly reduced duration MMN have been reported, as reviewed in the Introduction. On the other hand, some reports have suggested reduced MMN in clinically vulnerable populations (Oknina et al., 2005; Oades et al., 2006; Schreiber et al., 1992; Bar-Haim et al., 2003) and in first episode schizophrenia patients 1.5 years after first hospitalization (Salisbury et al., 2007). This result also contrasts with the pattern of results obtained for SPD subjects across several different domains where, if one applied a simple model of a linear progression of severity, SPD subjects were the least severely affected and chronic schizophrenia patients were the most severely affected. For example, less P50 suppression, a measure of sensory gating, has been found in SPD individuals (Cadenhead et al., 2000; 2002). A modestly reduced P300 has been also reported in SPD (Niznikiewicz et al., 2000; Salisbury et al., 1996). Reduced P300 has been found in first episode

schizophrenia thus bolstering the notion that disease related changes might be occurring before the first episode and that their first appearance may be documented in less affected populations such as prodromal individuals and, likely, in SPD, even though at a reduced level. In contrast, P300 amplitude reduction in chronic schizophrenia is a well described finding (Niznikiewicz et al., 2004). Progression of severity has also been documented for semantic operations. For example, the most abnormal N400, an index of semantic processes, was found in chronic schizophrenia while the least abnormal N400 was found in female SPD (Niznikiewicz et al., 1997; Niznikiewicz et al., 2002).

We believe that the results obtained in this study are important for our understanding of schizophrenia spectrum disorder for several reasons: First, our findings suggest that a simple linear model of schizophrenia spectrum disorders may not apply to all cognitive operations. Thus, the presence of abnormalities found in SPD in operations associated with sensory gating as marked by P50 suppression, auditory working memory, such as those indexed by the P300, as well as those associated with semantic operations as indexed by the N400, are consonant with the model of gradual progression of severity within schizophrenia spectrum disorders. On the other hand, abnormal pitch MMN found in SPD, and not found in first episode patients is not consonant with this model. Rather it is supportive of a model of the partial overlap between schizophrenia and schizotypal personality disorder. According to this view, some aspects of a cognitive breakdown characteristic of schizophrenia can be profitably studied using SPD as a model not complicated by chronicity and medication, while other aspects would have to be understood as unique features of schizotypy.

Second, these results underscore the importance of a careful characterization of the sample under investigation. SPD individuals examined in this study have been unique in the sense that they are not a college student-based population as reported in several previous publications. Following careful clinical examination, the SPD individuals in the current study, unlike college student samples, fulfilled five or more DSM-IV-defined criteria for SPD disorder. On the other hand, from the subjects' subjective perspective, they were not affected enough to seek clinical help: none of the SPD individuals was taking medication to alleviate their schizotypal symptoms, nor seeing a psychiatrist or visiting a psychiatric clinic to seek help with their problems. In addition, none of the subjects reported having a relative with schizophrenia. It is likely that these sample characteristics may have contributed to the present results.

Finally, yet another possible source of differences between this study and these studies in the literature that did not report MMN in first episode schizophrenia patients or schizophrenia relatives are methodological differences. We note here that Salisbury et al., 2002, 2007 study was methodologically the closest to the current study both in terms of the equipment and stimuli used. The two important factors in which the two studies differed were the age of the subjects (the subjects in the present study are older by about 5 years) and a distractor task: in the present study subjects were asked to read a book while in the Salisbury et al. studies, the subjects were asked to press a button to a checkerboard reversal. The remaining studies, as reviewed in the Introduction, varied also in terms of the stimuli used: typically lower frequency stimuli were used (e.g., 800 Hz for a standard and 600 Hz for a deviant).

In considering how these differences might influence the outcome measure, we will discuss two: age and the nature of the distractor task. If age is correlated with severity level then younger subjects would be expected to not manifest reduced MMN while older subjects would (Salisbury, personal communication 9/22/08). However, this argument is far from straightforward since severity level is not a simple function of age but also depends on genetic loading for schizophrenia and other possible environmental factors as studies reporting reduced MMN in prodromal and early first episode individuals seem to indicate (e.g., Oknina et al., 2005; Oades et al., 2006, and Baker et al., 2005). The nature of a distractor task also needs to be considered, especially in the context of reports of attentional influences on MMN (e.g., Sabri et al., 2006). For example, it is possible that attentional demands posed by different distractor tasks may be contributing to the differences between studies.

While these results suggest reduced MMN in the SPD group, they do not address a possible underlying cause for the reduction. One putative factor could be a structural abnormality in the regions identified as including MMN generators. For example, reduced left Heschl gyrus was found in male SPD (Dickey et al., 2002), and a volume of the left STG in female SPD was associated with odd speech (Dickey et al., 2003). Furthermore, in a recent fMRI study (Dickey et al., 2008) that used MMN-like paradigm (block design), more activation was found in the STG, bilaterally, to pitch deviants in the SPD relative to normal comparison individuals.

In summary, this is the first study to report reduced MMN ERP in a carefully diagnosed SPD population. As such, these results should be construed as preliminary and in need of replication. In addition, in this study, only pitch deviants were used. Previous reports in schizophrenia populations suggest that duration MMN may be more sensitive to early abnormalities in auditory processing. We are currently in the process of collecting both pitch and duration MMN data in an independent SPD sample.

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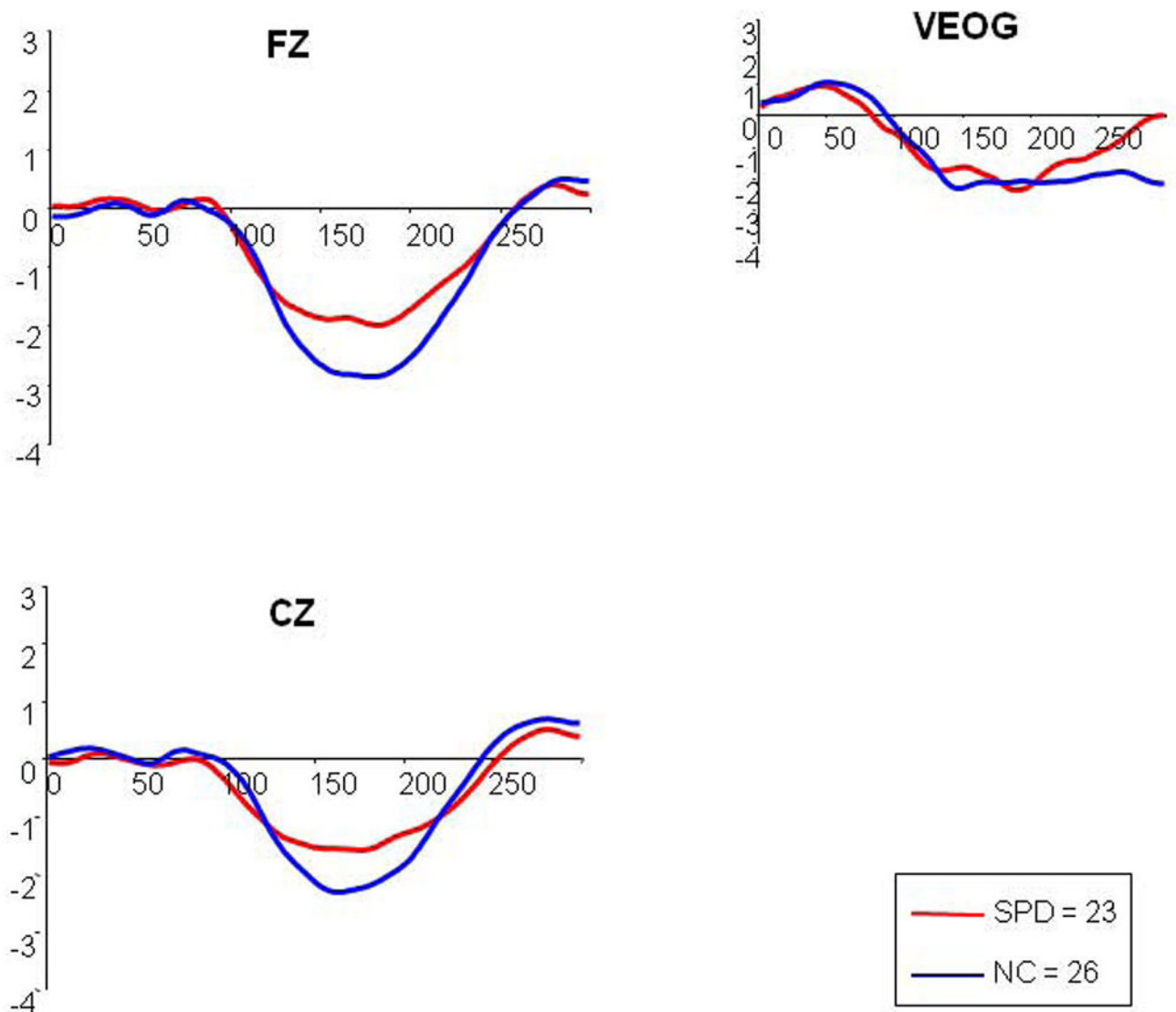
## References

- Ahveninen J, Jaaskelainen IP, Osipova D, Huttunen MO, Ilmoniemi RJ, Kaprio J, Lonnqvist J, Manninen M, Pakarinen S, Therman S, Näätänen R, Cannon TD. Inherited auditory-cortical dysfunction in twin pairs discordant for schizophrenia. *Biological Psychiatry*. 2006; 60(6):612–620. [PubMed: 16876141]
- Baker K, Baldeweg T, Sivagnanasundaram S, Scambler P, Skuse D. COMT Val108/158 Met modifies mismatch negativity and cognitive function in 22q11 deletion syndrome. *Biological Psychiatry*. 2005; 58(1):23–31. [PubMed: 15935994]
- Baldeweg T, Klugman A, Gruzelier J, Hirsch SR. Mismatch negativity potentials and cognitive impairment in schizophrenia. *Schizophrenia Research*. 2004; 69(2–3):203–217. [PubMed: 15469194]
- Baldeweg T, Wong D, Stephan KE. Nicotinic modulation of human auditory sensory memory: Evidence from mismatch negativity potentials. *International Journal of Psychophysiology*. 2006; 59(1):49–58. [PubMed: 16313986]



- Bar-Haim Y, Marshall PJ, Fox NA, Schorr EA, Gordon-Salant S. Mismatch negativity in socially withdrawn children. *Biological Psychiatry*. 2003; 54(1):17–24. [PubMed: 12842304]
- Bramon E, Croft RJ, McDonald C, Viridi GK, Gruzeliier JG, Baldeweg T, Sham PC, Frangou S, Murray RM. Mismatch negativity in schizophrenia: a family study. *Schizophrenia Research*. 2004; 67(1):1–10. [PubMed: 14741319]
- Brockhaus-Dumke A, Tendolkar I, Pukrop R, Schultze-Lutter F, Klosterkötter J, Ruhrmann S. Impaired mismatch negativity generation in prodromal subjects and patients with schizophrenia. *Schizophrenia Research*. 2005; 73(2–3):297–310. [PubMed: 15653275]
- Brooker BH, Cyr JJ. Tables for clinicians to use to convert WAIS-R short forms. *Journal of Clinical Psychology*. 1986; 42:983–986.
- Cadenhead KS, Light GA, Geyer MA, Braff DL. Sensory gating deficits assessed by the P50 event-related potential in subjects with schizotypal personality disorder. *Am J Psychiatry*. 2000 Jan; 157(1):55–9. [PubMed: 10618013]
- Cadenhead KS, Light GA, Geyer MA, McDowell JE, Braff DL. Neurobiological measures of schizotypal personality disorder: defining an inhibitory endophenotype? *Am J Psychiatry*. 2002 May; 159(5):869–71. [PubMed: 11986147]
- Dickey CC, McCarley RW, Voglmaier MM, Frumin M, Niznikiewicz MA, Hirayasu Y, Fraone S, Seidman LJ, Shenton ME. Smaller left Heschl's gyrus volume in patients with schizotypal personality disorder. *Am J Psychiatry*. 2002 Sep; 159(9):1521–7.
- Dickey CC, McCarley RW, Voglmaier MM, Niznikiewicz MA, Seidman LJ, Dimeo S, Frumin M, Shenton ME. An MRI study of superior temporal gyrus volume in women with schizotypal personality disorder. *Am J Psychiatry*. 2003 Dec; 160(12):2198–201. [PubMed: 14638590]
- Dickey CC, Morocz I, Niznikiewicz MA, Voglmaier M, Toner S, Khan U, Dreusicke M, Yoo SS, Shenton ME, McCarley RW. Auditory processing abnormalities in schizotypal personality disorder. An fMRI experiment using tones of deviant pitch and duration. *Schiz Res*. 2008 Aug; 103(1–3):26–39.
- Inami R, Kirino E, Inoue R, Arai H. Transdermal nicotine administration enhances automatic auditory processing reflected by mismatch negativity. *Pharmacology, Biochemistry, and Behavior*. 2005; 80(3):453–61.
- Javitt DC, Shelley A, Ritter W. Associated deficits in mismatch negativity generation and tone matching in schizophrenia. *Clinical Neurophysiology*. 2000; 111(10):1733–1737. [PubMed: 11018486]
- Javitt DC, Steinschneider M, Schroeder CE, Arezzo JC. Role of cortical N-methyl-D-aspartate receptors in auditory sensory memory and mismatch negativity generation: implications for schizophrenia. *Proceedings of the National Academy of Sciences of the United States of America*. 1996; 93(21):11962–11967. [PubMed: 8876245]
- Javitt DC, Steinschneider M, Schroeder CE, Vaughan HG Jr, Arezzo JC. Detection of stimulus deviance within primate primary auditory cortex: intracortical mechanisms of mismatch negativity (MMN) generation. *Brain Research*. 1994; 667(2):192–200. [PubMed: 7697356]
- Light GA, Braff DL. Mismatch negativity deficits are associated with poor functioning in schizophrenia patients. *Archives of General Psychiatry*. 2005; 62(2):127–136.
- Michie PT, Innes-Brown H, Todd J, Jablensky AV. Duration mismatch negativity in biological relatives of patients with schizophrenia spectrum disorders. *Biological Psychiatry*. 2002; 52(7):749–758. [PubMed: 12372666]
- Näätänen R. The mismatch negativity: a powerful tool for cognitive neuroscience. *Ear and Hearing*. 1995; 16(1):6–18. [PubMed: 7774770]
- Näätänen R, Tervaniemi M, Sussman E, Paavilainen P, Winkler I. Primitive Intelligence in the auditory cortex. *Trends in Neuroscience*. 2001; 24(5):283–288.
- Niznikiewicz MA, O'Donnell BF, Nestor PG, Smith L, Law S, Karapellou M, Shenton ME, McCarley RW. ERP assessment of visual and auditory language processing in schizophrenia. *Journal of Abnormal Psychology*. 1997; 106(1):85–94. [PubMed: 9103720]
- Niznikiewicz, MA.; Spencer, KM.; Salisbury, DF.; McCarley, RW. Event related potentials. In: Lawrie, SM.; Weinberger, DR.; Johnstone, EC., editors. *Schizophrenia: from Neuroimaging to Neuroscience*. Oxford: Oxford University Press; 2004. p. 293-330.

- Niznikiewicz MA, Shenton ME, Voglmaier M, Nestor PG, Dickey CC, Frumin M, Seidman LJ, Allen CG, McCarley RW. Semantic dysfunction in women with schizotypal personality disorder. *American Journal of Psychiatry*. 2002; 159(10):1767–1774. [PubMed: 12359685]
- Niznikiewicz MA, Voglmaier MM, Shenton ME, Dickey CC, Seidman LJ, Teh E, Van Rhoads R, McCarley RW. Lateralized P3 deficit in schizotypal personality disorder. *Biological Psychiatry*. 2000; 48(7):702–705. [PubMed: 11032982]
- Oades RD, Wild-Wall N, Juran SA, Sachsse J, Oknina LB, Ropcke B. Auditory change detection in schizophrenia: sources of activity, related neuropsychological function and symptoms in patients with a first episode in adolescence, and patients 14 years after an adolescent illness-onset. *Biomed Central Psychiatry*. 2006; 6:7. [PubMed: 16466573]
- Oknina LB, Wild-Wall N, Oades RD, Juran SA, Ropcke B, Pfueller U, Weisbrod M, Chan E, Chen EY. Frontal and temporal sources of mismatch negativity in healthy controls, patients at onset of schizophrenia in adolescence and others at 15 years after onset. *Schizophrenia Research*. 2005; 76(1):25–41. [PubMed: 15927796]
- Oranje B, van Berckel BN, Kemner C, van Ree JM, Kahn RS, Verbaten MN. The effects of a sub-anesthetic dose of ketamine on human selective attention. *Neuropsychopharmacology*. 2000; 22(3):293–302. [PubMed: 10693157]
- Pang EW, Fowler B. Dissociation of the mismatch negativity and processing negativity attentional waveforms with nitrous oxide. *Psychophysiology*. 1999; 36(5):552–8. [PubMed: 10442023]
- Rosburg T, Marinou V, Haueisen J, Smesny S, Sauer H. Effects of lorazepam on the neuromagnetic mismatch negativity (MMNm) and auditory evoked field component N100m. *Neuropsychopharmacology*. 2004; 29(9):1723–1733. [PubMed: 15127083]
- Sabri M, Liebenthal E, Waldron EJ, Medler DA, Binder JR. Attentional modulation in the detection of irrelevant deviance: a simultaneous ERP/fMRI study. *Journal of Cognitive Neuroscience*. 2006; 18(5):689–700. [PubMed: 16768370]
- Saint-Amour D, De Sanctis P, Molholm S, Ritter W, Foxe JJ. Seeing voices: High-density electrical mapping and source-analysis of the multisensory mismatch negativity evoked during the McGurk illusion. *Neuropsychologia*. 2007; 45(3):587–597. [PubMed: 16757004]
- Salisbury DF, Kuroki N, Kasai K, Shenton ME, McCarley RW. Progressive and Interrelated Functional Structural Evidence of Post-Onset Brain Reduction in Schizophrenia. *Archives of General Psychiatry*. 2007; 64:521–529. [PubMed: 17485604]
- Salisbury DF, Shenton ME, Griggs CB, Bonner-Jackson A, McCarley RW. Mismatch negativity in chronic schizophrenia and first-episode schizophrenia. *Archives of General Psychiatry*. 2002; 59(8):686–694. [PubMed: 12150644]
- Salisbury DF, Voglmaier MM, Seidman LJ, McCarley RW. Topographic abnormalities of P3 in schizotypal personality disorder. *Biological Psychiatry*. 1996; 40(3):165–172. [PubMed: 8830949]
- Schreiber H, Stolz-Born G, Heinrich H, Kornhuber HH, Born J. Attention, cognition, and motor preservation in adolescents at genetic risk for schizophrenia and control subjects. *Psychiatry Research*. 1992; 44(2):125–140. [PubMed: 1480678]
- Shelley AM, Ward PB, Catts SV, Michie PT, Andrews S, McConaghy N. Mismatch negativity: an index of a preattentive processing deficit in schizophrenia. *Biological Psychiatry*. 1991; 30(10):1059–62. [PubMed: 1756198]
- Umbricht DS, Bates JA, Lieberman JA, Kane JM, Javitt DC. Electrophysiological indices of automatic and controlled auditory information processing in first-episode, recent-onset and chronic schizophrenia. *Biological Psychiatry*. 2006; 59(8):762–772. [PubMed: 16497277]
- Umbricht D, Krljes S. Mismatch negativity in schizophrenia: a meta-analysis. *Schizophrenia Research*. 2005; 76(1):1–23. [PubMed: 15927795]
- Umbricht D, Schmid L, Koller R, Vollenweider FX, Hell D, Javitt DC. Ketamine-induced deficits in auditory and visual context-dependent processing in healthy volunteers: implications for models of cognitive deficits in schizophrenia. *Archives of General Psychiatry*. 2000; 57(12):1139–1147. [PubMed: 11115327]
- Valkonen-Korhonen M, Purhonen M, Tarkka IM, Sipila P, Partanen J, Karhu J, Lehtonen J. Altered auditory processing in acutely psychotic never-medicated first-episode patients. *Cognitive Brain Research*. 2003; 17(3):747–58. [PubMed: 14561460]



**Figure 1.**  
Grand average difference waveforms in 23 SPD and 26 healthy comparison individuals.

**Table 1**

Demographic data for the two groups of subjects (NC and SPD).

	NCs =26		SPDs = 23	
	Mean	SD	Mean	SD
Age	30.2	10.9	33.9	11.03
SES	3.5	1.6	3.05	1.6
PSES	3.9	.72	3.6	1.1
Educ.	17.2	2.8	16.4	2.5
IQ	118.5	14.2	113.3	17.4

**Table 2**

Scores on SCID in male and female SPD.

	<b>Male SPD (SD)</b>	<b>Female SPD (SD)</b>
Total number of SCID criteria met	5.36 (.92)	6.00 (.74)
Number of positive symptoms	3.91 (.94)	3.83 (.39)
Number of negative symptoms	1.55 (1.04)	2.17 (.78)
Ideas of reference	2.64 (.67)	2.75 (.45)
Odd beliefs/magical thinking	2.82 (.60)	3.0 (0.0)
Unusual perceptual experiences	2.73 (.65)	2.92 (.53)
Suspicious/paranoid ideation	2.55 (.82)	2.33 (.98)
Odd thinking and speech	2.4 (.92)	2.33 (.78)
Inappropriate/constricted affect	2.18 (.87)	2.25 (.96)
Odd/eccentric behavior or appearance	2.18 (.87)	2.33 (.88)
No close friends	1.82 (.75)	2.0 (.85)
Excessive social anxiety	2.18 (.87)	2.5 (.79)

**Table 3**

Mean amplitude and latency values for MMN in the two groups.

	NC =26		SPD =23	
	Amplitude ( $\mu$ V)	Latency (ms)	Amplitude ( $\mu$ V)	Latency (ms)
Fz	-2.5 (1.1)	172 (19)	-1.7 (1.1)	180 (22)
Cz	-1.8 (1.1)	162 (20)	-1.4 (1.0)	166 (23)