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Sensory-gating deficit of the N100 mid-latency auditory evoked potential in medicated schizophrenia patients

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ABSTRACT

The clinical and neuro-cognitive correlates of the P50 and N100 auditory evoked responses gating deficits in schizophrenia have thus far eluded identification. Based on our prior results, we hypothesized that, in addition to the P50, gating of the N100 is significantly decreased in schizophrenia and that this deficit correlates with the negative symptoms dimension of schizophrenia. Amplitudes and gating measures of the P50 and N100 were compared between stable out-patients ($N=45$) (mainly on atypical antipsychotics) with chronic schizophrenia and age- and gender-matched healthy controls ($N=49$) and the clinical correlates examined. All subjects underwent the paired-stimulus paradigm in 3 or 4 different days. Data from day one and the mean of all days (MOAD) were examined. P50 and N100 amplitudes and gating measures were correlated with PANSS and Wisconsin Card Sorting Test data. Utilizing day one data, no amplitude or gating measures were significantly different between the groups. Utilizing MOAD data, both P50 and N100 gating were significantly decreased in schizophrenia patients. The N100 gating deficit correlated with the negative-symptoms cluster and measures of frontal lobe dysfunction. The data suggest a correlation between N100 gating deficit and the negative-cognitive deficits dimensions of schizophrenia. Data also suggest that improving the signal to noise ratio (MOAD data) increases the sensitivity for detecting gating abnormalities and assessing their clinical correlates.

1. Introduction

The ability to inhibit or suppress the response to incoming irrelevant or redundant sensory input is a well documented characteristic of the central nervous system that is believed to have a protective mechanism that prevents the flooding of higher cortical centers with irrelevant information (Venables, 1964). The P50 auditory evoked potential (AEP) component functions as a tool to examine habituation or sensory gating (SG) in schizophrenia (Bramon et al., 2004). Thus far only SG at the P50 stage of information processing has been extensively examined (Bramon et al., 2004; Heinrichs, 2004). Sensory-gating occurring at the N100 stage of information processing is yet to be fully explored (Boutros et al., 1999, 2004). Reliability of the N100 as a gating index has been demonstrated (Smith et al., 1994; Fuerst et al., 2007). The paradigm for examining SG is widely accepted (Smith et al., 1994; Rentzsch et al., 2008).

Demonstrating a clinical association of gating deficits utilizing the P50 AEP has been a difficult task with reports suggesting no correlations (Adler et al., 1990; Boutros et al., 2004), or correlating with attentional deficit (Erwin et al., 1991, 1998), anxiety, depression and anergia (Yee et al., 1998). More recent studies support the notion that P50 gating abnormalities

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may be more represented in the disorganized and negative symptoms subgroups of schizophrenia patients (Ringel et al., 2004; Louchart-de la Chapelle et al., 2005).

The N100 gating literature remains extremely limited. Hsieh et al. (2004) reported an association between N100 gating and verbal learning in healthy controls but not in schizophrenia patients. Most recently, the N100 gating was shown to be significantly impaired in a mixed sample of schizophrenia patients with and without neuroleptic treatment (Brockhaus-Dumke et al., 2008).

The current study had three goals. Our first goal was to further document SG abnormalities occurring at the N100 phase of information processing in schizophrenia patients. Our second goal was to specifically ascertain whether the N100 gating deficit correlates with the negative symptoms dimension of schizophrenia. Thirdly, examining the correlation between N100 SG and frontal lobe executive functions. This goal was motivated by the accumulating literature for a frontal lobe involvement in mediating SG (Weisser et al., 2001; Grunwald et al., 2003; Korzyukov et al., 2007).

2. Methods

2.1. Subjects

Data from forty five schizophrenia patients and forty nine healthy control subjects were included in this study. Patients were recruited from the outpatient clinics of Yale University (2002–2004; total recruited subjects, 74/37 patients) and Wayne State University (WSU) hospitals (2005–2006; total recruited subjects 31/19 patients). The majority of patients were on atypical antipsychotics. Patients with head injury with loss of consciousness as well as patients with uncontrolled medical conditions (e.g., diabetes or hypertension) were excluded). None of the patients had a psychiatric hospitalization or a change in their psychotropic medications in the four weeks prior to or during the study. Among smokers, the number of packs per day was recorded. Healthy subjects were recruited through news paper ads. Healthy controls were matched for age and sex (as a group). The study was explained and all questions were answered before signing the written consent. All procedures were identical between the two study locations. The study was approved by the Yale and WSU Human Investigations Committees.

2.2. Clinical evaluation

Subjects were administered the Structured Clinical Interview for DSM-IV (SCID-I). Subjects meeting criteria for schizophrenia and who had no drug or alcohol use for the last 3 months (as verified by toxicology and confirmed by treating clinician) were administered the Positive and Negative Symptoms Scale (PANSS) and the Wisconsin Card Sorting Test (WCST).

2.3. Evoked potential paradigm

Each subject underwent one recording block using a paired-stimulus condition per each recording day. Subjects were invited to return for additional identical recordings three more times (four recording sessions total). This design was adopted in order to examine the test–retest reliability of the P50 and N100 gating measures. These data have been reported elsewhere (Fuerst et al., 2007). Briefly, all N100-derived measures showed good test–retest reliabilities while among the P50 gating measures the S2–S1 difference measure stood out as most reliable. This design also allowed the examination of possible beneficial effects of increasing the signal to noise ratio (SNR) by including more single trials in computing the AEPs. Recording sessions were maximally one week apart. If a patient's clinical condition changed (medication change or hospitalization) they were dropped of the study.

The recording procedure is described in detail elsewhere (Nagamoto et al., 1989; Boutros et al., 2004). Relevant to the current report is that sixty pairs of stimuli were presented and a minimum of 40 artifact-free trials were necessary to accept the resulting averages. Recording was made from the Fz, Cz, Pz, Oz, F7, F8, T3, T4, P5, and P6 locations and referred to linked ears. P50 and N100 measurements were made from the Cz electrode. Band-pass filters were set at .05 and 300 Hz and digitized at 1000 Hz for off-line averaging. Epochs were 300 ms starting 50 ms before stimulus. In order to improve the SNR, we further refiltered the EEG data between 1–50 Hz (Clementz et al., 1997).

Amplitudes of the P50 and N100 were measured both from peak to the preceding peak (PP) or from peak to baseline (PB). All components were identified independently by two fully trained research associates (SB and ME) who were blind to all rating scale scores and to theoretical predictions. Fig. 1 shows how these measures are calculated. In order to identify a component as the P50 (S1) the component had to have an amplitude of 0.5 μV or higher and be larger than the level of noise in the 50 ms pre-stimulus period. This procedure was adopted by this group to increase the confidence in the components identified as P50. Smaller components cannot be confidently distinguished from noise. For PB measurements, a portion of the P50 must be on the positive side of the baseline. If the entire component was on the negative side, the component was not selected for this measurement. If the S2 response could not be found within a 15 ms (for the P50) or 30 ms (for N100) of the latency of S1 response in the same trial, the response was

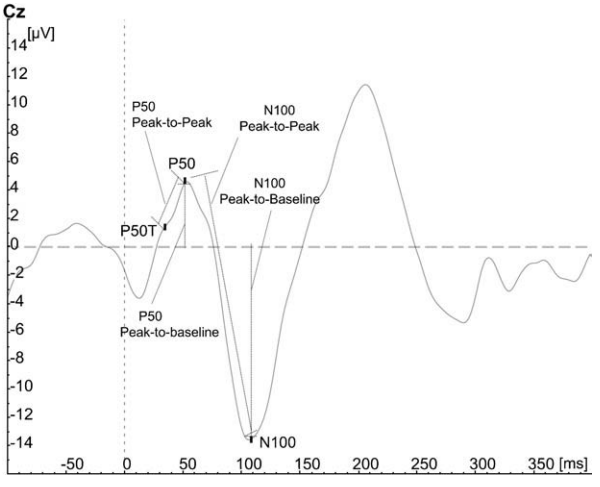

Fig. 1. Example of the P50, N100, P200 MLAER complex showing the points from which the P50 and N100 components are measured.

Table 1
Demographics of subjects for day 1 and for subjects entered in the mean-of all-days analyses.

Variable	Controls Day 1	Schizophrenia Day 1	Control all days	Schizophrenia all days
Sample size	49	45	46	40
Age	37.6 ± 13.3 (21–61)	41.3 ± 11 (21–65)	39.6 ± 13.3	45 ± 10
Sex (M–F)	25–24	29–16	24–22	28–12
Race	AA(14), C(26), H(3), A(6)	AA(21), C(19), H(4), A(1)	AA(14), C(25), H(3), A(4)	AA(20), C(17), H(2), A(1)
Smokers	11*	23*	7*	24*
Medications		Risperidone (17),olanzapine (10), Aripiprazole (5), Quetiapine (3), ziprasidone (1), clozapine (4), typicals (3), no meds (2).		Risperidone (15),olanzapine (10), Aripiprazole (4), Quetiapine (3), clozapine (3), typicals (3), no meds (2).

AA, African American, C, Caucasian, H, Hispanic, A, Asian.
*Significantly more smokers in the schizophrenia group; $p<0.001$.

assumed to have been completely attenuated. Tables 1 and 2 give the actual numbers of subjects entered into each analysis.

2.4. Statistical analysis

Sensory-gating ratio and difference measures were calculated. Ratios were restricted to a range from zero (complete attenuation of the response to S2) to 200 (S2 response twice as large as S1 response or larger). Lower S2/S1 ratios are assumed to reflect more intact SG. Second, we subtracted S2 amplitudes from S1 amplitudes (S1–S2 difference; heretofore called "difference"). Higher differences reflect better gating of the S2 responses.

Between groups ANOVA with S1 amplitudes and gating measures for Day 1 data with group (normal or schizophrenia) as the independent variable were calculated. We also recalculated these analyses with S1 as a covariate for ratio measures to determine if S1 amplitude made a significant contribution to the relationship. A mixed model ANOVA for gating measures with Day forming the repeated factor to determine if the days differed from one another was performed. When this analysis showed the days not to significantly differ (on any of the variables measured), data were collapsed across days to form an overall mean-of-all-days (MOAD), and the initial ANOVAs were repeated. In order to compute the MOAD averages, a minimum of 100 artifact-free trials were necessary. Based on a multivariant analysis of variance (MANOVA) test, there was no effect of site (Yale vs. WSU).

We then examined correlations between gating, S1 measures, and PANSS data (patients only). With the ratio variables limited to a range between zero and 200, the distribution was normal and Pearson correlations were most suitable for the data (Harris, 1985). For the Difference measures, no such limitation is imposed and the data was not-normally distributed and Spearman non-parametric correlations were applied. The primary correlation was with the three-main subscales (the three-factor model: positive, negative, and general psychopathology total scores) (Liddle et al., 1989), and separately with the five main subscales for the five-factor model (positive, negative, cognitive, emotional, and hostility components) (Bell et al., 1994). Finally, we correlated WCST measures with gating measures from MOAD, both overall ($N=48$), and in patients ($N=28$) and normal subjects ($N=20$).

All the above analyses were driven by specific predictions. We also looked at the effects of age, gender, smoking, and coffee consumption on gating measures using separate ANOVAs. These additional measures were exploratory. Demographics of the subjects included in the Day 1 and means of all days (MOAD) analyses are provided in Table 1.

3. Results

3.1. Day 1 results

The requirements that P50 components be larger than 0.5 μV and larger than the prestimulus noise level resulted in the exclusion of P50 data from 10 healthy and 9 schizophrenia patients. All N100 components were distinct and none were excluded. Means of all measurements are presented in Table 2.

Table 2
Means and standard deviations of Day 1 data.

Variable	Controls	Schizophrenia	Controls	Schizophrenia
Amplitude μV	PP	PP	PB	PB
P50 S1	3.9 ± 3.6 (39)	3.4 ± 2.9 (36)	3.4 ± 3.2 (35)	3.9 ± 3.4 (37)
P50 S2	2.3 ± 2.5	1.8 ± 2.5	2.2 ± 2.5	2.4 ± 2.5
N100 S1	10.9 ± 11.36 (49)	10.7 ± 9.7 (45)	8.6 ± 9.1 (49)	7.7 ± 7.7 (45)
N100 S2	4.1 ± 4.2	5.5 ± 4.9	2.7 ± 3	3.8 ± 3.5
Gating measures				
P50 ratio × 100	68 ± 65 (39)	66 ± 68 (36)	64 ± 78 (35)	71 ± 73 (37)
P50 diff μV	1.7 ± 2.7 (39)	1.6 ± 3 (36)	1.3 ± 2.6 (35)	1.5 ± 3 (37)
N100 ratio × 100	48 ± 41 (49)	65 ± 62 (49)	50 ± 47 (49)	58 ± 54 (49)
N100 diff μV	6.8 ± 8.8 (49)	5.2 ± 6.7 (49)	5.9 ± 8.1 (49)	3.9 ± 5.7 (49)

Numbers in () are the number of averages in this analysis. Ratio = S2 amplitude/S1 amplitude × 100.
Difference = S1 amplitude − S2 amplitude.

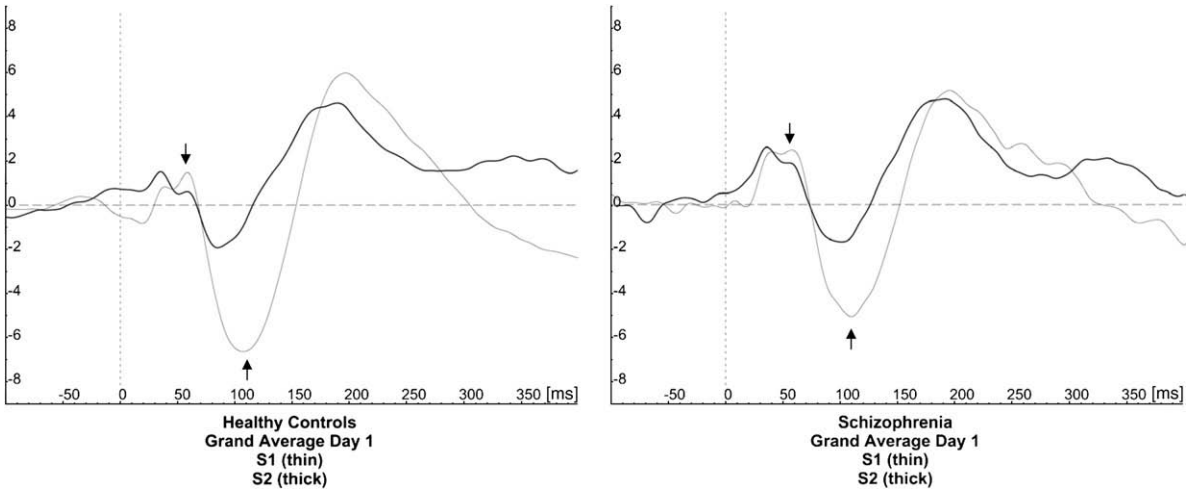

Fig. 2. Grand averages of the mid-latency auditory evoked responses of schizophrenia patients (S) and healthy control subjects (N) to S1 and S2 stimuli for day 1 data. Arrows indicate the P50 and N100 peaks.

ANOVAs for amplitudes and gating measures (P50 and N100 ratios and differences, PP and PB) and type (control vs. schizophrenic) revealed no significant differences between groups. The grand averages resulting from Day 1 data are presented in Fig. 2.

3.2. Means of all days (MOAD) analyses

ANOVAs for all gating measures (P50 and N100 ratios and differences, PP and PB) and group (control vs. schizophrenic) were significant for five of eight gating measures. For N100-derived measures, N100(PP) ratio ($F[1,84]=5.54$, $p<0.02$), N100 (PB) difference ($F[1,84]=5.96$, $p<0.03$) (Fig. 3), and N100 (PP) difference ($F[1, 83)=4.84, p<0.03$). For P50-derived gating measures, both ratio (PB) and difference (PB) were significantly worse in schizophrenia patients ($F[1,68]=12.3$, $p<0.001$ and $F[1,68]=11.35$, $p<0.001$ respectively). Neither the P50 nor the N100 S1 amplitudes differed significantly between the groups. When these analyses were rerun with S1 as a covariate for ratio measures to determine if S1 amplitude made a significant contribution to the relationship, all variables with significant differences remained significant (at the same level) suggesting minimal if any contribution from S1 amplitudes to the gating measures (Table 3).

None of the EP measures correlated with the total PANSS score or with any of the clusters when using a three-factor (positive, negative and general psychopathology) model (Liddle et al., 1989). Utilizing a five-factor model (positive, negative, cognitive, emotional and hostility (Bell et al., 1994) a significant positive correlation was found between the N100 (PP) ratio and the negative-component ($r=427$, $p<0.05$). This correlation is in the predicted direction of higher ratios correlating with higher scores on the negative scale. When applying the non-parametric Spearman correlations to the Difference measures, the N100 Difference (PB) also correlated

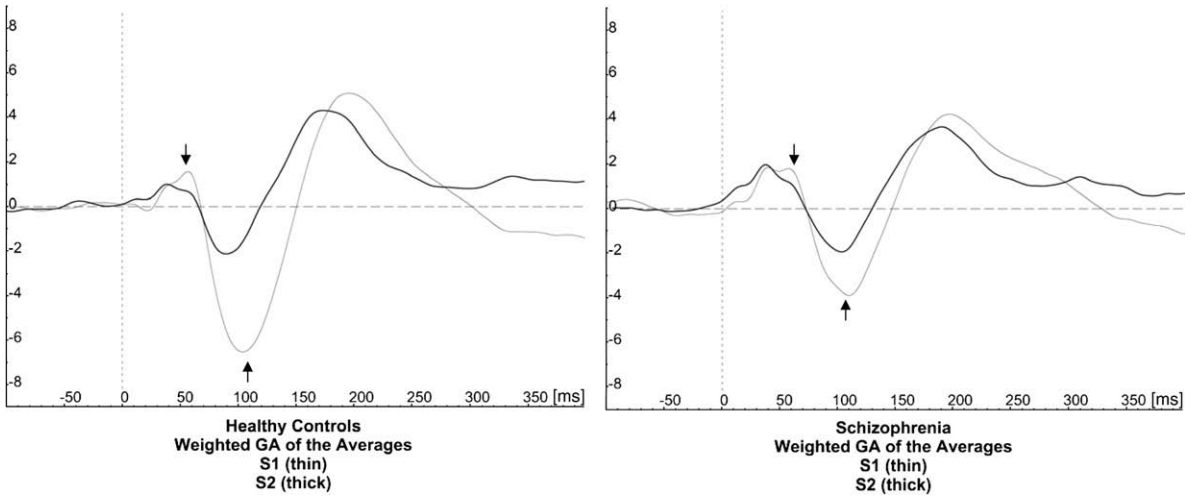

Fig. 3. Grand averages of the mid-latency auditory evoked responses of schizophrenia patients (S) and healthy control subjects (N) to S1 and S2 stimuli for grand averages of all days. Arrows indicate the P50, and N100 peaks.

Table 3
Means and standard deviations of means of all days (MOAD) EP variables in the two groups.

Variable	Controls	Schizophrenia	Controls	Schizophrenia
Amplitude μV	PP	PP	PB	PB
P50 S1	2.8 ± 2.5(36)	2.9 ± 2.7(35)	3.1 ± 2.2(31)	2.3 ± 2.4(35)
P50 S2	1.4 ± 1.5	2.0 ± 2.0	1.2 ± 1.2	1.8 ± 2.6
N100 S1	10.4 ± 9(45)	8.6 ± 7.3(40)	7.9 ± 6.9(46)	6.2 ± 5.5(40)
N100 S2	4.3 ± 3.8	5.1 ± 6	3.5 ± 3.2	3.9 ± 4.4
Gating measures				
P50 ratio × 100	67 ± 60 (35)	79 ± 65 (35)	41 ± 33(31)**	79 ± 53(35)**
P50 diff μV	1.4 ± 1.8(36)	1.0 ± 1.6(35)	1.9 ± 1.7(31)**	0.57 ± 1.6(35)**
N100 ratio × 100	47 ± 25(46)*	62 ± 33(40)*	52 ± 30(46)	64 ± 41(40)
N100 diff μV	6.1 ± 6.4(46)*	3.4 ± 4.9(40)*	4.3 ± 4.5(46)*	2.4 ± 3.3(40)*

Numbers in () are the number of averages in this analysis. Ratio = S2amplitude/S1amplitude × 100.
Difference = S1amplitude − S2 amplitude.
*$p<0.05$, **$p<0.01$.

with the negative component of the five-factors model ($r = -.446$, $p<0.02$). This correlation is also in the predicted direction of lower Difference scores with higher negative-component scores.

Correlations between gating measures and WCST scores are shown in Table 4. A number of significant correlations were found. The number of total errors, perseverative errors, categories completed and the number of trials to completing the first category correlated with N100 ratio (PP & PB). The correlations were in the predicted direction of worse gating correlating with worse performance on the WCST measures. The significance was largely due to schizophrenia patients. Within the control group with WCST data ($N = 20$) one subject scored beyond two standard deviations from all others on the WCST variables. Upon removing this one subject, all near significant correlations completely disappeared (see Table 4). It is of interest that this one healthy control subject had an elevated N100 gating ratio. This observation raises the interesting possibility that N100 gating deficit may correlate with frontal lobe dysfunction outside the context of schizophrenia. Within the schizophrenia group, N100 difference measures (both PP and BP) were related negatively to the number of trials administered (i.e., larger number of trials correlated with smaller differences reflecting worse gating). N100 ratios correlated positively with the number of perseverative errors (more perseverative errors correlating with higher ratios reflecting worse gating).

Table 4
WCST-EP correlations; mean of all days.

WCST variable	Gating variables	All subjects ($N = 48$)	Controls ($N = 20$)	Control ($N = 19$)	Schizophrenia ($N = 28$)
Total errors	N100RPT[a]	.44 **	.32	.01	.44*
	N100RPB[b]	.45**	.32	.04	.48*
Perseverative errors	N100RPT	.53***	.37	.09	.54**
	N100RPB	.44**	.38	.04	.43*
Categories completed	N100RPT	−.51**	−.47	−.18	−.48*
	N100RPB	−.42**	−.44	−.13	−.43*
Trials to complete 1st category	N100RPT	.44**	.26	.24	.45*
	N100RPB	.45**	.22	.28	.50*

* = $p<0.05$, ** = $p<0.01$, *** = $p<0.001$.
[a] N100RPT = N100 ratio measured peak to trough.
[b] N100RPB = N100 ratio measured peak to baseline.

3.3. Additional analyses

Using the MOAD data there was no main effect of smoking vs. non-smoking nor for the amount of cigarettes smoked per day as a covariate with group (schizophrenia or control). With respect to caffeine consumption, there was no main effect of caffeine found. Using caffeine consumption as a covariate, there was a significant association with P50(PP) difference measure ($F(1,75) = 10.43$, $p<0.01$), no effect of group but an effect of caffeine by group ($F(1,75) = 5.22$, $p<0.05$, with coffee drinkers showing better gating). There was no effect for the number of cups consumed/day. There was no effect for gender or age.

4. Discussion

The first important finding of this study is documenting a deficit of gating of the N100 component, in addition to the well-documented P50 gating deficit, in clinically stable medicated schizophrenia patients. This finding is in agreement with our prior preliminary findings (Boutros et al., 2004), as well as others (Clementz and Blumenfeld, 2001; Young et al., 2001). Whereas Turetsky et al. (2008) reports an N100 amplitude deficit in schizophrenia patients, they did not find an N100 gating deficit. In this paper the symptoms cluster composition of their patient sample is not reported. The Turetsky et al. (2009) provides more detail about the patient sample. Based on this paper it is possible to suggest that their patient sample is more of a positive symptom and less severe cohort. This factor could possibly account for the absence of an N100 gating deficit reported (Turetsky et al., 2008).

In our current patient sample, the responses to S1 stimuli were not statistically different between the groups (P50 or N100). When gating measures were co-varied with the amplitudes of the S1 responses, gating variables that were significant remained significant. This is an important finding as the question of whether the gating deficit effect seen in patients is mainly a result of a poor response to the first stimuli (S1) rather than a difficulty in attenuating the amplitude to the second stimuli (S2) is a core question for the entire SG field of research. Our data, derived from stable outpatients on atypical antipsychotics, revealed no amplitude abnormalities of the initial response (S1). The data thus strongly support the presence of a gating deficit in the absence of and independent from an S1 deficit.

The finding that significant deficits in P50 and N100 gating in the schizophrenia group was only detected when data from multiple recordings were averaged together is of importance to investigators in this field. A number of factors could contribute to inability to detect gating deficits in schizophrenia groups. Besides the use of atypical antipsychotic agents, a low signal to noise ratio (i.e., a small number of evoked potential trials entered into generating the averages), and the clinical composition of the patient sample could also influence the effect size of the abnormality. In the current study, improving the signal to noise ratio (by combining data from multiple recording sessions) indeed resulted in the differences in gating measures becoming detectable in a sample of stable patients receiving atypical antipsychotic medications. The above factors may have contributed to the six published lack of replications of the P50 gating deficit in schizophrenia (Kathmann and Engel, 1990; Grillon et al., 1991; Guterman et al., 1992; Guterman and Josiassen, 1994; Jin et al., 1998; Arnfred et al., 2003), and most recently Turetsky et al. (2009). Ringel et al. (2004) found the expected suppression deficit only in schizophrenia patients with the hebephrenic subtype compared to healthy controls, whereas in patients with brief/acute or transient psychotic disorder abnormalities in P50 suppression were absent.

The lack of a significant N100 amplitude deficit is at variance with our previous report of decreased N100 amplitudes in similarly treated schizophrenia patients in an independent sample (Boutros et al., 2004) and may be attributable to the majority of patients being on atypical antipsychotics (Yee et al., 1998). This observation suggests that the N100 amplitude deficit observed in schizophrenia, may be state and not trait-dependent. While the role of medications cannot be ascertained from our data, prior work have documented that the N100 amplitude deficit can be seen in unmedicated schizophrenia patients (Rosburg et al., 2008). The amplitude of an evoked potential has been shown to reflect the sum of the total resources allocated to the cerebral task to be performed in order to generate the response (Regan, 1988). Amplitude deficits reflect problems with the sensory registration of the information carried by these stimuli (Regan, 1988). Thus amplitude deficits and gating deficits reflect abnormalities of two distinct physiological functions.

PANSS data provide evidence for a correlation between deficit in gating the N100 component and the negative symptom cluster when using a five-factor model. We could not find a correlation using the three-factor model. The negative symptoms cluster of the three-factor model is comprised of seven items including difficulty in abstract thinking and stereotyped thinking. Both are grouped with the cognitive cluster of the five-factor model. On the other hand, three items that are included under the General Psychopathology Scale of the three-factor model (Preoccupation, motor retardation, and disturbance of volition) are grouped under the Negative cluster in the five-factor model adding up to eight factors for this symptoms cluster. It is possible that the correlation between gating and symptoms cluster is sensitive to the specific composition of the cluster. The lack of clinical correlations of P50 gating, despite higher significant difference from controls, suggests that P50 gating deficit is more fundamental to the entire group while N100 gating deficit may be more of a correlate of a subgroup of schizophrenia patients. Difficulty in correlating symptoms with gating measures (Adler et al., 1990; Boutros et al., 2004; Potter et al., 2006) may have also resulted from a low SNR in early studies utilizing small number of trials (40 or less). It should be noted that the patient sample was not selected for prevalence of negative symptoms. It remains to be seen if groups of schizophrenia patients with higher predominance of negative symptoms (e.g., deficit syndrome patients) would exhibit higher or more significant deviations of N100 gating indices.

WCST data highlight an important observation. While no correlations were found with Day 1 EP data, quite a number of correlations emerged when a higher SNR was assured via averaging a larger number of trials to generate grand averages. This finding strongly highlights the importance of the SNR variable in this field of research. To our knowledge, this is the first reported demonstration of a significant correlation between frontal executive dysfunction and gating measures. The data suggest that N100 gating deficit may be related to frontal lobe dysfunction. It is thus possible that the impact of frontal lobe dysfunction is more significant at the N100 stage of sensory-gating. It should be highlighted that in the current study only the WCST was utilized as a preliminary probe of frontal executive functions. Nonetheless, the highly significant correlation (particularly between N100 gating ratio and perseverative errors strongly suggest that more extensive exploration of frontal lobe executive dysfunction and N100 gating is warranted. It is indeed an interesting observation that the one healthy subject with some evidence of WCST difficulty also happened to exhibit N100 gating deficit.

While the different gating assessments based on base to peak or peak to peak measurements or deriving the ratios vs. the differences tend to be significantly correlated, the correlations tend to be modest and suggest that the different measures may be slightly different in their sensitivities to the different aspects of sensory-gating. The peak to preceding peak measurement may contain information pertaining more to the preceding peak. If both components (i.e., P50 and N100) gate, then this could represent a confounding factor. For the P50, this is unlikely to be a significant factor as the preceding P30 or N40 (from which trough the P50 is calculated in peak to peak measurements) has not been shown to gate (Naber et al., 1992). For the N100, this is also unlikely to be a major factor because the P50 amplitude is significantly smaller than the amplitude of the N100 and thus any contribution is likely to be small. Further research is certainly needed to firmly establish the most accurate methodology for assessing gating.

In conclusion, the most important finding in this report is the significant N100 gating deficit in schizophrenia patients who are stable outpatients and mostly on atypical antipsychotics. This effect is not secondary to a decreased responsiveness to the first stimuli (S1) as S1 responses were not significantly decreased in the current sample and co-varying the analysis using the S1 amplitudes did not result in a change of the level of significance of the gating measures. The correlation with negative symptoms while has been reported for the P50, this is the first report linking it to N100 gating deficit.

Not all possible symptoms clustering were examined (e.g., five subtypes proposed by the DSM-IV-TR, five-factors model

proposed by van der Gaag et al. (2006). It is of interest to point out that the large factorial analysis ($N = 5769$) conducted by van der Gaag et al.(2006) resulted in proposing a structure for the negative symptoms cluster rather similar to that proposed by Bell et al. (35) with the exception of not including "preoccupation". Removal of preoccupation from our analyses did not result in any change of statistical results. It is likely that only after a number of correlational studies with relatively large sample sizes are produced that a clearer picture of the clinical correlates of N100 gating deficit will become better established. Finally, secondary to the small number of channels used, we could not examine the sources of the demonstrated deficits. Both P50 and N100 are multi-components emanating from a number of cerebral sources. Examining the sources most affected and contributing to the scalp recorded deficit is an important goal and is subject for subsequent investigation.

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Contributors

Dr. N.N. Boutros designed and managed the study. Drs. K. Gjini and A. Vedeniapin helped with data analysis and manuscript preparation. Drs. A. Brockhaus-Dumke, and Dr. Keshavan helped with data interpretation and writing of the manuscript. Mr. M. Elfakhani and Mr. S. Burroughs performed all subject recruitment, evoked potential evaluations (including peak picking) and data tabulation (including cross checking for errors).

Conflicts of interest

None of the authors of this manuscript has any financial conflict or any form of conflict of interest with material presented. All authors had had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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None.

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