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Relationships between sensory “gating out” and sensory “gating in” of auditory evoked potentials in schizophrenia: a pilot study

Klevest Gjini^a, Cynthia Arfken^a, and Nash N. Boutros^a

^aDepartment of Psychiatry and Behavioral Neurosciences, Wayne State University, School of Medicine, 2751 E. Jefferson, Detroit, MI 48207

Abstract

The interrelationship between the ability to inhibit incoming redundant input (gating out) and the ability of the brain to respond when the stimulus changes (gating in), has not been extensively examined. We administered a battery of auditory evoked potential tests to a group of chronic, medicated schizophrenia patients (N=12) and a group of healthy subjects (N=12) in order to examine relationships between “gating out” measures (suppression with repetition of the P50, N100, and P200 evoked responses), and the mismatch negativity (MMN) and the P300 event related potentials as measures of “gating in”. Gating ratios for N100 and P200 in a visual attention paired-click task differed significantly between groups. Mismatch negativity and P300 potential amplitudes were also significantly reduced in the patient group. When including all subjects (N=24) a negative correlation was found between the P50 gating and the amplitude of the MMN. In healthy subjects this correlation was significantly stronger compared to schizophrenia patients. While no significant correlation was noted between the amplitudes of the P300 and any gating measures when all 24 subjects were included, a significant negative correlation was seen between the P200 gating and the P300 amplitudes in schizophrenia patients; an opposite trend was noted in healthy subjects. Finally, a positive correlation was seen between the P300 and MMN (to abstract deviance) amplitudes in healthy subjects, but the opposite was found in patients. These results suggest that further study of these interrelationships could inform the understanding of information processing abnormalities in schizophrenia.

Keywords

gating-in; gating-out; auditory evoked potentials; P50; N100; P200; MMN; P300; schizophrenia

1. Introduction

Abnormalities of the early as well as later stages of information processing have been documented in schizophrenia patients (Javitt et al., 1993; Jeon and Polich, 2001; Turetsky et

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Corresponding author Klevest Gjini, MD, PhD, Department of Psychiatry and Behavioral Neurosciences, Wayne State University, School of Medicine, UPC-Jefferson, Electrophysiology Lab, Suite #315, 2751 E. Jefferson, Detroit, MI 48207, tel.: 1-313-577-9994; fax: 1-313-577-5201, kgjini@med.wayne.edu.

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al., 2008). However, interrelationships between these abnormalities have not been extensively examined. Sensory “gating-out” has been conceptualized as a complex multi-stage function used to examine the ability of the CNS to inhibit incoming irrelevant sensory input (Boutros & Belger, 1999) and serves as a protective mechanism against flooding of the higher cortical centers with unnecessary information (Venables, 1964). The amplitude attenuation of the mid-latency auditory evoked potentials P50, N100, P200 in a paired-stimulus paradigm is used to examine this process. The mismatch negativity (MMN), and P300 can be used to examine the ability of the brain to detect and respond to stimulus changes (i.e., gating in: Brenner et al., 2009). All the above measures have been shown to be reduced in schizophrenia compared to healthy population (Adler et al., 1982; Boutros et al., 1999, 2004; Javitt et al., 1993; Näätänen and Kähkönen, 2009; Roth et al., 1981; Jeon and Polich, 2001). Brenner et al. (2009) concluded that there is aberrant sensory processing during stages of stimulus evaluation and saliency detection in schizophrenia.

Based on available literature, we postulated that the functions of gating-out and gating-in must be subserved by different but closely related neural systems (Boutros et al., 2004). Both gating of the P50 component and the MMN are believed to be pre-attentional reflecting an early gating-out/gating-in module (Näätänen et al., 1978). It is thus possible that some form of association would exist between the two variables. Similarly, gating of the N100/P200 components and the amplitude of P300 are significantly influenced by attentional manipulations reflecting a higher level gating-out/gating-in module (Pontifex et al., 2009).

MMN is an early evoked response related to automatic probing of auditory sensory traces of a repetitious stimulus by a deviant one (Näätänen et al., 1978; Sams et al., 1985). The P300 waveform represents processing of information at more advanced cognitive levels (Polich and Kok, 1995; Polich, 2007). Both the MMN and P300 can be seen as reflecting the ability of the CNS to “gate in” important information (Friedman et al., 2001).

Kisley et al. (2004) found a significant positive correlation between P50 sensory gating and the MMN amplitude (intensity deviation) in healthy individuals. In addition, Turetsky et al. (2009) reexamined these relationships in medicated schizophrenia patients and healthy controls. They were unable to find an association between gating of the P50 and the amplitude of the MMN measured either to duration or pitch deviance. They reported an association between the amplitudes of the N100, MMN and the P300 using factor analysis. In our prior work, we were unable to find an association between gating of the P50 and amplitudes of the P300 (Boutros et al., 2004). However a significant correlation between gating of the P200 and amplitude of the P300 was detected.

This study was motivated by the importance of further examining the reported associations among measures of sensory gating-out (P50, N100, P200 gating) and gating-in (MMN and P300) in healthy individuals and schizophrenia patients.

2. Materials and methods

Twelve chronic schizophrenia patients (11 males / 1 female, age 42.5 ± 11.7) and 12 healthy subjects (9 males / 3 females, age 38.3 ± 12.1) participated in this study.

One paired-click and three oddball tasks were administered in each of two recording days. We used a modified paired-click paradigm where subjects were asked to pay attention to a visual CPT while the auditory stimuli were being presented. The auditory stimulation was the standard paired-click paradigm (Boutros et al., 2004, 2009). Three oddball tasks were used. In the first oddball task, used to examine the P3b, the target (frequency-deviation) and two deviant tones (tone-duration and white-noise deviants) were presented randomly with a 10% frequency each. Subjects responded to the target tone. In the second oddball task, used

to elicit the MMN, three deviant tones (frequency-, duration- and white-noise deviants) were presented randomly with a 10% frequency each. Subjects responded to a target visual stimulus (1%). The third, paired-stimuli oddball paradigm, used to elicit the MMN to abstract violation, consisted in presentation of frequent, standard ‘ascending frequency’ tone-pairs and rare ‘descending frequency’ tone-deviants (Korzyukov et al., 2003). Subjects again responded to a target visual stimulus (1%).

Preprocessing of the EEG data included filtering, segmentation, baseline correction, artifact rejection and averaging to obtain the auditory evoked potentials of interest (P50, N100, P200, MMN and P300). The peak-to-peak amplitudes of the P50, N100 and P200 responses resulting from the S1 and S2 stimuli and gating ratios were defined following the methodology used in our previous studies (Boutros et al., 2004, 2009). MMN was scored from the difference waves (deviant rare stimulus – standard frequent stimulus). P3b to target stimuli was scored as the largest positivity in the interval 250–600 ms from the stimuli presentation. Grandaverage waveforms for data of two days were computed for each subject and variable scores from the latter were assessed (Boutros et al., 2009).

Statistics, including the correlational and regression analyses were carried out in SPSS. For a detailed description of the full methodology please see the online Supplementary Materials section.

3. Results

Assessment of the processing and gating deficits in the paired-click paradigm showed that gating ratios for N100 and P200 differed significantly between groups as expected ($t_{22}=2.82$, $p=0.01$ and $t_{22}=2.41$, $p=0.02$, respectively) (Table 1, Fig. 1). P50 gating ratio also was higher (i.e., less gating) in patients compared to controls (strong trend: $t_{22}=2.00$, $p=0.058$). MMN amplitudes were decreased in schizophrenia patients compared to controls for all measures (Table 1, Fig. 2) and reached significance only when elicited by white-noise deviants in the visual attention task ($t_{22}=2.58$, $p=0.02$). A trend in the same direction was noted for abstract MMN ($t_{22}=1.48$, $p=0.15$) (Figure 3). P3b amplitudes were decreased in schizophrenia patients (Table 1, Figure 4) and showed the largest difference when elicited by the white-noise deviants ($t_{22}=2.18$, $p=0.04$).

For the entire sample a significant negative correlation between P50 gating and MMN amplitudes for the abstract MMN was noted ($r=0.40$). This correlation was mainly due to healthy subjects’ strong negative correlation between P50 gating and the MMN ($r=0.86$, $p<0.01$) (i.e. decreased P50 gating associated with increased MMN amplitudes); in schizophrenia patients this correlation was nonsignificantly negative ($r=0.14$, $p=0.66$) (Figure 5).

When examining the correlation between P3b amplitudes and gating of the P200 in the entire group ($N=24$), no significant correlation was found ($r=-0.13$) (Table 2). However, schizophrenia patients exhibited a significantly negative correlation between the P200 gating and the P3b amplitudes ($r=0.56$, $p=0.05$), (i.e. decreased gating of the P200 associated with larger P3b amplitudes (Figure 6)). Healthy controls, in contrast, had a nonsignificant positive correlation (i.e., decreased gating of the P200 was correlated with lower amplitudes P3b) ($r=-0.38$, $p=0.22$). Finally, while a significant negative correlation between the P3b and MMN (to abstract deviance) was found in schizophrenia patients ($r=-0.83$, $p=0.001$), a nonsignificant positive correlation was seen between the two “gating-in” variables in healthy subjects ($r=0.51$, $p=0.09$) (Figure 7). For all of three association cases listed above (i.e., P50 gating - MMN, P200 gating - P3b, MMN - P3b), further comparison of correlation

coefficients between groups using the test for two independent correlation coefficients showed significant differences ($p < 0.05$; Table 2: cells shaded in gray).

A linear regression model with abstract MMN as dependent variable and P50 ratio, group and P50ratio*group interaction as independent variables, showed a significant difference in slopes of the fitted regression lines between the two groups (standardized coefficient for the P50ratio*group interaction: $\text{Beta} = -2.56$, $p < 0.001$, $N = 24$). Another linear regression model with P3b as dependent variable and P200 ratio, group and P200ratio*group interaction as independent variables, showed a trend in difference of slopes of the fitted regression lines between the two groups ($\text{Beta} = 2.44$, $p = 0.06$, $N = 24$). Lastly, a linear regression model with P3b as dependent variable and abstract deviant MMN, group and MMN*group interaction as independent variables, showed a difference in slopes of the fitted regression lines between the two groups ($\text{Beta} = -1.44$, $p = 0.02$, $N = 24$).

4. Discussion

In this study a number of significant correlations were found between measures of “gating out or habituating to repeating redundant stimuli” and “gating in or responding when the incoming stimuli takes on new or added significance”. Our most important finding is the significant correlation between gating of the P50 and amplitudes of the MMN to abstract deviance in healthy participants but not in schizophrenia patients. While the correlation was significant in the group as a whole, the correlations significantly differed between the two groups. In healthy individuals a strong negative correlation was detected (i.e., worse gating was associated with higher amplitudes MMN). This observation suggests the possibility that the MMN may be functioning as a safety or a second tier defense if the P50 gating was deficient. This correlation was significantly weaker in schizophrenia patients suggesting that this strong link between gating-out and gating-in in healthy subjects is affected in patients. It is worth highlighting that the distribution of P50 gating ratios in the two samples was very similar to our prior studies (see Figure 5; Fuerst et al, 2007; Rentzsch et al, 2008; Peterson et al, 2008). This is important as an unusual distribution could influence the results particularly with sample sizes like in the current study.

In previous studies with chronic schizophrenia patients, MMN amplitude reduction has been shown to be more robust to duration deviation (Magno et al., 2008; Todd et al., 2008). White-noise deviants were shown to produce larger, more robust differences in our group of chronic patients. Categorical abstract stimuli also prove to be good choices in eliciting robust differences in MMN between groups. The brain's capacity for abstraction and to detect important rule-violating events might underly the brain's adaptability to environmental demands (Bendixen and Schroger, 2008; Schroger et al., 2007). In this context, the abstract-rule violation MMN response (Saarinen et al., 1992; Korzyukov et al., 2003) would be an additional assessment to that based on the MMN response from concrete deviants.

In healthy controls, P3b amplitudes correlated positively with P200 gating (i.e., worse P200 gating related to lower P3b amplitudes) and abstract MMN amplitudes suggesting that these two components may be parts of one system that tends to work or fail together without one compensating for the other. In contrast, schizophrenia patients showed strong negative correlation between P3b amplitudes and the other two variables indicating that when P200 gating or MMN fails in a patient, more resources are allocated to the P3b as reflected by the higher amplitudes.

We reaffirm the observation that the sensory gating deficit pervades the entire mid-latency information processing stage (Boutros et al., 2004). The above data strongly suggests that

gating-out and gating-in are not independent functions and that additional research is needed to explore the underlying neural structures mediating the link between bottom-up and top-down processes (Klostermann et al., 2006).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Auditory evoked potentials (P50, N100, P200) elicited in the visual attention version of the paired-click paradigm (black arrows pointing at the consecutive peaks) – grandaverages (12 healthy subjects and 12 schizophrenia patients).

Figure 2. Mismatch negativity (MMN) elicited in the visual attention version of the oddball paradigm with white-noise as deviant (arrows pointing at MMN) – grandaverages (12 healthy subjects and 12 schizophrenia patients).

Figure 3. Mismatch negativity (MMN) elicited in the oddball paradigm with abstract rule violations (arrows pointing at MMN) – grandaverages (12 healthy subjects and 12 schizophrenia patients). Vertical bars represent the stimuli onset (within-pair interval is 0.12 s).

Figure 4.
P300 (P3b) elicited in the auditory oddball paradigm to target stimuli (arrows pointing at MMN) – grandaverages (12 healthy subjects and 12 schizophrenia patients).

Figure 5.
Association between P50 gating ratios and mismatch negativity (MMN) in healthy and schizophrenia samples (N=12 in each group).

Figure 6.

Association between P200 gating ratios and P300 amplitudes in healthy and schizophrenia samples (N=12 in each group).

Figure 7.

Association between MMN (abstract deviant) and P300 amplitudes in healthy and schizophrenia samples (N=12 in each group).

TABLE 1
Amplitudes and gating measures from the paired-click and oddball tasks

P50, N100, and P200 S1, S2 amplitudes and gating ratios (S2/21*100 in %), and MMN and P3b amplitudes shown as mean±SD for healthy subjects (N=12) and schizophrenia patients (N=12).

Measures mean ± (SD)	Schizophrenia	Healthy
P50 S1 amplitude (μV)	2.78 (2.32)	2.85 (1.33)
P50 S2 amplitude (μV)	2.00 (1.26)	1.59 (1.09)
P50 gating ratio (%)	99.56 (65.29)	61.15 (48.23)
N100 S1 amplitude (μV)	-6.71 (3.91) *	-10.23 (4.53)
N100 S2 amplitude (μV)	-4.81 (1.71)	-4.42 (1.51)
N100 gating ratio (%)	89.07 (54.26) **	46.03 (11.71)
P200 S1 amplitude	11.02 (4.31)	16.89 (12.83)
P200 S2 amplitude (μV)	6.56 (1.82)	5.78 (2.62)
P200 gating ratio (%)	69.62 (38.93) *	43.04 (18.41)
MMN amplitude (μV) (frequency deviance)	-3.42 (2.03)	-4.37 (3.39)
MMN amplitude (μV) (duration deviance)	-2.96 (1.35)	-3.77 (2.79)
MMN amplitude (μV) (white-noise deviance)	-3.43 (1.99) *	-5.62 (2.70)
MMN amplitude (μV) (abstract deviance)	-2.50 (1.47)	-3.55 (3.13)
P3b amplitude (μV) (frequency deviance)	4.37 (2.05) *	7.44 (5.42)
P3b amplitude (μV) (duration deviance)	4.58 (3.08)	4.78 (3.15)
P3b amplitude (μV) (white-noise deviance)	4.30 (2.84) *	8.16 (4.60)

**
p<0.01,

*
p<0.05; one-tailed independent samples t-tests

TABLE 2
Correlations between P50, N100, P200 gating ratios, MMN and P300 variables

Correlations between P50, N100, P200 gating ratios (S2/S1 *100), MMN and P300 variables, from the task requiring visual attention.

	P50 (ratio)	N100 (ratio)	P200 (ratio)	MMN (noise)	MMN (abstract)	P3b (target)
P50 (ratio)	1	0.36 -0.30 0.35	0.02 -0.73** 0.08	0.01 0.46 -0.07	0.40* 0.86** 0.14	-0.03 0.27 -0.19
N100 (ratio)		1	0.79** 0.56 0.78**	-0.39 0.28 -0.48	-0.16 -0.44 0.07	-0.18 -0.34 0.18
P200 (ratio)			1	-0.37 -0.26 -0.26	-0.44* -0.65* -0.37	-0.13 -0.38 0.56*
MMN (noise)				1	0.45* 0.52 0.12	0.41* 0.47 -0.26
MMN (abstract)					1	0.37 0.51 -0.83**
P3b (target)						1

*
p<0.05,

**
p<0.01; two-tailed tests

Note: In each single cell, top, middle and bottom correlation values belong to all (both groups), healthy and schizophrenia groups, respectively. Cells with significant differences between correlation coefficients in two groups are shaded in gray (test for two independent correlation coefficients).