P50, N100, and P200 Sensory Gating in Panic Disorder

Lars Thoma1,2,*, Johannes Rentzsch1,3,*, Katharina Gaudlitz1, Nicole Tänzer1, Jürgen Gallinat4, Norbert Kathmann2, Andreas Ströhle1, and Jens Plag1

Abstract
Panic disorder (PD) has been linked to abnormalities in information processing. However, only little evidence has been published for sensory gating in PD. Sensory gating describes the brain’s ability to exclude stimuli of low relevance from higher level information processing, thereby sustaining efficient cognitive processing. Deficits in sensory gating have been associated with various psychiatric conditions, most prominently schizophrenia. In this case-control event-related potential study, we tested 32 patients with PD and 39 healthy controls in a double click paradigm. Both groups were compared with regard to pre-attentive (P50), early-attentive (N100), and late-attentive (P200) sensory gating indices. Contrary to a hypothesized deficit, PD patients and healthy controls showed no differences in P50, N100 and P200 values. These results suggest that sensory gating seems to be functional across the pre-attentive, early-attentive, and late-attentive time span in this clinical population. Given this consistency across auditory sensory gating indices, further research aiming to clarify information processing deficits in PD should focus on other neurophysiological markers to investigate information processing deficits in PD (eg, P300, error-related negativity or mismatch negativity).

Keywords
panic disorder, sensory gating, amplitude suppression, P50, N100, and P200, electroencephalography (EEG), pre-, early-, and late-attentive information processing, anxiety disorders

Received July 17, 2019; revised November 26, 2019; accepted December 5, 2019.

Introduction
Panic disorder (PD) is characterized by recurrent panic attacks combined with worry about further occurrence of these attacks.1 Cognitive research has demonstrated that PD is associated with abnormalities in attention and information processing. In general, PD patients have been shown to attribute greater cognitive resources to threat-related stimuli such as body symptoms while neglecting their external environment.2–5 However, some studies also reported tendencies of patients with PD to process irrelevant information to a greater extent as compared with healthy control participants.6–9 Hence, cognitive abnormalities in PD may be characterized as disturbance in sensory filtering, that is, filtering relevant stimuli from irrelevant stimuli and adjusting cognitive resources accordingly.10 Potential deficits in signal to noise detection in PD are evidenced by event-related potential (ERP) studies. For instance, increased N100 amplitudes indexing intensified attention to monotonous stimuli were found in these patients.11–13 Additionally, PD patients have been shown to display reduced mismatch negativity amplitudes, signaling a reduced sensitivity to external stimulus changes.14 Further evidence in this condition includes elevated P300a and P300 amplitudes to rare stimuli reflecting changes in attentional processes,15,16 as well as reduced P300 amplitudes in panic disorder with atypical symptoms16 and increased error-related negativity.17 Although it needs to be noted that ERP trials in PD revealed mixed results,15,18 cumulative evidence tends to support the assumption of disturbed signal to noise detection in PD.

One further possibility to explore cognitive abnormalities in PD is sensory gating. It describes the brain’s faculty to discard possibly interfering stimuli before they reach higher level...
cognitive mechanisms.\textsuperscript{19,20} In sensory gating paradigms, ERPs in response to a stimulus shortly followed by another identical and thus redundant stimulus are compared, typically by calculating the ratio or the absolute difference of the second to the first amplitude.\textsuperscript{21} Low ratio (or high difference) scores signal adequate filtering of irrelevant information, while higher ratio (or lower difference) scores imply deficits in signal to noise detection which potentially indicate reduced cognitive functioning.

Abnormalities in sensory gating are of high interest in psychiatric research and have been studied mostly with P50, a positive amplitude occurring approximately 50 ms after auditory stimulus presentation, which likely reflects pre-attentive information processing.\textsuperscript{21-24} Alterations in P50 sensory gating have been found most prominently in schizophrenia.\textsuperscript{25-31} Furthermore, abnormalities in sensory gating have also been reported in a broader range of mental conditions, including antisocial personality disorder,\textsuperscript{32} posttraumatic stress disorder,\textsuperscript{13} schizotypal personality disorder,\textsuperscript{24-36} cocaine abuse,\textsuperscript{37,38} abstinent cannabis use,\textsuperscript{39} and bipolar affective disorder.\textsuperscript{40,41} Though one study reports normal sensory gating in bipolar disorder,\textsuperscript{42} in addition to the P50 response, sensory gating has been studied less frequently also with N100 and P200 evoked potentials, reflecting early and late attentive information processing, respectively.\textsuperscript{43,44} Impaired N100 sensory gating has been reported for schizophrenia\textsuperscript{45} and bipolar disorder.\textsuperscript{46} In addition, bipolar disorder has also been associated with impaired P200 sensory gating.\textsuperscript{46}

Despite this wealth of psychiatric research in sensory gating, little is known about sensory gating in PD. To the best of our knowledge, only one study has been published for P50 sensory gating, reporting increased P50 ratios in PD compared with HC, which possibly indicate an inability to filter internal stimuli according to their relevance,\textsuperscript{47} and no studies for N100 and P200 sensory gating in PD have been published. Due to the lack of robust evidence, it therefore remains unclear whether sensory gating across the pre-, early-, and late-attentive span is impaired.

Hence, the present study’s objective is to explore the functionality of sensory gating in PD as indexed by 3 different indices (P50, N100, and P200 amplitudes) in order to test whether earlier findings of impaired sensory gating in PD may be replicated.

**Method**

**Participants and Procedure**

We initially included 35 patients with panic disorder and 42 healthy controls (HC). During data analysis, 3 PD and 3 HC were excluded due to unidentifiable event related potentials (see EEG methods section for more detail). The final sample included thus 32 PD (15 without agoraphobia and 17 with agoraphobia, age between 19 and 51 years) and 39 HC (age between 22 and 50 years). This study is part of larger trial that investigated the effect of physical exercise on cognitive behavioral therapy and was already published elsewhere.\textsuperscript{14,48} Here we report baseline sensory gating data. All study procedures were performed according to the declaration of Helsinki.

Patients were approached through the Charité’s outpatient clinic for anxiety disorders. All patients were diagnosed by trained psychologists using the Mini-International Neuropsychiatric Interview (M.I.N.I.)\textsuperscript{49} with PD (with or without agoraphobia) according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Revision (DSM-IV).\textsuperscript{50} HC participants were approached through advertisement in the clinic’s environment. All participants provided written informed consent before participating in this study.

Inclusion criteria for both PD and HC included age between 18 and 70 years, as well as absence of past or current head trauma or neurological diseases. Furthermore, PD patients had to be free of anxiolytic medication for at least 4 weeks and showed no other primary psychiatric diagnoses. Additionally, duration of PD had to be for at least 6 months. HC were free of psychiatric diagnoses (assessed using M.I.N.I.) and did not consume drugs or psychotropic medication.

Panic severity and general anxiety were determined by using the Hamilton Anxiety Scale (HAMA),\textsuperscript{51} the self-rating version of the Panic and Agoraphobia Scale (PAS),\textsuperscript{52} and the Beck Anxiety Inventory (BAI).\textsuperscript{53} The Hamilton Depression Scale (HAMD-17)\textsuperscript{54} and the Beck Depression Inventory II (BDI-II)\textsuperscript{55} were applied to assess for symptoms of depression.

Sample characteristics are displayed in Table 1. The study groups did not differ in age, sex, and handedness. As expected, HC report less anxious and depressive symptoms than patients with PD.

**Auditory Stimulation**

Participants were seated in a sound-attenuated room. Participants were instructed to keep their eyes closed. Auditory stimulation consisted of 150 identical pairs of clicks (click duration 1 ms, interclick interval 500 ms) and 50 distractor sinus tones (1000 Hz, duration 400 ms, 80 dB) played in a pseudo-randomized sequence through headphones. The distractor stimuli were employed in order to facilitate steady attention.\textsuperscript{56} Participants were instructed to react to stimuli by pressing a button. A short interpair interval of 3400 ± 918 ms (range 3400-6044 ms) was employed instead of a long interval of 8 to 12 seconds to reduce recording time and thereby making the examination more tolerable for participants. Studies with HC have shown that suppression effects for P50, N100, and P200 can be detected with such shorter interpair intervals.\textsuperscript{57,58}

**Electroencephalographic Data**

EEG was recorded with 29 Ag/Ag-Cl electrodes according to the extended international 10/20 system using an electrode cap (EASYCAP GmbH, Herrsching, Germany) and a BrainAmp amplifier (Brain Products GmbH, Munich, Germany; digitized at 500 Hz; gain 5000; analog band pass filter: 0.15-100 Hz). Electrode impedances were kept below 10 kohm. Ocular movements were detected with an additional electrode located 1 cm
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lateral to the left eye. Electrodes were referenced to FCz and FPz served as ground.

Offline analysis was executed with Brain Vision Analyzer 2.0 (Brain Products, Munich, Germany) and EEGLab Version v13.1.1.59 EEG data were filtered (passband edges 0.5 and 70 Hz) before automatic artifact correction using the eeglab-plugins Artifact Subspace Reconstruction Version 0.1360 and Automatic Artifact Removal Version 1.3.61 Eye movement and electrocardiac artifacts that were not detected by these procedures were removed manually by use of independent component analysis (ICA). In the following, data were exported to Vision Analyzer and transformed to Current Source Density (CSD [in μV/m²]; order of splines 4, maximal degree of Legendre polynomials 10), filtered (10 Hz high-pass filter for P50 and 30 Hz low-pass filter for N100 and P200 evoked potential analysis, 12 dB/oct), segmented in relation to the first stimuli (−200 to 1000 ms) and baseline corrected (−200 to 0 ms). Segments showing amplitudes ±100 μV before transforming to CSD were excluded from further analyses. After averaging, automatic peak detection was performed at electrode Cz for the first and second click-evoked amplitudes. Latency ranges for peak identifications were estimated based on visual inspection of the grand averages’ mean from both groups and therefore slightly differ between the first and second click-evoked amplitude (latency ranges: first P50: 50-70 ms, second P50: 54-568 ms; first N100: 70-130 ms, second N100: 570-610 ms; first P200: 130-270 ms, second P200: 620-710 ms). Amplitudes were quantified as mean amplitudes within a 4-ms time frame around the amplitude peak. Three PD and 3 HC participants were excluded from analysis because no P50, N100, or P200 amplitude following click 1 was detectable. In line with common procedures applied in other studies, when no amplitude was detected after the second click, it was interpreted as maximal suppression and the amplitude therefore set to 0.001.38,62-64 Furthermore, ratio gating scores larger than 200% were restricted to 200 in order to prevent outliers from distorting group means,65,66 which did not occur preferentially in any of the 2 groups (n = 3 in PD, n = 3 in HC).

### Statistical Analysis

Sample characteristics were analyzed with 2-sample t tests as well as chi-square test. ERP latencies, amplitudes, and suppression scores were compared between groups with 2-sample t tests. Additionally, amplitudes between first and second click were analyzed through repeated measurement multivariate analysis of variance (MANOVA) with the within-subject factor time (click 1, click 2). Pearson correlations were used in order to test for correlations between clinical features or self-ratings and sensory gating indices.

An alpha level of .05 indicated significance in all analyses.

### Results

#### Mean Amplitudes

Mean amplitudes for P50, N100, and P200 after the first and second click are presented in Table 2. Amplitudes did not differ between the two groups. Repeated measurement analysis yielded a significant effect of time (click 1, click 2) on P50, F(1, 69) = 54.93, P < .001; N100, F(1, 69) = 29.9, P < .001; and P200 amplitude, F(1, 69) = 78.2, P < .001, indicating an amplitude reduction from first to second click stimulus.

#### Amplitude Suppression

Aggregated waveforms are displayed in Figure 1a (for P50) and in Figure 1b (for N100 and P200). Difference and ratio

### Table 1. Demographic and Clinical Characteristics of the Panic Disorder Group and Healthy Control Group With Comparison Statistics (t Test and χ² Test).

<table>
<thead>
<tr>
<th></th>
<th>Panic Disorder Group, n = 32</th>
<th>Healthy Control Group, n = 39</th>
<th>Comparison Statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M ± SD</td>
<td>M ± SD</td>
<td></td>
</tr>
<tr>
<td>Sex (female)</td>
<td>18 / 53.3%</td>
<td>24 / 61.5%</td>
<td>χ²(1) = 0.2, P &gt; .6</td>
</tr>
<tr>
<td>Right-handedness</td>
<td>30 / 93.8%</td>
<td>38 / 94.4%</td>
<td>χ²(2) = 1.2, P &gt; .5</td>
</tr>
<tr>
<td>Age, years</td>
<td>31.8 ± 7.0</td>
<td>33.9 ± 9.7</td>
<td>t(67.8) = 1.0, P &gt; .8</td>
</tr>
<tr>
<td>Age of onset, years</td>
<td>29.8 ± 7.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of illness, months</td>
<td>40.7 ± 53.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HAM-A</td>
<td>19.5 ± 9.4</td>
<td>1.7 ± 2.4</td>
<td>t(69) = 11.5, P &lt; .001</td>
</tr>
<tr>
<td>BAI</td>
<td>18.8 ± 10.1</td>
<td>1.7 ± 2.1</td>
<td>t(69) = 10.3, P &lt; .001</td>
</tr>
<tr>
<td>PAS</td>
<td>18.8 ± 9.3</td>
<td>0.1 ± 0.3</td>
<td>t(69) = 12.7, P &lt; .001</td>
</tr>
<tr>
<td>HAMD-17</td>
<td>7.0 ± 4.6</td>
<td>0.4 ± 0.8</td>
<td>t(69) = 8.8, P &lt; .001</td>
</tr>
<tr>
<td>BDI-II</td>
<td>11.4 ± 9.2</td>
<td>1.7 ± 2.1</td>
<td>t(69) = 6.4, P &lt; .001</td>
</tr>
</tbody>
</table>

Abbreviations: HAM-A, Hamilton Anxiety Rating Scale; BAI, Beck Anxiety Inventory; PAS, Panic and Agoraphobia Scale; HAMD-17, Hamilton Rating Scale for Depression; BDI-II, Beck Depression Inventory II.
scores for sensory gating are presented in Table 3. We found no significant differences in amplitude suppression between PD patients and HC. These results did not change when participants with ratio scores larger than 200% were excluded from the analysis.

**Correlations Between Clinical Features and Sensory Gating Indices**

There were no statistically significant correlations between clinical features or self-ratings and any sensory gating indices (data not shown; all $r(30) < .29$, all $P > .1$)

**Discussion**

The objective of this trial was to test replicability of P50 sensory gating deficits as well as to first investigate N100 and P200 sensory gating indices in PD. As a result, the present study found no differences for pre-attentive P50, early-attentive N100, and late-attentive P200 sensory gating between PD patients and HC.

Our results are in contrast to those reported by Ghisolfi et al who found higher P50 suppression ratios in a sample of 28 patients with PD as compared with 28 HC. Some methodological differences need to be considered in relation to these divergent results. We used a modified paired-stimulus protocol with distractor stimuli to control for attention and shorter inter-stimulus intervals than Ghisolfi and colleagues. Controlling for attention is important as attention has been evidenced to confound P50 sensory gating group differences in schizophrenic patients. Furthermore, participants in our study were instructed to keep their eyes closed (eyes open in Ghisolfi and colleagues’ study). Thus, we cannot rule out that our specific methodology may have biased our results. It is worth mentioning though that evidence from a study with HC found no P50 sensory gating differences in relation to testing with eyes open or closed. However, it is unclear whether eyes open or eyes closed status has any impact on P50 sensory gating in PD. Additionally, sample heterogeneity between the present and Ghisolfi and colleagues’ study need to be noted: In our study only unmedicated PD patients without other psychiatric diagnoses were included, whereas Ghisolfi and colleagues also included comorbid patients (with depression, dysthymic disorder, generalized anxiety disorder, social phobia) and more severely affected patients as well as patients medicated with antidepressants and benzodiazepines (22 out of 28 patients). Analyses in Ghisolfi and colleagues’ study revealed that these factors may have a differential impact on P50 sensory gating. More precisely, comorbidity with social phobia and generalized anxiety disorder seems to increase P50 ratios (that is impair sensory gating), while benzodiazepines may decrease P50 ratios (ie, improve sensory gating). The latter finding is in line with other studies that reported impaired P50 sensory gating in relation to medication. More precisely, selective serotonin reuptake inhibitors (SSRIs) and dual-acting antidepressants have been found to impair sensory gating in HC. Additionally, no P50 sensory gating deficits were found in unmedicated patients affected by obsessive-compulsive disorder, whereas obsessive-compulsive disorder patients medicated mostly with SSRIs displayed impaired P50 sensory gating.

The present trial is the first to test sensory gating in PD across P50, N100, and P200 time frames. Our results indicate that sensory gating in PD is unaltered across the pre-, early-, and late-attentive stage of sensory information processing. Hence, sensory gating deficits might be of lower relevance in PD as compared with psychotic disorders. In fact, P50 sensory gating deficits seems to be a more robust finding in schizophrenia for a meta-analysis and bipolar disorders with a history of psychosis, but deficits are also consistently reported for posttraumatic stress disorder. In other mental disorders, sensory gating is investigated less frequently or subject to contrasting findings such as in obsessive-compulsive disorder. However, further research is needed in order to replicate these results. Depending on further studies, it is also conceivable that sensory gating is affected only in a subgroup of PD patients.

Abnormal sensory information processing in PD has been evidenced by various ERPs such as mismatch negativity and N100 potentials. However, the present study adds to evidence for functional information processing indices such as normal N100 or normal N200 and P200. These at times mixed results need to be interpreted in light of considerable variations in medication status and comorbidity of study participants. As a consequence, this heterogeneity in study samples naturally reflects in slightly heterogeneous results. It therefore seems to be possible that some information processing deficits found in former ERP trials are not directly related to the core symptoms of PD.

Limitations to this study need to be considered. First, we did not assess smoking status. Smoking has been found to normalize impaired sensory gating in schizophrenic patients. However, as preparation and testing took approximately 2 hours, acute
Figure 1. (a and b) P50, N100, and P200 amplitudes at Cz evoked by first and second click stimulus. Click stimuli were presented at time zero (first click) and at 500 ms (second click). Please note different y-axis and different filter settings for P50 (high-pass 10 Hz) and for N100/P200 (low-pass 30 Hz) evoked potentials.

Table 3. Amplitude Suppression for P50, N100, and P200 Calculated as Difference Score (Click 2 – Click 1) and as Ratio (Click 2/Click 1) for Panic Disorder Patients and Healthy Controls With Means and Standard Deviations, as Well as t-Test Comparison Statistic.

<table>
<thead>
<tr>
<th></th>
<th>Panic Disorder Group</th>
<th>Healthy Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>SD</td>
</tr>
<tr>
<td>Difference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>dP50</td>
<td>3.09</td>
<td>3.8</td>
</tr>
<tr>
<td>dP50 BC</td>
<td>3.01</td>
<td>3.78</td>
</tr>
<tr>
<td>dN100</td>
<td>-4.41</td>
<td>6.9</td>
</tr>
<tr>
<td>dN100 BC</td>
<td>-4.97</td>
<td>6.75</td>
</tr>
<tr>
<td>dP200</td>
<td>7.10</td>
<td>6.33</td>
</tr>
<tr>
<td>dP200 BC</td>
<td>6.34</td>
<td>6.03</td>
</tr>
<tr>
<td>Ratio</td>
<td></td>
<td></td>
</tr>
<tr>
<td>gP50</td>
<td>52.3</td>
<td>45.6</td>
</tr>
<tr>
<td>gP50 BC</td>
<td>55.8</td>
<td>40.9</td>
</tr>
</tbody>
</table>

Note that BC indicates values that are corrected by the baseline before the second (instead of the first) click.

nicotine effects can be ruled out. A further limitation consists in the specific protocol with shorter interstimulus intervals as discussed above. If sensory gating represents a robust construct, however, it should be expected to be detected across varying protocols. The use of varying protocols therefore may be advantageous in some degree to increase the generalizability of results.
In conclusion, the present study is the first to reveal comparable P50, N100, and P200 sensory gating indices between PD patients and HCs. These results suggest that auditory sensory gating seems to be generally unaltered in PD and further research should rather focus on further neurophysiological markers to investigate information processing deficits in PD such as P300, mismatch negativity or error-related negativity.

Authors’ Note

This trial was approved by the ethics committee at Charité—Universitätsmedizin Berlin (EA1/129/08) and is registered at “ClinicalTrials.gov” (identifier: NCT01788800).

Author Contributions

LT: substantially contributed to conception or design; drafted the manuscript; critically revised the manuscript for important intellectual content; gave final approval; agrees to be accountable for all aspects of the work in ensuring that questions relating to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

JR: substantially contributed to conception or design; substantially contributed to conception or design; drafted the manuscript; critically revised the manuscript for important intellectual content; gave final approval; agrees to be accountable for all aspects of the work in ensuring that questions relating to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

KG: substantially contributed to conception or design; substantially contributed to conception or design; critically revised the manuscript for important intellectual content; gave final approval; agrees to be accountable for all aspects of the work in ensuring that questions relating to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

NT: substantially contributed to conception or design; critically revised the manuscript for important intellectual content; gave final approval; agrees to be accountable for all aspects of the work in ensuring that questions relating to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

NK: substantially contributed to conception or design; critically revised the manuscript for important intellectual content; gave final approval; agrees to be accountable for all aspects of the work in ensuring that questions relating to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

AS: substantially contributed to conception or design; substantially contributed to conception or design; critically revised the manuscript for important intellectual content; gave final approval; agrees to be accountable for all aspects of the work in ensuring that questions relating to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

JP: substantially contributed to conception or design; substantially contributed to conception or design; critically revised the manuscript for important intellectual content; gave final approval; agrees to be accountable for all aspects of the work in ensuring that questions relating to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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