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Short communication

# Auditory sensory gating in patients with bipolar disorders: A meta-analysis

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ABSTRACT

*Background:* Sensory gating (SG) refers to the attenuation of neural response to the second identical stimulus and is conceptualized as an automatic process to inhibit redundant information. Although its deficit in schizophrenia has been well-documented, the degree to which SG is modulated by bipolar disorders (BD) remains elusive. Thus, the present meta-analysis study aimed to explore the pooled effect sizes of SG ability in BD patients.

*Methods:* Ten studies consisting of 14 individual investigations were included, consisting of 699 healthy controls and 568 BD patients. The effect sizes, calculated as Cohen's d, were estimated individually for S2/S1 ratio and S1 − S2 difference. Additionally, S2/S1 ratio was examined in two conditions: BD with and without a history of psychosis.

*Results:* We found that BD patients with ($d=0.847$, $p<0.001$) or without ($d=0.589$, $p<0.001$) a psychotic history exhibited an impaired SG ability compared to the healthy controls. Furthermore, both S1 − S2 difference score and S2/S1 ratio, at a group level, can differentiate BD patients from healthy controls.

*Limitations:* We were not able to divide patients with BD into different subtypes, and thus our data should be interpreted with cautions.

*Conclusion:* These findings suggest BD itself impairs SG ability, which worsens with a psychotic history. The current understanding invites future research to ascertain the role of SG in subtypes of BD.



## 1. Introduction

Bipolar disorders (BD) are characterized by uncontrolled mood fluctuation and associated with many aspects of cognitive impairments, including the sensory gating (SG) ability (Olincy and Martin, 2005; Schulze et al., 2007; Hall et al., 2015). SG, referring to the brain's ability to automatically filter out redundant sensory stimuli, is considered as a protective mechanism to prevent a flooding of irrelevant information to the higher cortical centers (Boutros and Belger, 1999). Although SG occurs at the early stage of information processing, its influences manifest across the whole cognitive operations (Wan et al., 2008; Cheng et al., 2016). In the event-related potential (ERP) studies, auditory P50 gating ratio (Stimulus 2 over Stimulus 1, S2/S1) is typically assessed by the paired-click paradigm. A larger ratio is indicative of reduced cortical inhibition. This electrophysiological measure has been widely applied in patients with schizophrenia. Recently, the assessments of SG have received increased attention in patients with BD to identify the potential pathophysiological similarities and differences with other psychiatric diseases (Hall et al., 2015).

Despite considerable effort, the progress in regular utilization of the P50 SG method in BD clinical research has been challenged due to the complexity of the disease. One of the major factors that led to the controversial findings might be the comorbidity/history of psychotic symptoms in these patients. It is estimated that approximately 65% of BD patients have accompanying psychotic symptoms (Coryell et al., 2001). Olincy and Martin, (2005) reported that BD patients with a lifetime history of psychosis demonstrated impaired P50 SG compared to those without psychotic symptoms. Furthermore, the P50 SG ratio in BD patients without a history of psychosis did not differ from that of healthy controls, suggesting this defect might be associated with psychosis in

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general (Olincy and Martin, 2005; Sanchez-Morla et al., 2008). In contrast, some contradictory results showed that P50 gating ratio did not significantly vary as a function of psychosis, suggesting BD *per se* might lead to SG impairment (Carroll et al., 2008; Patterson et al., 2009).

In addition to S2/S1 ratio, SG ability can be expressed as the difference score between the S1 and S2 neural responses (S1 − S2). A smaller S1 − S2 value reflects a poorer gating ability. Although the gating ratio has been studied in most of the SG research, the P50 S1 − S2 difference score has been proved to be more reliable than the P50 S2/S1 ratio (Rentzsch et al., 2008). As a result, recent studies attempted to report the data of S2/S1 ratio and S1 − S2 score simultaneously (Terada et al., 2015; Vuillier et al., 2015). Nevertheless, it is still less understood which measuring parameter is more effective to differentiate BD patients from healthy controls.

Meta-analysis plays an important and objective role in summarizing the results that show heterogeneity. To the best of our knowledge, no statistical review of SG in BD patients has been conducted. Specifically, the purpose of the present study was twofold. First, we aimed to evaluate whether BD patients demonstrated a deficient SG ability compared to the healthy controls. The effect sizes of SG ability in those patients with or without a history of psychosis were also examined. Second, the effect sizes of different computational methods (S2/S1 ratio and S1 − S2 score) were compared to determine which one could better differentiate BD patients from healthy subjects.

## 2. Methods

### 2.1. Data source and study selection

The published literature was searched in Medline and PubMed (1990–2016 January), using the following keywords, “sensory gating” and “bipolar disorder”. The reference lists of the selected articles were also searched as additional studies.

Two reviewers (Cheng and Chan) independently reviewed and identified articles that met the following criteria: (1) they involved ERP or event-related field (ERF) experiments, (2) the subjects were divided into at least controls and BD patients, (3) SG ability was measured as S2/S1 ratio or S1 − S2 difference, and (4) they were written in English.

### 2.2. Data extraction

The necessary data of each study regarding the number of participants, age, subtypes of BD, a psychotic history or not, stimulus characteristics, means (M), and standard deviations (SD) of SG ability for each group were extracted by Cheng and checked by Chan. Disagreements with study criteria or data coding were resolved by consensus. If the study was composed of more than one comparison, such as BD patients with or without a history of psychosis, then each comparison served as an individual investigation.

### 2.3. Data synthesis

The collected data were analyzed by using Comprehensive Meta Analysis 2.0 software (Biostat Inc., Englewood, NJ). The effect size (Cohen's d) was calculated based on the mean differences between BD patients and controls, divided by the pooled SD. M and SD from one of the studies (Patterson et al., 2009) was estimated from the bar graph. In order to overcome the influences of sample sizes on the effect sizes, an inverse variance weighting factor was used to give more weight on studies with larger sample sizes. Effect sizes between 0.2 and 0.5 were considered to be small, those between 0.5 and 0.8 were considered to be medium, and those above 0.8 were considered to be large. The heterogeneity of each effect size was evaluated by Q-statistics and $I^2$ index. When obvious heterogeneity was present, a random effect model was applied. Otherwise, a fixed model was selected.

A funnel plot was created to detect if the included studies suffered from publication bias. Moreover, Begg and Mazumdar (1994) rank correlation and Egger et al. (1997) regression intercept test were used to assess whether a bias exists. *P* values less than 0.05 were considered as the significant levels.

## 3. Results

### 3.1. Study characteristics

An initial search yielded 49 results. Based on the title and abstract, 24 potentially eligible articles were identified. The two authors conducted a full-text review and determined that 10 articles fulfilled the inclusion criteria (Olincy and Martin, 2005; Carroll et al., 2008; Hall et al., 2008; Sanchez-Morla et al., 2008; Lijffijt et al., 2009; Patterson et al., 2009; Cabranes et al., 2013; Wang et al., 2014; Hall et al., 2015; Vuillier et al., 2015). Six of these studies consisted of more than one comparison, and thus a total of 14 and 8 individual investigations for S2/S1 ratio and S1 − S2 difference score, respectively, were included in the meta-analysis.

Table 1 summarizes the clinical information and experimental data of the 10 included studies. Among these investigations, seven involved comparisons between controls and BD patients with a psychotic history, and six involved comparisons between controls and BD patients without a psychotic history.

### 3.2. Effect sizes

Fig. 1(A) depicts the effect sizes and 95% confidence intervals (CIs) of S2/S1 ratio for each investigation. The meta-analysis revealed a pooled effect size of 0.736 with 95% CI ranging from 0.625 to 0.848 ($p < 0.001$). The heterogeneity was not significant ($Q = 14.97$, $I^2 = 8.43\%$, $p = 0.36$), and thus the fixed model was applied. Fig. 1(B) and (C) show the effect sizes of S2/S1 ratio of BD patients with and without a psychotic history, respectively. The pooled effect size (fixed model) of S2/S1 ratio between BD patients with a psychotic history and healthy controls was 0.847 with 95% CI ranging from 0.710 to 0.985 ($p < 0.001$). The pooled effect size (fixed model) of S2/S1 ratio between BD patients without a psychotic history and control subjects was 0.589 with 95% CI ranging from 0.374 to 0.804 ($p < 0.001$).

We further computed the effect sizes of S1 − S2 difference score between control subjects and BD patients. The pooled effect size (fixed model) of S1 − S2 difference score was 0.451 with 95% CI ranging from 0.298 to 0.604 ($p < 0.001$).

### 3.3. Publication bias

The funnel plot of S2/S1 ratio displays a symmetric shape, suggesting no publication bias between smaller-size and larger-size studies (Supplementary Data). The Begg and Mazumdar rank correlation ($tau = -0.34$, $p = 0.09$) and Egger's regression intercept ($intercept = -1.23$, $p = 0.15$) also confirmed that these meta-analysis results did not suffer from publication bias.

## 4. Discussion

This meta-analysis yielded two important insights into the nature of SG impairment in BD. Firstly, BD patients, either with or