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Review

# Inhibitory deficits in prepulse inhibition, sensory gating, and antisaccade eye movement in schizotypy

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ABSTRACT

Schizotypy is a term that refers to a continuum of personality characteristics, emerging from mental states ranging from organized and normal to unorganized and disordered; with the latter tending to include individuals with high schizotypal scores as well as those diagnosed with schizotypal personality disorder. Evidence from psychophysiological studies has found a relative weakness in the inhibitory functioning, including prepulse inhibition (PPI), sensory gating (SG), and antisaccade eye movement (AEM) in schizotypy and schizophrenia. As schizotypy and schizophrenia are in the same spectrum, understanding the nature of sensory and motor inhibitory weakness associated with schizotypy will optimize the prevention and intervention for both schizotypy and schizophrenia populations.

This review aims at examining the deficits of sensory gating, saccade control, and prepulse inhibition in schizotypy; examining the relationship between the three measures and schizotypal symptoms and traits; examining the effect of nicotine on the three measures; and examining the relevant brain regions to the three measures. We searched multiple databases (such as MEDLINE, Pubmed, PsychINFO, Google Scholar) using combinations of the keywords: schizotypy, schizotypal personality disorder, prepulse inhibition, sensory gating and antisaccade for articles published in English since 1980.

We found that three measures (SG, PPI and AEM) are associated with major schizotypal symptoms, suggesting that three measures could be used to predict the disease etiology and prognosis. Secondly, the three measures are modulated by nicotine administration at a certain level, providing a potential tool to study the role of nicotine in the cognition and symptom improvement in schizotypy. Thirdly, brain-imaging studies have localized activity in brain regions associated with sensory gating, saccade control, and prepulse inhibition, narrowing the search for brain regions to target for the treatment and prevention of schizotypy. Overall, the three measures are suggested to be a valuable tool to study the inhibitory deficits in schizotypy, and maybe used as a tool for the prevention and treatment of schizotypy as well.



## 1. Introduction

Schizotypy provides a particularly useful framework for investigating schizophrenia spectrum disorders because it places individuals' psychotic symptoms and personality characteristics on a continuum ranging from personality to psychosis. Since the schizotypy framework uses a continuum rather than discrete categories, vulnerabilities to schizophrenia spectrum disorders can be expressed as a multidimensional personality organization (Barrantes-Vidal et al., 2015). This framework is valuable for studying the development of schizophrenia because adolescents who meet diagnostic criteria for schizotypy or have schizotypal personality disorder are at an increased risk for developing schizophrenia, implicating the role of pre-existing risk factors for schizophrenia. While limited studies have documented an increased risk for developing schizophrenia as an adolescent with schizotypy (Angst and Clayton, 1986), evidence for the increased likelihood of schizotypal personality disorder adolescents progressing to schizophrenia has been more widely studied with rates between 20% and 40% (Yung, et al., 2003; Walker, et al., 2004) including a 15-year follow-up study that reported 40% of the individuals with schizotypal personality disorder were diagnosed with schizophrenia later in life (Fenton and McGlashan, 1989). The disparity in the research on schizotypal personality disorder and schizotypy in terms of one's tendency to develop schizophrenia may be due to the pathologic nature of schizotypal personality disorder, while schizotypy pertains to a latent personality construct. The tendency for individuals with schizotypy or schizotypal personality disorder to develop schizophrenia suggest that these two disorders possess a liability for developing schizophrenia

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(Walker and Gale, 1995), making schizotypy research the crux to identifying targets for treatment and prevention.

Deficits in the basic process inhibition functioning (such as sensory and motor) among schizophrenia patients have been studied using various techniques including sensory gating, anti-saccade, prepulse inhibition (PPI); all of which have been well characterized among schizophrenia populations. Patients with schizophrenia have abnormal sensory gating to irrelevant stimuli (Adler et al., 1982; Siegel et al., 1984). The increased sensory response to irrelevant stimuli in schizophrenia appears to be due to poor selective sensory inhibition, resulting in the flooding of sensory input into higher cortex. The abnormal sensory gating has been found to be linked to the negative symptoms in schizophrenia, as well as sensory overload and cognitive fragmentation in schizophrenia (Louchart-de la Chapelle et al., 2005a, 2005b). In addition, schizophrenia patients have demonstrated poor inhibition of eye movements and have demonstrated an increased proportion of antisaccade errors (Fukushima et al., 1990). In fact, saccade studies have found increased inhibition errors during the antisaccade task, particularly in schizophrenia patients with more severe negative symptoms (Ettinger et al., 2004; Nkam et al., 2001). Moreover, PPI has been reported as being reduced in schizophrenia. This effect is maximized with stronger prepulses and tends to be linked to positive and negative symptoms (Braff et al., 1999). As this deficit appears to be a stable trait associated with schizophrenia and is not modulated by clinical state, PPI deficits are considered to be an endophenotype of schizophrenia (Braff and Freedman, 2002; Gottesman and Gould, 2003).

Sensory gating, antisaccade eye movement and PPI have been widely studied in schizophrenia, and the deficits in these three measures have been consistently measured in schizophrenia. As schizotypy and schizophrenia are in the same disease spectrum and a certain percentage of schizotypal personality disorder finally develops into schizophrenia, studying the three inhibitory deficits in schizotypy will complete the understanding of the schizophrenia spectrum, and optimize the prevention and intervention for both schizotypy and schizophrenia.

This review aims at examining the deficits of sensory gating, saccade control, and prepulse inhibition in schizotypy, including individuals with high schizotypal scores and patients with schizotypal personality disorder; examining the relationship between these three measures and schizotypal symptoms and traits; examining the effect of nicotine on the three measures in schizotypy; and examining the relevant brain regions to the three measures in schizotypy.

We have searched multiple databases using combinations of the keywords: schizotypy, schizotypal personality disorder, prepulse inhibition, sensory gating and antisaccade for articles published in English since 1980. We have searched MEDLINE/Pubmed database for 63 articles and PsychINFO database for 56 articles. Additional articles were identified through other sources, such as Google Scholar. We have searched hundreds of articles by using combined keywords. After the duplicates removed, we have 87 articles left. Our inclusive criteria are: 1) human studies; 2) psychophysiological studies; 3) brain imaging studies. Our exclusive criteria are: 1) animal studies; 2) biological studies; 3) review paper; 4) biochemistry studies; 5) studies published before 1980; 6) studies published in languages other than English. Therefore, 30 of 87 articles were excluded. We have 57 full-text articles assessed for eligibility. Among them, 33 studies were included in the tables, and 24 were included in the brain structure section.

### 1.1. Sensory gating

Sensory gating is a mechanism utilized by the central nervous system to prevent irrelevant sensory stimuli from entering into the higher cortex, ensuring normal information processing (Adler et al., 1998). Deficits in sensory gating result in an overflowing of irrelevant stimuli into the higher cortex for processing, which tend to be associated with behavioral disorders and psychotic symptoms (McGhie and Chapman, 1961).

Sensory gating is usually measured by the change of P50 amplitude. The P50 is a mid-latency auditory evoked response, and it appears in the electroencephalograph (EEG) about 50 ms after administrating an auditory stimulus. During the test, the subject is given a pair of single-sound stimuli: S1 (also called conditioning stimulus) and S2 (also called test stimulus). Both of them are the same in intensity, frequency and pitch. The sensory gating efficacy is measured either using a ratio of the P50 amplitudes of S2 over S1, or by the difference between the amplitudes of S2 and S1. A low ratio or large difference represents better sensory gating capability (Freedman et al., 1983). Evidence shows that normal subjects can reduce the amplitude of S2 by 80–90% of the amplitude of S1, and schizophrenia subjects only reduce the amplitude of S2 by 10–20% (Freedman et al., 1983).

a. Individuals with high schizotypal scores

The degree of schizotypy is usually measured with questionnaires, including the Schizotypal Personality Questionnaire (SPQ; Raine et al., 1991), O-LIFE questionnaire (Mason and Claridge, 2006), etc. The schizotypal scores tend to be negatively associated with P50 gating. For example, individuals high in the dimension of unreality tend to be poorer sensory gates than individuals low in unreality, indicating that P50 gating deficits are related to the unreality aspects of schizotypy (Croft et al., 2001). Similarly, among non-clinical Japanese individuals, P50 suppression ability negatively correlated with total SPQ score, extraversion, and neuroticism. Moreover, when controlled for extraversion or neuroticism, a significant partial correlation of P50 suppression with the total SPQ score persisted (Wang et al., 2004). Reduced P50 gating and smaller P50 amplitude to S1 have been linked to cognitive disorganization, but not to positive or negative symptoms of schizotypy (Evans et al., 2007). By using the O-LIFE questionnaire, P50 suppression was significantly reduced in those with high schizotypal scores, compared to the low-scoring individuals. In addition, cognitive disorganization and impulsive non-conformity are associated with the degree of deficit in P50 gating (Park et al., 2015).

Smoking has been found to facilitate P50 gating (Crawford et al., 2002). P50 gating is positively correlated to schizotypal personality scores in heavier smokers, and negatively related to schizotypal personality scores in non-smokers and those who smoked little (Croft et al., 2004). Interestingly, in a college student sample, high schizotypal personality score and better P50 gating have been found in smokers, while low schizotypal personality score and worse P50 gating have been found in non-smokers. Among non-smokers, better P50 gating occurred in the low schizotypal group than the high schizotypal group; among smokers, better P50 gating occurred in the high schizotypal group than the low schizotypal group (Wan et al., 2006, 2007). The study indicates a facilitating effect of the tendency to smoke on P50 gating for individuals with high SPQ scores, but not individuals with low SPQ scores.

b. Patients with schizotypal personality disorder

Schizotypal personality disorder is usually assessed with the Structured Clinical Interview for DSM-IV Axis I Disorders/Non-Patient (SCID-I/NP) and with the Structured Interview for DSM-IV Personality (SIDP). Cadenhead et al. (2000a, 2000b)'s study found that patients with schizotypal personality disorder had significantly less P50 suppression than did the normal subjects. A linear stepwise pattern was observed when Hazlett et al. (2015) measured P50 suppression in healthy controls, schizotypal personality disorder, and schizophrenia groups demonstrating a relationship between schizotypy level and degree of P50 gating deficit. Both schizotypal and schizophrenia groups had lower S1 amplitudes and smaller S2-S1 amplitude differences than controls. Among the patient groups, greater conditioning-response P50 amplitude deficits were associated with greater clinical symptom severity.