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# Differential sensory gating functions between smokers and non-smokers among drug-naive first episode schizophrenic patients

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ABSTRACT

Although an acute effect of cigarette smoking and nicotine on sensory gating of schizophrenias has been investigated in published papers, the chronic effect of cigarette smoking on this phenomenon has not yet been reported. We report the effects of chronic cigarette smoking, without new acute exposure before testing, on sensory gating using the P50 auditory evoked potential in a group of drug-naive first episode schizophrenic smokers and healthy smokers. Sensory gating was evaluated using auditory P50 suppression elicited using the conditioning (S1)–testing (S2) paradigm. Fifty six male drug-naive first episode schizophrenic patients were compared to 41 healthy male controls. Patients were classified into subgroups of current smokers ($n=18$) and non-smokers ($n=38$) to explore the effects of smoking on sensory gating. All subjects did not smoke a cigarette for at least 1 h prior to testing. Schizophrenic patients showed an increased S2 amplitude and a poorer sensory gating as measured by both S2/S1 ratio and S1–S2 difference of P50 amplitude, as compared to healthy controls. However, smokers showed an increased S1 amplitude and better sensory gating than did non-smokers both in schizophrenia patients and healthy controls. Our findings support a sensory gating deficit among first episode schizophrenic patients. However, it was less pronounced among schizophrenic patients who were current cigarette smokers, suggesting a positive effect of chronic cigarette smoking on ameliorating this sensory gating deficit in schizophrenia. Our findings of the present study present new evidence supporting the self-medication hypothesis of self-medication by cigarette smoking in schizophrenia to possibly ameliorate pre-existing functional deficits.



## 1. Introduction

The prevalence of tobacco use or cigarette smoking in schizophrenia is very high. About 80% of individuals with schizophrenia are cigarette smokers compared to 25% of the general population (de Leon and Diaz, 2005; Zhang et al., 2010). Schizophrenic smokers often smoke high-tar cigarettes or smoke more cigarettes than do control smokers (Olincy et al., 1997; Strand and Nyback, 2005). A hypothesis of self-medication by cigarette smoking to correct pre-existing functional deficits has been suggested to explain the reasons of widespread smoking behavior seen in schizophrenia (Kumari and Postma, 2005; Leonard et al., 2007). Smoking might serve as a form of self-medication to reduce the side effects of antipsychotic medications (Goff et al., 1992; Yang et al., 2002), to enhance the therapeutic effect of antipsychotics to alleviate negative symptoms (Smith et al., 2002), and/or to improve and cognitive deficits (Sacco et al., 2004) and illness-related sensory gating (Adler et al., 1992, 1993; Griffith et al., 1998). The effect of nicotine or cigarette smoking on of sensory gating of visual or auditory stimuli in the brain has attracted much interest among researchers.

Sensory gating refers to the function of "filtering" irrelevant sensory input in the brain (Braff and Geyer, 1990). It is one of the fundamental mechanisms that the brain uses to organize and prioritize the salience on incoming stimuli, and prevent sensory overload with irrelevant stimuli. The sensory gating function is often assessed by measuring suppression of the auditory P50 evoked response. It has been examined using a conditioning–testing paradigm, in which the first click stimulus (S1) initiates or conditions the inhibition and the second (S2) tests its strength (Eccles, 1969; Boutros and Belger, 1999). Sensory gating is measured by the ratio of P50 amplitude evoked by S2 to P50 amplitude evoked by S1. The lower the S2/S1 ratio, the better the sensory gating function. In addition, the amplitude difference between S1 and S2 has also been utilized as a reliable measure of sensory gating (Smith et al., 1994).

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Sensory gating has been observed in several brain regions, including the hippocampus, the temporoparietal region and prefrontal cortex (Grunwald et al., 2003). It is suggested that sensory gating may be a multistep process with an early temporoparietal and prefrontal phase and a later hippocampal phase (Turetsky et al., 2007). The potential synaptic mechanisms underlying the P50 response have been investigated in several studies. The CA3–CA4 area of the hippocampus generates a response 50 ms poststimulus which quickly diminishes on repeated stimulation (Goff et al., 1980; Wilson et al., 1984). Activation of the CA3–CA4 interneurons' nicotinic receptors by cholinergic medial septal inputs might be the final mechanism for suppression (Luntz-Leybman et al., 1992).

The tobacco alkaloid nicotine is known to be a potent cholinergic stimulant that affects brain functioning. Smoking tobacco may impact sensory gating through two different neurochemical pathways (Crawford et al., 2002). The first one is associated with nicotine-stimulated release of dopamine (DA) via nicotinic receptors on DA neurons (Cooper et al., 1996), which would impact both synthesis-modulating and release-modulating autoreceptors. It is sensitive to nicotine levels, and the effect is short-lived because nicotinic receptors desensitize rapidly. Therefore, this pathway is mainly related to the acute effect of cigarette smoking. The second pathway is associated with monoamine oxidase (MAO) level. MAO is the major enzyme that regulates the central DA level in brain. Chronic inhibition of MAO, which has been found in the brains of smokers (Fowler et al., 1996), leads to more DA excitement in central nervous system (CNS) and enhances the sensory gating. The second pathway is possibly related to the chronic effect of cigarette smoking (Crawford et al., 2002; Wan et al., 2006) that may influence MAO activity. There are several studies investigating both acute and chronic effects of cigarette smoking on P50 suppression among healthy controls. In the design of these studies, the acute effect of smoking or nicotine referred to the difference in sensory gating measures between baseline statuses vs. transient status after smoking a cigarette. The chronic effect of cigarette smoking referred to the difference of sensory gating between smokers vs non-smokers. Crawford et al. (2002) examined the auditory P50 response potential from smokers after they had abstained from smoking overnight and after smoking a cigarette, and compared the response to never-smokers. They did not find an acute effect of smoking, but found a chronic effect; chronic smokers showed better sensory gating than never-smokers across both conditions. Croft et al. (2004) replicated the finding that P50 sensory gating was better in smokers than non-smokers among university students, but also reported that this effect was moderated by schizotypal beliefs. Like Crawford et al. (2002), Wan et al. (2006, 2007) did not find an acute effect of smoking on sensory gating. However, they reported that smokers showed a poorer sensory gating than non-smokers among undergraduates with low schizotypal personality, and no difference of sensory gating between smoker and non-smokers among undergraduates with high schizotypal personality. These inconsistent findings suggested that it was necessary to further confirm the chronic effect of smoking on sensory gating among non-psychotic controls.

A deficit in sensory gating has been extensively reported among schizophrenia populations (e.g. Adler et al., 1982; Freedman et al., 1983; Siegel et al., 1984; Adler et al., 1998a,b; Boutros et al., 1991). Compared with healthy controls, individuals with schizophrenia often present a similar P50 response to conditioning stimulus but a larger P50 response to testing stimulus, resulting in a higher S2/S1 ratio or a smaller S1–S2 difference. Among healthy controls, the mean S2/S1 ratio is usually smaller than 0.5; whereas among most studies of schizophrenic patients the mean ratio is usually larger than 0.5 (e.g., Freedman et al., 1983, 1991; Boutros et al., 1991; Judd et al., 1992; Clementz et al., 1998a,b). For schizophrenia, P50 suppression deficits are persistent and found in both acutely ill schizophrenics as well as more stable outpatients (Adler et al., 1982; Franks et al., 1983; Freedman et al., 1983; Ward et al., 1996). A meta-analysis by Bramon et al. (2004) revealed that the effect size of P50 ratio between schizophrenia patients and controls was −1.56 (95% CI: −2.05 to −1.06). The P50 suppression deficits have also been replicated in several studies among first episode schizophrenic patients (Chen et al., 2005; Brockhaus-Dumke et al., 2008; Devrim-Uçok et al., 2008; Hong et al., 2009), except in one study by de Wilde et al. (2007), suggesting that the P50 sensory gating this abnormality may be a primary trait characteristic of both acute and chronic schizophrenia.

The deficient sensory gating among schizophrenics may lead to their brains being overloaded by many confusing or irrelevant stimuli and this may contribute to cognitive deficits repeatedly reported in schizophrenia patients and possibly to other psychiatric symptoms (Light and Braf, 2003). Factors, which possibly normalize P50 suppression deficits of schizophrenia, have been explored. Clozapine showed a consistent beneficial effect (Arango et al., 2003; Adler et al., 2004a,b). Risperidone had only a marginal effect on P50 suppression, and the data on olanzapine remain inconsistent (Light et al., 2000; Arango et al., 2003; Adler et al., 2004a,b). Ondansetron, a highly selective 5-HT3 antagonist, significantly enhanced P50 auditory gating in schizophrenic patients treated with typical antipsychotics (Adler et al., 2005). In general, the effect of most antipsychotics, including the second generation of antipsychotics, is relatively limited. However, cigarette smoking was found to normalize the P50 sensory gating deficit among schizophrenics (Adler et al., 1993; Griffith et al., 1998) and their first-degree relatives (Adler et al., 1992), though this effect is just a transient acute effect of cigarette smoking, usually disappearing after 1 h. In addition, new drugs are being developed to mimic some of the effects of nicotine, and drugs which specifically effect the α-7 nicotinic receptor have been selected as a major target for drug development for cognitive deficits in schizophrenia. A direct α-7 nicotinic receptor agonist, 3-(2,4-dimethoxybenxylidene) anabaseine (DMXB-A), produced improvements in both the sensory processing P50 deficit and in some aspects of cognition in a double-blind, in a placebo-controlled study of 12 patients with schizophrenia (Olincy et al., 2006). DMXB-A also improved clinical ratings of negative symptoms that are generally resistant to treatment with dopamine antagonist antipsychotic drugs (Freedman et al., 2008). These findings are consistent with the hypothesis that smoking in schizophrenia may also be a form of self-medication as an attempt to correct underlying neuropathologies (Kumari and Postma, 2005; Leonard et al., 2007). However, the chronic effect of cigarette smoking on sensory gating has not yet been reported among schizophrenia patients; effects on the P50 response in chronic schizophrenic smokers could provide additional support for the self-medication hypothesis.

The main purpose of the present study was to investigate the chronic effect of smoking tobacco in individuals with schizophrenia by comparing the responses of P50 auditory evoked potentials in regular cigarette smokers vs. non-smokers. In order to exclude the possible confounding factors of treatment with different antipsychotics and illness duration, only drug-naive and first episode schizophrenia patients were recruited. The significance of gathering drug naive patients is that it could exclude the reported effects on sensory gating by antipsychotics (Light et al., 2000; Arango et al., 2003; Adler et al., 2004a,b; Devrim-Uçok et al., 2008) and by the interactions of antipsychotics with smoking (Levin et al., 2005). Because smoking is much higher among males than in females in China (Tang et al., 2007), we only included male subjects in the present study.

## 2. Methods

### 2.1. Subjects

Male patient subjects were recruited from those who first came to Shanghai Mental Health Center between January 2005 and December 2007, had no history of antipsychotic medications, and met International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) diagnosis criteria of schizophrenia