

Medication status affects the relationship of symptoms to prepulse inhibition of acoustic startle in schizophrenia

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Abstract

Inhibition of the acoustic startle response by a smaller preliminary nonstartling stimulus is termed prepulse inhibition (PPI). Schizophrenia patients have impairments in PPI that may not fully normalize even when they are clinically stable on medication, particularly typical antipsychotics. There is evidence that more severe symptoms are associated with more severe PPI abnormalities, but the effect of antipsychotics on this relationship is not clear. Seventy-three male schizophrenia patients underwent acoustic startle and PPI testing. Symptom ratings were performed using the Brief Psychiatric Rating Scale (BPRS) and its subscales. Fifty-two subjects were treated with antipsychotic medication at time of testing; 21 were unmedicated. For all subjects, PPI was negatively correlated with the BPRS psychological discomfort subscale but not with BPRS total symptoms, BPRS positive symptoms or BPRS negative symptoms. For medicated subjects analyzed separately, there were no correlations with BPRS total scores or any subscales. For the unmedicated subjects analyzed separately, there were significant correlations of lower PPI with greater severity of BPRS total symptoms, positive symptoms and the psychological discomfort subscale. These data indicate that more severe symptoms are associated with lower PPI, but that medication status is an important factor in the relationship between symptom severity and sensorimotor gating.

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1. Introduction

Patients with schizophrenia have difficulty automatically screening out or “gating” irrelevant thoughts and sensory information from conscious awareness (Venables,

1960; Braff and Geyer, 1990; Braff, 1993). These “sensorimotor gating deficits” are hypothesized to contribute to sensory overload, interceptive stimuli and cognitive fragmentation, resulting in psychotic symptoms and cognitive deficits (McGhie and Chapman, 1961; Braff and Geyer, 1990; Braff, 1993). The acoustic startle response is a reflex contraction of the skeletal muscles in response to a sudden acoustic stimulus (Landis and Hunt, 1939). The inhibition of the acoustic startle response by a preliminary nonstartling acoustic stimulus, termed prepulse inhibition

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(PPI), is used as an operational measure of sensorimotor gating (Hoffman and Searle, 1968; Graham, 1975). While the acoustic startle reflex itself is mediated by a simple subcortical circuit (Davis et al., 1982; Lee et al., 1996; Davis, 1997; Koch, 1999; Fendt et al., 2001), PPI is modulated by a number of cortical and subcortical brain areas such as hippocampus, prefrontal cortex, thalamus and limbic areas (Swerdlow et al., 2001; Kumari et al., 2003), many of which are implicated in the pathophysiology of schizophrenia.

Schizophrenic patients, hypothesized to suffer from sensorimotor gating deficits, were first shown to have decreased PPI by Braff et al. (1978). Numerous other studies have subsequently shown PPI deficits in patients with schizophrenia (Braff et al., 1992; Grillon et al., 1992; Dawson et al., 1993; Cadenhead et al., 2000; Dawson et al., 2000; Parwani et al., 2000; Ludewig et al., 2002). These studies were conducted with schizophrenia subjects who were clinically stable on antipsychotic medication, indicating that the abnormality is not fully normalized with medication. Some studies (Kumari et al., 1999, 2000; Weike et al., 2000; Leumann et al., 2002; Kumari et al., 2002; Oranje et al., 2002; Meincke et al., 2004) but not all (Mackeprang et al., 2002; Perry et al., 2002; Duncan et al., 2003a,b) indicate that schizophrenia subjects on atypical antipsychotics have less impaired PPI than unmedicated subjects or subjects on typical antipsychotics (for reviews, see Hamm et al., 2001; Kumari and Sharma, 2002).

A number of studies in the literature have examined whether current symptomatology correlates with PPI deficits in schizophrenia. Results in the literature are mixed: some studies have found significant correlations between the degree of PPI impairment and symptom severity (Perry and Braff, 1994; Perry et al., 1999; Braff et al., 1999; Weike et al., 2000; Meincke et al., 2004), although other studies did not find such a relationship (Kumari et al., 2000; Parwani et al., 2000). In all these studies examining symptom correlates, most or all of the subjects were on medication at the time of testing. Given the robust effect of antipsychotic medication on schizophrenia symptoms, it is possible that medication status could affect the relationship between current symptoms and the degree of PPI impairment in a study population. We hypothesized that unmedicated subjects would show a more robust relationship between PPI and symptom severity than medicated subjects since there would be no confounding influence of antipsychotic treatment. Hence, in the current study, the relationship of PPI and symptom severity was evaluated in two subject groups: those who were clinically stable on antipsychotic medication and those who had discon-

tinued antipsychotic treatment and were unmedicated at the time of testing.

2. Methods

2.1. Subjects

Participants were recruited from the New York Harbor Veterans Affairs Medical Center (NY VAMC) and the Atlanta Veterans Affairs Medical Center. All study procedures were approved in New York by the Human Subjects Subcommittee at the NY VAMC and the Institutional Review Board at New York University School of Medicine, and in Atlanta by the Human Subjects Subcommittee at the Atlanta VAMC and the Institutional Review Board at Emory University School of Medicine. Seventy-eight adult male schizophrenia subjects met study inclusion criteria and signed informed consent to participate. The diagnosis of schizophrenia was established on the basis of chart review and the Structured Clinical Interview for DSM-IV, Axis-I (SCID-P) conducted by an experienced mental health clinician (E.D., M.K., A.P.) or a SCID-trained researcher with at least two years of experience with schizophrenia subjects (S.S., B.L.). Potential participants were excluded if they had current clinically unstable medical illness, renal failure or disease, any history of head trauma or neurological disease, mental retardation or any recent history of significant drug or alcohol abuse. All subjects had negative urine toxicologies at time of testing. Five subjects were excluded for having startle responses too low for the reliable computation of PPI (see Section 2.3). Of the remaining 73 analyzable subjects, 52 were being treated with antipsychotic medication at time of testing and 21 were unmedicated for a mean \pm S.D. of 86.6 ± 135.3 days. The unmedicated group had chosen to stop their medication as outpatients and were tested prior to restarting antipsychotic treatment. See Table 1 for demographics and medication information. Between group and test–retest PPI data have been reported on 46 of these subjects in prior publications examining the effects of medication status on PPI (Duncan et al., 2003a,b).

2.2. Symptom ratings

Participant's symptoms were rated with the Brief Psychiatric Rating Scale (BPRS, 18 item 1–7 version, Guy, 1976). In addition to BPRS total scores (BPRS-tot), validated subscale scores were used to examine the relationship of PPI to specific symptom domains. Subscale scores and the individual BPRS items comprising them are

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