



## Sensitization and habituation of the acoustic startle reflex in patients with schizophrenia

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### Abstract

Assessments of prepulse inhibition and habituation of the acoustic startle response have proved to be valuable tools for assessing deficits of sensorimotor gating and information processing in schizophrenia patients. Recent studies, however, have reported inconsistent results regarding startle habituation deficits in schizophrenia using block-to-block analyses. Some of these inconsistencies may be due to abnormal initial sensitization effects to startle-eliciting stimuli. In a longitudinal study during the course of an acute psychotic episode, 34 medicated inpatients were examined with regard to sensitization and habituation effects in a trial-by-trial analysis and compared with 18 normal control subjects. On two examinations—10 days after admission and after psychopathological improvement 2–3 weeks later—schizophrenia patients exhibited an exaggerated magnitude increment across the first few startle-eliciting stimuli and habituation deficits that were evident when the effect of sensitization was removed from analysis. In the present study, both increased sensitization and reduced habituation appeared to be trait markers of schizophrenic psychoses. The enhanced sensitization effect—presumably due to an abnormal arousal modulation—reflects abnormal stimulus processing in schizophrenia, i.e. the diminished ability to learn the irrelevance of simple identical stimuli. In addition, the present data have important implications for designing startle studies to assess sensitization, habituation and prepulse inhibition in one session.

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### 1. Introduction

Attentional and information-processing dysfunctions are known to be core symptoms in schizophrenia disorders and are of considerable relevance for functional outcome and rehabilitation (e.g.

Green, 1996). Bleuler underscored attention impairments due to a reduced ability to filter out irrelevant stimuli (Bleuler, 1911). Based on the influential clinical reports of McGhie and Chapman in schizophrenia patients (e.g. McGhie and Chapman, 1961), sensory overload due to impairments in preattentive inhibitory stimulus processing is believed to play an important role in the

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pathogenesis of schizophrenia (reviews: Nuechterlein and Dawson, 1984; Braff, 1993). This hypothesis is supported by experimental findings in normal subjects (Gottschalk et al., 1972; Lipowski, 1975) as well as by operational measures of preattentive processing of acoustic stimuli in patients with schizophrenia spectrum disorders. In particular, many studies have demonstrated deficits in prepulse inhibition (PPI) and habituation of the acoustic startle reflex in schizophrenia (review: Braff et al., 2001).

Habituation is most often defined as the decrement in behavioral responses to repeated presentations of an identical, initially novel stimulus that is not due to sensory adaptation or effector fatigue (e.g. Geyer and Braff, 1982). However, many researchers reported an initial increase in the magnitude of the startle reflex across a series of intense white noise bursts in the rat (Payne and Anderson, 1967; Szabo and Kolta, 1967; Groves and Thompson, 1970; Davis, 1972; Geyer and Braff, 1987) and in humans (Davis and Heninger, 1972; Ornitz and Guthrie, 1989), followed then by an exponential magnitude decrement. Based on this robust phenomenon, Groves and Thompson (1970) developed their influential dual-process theory regarding the processing of repetitive stimuli. They proposed that stimuli presented repeatedly engage both a decremental process called habituation and an opposing, independent and superimposed incremental process called sensitization.

In the view of Groves and Thompson, sensitization is due to a change of the subject's 'state'—a theoretical construct that reflects the level of general excitability and arousal. It enhances the reflex magnitude after presentation of a novel stimulus. Depending on stimulus intensity, the startling stimulus itself may represent an aversive and therefore relevant event mediating a sensitizing influence on startle magnitude in subsequent trials. However, after further repetitive presentation of identical startle stimuli, the process of sensitization wanes. The reflex net magnitude is then predominantly determined by the mechanism of habituation resulting in an exponential decrement during the experimental session (Groves and Thompson, 1970).

In schizophrenia, some studies have demonstrated significant (Geyer and Braff, 1982; Bolino et al., 1992, 1994; Parwani et al., 2000) or marginal habituation deficits (Braff et al., 1992; Perry et al., 2001, 2002; Ludewig et al., 2002) of the startle reflex. Reduced habituation in schizophrenia patients has been interpreted to reflect impaired gating of repeatedly presented trivial stimuli that may result in cognitive disruption by sensory overload (Braff et al., 1992; Geyer and Braff, 1987). Nevertheless, other studies failed to replicate habituation deficits in schizophrenia (Braff et al., 1999; Cadenhead et al., 2000; Kumari et al., 2000, 2002). In this context, it is important to point out that assessment of habituation, especially in studies with a small number of trials, may be confounded by altered sensitization processes in schizophrenia. So far, the influence of sensitization has not been investigated systematically except in one study (Geyer and Braff, 1982). However, precise trial-by-trial analysis of startle magnitude across repetitive presentation of intense acoustic stimuli may provide an operational measure for excitatory processing of novel aversive stimuli in healthy subjects and patients with schizophrenia. Since it is known that startle magnitude is potentiated when subjects are in an aversive or anxious state (Lang et al., 1990; Grillon et al., 1991), suspicious and hostile schizophrenia patients with persecutory delusions or psychotic anxiety might show higher magnitudes and increased sensitization effects across a train of loud startle stimuli. However, sensitization of acoustic startle might be low in patients with predominantly negative symptoms, especially affective flattening, who are known to exhibit diminished expressiveness to emotional stimuli (e.g. Berenbaum and Oltmanns, 1992). An enhancement of sensitization in an acute psychotic state might subsequently be attenuated after psychopathological improvement, especially after partial remission of positive symptoms.

To test these hypotheses, sensitization and habituation of acoustic startle were investigated longitudinally in schizophrenia inpatients across an acute psychotic episode. Relationships between sensitization and habituation to clinical variables and psychopathological symptoms evaluated in

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