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Pre-attentive information processing and impulsivity in bipolar disorder

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ABSTRACT

Early responses to stimuli can be measured by sensory evoked potentials (EP) using repeated identical stimuli, S1 and S2. Response to S1 may represent efficient stimulus detection, while suppression of response to S2 may represent inhibition. Early responses to stimuli may be related to impulsivity. We compared EP reflecting stimulus detection and inhibition in bipolar disorder and healthy controls, and investigated relationships to impulsivity. Subjects were *48 healthy controls without family histories of mood disorder* and 48 with bipolar disorder. EP were measured as latencies and amplitudes for auditory P50 (pre-attentional), N100 (initial direction of attention) and P200 (initial conscious awareness), using a paired-click paradigm, with identical stimuli 0.5 s apart. Impulsivity was measured by questionnaire and by laboratory tests for inability to suppress responses to stimuli or to delay response for a reward. Analyses used general linear models. S1 amplitudes for P50, N100, and P200, and gating of N100 and P200, were lower in bipolar disorder than in controls. P50 S1 amplitude correlated with accurate laboratory-task responding, and S2 amplitude correlated with impulsive task performance and fast reaction times, *in bipolar disorder*. N100 and P200 EP did not correlate with impulsivity. These findings were independent of symptoms, treatment, or substance-use history. EPs were not related to questionnaire-measured or reward-based impulsivity. Bipolar I disorder is characterized by reduced pre-attentional and early attentional stimulus registration relative to controls. Within bipolar disorder, rapid-response impulsivity correlates with impaired pre-attentional response suppression. These results imply specific relationships between ERP-measured response inhibition and rapid-response impulsivity.

1. Introduction

1.1. Pre-attentional and early attentional sensory responses in psychiatric disorders

Cognition and action require processes that precede conscious attention (Naatanen and Winkler, 1999). Disruption of these processes could interfere with filtering of inappropriate stimuli, leading to overstimulation or poorly modulated behavioral responses (Freedman et al., 1987). Abnormal pre-attentive and early attentive responses have been reported in psychiatric disorders, but relatively little is known about their relationships to behavior. Early screening processes are potentially related to impulsivity (Moeller et al., 2001), a central aspect of bipolar disorder. In this study we investigated relationships between pre-attentive or early attentive information processing and impulsivity in patients with bipolar disorder and in healthy control subjects without family history of affective disorder.

Measured by evoked potentials (EP), an auditory stimulus initiates a series of events including, at 50 ms, pre-attentive registration (P50); at 100 ms, initial direction of attention (N100); and, at 200 ms, initial conscious awareness of the stimulus (P200). The P50 reflects pre-attentive automatic registration or detection, and the N100 and P200 may be part of the orienting reflex potentially modulated by arousal and attention (Naatanen and Winkler, 1999). If the initial auditory stimulus (S1) is followed shortly by an identical stimulus (S2), EP are suppressed. Suppression of the evoked potential in response to S2 represents inhibition of response to an irrelevant stimulus. Gating, the extent to which S2 is smaller than S1, is a combination of stimulus encoding and suppression of responses to irrelevant stimuli. Although gating is expressed mathematically in terms of S1 (encoding) and S2 (inhibition), stimulus

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encoding and suppression have different but interacting neural substrates, while gating results from top-down suppression of the pre-attentional stimulus (Korzyukov et al., 2007; Kurthen et al., 2007). Therefore, "gating" can potentially be regarded as distinct from the responses reflecting stimulus encoding.

Pre-attentional and early attentional EP are abnormal in bipolar disorder (Lijffijt et al., 2009d). Impaired P50 gating has been reported in bipolar disorder during mania (Baker et al., 1990), or regardless of clinical state (Sanchez-Morla et al., 2008; Lijffijt et al., 2009d), whether patients were psychotic (Olincy and Martin, 2005) or non-psychotic (Carroll et al., 2008; Lijffijt et al., 2009d). Further, P50 gating was impaired in nonaffected twins or other relatives (Hall et al., 2007), suggesting that it could be an endophenotype for bipolar disorder (de Geus, 2010).

In addition to the pre-attentional P50 potential, gating of N100 and P200 are reduced in bipolar disorder (Lijffijt et al., 2009d). In healthy subjects, these gating mechanisms have differential relationships with response inhibition, signal-noise discrimination, and working memory (Lijffijt et al., 2009a), and with cognitive aptitude and age (Lijffijt et al., 2009b).

1.2. Early information processing and behavioral regulation: impulsivity

Impulsivity involves dysregulation of early behavioral responses to stimuli, resulting in action without the conscious decision to act, and is prominent in bipolar disorder (Moeller et al., 2001). P50 amplitudes and/or gating are reduced in impulsivity-related conditions, including antisocial personality disorder (Lijffijt et al., 2009c), impulsive aggression (Houston and Stanford, 2001), and cocaine abuse (Fein et al., 1996), and correlate with marijuana use in controls (Rentzsch et al., 2007). Because impulsivity may involve behavior occurring without conscious reflection, it may be differentially related to pre-attentional vs attentional EP. Impulsivity is complex; specific aspects are measured with questionnaires or human laboratory tasks (Barratt and Patton, 1983; Evenden, 2000; Swann et al., 2002; Gorlyn et al., 2005).

Trait impulsivity, measured by the Barratt Impulsiveness Scale (BIS-11) (Barratt and Patton, 1983; Stanford et al., 2009), is increased in bipolar disorder, regardless of treatment or clinical state, consistent with a general propensity toward impulsivity (Swann et al., 2009a).

Rapid-response impulsivity, resulting from failure of response suppression, can be measured by stop-signal or continuous performance tests (Dougherty et al., 2003; Swann et al., 2002). Rapid-response impulsivity leads to action without conscious deliberation and could be consistent with disrupted pre-attentive responses to stimuli. Impulsive (commission) errors are increased in bipolar disorder during mania (Swann et al., 2003; Fleck et al., 2005; Sax et al., 1998), and with history of substance-use disorder (Swann et al., 2004), or many previous episodes (Swann et al., 2009b), but may not be otherwise (Swann et al., 2009b).

Reaction times are slow and response bias is conservative in bipolar disorder (Fleck et al., 2001; Swann et al., 2009b), consistent with an adaptation that could reduce impulsive responses. Reaction times are faster and impulsive errors are increased with histories of many episodes or of a substance-use disorder (Swann et al., 2009b), medically severe suicide attempt (Swann et al., 2005), comorbid antisocial personality disorder (ASPD) (Swann et al., 2011b), or criminal conviction (Swann et al., 2011a). Therefore, accelerated reaction times and increased commission errors may be associated with severity or progression of bipolar disorder, possibly representing loss of an adaptive mechanism protecting against impulsive behavior in bipolar disorder (Swann et al., 2009b).

Reward-delay impulsivity, inability to delay response for reward, is measured as choice between a smaller-sooner and larger-later reward (Dougherty et al., 2003; Cherek et al., 1997). Reward-delay impulsivity may be increased in bipolar disorder (Swann et al., 2009b), possibly related to comorbidities (Rogers et al., 2010; Swann et al., 2011b) or affective state (Strakowski et al., 2009). Because reward-based impulsivity involves anticipated consequences of action, while rapid-response impulsivity essentially ignores consequences, rapid-response impulsivity may be more strongly related than reward-based impulsivity to early neurophysiological responses.

1.3. Rationale and hypotheses

In a preliminary study, P50, N100, and P200 gating were impaired in bipolar disorder (Lijffijt et al., 2009d). Here, we investigated EPs in more detail in a larger group of bipolar disorder and control subjects, taking potential confounds into account. Specific hypotheses were: 1) Rapid-response impulsivity would be related specifically to pre-attentional P50 EPs; 2) Impaired pre-attentional response suppression (increased P50 S2 amplitude and S2/S1 ratio) would be related to impulsive errors and shorter reaction time on a measure of rapid-response impulsivity; 3) Pre-attentional (P50) stimulus registration (S1 amplitude) would correlate with correct detections; 4) In bipolar disorder EP would be independent of symptoms or treatment.

2. Methods

2.1. Subjects

The study was approved by the Committee for the Protection of Human Subjects, Institutional Review Board (IRB) for the University of Texas Health Science Center at Houston (protocol HSC-MS-05-0036). Subjects were recruited from the community by IRB-approved notices and advertisements, with full discussion of the study and its risks and written informed consent before study-related procedures.

There were 48 healthy controls (18 men, age 31.2 ± 9.8 years, education 13.9 ± 2.3 years; 30 women, age 32.2 ± 10.6, education 14.3 ± 1.8) and 48 subjects with bipolar disorder (26 men, age 40.8 ± 9.6, education 13 ± 2.7; 22 women, age 35.2 ± 10.4, education 13 ± 2.7). Subjects with bipolar disorder were older ($F(1,96) = 9.1$, $p = 0.003$) and had fewer years of education ($F(1,96) = 4.6$, $p = 0.03$) than controls. Sex had no significant effects or interactions on age or years of education ($F < 2.5$).

Diagnoses (DSM-IVTR) used SCID-I (First et al., 1996) and -II (First et al., 1997). Symptoms (mania, depression, anxiety, and psychosis) were assessed by the Schedule for Affective Disorders and Schizophrenia, Change version (SADS-C) (Spitzer and Endicott, 1978). Subjects with bipolar disorder could have past substance-use disorders, but could not meet criteria for current substance-abuse or -dependence. Healthy controls were required never to have met DSM-IVTR criteria for any Axis I or Axis II disorder, and not to have any first degree relatives with history of an affective or psychotic disorder. Subjects with bipolar I disorder were required never to have met criteria for any other Axis I disorder except anxiety or past substance-use disorder. Thirty-five subjects had histories of psychosis, 31 of substance-use disorder (alcohol, marijuana, and/or stimulant), and 25 of tobacco smoking. On study days, urine drug screens and expired air alcohol were obtained; if positive, subjects were rescheduled and, if positive on three occasions, dropped from the study.

Subjects *with bipolar disorder* were required to be in outpatient treatment; prospective subjects not in treatment were referred and