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Eyeblink conditioning deficits indicate timing and cerebellar abnormalities in schizophrenia☆

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Abstract

Accumulating evidence indicates that individuals with schizophrenia manifest abnormalities in structures (cerebellum and basal ganglia) and neurotransmitter systems (dopamine) linked to internal-timing processes. A single-cue tone delay eyeblink conditioning paradigm comprised of 100 learning and 50 extinction trials was used to examine cerebellar timing circuits in 13 medicated patients with schizophrenia and 13 age- and sex-matched controls. Patients with schizophrenia showed impaired learning of the conditioned response compared to controls and also greater within-subject variability in the timing of their responses. These findings are consistent with models of schizophrenia in which timing deficits underlie information-processing abnormalities and clinical features of the disorder.

1. Introduction

Intra-individual response variability and behavioral heterogeneity were recognized as essential features of schizophrenia (SZ) in the influential nosologies of Bleuler (1911/1950) and Kraepelin, Barclay, and Robertson (1919). In fact, classic symptoms of SZ such as formal thought disorder, disorganized and bizarre behavior, and soft neurological signs can be viewed as manifestations of a disturbance of temporal coordination of information processing in the central nervous system. Some contemporary theoretical models describe intra-subject response variability as a "fundamental characteristic" (Lehmann & Cancro, 1985) and qualitative feature of SZ (Meehl, 1990). Not surprisingly, short-interval timing deficits in SZ have been reported using a variety of methods, including time estimation as well as temporal production and reproduction tasks (Densen, 1977; Johnson & Petzel, 1971; Tracy et al., 1998; Tysk, 1983, 1990; Volz et al., 2001). In addition, reaction time (e.g., Manoach et al., 2001; Shakow, 1962) and event-related brain potential studies (e.g., Ford, White, Lim, & Pfefferbaum, 1994; Matthysse, Levy, Yingnian, Rubin, & Holzman, 1999; Patterson et al., 2000) report greater within-subject temporal response variability among individuals with SZ compared to non-patient comparison groups. The purpose of the present investigation is to use eyeblink conditioning methodology to examine the integrity of cerebellar and related neural-timing circuits in SZ. The impetus for the present research arises from models of SZ in which within-subject timing deficits underlie information-processing abnormalities and clinical features of the disorder.

Although relatively little theoretical consideration has been given in the literature to within-subject response variability in SZ, a hand-full of models of SZ

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assert that increased intra-individual response variability is an underlying feature of the illness and specifically predict variable response timing. For example, Meehl (1962, 1989, 1990) postulated that the fundamental problem in SZ is a ubiquitous neural integrative defect, termed schixotaxia, that is associated with aberrant post-synaptic firing probabilities. This deficit is said to produce psychophysiological and soft neurological aberrations and forms of cognitive "slippage," such as loose associations and thought disorder (Meehl, 1989, 1990). Meehl (1990) reasoned that this "molar slippage" in cognitive and cognitive-affective processes was indicative of "microslippage" at the neuronal level. Accordingly, the model predicts that "microslippage," via aberrations in the synaptic control of neuronal firing probabilities, introduces intra-individual temporal response variability in SZ.

Another influential model to emerge from the cognitive information-processing revolution of the 1950s and 1960s was the segmental set theory proposed by Shakow (1962, 1963). Shakow postulated that perceptual, integrating, and organizing functions of the brain, which underlie the establishment of generalized states of readiness for responding to incoming stimuli, are impaired in SZ. In the healthy individual, major "sets" facilitate and economize information processing and responding by providing a parsimonious and consistent strategy for processing and responding to stimuli in the environment. Shakow proposed that individuals with SZ have difficulty maintaining the optimal, situationally determined "state of readiness" (Nopoulos, Ceilly, Gailis, & Andreasen, 2001, p. 9) for responding to external and internal inputs due to susceptibility to distraction by irrelevant aspects of the stimulus environment (both internal and external). This inability to maintain the contextually relevant set is secondary to a tendency to form multiple, disarticulated, segmented sets (or minor sets) that are elicited by transient situational irrelevancies. Temporal response variability, then, occurs because successive adoption of minor, segmented sets disrupts and precludes the fluid processing of information through the central nervous system.

In a similar and more recent theoretical formulation, Matthysse et al. (1999) proposed that SZ is associated with intermittent lapses or degradation of performance, termed dialipsis, which is caused by impaired cognitive control mechanisms that modulate the effect of motives on cognition and perception. According to the authors, "The intermittent degradation model accounts for the higher variance within individuals in the schizophrenic group by the erratic presence of the dialipsis component, and for the variability of the variance from person to person within that group" (p. 20). The authors postulate that not all individuals with SZ are susceptible to dialipsis. As with Meehl and Shakow, Matthysse and colleagues proposed that the organismic instability of perceptual and cognitive processes, which characterizes dialipsis in affected patients, underlies core features of SZ such as thought disorder.

"Disconnection" models of SZ (Friston, 1998) offer additional ways to understand the possible role of timing problems in SZ. One of the more prominent of such models, Andreasen's (1999) "cognitive dysmetria" model, states that the symptoms of SZ indicate a disturbance in the fluid temporal coordination of motor, perceptual, and cognitive sequences of behavior. She hypothesized that this synchronous, temporally coordinated organization of behavior is controlled by a neural circuit comprised of cortico-cerebellar-thalamic-cortical (CCTC) connections. Interestingly, Andreasen proposed that the heterogeneity of the symptoms of SZ, including thought disorder, disorganized behavior, and soft neurological signs, may be unified by postulating a basic cognitive deficit that results from abnormalities in the CCTC circuit.

Taken together, these theoretical models provide strong impetus for examining the functional integrity of neural timing mechanisms in SZ. However, there is generally a paucity of empirical research linking timing deficits in SZ to specific neural circuits and/or mechanisms. Exceptions can be found in the work of Andreasen and her colleagues (Andreasen, Paradiso, & O'Leary, 1998) and others (Buhusi & Meck, 2002; Meck, 1996; Rammsayer, 1997; Tysk, 1983, 1990; Volz et al., 2001), which in various combinations relate timing deficits and structural brain abnormalities or neurotransmitter systems to SZ.

There is accumulating evidence that brain structures linked to response timing (e.g., cerebellum and basal ganglia) are abnormal in SZ. For example, deficits in the cortical and thalamic nodes of the CCTC circuit have been clearly demonstrated (Nopoulos, Ceilly, Gailis, & Andreasen, 1999; Staal et al., 2001; Volz, Gaser, & Sauer, 2000), in addition to abnormalities in the cerebellar node (Andreasen et al., 1996, 1997; Vrtunski, Simpson, & Meltzer, 1996), which has been widely linked to response timing (e.g., Fiala, Grossberg, & Bullock, 1996; Ivry & Keele, 1989; Spencer, Zelaznik, Diedrichsen, & Ivry, 2003; Steinmetz, 2000; see below). In addition, decreased cerebellar size has been observed in SZ (e.g., Ichimiya, Okubo, Suhara, & Sudo, 2001; Lippman et al., 1982; Loeber, Cintron, & Yurgelun-Todd, 2001; Nopoulos et al., 1999; Weinberger, Torrey, & Wyatt, 1979; but see negative findings from Nasrallah, McCalley-Whitters, & Jacoby, 1982) and is a reliable indicator of poor long-term outcome (Wassink, Andreasen, Nopoulos, & Faum, 1999). A correlation between reduced cerebellar vermal volume and total BPRS Depression and Paranoia subscore has also been reported (Ichimiya et al., 2001). Moreover, the observed cerebellar volume deficits are correlated with greater cognitive dysfunction