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Autonomic regulation predicts performance on Wisconsin Card Sorting Test (WCST) in adults with schizophrenia

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ABSTRACT

Although executive functions have been associated with autonomic regulatory capacity in healthy adults, there appear to be no reports of these relations in adults with schizophrenia to date. We tested whether baseline autonomic regulation was associated with performance on the Wisconsin Card Sorting Test (WCST) in a group of 42 stable community outpatients with schizophrenia. Patients exhibited faster resting heart rates and lower respiratory sinus arrhythmia (RSA) than age-matched controls, consistent with previous research. Patients also completed relatively few WCST categories and made many perseverative errors, replicating prior studies. Within the patient group, relatively better WCST performance was associated with slower resting heart rate and higher RSA, suggesting that inefficient executive and autonomic functioning in schizophrenia may be linked. WCST performance and autonomic regulatory capacity were further reduced in a subset of patients receiving clozapine, but relations between WCST performance and autonomic regulatory parameters did not differ from those of other patients. Findings extend the neurovisceral integration model of autonomic regulation to adults with schizophrenia and attest to the reliability of the model.

1. Introduction

1.1. Executive functioning in schizophrenia

Schizophrenia has been characterized by three broad dimensions, including psychosis, disorganized thought patterns, and deficits in emotional expression (Andreasen, 1995). The first two dimensions reflect the presence of positive symptoms of the disorder, such as delusions and hallucinations. Negative symptoms refer to deficits in functioning, i.e., the absence of behaviors such as affective expression that are expected in the course of normal social engagement.

Along with the presence of disorganized thinking, deficits in cognitive flexibility, self-monitoring, and inhibitory control are widely reported in schizophrenia (e.g., Heinrichs, 2005; Waford and Lewine, 2010), even among patients with average intelligence (e.g., Evans et al., 1997). Perseveration – the tendency to repeat the same errors, despite informative feedback – is considered a hallmark of the condition. Deficits in set-shifting ability and inhibitory control may reflect a broad phenotype of schizophrenic disorder, as even first-degree relatives of patients with schizophrenia may demonstrate perseverative tendencies (Laurent et al., 2001; Liu et al., 2003). These deficits, considered "executive" in nature, have been associated with lower levels of coping and insight (Drake and Lewis, 2003; Lysaker and Bell, 1994; Young et al., 1993), and poor functional outcomes in this population (Green and Nuechterlein, 1999; Rocca et al., 2009). Indeed, some authors have described schizophrenia as a primarily neurocognitive disorder in which poor insight may be closely related to neurologically based cognitive impairments, rather than to psychotic symptoms per se (Green and Nuechterlein, 1999; Lysaker and Bell, 1994).

In studies of neurotypical populations, executive functions have been positively associated with autonomic regulatory capacity, suggesting a high degree of coordination between autonomic nervous system (ANS) activity (responsible for involuntary control of the heart and other organs) and activity in the central nervous system. In a model of neurovisceral integration, Thayer and his colleagues account for this coordination by positing a common inhibitory network of prefrontal and brainstem cardioregulatory circuits that is active during cognitive, affective, and physiological regulation (Thayer and Lane, 2000; Thayer et al., 2009). Despite considerable evidence for deficits in both executive processing and autonomic regulatory capacity in patients with schizophrenia, there appear to be no reports to date linking the two phenomena in this population. Nonetheless, understanding the role

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of physiological regulation in executive control could potentially yield helpful information with respect to cognitive functioning in schizophrenia and its close association with negative symptoms of the disorder (Breier et al., 1991; Laurent et al., 2001; Waford and Lewine, 2010).

Traditionally, executive abilities in schizophrenia have been assessed with the Wisconsin Card Sorting Test (WCST; for a review, see Li, 2004, a task thought to index aspects of higher order thinking, including abstract concept formation, set-shifting, and inhibitory control (Axelrod et al., 1996; Heaton, 1981; Milner, 1963; Miyake et al., 2000; Rocca et al., 2009)). For healthy young adults, the strongest indicator of the ability to shift set following an unexpected change in the sorting principle may be the number of perseverative errors they make (Lezak, 1995). Adults with schizophrenia have a marked tendency to perseverate and tend to complete fewer categories than unimpaired adults (e.g., Lysaker and Bell, 1994; Saoud et al., 2000). Moreover, unlike other neuropsychological tests of executive skills (e.g., Trail-making and color Stroop; Buchanan et al., 1994; McGrath et al., 1997; Seidman et al., 1991), performance of the WCST does not tend to improve over time in patients with schizophrenia (e.g., McGrath et al., 1997; Seidman et al., 1991), suggesting that these executive deficits are very robust. Their obdurate nature also underscores the potential utility of exploring their physiological underpinnings.

1.2. Autonomic functioning in schizophrenia

In the past decade, a considerable body of work has accumulated suggesting that autonomic regulation is altered in patients with schizophrenia (e.g., Bär et al., 2005; Boettger et al., 2006; Castro et al., 2008; Jindal et al., 2009; Toichi et al., 1999; Valkonen-Korhonen et al., 2003) and their unaffected, first-degree relatives (e.g., Bär et al., 2009; Castro et al., 2009). Autonomic manifestations of the disorder include increased sympathetic activity (Schell et al., 2005; Schiffer et al., 1996), impaired capacity for autonomic adjustment (Castro et al., 2008; Valkonen-Korhonen et al., 2003), and altered diurnal variation in autonomic parameters (Boettger et al., 2006; Mujica-Parodi et al., 2005). Evidence from medicated (Castro et al., 2008; Toichi et al., 1999), unmedicated (Chang et al., 2009; Jindal et al., 2009) and first-episode patients (Bär et al., 2005; Valkonen-Korhonen et al., 2003), suggests that parasympathetic regulation, in particular, is reduced in schizophrenia. Inefficient parasympathetic regulation has been implicated in precipitating psychosis (Castro et al., 2008), in the development of dangerous ventricular arrhythmias after exercise (Kannankeril et al., 2004), and in a small but elevated risk of sudden death (Boettger et al., 2006; Mortensen and Juel, 1993) – a risk that in schizophrenia is already estimated to be two-to-three times that of the general population (Brown et al., 2000; reviewed in Koponen et al., 2009).

Autonomic regulation may be further impacted by the use of antipsychotic medications (Agelink et al., 2001; Ray et al., 2009; Rechlin et al., 1998) and poor lifestyle choices (e.g., smoking, sedentary habits, poor diet, and lack of attention to health care) (Brown et al., 2000; Hennessy et al., 2002). As autonomic regulatory capacity declines with increased age (e.g., Antelmi et al., 2004; Korkushko et al., 1991) and duration of illness (Bär et al., 2005), the autonomic burden of schizophrenia is likely to increase as patients age.

1.3. Integration of the central and autonomic nervous systems in unimpaired adults and adults with schizophrenia

Cardiovascular output is regulated by competing innervation from the sympathetic and parasympathetic nervous systems in response to changing environmental conditions. When cognitive effort, emotional arousal, or metabolic demands increase, the sympathetic nervous system enhances the speed and strength of myocardial contractions by releasing norepinephrine to adrenergic receptors in the heart's pacemaker and the vasculature. Conversely, the parasympathetic nervous system releases acetylcholine, which is taken up by muscarinic receptors in the pacemaker to slow heart rate to meet the reduced physiological demands of a resting situation. Because of differences in the pharmacokinetics of their respective neurotransmitters, the parasympathetic system responds more quickly than the sympathetic system, and is thus responsible for fine-grained, beat-to-beat variation in heart rate.

All of the mechanisms of cardio-respiratory control are integrated by the central nervous system (Spyer, 1994) via a functional network of cortical and subcortical brain regions known as the central autonomic network (CAN, Benarroch, 1993; Napadow et al., 2008). Structurally, the CAN includes prefrontal and orbitofrontal cortices, the anterior cingulate, insula, amygdala, hypothalamus, and subcortical brain regions. Output from this network influences the activity of the parasympathetic efferent traffic that controls cardiac motor circuits (Devinsky et al., 1995; Saul, 1990; Ter Horst and Postema, 1997). The interplay between these central modulatory regions and parasympathetic activity is reflected in peripheral measures of heart rate variability (HRV), i.e., variation in the length of the interbeat interval (Thayer et al., 2009; Thayer and Lane, 2000), and a high-frequency irregularity in heart rate known as respiratory sinus arrhythmia (RSA). Resting RSA is frequently used as a proxy measure of phasic parasympathetic control of heart rate (Berntson et al., 2007). Normally, the cardiac signal exhibits high levels of HRV and RSA, but when parasympathetic control is reduced, HRV and RSA are substantially reduced as well (Bär et al., 2005). Greater variability in the cardiac signal is associated with better health (Fallen, 2000) and self-regulation (Thayer and Friedman, 2002).

There are substantial and reliable individual differences in the relative contributions of sympathetic and parasympathetic output to the performance of psychological tasks (Berntson et al., 1994; Pitzalis et al., 1996). High HRV and RSA have been associated with optimal executive functioning in younger (e.g., Hansen et al., 2003; Johnsen et al., 2003; Sütterlin et al., 2011; Thayer et al., 2009) and older adults (Kim et al., 2006; Mathewson et al., 2011), as well as efficient emotion regulatory processes (e.g., Appelhans and Luecken, 2006; Phillips et al., 2003; Thayer and Siegle, 2002). Conversely, both human (e.g., Jefferson et al., 2007; Robbins et al., 2005) and non-human animal models (e.g., Moore et al., 2002) suggest that cognitive processing, especially executive functions, may be impaired in cardiovascular disease states where autonomic regulatory capacity is reduced, such as hypertension. Based on studies of neurotypical adults, we reasoned that deficits in parasympathetic control may be related to executive capacities in schizophrenia.

Few researchers to date have explored autonomic functioning in relation to cognitive performance in patients with schizophrenia. However, in one report, Valkonen-Korhonen et al. (2003) examined HRV in first-episode patients both at rest and while they completed tasks with differing mental "loads" – an oddball task and the WCST. Resting HRV, and autonomic reactivity for task performance, were both lower in patients than control participants. Nonetheless, no correlations between autonomic parameters and task performance were assessed. In another study, WCST performance was evaluated in conjunction with regional cerebral blood flow (rCBF) in stable outpatients and matched control participants (Toone et al., 2000). Toone and colleagues found that in the control group, good performance was associated with increased rCBF in prefrontal regions during the execution of the task. In contrast, patients with schizophrenia performed more poorly than their unimpaired peers and exhibited only a moderate increase in rCBF that was limited to the left anterior cingulate. Similarly, Weinberger et al. (1986), reported differential group increases in prefrontal rCBF during WCST performance, but in addition, found