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Circadian rhythms in cognitive functioning among patients with schizophrenia: Impact on signal detection in clinical trials of potential pro-cognitive therapies☆,☆☆

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ABSTRACT

Objective: Cognition is affected by circadian rhythms over the course of a day. Circadian rhythms in cognitive functioning are driven by a variety of both endogenous and exogenous factors. Patients with schizophrenia are known to have disturbed circadian rhythms that can affect their cognitive functioning. We examined the impact of time of day on cognitive test scores from subjects participating in clinical trials of potential pro-cognitive therapies for schizophrenia and then explored how this diurnal variation affected signal detection.
Method: Baseline data from 8 separate schizophrenia clinical trials using the MATRICS Consensus Cognitive Battery (MCCB) were aggregated (Total N = 2032). The MCCB assessments were divided into five 2-hour time intervals based on the start-time of the assessments (varying from 8:00 am to 5:59 pm) and then analyzed for differences by time interval. Next, data from two Phase 2 schizophrenia clinical trials of potential pro-cognitive therapies were analyzed to explore the impact of this diurnal variation on placebo separation.
Results: Time of day exerted a significant effect on baseline composite MCCB scores ($p = .002$). Follow-up comparisons revealed significant differences among multiple temporal epochs. In both Phase 2 clinical trials, subjects whose cognitive functioning was assessed at consistent times of day between their baseline and endpoint visits showed a more robust treatment response as compared to subjects assessed at inconsistent times of day.
Conclusion: Cognitive functioning ebbs and flows over the course of the day. Maintaining consistency in the time of day of cognitive test administrations between visits can help to reduce the noise introduced by circadian rhythms, thereby enhancing signal detection in clinical trials of potential pro-cognitive therapies.

1. Introduction

Over one hundred years ago, while performing groundbreaking research into human learning, memory, and forgetting, Hermann Ebbinghaus made the following observation about the impact of time of day on cognitive functioning:

> "*In the later hours of the day mental vigor and receptivity are less. The series learned in the morning and then relearned at a later hour, aside from other influences, require more work for relearning than they would if the relearning were done at a time of mental vigor equal to that of the original learning.*"
>
> [Ebbinghaus (1885)]

From this simple observation regarding the impact of time of day on the learning of nonsense syllables, a wealth of studies has now established that circadian rhythms in cognitive functioning are pervasive and affect a wide variety of cognitive processes, including attention

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(Valdez et al., 2005), vigilance (Buysse et al., 2005; Hoffman et al., 2005), phonological and visual working memory (Ramirez et al., 2006), declarative memory (Johnson et al., 1992), procedural memory (Cajochen et al., 2004), dual-task processing (Van Eekelen and Kerkhof, 2003), inhibition (May and Hasher, 1998), cognitive flexibility (May et al., 1999), and a wide variety of executive functions (Blatter and Cajochen, 2007; Schmidt et al., 2007). These variations in functioning also tend to follow a pattern over the course of a day and are not simply random noise. A typical pattern of diurnal variation in cognitive functioning reflects that performance often peaks mid-morning and then gradually decreases over the course of the day (Blatter and Cajochen, 2007), sometimes with an exacerbation of poor performance in the mid-afternoon (Wertz et al., 2006; Wright et al., 2012). Inter-individual differences in circadian rhythms, called chronotypes, have also been identified. For example, differences in morning versus evening chronotypes have been found to vary by age, with the performance of young adults sometimes improving over the day, while it deteriorates among older adults, especially among executive and memory domains (Hasher et al., 1999; Schmidt et al., 2007).

Circadian rhythms in cognitive functioning are driven by a variety of both endogenous and exogenous factors. Endogenous factors affecting diurnal variation in cognitive performance include sleep pressure, which increases with time spent awake and is reflected in increases in fatigue and sleepiness. Another endogenous factor is the circadian time process (i.e., the circadian 'pacemaker'), which is a nearly 24-hour oscillatory variation in sleep propensity. This circadian pacemaker affects brain arousal through projections from the master circadian clock, located in the hypothalamic suprachiasmatic nuclei, and via clock gene oscillations in a variety of brain tissues (Wright et al., 2012). A variety of exogenous factors can also impact diurnal variation in cognitive performance, including food intake and its resulting changes in blood glucose, caffeine intake, motivation, and lighting, to name just a few (Wertz et al., 2006; Schmidt et al., 2007).

Patients suffering from a variety of psychiatric disorders have been found to have disturbed circadian rhythms, including major depressive disorder (Courtet and Olié, 2012), bipolar disorder (Ciarleglio et al., 2011), and schizophrenia (Wulff et al., 2012). In regard to schizophrenia specifically, sleep disturbances are known to adversely affect cognition (Manoach and Stickgold, 2009). Clinically, sleep disturbance may predict the onset of psychosis (Ruhrmann et al., 2010) and psychotic relapse following therapy with antipsychotics (Chemerinski et al., 2002). Some researchers have postulated that the common comorbidity between sleep disturbances and schizophrenia may reflect shared biological diatheses underlying both conditions (Pritchett et al., 2012).

Recently, several small studies have specifically examined circadian rhythm abnormalities among patients with schizophrenia. Wulff et al. (2012) conducted a 6-week study of 20 outpatients with schizophrenia and 21 healthy controls and examined the magnitude of circadian disruptions by collecting sleep-wake data using actigraphy along with weekly 48-hour profiles of a urinary metabolite of melatonin. A markedly delayed and/or free-running sleep-wake cycle was seen among 50% of the patients with schizophrenia, implying a lack of synchrony between the body's internal rhythm and the external day-night cycle. No evidence was found that the dose of antipsychotic medication was related to any of the circadian abnormalities, which is consistent with the broader literature suggesting that sleep disturbances in schizophrenia are not merely side effects of antipsychotic therapy (Pritchett et al., 2012). Bromundt et al. (2011) examined the connection between circadian abnormalities and cognitive functioning among 14 patients with schizophrenia using a combination of continuous wrist actigraphy, salivary samples of melatonin secretions, and repeated assessments of patients' neuropsychological functioning and clinical symptoms over 3 weeks. Despite the small sample size, the relative amplitude of sleep-wake cycles significantly predicted performance on all of the cognitive measures, and was superior to all other predictors of cognitive performance, including age, positive and negative symptom scale scores on the Positive and Negative Syndrome Scale (PANSS), and sleep efficiency. Lastly, D'Reaux et al. (2000) examined the impact of time of day on cognitive functioning between a group of 14 patients with schizophrenia and contrasted them to a group of 14 normal controls. They found that time of day of testing did have a significant effect on cognitive performance for both healthy controls and patients. In particular, the patients with schizophrenia had both poorer performance and a distinct pattern of time of day effects in terms of their cognitive functioning as compared with the normal controls, with patients having better afternoon cognitive performance on measures of visual memory and motor measures as compared to their morning performance.

Numerous clinical trials focused on cognitive impairments in schizophrenia have been conducted focusing on a wide variety of potential mechanisms of action for pro-cognitive activity, from nicotinic alpha-7 receptor agonism to 5-HT_{2A} antagonism. However, to date the majority of these trials have been negative. It is not well understood at present the extent to which these trials failed because of inadequate or misfocused psychopharmacology, methodological issues that may have precluded signal detection, or a combination of both or other factors.

Based on the literature review above, we hypothesized that patients with schizophrenia would exhibit a circadian rhythm in their cognitive functioning. Moreover, we hypothesized that taking into account this diurnal variation in cognitive functioning would serve to enhance signal detection in clinical trials of potential pro-cognitive therapies by eliminating an important source of error variance from the data. To test these hypotheses, we first examined the impact of time of day on patients' baseline performance on the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB) (Nuechterlein et al., 2008) across 8 large Phase 2, US-based, schizophrenia clinical trials. Next, we compared placebo separation between groups of subjects with consistent versus inconsistent timing of cognitive battery administrations by analyzing their change from baseline scores. This enabled us to determine whether subjects tested at consistent times of day, thus reducing diurnal variation, would show enhanced placebo separation as compared to subjects tested at inconsistent times of day. For these analyses, we examined data from two Phase 2 potential pro-cognitive schizophrenia clinical trials, one of an adjunctive alpha-7 nicotinic acetylcholine receptor agonist, and the other of a broad-spectrum γ-aminobutyric acid-enhanced antipsychotic agent.

2. Methods

First, MCCB baseline assessments were aggregated across 2032 subjects from US sites in 8 different schizophrenia clinical trials for the diurnal variation analyses. These 8 clinical trials were chosen because data from them were available for these analyses. Consistent with the construction and use of the MCCB in clinical trials, we focused our analyses on the composite score, which is derived from the ten subtests and resulting 7 domain scores, that comprise the battery (Nuechterlein et al., 2008). The cognitive assessments were administered between December 2007 and September 2011. The analyses are based on 1915 subjects who had composite scores available and tests beginning between 8:00 am and 5:59 pm. Subjects were excluded from the analyses if their MCCB total test time was less than 40 min, exceeded 2.5 h, or if the test administration spanned 2 days. MCCB assessments were divided into five 2-hour time intervals based on their start-time. Mean overall composite scores for each 2-hour period were compared with a 4-*df* analysis of covariance (ANCOVA), adjusting for age, gender, and study protocol. If this analysis yielded an overall time-of-day group difference ($p < .05$), then the Tukey–Kramer procedure was used to assess for significant differences among the 10 possible pairwise comparisons (Kramer, 1956; Tukey, 1994). Additionally, interactions between time of assessment and the covariates were explored.