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# A pilot study of actigraphy as an objective measure of SSRI activation symptoms: Results from a randomized placebo controlled psychopharmacological treatment study

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## ABSTRACT

Selective serotonin reuptake inhibitors (SSRIs) are an efficacious and effective treatment for pediatric obsessive-compulsive disorder (OCD) but have received scrutiny due to a potential side effect constellation called activation syndrome. While recent research introduced a subjective measure of activation syndrome, objective measures have not been tested. This pilot study, using data from a larger randomized-controlled trial, investigated the potential of actigraphy to provide an objective measure of activation symptoms in 44 youths with OCD beginning an SSRI medication regimen. Data were collected over the first four weeks of a multi-site, parallel, double-blind, randomized, placebo controlled psychopharmacological treatment study and statistical modeling was utilized to test how activation syndrome severity predicts daily and nightly activity levels. Results indicated that youths with higher activation symptoms had lower daytime activity levels when treatment averages were analyzed; in contrast youths who experienced onset of activation symptoms one week were more likely to have higher day-time and night-time activity ratings that week. Results support actigraphy as a potential objective measure of activation symptoms. Subsequent studies are needed to confirm these findings and test clinical applications for use by clinicians to monitor activation syndrome during SSRI treatment. National Institutes of Health (5U01 MH078594-01); NCT00382291.

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## 1. Introduction

Selective serotonin reuptake inhibitors (SSRIs) have been linked to the development of a distinct constellation of behavioral side effects, variably referred to as “Behavioral Activation”, “Activation Syndrome”, and “Antidepressant-Induced Jitteriness/Anxiety Syndrome” (Dimidjian et al., 2006; Harada et al., 2008; Sinclair et al., 2009). The varying terminology likely reflects the heterogeneous presentation of these SSRI-linked adverse events and to date, no strict diagnostic criteria have been defined for activation syndrome. The U.S. Food and Drug Administration (FDA) described a symptom set consisting of anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, akathisia (psychomotor restlessness), hypomania, and mania that

might be linked to worsening depression and suicidal ideation development (FDA, 2010). Reid et al. (2010) proposed organizing the most common activation symptoms into five symptom clusters (i.e., irritability, akathisia, disinhibition, mania, and self-harm) and, in combination with work by Bussing et al. (2013), psychometrically validated the first dimensional parent-report measure for activation symptoms called the Treatment Emergent Activation Syndrome Assessment Profile (TEASAP). The TEASAP uniquely measures these symptom clusters, producing five subscale scores and an overall activation score.

To enhance research into the phenomenology and etiology of activation syndrome, additional objective and clinically feasible measurement approaches are needed. Since restlessness, behavioral disinhibition and increased energy are all associated with activation syndrome (Sinclair et al., 2009), actigraphy may be a plausible assessment tool warranting further investigation. Actigraphy involves participants wearing a wrist-like device that tracks light and movement, providing accurate feedback regarding activity levels over extended time periods. Actigraphy devices have

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strong psychometric support (Berlin et al. 2006) and extensive use in sleep disorder (Sadeh and Acebo, 2002), attention-deficit hyperactivity disorder (De Crescenzo et al., 2014) and depressive disorder research (Burton et al., 2013). Preliminary research has employed actigraphy in research addressing sleep in anxiety disorders (e.g., Alfano and Kim, 2011; Drummond et al., 2012) and developmental disorders (e.g., Tryon et al., 2006).

A large literature links higher depressive symptoms to lower activity levels (e.g., Jacka et al., 2011; Mangerud et al., 2014). Notably, 60% of children and adolescents with depressive disorders have low activity compared to 40% of those with anxiety disorders (Mangerud et al., 2014). To the best of the authors' knowledge, activity levels in pediatric OCD have never been reported and little theoretical research has even postulated an association between obsessive-compulsive symptoms and activity (Abrantes et al., 2012; Albert et al., 2013). Therefore, studying the association between activation and actigraphy in an OCD sample (compared to a depressive disorder sample) may allow for a less biased analysis than a depressive disorder sample because findings would be less clouded by the impact of primary psychopathology on activity.

The goal of this pilot study was to investigate the utility of actigraphy to capture symptoms of activation syndrome in youths beginning an SSRI regimen to treat obsessive-compulsive symptoms. The two aims of this study are to: (1) document if actigraphy is sensitive to average changes in activation symptoms across treatment, and (2) examine week-to-week fluctuations in activation symptoms. Based on the review above, it is hypothesized that emerging symptoms of activation syndrome on the TEASAP will predict higher activity levels. Data analyzed in this study come from a larger randomized-controlled trial.

## 2. Methods

### 2.1. Participants and procedures

Participants consisted of 56 treatment seeking youths recruited between February 2009 and January 2011 that enrolled in a double-blind randomized controlled study conducted at two large southeastern university clinics. Institutional Review Boards approved the study at both site locations and parental consent and child assent was acquired for all subjects. Participants were recruited until sample size goals were obtained. Forty-four (79%) of the 56 participants (25 at site 1, 19 at site 2) consented to wear an actigraphy device during the first 4 weeks of study participation and produced usable data. These participants consisted of 21 (48%) females; 43 (98%) identified as Caucasian and one (2%) identified as Hispanic. The average participant age was 11.8 years (S.D. = 3.3 years; range 7–17 years). For a more detailed description of baseline characteristics specific to each randomization group, please refer to Table 1.

At the screening visit, study eligibility was determined and those eligible for inclusion were instructed to wear the actigraphy device starting one week before their next visit, the baseline visit. Eligible children and adolescents met criteria for OCD of at least moderate clinical severity (as reflected in Children's Yale-Brown Obsessive-Compulsive Scale total score  $\geq 18$ ; Scahill et al., 1997). Children and adolescents meeting criteria for substance abuse, bipolar disorder, autism,

schizophrenia, mental retardation or chronic degenerative neurological disease were excluded. Participants were excluded if they were taking any other psychopharmacological medication with the exception of stimulants and PRN sedative/hypnotics for insomnia. Diagnoses were consistent with the Diagnostic and Statistical Manual, Fourth Edition, Text Revision (American Psychiatric Association, 2000) and were ascertained through clinical interview and a semi-structured diagnostic interview (Schedule for Affective Disorders and Schizophrenia for School-Age Children; Kaufman et al., 1997). In addition to OCD, seven (16%) participants met diagnostic criteria for comorbid ADHD; 25 (57%) for a comorbid anxiety disorder, seven (16%) for a comorbid tic disorder, two (5%) for comorbid depressive disorder and eight (18%) for other disorders (i.e., elimination disorders, oppositional defiant disorder and phonological disorder). Altogether eight (20%) participants met criteria for an OCD diagnosis and no comorbid diagnoses, 20 (46%) for one comorbid diagnosis, and 10 (23%) for two or more comorbid diagnoses. Please refer to Fig. 1 for a study flow chart.

At baseline, participants were randomized in a parallel design to one of three medication arms: regular sertraline titration, slow sertraline titration or placebo (1:1:1 allocation); computer generated randomization sequence stratified by age (7–12 year old and 13–17 year old groups). All participants and study investigators/clinicians remained blind until the conclusion of treatment; assignment of participants to intervention group was conducted by one unblinded study nurse not involved in assessments. The primary aim of the randomized-controlled trial was to investigate impact of titration speed on activation symptom presentation. The current study displays findings for a secondary outcome of interest from the trial related to the ability of actigraphy to objectively measure symptoms of activation syndrome. To investigate this research aim, participants were closely monitored for symptoms suggestive of activation syndrome for one week prior to randomization and during the first three weekly follow-up visits of the randomized-controlled trial. Actigraphy devices were worn and sleep diaries were completed during these four weeks. This time period did not include any exposure to cognitive behavioral therapy, which was initiated at week 4.

### 2.2. Measures

#### 2.2.1. Schedule for Affective Disorders and Schizophrenia for School-Age Children, Present and Lifetime Version (K-SADS-PL)

The K-SADS-PL (Kaufman et al., 1997) is an adapted version of the K-SADS, a parent-child interview measure used to diagnose several childhood psychiatric disorders and their severity. The K-SADS-PL extends upon previous versions as it includes several new disorders (attention-deficit hyperactivity disorder, posttraumatic stress disorder, and tic disorders), assesses global functioning, and includes both lifetime and current psychopathology. In addition to the disorders already mentioned, the K-SADS-PL assesses depressive disorders, bipolar disorder, anxiety disorders, conduct disorder, and oppositional defiant disorder. The K-SADS-PL has high test-retest reliability, inter-rater reliability, as well as strong agreement with other diagnostic instruments used to assess specific disorders (Kaufman et al., 1997).

#### 2.2.2. Sleep diary

The sleep diary is a brief self-report log of sleep habits that combined with actigraphy data, is the gold standard for measuring sleep (Espie, 2000; Wolfson et al., 2003; Buysse et al., 2006). The sleep diary was completed daily from screening through the end-of week-3 visit upon awakening and required approximately 3 min/day to complete (Lichstein et al., 1998).

#### 2.2.3. Actigraphy

Participants wore wrist-band style Mini Mitter Actical<sup>®</sup> actigraphy devices (Starr Life Sciences Corp., USA) on their non-dominant wrist daily for 4 weeks starting at the baseline visit. The device detects frequency and intensity of motion and has been shown to be valid and reliable for recording general activity levels (Chang et al., 1999; Swanson et al., 2002) and SSRI related motor activity (Putzhammer et al., 2005). The study reports average activity units, converted to a rate per minute of real time, for day and night-time periods.

#### 2.2.4. Treatment-Emergent Activation and Suicidality Assessment Profile (TEASAP)

The TEASAP (Bussing et al., 2013) is a parent-rated assessment of activation symptom severity that captures five identified symptom clusters related to Activation Syndrome: (1) irritability (nine items), (2) akathisia/hyperkinesia/somatic anxiety (six items), (3) disinhibition/impulsivity (seven items), (4) mania (10 items), and (5) self-injury/suicidality/harm to others (six items). Parents rate the child's behavior in the past week, considering frequency and impairment associated with the behavior on a four-point Likert-style scale (0 = none; 1 = mild; 2 = moderate; and 3 = severe). The five subscales are summed to create a Total Score of activation symptom severity used for all analyses in this study. The TEASAP has strong psychometric properties, including the ability to capture week-to-week fluctuation in activation symptom severity (Bussing et al., 2013).

**Table 1**  
Demographic and baseline clinical characteristics of the sample.

	RegSert + CBT (n = 14)	SloSert + CBT (n = 17)	PBO + CBT (n = 13)
Gender N	50.00	52.90	38.50
(% female)			
Age, M (S.D.)	11.70 (2.70)	11.24 (3.45)	12.01 (3.86)
CY-BOCS total	23.71 (4.03)	25.71 (4.33)	26.15 (3.67)
Psychiatric comorbidity, N (%)			
Internalizing	7 (50%)	8 (47.01%)	9 (69.23%)
Externalizing	3 (21.4%)	1 (5.88%)	3 (23.07%)
Tic disorder	3 (21.4%)	2 (11.76%)	3 (23.07%)

Note. CY-BOCS = Children's Yale-Brown Obsessive-Compulsive Scale.

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