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Dimensional Characteristics of Children and Adolescents with Mood Disorders and Autism Spectrum Disorders

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ABSTRACT

Objective: We sought to identify clinical discriminators between predominantly mood disordered and predominantly autism spectrum disordered research subjects that may reflect phenotypic state and treatment response characteristics. **Method:** Participants were 26 boys and 4 girls aged 2 to 18 years (Mean Age = 7.70). Subjects with DSM-IV diagnoses of Major depression (N = 2), Bipolar Disorder (N = 4) and Mood Disorder not otherwise specified (NOS) (N = 11) represented the mood disorder group (MD) (N = 17, Mean Age = 8.2) and those with diagnoses of Autistic Disorder (N = 1), Asperger's Disorder (7) or Pervasive Developmental Disorder (NOS) (N = 3) comprised the autism spectrum disorder (ASD) group (N = 9, Mean Age = 6.8). Primary outcome measurements were continuous actigraphic measurements collected over one to three week periods. Secondary outcomes included personality and observational measurements. Personality characteristics reflected significant cross-group impairments related to self-control and self-discipline and differed relative to intellectual measures. Observational measurements reflected greater general impairments among the ASD group. **Results:** Predominantly mood disordered children demonstrated greater impairments related to sleep (P = 0.000) and sleep onset latency (P = 0.000) and were more active than ASD children during evening periods (P = 0.000). ASD children had lower verbal functioning and greater deviations from the norm on measures of cognitive development (P = 0.003) and psychosis (P = 0.047). **Conclusions:** Sleep disturbances, evening activity levels and phase delayed sleep appear to differentiate predominant mood and autism spectrum disordered children suggesting future areas for further exploration of neurological and phenotypic treatment response characteristics.

Keywords: Autism Spectrum Disorders; Mood Disorders; Children; Actigraphy; Sleep

1. Introduction

Children with mood disorders (MD) and autism spectrum disorders (ASD) typically share co-morbid symptoms [1-3]. The pathophysiological mechanisms which underlie these two broad categories of disorders are multivariate and, in some cases, may overlap. The DSM-IV categorical disorders including these two broad groups have been poor guides to effective pharmacologic treatment.

ASD and MD can be examined both clinically and physiologically for dimensional abnormalities that reflect dysregulated neurophysiology. Actigraphic measurements give objective data regarding such dysregulation and might identify neurophysiologic subtypes among children with similar or overlapping symptoms. For example, such a study might clarify whether or not the presence of phase delayed sleep, which has been proposed to be characteristic of pediatric bipolar syndromes [4], is an important marker for clinical intervention. A variety of childhood circadian abnormalities, regardless of etiology, may have pathogenic potential, *i.e.*, may adversely impact subsequent biologic and psychosocial development. If so, early identification and treatment of these markers might be extremely important [5].

In this analysis, we evaluate measurements of sleep and activity, personality, cognitive functioning, and observed behaviors, in an attempt to better differentiate these complex childhood clinical groups. We propose that there is the value in sub-typing clinical pediatric subjects as either predominantly mood disordered or predominantly autism spectrum disordered. This analysis seeks to determine whether or not there are significant differences between the two broad groups. We hypothesize that despite shared behavioral and emotional symp-

toms there will be significant differences between groups in the nature and variation of their activity patterns and sleep characteristics.

2. Methods

Descriptions of age, gender and age of onset (age at which the parents first became concerned that their child had a significant problem) are examined along with dimensional characteristics that include activity and activity patterns, sleep onset latency, sleep efficiency, sleep time, cognitive measurements, multi-dimensional personality factors and operationally defined and repeated observations. A baseline assessment included a review of a biopsychosocial history, clinical and available educational testing and records, a mental status examination, operationally defined symptom history and psychological assessment. DSM IV criteria were applied and those with major depressive disorder, bipolar disorder, mood disorder, NOS, autistic disorder and pervasive developmental disorder, NOS were invited to participate in the study as actigraphic devices were available.

Children were recruited to the study between August 2010 and August of 2011 from an out-patient child evaluation and treatment clinic. The study had three actigraphic devices available. The limited availability of actigraphic devices imposed a randomization effect, with the children meeting the selection criteria being recruited when an actigraphic device was available at the time of that determination. During the study period one actiwatch was lost, further limiting device availability for the duration of the study. Most children wore the watches without difficulty or complaint and two children (one from each group) who were invited to participate in the study declined because they didn't want to wear the actiwatch. Another subject, diagnosed with autistic disorder was determined ineligible due to the parent's assessment that the child would destroy the actiwatch.

The thirty participants were two to eighteen years of age (Mean Age = 7.7) 26 of whom were males and four who were female.

Despite overlapping mood and behavioral symptomatic presentations in those with autistic characteristics and children that are primarily mood disordered there are clearly distinctions that separate the two broad groups. This study sub-typed clinical pediatric subjects, as either predominantly mood disordered or predominantly autism spectrum disordered. Subjects with DSM-IV diagnoses of Major depression (N = 2), Bipolar Disorder (N = 6) and Mood Disorder not otherwise specified (NOS) (N = 11) represented the mood disorder group (MD) (N = 19, Mean Age = 8.2) and those with diagnoses of autistic disorder (N = 1), Asperger's Disorder (7) or Pervasive Developmental Disorder (NOS) (N = 3) comprised the autism spectrum disorder (ASD) group (N = 11, Mean Age = 6.8). The subjects categorized within the autism spectrum group scored within a range of mild to severe on either the Childhood Autism Rating Scale [6] or the Asperger's Syndrome Diagnostic Scale [7].

The primary outcome measurements of the study were actigraphic measurements recorded every 30 seconds during one to three-week measurement periods. Actigraphy has been demonstrated to be a valid method for estimating sleep and wakefulness in a bipolar population and has demonstrated concordance with polysomnography in the presence of sedating medication use and in those with clinical sleep disturbances [8]. Both the referenced Kaplan study and our analysis utilized a medium threshold for sleep detection and analyzed the actigraphy data using Actiware 5.59 (Mini Mitter Philips Respironics Inc.).

The measurements were made utilizing an Actiwatch [9] (AW-64 Phillips-Respironics, Inc.) placed on the subject's non-dominant wrist. Actigraphic measurements collected at this frequency record motor activity detecting mobility, immobility, sleep states, sleep duration and sleep disruptions.

Secondary outcome measurements included baseline standardized personality and cognitive assessments and episodic repeated measurements utilizing the Systematic Observation Scale TM [10] during the measurement periods.

Although there were no matched controls and the two groups were not able to be gender and age matched, standardized measures of cognition and age and gender-normed personality inventories were incorporated in a baseline assessment battery. This study did not attempt to differentiate these MD probands into non-polar versus bipolar subgroups nor sub-type the ASD probands.

Statistics

Analysis was conducted utilizing the Statistical Package for Social Sciences (SPSS 19.0). Nonparametric analysis of group independence (Independent Samples Mann-Whitney U Test) was applied to the actigraphic, personality and observational measurements. An analysis of variance was applied to determine significance of variance related to the standardized cognitive measurements.

3. Results

3.1. Dimensional Characteristics

Descriptive characteristics of the subjects by Gender, Mean Age of Onset (The age at which the parent first felt their child had a significant difficulty) and Diagnostic Category are shown in **Table 1**.

Actigraphic measurements were analyzed by active, rest and sleep intervals. The active interval represented

the time from awakening to that of early evening hours. The rest interval followed the active interval until sleep onset was established and the sleep period began and remained until awakening.

Table 2 presents the means of the actigraphy measures and related tests of independence between the MD and ASD groups. The mood disordered and autistic spectrum disordered groups differed in all intervals with two exceptions. Both groups had similar periods of sleep and immobility during the active period.

Figure 1 is a 24-hour activity graph of a six year old mood disordered male reflecting delayed sleep onset and disrupted sleep.

Asymptotic significances are displayed. The significance level is .05.

Although the MD and ASD groups were similar during active period related to wakefulness and immobility, the ASD group had a significantly greater percentage of immobility related to sleep time during the active interval.

Total activity levels and average activity per minute differed between the two groups across interval types. Similarly onset latency, sleep time and sleep efficiency were also demonstrated to be different between the groups.

Table 1. Combined subject pool by gender, mean age of onset* and diagnostic category.

N	N	ASD	
Male	26	17	9
Female	4	2	2
Total	30	19	11

Table 2. Means of actigraphy measures and test of independent samples mann-whitney U test.

Measures	N	MD	N	ASD	Sig	Interval
Total activity	699	675923.67	279	514720.63	0.000	Active
Total activity	639	13213.06	346	10659.90	0.000	Rest
Total activity	639	11679.53	345	9864.48	0.000	Sleep
Average activity/min	699	780.1154	279	609.7672	0.000	Active
Average activity/min	639	23.5679	346	18.3404	0.000	Rest
Average activity/min	639	22.0053	345	17.4807	0.000	Sleep
Sleep onset	639	9.79	345	6.18	0.000	Sleep
Sleep efficiency	639	75.07	345	80.66	0.000	Sleep
Sleep time	639	489.60	346	524.75	0.000	Rest
Sleep time	639	422.91	345	473.66	0.000	Sleep
Immobile time	639	491.074	346	528.540	0.000	Rest
Immobile time	639	469.806	345	517.701	0.000	Sleep

Asymptotic significances are displayed. The significance level is 0.05.

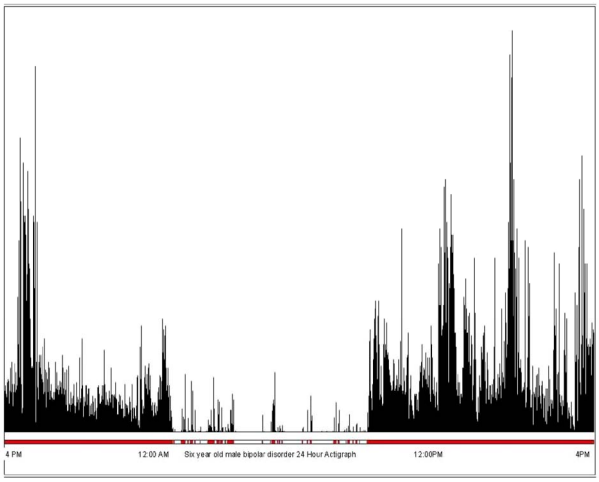

Figure 1. Six year old male bipolar 24-hour actigraph.

3.2. Cognitive Characteristics

Cognitive characteristics were determined utilizing the Kaufman Brief Intelligence Test II [11]. The ASD group, relative to the autism spectrum in general, was high functioning. Statistically significant differences in verbal functioning differentiated the two groups with statistical significance between verbal scores (ASD = 91.3 MD = 102.33 P = 0.049) and a lack of significance between non-verbal measures (ASD = 99.2 MD = 96.7 P = 0.763). It was expected, given known verbal processing issues in ASD, that those with autism spectrum disorders would have lower verbal function. Statistically significant differences were not seen between the groups on nonverbal functioning, however, a trend for the mood disordered toward lower nonverbal scores may reflect cognitive impairment secondary to mood instability or other impairment. The autistic spectrum group, relatively speaking, has nonverbal strengths.

3.3. Personality Characteristics

The Personality Inventory for Children-Revised (PIC-R) [12] is an age and gender referenced objective multidimensional measurement of affect, behavior, ability and family function. The PIC-R was administered at the time of the initial evaluation and provided standardized age and gender-normed values. These values are presented as T scores whose means are 50 and standard deviations are 10. Upward deviations from the norm indicate pathological associations with the measured dimension. As a matter of practical application, scores exceeding one and a half standard deviations *i.e.* >65 are frequently clini-

cally significant.

The results of the PIC-R indicated both similarities and differences in symptom presentations and associated impairments. The Personality Inventory for Children includes four broad factorial derived dimensions, scales measuring general adjustment and informant response style, developmental, cognitive and clinical scales. Both the mood disordered and autism spectrum groups reflect significant impairment related to self-control and self-discipline. Both groups deviate from the norm by over two standard deviations.

Difficulties in social competence between the two groups approached but did not meet statistical significance. Both group's scores suggest social impairments and deviate from the norm. The ASD group demonstrated a statistically non-significant, but higher degree of impairment in the domain of social competence. Differences between groups related to somatic concerns and internalization were not significant with means of 62.89 to 66.55. Statistically significant differences existed between the mood disordered and autism spectrum disorder groups related to general issues of cognitive development.

Other scaled personality dimensions derived from the Personality Inventory for Children that contributed to characterizing and differentiating between children with autism spectrum disorder and children with mood disorders included the dimensions of intellectual screening and psychoses. These distinctions are noted in **Table 3**.

3.4. Observational Characteristics

The observational characteristics were based on the percentage of symptom presence observed on over 72 operationally defined symptoms and the repeated measurements that were collected intermittently throughout the study period. The Systematic Observation Scale utilizes operationally defined symptoms [13] that are presented to a primary observer (usually a self-observer or a parent) for determination regarding the percentage of time symptoms are present.

These measurements are the most limited of the measurements presented. Although the observations provided meaningful individual clinical response data, they are not standardized measurements and do not have inter-rater reliability. And, as previously noted, various therapeutic interventions occurred across the study period that were not consistent across the groups. These confounding factors resulted in few items differentiating the two groups. Nevertheless, the observational symptoms that broadly demonstrated group differences are shown in **Table 4**.

Table 3. Personality dimension T scores and test of independent samples Mann-Whitney U test.

Description	DM	DSA	giS
Cognitive development	58.79	83.91	0.003*
Intellectual screening	55.32	84.18	0.006*
Psychosis	80.32	98.45	0.047*

Asymptotic significances are displayed. The significance level is 0.05.

4. Discussion

It is not the authors' intention to suggest that all child psychiatric patients can be placed into the two broad groups we have examined. But, despite similar symptomatic expressions of dysregulated mood, irritability and other impairments there is a clinically discernible difference in social relatedness among the autism spectrum group. The fundamental neurodevelopmental nature of autism spectrum disorders suggests neurophysiologic differences despite elements of common symptomatic presentations. In our sample the activity patterns and sleep characteristics differ between the included major depressive disorder, bipolar disorder and unspecified mood disorder from our ASD sample. The ASD sample of this study was limited by those available in a setting where a "high functioning" bias existed. Nevertheless, there appear to be significant differences between the broad groups of mood disorder and autism spectrum disorders that can be further defined by applying objective measures to determine treatment response phenotypes and as a method to support and measure specific related categorical diagnoses.

The broadly defined MD and ASD groups of this study had similar self-control and behavioral impairments, but exhibited significant differences in circadian sleep and motor activity characteristics. These findings are limited but point to the potential of further characterizing these and other differences. Although both groups in this study had sleep complaints the predominantly mood disordered exhibited significantly different sleep characteristics than did those with autism spectrum diagnoses. The autism spectrum group also exhibited significantly less total activity than the mood disordered group. Phenotypic characteristics such as these may be associated with

Table 4. Mean percentage present of operationally defined symptoms and test of independent samples Mann-Whitney U test.

Observational measure	MD	ASD	Sig
Tics/mannerisms	7.56	26.36	0.048
Picky eater	15.74	35.14	0.010
Bed wetting	6.39	32.50	0.001
Whiny	14.81	32.55	0.048

treatment response variance and may, once fully characterized, reveal pathological processes that precede or contribute to chronically established impairments.

The clinical implications of variations of activity and sleep disruptions are numerous and include their relationship to mood, cognition and development. Sleep is closely related to emotional regulation and cognitive functioning. Dysphoric mood states [14]; completed suicides [15] the onset of manic symptoms worsening [16] and possible long lasting learning deficits have each been associated with sleep disturbances [17]. Approximately 85% of bipolar children and adolescents exhibit sleep disturbance [18] (4). And, bipolar individuals experience sleep problems during periods of relative euthymia [19] [16] as well as during episodic worsening of affective illness. Bipolar children may be especially likely to exhibit low sleep efficiency, frequent awakenings [20] and phase-delayed sleep [4].

Sleep disturbances are associated with poorer academic performance among children diagnosed as having autism and attention deficit hyperactivity (ADHD) disorders, but not among normal control children [21]. Our results suggest that predominantly mood-disordered children have significantly more severe sleep impairment than do those with autism spectrum diagnoses. If a strong association exists between sleep disturbance and academic performance among predominantly mood-disordered children, as seems very likely, it would be particularly important to address sleep symptoms during clinical treatment of these children and adolescents.

Circadian rhythm disorders are associated with cognitive impairment, mood disturbances and increased risk of cardio-metabolic disorders and can be treated by light management, scheduled sleep-wake time adherence, timed low-dose melatonin and other pharmacological agents [22]. Melatonin has demonstrated effectiveness in advancing sleep-wake rhythm and endogenous melatonin rhythm in delayed sleep phase disorder [23].

Sleep and activity measurements are reflections of neurophysiological states and are measureable treatment targets. Insomnia and hypersomnia, sensitivity to shifts in circadian rhythm, difficulties awakening, and prolonged sleep latency may act as vulnerability factors prior to the manifestation of manic episodes [16].

Effective reduction of sleep disturbances in children and adolescents, particularly those with predominant mood disorder symptoms, perhaps should be a primary goal. Sleep disturbed adult bipolar probands treated with ramelteon, a selective melatonin receptor agonist, were approximately half as likely to relapse as those treated with placebo through a 24 week treatment period [24]. Symptoms of delirium have been correlated with circadian rhythm disturbances and are reported to have been improved by treatment with ramelteon [25]. Although the pathophysiology of mood disorders is unknown, the disruptions in daily rhythms associated with major depressive disorder and bipolar disorder have led to consideration of circadian pathophysiology as a contributing causal factor [26,27].

5. Conclusion

Limitations of this study are significant and include that: this is a small unmatched sample; subjects represented various developmental states; the ASD subjects are heavily weighted toward high functioning and are not representative of a broad ASD group; some subjects were drug naïve at baseline while others were not; and, subjects in both diagnostic categories received various pharmacological interventions during actigraphy measurement periods. Despite these limitations we propose that low budget or no budget clinical investigations such as these can assist in clinical management and incrementally shed light on phenotypic differences worthy of further investigation.

The results of this study are consistent with sleep disturbances reported in studies of pediatric bipolar subjects [18] and demonstrate the value of utilizing objective measurements for the differentiation of complex phenoltypic neurodevelopmental and neuropsychiatric disorders. Phenotypic differences may be a factor in lower antidepressant and other variant medication efficacies seen in the ASD population [28].

Future studies may identify phenotypic subtypes of complex disorders that reveal dimensional aspects underlying neurophysiological effects and states. Identification of these characteristics enhances phenotypic differentiation and neurodevelopmental opportunities to mitigate or reduce pathological development.

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