Sleep and COMT Polymorphism in ADHD Children: Preliminary Actigraphic Data

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ABSTRACT

Objective: To examine whether COMT (catechol-O-methyltransferase) polymorphism modulates aspects of sleep in children diagnosed with attention-deficit/hyperactivity disorder (ADHD). Method: Nightly sleep actigraphic recordings during a double-blind, placebo-controlled, crossover clinical study (1 week of 0.5 mg/kg MPH; 1 week of placebo) were obtained for 34 children, 7.4 to 12 years old, diagnosed with ADHD (DSM-IV). Diagnosis was generated by the Diagnostic Interview Schedule for Children and was confirmed by multidisciplinary consensus. Results: Children who were Val allele carriers had poorer sleep continuity compared with children with the Met-Met genotype while receiving a placebo and while receiving methylphenidate. Conclusions: The findings of the present study support the hypothesis that sleep disturbances in children with ADHD are related to the underlying pathophysiology of the disorder. J. Am. Acad. Child Adolesc. Psychiatry, 2006;45(8):982–989. Key Words: attention-deficit/hyperactivity disorder, catechol-O-methyltransferase, COMT, sleep, genotype.

Attention-deficit/hyperactivity disorder (ADHD) is characterized by developmentally inappropriate symptoms of inattention and/or impulsivity/hyperactivity, which begin in childhood and lead to functional impairment in various life settings (American Psychiatric Association, 1994). A recent report demonstrated that 50% of children diagnosed with ADHD show clinically significant symptoms and impairment as young adults (National Center on Birth Defects and Developmental Disabilities [NCBDDDD], 2001). The Centers for Disease Control and Prevention have labeled ADHD “a serious public health problem” (NCBDDDD, 2001), citing the large estimated prevalence of the disorder, the significant impairment in the areas of school performance and socialization, the chronicity of the disorder, the limited effectiveness of current interventions to attend to all of the impairments associated with ADHD, and the inability to demonstrate that intervention provides substantial benefits for long-term outcomes.

Although the etiology of ADHD is obscure, family aggregation and twin studies suggest that genetic factors may be significant in this disorder. Imaging studies, animal models, and the clinical efficacy of stimulants such as methylphenidate (MPH) in the treatment of ADHD suggest that genes coding for neurochemical elements that are involved in dopaminergic transmission are likely candidates for the etiology of this disorder (Bobb et al., 2005; Faraone et al., 2005; Pliszka, 2005).

Parental reports indicate a two- to threefold higher prevalence of sleep problems including difficulty falling...
asleep, night awakenings, and restless sleep in children with ADHD compared with controls (see Owens, 2005 for a review). Most of the objective studies have failed to find consistent significant differences in sleep architecture between children with ADHD and controls (Owens, 2005). Actigraphy studies have suggested that activity during sleep in children with ADHD is higher and that children with ADHD tend to have unstable sleep patterns (Gruber and Sadeh, 2004; Gruber et al., 2000; Konofal et al., 2001). Studies regarding the association between sleep and neurobehavioral functioning in children with ADHD and sleep-disordered breathing (Archbold et al., 2004; Chervin et al., 1997; O’Brien et al., 2003a) and in children with ADHD and restless leg syndrome/periodic leg movement disorder (Picchietti et al., 1999) consistently showed that in these populations, sleep disruption was associated with hyperactivity and inattention.

The use of stimulants has also been associated with increased sleep problems in this population (for a review, see Cohen-Zion and Ancoli-Israel, 2004). Because of the mixed reports that associate sleep problems with the clinical presentations of the disorder and with the commencement of the pharmacological intervention, it is not clear whether sleep problems in children with ADHD are caused by intrinsic (e.g., cholinergic, dopaminergic, and noradrenergic mechanisms) or extrinsic (e.g., MPH) factors.

There is some published evidence that suggests that catechol-O-methyltransferase (COMT), a gene coding for dopamine that has been associated with ADHD, is involved in the regulation of sleep. COMT is involved in the inactivation of DA and has been localized to the chromosomal region 22q11 (Grossman et al., 1992; Lundstrom et al., 1995). A functional polymorphism of this gene, involving a substitution of valine (Val) for methionine (Met) at codon 108/158 (Val_108/158 Met), results in a fourfold variation in enzymatic activity. Recently, the role of COMT has been explained from the perspective of the tonic-phasic dopamine hypothesis (Bilder et al., 2004). According to this model, the Met allele increases the release of tonic dopamine (baseline steady-state levels of dopamine), decreases the release of phasic dopamine (large, brief, pulses of dopamine) in subcortical regions, and increases DA concentrations in cortex, thereby enhancing the functions associated with tonic dopamine system activity. The Val allele has complementary effects, increasing phasic dopamine transmission, while decreasing tonic dopamine neurotransmission subcortically (Bilder et al., 2004).

COMT activity has been found to be associated with sleep in narcolepsy (Dauvilliers et al., 2001) and in Parkinson’s disease (Frauscher et al., 2004), clinical conditions in which a dysfunction in the dopamine system is presumed to play an important etiological role (e.g., Eisensehr et al., 2003; Maguire-Zeiss et al., 2005). It has been suggested that COMT activity contributes to sleep problems because of its involvement in the metabolism of dopamine (Frauscher et al., 2004). Additional support for the association between dopamine and sleep is provided by studies that explore the anatomy and state-related function of midbrain dopamine neurons, as well as from animal studies, clinical observations, and studies showing exogenous dopaminomimetic effects on sleep–wake state (for reviews, see Gottesmann, 2002; Rye, 2004).

Convergent lines of research have implicated that dopamine-related genes that have been associated with ADHD may also be associated with the regulation of sleep. However, the association between sleep and genes coding for dopamine in children with ADHD has not been investigated. In the present study, we set out to examine whether COMT polymorphism modulates aspects of sleep in children diagnosed with ADHD. To determine whether differences in sleep parameters are related to intrinsic or extrinsic mechanisms, a double-blind, placebo-controlled, within-subject (crossover) design was used to assess sleep in children diagnosed with ADHD of different COMT genotypes, both while they were taking medication and while they were taking placebo.

**METHOD**

**Subject**

Thirty-four children (29 boys, 5 girls) between the ages of 6 and 12 years (mean age 9.2; SD = 1.88) with a DSM-IV (American Psychiatric Association, 1994) diagnosis of ADHD were included in the study. The diagnosis of ADHD was determined by criteria from DSM-IV. The Diagnostic Interview Schedule for Children (DISC-IV; Shaffer et al., 2000), which generates DSM-IV diagnoses, was administered to parents. The ADHD diagnosis that was generated by the DISC was confirmed by multidisciplinary consensus after reviewing interview data, psychological testing, behavior rating scales obtained from teachers and from parents including the Child Behavior Checklist, the Conners Parent and Teacher Rating Scales,
information obtained from teachers in a telephone interview, and a
psychiatric examination.

Of the 34 children who met the DSM-IV criteria for ADHD, three met the criteria for the inattentive subtype, three met the criteria for the hyperactive-impulsive subtype, and 28 fulfilled the criteria for combined subtype. Subjects were excluded if they had an IQ <80 on WISC-III (Wechsler, 1991) or if they had a diagnosis of Tourette’s syndrome, pervasive developmental disorder, or psychosis. Children taking any medication other than MPH or having shown previous intolerance or allergic reaction to any psychostimulant were also excluded. The children were recruited from the Disruptive Behavior Disorders Program and from the outpatient department of Douglas Hospital in Montreal, a psychiatric university teaching hospital. The study was approved by the Research Ethics Board of Douglas Hospital. Parents signed informed consent forms, and all of the children assented to participation in the study.

Study Design

A double-blind, placebo-controlled, within-subject (crossover) design was used to assess sleep with participants who were either taking a placebo or MPH. The children received a placebo and a daily 0.5-mg/kg dose of MPH, the dose usually prescribed in clinical and research settings (Gadow et al., 1995; Sprafkin and Gadow, 1996), divided in two equal doses (morning and noon) each for a 7-day period. The order of administration (MPH and placebo) was counterbalanced and determined by random assignment such that an equal number of children received either the placebo or MPH during a given 7-day period. MPH and the placebo were prepared in colored gelatin capsules by the hospital’s clinical pharmacist, who was not involved in the study in any other way. Capsules were sealed in individual, daily envelopes to help control for accurate administration. Parents were instructed to maintain the child’s regular sleep schedule and routines. All of the children were monitored during regular school days (i.e., excluding weekends and holidays). The children were instructed to attach a miniature actigraph (AW64 series, Mini-Mitter Co., Bend, OR) to their nondominant wrist in the evening when preparing for sleep and remove it in the morning for 2 weeks. In addition, parents were asked to document the child’s sleep schedule in nightly sleep logs.

Isolation of DNA and Genotyping. The Val<sup>108/158</sup> Met polymorphism of the COMT gene was genotyped using a polymerase chain reaction (PCR)—based method as previously described (Lachman et al., 1996). The PCR was performed in a 25-μL total reaction volume containing 1X PCR buffer, 200 μmol/L deoxyribonucleoside triphosphate, 200 ng of primers (5’-GGGATGTTGGG CACTCCAAGC; 5’-TGGAGAGGCTAGGGTCGAC), 1 unit of Taq DNA polymerase, and 100 ng of genomic DNA. PCR products were electrophoresed on agarose-TAE gel along with 1-kb and 100-bp DNA ladders, visualized under ultraviolet light and coded according to the length of the PCR product. Genotypes were called by two independent and experienced technicians who were blind to all of the clinical data. No discordance in any of the readings was noted.

Sleep Assessment. In the present study, monitoring by actigraphs (AW64 series, Mini-Mitter Co.) was used to assess the sleep patterns of the children in their natural home environment. The term actigraphy refers to the use of computerized wristwatch-like devices, actigraphs, to monitor and collect data generated by movement. These are small, easy-to-use devices that are only minimally invasive. They allow sleep to be reliably recorded over an extended period of time without interfering with the family’s routine. Actigraphy has been widely used to assess sleep in both clinical trials and studies requiring multiple measurements. It has been validated against polysomnography with agreement rates for minute-by-minute sleep-wake identification higher than 90% (Ancoli-Israel et al., 2003; Sadah and Acebo, 2002). Actigraphic data were analyzed during each sleep episode based on 1-minute epochs. The reported bedtime and wake time (provided by the sleep logs) were used as the start and end times for the analyses. For each 1-minute epoch, the total sum of activity counts was computed. If they exceeded a threshold (threshold sensitivity value = mean score in active period/45), then the epoch was considered waking. If it fell below that threshold, then it was considered sleep. Actigraphic sleep measures included the following parameters: sleep time: sleep period; wake time: the amount of time spent awake during the night; sleep efficiency: sleep time excluding all periods of wakefulness; wake time percentage: the percentage of sleep time that was actually spent awake, motionless sleep time: the summation of the time in which the subject does not move, motionless sleep percent: motionless time out of sleep period; and movement and fragmentation index: the percentage of time in which changes from sleep to wake state occurred.

Daily Sleep Logs. The daily sleep logs completed by the parents included information about children’s sleep nighttime and waking time.

Reported Sleep Problems. To supplement the daily information on daytime sleepiness with a general overview of the child’s sleep habits, at the screening stage of the study, we had each mother complete a questionnaire that included a 3-point Likert-type scale with items regarding their child’s sleep habits. Mothers were asked to indicate whether the child never (0), sometimes (1), or often (2) sleeps less than most kids; talks or walks in sleep; has nightmares; has trouble sleeping. In addition, parents were asked to indicate whether their child “sleeps more than most kids during the day.” The internal consistency value was 0.70.

Data Analysis

The Val<sup>108/158</sup> Met polymorphism consists of both the low-activity Met and high-activity Val alleles. Subjects were divided into two groups: Val carriers (Val-Val and Val-Met genotypes) and Met homozygous genotypes.

Different demographics and intellectual and psychiatric characteristics were considered to be dependent variables and were compared across the genotypes using either one-way analysis of variance or χ<sup>2</sup> analysis, depending on the nature of the data. Principal component analyses were used to reduce the number variables and to aggregate sleep measures into reliable indices reflecting the integrity of sleep-related dimensions.

The polymorphism in the COMT gene in relation to sleep patterns of children with ADHD was examined using multivariate analyses of variance, in which COMT (Val carriers, Met-Met: 2) was the between-subject independent factor, condition (MPH, placebo) (2) was the repeated, within-subject, independent factor, sleep factors (sleep continuity, sleep quantity) (2) as the dependent variables, and child’s age and sex as covariates.

Parental report of sleep problems were considered as dependent variables and were compared across the genotypes using two-way analysis of covariance with child’s age and sex as covariates.

SPSS 12.0 for Windows (SPSS, Chicago) was used for all of the statistical analyses. p Values <.05 were considered to indicate statistical significance.
RESULTS

Of the 34 patients, 9 (26.5%) had Met-Met, 20 (58.8%) had Val-Met, and 5 (14.7%) had Val-Val genotypes. Val allele carriers (Val-Val and Val-Met genotypes) were compared to subjects with the Met-Met genotype. In Table 1, we present the means and the SDs on the demographic and clinical characteristics of children with ADHD divided into groups according to their COMT groups. A series of analyses of variance was conducted to determine whether the COMT groups differ in age, IQ, externalizing and internalizing total scores on the CBCL, and their ADHD symptoms. No significant differences between the COMT genotypes were observed on any of these measures. Chi-square tests were used to examine differences in the prevalence of boys and girls and to examine differences in the prevalence of opposition defiant disorder or conduct disorder between the COMT groups. No significant differences between the COMT groups were observed on any of these measures.

Factor Analyses

Principal-component analyses with Varimax rotation produced similar two-factor solutions for the sleep measures that were obtained while the children were taking placebo and while the children were taking MPH. These factors accounted for 82.5% and 83.2%, respectively, of the variance. Interpretation and labeling of each component were based on component loadings of 0.6 or higher (Table 2). The first factor (eigenvalues 3.95 and 4.45, respectively) was weighted by scores from the movement and fragmentation index, wake time percentage, motionless sleep percentage, and wake time. This component appears to reflect the continuity of sleep and therefore was labeled sleep continuity. The second factor (eigenvalues 1.83 and 1.34, respectively) was weighted by scores of motionless sleep time and sleep time. This component appears to reflect the duration of sleep and was therefore labeled sleep quantity. Individual scores for each factor were calculated by weighting the items according to the factor loadings presented in Table 2.

Comparing Actigraphic Sleep Measures in the COMT Group

The multivariate analyses of variance that were conducted to determine differences between the COMT groups revealed a significant COMT main effect on sleep continuity ($F_{1,29} = 4.89, p < .05$). Children who were Val allele carriers had poorer sleep continuity compared with children with the Met-Met genotype while receiving placebo and while receiving MPH. There were no significant differences in sleep continuity or sleep quantity between the condition in which the children were receiving MPH and the condition in which they were receiving placebo.

### TABLE 1

Demographic and Clinical Characteristics of Children With ADHD Separated According to COMT Group Status

<table>
<thead>
<tr>
<th></th>
<th>Met-Met ($n = 9$)</th>
<th>Val Carriers ($n = 25$)</th>
<th>$\chi^2$</th>
<th>df</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, M/F</td>
<td>8/1</td>
<td>21/4</td>
<td>0.13</td>
<td>1</td>
<td>.72</td>
</tr>
<tr>
<td>Age, yr</td>
<td>9.7 (1.8)</td>
<td>9.3 (1.9)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IQ</td>
<td>96.89 (16.3)</td>
<td>98.5 (15.5)</td>
<td>$F_{1,32} = 0.45$</td>
<td>.51</td>
<td></td>
</tr>
<tr>
<td>CBCL (total score)</td>
<td>68.44 (9.13)</td>
<td>70.6 (10.12)</td>
<td>$F_{1,32} = 0.30$</td>
<td>.59</td>
<td></td>
</tr>
<tr>
<td>CBCL, Internalizing</td>
<td>63.22 (10.93)</td>
<td>63.28 (9.86)</td>
<td>$F_{1,32} = 0.55$</td>
<td>.99</td>
<td></td>
</tr>
<tr>
<td>CBCL, Externalizing</td>
<td>66.22 (9.9)</td>
<td>72.6 (10.81)</td>
<td>$F_{1,32} = 2.3$</td>
<td>.13</td>
<td></td>
</tr>
<tr>
<td>Conners-total</td>
<td>74.4 (7.8)</td>
<td>72.9 (13.4)</td>
<td>$F_{1,32} = 0.28$</td>
<td>.60</td>
<td></td>
</tr>
<tr>
<td>DISC-IV Inattention items</td>
<td>7.11 (1.69)</td>
<td>7.4 (1.66)</td>
<td>$F_{1,32} = 0.2$</td>
<td>.67</td>
<td></td>
</tr>
<tr>
<td>DISC-IV Hyperactivity items</td>
<td>6.44 (2.5)</td>
<td>6.7 (1.84)</td>
<td>$F_{1,32} = 0.09$</td>
<td>.78</td>
<td></td>
</tr>
<tr>
<td>DISC-IV total items</td>
<td>13.6 (3.32)</td>
<td>14.1 (2.63)</td>
<td>$F_{1,32} = 0.23$</td>
<td>.64</td>
<td></td>
</tr>
<tr>
<td>Inattentive subtype</td>
<td>1/9</td>
<td>2/25</td>
<td>$F_{1,32} = 0.35$</td>
<td>.60</td>
<td></td>
</tr>
<tr>
<td>Hyperactive-impulsive subtype</td>
<td>2/9</td>
<td>1/25</td>
<td>$F_{1,32} = 1.5$</td>
<td>.21</td>
<td></td>
</tr>
<tr>
<td>Combined subtype</td>
<td>6/9</td>
<td>21/25</td>
<td>$F_{1,32} = 0.73$</td>
<td>.40</td>
<td></td>
</tr>
<tr>
<td>Comorbid ODD</td>
<td>5/9</td>
<td>19/25</td>
<td>$\chi^2 = 1.33$, df = 1, $p = .25$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comorbid CD</td>
<td>3/9</td>
<td>11/25</td>
<td>$\chi^2 = 1.2$, df = 1, $p = .54$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comorbid major depression</td>
<td>1/9</td>
<td>3/25</td>
<td>$\chi^2 = 0.71$, df = 1, $p = .25$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comorbid generalized anxiety disorder</td>
<td>1/9</td>
<td>1/25</td>
<td>$\chi^2 = 1.33$, df = 1, $p = .25$</td>
<td></td>
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</tr>
</tbody>
</table>

Note: Values are mean (SD). COMT = catechol-O-methyltransferase; ADHD = attention-deficit/hyperactivity disorder; CBCL = Child Behavioral Checklist; DISC-IV = Diagnostic Interview Schedule for Children, Fourth Edition; ODD = oppositional defiant disorder; CD = conduct disorder; LD = learning disability.
and demonstrated that within the population of children with ADHD, there is a possible genetic link between ADHD and sleep continuity.

The study extended previous research in several ways: first, by using a double-blind, placebo-controlled, within-subject (crossover) design to assess sleep in children with ADHD of different COMT genotypes; second, by using objective methodology rather than parental report for the assessment of sleep by assessing sleep in the children’s natural home environment for 2 weeks; finally, by relying on a sample that was composed of children who met the diagnosis for ADHD.

Children with ADHD carrying the COMT high-activity allele (Val-Val or Val-Met genotypes) had poorer sleep continuity compared to those with the Met-Met genotype while they were taking MPH and placebo. These findings are consistent with those of recent studies that establish a connection between sleep and COMT in narcolepsy and Parkinson’s disease. ADHD, narcolepsy, and Parkinson’s disease share several clinical features, such as increased daytime sleepiness, subjective reports regarding disrupted sleep, perturbations in markers for dopamine transmission in striatal circuits, and favorable responses to dopaminomimetics (Rissling et al., 2004; Rye and Jankovic, 2002; Silber and Rye, 2001; Tolosa et al., 2004). These similarities between these disorders, combined with the findings of the present study, support the hypothesis that sleep disturbances in children with ADHD are related to the underlying pathophysiology of the disorder. Additional research assessing the association between arousal and sleep in children with ADHD of different COMT genotypes is warranted to further investigate the associations between sleep and ADHD.

Comparing Subjective Sleep Measures in the COMT Groups

No significant differences were found in the daily sleep logs.

Comparing Reported Sleep Problems in the COMT Group

In Table 3, we present the means and SDs of the reported sleep problems scale. The analyses of covariance that were conducted to determine differences between the COMT groups revealed a marginal effect on the item “does your child have trouble sleeping” (F\(_{1,29} = 3.08, p < .09\)). Children who were Val allele carriers tended to have more reported sleep problems compared with children with the Met-Met genotype.

DISCUSSION

This is the first published study that has compared sleep parameters assessed with actigraphy in children diagnosed with ADHD of different COMT genotypes

### TABLE 2
Means, SDs, and Rotated Factor Loadings for the Actigraphic Sleep Measures While Taking Placebo and Taking MPH

<table>
<thead>
<tr>
<th>Items</th>
<th>Placebo</th>
<th>MPH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Met-Met (n = 9)</td>
<td>Val Carriers (n = 25)</td>
</tr>
<tr>
<td>Sleep time (hr:min)</td>
<td>8:21 (0:23)</td>
<td>8:12 (0:49)</td>
</tr>
<tr>
<td>Wake time (hr:min)</td>
<td>1:10 (0:22)</td>
<td>1:28 (0:21)</td>
</tr>
<tr>
<td>Sleep efficiency (%)</td>
<td>84.26 (3.09)</td>
<td>80.13 (3.8)</td>
</tr>
<tr>
<td>Wake time, %</td>
<td>12.23 (3.53)</td>
<td>14.21 (4.28)</td>
</tr>
<tr>
<td>Motionless sleep time</td>
<td>492 (23)</td>
<td>487.5 (40)</td>
</tr>
<tr>
<td>Motionless sleep time, %</td>
<td>86.1 (3.5)</td>
<td>83.12 (3.25)</td>
</tr>
<tr>
<td>Movement and fragmentation index</td>
<td>27.58 (5.14)</td>
<td>31.55 (6.73)</td>
</tr>
</tbody>
</table>

Note: Values are mean (SD). All loadings >0.6 shown in bold. MPH = methylphenidate.
COMT has been associated with prefrontal cognition. For example, Egan et al. (2001) demonstrated that patients with schizophrenia, unaffected siblings, and controls with the Met allele (low activity) performed better on the Wisconsin Card Sorting Test, a neurocognitive test of prefrontal cognition. This effect was more prominent when an individual had two copies of the Met allele. These findings have subsequently been replicated in other studies (Blasi et al., 2005; Joober et al., 2002; Malhotra et al., 2002; Rosa et al., 2004). The findings of the present study suggest that children with two copies of the Met allele had better sleep continuity. It has been suggested that sleep is associated with better performance on complex neurobehavioral tasks (Durmer and Dinges, 2005; Sadeh et al., 2002). Based on the findings of the present study, we speculate that sleep and attention in ADHD may be related to overlapping neurochemical and structural abnormalities in the brain that may account for both.

Previous studies that used objective measures of sleep have yielded contradictory results with respect to the incidence of sleep problems in children with ADHD (Cohen-Zion and Ancoli-Israel, 2004; Corkum et al., 1999). A number of potential methodological issues in sleep research with ADHD may have contributed to these conflicting findings, including small sample sizes, inconsistent diagnostic criteria, lack of exclusion diagnostic criteria, inadequate control procedures, heterogeneity of sleep parameters, and difficulties with adaptation to the procedure required for going through assessment of sleep in a laboratory. Although these methodological shortcomings are relevant, we suggest that the inconsistency in the finding may also be related to the genotypes of the subjects, for example, their COMT allele risk status. Sleep is a complex phenotype that is regulated by many genes. Sleep continuity, as well as other aspects of sleep, may be determined by various genes. Further studies that examine sleep and genes in relation to ADHD, using both animal models and different genetic techniques (Dauvilliers et al., 2005), are needed to further elucidate the nature of sleep patterns in children with ADHD.

The differential impact of tonic and phasic dopamine on sleep is unknown. Rapid eye movement (REM) sleep was not evaluated in the present study. However, there is evidence that phasic dopamine release is associated with burst discharge of dopamine during REM sleep (Jones, 2003). According to the tonic-phasic dopamine perspective regarding COMT, the Val allele increases phasic dopamine transmissions (Bilder et al., 2004). Previous studies found alterations in REM sleep in nonmedicated children with ADHD (Kirov et al., 2004; O’Brien et al., 2003a,b; Picchietti et al., 1999). The findings of the present study that suggest that the Val allele was associated with poorer sleep, coupled with previous findings suggesting REM-related abnormalities in the sleep of children with ADHD, highlight the need for further examination of the relationship between the COMT polymorphism and REM sleep in children with ADHD by means of polysomnography.

The present findings indicating similar patterns of sleep when the children were taking MPH and taking a placebo concur with those of previous studies (e.g., O’Brien et al., 2003a,b). Children with ADHD carrying the COMT high-activity allele (Val-Val or Val-Met genotypes) had poorer sleep continuity compared with those with the Met-Met genotype while they were receiving MPH and while they were receiving a placebo. The absence of medication differences in sleep continuity may suggest either that the Val allele effect on sleep is not affected by MPH or that the medication effects had worn off by the time sleep was measured. Future studies using polysomnography are needed to further assess the impact of medication on sleep in children with ADHD of different COMT genotypes.

This is particularly important given recent concerns regarding the potential for chronic administration of MPH to have an impact on growth in children with ADHD (MTA Cooperative Group, 2004). Growth hormone secretion occurs in pulses throughout the day. The growth hormone release during sleep can amount to two thirds of the total growth hormone secreted in 24 hours in young males. Sleep deprivation tends to suppress growth hormone secretion, and large growth hormone releases occur during recovery sleep (Kimura and Tsai, 1984; Sassin et al., 1969; Takahashi et al., 1981). Therefore, further studies are needed to investigate whether dopaminergic effects on sleep have an impact on the secretion of growth hormone (during day or night) and as a result on the growth of children with ADHD.

The field of sleep genetics is only now emerging (Lavie, 2005) and faces major challenges because of the complexity of sleep behavior. Identifying simple, objective, and quantifiable behaviors that are amenable to genetic dissection is a critical step in the identification of the links between sleep and behavior in children with ADHD. The present study highlighted the utility...
of actigraphy-derived sleep measures as a phenotypic behavior in sleep studies of children with ADHD. Future studies using polysomnography are needed to investigate further the association between sleep, ADHD, and genetic features of the disorder.

Clinical Implications

Knowledge about presumed mechanisms of sleep in ADHD could direct investigations regarding candidate genes predicting the risk of sleep problems, as well as studies that will examine whether these polymorphisms predict response to sleep treatment or side effects associated with medication. Development of individualized sleep regimens based on patient genetic variability may lead to optimized symptom reduction. Future studies should emphasize large, prospective trials assessing the impact of intervention that target sleep in children with ADHD and consider patterns of genetic variation that will guide design of optimal individually tailored sleep treatment regimens as a supplement to other interventions.

Limitations and Future Research

A number of limitations of the study need to be addressed. First, because of the small number of patients, these results should be considered preliminary and require replication by future studies. Another limitation of the study is the lack of objective measures of daytime sleepiness or alertness (e.g., the Multiple Sleep Latency Test, the Maintenance of Wakefulness Test). Such measures could indicate whether hypoaousal during the day (e.g., increased daytime sleepiness or reduced vigilance) are associated with the COMT polymorphism in children with ADHD. The relationships among the COMT polymorphism, sleep, and arousal in children with ADHD of different COMT genotypes require additional research efforts.

Actigraphy allows the reliable, continuous recording of the child’s sleep in his or her home environment. Therefore, it is a valuable method for assessing sleep in children. However, it does not allow the sleep architecture to be recorded. Future studies would benefit from using both polysomnography and actigraphy to further investigate the association between sleep and ADHD in children of different COMT genotypes.

Finally, given that we have identified an association between sleep parameters and the COMT genotype in children with ADHD, we believe that exploring the effect of different treatment regimens (long acting, t.i.d. regimens of short acting) and higher doses of MPH on the sleep patterns of children of different COMT genotypes is warranted.

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