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Title: Sleep disturbances and behavior in Smith-Magenis syndrome

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Highlights

- *complaints of sleep problems are very frequent in SMS.
- *Sleep problems impact behavior and cognitive functions.
- *The relation of specific sleep disturbances and behavior problems is unclear in SMS .

Abstract

Background: The Smith–Magenis syndrome (SMS) shows a collection of neurodevelopmental problems including mild to moderate intellectual disability, change-related anxiety, impulsivity, speech delay, Attention-Deficit/Hyperactivity Disorder (ADH) and sleep disturbances. Sleep disorders, when present, have been treated in several populations with consecutive improvements in cognitive and behavioral aspects.

Aims: To better understand the existing relationships between sleep disturbances and behavioral problems in SMS syndrome this study describes the sleep and behavior problems in the SMS and explores the possible relation between both.

Methods and Procedures: 17 individuals with SMS (50% males; 11.2 ± 4.9 years old) and 12 individuals with typical development (50% male; 11.1 ± 4.4 years old) were investigated using the Sleep Disturbance Scale for Children and the Child Behavior Checklist.

Results: A high percentage (60%) of individuals with SMS have an indication of sleep disorders, being the most frequent disorders the sleep-wake transition disorders, and

disorders of initiating and maintaining sleep with sleep latency higher than acceptable and total sleep time below acceptable. More than 94% of the SMS group presented clinical or borderline scores on the total behavioral problems scale. The most common behavioral problems were Externalizing Problems, Thought and Attention, ADH and Aggressive problems. There was a positive correlation between disorders of initiating and maintaining sleep, sleep-wake transition disorders, disorders of arousal, disorders of excessive somnolence and behavioral problems.

Conclusions and Implications: The worse the sleep disturbances investigated, the more severe the behavioral problems characteristics reinforcing the importance to address the sleep problems in the treatment of SMS individuals.

Keywords: neurodevelopmental disorder, Sleep, Smith Magenis syndrome, behavior.

What this paper adds:

- *60% of individuals with SMS have indicative for sleep disorders
- *94% of the SMS group presented clinical or borderline scores for behavioral problems
- * Specific sleep disorders are related with specific behavior problems in SMS.
- * The worse the sleep disturbances, the more severe the behavioral problems in SMS.

Introduction

Smith–Magenis syndrome (SMS) is a complex neurodevelopmental disorder caused by an interstitial deletion of chromosome 17p11.2 including the retinoic acid-induced 1 (RAI1) gene (Slager et al., 2003; Vlangos et al., 2003; Elsea and Girirajan,

2008; Finucane et al., 2021). RAI1 is considered to be responsible for most of the clinical abnormalities presented in those diagnosed with SMS, such as physical appearance, sleep and behavioral disorders (Elsea and Girirajan, 2008; Finucane et al., 2021). Approximately 10% of cases may also be secondary to pathogenic variants in the RAI1 gene itself (Acquaviva et al., 2017).

The syndrome presents a prevalence of 1/15,000—25,000 births (Elsea and Girirajan, 2008; 2009) and is currently underdiagnosed. It shows a collection of problems that are present to a greater or lesser degree in the SMS population such as neurodevelopmental disorders, mild to moderate intellectual disability (Udwin et al, 2011; Garayzábal et al, 2011, 2021; Osorio et al, 2013), Attention-Deficit/Hyperactivity Disorder (ADHD), and several congenital problems such as scoliosis, ophthalmological problems and deafness, among others (Greenberg et al, 1996; Gropman et al., 1998; Udwin et al., 2001; Howlin & Udwin, 2002; Wolters et al., 2009; Garayzábal et al., 2011; Osório et al. 2012; Rive Le Gouard et al., 2021). Furthermore, sleep disturbances are very common symptoms of the SMS (Wilde et al., 2013; Angriman et al., 2015; Shayota & Elsea, 2019; Rive Le Gouard et al., 2021).

Specifically focused on sleep disturbances there is a high prevalence of severe sleep disorders associated mainly with an inverted circadian rhythm of melatonin (Boudreau et al., 2009) which, in turn, is thought to be a by-product of dysregulation of the RAI1 gene (Falco, Amabile, & Acquaviva, 2017). The variation of RAI1 alters the expression of many other genes such as CLOCK, PER2, PER3, CRY1 related to the regulation of circadian rhythms; or genes such as BDNF, related to obsessive behaviors (Burns et al., 2010; Nováková et al., 2012; Chen et al., 2015; Mullegama et al., 2015; Abad et al., 2018).

In addition, the individuals with SMS have a high prevalence of clinical health conditions including constipation, otitis media, gastrointestinal reflux and scoliosis (Dagli et al., 2017; Glassman et al., 2017; Osorio et al., 2013; Gropman, Duncan, & Smith, 2006) which have been linked to poor sleep in several conditions (Buie et al., 2010; Mannion et al., 2013; Trickett et al., 2018).

This picture of difficulties seems to indicate that in the SMS co-occur both behavioral and physical sleep problems that have great impact in their quantity and quality of sleep which lead to a significant disruption in the lives of patients and their families (Wolters, Gropman and Martin, 2009; Agriman et al., 2015; Trickett et al., 2018; Shayota and Elsea, 2019; Agar et al., 2020).

There is a specific behavioral phenotype that accounts for the SMS in which maladaptive behaviors are found to be good predictors of parental and familial problems (Hodapp et al., 1998 Fidler et al., 2000). These maladaptive behaviors can be summarized as attentional problems, hyperactivity, temper tantrums, impulsivity, aggressiveness, self-injurious behaviors, stereotypes, a high pain threshold and food-seeking behaviors (Greenberg et al., 1996; Bouras et al., 1998; Smith et al., 2001; Udwin et al, 2001; Howlin and Udwin, 2002; Elsea and Williams, 2011; Hildenbrand and Smith., 2012; Osorio et al, 2013; Garayzábal & Lens, 2014; Gnanavel, 2014; Shayota and Elsea, 2019). The self-injury described in SMS compared to other genetic syndromes with behavioral disorders appears very early, approximately at the age of two (Huisman et al., 2018).

These behavioral characteristics constitute important challenges to caregivers, and the search for possibilities of behavior improvement in this population is extremely important, considering the serious behavioral condition presented from adolescence onwards (Finucane and Haas-Givler, 2009). In several pathological conditions where it has been shown that there are correlations between sleep disturbances and behavior, the

identification and treatment of sleep disturbances leads to behavioral enhancement. This improvement has also been observed in the SMS population when sleep problems have been treated (De Leersnyder et al., 2001; De Leersnyder et al., 2003; Shayota and Elsea, 2019).

Osorio et al. (2013) and Garayzábal et al. (2011) assume there should be an important correlation between sleep disorders and disruptive behaviors due to lengthy and continuous night awakenings that result in sleepiness and lack of attention.

Moreover, in Garayzábal et al. (2011) it is even proposed that it would be a good idea to work with and evaluate these people early in the day, since as they become drowsier, their behavior becomes more aggressive and attention decreases considerably. This is further evidence that behavior and rest in the SMS population are closely related.

The information given above highlights the need to better understand the existing relationships between sleep disturbances and behavioral problems in SMS syndrome. Thus, the primary aim of the current study is to describe sleep and behavior problems in the SMS. A secondary aim is to correlate the behavioral data with sleep in this group.

The results of the present study would be further evidence that it is very important to address the sleep problems of people with SMS, because this has a significant impact on their behavior.

2. Methods

This cross-sectional clinical study was conducted in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans, and was approved by the local ethics committee. The study gathered 17 individuals with SMS (50% males; 11.2 ± 4.9 years old) with clinical and molecular cytogenetic SMS diagnostics by Fluorescence *in situ* hybridization (FISH). The control

group consisted of 12 individuals with typical development (TD) (50% male; 11.1 ± 4.4 years old).

2.2. Procedures

2.2.1. Sleep Disturbance Scale for Children (SDSC)

To identify individuals with SMS who had sleep problems, we used the SDSC, which contains 26 items, for the assessment of sleep in children and adolescents aged three to 18 years. Each item is scored from one (never) to five (always) according to its frequency in the last six weeks. Thus, higher numeric values reflect greater severity of clinical symptoms.

The SDSC contains six subscales: disorders of initiating and maintaining sleep-DIMS (including sleep duration, sleep latency, going to bed without being sleepy, difficulty sleeping, sleep without anxiety, and nocturnal awakenings), sleep-breathing disorders-SBD (including breathing difficulties, sleep apnea, and snoring), disorders of arousal-DA (including sleepwalking, sleep terrors, and nightmares), sleep-wake transition disorders-SWTD (including hypnic jerks, rhythmic movement disorders, hypnagogic hallucinations, nocturnal hyperkinesias, and bruxism), disorders of excessive somnolence-DES (including difficulty waking up, waking up tired, sleep paralysis and daytime sleepiness) and sleep hyperhidrosis-SHY (including sweating during sleep and perspiring during the night). The sum of the scores provides an overall score of sleep disturbance.

2.2.2. Child behavior inventory

The behavioral profiles of individuals with SMS were obtained from the “Child Behavior Checklist for ages six–18” (CBCL/6–18). This questionnaire is given as a direct

interview with parents and consists of 113 items that are related to behavior problems; the informant classifies the behavior as not true or absent (score = zero), partially or sometimes true (score = one), or very true or often true (score = two) over the last six months. The sum of scores allows the evaluator to draw a behavioral profile of the child or adolescent (internalizing problems or externalizing problems) that is derived from an analysis of eight groupings of items: anxious/depressed, attention problems, delinquent behavior, social problems, thought problems, withdrawn, somatic complaints and aggressive behavior.

The raw scores on each factor were transformed into T scores at three levels, representing unaffected to the most severely affected individuals with symptoms ranging from non-clinical to clinical, respectively. The score for the non-clinical category is ≤ 67 ; the score for the borderline category is 67–70, inclusive; the score for the clinical category is ≥ 70 . For internalizing and externalizing problems, this ratio should be ≤ 60 for the non-clinical category, from 60 to 63 for the neighboring category, and ≥ 63 for the clinical category.

3. Results

3.1. Sleep

About 60% of individuals with SMS had an indication of sleep disorders, the most frequent disorders were sleep-wake transition disorders (SWTD) and disorders of initiating and maintaining sleep (DIMS). Approximately 7% of the group of TD individuals had an indication of disorders of initiating and maintaining sleep.

About 35% of the group of individuals with SMS had sleep latency higher than acceptable (> 15 min) and 47% had total sleep time below than acceptable (< 7 hours).

While 21% of the group of TD individuals slept less than 7 hours. The group SMS showed higher mean scores than the group TD in all SDSC subscales (Figure 1).

3.2 Behavior

The results of the CBCL showed that more than 94% of the SMS group presented clinical (C) or borderline scores (B) on the total behavioral problems scale. The most common behavioral problems were Externalizing Problems (82.3% C), Thought problems (more than 70% C), ADH problems (70.59% C), and Aggressive behavior (64.7% C). Clinical scores for Affective and Anxiety problems were found in more than 50% and for Social and Internalizing problems in more than 40% (Table 1). The typical developmental group showed 8% of individuals with borderline scores for Anxiety, Affective and Internalizing problems.

When comparing the CBCL scores between the TD and SMS groups, higher scores were found for the SMS than for TD individuals in Anxious/depressed behavior, somatic complaints, social problems, thought problems, attention problems, rule-breaking behavior and aggressive behavior (Figure 2); Internalizing problems, externalizing problems and overall score of problems (Figure 3); affective problems, anxiety problems, somatic problems, attention problems, oppositional problems and conduct problems (Figure 4), Sluggish Cognitive Tempo, Obsessive-Compulsive Problems and Post-traumatic Stress Problem (Figure 5).

3.3. Correlation between sleep disturbances and behavior

The investigation of possible relationships between sleep disorders and behavior problems found in individuals with SMS showed that there was a positive correlation between disorders of initiating and maintaining sleep-DIMS and behavioral problems:

somatic complaints, social problems, thought problems, attention problems, rule-breaking behavior, aggressive behavior, internalizing problems, externalizing problems and total score of behavior problems (Figure 6), affective problems, anxiety problems, somatic problems, attention deficit/hyperactivity problems, oppositional defiant problems, conduct problems, Sluggish Cognitive Tempo and Post-traumatic Stress Problem (Figure 7).

The sleep-wake transition disorders-SWTD also showed positive correlation with behavior problems: social problems, thought problems, aggressive behavior, anxiety problems, oppositional defiant problems and conduct problems (Figure 8).

The disorders of arousal-DA showed positive correlation with behavior problems of anxious/depressed, somatic complaints, social problems, thought problems, attention problems, rule-breaking behavior, aggressive behavior, externalizing problems, total score of behavior problems, affective problems, anxiety problems, oppositional defiant problems, conduct problems, sluggish cognitive tempo, post-traumatic stress problem (Figure 9).

The disorders of excessive somnolence-DES showed positive correlation with behavior problems of somatic complaints, thought problems, attention problems, rule-breaking behavior, affective problems, somatic complaints, oppositional defiant problems, conduct problems, Sluggish Cognitive Tempo (Figure 10).

The overall score of sleep disturbance (TS) showed positive correlation with behavior problems of somatic complaints, social problems, thought problems, attention problems, rule-breaking behavior, aggressive behavior, internalizing problems, externalizing problems and overall score of behavior problems (Figure 11), affective

problems, anxiety problems, somatic complaints, attention problems, oppositional defiant problems, conduct problems, sluggish cognitive tempo, obsessive-compulsive problems and post-traumatic stress problems (Figure 12).

4. Discussion

After an extensive statistical analysis of the results, it is possible to take a closer look at the findings achieved.

The overall aim of this work is to better understand the existing relationships between sleep disturbances and behavioral problems in SMS syndrome. As described in the procedure section, the population samples consisted of an SMS group and a typically developing group. Their sleep and behavioral profiles were measured using the Sleep Disturbance Scale for Children (SDSC) and the Child Behavior Checklist (CBCL/6–18) in order to observe whether there is a correlation between the behavioral disorders of the SMS population and their sleep problems.

First, sleep disorders were present in 60% of the SMS group. More specifically, initiating and maintaining sleep (DIMS), and sleep-wake transition disorders (SWTD) disorders were prevalent. This result was expected since this population has several biological and behavioral characteristics which lead to a high incidence of sleep disorders (Boudreau et al., 2009; Spruyt et al., 2016; Nováková et al. 2012; Dagli et al., 2017; Glassman et al., 2017; Osorio et al., 2013; Gropman, Duncan, & Smith, 2006). Among these the most relevant would be the inverted pattern of the hormone melatonin, which peaks during the day and falls during the night (De Leersnyder et al., 2001; Potocki et al., 2000). In 2001, De Leersnyder and colleagues administered a beta-blocker early in the day for six months to nine cases with SMS. The aim was to avoid the melatonin peaks

that occur during the day in the SMS population in order to regulate their circadian rhythm. The results were evident before six months: daytime sleepiness decreased, hours of night-time rest increased and the number of weekly tantrums decreased considerably (De Leersnyder et al., 2001). This was one of the first pieces of evidence that improving the sleep pattern in the SMS population also enhances their behavior.

Secondly, in the present study 94% of the SMS group had behavioral problems. Above all, very high values were detected in the following items: externalizing problems, thought and attention, ADH problems, and aggressive behavior. In the comparison of the CBCL results, the differences between the SMS group and the TD group were statistically significant in almost all variables. Only "Withdrawn/depressed" CBCL variable showed no significant difference.

In general, if we take a look at figures 6–12, correlation between sleep and behavioral values show statistical significance. Sleep variables that seem to most influence the behavioral problems in the SMS group are disorders of initiating and maintaining sleep (DIMS), followed by disorders of arousal (DA), while behavioral problems in the SMS group more related to sleep disorders are: social problems, attention problems, aggressive behavior and oppositional defiant problems.

In greater detail, we can see that the value showing the highest correlation with the CBCL variables was DIMS – disorders of initiating and maintaining sleep (Figures 6 and 7). Specifically, the CBCL variable with the highest correlation with DIMS was "Attention problems", followed by the "Oppositional defiant problems", and "Affective problems" variables. The correlation detected between DIMS and the total score of the behavioral profile was significant.

Furthermore, statistical significance was found between disorders of arousal (DA) and 9 variables measured in the CBCL (Figure 9). There were also correlations between DA and "Anxiety problems" and "Social problems". Thus, the correlation between sleep disturbance scale (SDSC) total score and the variables measured with the CBCL was significant (Figures 11 and 12). "Conduct problems" and "Social problems" were remarkable. The correlation between total scores of SDSC and CBCL showed a significant result.

These behavioral problems have traditionally been identified in the behavioral profile of individuals with SMS (Udwin et al, 2001; Howlin and Udwin, 2002; Elsea and Williams, 2011; Hildenbrand and Smith., 2012; Osorio et al, 2013; Garayzábal & Lens, 2014; Gnanavel, 2014; Shayota and Elsea, 2019), and they may, in part, be related to neurocognitive impairment, environmental contingencies, change-related anxiety, level of impulsivity, speech delay and the degree of sleep disturbance (Sloneem et al., 2011; Poisson et al., 2015; Shayota and Elsea, 2019).

Sleep problems have been associated with poor attention abilities and emotional regulation problems (Dahl & Lewis, 2002; Gregory & Sadeh, 2012; Gruber, 2014); some studies have pointed out sleep problems in people with behavioral disorders such as attention deficit, hyperactivity and self-regulation problems (Carskadon et al, 2004; Aronen et al, 2014); also other studies have found that in preadolescence, sleep problems are closely related to anxiety problems (Dahl & Lewis, 2002; El-Sheikh, 2012; Hansen et al, 2013), which interestingly coincides with the observations of parents of children with SMS, who report that it is around the age of 8 and up to the age of 15 that sleep problems are most striking in their children (unofficial conversations).

After having observed the correlations between SDSC and CBCL, it could be argued that the characteristic behavioral phenotype of SMS may be partly due to sleep disorders in general and, particularly, to difficulties in initiating and maintaining sleep at night, as well as to arousal disorders. These findings are in line with previous studies evidencing the strong correlation between sleep quality and behavior (Dahl & Lewis, 2002; Carskadon et al, 2004; Gregory & Sadeh, 2012; El-Sheikh, 2012; Hansen et al, 2013; Aronen et al, 2014; Gruber, 2014). Likewise, the results seem to be in line with studies that focus on other dimensions of the syndrome, such as language or behavior, without taking sleep into account. These studies reinforce the idea that improving sleep would have a positive effect on them (De Leersnyder et al., 2001; De Leersnyder et al., 2003; Garayzábal et al., 2011; Osório et al., 2013; Shayota and Elsea, 2019).

In summary, a high percentage of individuals with SMS showed indication of sleep disorders with higher sleep latency and shorter sleep time period. The SMS group presented the clinical category in almost all behavioral problems explored in the CBCL. The most common behavioral problems were Externalizing Problems, Thought and Attention, ADH problems, and Aggressive behavior. The worse the sleep disturbances investigated, the more severe the behavioral characteristics reinforcing the importance to address the sleep problems in the treatment of SMS individuals.

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TABLE 1. Percentual (%) of individuals with SMS that showed Clinical (C) or Borderline Clinical (B) range in the “Child Behavior Checklist for ages six–18” (CBCL/6-18) parameters.

	Anxious/ depressed	Withdrawn/ depressed	Somatic complaints	Social problems	Thought problems	Attention problems	Rule- breaking behavior	Aggressive behavior	Internalizing problems	Externalizing problems
% C	5.88	5.88	29.41	41.18	70.59	52.94	-	64.71	41.18	82.35
% B	11.76	5.88	17.65	35.29	23.53	23.53	29.41	17.65	35.29	5.88
	Total problems	Affective problems	Anxiety problems	Somatic problems	ADH problems	Oppositional defiant problems	Conduct problems	Sluggish Cognitive Tempo	Obsessive- Compulsive Problems	Post- traumatic Stress Problems
% C	88.24	58.82	52.94	-	70.59	29.41	11.76	11.76	5.88	29.41
% B	5.88	17.65	23.53	17.65	11.76	29.41	47.06	29.41	17.65	23.53

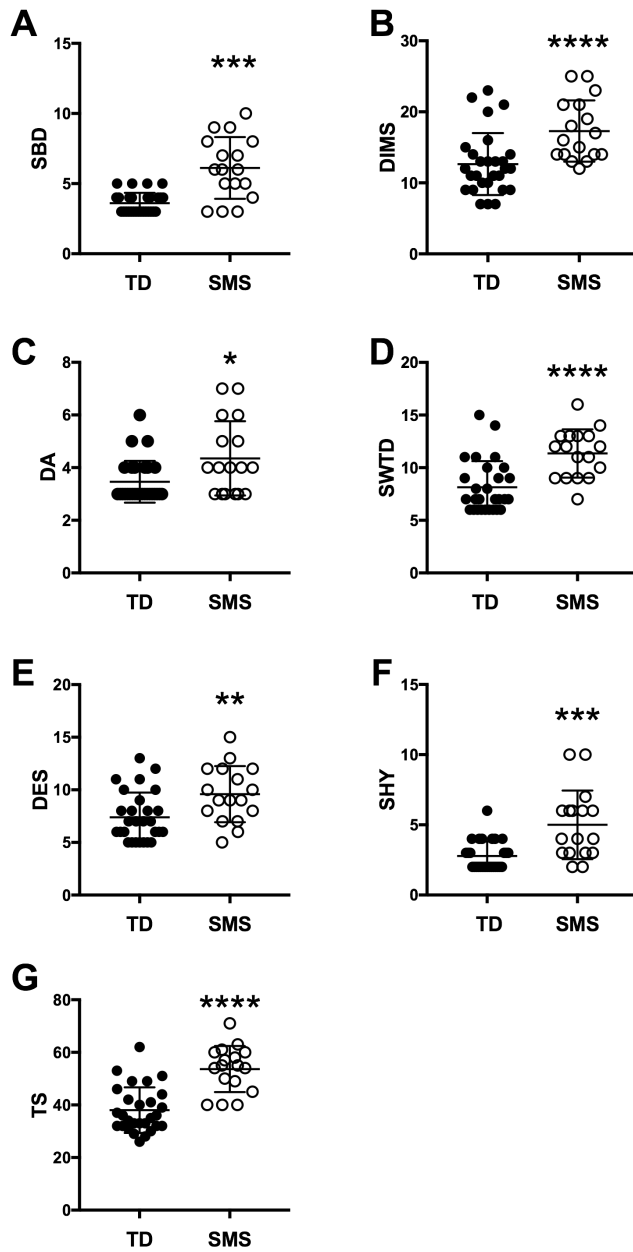


FIGURE 1. Scores of Sleep Disturbance Scale for Children, comparison between typical developmental (TD) and Smith Magenis Syndrome (SMS) individuals; SBD sleep-breathing disorders; DIMS- disorders of initiating and maintaining sleep; DA disorders of arousal; SWTD- sleep-wake transition disorders; DES- disorders of excessive somnolence; SHY- sleep hyperhidrosis; TS- overall score. * means $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; **** $p < 0.0001$.

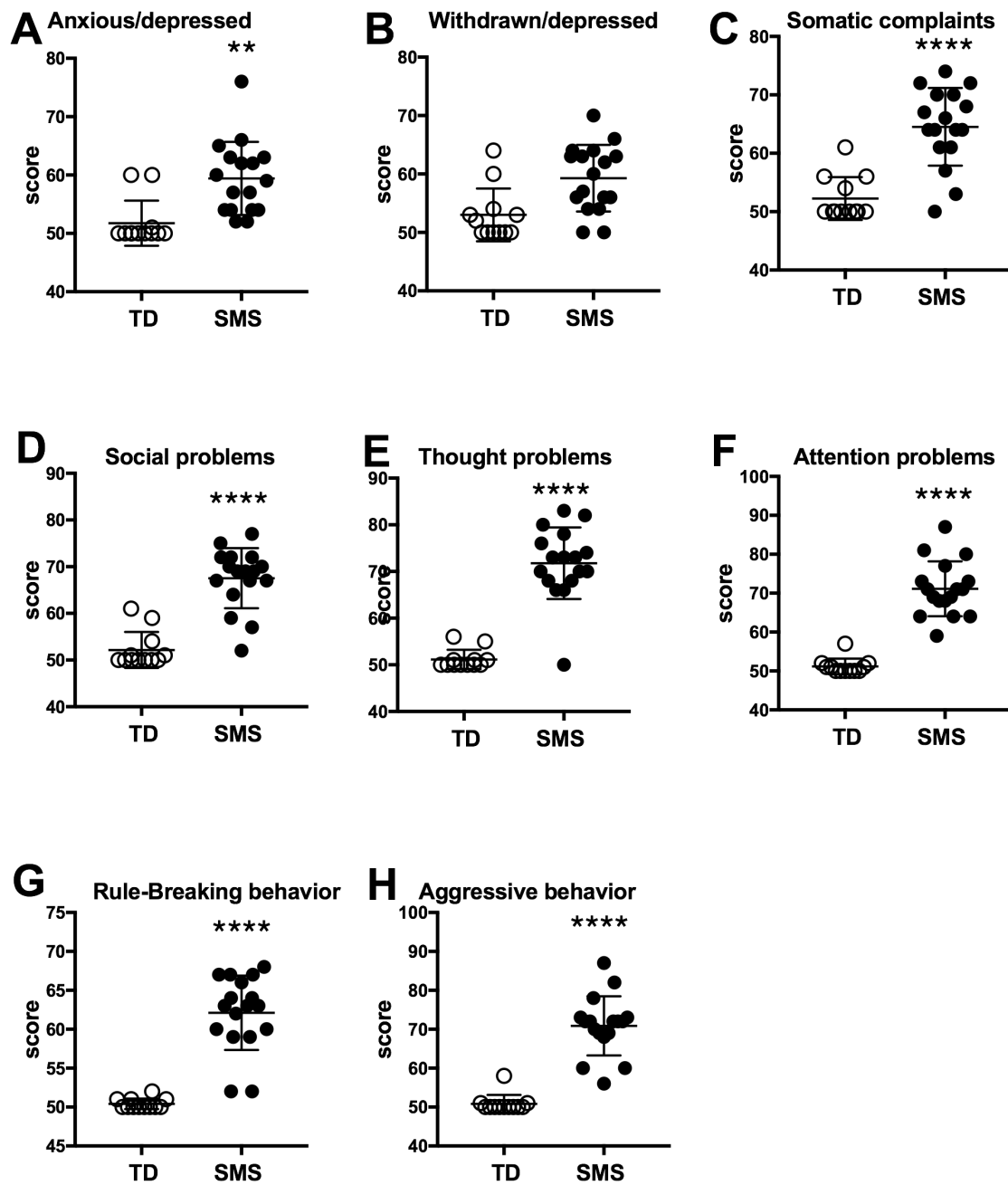


FIGURE 2. Scores of the Child behavior inventory, comparison between typical developmental (TD) and Smith Magenis Syndrome (SMS) individuals on behavior problems of anxious (A); withdrawn (B); somatic complaints (C); social problems (D); thought problems (E); attention problems (F); rule-breaking behavior (G); aggressive behavior (H); $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; **** $p < 0.0001$.

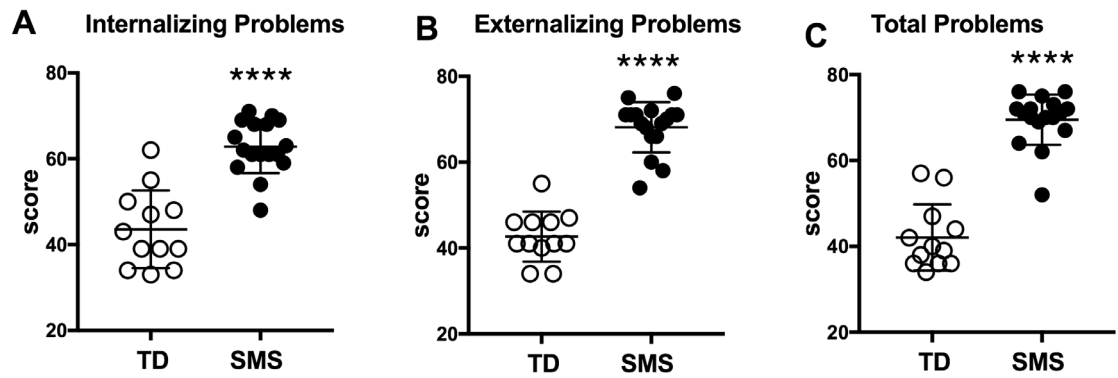


FIGURE 3. Scores of the Child behavior inventory, comparison between typical developmental (TD) and Smith Magenis Syndrome (SMS) individuals on behavior problems of internalizing problems (A); externalizing problems (B); overall score of behavior problems (total problems) (C). $p < 0.05$; $** p < 0.01$; $*** p < 0.001$; $**** p < 0.0001$.

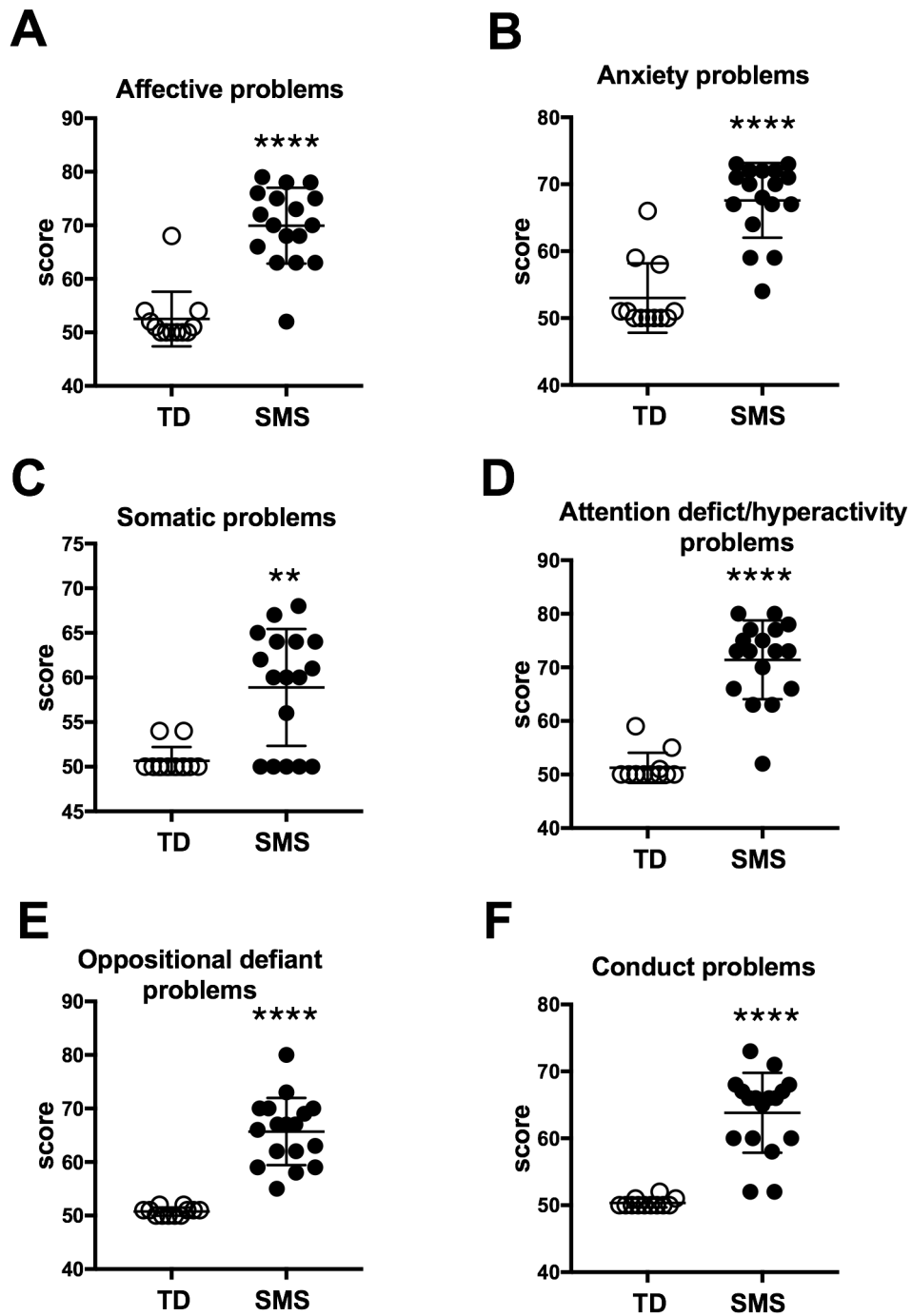


FIGURE 4. Scores of the Child behavior inventory, comparison between typical developmental (TD) and Smith Magenis Syndrome (SMS) individuals on behavior problems of affective problems (A); anxiety problems (B); somatic problems (C); attention problems (D); oppositional defiant problems (E); conduct problems (F). $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; **** $p < 0.0001$.

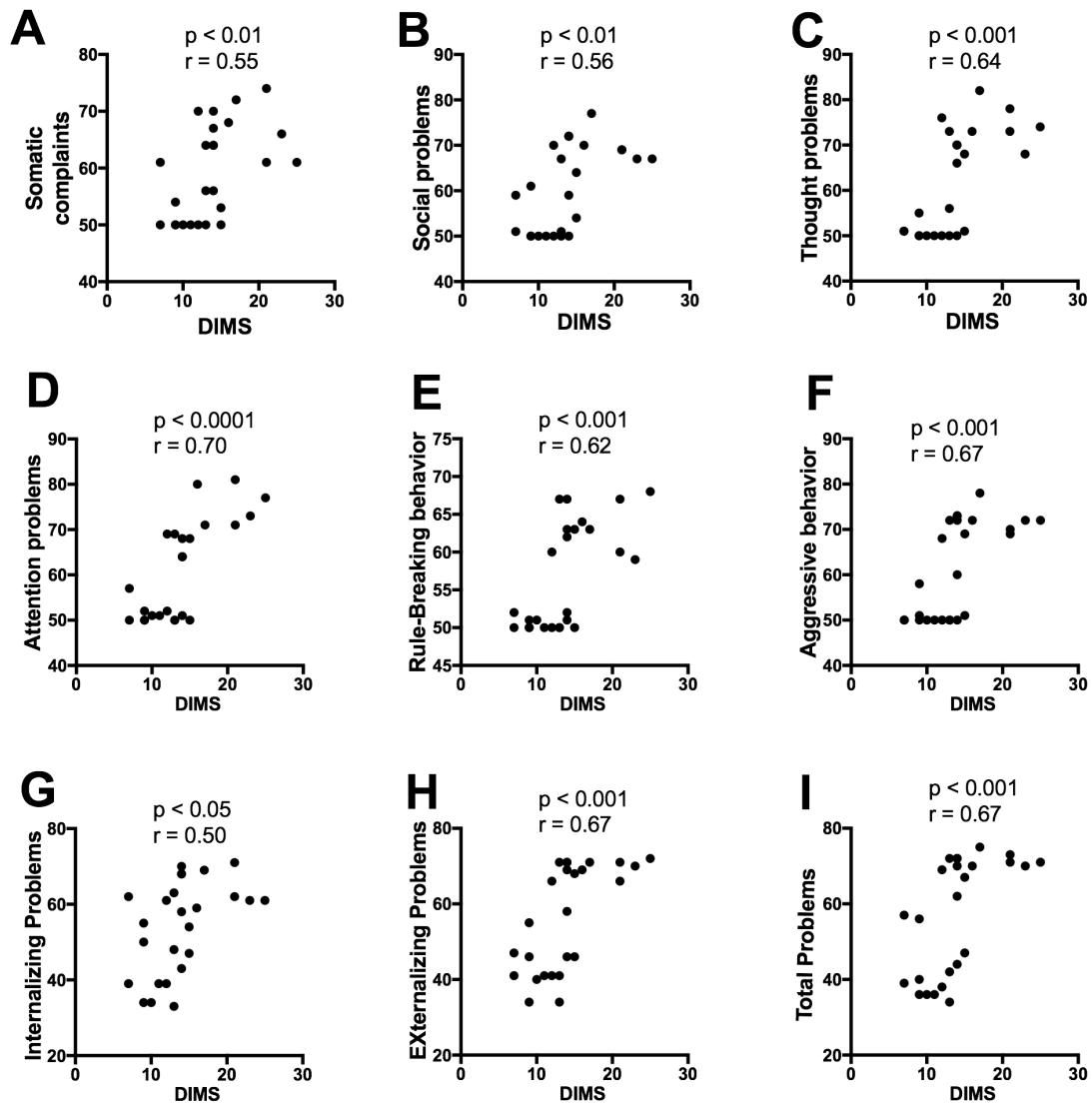


FIGURE 6. Correlation between the Scores of the disorders of initiating and maintaining sleep-DIMS and the Child behavior inventory on behavior problems of somatic complaints (A); social problems (B); thought problems (C); attention problems (D); rule-breaking behavior (E); aggressive behavior (F); internalizing problems (G); externalizing problems (H); overall score of behavior problems (total problems) (I).

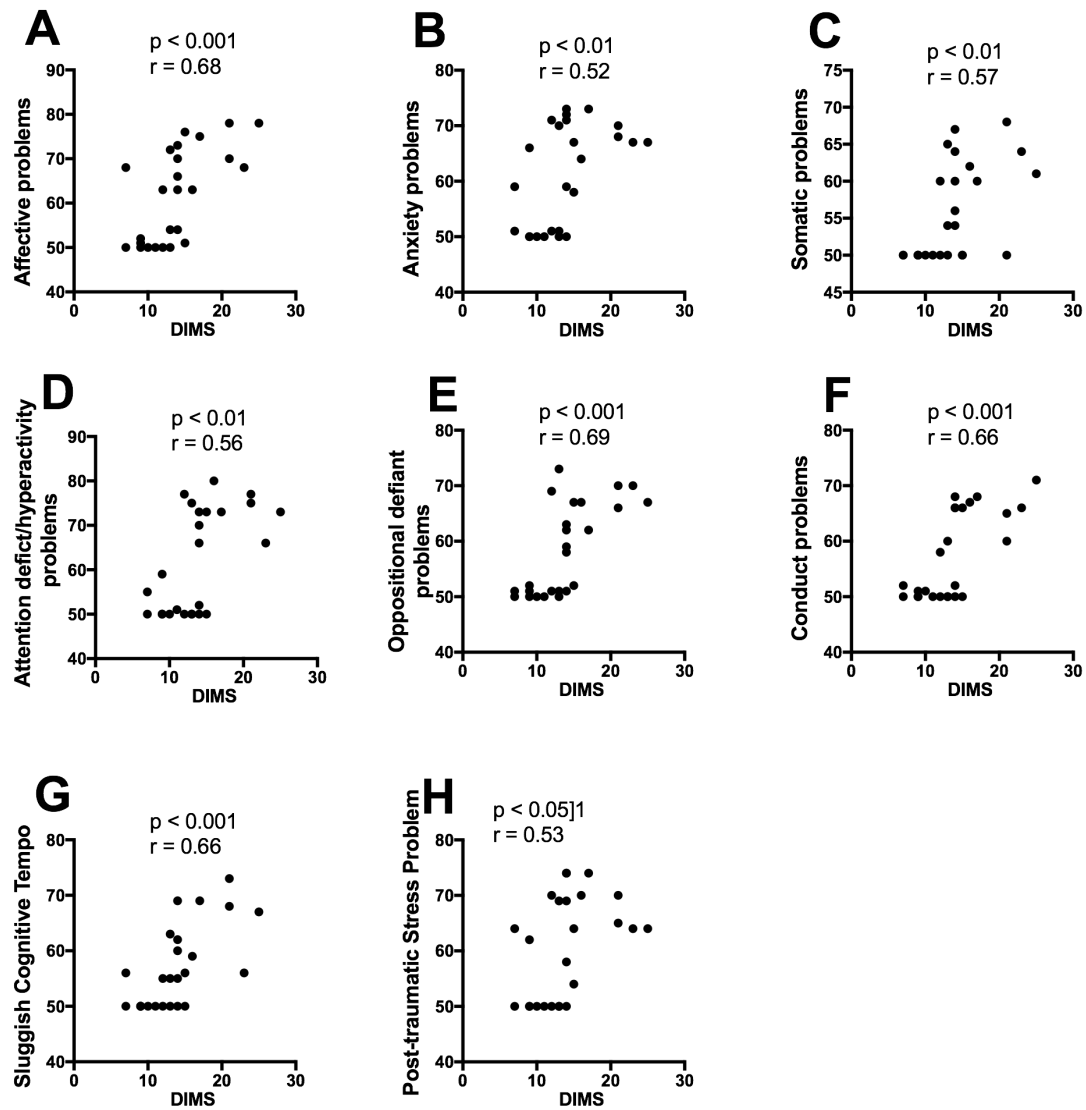


FIGURE 7. Correlation between the Scores of the disorders of initiating and maintaining sleep-DIMS and the Child behavior inventory on behavior problems of affective problems (A); anxiety problems (B); somatic problems (C); attention deficit/hyperactivity problems (D); oppositional defiant problems (E); conduct problems (F); sluggish cognitive tempo (G); post-traumatic stress problem (H).

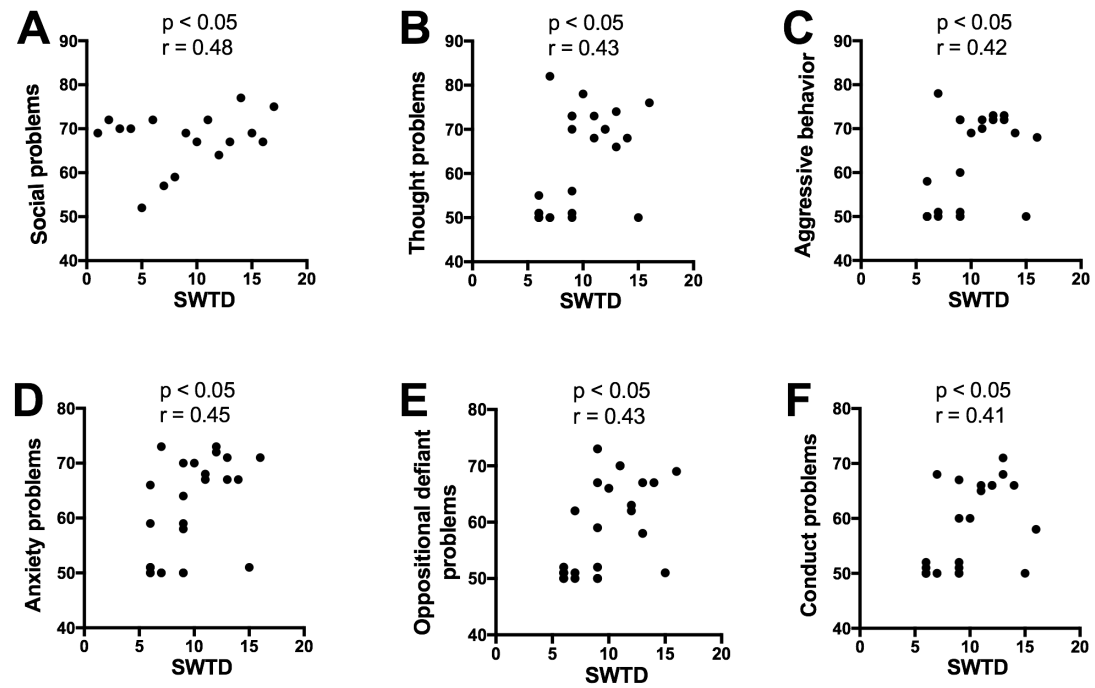


FIGURE 8. Correlation between the Scores of sleep-wake transition disorders-SWTD and the Child behavior inventory on behavior problems of social problems (A); thought problems (B); aggressive behavior (C); anxiety problems (D); oppositional defiant problems (E); conduct problems (F).

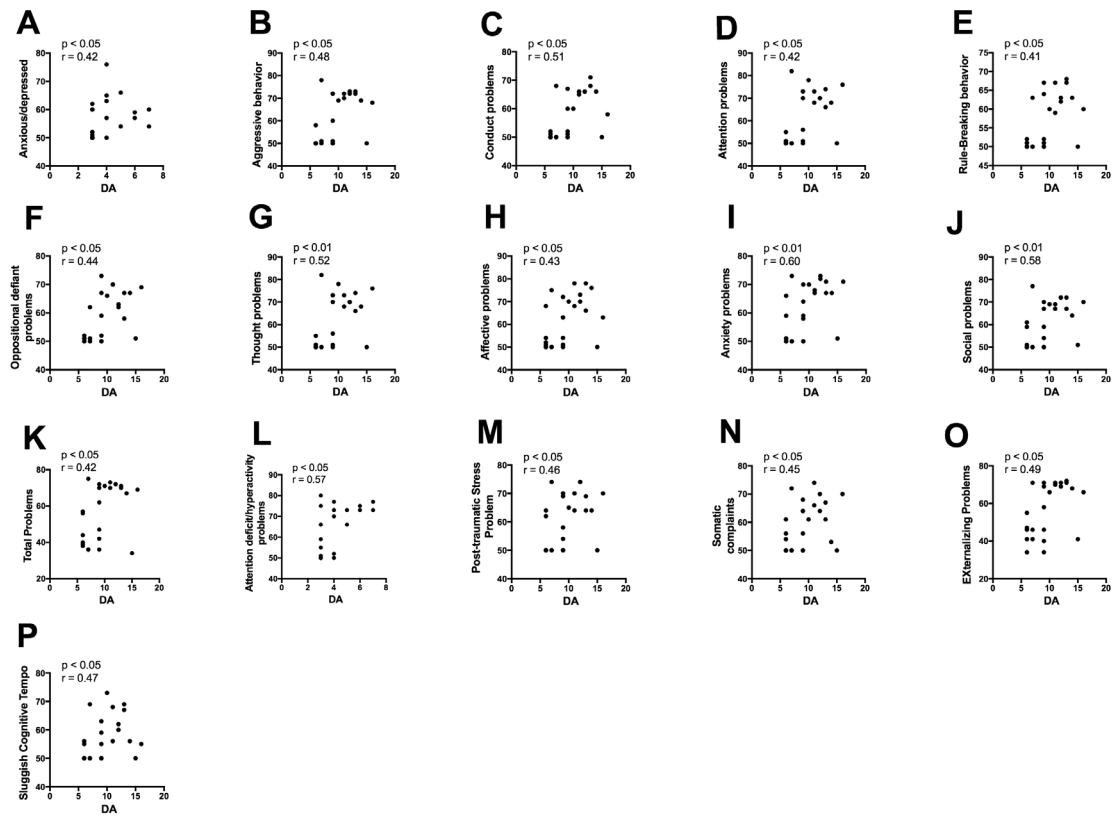


FIGURE 9. Correlation between the Scores of disorders of arousal-DA and the Child behavior inventory on behavior problems of anxious/depressed (A) somatic complaints (B); social problems (C); thought problems (D); attention problems (E); rule-breaking behavior (F); aggressive behavior (G); externalizing problems (H); total score of behavior problems (I), affective problems (J); anxiety problems (K); oppositional defiant problems (L); conduct problems (M); sluggish cognitive tempo (N); post-traumatic stress problem (O).

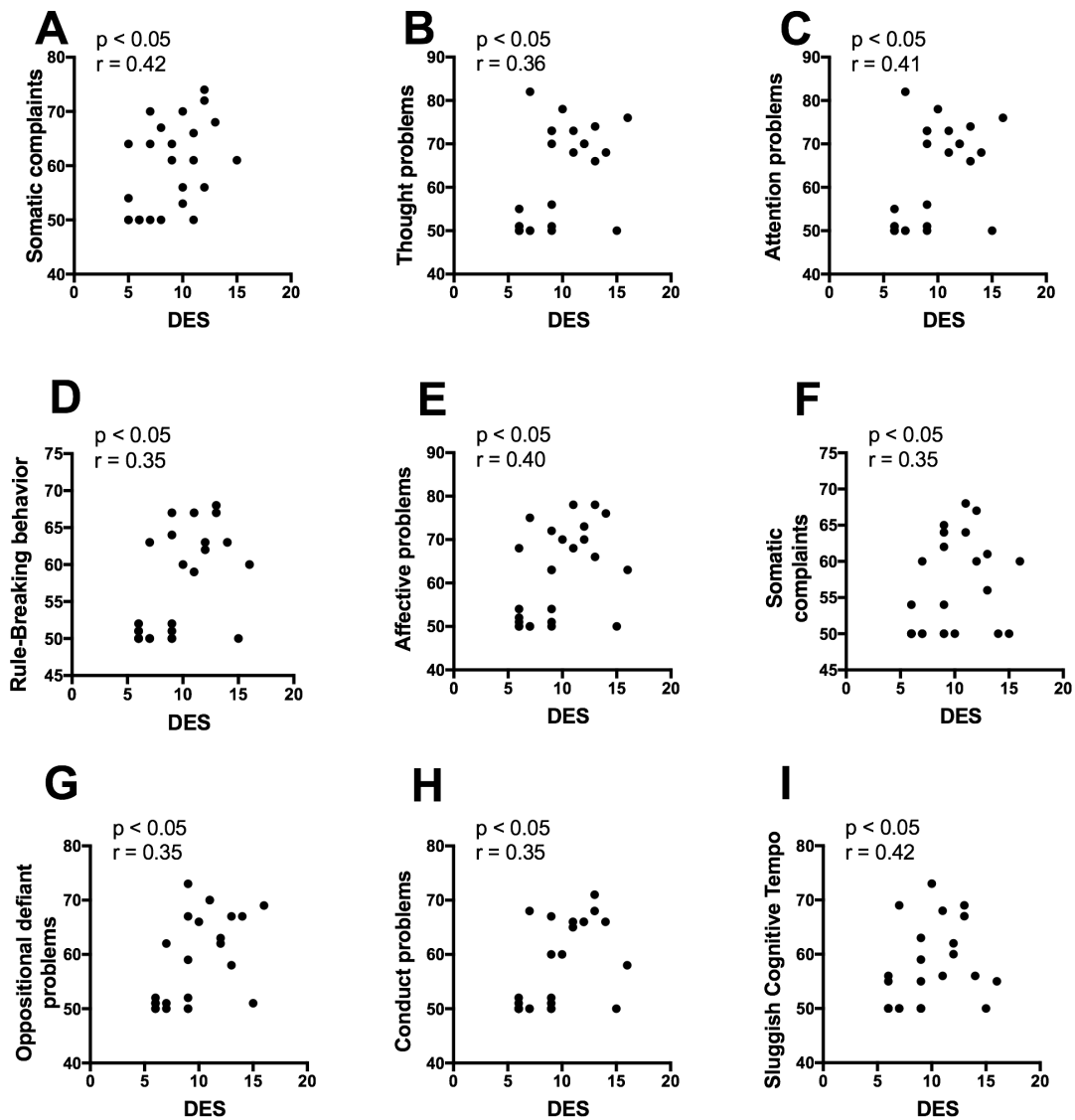


FIGURE 10. Correlation between the scores of disorders of excessive somnolence-DES and the Child behavior inventory on behavior problems of somatic complaints (A); thought problems (B); attention problems (C); rule-breaking behavior (D); affective problems (E); somatic complaints (F); oppositional defiant problems (G); conduct problems (H); sluggish cognitive tempo (I).

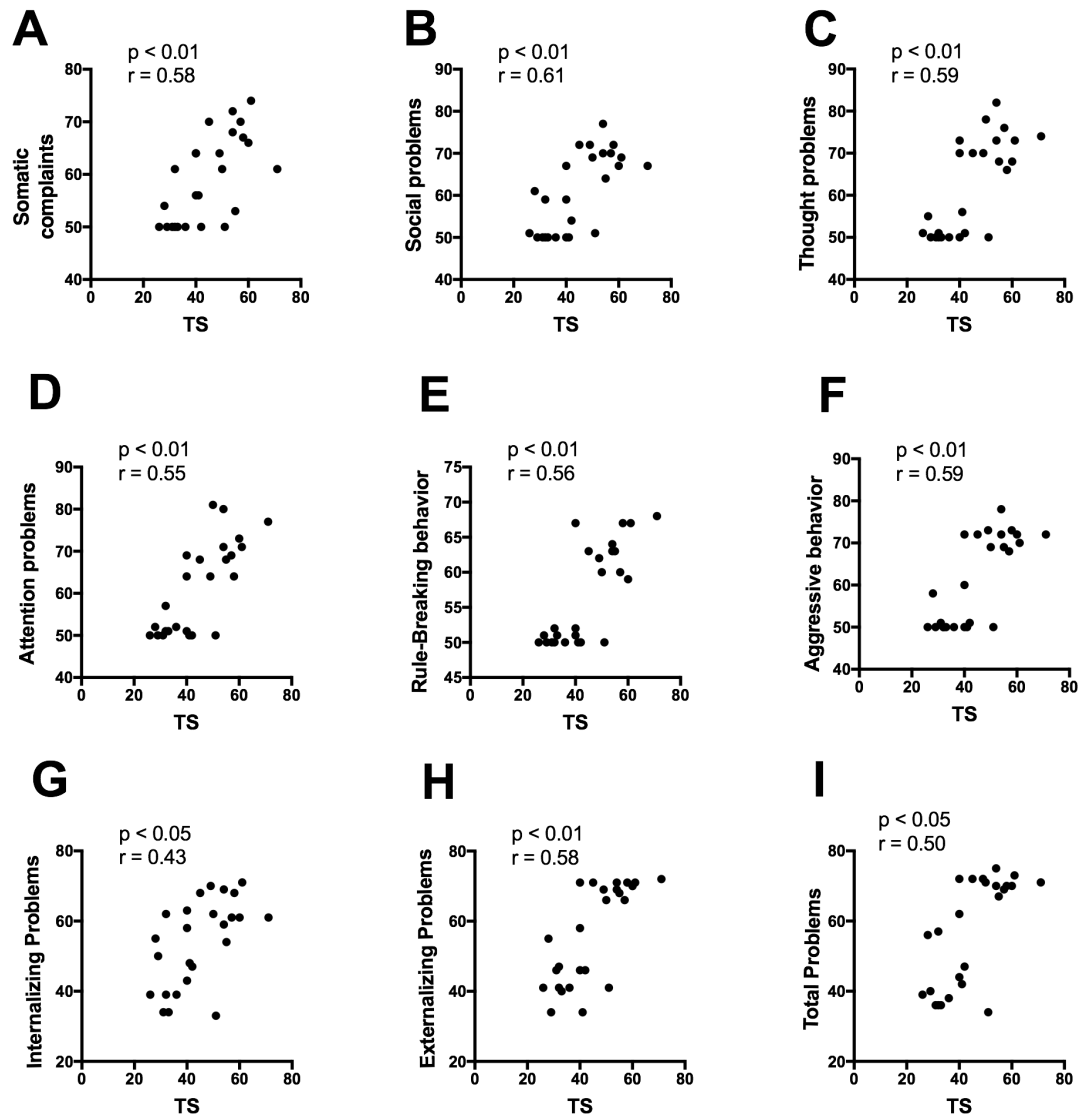


FIGURE 11. Correlation between the overall score of sleep disturbance (TS) and the Child behavior inventory on behavior problems of somatic complaints (A); social problems (B); thought problems (C); attention problems (D); rule-breaking behavior (E); aggressive behavior (F); internalizing problems (G); externalizing problems (H); overall score of behavior problems (total problems) (I).

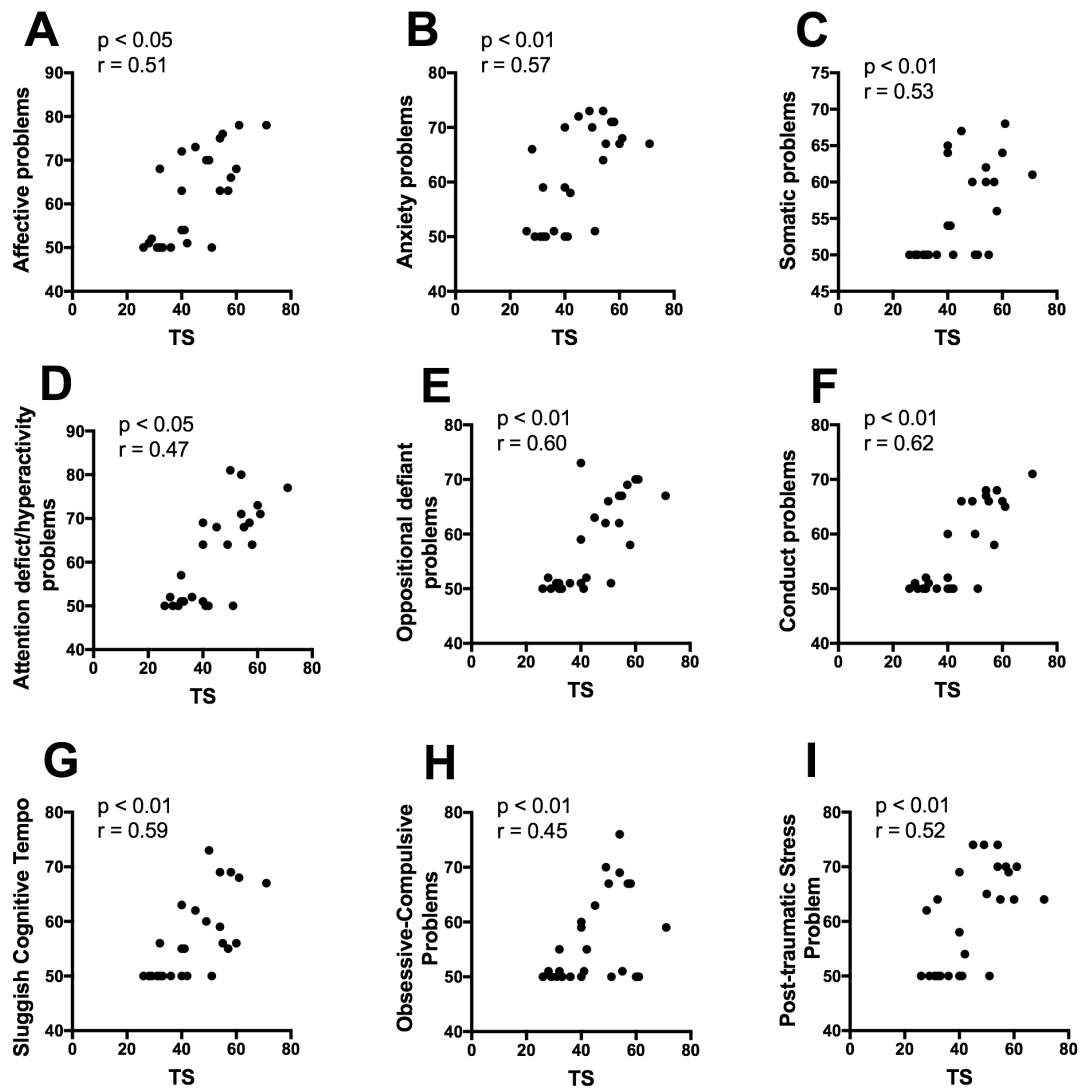


FIGURE 12. Correlation between the overall score of sleep disturbance (TS) and the Child behavior inventory on behavior problems of affective problems (A); anxiety problems (B); somatic complaints (C); attention problems (D); oppositional defiant problems (E); conduct problems (F); sluggish cognitive tempo (G); obsessive-compulsive problems (H); post-traumatic stress problem (I).