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Behavioral abnormalities and sleep problems in SATB2-associated syndrome.

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ABSTRACT

AIM: To determine the nature and frequency of behavioral abnormalities and sleep disturbances in individuals with SATB2-associated syndrome (SAS).

METHODS: The Strengths and Difficulties Questionnaire (SDQ) along with an age-appropriate sleep questionnaire were distributed to the parents of individuals with SAS. All scores were compared to available normative data.

RESULTS: Thirty-one individuals completed the assessment. Individuals with SAS had significantly higher Total Difficulty scores than the normative sample (14.9±5.8 vs 7.1±5.7, p<0.0001). A high frequency of emotional problems (22.6% vs 8%, p=0.01), peer problems (48.4% vs 10%, p<0.0001), hyperactivity (48.4% vs 9%, p<0.0001), and low prosocial behaviors (45.2% vs 9%, p<0.001) contribute to the behavioral profile in SAS. Concurrent sleeping difficulties were also frequently identified. Ten individuals (48%) in the 5 to 15 years of age range had at least one sleep disorder (mean Sleep Disorder Scale for Children total score =40.9±8.4 vs 35.1±7.7, p<0.001).

INTERPRETATION: With previous limited available objective neurobehavioral data in the SAS population, we provided evidence of high risk for a broad spectrum of burdensome behavioral abnormalities and concurrent sleeping difficulties, the latter being particularly prevalent during early childhood. Routine assessment and treatment for behavioral issues and sleep problems is recommended.

Short title: SATB2-associated syndrome behavior and sleep
WHAT THIS PAPER ADDS:

- SDQ Total Difficulty score was abnormal in 45% of individuals.
- Emotional and peer problems, hyperactivity, and low prosocial behavior are common in SAS.
- Behavioral difficulties are perceived as burdensome to over half of the parents.
- Nearly half of individuals have at least one sleep disorder.
- Sleep-wake transition disorders were most common.
SATB2-associated syndrome (SAS) is an autosomal dominant multisystemic disorder that results from alterations to the *SATB2* gene. The main features can be remembered using the SATB2 acronym: Severe speech anomalies; Abnormalities of the palate; Teeth anomalies; Behavioral issues with or without Bone or Brain anomalies, and age of onset before 2 years of age.\(^1\) The true prevalence of SAS is unknown; however, previous studies suggest that between 0.24-0.3% of patients who have intellectual disability or developmental delay are affected by this syndrome.\(^1,5\)

While behavioral problems have been described as one of the core features of SAS, little is known about the specific spectrum of abnormalities in this population.\(^2\) Overall, children have been described as having pleasant and happy dispositions but being at high risk for autistic tendencies, aggressive behavior, obsessions/compulsions, and hyperactivity.\(^4\) In children, behavioral difficulties are described as frequent tantrums, difficulties with transitions/changes, and meltdowns with poor tolerance for frustration while older individuals seem to be at higher risk of developing aggression towards themselves and others.\(^4\) Sleep disturbances with difficulties falling asleep or maintaining sleep have also been reported in several individuals.\(^2,4\)

The main aims of this study were to (1) characterize the spectrum and frequency of behavioral abnormalities, and (2) describe the nature of sleep disturbances, in individuals with SAS as compared with normative data.

**METHODS**

**Participants**

As part of a multidisciplinary international SAS clinic that took place in 2018, all individuals with confirmed diagnosis of SAS were evaluated by child and adolescent
Behavioral and sleep measures were collected during clinic visit time and available clinical data were abstracted from the medical records. Data was de-identified by assigning a research identification number to each participant. All families reported gave informed consent and were enrolled under a research clinical registry protocol approved by the Institutional Review Board of the University of Arkansas for Medical Sciences.

**Behavioral Measures**

To assess general psychosocial well-being and ongoing behavioral problems, the parents of each child were given the Strengths and Difficulties Questionnaire (SDQ) for ages 2-4 or 4-17 years. The SDQ is a brief dimensional measure of behavioral abnormalities among children that has been extensively validated in the clinical and research setting for both typically developing children, as well as young people with intellectual disability (ID). The SDQ contains 25 items that make up 5 scales of 5 items each: (i) the Emotional Problems scale, (ii) the Conduct Problems scale, (iii) the Hyperactivity/Inattention scale, (iv) the Peer Relationships scale, and (v) the Prosocial scale. As the prosocial items ask about the presence of prosocial behavior, high score on this sub-scale reflects strength, while high scores on the other four SDQ sub-scales represent increasing impairment which are summed to provide the Total Difficulty score.

The SDQ supplemental Impact subscale measures chronicity, distress, social impairment, and burden to others. A score greater than zero represents the total impact on functional capacity the reported difficulties have. For all SDQ scores, a four-band categorization model was applied: close to average, slightly raised (/slightly lowered),
high (/low) and very high (/very low). A SDQ score in the abnormal range was defined as those within either the high (/low) or very high (/very low) categories.

Scores on the SDQ were pro-rated per author scoring guidelines to account for missing values. Twenty-three values (2.97% of the total) were missing from a total of five subjects’ (16%) SDQs, none of which were from the Impact Scale. SDQ scores as collected from parents of individuals with SAS, were compared with parent-reported SDQ scores from a normative sample of 10,367 individuals aged 4 to 17 years old in the United States.6

**Sleep Disorder Measures**

The sleep questionnaire that each parent completed varied depending on the age of the child: the Children’s Sleep Wake Scale (CSWS) for children younger than 5 years of age, the Sleep Disturbances Scale for Children (SDSC) for children ages 5-15, and the Adolescent Sleep Wake Scale (ASWS) for those individuals over the age of 15.

The CSWS, is a 25-item parent/caregiver-report measure of behavioral sleep quality validated in children ages 2 to 8 years old.10 A 6-point Likert scale is used for rating and higher scores indicate better sleep quality. The CSWS provides 5 sub-scale scores and an overall sleep quality score. The SDSC is a 26-item rating scale developed to categorize sleep disorders that has been validated in children with disability, as well as healthy children ages 5-15 years.11-14 It is categorized into 6 subscales that are scored on a 5-point Likert scale with higher scores indicating more acute sleep disturbances.12 A table, based on normative data, converts the raw scores of the individual factors and the total scores into T-scores. A T-score of more than 70 (>95th percentile) was regarded as abnormal. The ASWS is the modified version of the CSWS validated for use in
adolescents between ages 12-18. This modified version, similar to the CSWS, measures overall sleep quality in 5 sub-scale domains as well as overall sleep quality. It is rated on a 6-point Likert scale as described above. Results of surveys assessing sleep disturbances (CSWS and SDSC) were compared to their respective published normative data.

**Statistical analysis**

Differences in mean scores for each of the SDQ items between individuals with SAS and the normative sample were assessed with two sample independent t-tests. Differences in the proportion of individuals with SAS scoring within the “abnormal” clinical range for each of the SDQ scores, compared with normative sample, were assessed with Fisher’s exact tests. All individuals with SAS were included in the comparison with the normative sample, as were subgroups of individuals with SAS by age (ages 2-4, and ages 5-17). Statistically significant differences were identified from p-values of <0.05.

**RESULTS**

Without further exclusion criteria, all individuals under age 18 who attended the clinic in July 2018 and had a diagnosis of SAS were included in the study (Figure 1). Baseline demographics and summary of SDQ and sleep scores are presented in Supplementary table 1. After excluding an individual that was older than 18 years, the final study cohort was made of 31 individuals from 30 families (a pair of monozygotic twins was included). Each subject presented with his or her parent(s), who participated in the evaluation and completed the assessments. Eighteen individuals (58%) were female and mean age was 7 years 3 months (SD=4.2) with ages ranging from 2 to 16 years. Different underlying
molecular mechanisms of disease were also represented, with 14 individuals (45.2%) having truncating variants.

**Strength and Difficulties Questionnaire Scores**

Based on SDQ authors’ recommended age ranges, charts were divided into ages 2-4 (n=8) and 5-17 years (n=23). Total and subscale scores for each individual by age are represented in Supplementary Figure 1 and summarized in Table 1.

For Emotional problems, Conduct problems, Hyperactivity/Inattention, and Peer Relationships, mean SDQ scores were significantly higher among individuals with SAS compared with normative data. Alternatively, Prosocial scores were significantly lower among individuals with SAS. Likewise, the frequency of individuals with abnormal screening results was higher for most SDQ measures (Table 1). These differences were seen regardless of age subgroup. Remarkably, the Total Difficulty score, a score that represents overall functional impairment, was abnormal in 45% of individuals compared with only 9% in the normative data (p<0.001).

Behavioral difficulties were also often perceived as a burden as reflected in the total Impact score, which differed significantly from the normative sample (58.1% v 8%, p<0.0001) (Table 1). Half of individuals (n=4) in the 2-4 age range and 56.5% (n=13) in the 5-17 age group scored in the very high range (Supplementary Figure 1). Overall, distress was noted by parents and this worsened with age. Across all age groups, 40.6% (n=13) of parents ranked overall distress as “a medium amount” and 15.6% (n=5) ranked it as “a great deal.” Across all age groups, 25.0% (n=8) had “a medium amount” of trouble at home and 28.1% (n=9) had this level of impairment at leisure, while 34.4%
(n=11) and 31.3% (n=10) described trouble among friends and in a learning environment, respectively.

**Sleep Disorder Scales**

Subjects were divided into three categories based on age, ages 2-4 (n=8), ages 5-15 (n=21), and ages 16-18 (n=2). Age normed sleep questionnaires were used for each of these groups.

*Children’s Sleep Wake Scale (CSWS) and Adolescent Sleep Wake Scale (ASWS)*

For the 2 individuals in the 16 to 18 years age group, no distinctive sleep abnormalities were identified (Supplementary Figure 2). On the other hand, compared with normative data, individuals in the 2 to 4 years age group had lower mean scores for falling asleep (FA, 3.6±0.9 vs 4.25±1, p=0.068), maintaining sleep (MS, 3.6±0.5 vs 4.6±1, p=0.0048), and retaining sleep (RS, 3.3±1.7 vs 4.14±1.2, p=0.05) (Supplementary Figure 2). No statistical differences in the total sleep quality score were observed.

**Sleep Disorder Scale for Children (SDSC)**

Total and subscale scores for each individual and by age group are represented in Figure 2 and Supplementary Figure 3, and summarized in Table 2. The mean SDSC total score and T-score for children aged 5-15 years (n=21) were 40.9 (±8.4) and 57.9 (±10.6), respectively. As a group, 3 individuals (14.3%) with SAS had an abnormal total sleep T-score (>70). Ten individuals (48%) had an abnormal score on at least one of the following SDSC factors: (1) DIMS, with T-scores ranging between 38 and 100 (mean 56.6±16.3), and 4 having abnormal scores (19.0%), (2) SBD, with T-scores ranging between 45 and 100 (mean 55.0±14.5), and 3 having abnormal scores (14.3%), (3) SWTD, with T-scores ranging between 41 and 100 (mean 67.3±15.5), and 8 having
abnormal scores (38.1%), and (4) SHY, with T-scores ranging between 45 and 75 (mean 49.3±8.8), and a single individual having abnormal scores (4.8%). No individuals had abnormalities in the DA or DOES subscales.

**SDSC results and age**

Most of the individuals with abnormal scores were noted to be younger in age. Sixty percent (9/15) of individuals 8 years or younger had an abnormal score on at least one of the SDSC factors compared with 16% (1/6) in the 9 to 15 years of age group. Higher mean scores for SBD (p=0.007) and DA (p=0.01) scores were also seen in the 5-8 year age group compared with their older counterparts (Table 2). Lastly, a higher total sleep score (43±8.7) was found in the younger age group but this did not reach statistical significance (p=0.07).

**DISCUSSION**

In this study we assess the frequency, spectrum, and impact of neurobehavioral and sleeping difficulties in the largest cohort of individuals with SAS, to date, using validated tools. Based on our findings, it is clear that children with SAS are at risk for behavioral and sleep difficulties.

The SDQ is one of the most widely used measures of behavioral and emotional problems in young people in both research and practice. Using this screening we documented that individuals with SAS had an overall high frequency of emotional problems (22.6%), peer problems (48.4%), hyperactivity (48.4%), and low prosocial behaviors (45.2%). High scores on the Emotional Problems subscale indicate a propensity towards depressive and anxiety symptoms. Similarly, high scores on the Peer Problems subscale indicate problems with social interactions in a peer group, and could
contribute to emotional distress. In fact, a high combined Emotional and Peer Problems score can be a proxy for “Internalizing” problems, which essentially means the reaction to stressors is directed towards the self rather than outwardly expressed. In this cohort of children who have communication difficulty at baseline, this is particularly concerning. In contrast, a high combined score on the Hyperactivity/Inattention and Conduct Problems subscales can be classified as having “Externalizing” problems, which is characterized by reacting to stressors in the external world with acting out, aggression, and anti-social behaviors.

The SDQ Total Difficulty score, a score that represents overall functional impairment, was abnormal in 45% of individuals with SAS. These difficulties were also often perceived as burdensome to parents as reflected by the abnormal Impact score in 58% of the study population. Of note, only parents of children (5-17 years) ranked distress as “a great deal” suggesting that young children (<5 years) lack awareness of their impairment and that older children struggle more given the greater social and academic demands placed on them. In SAS, the high impact score reflects the chronicity of behavioral symptomatology and the high level of distress, social impairment, and burden to parents.

Children with neurodevelopmental disorders experience sleep problems at higher rates than the general population with prevalence estimates range from 13% to 86%. With the use of validated screening tools, our results confirm that sleep disorders represent a common problem in a sample of individuals with SAS. In this study, we found that nearly half of individuals in the 5 to 15 years of age range had at least one sleep disorder. The sleep disorders reported in our sample were disorders in initiating and
maintaining sleep (19%), sleep breathing disorders (14.3%), sleep-wake transition disorders (38.1%), and hyperhidrosis (4.8%). The relatively high frequency of sleep-wake transition disorders in this population could be related to increased prevalence of bruxism and abnormal electroencephalographic abnormalities during sleep that could lead to perceived body jerking while falling asleep and frequent twitching while asleep. Given the limited amount of patients in this data set, we were unable to provide correlation with seizure activity or other comorbidities.

Our results also indicate that sleeping difficulties tend to be influenced by age, with younger individuals having more problems. In the 2 to 4 years age group, children were documented to have lower mean scores for falling asleep, maintaining sleep, and retaining sleep scores compared to normative data. The trend for sleeping difficulties continues in the 5 to 8 years of age category with 60% of individuals scoring abnormal for at least one of the SDSC factors. Finally, sleeping anomalies seem to become milder or less perceptible after 9 years of age. If this apparent improvement is the result of true developmental maturation of the brain or not, remains unclear.

There are several limitations to this study. First, the SDQ and the sleep scales used are primarily intended to assess mental well-being and sleep related disorders but they do not provide an accurate clinical diagnosis. SDQ provides a general ideal of the behavioral difficulties in children, and other scales like the Child Behavioral Checklist (CBCL, Achenbach) may be useful to identify more specific problematic behaviors in future research. Also, to assess sleep difficulties, we had to use different sleep measures validated for different age ranges, which made it difficult to compare and interpret scores across ages. The behavioral and sleep measures utilized in this study provide only a
snapshot of symptoms and difficulties in this population. Second, the data generated is dependent on the use of parental questionnaires for the behavioral screening and assessing sleep characteristics as provided by the families that were able to attend the dedicated SAS clinic. Families were invited to attend the clinic through social medial and support group advertisement. While the influence of psychosocial or cultural differences was not actively measured, families attending the clinic were not preselected based on affordability of services, medical coverage, country of origin, or socioeconomic status. Third, the effect of concurrent medications and co-existing medical conditions was not conducted given the limited sample size. However, this can be explored in future studies as some of these medications can have an impact on behavior and sleep regulation. Fourth, published normative data was used for comparison rather than own control population. Lastly, while this study includes a relatively large cohort of individuals with a very rare condition, direct inferences and generalization of these findings should made with caution. Despite these limitations, our results provide a more detailed outline about the behavioral and sleep problems in SAS.

Given the high frequency and impact of behavioral and sleep problems in this population, we recommend to specifically screen for sleep problems and consider a referral to a mental health specialist or developmental pediatrician to assess and manage comorbid neurobehavioral disturbances. In the presence of sleeping difficulties, consideration for overnight electroencephalographic evaluation should take place. If sleep problems are mild to moderate, we generally recommend starting with low dose melatonin supplement and titrating the dose upwards for symptom control. Alpha-agonist medications like guanfacine or clonidine can be helpful for both sleep initiation problems
and daytime hyperactivity. Other medications that can be considered for sleep disturbance include the antidepressant trazodone in lower doses or the antiepileptic medication gabapentin. A behavior management plan including the use of evidence-based treatment for autism (eg. Applied Behavioral Analysis) may be considered for aggressive behaviors. When diagnosis is uncertain, a psychological evaluation may be considered to rule out underlying or comorbid mental health issues. Although some medications do not have a good evidence base for use in behavioral problems, certain medications including aripiprazole and risperidone are approved by the US Food and Drug Administration (FDA) for severe irritability associated with autism. Other medication options may help with the comorbidity associated with behaviors, and may require treatment with an antidepressant, a stimulant, or a mood stabilizer. While several individuals with SAS have been on some of these medications to manage behaviors⁴, a certain level of provider experience and caution is needed. Of importance, family therapy should be considered as an option to deal with caregiver burnout, or conflict with sibling behaviors. Lastly, children with SAS may be able to function in the school setting with appropriate educational evaluation as well as testing for speech, occupational, and physical disorders interfering with learning. Parents may work with teachers and school administration to develop an individualized educational plan (IEP) which outlines goals and objectives related both to academics and to indicated therapies, appropriate to the child’s level of functioning. With a larger sample, future research can look at several other unanswered questions such as the variability of behavioral phenotypes according to genotype, relationship between treatment of possible nocturnal seizures and sleep, and the overall influence of sleep issues on other spheres of functioning such as, behavior and learning.
REFERENCES


16 Stone LL, Otten R, Engels RC, Vermulst AA, Janssens JM. Psychometric properties of the parent and teacher versions of the strengths and difficulties


### Table 1. Parent report of Strengths and Difficulties Questionnaire (SDQ) subscales by age group and overall compared with normative data

<table>
<thead>
<tr>
<th>SUBSCALE</th>
<th>2-4 age range (n=8)</th>
<th>5-17 age range (n=23)</th>
<th>All SAS (n=31)</th>
<th>Normative sample (n=10367)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean score (SD)</td>
<td>p-value^a</td>
<td>Abnormal (p-value^b)</td>
<td>Mean score (SD)</td>
</tr>
<tr>
<td>Emotional Problems</td>
<td>2.6 (1.4)</td>
<td>0.116</td>
<td>25.0% (0.130)</td>
<td>2.7 (2)</td>
</tr>
<tr>
<td>Conduct problems</td>
<td>1.8 (0.7)</td>
<td>0.0836</td>
<td>0.0% (1)</td>
<td>2 (1.4)</td>
</tr>
<tr>
<td>Hyperactivity Peer Problems</td>
<td>(2.3) &lt;0.0001</td>
<td>50.0% (0.003)</td>
<td>(2.7) &lt;0.0001</td>
<td>(2.7) &lt;0.0001</td>
</tr>
<tr>
<td>Conduct problems</td>
<td>(2.5) &lt;0.0001</td>
<td>37.5% (0.016)</td>
<td>(2.1) 0.059</td>
<td>(2.4) &lt;0.0001</td>
</tr>
<tr>
<td>Impact score</td>
<td>2.5 (5.8)</td>
<td>0.0001</td>
<td>40.0% (0.003)</td>
<td>2.5 (5.8)</td>
</tr>
</tbody>
</table>

All p-values generated when compared with normative data by either ^a t-test, accounting for equality in variance or ^b Fisher's Exact test.
Table 2. Sleep Disturbance Scale for Children (SDSC) by age group compared with normative data

<table>
<thead>
<tr>
<th>SUBSCALE</th>
<th>5 to 8 years (n=15) p-value versus 8-15</th>
<th>8-15 years (n=6) p-value versus normative</th>
<th>Total (n=21) p-value versus normative</th>
<th>Normative sample (n=1157) Mean score</th>
</tr>
</thead>
<tbody>
<tr>
<td>DIMS score</td>
<td>Mean score 12.9 (5.9) p-value 0.203</td>
<td>Mean score 9.5 (3.3) p-value 0.069</td>
<td>Mean score 11.9 (5.4) p-value 0.106</td>
<td>Mean score 9.9 (3.1)</td>
</tr>
<tr>
<td>SBD score</td>
<td>Mean score 5.1 (2.3) p-value 0.007</td>
<td>Mean score 3.2 (0.4) p-value 0.047</td>
<td>Mean score 4.5 (2.1) p-value 0.14</td>
<td>Mean score 3.8 (1.5)</td>
</tr>
<tr>
<td>DA score</td>
<td>Mean score 3.5 (0.7) p-value 0.015</td>
<td>Mean score 3 (0.0) p-value &lt;0.0001</td>
<td>Mean score 3.4 (0.7) p-value 0.570</td>
<td>Mean score 3.3 (0.8)</td>
</tr>
<tr>
<td>SWTD score</td>
<td>Mean score 12.5 (4.2) p-value 0.671</td>
<td>Mean score 11.7 (2.6) p-value 0.0003</td>
<td>Mean score 12.3 (3.8) p-value &lt;0.0001</td>
<td>Mean score 8.1 (2.4)</td>
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<tr>
<td>DOES score</td>
<td>Mean score 6.5 (1.7) p-value 0.360</td>
<td>Mean score 5.8 (1.0) p-value 0.026</td>
<td>Mean score 6.3 (1.6) p-value 0.036</td>
<td>Mean score 7.1 (2.6)</td>
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<tr>
<td>SHY score</td>
<td>Mean score 2.8 (1.6) p-value 0.685</td>
<td>Mean score 2.5 (1.2) p-value 0.565</td>
<td>Mean score 2.7 (1.5) p-value 0.592</td>
<td>Mean score 2.9 (1.7)</td>
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<tr>
<td>Total sleep score</td>
<td>Mean score 43.0 (8.7) p-value 0.069</td>
<td>Mean score 35.7 (4.7) p-value &lt;0.0001</td>
<td>Mean score 40.9 (8.4) p-value 0.0006</td>
<td>Mean score 35.1 (7.7)</td>
</tr>
</tbody>
</table>

All p-values generated when compared with normative data by t-test.
DIMS, disorders of initiating or maintaining sleep; SBD, sleep breathing disorders; DA, disorders of arousal; SWTD, sleep–wake transition disorders; DOES, disorders of excessive somnolence; SHY, sleep hyperhidrosis;
FIGURE LEGENDS

Figure 1: Individuals with SAS are often described as jovial. Left: SATB2-026, Middle: SATB2-060, Right: SATB2-085.

Figure 2: Percentage of children with abnormal Sleep Disturbance Scale for Children (SDSC) scores by age groups. DIMS, disorders of initiating or maintaining sleep; SBD, sleep breathing disorders; SWTD, sleep–wake transition disorders; SHY, sleep hyperhidrosis.
**Supplementary Table 1.** Baseline demographic and clinical data for 31 individuals with SATB2-associated syndrome. Abnormal SDQ and sleep scores scales are also presented.

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Molecular SATB2 alteration</th>
<th>Age (years)</th>
<th>Gender</th>
<th>ADHD</th>
<th>Autism</th>
<th>Seizures</th>
<th>Sleep Aid</th>
<th>Other medications</th>
<th>SDQ abnormally scaled</th>
<th>SDSC abnormally subscaled</th>
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<td>SATB2-089</td>
<td>Nonsense</td>
<td>2</td>
<td>F</td>
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<td></td>
<td></td>
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<td>SATB2-132</td>
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+, feature present
-, feature not present
?, unknown

CP, conduct problems; EP, emotional problems; F, female; Hyp, hyperactivity; IS, impact score; M, male; N/A, not applicable; PP, peer problems; PS, prosocial; TD, total difficulties