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The behavioural profile of SYNGAP1-related Intellectual Disability

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The behavioural profile of SYNGAP1-related Intellectual Disability

Abstract

This study aimed to describe the behavioural profile of individuals with SYNGAP1-ID.

Parents/carers of 30 individuals aged 3-18 years old with a diagnosis of SYNGAP1-ID and 21 typically-developing individuals completed the Vineland-3 Adaptive Behaviour Scale and the Child Behavior Checklist.

We found that those with SYNGAP1-ID showed fewer adaptive behaviours and higher levels of internalising and externalising behaviours across almost all domains compared to typically developing controls. There was some evidence that these differences were greatest in older children, and more apparent in those with co-occuring epilepsy.

This characterisation of the phenotype of SYNGAP1-ID significantly aids our understanding of the behavioural profile of this population and is a step towards the development of tailored interventions.

Keywords: SYNGAP1-related ID; Adaptive; Maladaptive; Intellectual Disability; Behavioural phenotype; Autism

Introduction

Intellectual disability (ID) is a heterogenous neurodevelopmental disorder characterised by global cognitive impairment (specifically an IQ < 70) and impairments in adaptive functioning. It is increasingly recognised that an important genetic cause of ID is pathological variation of the *SYNGAP1* gene. *SYNGAP1* encodes the ras-GTPase activating protein SYNGAP which plays a vital role in brain function and development. Most individuals have been identified with *de novo* truncating variants, although missense and microdeletions have also been reported which are likely to produce haploinsufficiency (Mignot et al., 2016; Writzl & Knegt, 2013; Zollino et al., 2011). Although the exact prevalence of SYNGAP1-related intellectual disability (hereafter referred to as SYNGAP1-ID) is unclear it is thought to be one of most common causes of sporadic ID and may explain up to 1% of all cases (Berryer et al., 2013; Fitzgerald et al., 2015; Hamdan et al., 2009, 2011; Rauch et al., 2012). It was first identified in 2009 with its phenotypic features including moderate to severe intellectual disability, epilepsy, and autism (Hamdan et al., 2011; Mignot et al., 2016; Wright et al., 2022). A recent study, in a cohort of 57 individuals highlighted other features including high pain threshold (72%), eating problems (68%), sleep problems (62%), ataxia/gait issues (51%) and aggression (73%) (Vlaskamp et al., 2019). Despite the increasing understanding of the phenotypic features of this disorder, there has been no standardised examination of its behavioural profile.

Adaptive functioning

Adaptive functioning refers to the conceptual, practical, and social skills that are learnt to allow an individual to be able to live their everyday lives. For instance, it refers to a wide range of behaviours including personal care, the expression of needs, obeying rules/following instructions, and the building and maintaining of relationships. Difficulties with adaptive behaviours are part of the Diagnostic and Statistical Manual of Mental Disorders, 5th edition

(DSM-5) definition of ID, and as such, it is a critical parameter of ID, along with intellectual impairment (IQ <70). Adaptive skills typically develop as an individual ages, and as a result there is usually a higher level of adaptive functioning in those that are older.

Adaptive functioning is also an important factor in relation to education and employment. Children with lower adaptive functioning are more likely than IQ matched individuals with higher adaptive functioning to attend schools for severe learning problems (de Bildt et al., 2005). Moreover, Woolf et al. (2010) reported that adaptive behaviour accounted for 45% of the variance in work and residential independence for adults with ID, indicating that those with lower adaptive abilities were more likely to need higher levels of community support.

Currently, there are a number of individualised, standardised behaviour scales available to measure adaptive behaviour (Tasse et al., 2012). The most widely used of these is the Vineland Adaptive Behaviour Scale. Using this scale, adaptive behavioural profiles have been identified for a number of genetic syndromes that are associated with ID including Prader-Willi syndrome (Dykens et al., 1992), Cri-du-Chat syndrome (Cornish et al., 1998), Phelan-McDermid syndrome (Oberman et al., 2015) and Down syndrome (Dykens et al., 2006) which have focused on identifying relative strengths and difficulties within these syndromes. For example, for those with Prader-Wili syndrome they have shown relative strengths in daily living skills and relative difficulty in socialisation; whilst for individuals with Down syndrome they have tended to demonstrate relative strengths in socialisation and with relative difficulty in communication abilities (Dressler et al., 2010; Dykens et al., 2006; Fidler et al., 2006; Van Duijn et al., 2010).

Behavioural problems

Emotional and behavioural problems are frequently reported in those with ID (Bregman, 1991; Dykens, 2000; Rutter et al., 1970). Rutter et al. (1970) found that children with ID had three to four times more behavioural problems than children with IQ in the typical range (Rutter et al., 1970). Those with ID are more likely to demonstrate a range of behavioural issues including aggressive/destructive, stereotypic, self-injurious behaviours along with attentional and social issues (Dekker, Koot, van der Ende, and Verhulst, 2002; Mederios et al., 2014; Rojahn et al., 2011). The Child Behavior Checklist (CBCL; Achenbach, 1991) is a widely used instrument that has often been employed to assess emotional and behavioural problems. Profiles of emotional and behaviour issues have been produced for various genetic syndromes, including Angelman syndrome (Summers et al., 1995), fragile X syndrome (Einfeld et al., 1994; Fisch et al., 1996; Turk, 1995), Cri-du-Chat (Cornish et al., 1998), and Prader-Wili syndrome (Einfeld et al., 1999).

Despite the increasing number of patients diagnosed with SYNGAP1-ID, no studies have yet been conducted using a standardised assessment of adaptive and maladaptive behaviours within this population and consequently our understanding of these in this population remains limited. Using parent report questionnaires that examine both adaptive behaviours and emotional / behavioural problems we therefore set out to address two main questions:

(1) To what extent does the adaptive behaviour profile of SYNGAP1-ID differ from typically developing controls? We hypothesised that those with SYNGAP1-ID will demonstrate lower levels of adaptive behaviours than typically developing controls. Subsequently, we aimed to examine areas of relative adaptive strength and weakness and uncover the factors associated with lower adaptive functioning in SYNGAP1-ID.

(2) Does the emotional and behaviour profile of SYNGAP1-ID as highlighted by the CBCL differ from typically developing controls? We hypothesised that those with individuals

with SYNGAP1-ID will have higher levels of emotional and behavioural problems than typically developing controls. We also aimed to examine whether there were any areas of particular difficulty.

Method

Participants

Information was obtained about individuals who had received a diagnosis of SYNGAP1-ID and a group of typically developing controls. Participants were recruited through patient and family organisations (SYNGAP1 UK Foundation and SynGAP Research Fund) and from our own research centre contact database. Control participants were recruited from family members of those with SYNGAP1-ID and through our contact database. Participant characteristics (i.e., age biological sex, ASD diagnosis, ADHD diagnosis, epilepsy diagnosis, and non-verbal IQ) are presented in Table 1 and were collected alongside the completion of the measures. Informed consent was obtained from all parents and legal guardians for participants to be included in the study. Assessments of capacity to consent for themselves were made, however none were deemed to have capacity to do this, and as a result proxy consent was sought. The study protocol was reviewed and approved by NHS Scotland A Research Ethics Committee.

Measures

Parents and caregivers were administered the comprehensive parent/caregiver version of the Vineland Adaptive Behaviour Scale (VABS) Third edition (Sparrow et al., 2016). The VABS is a standardised assessment tool to measure adaptive behaviour in children with developmental disorders (Pepperdine & McCrimmon, 2018), which has been shown to have good validity and reliability (Balboni et al., 2001). Items are centred on four domains, each of which is divided into subdomains: Communication (Receptive, Expressive, and Written), Daily Living Skills

(Personal, Domestic, and Community), Socialisation (Interpersonal Relationships, Play and Leisure, and Coping Skills) and motor skills (Gross and Fine Motor). Each item is scored on a 3-point Likert scale (‘0’ never; ‘1’ sometimes, partially; or ‘2’ usually). Standard scores from the communication, daily living skills and socialisation domains are then summed to provide an Adaptive Behaviour Composite (ABC). The norm-referenced standard scores have a population mean of 100, with a standard deviation of 15. Higher scores correspond to more advanced adaptive behaviours. Age-equivalent scores can also be produced from raw scores.

The Child Behavior Checklist (CBCL; Achenbach, 1991) is a widely-used parent report form used to examine emotional and behavioural problems. Parents report how true each item of behaviour was in the last 6 months on a 3-point Likert scale (‘0’ not true; ‘1’ somewhat/sometimes true; ‘2’ very true). There is a pre-school (CBCL 1.5-5) and a school age (CBCL 6-18) version of the CBCL. The CBCL 1.5-5 is a 100-item parent report that examines emotional and behavioural issues in those aged between 1.5-5 years old. It consists of seven syndrome subscales: emotionally reactive, anxious/depressed, somatic complaints, withdrawn, sleep problems, attention problems and aggressive behaviours. Along with the syndrome subscales there are also five DSM-5 orientated subscales: affective problems, anxiety problems, pervasive developmental problems, attention deficit/hyperactivity problems, and oppositional defiant problems. The CBCL 6-18 is for those aged between 6-18 years old and consists of 118 items which contribute to seven syndrome subscales: anxious/depressed, withdrawn/depressed, somatic complaints, social problems, thought problems, attention problems, and rule breaking behaviour. Alongside these subscales, there are also five DSM-5 orientated scales: Affective problems, anxiety problems, somatic problems, Attention Deficit/Hyperactivity problems, Oppositional Defiant Problems and Conduct Problems.

For both the CBCL 1.5-5 and the CBCL 6-18 the scores from the subscales are summed to produce three summary scales (Internalising, externalising, and total score), with higher

scores indicating more severe behavioural problems. The raw scores were converted into t-value scores. T-scores of 65 or more on the subscales are considered to be in the clinical range, indicating more problems than reported by 97% of the normative sample. The CBCL has been shown to have well-established reliability and validity (Achenbach 1991; Borthwick-Duffy, Lane, and Widaman, 1997; Embregts, 2000) and it has been successfully used in other studies focused on individuals with ID (e.g. (Dykens et al., 2002; Rosner et al., 2004).

To estimate non-verbal IQ (NVIQ) the Leiter-3 International Performance scale (3rd edition; (Roid et al., 2013) was utilised. The Leiter-3 is comprised of two groupings of subtests – the cognitive battery and the attention/memory battery. A NVIQ composite is produced based on the scores obtained from four subtests of the cognitive battery (Figure ground, form completion, sequential order and classification/analogies). The raw scores from each of the subtests were converted to normalised scaled scores, which were then summed to produce a NVIQ composite. The normalised NVIQ composite had a mean of 100 (SD =15). An NVIQ score was obtained from 31 individuals (20 SYNGAP1-ID; 11 typically developing controls), as not all of our sample were able to visit our research site to complete this assessment.

Analysis

For the VABS, all statistical analysis was performed on the standard scores from the communication, daily living skills, socialisation, motor skills and adaptive behaviour composite domains. For these domains, a standard score of 20 is the floor. For the motor domain there is a ceiling effect for those over 7 years so motor scores are not produced by the VABS for these participants (n = 8 SYNGAP1-ID; 5 typically developing controls). For the CBCL, t-scale scores are reported for all scales and used for analysis. When examining the internalising, externalising and total score subscales we combined the t-scores from the CBCL 1.5-5 and the CBCL 6-18. This approach of combining scores across CBCL's has previously

been used in other research examining emotional behavioural problems in children and adolescents with autism (e.g. Guerrera et al., 2019).

All data was examined for normality of distribution and descriptive statistics were calculated. For comparing groups, Mann-Whitney U non-parametric tests were used. Spearman's rank order correlations were calculated for NVIQ, age, and the standard scores of the VABS and the CBCL subscales.

Results

Participant characteristics

Information was obtained concerning 30 (12 males; mean age 90 months (7.5 years)) individuals who had all received a diagnosis of SYNGAP1-ID and 21 (7 males; mean age 98 months (8.1 years)) typically developing controls (Table 1). For those with SYNGAP1-ID, 12 had received a diagnosis of ASD, whilst 2 had a diagnosis of ADHD, and 19 had a diagnosis of epilepsy. Of these, one individual had received a diagnosis of ASD, ADHD and epilepsy, 6 had a dual diagnosis of ASD and epilepsy, one had dual diagnosis of ADHD and epilepsy, 11 had just a diagnosis of epilepsy, whilst 5 had just an ASD diagnosis and another 5 had reported no diagnoses for either ASD, ADHD or epilepsy. Nonverbal IQ mean was 62 (SD 15.1; range 30-91) for those with SYNGAP1-ID (see Table 1). None of the typically developing controls were reported to have a received a diagnosis of either ASD, ADHD or epilepsy. A Mann-Whitney U test showed that there was no significant difference in age between the groups; whilst NVIQ was found to be significantly higher ($U = 2.0$, $p < .0001$) for the typically developing controls than for those with SYNGAP1-ID.

Table 1. *Participant characteristics of each group.*

[Table 1]

Medication Use

Information on medication use was also obtained. For the SYNGAP1-ID group most (N=20) reported being on some form of medication, with many being on more than one. Potentially psychotropic medications described were: Sodium Valporate (N= 6), Lamotrigine (N=5), Clobazam (N=5), Melatonin (N=5), Levetiracetam (N=4), Ethosuximide (N=3), Risperidone (N=1), Flupentixol (N=1), Atomoxetine hydrochloride (N=1), Hyoscine (N=1), Fluoxetine (N=1), and CBD oil (N=1). None of the typically developing controls reported being on any medication. We did not have medication use data from one individual with SYNGAP1-ID.

Genetic profile

Among the SYNGAP1-ID group, variants were distributed across exons 4-19, with most occurring in exon 15 (See Figure 1). There was one individual who we did not have genetic information for.

[Figure 1 here]

Figure 1. Location of the variants of our SYNGAP1-ID group. (A) Variants mapped on to the *SYNGAP1* domains. (B) Variants mapped on to the *SYNGAP1* exons. Localisation of the *SYNGAP1* variants based on NM_06772.2 using GRCh37/hg19.

Adaptive functioning

Vineland - Domain scores

We first examined the four main domains of communication, daily living skills, socialisation, motor skills and the adaptive behaviour composite. The standard scores for all these domains were significantly lower for the SYNGAP1-ID group compared to the typically developing controls (Communication $U = 7$, $p < 0.001$; Daily living skills $U = 17$, $p < 0.001$; Socialisation $U = 23.5$, $p < 0.001$; Adaptive behaviour composite $U = 0$, $p < 0.001$; Motor skills $U = 0$, p

<0.001) (Figure 2). For those with SYNGAP1-ID, comparing each domain, scores were highest in the motor skills (Median 62, IQR 51-71) and lowest for communication (Median 42; IQR 23.5- 55).

For the SYNGAP1-ID group, we were interested in whether participant characteristics impacted on adaptive functioning. Firstly, we examined how ASD diagnosis related to adaptive behaviour. However, standard scores on all domains did not significantly differ between those with and those without an ASD diagnosis. Secondly, standard scores were found not to be significantly different between males and females and so no additional analysis was conducted on biological sex. Thirdly, when looking at adaptive functioning in those with and without an epilepsy diagnosis, scores were lower on all domains for those with diagnoses of SYNGAP1-ID and concurrent epilepsy compared to those with just a SYNGAP1-ID diagnosis. Analysis revealed that there were significant differences on daily living skills ($U=46.5$, $p = 0.024$) and the adaptive behaviour composite ($U= 50.5$, $p= 0.04$) between those with diagnoses of SYNGAP1-ID and concurrent epilepsy compared to those without epilepsy. There were no significant differences in NVIQ between those with those with diagnoses of SYNGAP1-ID and concurrent epilepsy and those with only a SYNGAP1-ID diagnosis.

To examine the association between adaptive functioning and sample characteristics including age (Figure 3) and NVIQ (Figure 4), Spearman's rank order correlations were undertaken. For the SYNGAP1-ID group, communication ($r (29) = -0.399$, $p = 0.032$), daily living skills ($r (29) = -0.569$, $p = 0.001$), socialisation ($r (29) = -0.542$, $p = 0.002$), and adaptive behaviour composite ($r (29) = -0.506$, $p = 0.005$) all showed strong negative statistically significant correlations with age. For NVIQ, there were strong positive statistically significant correlations with communication ($r (19) = 0.809$, $p < .001$), daily living skills ($r (19) = 0.803$, $p < .001$), socialisation ($r (19) = 0.810$, $p < .001$), adaptive behaviour composite ($r (19) = 0.834$, $p <.001$), and motor skills ($r (19) = 0.896$, $p <.001$), indicating that those with higher NVIQ

demonstrated higher adaptive functioning across all domains. See supplementary materials for correlations between those with diagnoses of SYNGAP1-ID and concurrent epilepsy compared to those without epilepsy with age.

[Figure 2 Here]

Figure 2. Standard scores of the Vineland Adaptive Behaviour Scale domains for the SYNGAP1-ID (SYN) group and typically developing controls (TDC). Solid line indicates population mean whilst dotted lines denote standard deviations. Boxes correspond to interquartile range (25^{th} to 75^{th}), with the minimum/maximum whiskers calculated as Q1/Q3 -/+ 1.5 times IQR.

[Figure 3 Here]

Figure 3. Correlations with age (months) and standard domain scores on the Vineland Adaptive Behaviour Scale for those with SYNGAP1-ID (SYN; Red line) and typically developing controls (TDC; Blue line). A) Association of standard domain scores for communication with age. B) Association of standard domain scores for daily living skills with age. C) Association of standard domain scores for socialisation with age. D) Association of adaptive Behaviour Composite scores with age. E) Association of standard domain motor skills scores with age. Lines denote linear model regression with its confidence interval as shaded areas

[Figure 4 Here]

Figure 4. Correlations with non-verbal IQ (NVIQ) and standard scores on the Vineland Adaptive Behaviour Scale for those with SYNGAP1-ID (SYN; Red line) and typically developing controls (TDC; Blue line). A) Association of standard domain scores for communication with NVIQ. B) Association of standard domain scores for daily living skills with NVIQ. C) Association of standard domain scores for socialisation with NVIQ. D)

Association of adaptive behaviour composite scores with NVIQ. E) Association of standard domain scores for motor skills with NVIQ. Lines denote linear model regression with its confidence interval as shaded areas

Emotional and Behavioural Problems

Child Behavior Checklist 1.5-5 and 6-18

We first looked at internalising, externalising and total scores by combining these scores together from the pre-school (CBCL 1.5-5) and school age (CBCL 6-18) versions of the CBCL (Figure 5). Those with SYNGAP1-ID had significantly higher total scores than typically developing controls (SYNGAP1-ID Median 63.96 IQR 58.5-70; TDC Median 39.5, IQR 30.5-45.75; $U = 2.5$, $p<.001$), with scores also higher for externalising (SYNGAP1-ID Median 63, IQR 55-67; TDC Median 39.5, IQR 34-44; $U =16$, $p<.001$) and internalising (SYNGAP1-ID Median 63, IQR 50-68; TDC Median 43, IQR 39-47.75; $U = 78$, $p<.001$) behaviours. In terms of the standardised cut-offs for the CBCL, 21 (70%) SYNGAP1-ID individuals scored within the borderline/clinical range on the total score. For the internalising score, 16 (53%) SYNGAP1-ID individuals scored within the borderline/clinical range; whilst for the externalising scale, 15 (50%) SYNGAP1-ID individuals scored within the borderline/clinical range.

Within the SYNGAP1-ID group, there were no significant differences in internalising, externalising or total score between those with and without an autism diagnosis. The presence or absence of epilepsy did significantly affect scores such that those with concurrent epilepsy demonstrated significantly higher total CBCL scores than those without ($U = 47$, $p=0.019$). There were no significant correlations between for internalising, externalising, or total score with either age or NVIQ. There were no significant differences in scores between SYNGAP1-

ID males and SYNGAP1-ID females for either externalising, internalising or total score on the CBCL.

[Figure 5 Here]

Figure 5. Child Behavior Checklist scale scores for those with SYNGAP1-ID (SYN) and typically developing controls (TDC). Internalising, externalising and total scores combined from the 1.5-5 & 6-18 versions of the CBCL for both those with SYNGAP1-ID and typically developing controls. Dotted lines denote borders between typical (t-score <60), borderline (t-score 60-64) and clinical range (t-score >65). Boxes correspond to interquartile range (25^{th} to 75^{th}), with the minimum/maximum whiskers calculated as Q1/Q3 -/+ 1.5 times IQR.

[Figure 6 here]

Figure 6. Scores on the CBCL 1.5-5 for those with SYNGAP1-ID (SYN) and typically developing controls (TDC). Dotted lines denote borders between typical (t-score <65), borderline (t-score 65-69) and clinical range (t-score >70). Boxes correspond to interquartile range (25^{th} to 75^{th}), with the minimum/maximum whiskers calculated as Q1/Q3 -/+ 1.5 times IQR.

To develop a clear profile of emotional and behavioural problems for those with SYNGAP1-ID we next looked at the pre-school (CBCL 1.5-5) and a school age (CBCL 6-18) versions of the CBCL individually:

Child Behavior Checklist 1.5-5

There were significant differences between the SYNGAP1-ID group and the typically developing controls on all of the scales except anxious / depressed and somatic complaints (Emotionally reactive U= 1.5, p =0.008; Withdrawn U= 0, p=0.004; Sleep problems U= 0, p=0.004; Attention problems U= 0, p=0.004; Aggressive behaviours U=0, p=0.004; Figure 6).

For those with SYNGAP1-ID, median scores in the clinically impaired range were seen for withdrawn (Median 74.5, IQR 71.5-80.5), and attention problems (Median 75, IQR 70.25-77.75). The typically developing participants in this 1.5-5 age group all scored below the clinical cut-off for all of the subscales.

Next, we examined correlations between age and NVIQ and the scales on the CBCL 1.5-5. Analysis showed that there were no significant correlations between the scores on the CBCL 1.5-5 scales and age for either group. For NVIQ and scores on the CBCL 1.5-5 for those with SYNGAP1-ID, there were strong significant negative correlations with NVIQ and withdrawn behaviours ($r(5) = -0.9$, $p=0.037$) suggesting that those in this age range those with lower NVIQ were likely to show more affective and withdrawn behaviours.

Child Behavior Checklist 6-18

There were significant differences between the SYNGAP1-ID group and the typically developing controls on all of the subscales (Anxious/Depressed $U = 86$, $p =0.009$; Withdrawn/Depressed $U=65$, $p = 0.001$; Somatic complaints $U= 73$, $p=.003$; Thought problems $U= 20$, $p< 0.001$; Attentional problems $U = 2$, $p<0.001$, Rule breaking behaviours $U = 47$, $p<0.001$; Aggressive behaviours $U = 22$, $p<0.001$; Figure 7). For those with SYNGAP1-ID, median scores in the clinically impaired range were seen for social (median 67; IQR 59-70) and attention problems (median 73; IQR 67-76). For the typically developing controls, all individuals scored below the clinical cut-off for all of the subscales.

Bivariate Spearman's rank correlations were conducted in order to investigate the relationships between the CBCL subscales with age (Figure 8) and nonverbal IQ (Figure 9) within the SYNGAP1-ID group. Within this group, age showed a significant positive correlation with somatic complaints ($r (19) = 0.649$, $p = 0.003$). There were non-significant

positive trend for rule breaking behaviours r(19)=0.394, p<0.1). For NVIQ, there was a significant negative correlation with thought problems (r (14) = -0.588, p = 0.027).

[Figure 7 Here]

Figure 7. Scores on the CBCL 6-18 for those with SYNGAP1-ID (SYN) and typically developing controls (TDC). Dotted lines denote borders between typical (t-score <60), borderline (t-score 65-69) and clinical range (t-score >70). Boxes denote interquartile range (25^{th} to 75^{th}), with the minimum/maximum whiskers calculated as Q1/Q3 -/+ 1.5 times IQR.

[Figure 8 Here]

Figure 8. Correlations with age (months) and t-scale scores of the CBCL 6-18 subscales for those with SYNGAP1-ID (SYN; Red line) and typically developing controls (TDC; Blue line). (A) Association of anxious/depressed behaviours CBCL subscale scores with age. (B) Association of withdrawn CBCL subscale scores with age. (C) Association of somatic complaints CBCL subscale scores with age. (D) Association of social problems CBCL subscale scores with age. (E) Association of thought problems CBCL subscale scores with age. (F) Association of attention problems CBCL subscale scores with age. (G) Association of rule breaking behaviours CBCL subscale scores with age. (H) Association of aggressive behaviours CBCL subscale scores with age. Lines denote linear model regression with its confidence interval as shaded areas.

[Figure 9 Here]

Figure 9. Correlations with non-verbal IQ (NVIQ) and t-scale scores of the CBCL 6-18 subscales for those with SYNGAP1-ID (SYN; Red line) and typically developing controls

(TDC; Blue line). (A) Association of anxious/depressed behaviours CBCL subscale scores with NVIQ. (B) Association of withdrawn CBCL subscale scores with NVIQ. (C) Association of somatic complaints CBCL subscale scores with NVIQ. (D) Association of social problems CBCL subscale scores with NVIQ. (E) Association of thought problems CBCL subscale scores with NVIQ. (F) Association of attention problems CBCL subscale scores with NVIQ. (G) Association of rule breaking behaviours CBCL subscale scores with NVIQ. (H) Association of aggressive behaviours CBCL subscale scores with NVIQ. Lines denote linear model regression with its confidence interval as shaded areas.

Discussion

In this population of children and adolescents with pathological variations in SYNGAP1-ID we identified broad impairments of adaptive functioning which were most apparent in those with concurrent epilepsy. We also found that the gap in adaptive function between affected individuals and typically developing controls was highest in older individuals. Differences in behavioural and emotional difficulties between the groups were also apparent; again those with epilepsy were more affected than those without, and there was some evidence of greater difficulties in older participants particularly in the 6-18 year old group.

Adaptive behaviour reflects the conceptual, practical and social skills that an individual uses in their daily lives. While impairments in those with SYNGAP1-ID were seen across all domains it is useful to note that they had relative strengths in motor skills and particular relative weaknesses in communication. This relative strength in motor skills is consistent with previous SYNGAP1-ID reports (Jimenez-Gomez et al., 2019). It is worth noting that whilst relatively high compared to other areas of their adaptive functioning, their motor skills were still significantly lower than typically developing controls, in keeping with previous reports of

SYNGAP1-ID, which have highlighted the presence of ataxia and gait abnormalities (Agarwal et al., 2019; Mignot et al., 2016; Parker et al., 2015; Vlaskamp et al., 2019; Wright et al., 2022). Similarly, the deficits in receptive and expressive language skills in SYNGAP1-ID were in keeping with previous reports (Mignot et al., 2016).

In terms of emotional and behavioural problems, those with SYNGAP1-ID demonstrated higher levels of these compared with the typically developing controls. Within the SYNGAP1-ID group, difficulties with attention were common across the entire age range examined. Although to our knowledge, inattention has not been reported in the SYNGAP1-ID literature before, the related symptomology of hyper-excitability has been (e.g. Parker et al., 2015). Interestingly, the high levels of inattention in our sample are not reflected in the numbers reporting a diagnosis of ADHD. This may be the result of diagnostic overshadowing and raises the possibility that ADHD is a potentially under-recognised and therefore under-treated component of the SYNGAP1-ID behavioural phenotype. It is important to note however that the diagnosis of ADHD, especially the inattentive subtype, in individuals with significant cognitive impairment is extremely complex and requires detailed multidisciplinary assessment and observation. The DSM-5 criteria for an ADHD diagnosis require symptoms to be present which are "inappropriate for developmental level", a judgement which is difficult to make in those with moderate to severe intellectual disability. Our data suggest the possibility that inattentive ADHD may be a significant issue but more detailed clinical diagnostic studies, and potentially treatment trials, are required to confirm or refute this. In addition, younger children were reported to be particularly withdrawn which may reflect the high frequency of autism diagnoses in this population. We found no association between biological sex and either adaptive behaviour or emotional and behavioural difficulties, suggesting that this does not underlie the phenotypic heterogeneity of SYNGAP1-ID in these domains.

When considering the effects of epilepsy, we found that an epilepsy diagnosis was associated with lower levels of adaptive behaviour, both globally and with specific reference to the daily living skills subscale. Similarly, those with SYNGAP1-ID and an epilepsy diagnosis demonstrated significantly higher total scores on the CBCL than those with SYNGAP1-ID without a diagnosis of epilepsy. Interestingly, there was no difference in NVIQ between those with an additional epilepsy diagnosis and those without suggesting that NVIQ does not seem to be a contributing factor to this difference in skills (despite the known association between low IQ and epilepsy reported more broadly). As such, it appears that epilepsy is independently associated with fewer adaptive behaviours and a greater number of emotional and behavioural problems. Unfortunately, we did not collect in-depth information about whether epilepsy for our SYNGAP1-ID group was intractable or not, which would have provided greater knowledge of how this impacts on adaptive behaviour.

Within our sample participants reported being on multiple medications with potentially psychotropic effects which could affect behaviour. Unsurprisingly, anti-epileptics were the most commonly prescribed medication, given their licensed purpose of treating epilepsy. Separating the effects on behaviour of medication use and seizure frequency in this population would be interesting but would require a larger sample size, ideally with prospective data collection. Perhaps somewhat more surprisingly, despite significant behavioural difficulties being reported, very few participants were taking medication to manage these difficulties, or were being treated for conditions such as anxiety or ADHD, which could underlie such difficulties. Unfortunately we did not have enough participants taking any single class of medication to examine whether or not there were significant relationships with behaviour.

Interestingly, we found significant negative relationships between age and adaptive functioning suggesting that the gap between individuals with SYNGAP1-ID and their age-matched peers might increase through development. It is noteworthy that the raw scores of the

VABS subdomains do not decrease in the SYNGAP1-ID group with age and in some domains appear to increase (see supplementary materials figure 2), indicating that the SYNGAP1-ID group do not generally regress and may continue to acquire skills, albeit at a slower rate than the typically developing controls. In terms of emotional and behavioural problems, there was some evidence of increasing difficulty with age in the SYNGAP1-ID 6-18 age group for somatic complaints, but also a trend towards increased rule breaking behaviours.

Our study has a number of limitations that need to be taken into account when considering the findings. Firstly, the limited sample size may restrict strong inferences from being made particularly concerning those aged under five. Alongside this, with the study only including those up to the age of 18 years it still remains an open question as to the behavioural profile of those above this age and how it changes with age. Secondly, assessment of nonverbal IQ could not be performed on the whole sample, making interpretations regarding the influence of cognitive ability on the behaviour profile difficult. This is particularly important especially due to the strong link between intellectual functioning and adaptive behaviours. The study is also cross-sectional therefore any age relationships we report require to be confirmed in a longitudinal study to more closely examine developmental trajectories.

In conclusion, we have set out the behavioural profile of those with SYNGAP1-ID consisting of low adaptive functioning alongside high levels of emotional and behavioural problems. In particular, across all ages they demonstrated particular difficulties with attention, whilst those aged 1.5-5 also had issues with withdrawn behaviours and those aged 6-18 had issues with social behaviours. Those with a concurrent diagnosis of epilepsy appeared to have lower levels of adaptive behaviours and more emotional and behavioural problems. This understanding of the relative strengths and weakness in relation to adaptive functioning and behavioural issues experienced by those with SYNGAP1-ID helps to identify areas in which extra support and specific interventions may be required.

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Figure1

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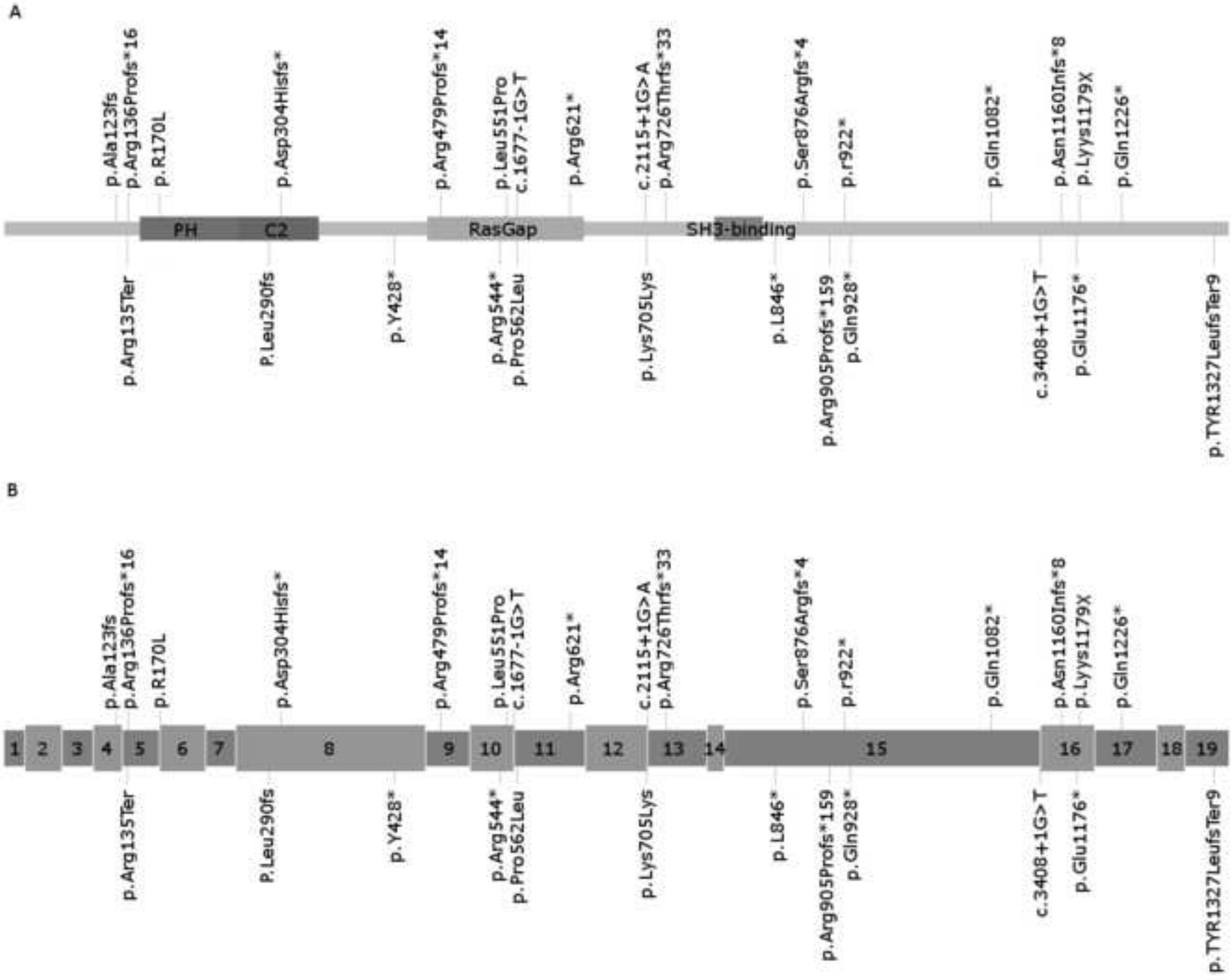

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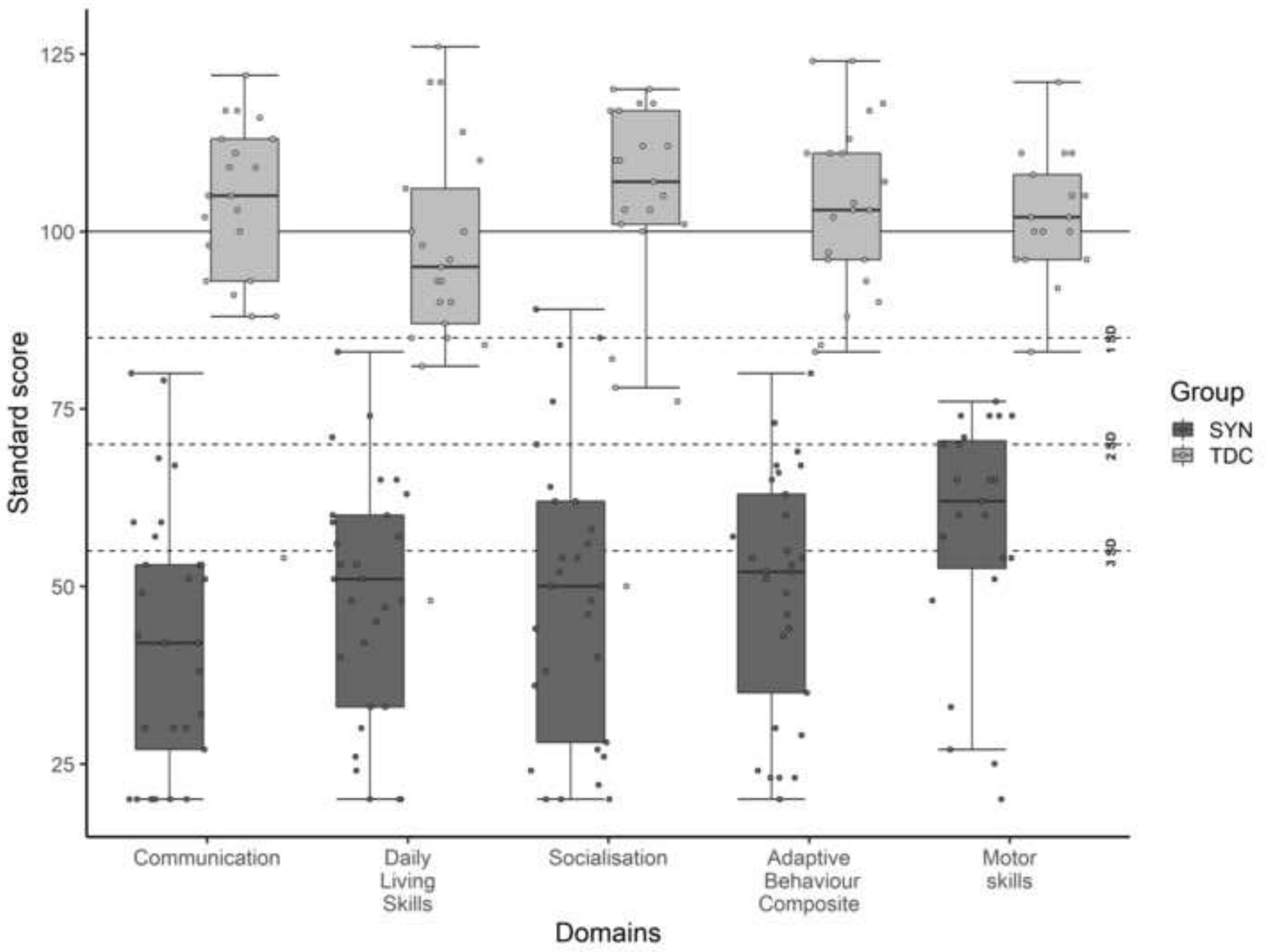

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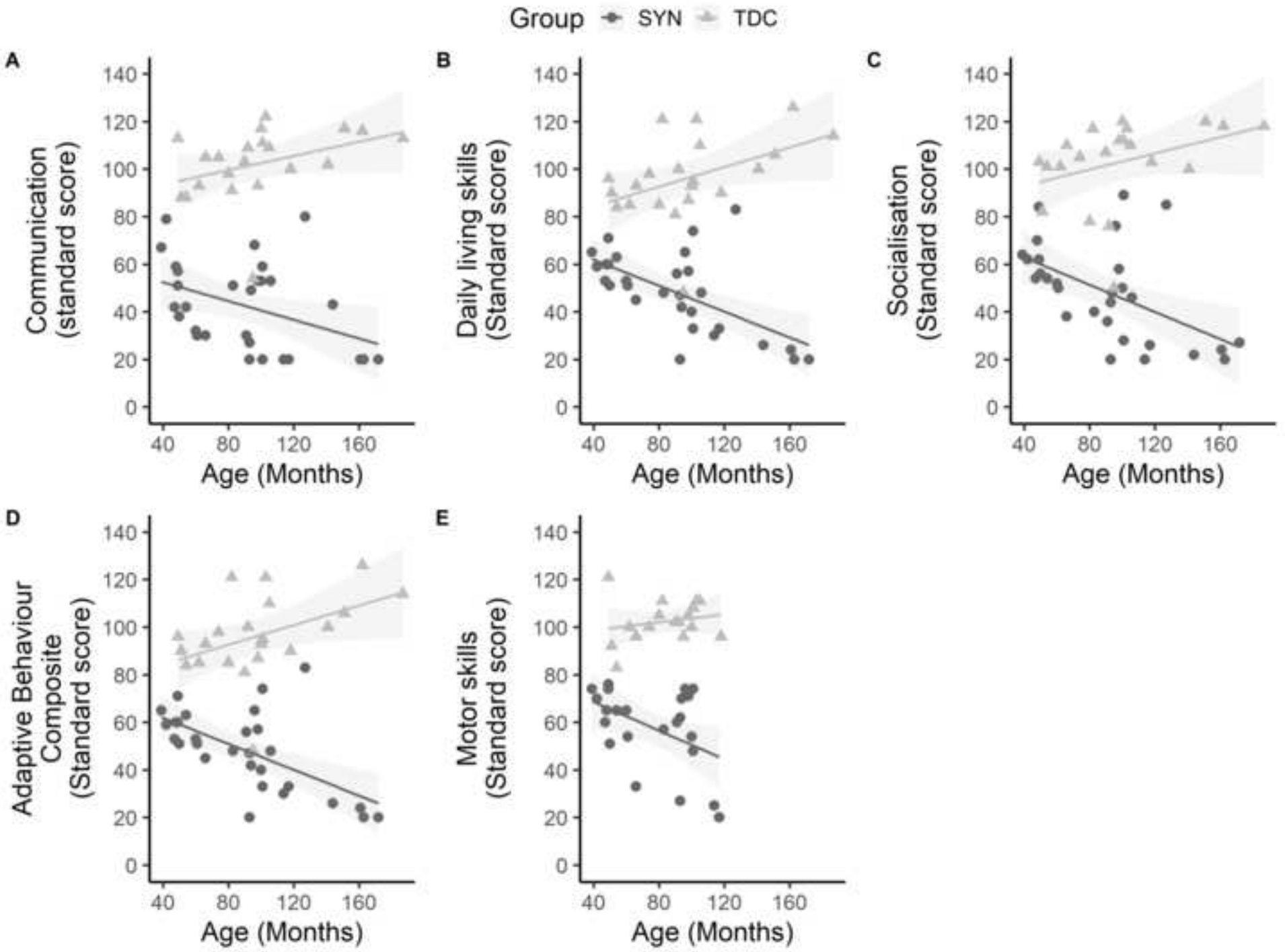

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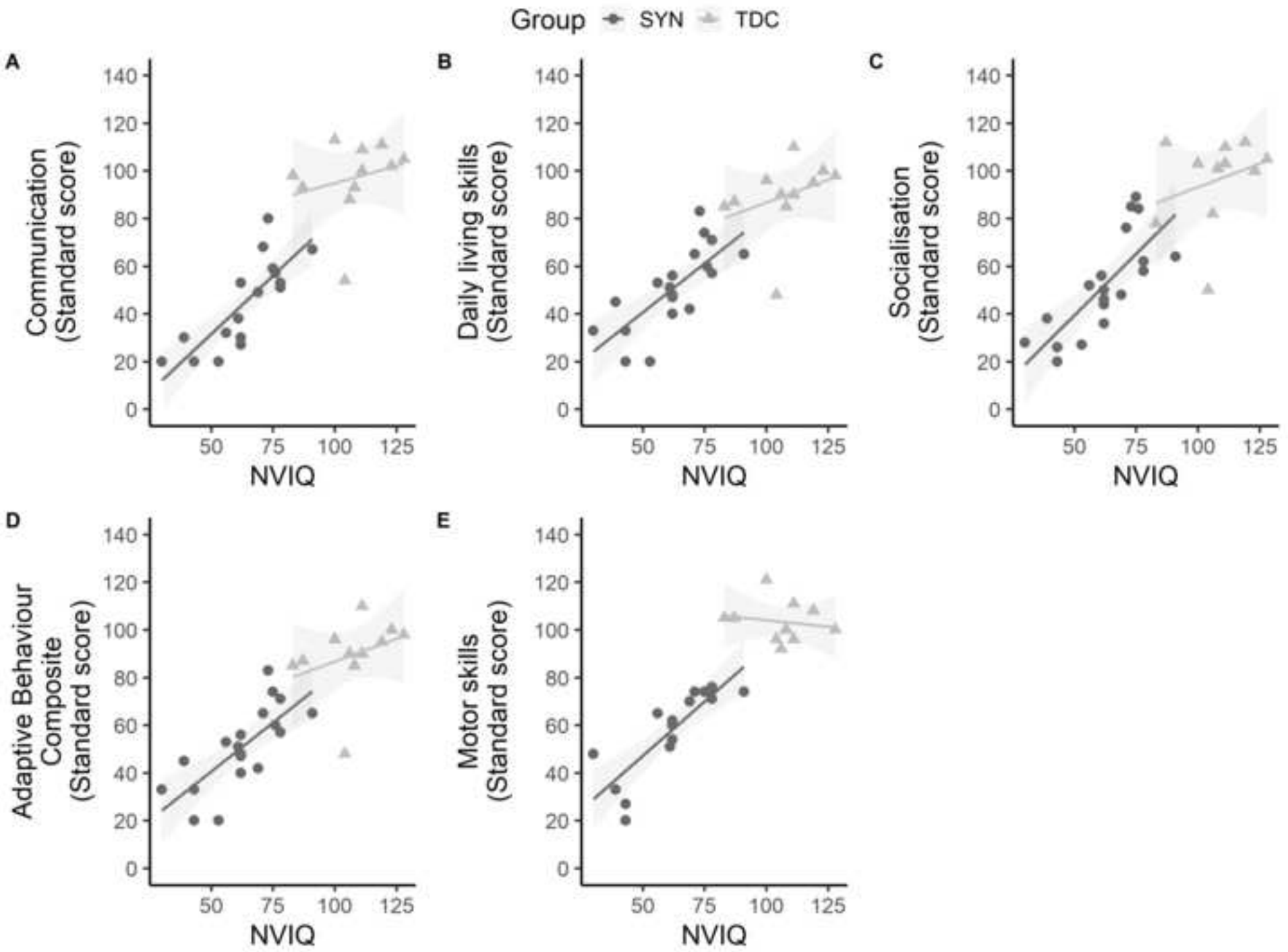

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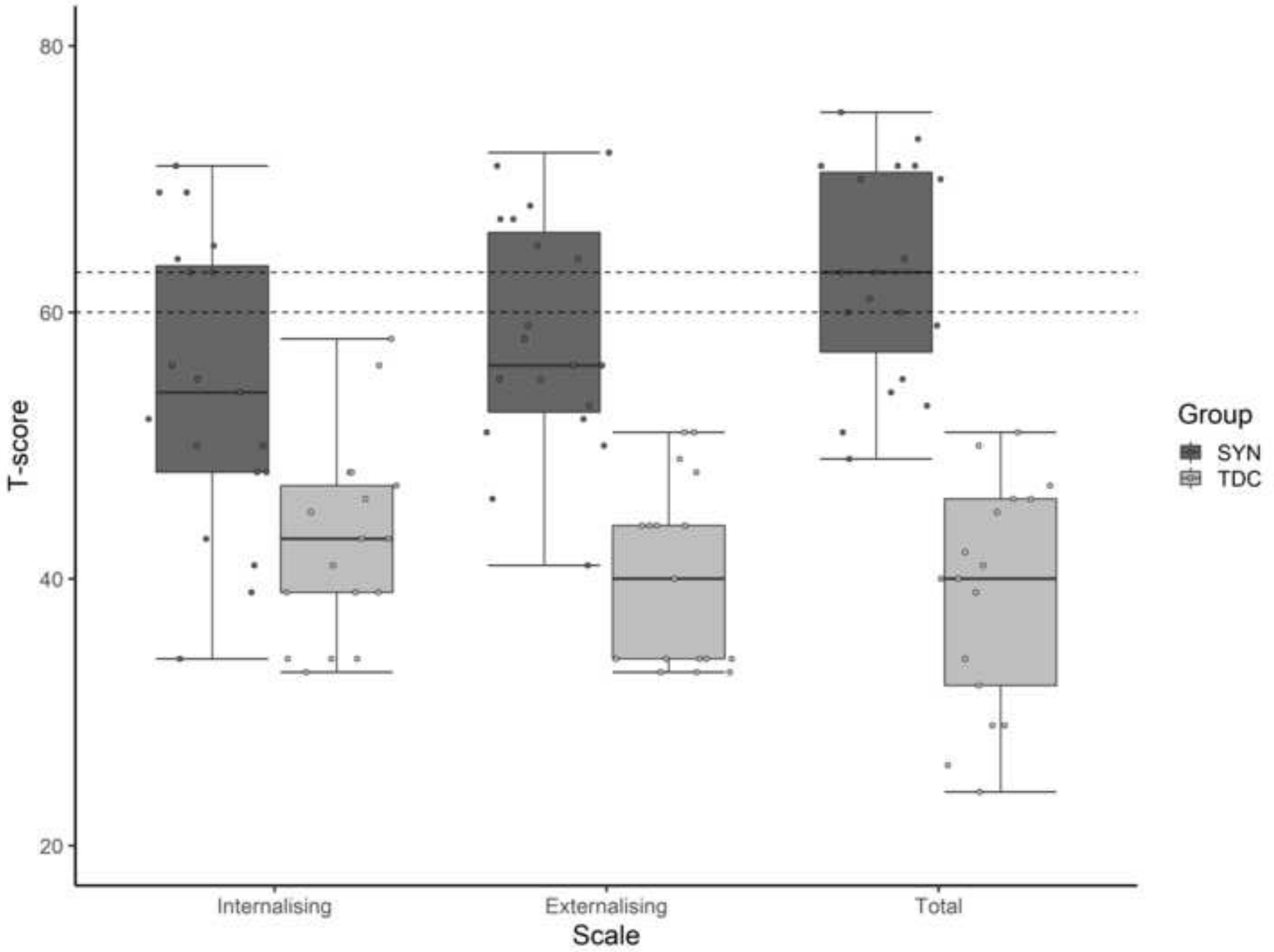

Figure6

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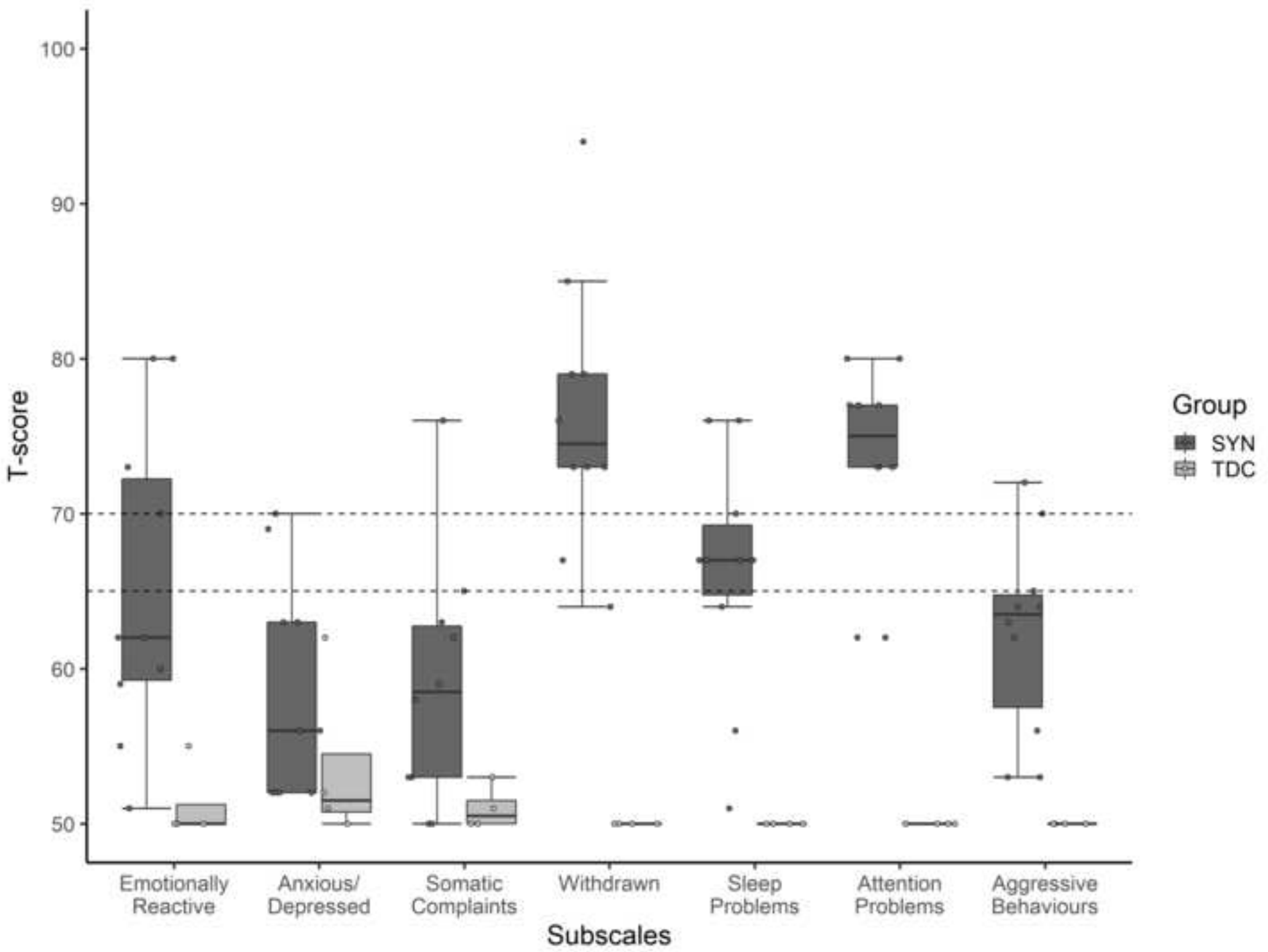

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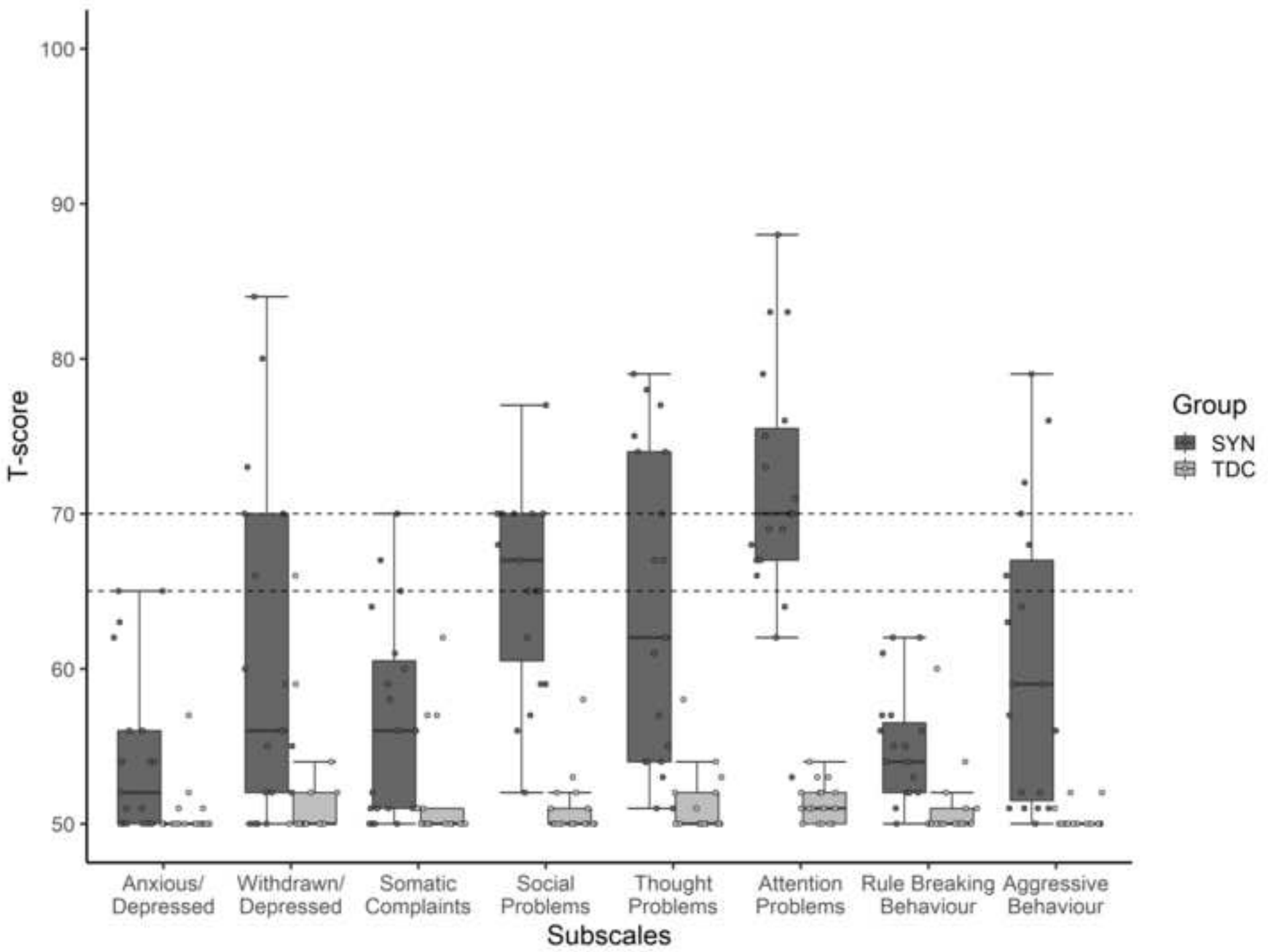

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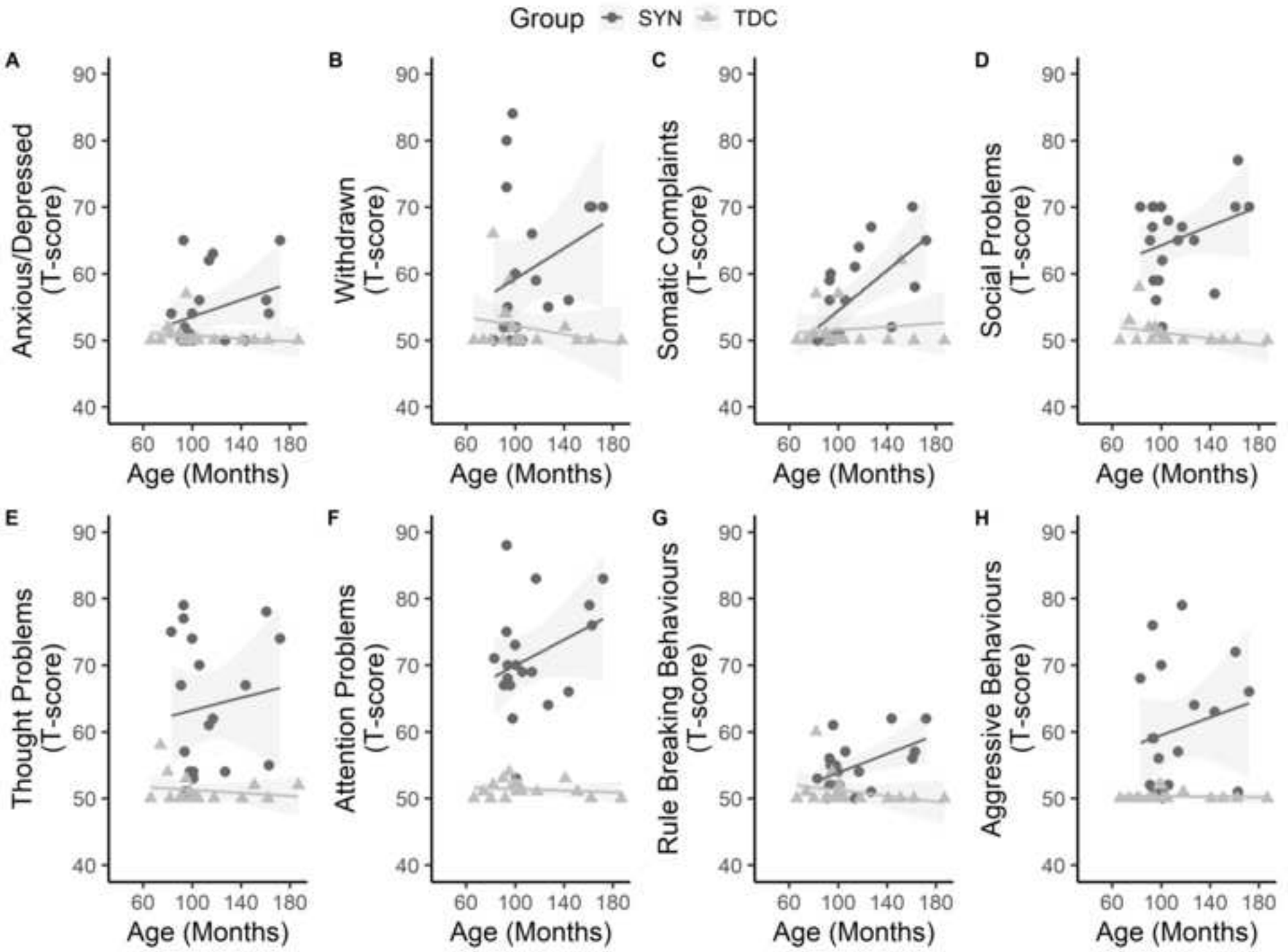

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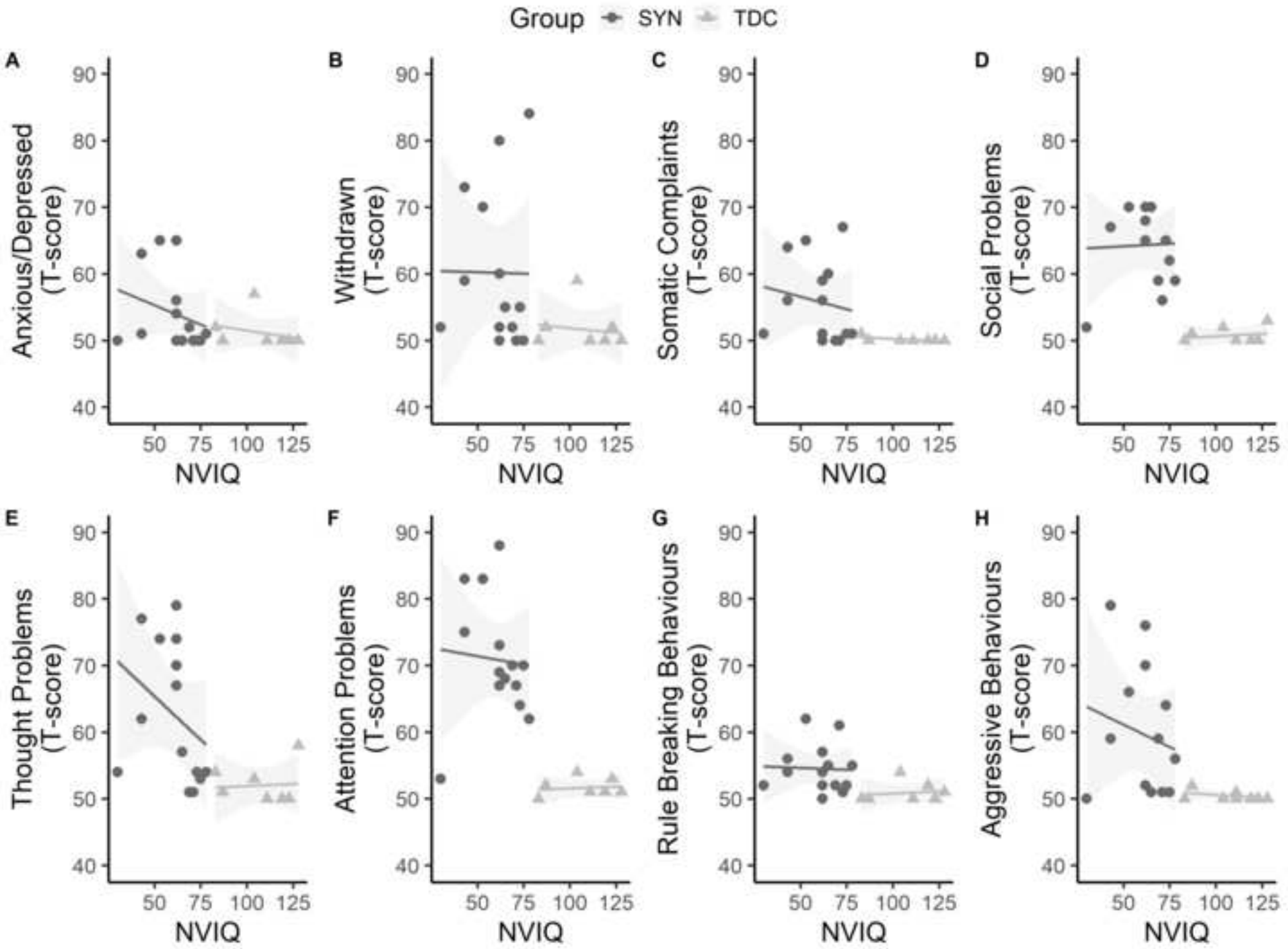

Table 1.

	SYNGAP1 **(N=30)**	**Typically developing controls (N=21)**
Age (Mean)	90 Months (SD 37)	98 Months (SD 37)
Gender (N)	12 Males	7 Males
ASD diagnosis (N)	12	0
ADHD diagnosis (N)	2	0
Epilepsy diagnosis (N)	19	0
Non-verbal IQ (Mean)	62 (SD 15.1)	107 (SD 13.8)