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Exploring the approximate number system in Sotos syndrome: insights from a dot comparison task

Chloe Lane*[1], Jo Van Herwegen[2], Megan Freeth[1]

[1]Department of Psychology, University of Sheffield, UK

[2]Department of Psychology and Human Development, UCL Institute of Education, UK

***Correspondence to:** Chloe Lane, Department of Psychology, The University of Sheffield, Sheffield, UK, S1 2LT; Email: chloe.lane@sheffield.ac.uk

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Abstract

Background

Sotos syndrome is a congenital overgrowth condition associated with intellectual disability and an uneven cognitive profile. Previous research has established that individuals with Sotos syndrome have relatively poor mathematical ability but domain-specific numeracy skills have not been explored within this population. This study investigated the approximate number system (ANS) in Sotos syndrome.

Method

A dot comparison task was administered to 20 participants with Sotos syndrome (mean age in years = 18.43, SD = 9.29). Performance was compared to a chronological age matched typically developing control group (n = 25) and a mental age matched Williams syndrome group (n = 24).

Results

The Sotos group did not display an ANS deficit overall when compared to chronological age matched control participants. However, for trials where the size of the individual dots and the envelope area were negatively correlated with the total number of dots (incongruent trials), the Sotos group were less accurate than the TD group but more accurate than the WS group, suggesting an inhibitory control deficit. Better accuracy on incongruent trials, but not congruent trials, was associated with higher quantitative reasoning ability for participants with Sotos syndrome.

Conclusion

Overall, the findings suggest that ANS acuity is not impaired in Sotos syndrome but that numerical difficulties may be associated with an inhibitory control deficit for individuals with Sotos syndrome.

Keywords

Sotos syndrome; numeracy; approximate number system; congruency

Exploring the approximate number system in Sotos syndrome: insights from a dot comparison task

Background

Sotos syndrome is a congenital overgrowth condition associated with intellectual disability. Intellectual functioning is variable but the majority of individuals within this population have mild to moderate intellectual disability (Lane et al., 2016). The syndrome has an estimated incidence of approximately 1 in 14,000 and is caused by a pathogenic variant of the NSD1 (nuclear receptor binding SET domain protein 1) gene (Kurotaki et al., 2002, Tatton-Brown and Rahman, 2004). Recent research has established that Sotos syndrome is associated with an uneven cognitive profile, characterised by relative strength in verbal ability and visuospatial memory but relative weakness in non-verbal reasoning ability, particularly quantitative reasoning (Lane et al., 2018). Anecdotal reports of relatively poor numeracy have also been reported (Cole and Hughes, 1994). Findings from both of these studies indicate that numerical difficulties are common in individuals with Sotos syndrome but the specific nature of these difficulties has not yet been explored.

The development of numeracy is a complex process and multiple skills, including both domain-specific and domain-general skills, have been implicated in this developmental process. Evidence from typical populations indicates that domain-specific numeracy skills such as estimation, symbolic and non-symbolic magnitude processing, counting and cardinality (i.e. understanding that the last number in a counting set represents the total number of items in the set) are associated with mathematical achievement (Sasanguie et al., 2013, Schneider et al., 2017). In addition, domain-general abilities such as language, visuospatial processing, attention and executive functions have been associated with mathematical achievement in typically developing populations (Bull and Scerif, 2001, Cragg

and Gilmore, 2014, LeFevre et al., 2010, Simms et al., 2016). Furthermore, evidence from atypical populations indicates that different factors may underlie mathematical difficulties in distinct populations, as well as different factors having an impact at different stages of development (Brankaer et al., 2017, Paterson et al., 2006). Thus, it is important to investigate skills associated with mathematical achievement in both typical and atypical populations in order to advance understanding of factors underlying numerical difficulties. This will ensure that appropriate interventions are utilised for those at risk of developing numerical difficulties.

The approximate number system (ANS) supports the representation and processing of non-symbolic quantities and enables individuals to compare quantities without counting them. The ANS has commonly been assessed using dot comparison tasks, in which individuals must determine which array, in a set of two, has the most dots. This relies upon non-verbal magnitude representations. Better accuracy on this task has been associated with higher mathematical achievement in typically developing populations, suggesting that non-symbolic number processing is important for mathematics (Chen and Li, 2014, Dehaene, 2001, Mazzocco et al., 2011b, Halberda et al., 2008). It is important to note that this relationship has been found to be stronger in children aged 6 years and younger, indicating that the ANS has a greater impact on the early acquisition of mathematics (Fazio et al., 2014). However, in developmental disorders, such as dyscalculia, impaired ANS acuity has been found in older children, indicating that impairments early in development affect mathematical abilities throughout the lifespan for individuals with developmental disorders (Mazzocco et al., 2011a, Piazza et al., 2010).

One of the features of dot comparison tasks is that they often include both congruent and incongruent trials. In congruent trials, stimulus characteristics (e.g. size of dots and envelope area) are positively correlated with the number of dots, whereas these

characteristics are negatively correlated with the number of dots in incongruent trials. This means that relying upon stimulus characteristics alone, such as the size of the individual dots, would result in incorrect responses for incongruent trials but correct responses for congruent trials. Consequently, poor performance on incongruent trials of the dot comparison task has been associated with poor inhibitory control, as these trials require the participant to inhibit a response based purely on stimulus characteristics (Gilmore et al., 2013, Clayton and Gilmore, 2015). Thus, it has been suggested that the relationship between the ANS and mathematical achievement is attributable to the confound of inhibitory control (Gilmore et al., 2013).

Cross-syndrome comparisons are useful for identifying syndrome-specific phenotypic differences which can be used to inform syndrome-specific interventions. Williams syndrome (WS) is a congenital syndrome associated with intellectual disability (overall mean IQ score of 56, range 50 – 70, on average), as well as impaired numeracy skills from infancy onwards (Ansari et al., 2007, Ansari et al., 2003, Van Herwegen et al., 2008). Previous research using cross-syndrome comparisons to assess domain-specific numeracy skills, such as counting and magnitude processing, have identified syndrome-specific differences in relation to these skills (Paterson et al., 2006, Karmiloff-Smith et al., 2012). As WS is associated with similar overall intellectual ability to Sotos syndrome and a cognitive profile of better verbal ability compared with non-verbal reasoning ability, WS provides an ideal comparison group for investigating domain-specific numerical skills, as differences in task performance can be interpreted as syndrome-specific, as opposed to resulting from general cognitive impairment (Martens et al., 2008).

As the ANS has been implicated in mathematical achievement and Sotos syndrome is associated with numerical difficulties, it is important to assess the ANS within this population. To date, domain-specific numeracy skills have not been investigated in individuals with Sotos syndrome so it is not yet known whether ANS acuity is impaired

within this population. It will be useful to assess the ANS in order to determine whether the representation and processing of non-symbolic quantities is particularly problematic for individuals with Sotos syndrome. This will inform appropriate strategies and interventions for supporting poor numeracy within this population. Therefore, the primary aim of this study was to explore the ANS in individuals with Sotos syndrome by assessing performance on a dot comparison task. In order to establish whether the Sotos syndrome participants had impaired ANS acuity, performance was compared to a TD control group matched on chronological age. Furthermore, a cross-syndrome approach was used to establish whether the Sotos syndrome group had similar ANS acuity to a group of individuals with WS, matched on mental age. A secondary aim of this study was to investigate relationships between accuracy on congruent and incongruent trials and quantitative reasoning ability for participants with Sotos syndrome.

Method

Participants

The sample comprised 20 individuals with Sotos syndrome, 25 typically developing individuals matched on chronological age and 24 individuals with WS (see Table 1 for participant characteristics). Participants with Sotos syndrome were recruited via the Child Growth Foundation (CGF; a UK charity that supports families of individuals affected by growth conditions) and advertisements on a Sotos syndrome support group on social media. Participants in the typically developing control group were recruited using established contacts from the Child Development and Learning Difficulties Unit at Kingston University. All typically developing control participants had English as their first language and none had any reported learning difficulties, according to a parental questionnaire. Participants in the WS group were part of a larger study on mathematical foundations in neurodevelopmental

disorders, led by the second author. These participants were recruited via the Williams Syndrome Foundation in the UK.

[Insert Table 1 about here]

Measures

In order to match the syndrome groups, the Sotos syndrome participants and WS participants completed a matrices task which provided an indication of the non-verbal reasoning ability of these groups. Participants with Sotos syndrome completed the matrices task from the British Ability Scales, third edition (BAS3) and participants with WS completed the Raven's Coloured Progressive Matrices task. Both of these standardised tasks provide mental age equivalents which were used to match participants.

Dot comparison

A dot comparison task, based on Gebuis and Reynvoet (2011), was used to assess ANS acuity. This was a computerised task in which participants were presented with two arrays of dots; one with blue dots and one with red dots, presented simultaneously on the left and right of the screen. The number of dots included in each array ranged from 5 to 20. The ratio between the two arrays in each trial was either 0.5, 0.6, 0.7 or 0.8 and the number of trials using these ratios was distributed evenly across the 48 trials. The array with the greatest number of dots was counterbalanced, appearing on either the left or right side of the screen. In half of the trials, the size of the individual dots and the envelope area were positively correlated with the total number of dots (congruent trials) and in the other half of the trials, the size of the individual dots and the envelope area were negatively correlated with the total number of dots (incongruent trials). Participants were asked "which side has more dots?" and

were instructed to choose the array with more dots by pointing, or stating the colour of the array with the most dots. Participants received a score of 1 for each correct trial (minimum score = 0, maximum score = 48).

Before completing the dot comparison task, participants were administered a practice task using two dot arrays, where the ratio between the number of dots in the two arrays was 3:1. The practice task included both congruent and incongruent trials and verbal feedback was provided for incorrect responses. Participants completed up to 24 trials of this task and progression to the main dot comparison task was dependent upon responding correctly to 8 consecutive practice trials (see Van Herwegen et al., 2018 for a similar approach).

Quantitative reasoning ability

Quantitative reasoning ability was assessed using the quantitative reasoning task from the school age battery of the BAS3. This task was only completed by participants with Sotos syndrome and T-scores (M = 50, SD = 10) were used for the purpose of analysis.

Procedure

Participants took part in the study in a quiet room at their home, school or organisation centre. Participants aged 18 years and over provided written informed consent and for children under the age of 18 years, the parent/caregiver of the participant was required to give written informed consent. All participants provided verbal assent. The study received ethical approval from the departmental ethics committee.

Results

One of the Sotos syndrome participants did not respond correctly to 8 consecutive trials on the practice task and therefore did not complete the main task. So, only 19 participants with Sotos syndrome (11 males and 8 females; mean age = 18.97 years, SD = 9.21 years) were included in the subsequent analyses. There was no significant difference in

chronological age between the three groups; $F(2, 65) = 0.49$, $p = .618$, $\eta\rho^2 = .015$. There was no significant difference between mental age equivalents (in years;months) for the matrices tasks between the Sotos (M = 6;11, SD = 2;9) and WS (M = 6;1, SD = 1;5) groups, $t(41) = 1.23$, $p = .225$, $d = 0.38$.

Approximate number system acuity

ANS acuity on both congruent and incongruent trials in individuals with Sotos syndrome was assessed and compared with the TD and WS groups. A total congruent score was calculated as the sum of correct responses on the 24 congruent trials for the Sotos (M = 21.00, SD = 3.40, range = 13 – 24), TD (M = 20.72, SD = 3.53, range = 11 – 24) and WS (M = 21.33, SD = 3.03, range = 10 – 24) participants and a total incongruent score was calculated as the sum of correct responses on the 24 incongruent trials for the Sotos (M = 18.53, SD = 5.12, range = 4 – 24), TD (M = 21.40, SD = 3.29, range = 13 – 24) and WS (M = 14.63, SD = 4.87, range = 3 – 22) participants. In order to determine whether accuracy differed between congruent trials and incongruent trials for the three groups, a 2 x 3 (trial type: congruent/incongruent x group: Sotos/TD/WS) mixed measures analysis of variance (ANOVA) was used to compare total congruent scores and total incongruent scores between the three groups. The analysis identified a significant main effect of congruency, $F(1, 65) = 23.75$, $p < .001$, $\eta\rho^2 = .268$, a significant congruency x group interaction, $F(2, 65) = 14.81$, $p < .001$, $\eta\rho^2 = .313$ and a significant main effect of group, $F(2, 65) = 6.03$, $p = .004$, $\eta\rho^2 = .156$. This indicates that there was a significant difference between accuracy on congruent and incongruent trials, there were overall differences in performance between the groups and that performance on the trial types differed between the groups[1].

[1] The nature of these results did not change when controlling for age using an ANCOVA: a significant main effect of congruency, $F(1, 64) = 14.83$, $p < .001$, $\eta\rho^2 = .188$, a significant congruency x group interaction, $F(2, 64) = 16.13$, $p < .001$, $\eta\rho^2 = .335$ and a significant main effect of group, $F(2, 64) = 7.90$, $p = .001$, $\eta\rho^2 = .198$.

As our research question was to investigate how ANS acuity in Sotos syndrome compares to both TD and WS and the initial analysis identified a significant group x trial type interaction, separate analyses were used to identify whether there were specified group differences in performance. A 2 x 2 (trial type: congruent/incongruent x group: Sotos/TD) mixed measures ANOVA was used to compare total congruent scores and total incongruent scores between the Sotos and TD groups in order to establish whether performance was impaired in the Sotos group. Specifically, a significant main effect of group would indicate that Sotos syndrome is associated with an ANS deficit, whilst a significant interaction would indicate that Sotos syndrome is associated with an inhibitory control deficit, rather than an ANS deficit. A significant main effect of group and a significant interaction would suggest that Sotos syndrome is associated with both an ANS deficit and an inhibitory control deficit.

The analysis identified a significant congruency x group interaction, $F(1, 42) = 5.92$, $p = .019$, $\eta\rho^2 = .123$, but no main effect of congruency, $F(1, 42) = 1.91$, $p = .174$, $\eta\rho^2 = .044$ and no main effect of group, $F(1, 42) = 1.78$, $p = .190$, $\eta\rho^2 = .041$. As the analysis identified a significant interaction, post-hoc comparisons (using a Bonferroni correction $p < .025$ required for significance) were used to compare total congruent scores and total incongruent scores between the groups. The comparisons revealed no significant difference between total congruent scores for the Sotos and TD groups, $t(42) = 0.27$, $p = .792$, $d = 0.08$, indicating no difference in accuracy on congruent trials between the groups. There was a trend for the Sotos group to have lower total incongruent scores than the TD group, $t(42) = -2.26$, $p = .029$, $d = 0.70$, and this was a medium-sized effect. This suggests that Sotos syndrome is associated with an inhibitory control deficit but not an ANS deficit.

A 2 x 2 (trial type: congruent/incongruent x group: Sotos/WS) mixed measures ANOVA was used to compare total congruent scores between the Sotos and WS groups in order to establish whether there were syndrome-specific differences in performance. The

analysis identified a significant main effect of congruency, $F(1, 41) = 27.32$, $p < .001$, $\eta\rho^2 = .400$, a significant congruency x group interaction, $F(1, 41) = 5.81$, $p = .02$, $\eta\rho^2 = .124$, but no main effect of group, $F(1, 41) = 3.61$, $p = .065$, $\eta\rho^2 = .081$. As there was a significant interaction, post-hoc comparisons (using a Bonferroni correction $p < .025$ required for significance) were used to compare total congruent scores and total incongruent scores between the groups. The comparisons revealed no significant difference between total congruent scores for the Sotos and WS groups, $t(41) = -0.34$, $p = .736$, $d = 0.11$, indicating no difference in accuracy on congruent trials between the groups. The Sotos group had significantly higher total incongruent scores than the WS group, $t(41) = 2.55$, $p = .015$, $d = 0.80$, and this was a large effect. Overall, these results suggest that the WS group had more inhibitory control difficulties than the Sotos group. Figure 1 shows the mean congruent total scores and mean incongruent total scores for the Sotos group, TD group and WS group.

[Insert Figure 1 about here]

Relationships between approximate number system acuity and quantitative reasoning ability

A quantitative reasoning task was administered to 17 participants with Sotos syndrome (10 males and 7 females; mean age = 19.13 years, SD = 8.51 years). Quantitative reasoning T-scores ranged from 20 – 59 (M = 29.41, SD = 10.62). The association between accuracy on congruent and incongruent trials and quantitative reasoning ability was assessed. Spearman's rank identified a weak, non-significant relationship between total congruent scores and quantitative reasoning T-scores, $r_s = .139$, $N = 17$, $p = .595$. Spearman's rank identified a strong positive relationship between total incongruent scores and quantitative

reasoning T-scores, $r_s = .597$, $N = 17$, $p = .011$. This indicates that, for individuals with Sotos syndrome, better accuracy on incongruent trials, but not congruent trials, is related to higher quantitative reasoning ability.

Discussion

The primary aim of this study was to explore the ANS in individuals with Sotos syndrome, using a dot comparison task, in order to establish whether ANS acuity is impaired within this population. In addition, a cross-syndrome approach was used to investigate syndrome-specific differences in task performance, in relation to a matched group of individuals with WS. The relationship between performance on congruent and incongruent trials and quantitative reasoning ability was assessed for participants with Sotos syndrome. The findings indicate that ANS acuity is not impaired in Sotos syndrome, as evidenced by no significant difference in total congruent scores between the Sotos syndrome and the chronological age matched TD group. However, the Sotos syndrome group was less accurate on incongruent trials than the TD group, suggesting an inhibitory control deficit. Furthermore, cross-syndrome comparisons identified no significant difference in performance on congruent trials between the Sotos and WS groups. However, the Sotos syndrome group were significantly more accurate on incongruent trials, compared with the WS group, indicating that inhibitory control is less impaired in Sotos syndrome than WS. A significant relationship was identified between accuracy on incongruent trials and quantitative reasoning ability for participants with Sotos syndrome, indicating that better accuracy on incongruent trials is associated with higher quantitative reasoning ability. As these trials require inhibitory control, this suggests that poor inhibition skills may contribute to numerical difficulties within this population.

Comparison of performance on congruent and incongruent trials revealed a significant difference in performance on these trial types of the dot comparison task for the Sotos and TD groups. Specifically, although ANS acuity was not impaired for individuals with Sotos syndrome, these participants were less accurate on incongruent trials, compared with the TD control group. Furthermore, a cross-syndrome approach enabled performance of the Sotos syndrome participants to be interpreted in relation to participants with WS. Specifically, this revealed that the Sotos syndrome participants were more accurate on incongruent trials, compared with the WS group. This indicates that, although the Sotos group were less accurate than the TD group, the congruency effect was more pronounced in the WS group, compared with the Sotos group, suggesting that inhibitory control is more impaired in WS than Sotos syndrome. Previous research has established that individuals with WS have difficulties with inhibition so this could account for the lower accuracy observed on the incongruent trials for this group (Mobbs et al., 2007, Porter et al., 2007). To date, inhibitory control has not been directly investigated within the Sotos syndrome population, so this will be an important direction for future research.

Previous research has reported that the ANS is associated with mathematical achievement in typically developing populations (Chen and Li, 2014, Dehaene, 2001, Mazzocco et al., 2011b, Halberda et al., 2008). Furthermore, it has been suggested that accuracy on incongruent trials, rather than congruent trials, is related to mathematical achievement and that the relationship between the ANS and mathematical achievement can be attributed to the confound of inhibitory control (Gilmore et al., 2013, Clayton and Gilmore, 2015). Specifically, poor inhibitory control may result in difficulty inhibiting an incorrect response to incongruent trials, resulting in participants selecting the set with larger individual dots, rather than a larger quantity of dots. This means that participants use an inferior strategy to complete the task by relying on the size of the individual dots as an

indicator of the total quantity of dots. The findings from the present study indicate that inhibitory control is associated with quantitative reasoning ability for individuals with Sotos syndrome, as evidenced by a significant association between total incongruent scores and quantitative reasoning ability. In addition, there was no association between total congruent scores and quantitative reasoning ability, indicating that performance on these trials is not associated with mathematical ability for individuals with Sotos syndrome. Thus, the findings from the present study indicate that poor inhibition skills may contribute to the numerical difficulties observed within the Sotos syndrome population.

In typically developing individuals, domain-general abilities such as language, visuospatial processing, attention and executive functions have been identified as important contributors to numerical development (Bull and Scerif, 2001, Cragg and Gilmore, 2014, LeFevre et al., 2010, Simms et al., 2016). As Sotos syndrome is associated with developmental delay, an uneven cognitive profile and motor difficulties, it will be important to investigate the phenotype more broadly in order to determine specific factors which may be associated with numeracy development within this population. Furthermore, assessing a range of domain-specific numeracy skills and relationships between these skills and mathematical achievement will advance understanding of potential mechanisms underlying numerical difficulties for individuals with Sotos syndrome.

The present study used a relatively small sample, in order to gain a preliminary insight into the ANS and to establish the feasibility of assessing domain-specific numeracy skills within this population, despite intellectual disability and relatively poor numerical reasoning ability (Lane et al., 2018). Only one of the Sotos syndrome participants failed to progress to the main dot comparison task, indicating that this task was appropriate for this population. However, it is important to note that the present study only included a sample with a minimum age of 8 years and that the participant who did not pass the practice trials

was 8 years of age. Therefore, it will be important for future research to determine whether ANS acuity is typical or impaired in younger children with Sotos syndrome and the feasibility of assessing the ANS in a younger sample of children within this population. Furthermore, as research with typical populations has suggested that the relationship between ANS and mathematical achievement is stronger in young children, it will be useful to establish whether this is also apparent within the Sotos syndrome population (Fazio et al., 2014). This has important implications for considering appropriate interventions to support numeracy development within the Sotos syndrome population and the age at which these may be most effective.

In summary, this is the first study to explore the ANS in Sotos syndrome. The findings indicate that ANS acuity is not impaired in individuals with Sotos syndrome. However, the Sotos syndrome participants showed a congruency effect, with worse accuracy on incongruent trials, compared to the TD participants. Furthermore, cross-syndrome comparisons revealed no differences in accuracy on congruent trials between the syndromes but the Sotos syndrome participants were more accurate on incongruent trials than the WS group. Better accuracy on incongruent trials was associated with higher quantitative reasoning ability for individuals with Sotos syndrome, indicating that inhibitory control is important for numeracy within this population. In order to further understanding of the numerical difficulties associated with Sotos syndrome, it will be important for future research to investigate other domain-specific numeracy skills, as well as the role of domain-general abilities, such as executive functions, in the development of these skills, across development. Ultimately, this approach will enable appropriate and effective strategies to be implemented to support numerical development within this population.

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Table 1. Participant characteristics

Characteristics	Sotos syndrome (n = 20)	TD controls (n = 25)	WS (n = 24)
Chronological age (in years)			
Mean	18.43	18.04	21.04
SD	9.29	8.68	13.67
Range	8.00 – 37.42	7.92 – 42.08	8.00 – 52.25
Sex (n)			
Males	11	12	7
Females	9	13	17
Mental age (in years)			
Mean	6.95	-	6.13
SD	2.80	-	1.48
Range	3.83 – 13.75	-	3.33 – 8.83

Figures

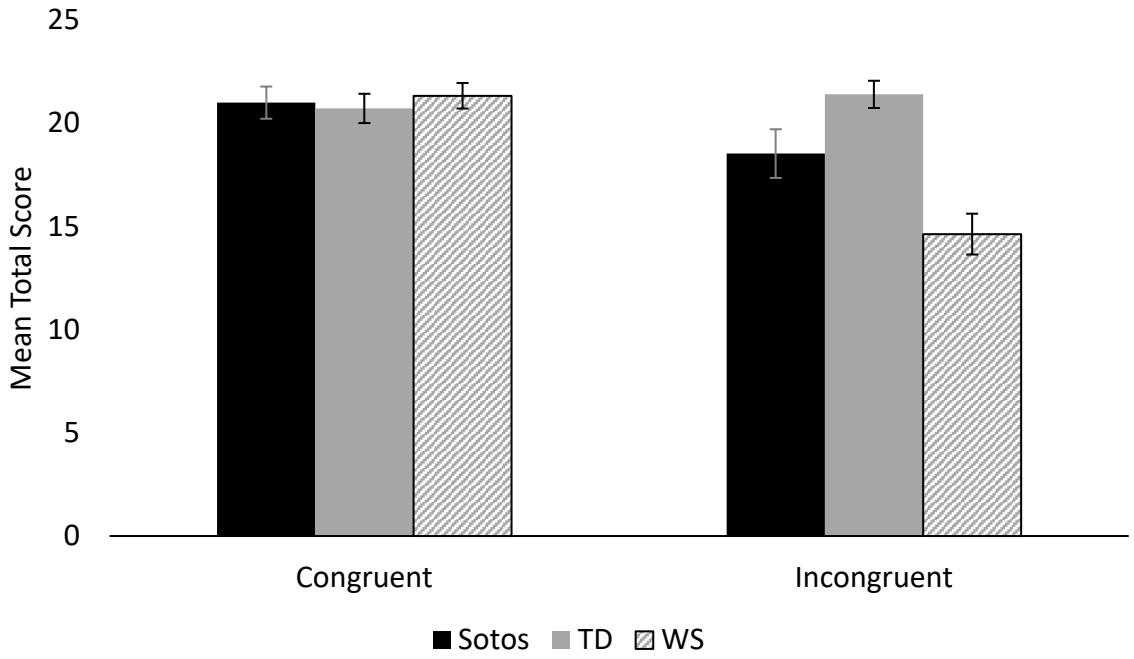

Figure 1. Mean total congruent scores and total incongruent scores for the Sotos syndrome group, typically developing (TD) group and Williams syndrome (WS) group. Error bars show +/- 1 standard error.