CANDY

Comorbid Analysis of Neurodevelopmental Disorders and epilepsY

Deliverable D2.7

Report on prototype of tablet based translational test battery for pre-schoolers

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1 Executive summary

Currently, our ability to assess social, cognitive and emotional development in neurodivergent children is hampered by the lack of suitable, validated tests. For example, many preschoolers (and notably those with neurodevelopmental conditions and/ or developmental delay) find it difficult to understand verbal task instructions, and the majority of neuropsychological tests can be fairly long and "boring", so that children are either unwilling or unable to complete the tests. Moreover, for some domains, such as reward or sensory processing, relevant preschool versions are altogether lacking.

The goal of Deliverable 2.7 is to optimise and validate a set of touch screen tests in preschoolers with neurodevelopmental conditions (autism, ADHD, ID and/or epilepsy), and to implement the battery in clinical studies carried out in WP4 (the Preschool Brain Imaging and Behaviour Project) and WP5 (Multiplex Family Study.

The majority of these tasks were initially developed between 2018-2020, and form part of a larger research project funded by the Simons Foundation for Autism Research (SFARI) to develop touch screen tests covering six bio-behavioural domains (social, cognitive, reward, emotional, un/predictability and sensory processes) and that are suitable for children from 3 years to adulthood.

As part of CANDY WP2, Task 2, we focused specifically on optimising and validating sub-tests of relevance for ADHD and developmental delay (inhibitory control, social and 'non-social' reward processing, sustained attention, temporal discounting). We added to this a 'translational test' of social novelty (aligned with WP2, Task 1). Task development has been an iterative process. Evaluation criteria involve acquisition rates, face validity, construct validity, split-half and test-retest reliability (as well as sensitivity to change). If a task does not meet acceptable thresholds on one or more criteria, the task was revised and then administered to a new group of children.

Version 0.8.6 of the above tests was implemented in the AIMS-TRIALS/ CANDY Preschool Brain Imaging and Behaviour Study. We report preliminary analyses of these tests as well as parallel work aimed at developing robust clustering techniques to identify "cognitive subgroups" based on the combination of test performance across domains.

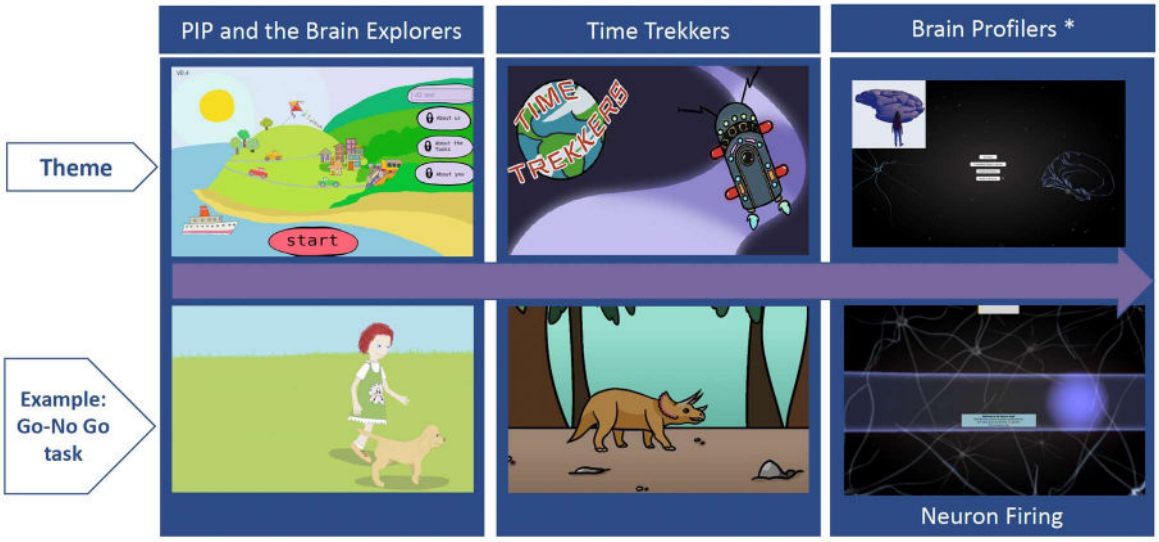
In additional task development work (Version 0.87 to 0.89) we used Bayesian Adaptive Optimatisation (an artificial intelligence algorithm) to "optimise" test components (speed, complexity) depending on a child's performance and to create a shorter version of some subtests to increase acquisition rates in preschoolers with ID (such as rare genetic syndromes)

2 Introduction

Detailed assessment of children's social, cognitive, motivational and emotional development is critical to 1) understand a child's (relative) strengths and difficulties as a basis to informing treatment/ support needs, 2) identify potential clinically-relevant subgroups that may help us to make more accurate prognoses of developmental trajectories.
While standardised tests of several cognitive processes (most notably "IQ tests") exist, we do not have comparable "transdiagnostic" measures of many domains that are relevant for neurodevelopmental conditions, such as social, reward, un/predictability or sensory processes. Moreover, many existing tests are not suitable for preschoolers with neurodevelopmental conditions, many of whom have limited attention span or motivation to complete formal tests.

As part of a SFARI funded projected, we have created a touch screen battery that comprises three versions: A preschool version called "Pip and the Brain Explorers" for children aged 3-6 years (or neurodivergent children with lower cognitive ability levels/ mental ages) a school-going version ("Time Trekkers") for children aged 6-14 years (which increased the 'gaming' character of tests to make tests more attractive) and an adolescent/ young adult version ("Brain Rangers", from 13 years +). Each version includes most of the same tests, which however vary in terms of surface features and task difficulty/ complexity. Figure 1 gives an overview of the platform.

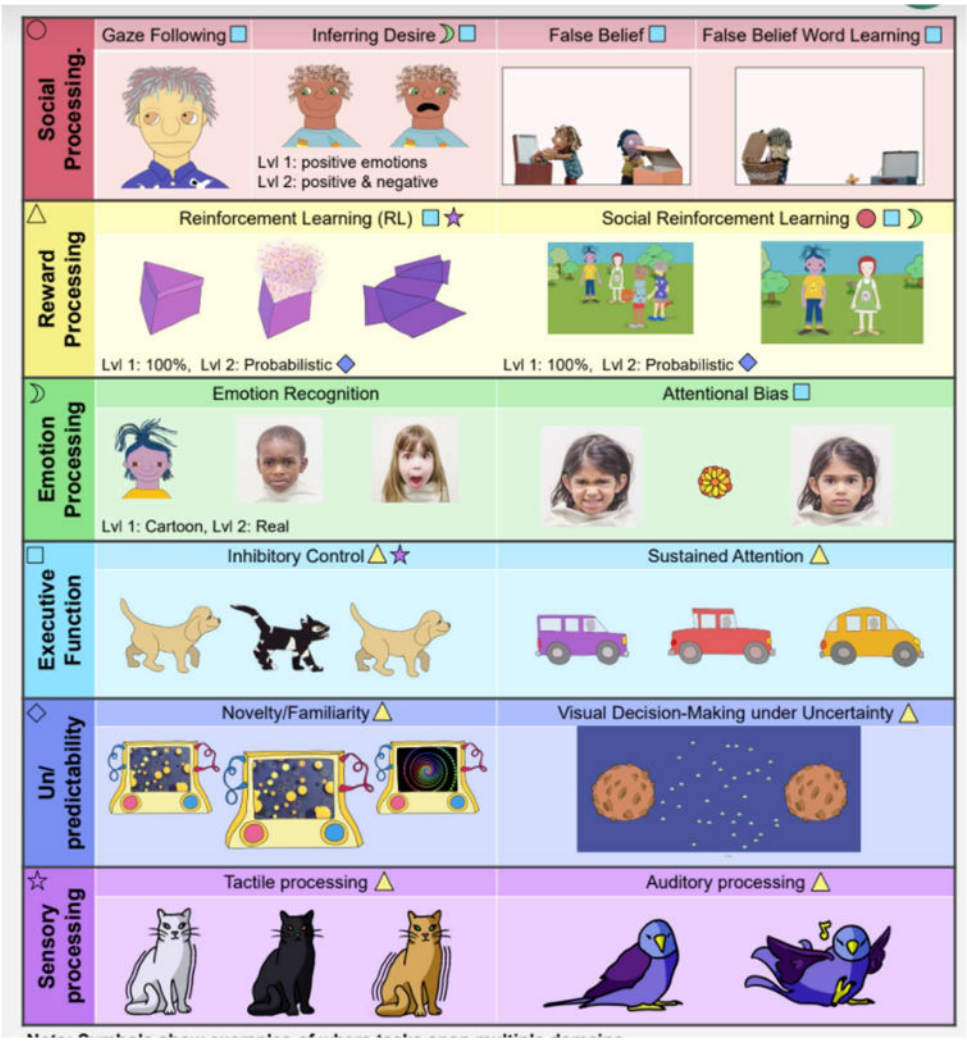
Figure 1. Three versions of the touch screen battery for preschoolers (and children/ people with intellectual disability), school-going children, and adolescents/ young adults



In the following we predominantly report on the preschool version (see Figure 2), which consists of 12 subtests.
The tasks were programmed in the Unity Game Engine Environment using the C# coding language. They can be downloaded as app onto any tablet system. The cartoon characters include children of multiple ethnicities; some have autistic or ADHD traits or are non-verbal. Subtests are arranged modular around a continuous theme (Pip's world) and include recurrent features (e.g., Pip's car, butterflies, trains, Pip's puppy, kite). To appeal to the 'literal mind' of many neurodivergent children and avoid confusion, we ensured that all tests follow an intrinsically plausible narrative/ structure. Task instructions are kept to a minimum. A demonstration (animated cartoon), presented by the

characters (Pip, the "Scientist") to standardize instructions and enable the use of these tablet tasks at home, with minimal input required from parents (researchers). The character of our demonstration/ instruction videos are similar to the "Pip and the Brain Explorers" video. (see https://vimeo.com/251640114). We record full tablet interaction (how it is moved, where and how frequently it is touched), which allows us to complement standard cognitive metrics (e.g., response time) with non-conventional ones to account for factors in responses that may be more frequently associated with ASD/ ID. We also developed SOPs and user manuals, and more recently, a demonstration video for users. Across subtests, 1 to 6 pilot versions were created and iteratively refined with lived-experience input.

Figure 2. Overview of the Domains and Subtests comprising the Preschool Task Battery



Version 0.8.6 was implemented into the Preschool Brain Imaging and Behaviour Project. In collaboration with AIMS-2-TRIALS/ CANDY staff, we translated the preschool battery into Dutch, Swedish, and French. In parallel, the tasks have been administered online to ~50 families, and in person to 500-1200 children aged 4-14 years who took part in the South African Safe Passage BONO study.

3 Main section

3.1 Task Validation

3.1.1 Task validation in the Preschool Brain Imaging and Behaviour Study

Interim analyses of 82 to 123 children (including 21 autistic children) aged 2.5 to 4.5 years across different subtests (e.g., inhibitory control, reward learning) were carried out in January 2023. Validation criteria included 1) data acquisition rates, which includes children's comprehension of task/ task instructions, motivation to complete the task 2) several psychometric properties, including split- half reliability (consistency, and order/ fatigue effects), test-retest reliability, construct validity, effect of assessment procedures (i.e. researcher administered during lab-visit vs. tested at home by parents [this includes the period between 2020-2022 where several labs underwent COVID-19 restrictions and KCL implemented a 'remote-testing protocol'). In addition, we tested in a subsample 3) the effect of version/ surface features (ie., comparison between preschool and school going task versions of the same task level/ difficulty) as well as devices (smartphone vs. tablet).
Data acquisition rates for the vast majority of subtests were higher for the neurotypical group (inhibitory control: neurotypical: 92%, neurodivergent: 68% , sustained attention: neurotypical:81%, neurodivergent: 64%, reward learning: neurotypical: 95%, neurodivergent: 89%, social reward learning: neurotypical: 80%, neurodivergent: 59%

As the data freeze of the CANDY groups (children with ID, ADHD, and epilepsy) has been extended to December 2023, below we report on preliminary analyses of 239 children (142 typically developing children, 82 autistic children, and 15 children with a 'suspected' autism diagnosis, who were undergoing referral processes or were on a 'waiting list' at the time of the assessment. Table 1 summarises the acquisition rates of children with ID and ADHD. These data are however not include in the between-group and clustering analyses reported below.

Table 1. Touchscreen **data acquisition rates**[1] with a subset of baseline data from the CANDY clinical groups in the PIP study including data available up to September 2023

[1]Data acquisition rates are based on observations (clinical record forms) from the data collection team at each site. Partial % is when some trials were collected but the task was incomplete (i.e. less than 50% of trials completed).

Task	**ADHD (N = 19)**	**Developmental Delay (N = 28)**
Bubbles	Complete: 95% Partial: 5% Not complete: 0%	Complete: 86% Partial: 0% Not complete: 14%
Find the puppy	Complete: 90% Partial: 10% Not complete: 0%	Complete: 50% Partial: 7% Not complete: 43%
Magic box	Complete: 90% Partial: 10% Not complete: 0%	Complete: 68% Partial: 11% Not complete: 21%
Come play with me	Complete: 90% Partial: 0% Not complete: 10%	Complete: 54% Partial: 7% Not complete: 39%
What does PIP want	Complete: 84% Partial: 0% Not complete: 16%	Complete: 32% Partial: 11% Not complete: 57%
Pip's car	Complete: 68% Partial: 16% Not complete: 16%	Complete: 43% Partial: 7% Not complete: 50%
Good days, bad days	Complete: 79% Partial: 5% Not complete: 16%	Complete: 21% Partial: 4% Not complete: 75%
False belief	Complete: 84% Partial: 0% Not complete: 16%	Complete: 36% Partial: 4% Not complete: 60%
False belief (word)	Complete: 84% Partial: 0% Not complete: 16%	Complete: 32% Partial: 4% Not complete: 64%

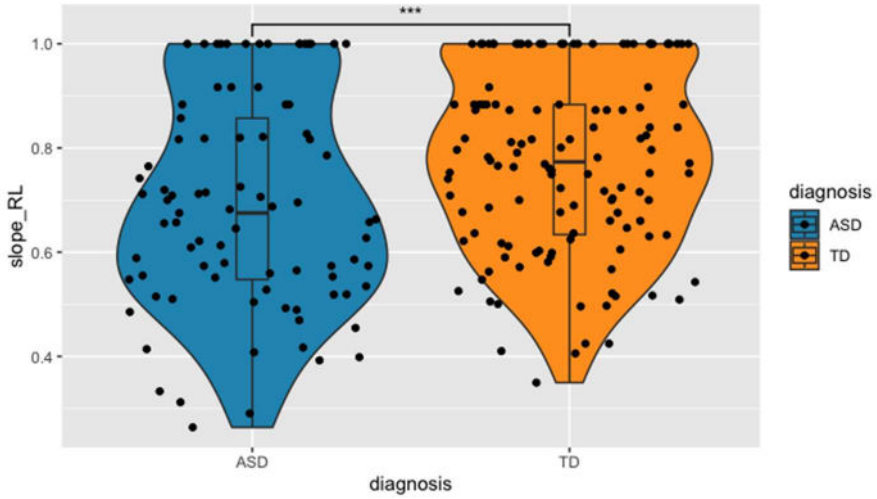
As there were no significant group differences either in clinical profile or neurocognitive task performance between the autistic and suspected-autistic children (except for key dependent variables on the reward learning task) they are collapsed into one group below.

Variable	N	ASD, N = 82[1]	ASD_S, N = 15[1]	TD, N = 142[1]	p-value[2]
gender	239				0.011
F		21 (26%)	2 (13%)	59 (42%)	
M		61 (74%)	13 (87%)	83 (58%)	
Go-No Go accuracy	144	83 (64, 94)	76 (66, 96)	85 (73, 93)	0.4
Go-No Go d'	144	2.08 (0.82, 2.50)	1.65 (0.79, 2.86)	2.19 (1.35, 2.75)	0.5
Go-No Go mean RT	144	0.85 (0.73, 0.96)	1.00 (0.87, 1.08)	0.90 (0.77, 1.00)	0.2
Sustained attention accuracy	153	0.92 (0.87, 0.96)	0.89 (0.87, 0.94)	0.92 (0.88, 0.95)	0.5
Sustained attention d'	153	2.37 (1.64, 3.06)	2.27 (0.83, 2.77)	2.27 (1.61, 2.91)	0.7
Sustained attention mean RT	144	0.96 (0.89, 1.07)	0.92 (0.75, 0.95)	1.02 (0.88, 1.16)	0.091
Non-Social Reward Learning Accuracy	227	0.67 (0.57, 0.80)	0.67 (0.55, 0.75)	0.73 (0.60, 0.83)	0.059
Non-Social Reward learning mean RT	227	1.78 (1.50, 2.16)	1.95 (1.56, 2.62)	2.00 (1.69, 2.52)	0.033
Non-Social Reward Learning Rate	227	0.66 (0.53, 0.83)	0.71 (0.56, 0.96)	0.78 (0.63, 0.96)	0.009
Non-Social Reward Learning Criterion	227	22 (11, 30)	17 (10, 30)	14 (9, 25)	0.028

[1] n (%); Median (IQR)

[2] Pearson's Chi-squared test; Kruskal-Wallis rank sum test

As expected, we found significant age effects on inhibitory control (accuracy), sustained attention (d-prime), and non-social reward learning (accuracy, learning rate)
There were also significant relationships of IQ to inhibitory control (accuracy), sustained attention (d-prime), and Response Time Variability (RTV), and non-social reward learning (all dependent variables).
We found significant mean-group differences in Response Time Variability; a parameter that has previously been linked to ADHD, on the Inhibitory Control task but not on the key dependent variables (inhibitory control index) as well as significant group differences in terms of reward learning (with lower accuracy and learning rates in the autism group). There were no significant group differences in terms of sustained attention.



Density-based clustering

We then used a novel density-based clustering approach (developed by collaborator Prof Mick Brammer, which has capacity to deal with different categorical, rank and parametric variables) to identify subgroups based on the combined performance across the three tasks. In this analysis, we used key performance variables only. For children who moved on to the main trials, but were not able to reliably complete the task, we imputed low values which indicate poor performance. This yielded a sub-sample of 170 children. We identified a four-cluster solution. The clusters (subgroups) differed on the total score on the ADHD Rating Scale ($p<0.01$), as well as on the inattention ($p<0.01$) and hyperactivity-impulsivity subscale ($p<0.05$). The subgroups also showed significant differences in terms of social-communicative features (SRS total score), and the total score on the Sensory Experience Questionnaire ($p<0.01$) and the hypo-responsiveness sub-scale ($p<0.01$).

After correcting for multiple comparisons, the ADHD-likelihood cluster (Subgroup 1) showed a significant difference with cluster 2 and cluster 4, but not cluster 3 on all clinical measures, apart from the SRS Restrictive and Repetitive Behaviours. The subgroups also differed on all in-model measures derived from the neurocognitive tasks apart from the mean response time on the reward learning task.

Further analyses including the "Candy" clinical groups ADHD, ID and epilepsy are planned. Additional validation will include comparing subgroups on brain anatomical indices in brain networks implicated in inhibitory control (prefrontal areas) and reward processing (subcortical areas of the ventral striatum and amygdala).

Cluster	N	1, N = 21[1]	2, N = 97[1]	3, N = 18[1]	4, N = 34[1]	p-value[2]
diagnosis	170					<0.001***
Autism		12 (57%)	27 (28%)	15 (83%)	13 (38%)	
TD		9 (43%)	70 (72%)	3 (17%)	21 (62%)	
gender	170					0.3
F		5 (24%)	34 (35%)	3 (17%)	8 (24%)	
M		16 (76%)	63 (65%)	15 (83%)	26 (76%)	
Age (days)	170	1,133.10 (±306.76)	1,322.43 (±211.18)	1,253.78 (±371.68)	1,254.71 (±337.80)	0.056
Inattention Score	144	11.06 (±4.96)	6.76 (±5.33)	8.62 (±5.56)	5.52 (±4.21)	0.002**
Hyperactivity-Impulsivity Score	147	11.94 (±5.75)	8.29 (±5.94)	9.00 (±7.16)	6.47 (±4.56)	0.027*
ADHD Rating Scale Total Score	143	23.29 (±10.39)	15.05 (±10.69)	17.62 (±12.33)	12.30 (±7.59)	0.007**
Total SRS score	131	71.88 (±40.77)	46.01 (±34.73)	70.89 (±43.31)	42.12 (±25.56)	0.007**
SRS Social Awareness	145	10.58 (±3.76)	8.65 (±3.84)	11.57 (±4.05)	8.07 (±3.02)	0.004**
SRS Social Motivation	145	12.05 (±6.73)	7.90 (±6.46)	10.58 (±6.30)	7.21 (±4.36)	0.020*
SRS Restrictive and Repetitive Behaviours	146	11.11 (±9.22)	6.03 (±6.89)	11.82 (±9.84)	5.57 (±4.50)	0.018*
SRS Social Communication	142	23.29 (±13.83)	13.99 (±12.98)	24.00 (±12.27)	12.36 (±9.41)	<0.001***
SRS Social Cognition	144	15.22 (±8.61)	8.85 (±7.10)	14.82 (±8.46)	8.86 (±6.03)	0.004**
SDQ Hyperactivity	135	5.22 (±2.69)	3.90 (±2.95)	5.42 (±3.12)	4.04 (±2.62)	0.2
SDQ Prosocial Behaviour	136	5.06 (±2.34)	7.13 (±2.65)	4.18 (±2.79)	7.18 (±2.54)	<0.001***
Early Learning Composite on the Mullen	162	90.68 (±25.32)	104.61 (±24.30)	67.57 (±18.05)	104.30 (±20.18)	<0.001***
Sensory Experiences Questionnaire Total Score	136	44.56 (±16.88)	33.58 (±19.01)	46.85 (±21.65)	32.14 (±13.52)	0.010*
Sensory Hyporesponsiveness	132	6.31 (±4.11)	4.16 (±3.82)	7.33 (±4.83)	3.34 (±2.55)	0.007**
Sensory Hyperresponsiveness	134	17.65 (±9.16)	12.32 (±8.64)	14.46 (±8.21)	12.17 (±5.82)	0.076

[1] n (%); Mean (±SD)
[2] *p<0.05; **p<0.01; ***p<0.001

3.1.2 Task validation in the South African Safe Passage BONO Study

The school going version (“Time Trekkers”) including comparable versions of inhibitory control (“Dino go”), probabilistic reward learning (“Treasure Chest”), social reward learning (“Royal feast”, “let’s play”), sustained attention (“Pirate ships”) was implemented in a study of currently 900 South African children aged 6-14 years.

3.2. Task Optimisation

(1) Fudge Factor Test: to explore the fudge factor’s influence on user performance, 3 versions of the “Bubble Pop” tasks have been created with different fudge factors.

(2). “Find the Puppy”: to make the task shorter, two more versions were added. Version 1 reduced the original task’s main trial length. Version 2 reduced the original task’s main trial length and deleted the practice trial session. These versions are currently tested in children with rare genetic syndromes and intellectual disability in a collaboration with Dr Caroline Richards and Rory O’Sullivan at the University of Birmingham.

3. New Technical Capabilities

Several technical capabilities were added, including:

(1). A deep learning-based voice clone pipeline was developed to replace the time consuming and expensive voiceover workflow. It provides an efficient way to customize the audio content to new languages. A Slovenian version for all tasks has been developed based on this pipeline without introducing extra costs. A Chinese version is currently under development.

This will enable us to acquire data with Slovenian and Chinese collaborators, and to validate findings across different countries and cultures.

(2). Logging file conversion pipeline. The logging files are tsv format which is not supported in mainstream analysis software e.g. R. Manual conversion of the tsv files is time consuming. So we wrote a Python based auto-conversion pipeline which can automatically convert tsv to csv to facilitate analysis.

3.3. Additional task development

We added a translational social habituation task to the Time Trekkers battery. The task consists of an adapted version of the children's game "Rock, paper scissors" where participants can choose after a habituation period to either continue playing with a familiar character or new opponents. The task was developed together with preclinical experts at UNIBAS and inspired by recent findings that genetic abnormalities in neurologin-3 impact oxytocin signalling in dopaminergic neurons in the ventral tegmental area, as well as social habituation/ novelty response. Both molecular and behavioural responses could be 'rescued' by a specific MNK that restored oxytocin signalling through resetting of translational regulation [1]. Back-translation of the social habituation paradigm may help us to identify in the future a potential subgroup for treatment with this MNK Inhibitor, or serve as secondary (surrogate) outcome measure.

4. Conclusions

Tests of inhibitory control and reward processing work well with the majority of typically developing preschool children from the age of 3 years.

5. Glossary

6. Abbreviation / acronym	Description
ADHD	Attention deficit / Hyperactivity Disorder
ASD	Autism Spectrum Disorder
ID	Intellectual Disability
IQ	Intellectual Quotient
MNK	MAPK-Interacting Kinases
RTV	Response Time Variability
SFARI	Simons Foundation Autism Research Initiative
SOP	Standard Operating Procedure
SRS	Social Responsiveness Scale
WP	Work Package

7. Bibliography

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