Behavior and cognitive functioning in Witteveen–Kolk syndrome

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Abstract
Witteveen–Kolk syndrome (WITKOS) is a rare neurodevelopmental disorder characterized by developmental delay/intellectual disability, facial dysmorphisms, and short stature. The syndrome is caused by loss of function of switch-insensitive 3 transcription regulator family member A (SIN3A). Regarding behavioral functioning, Autism Spectrum Disorders (ASD), obsessive–compulsive behaviors, as well as Attention-Deficit/Hyperactivity Disorder symptoms (ADHD) have been suggested. The present study explores various aspects of neurocognitive functioning in five individuals (age range 10–23) with WITKOS. Medical records and results of extensive neuropsychological assessment are used to describe developmental trajectories and neurocognitive profiles. Systematic analysis of medical records displays developmental difficulties described as ASD or ADHD in childhood, sleep problems and internalizing problems during adolescence. Results of cognitive assessments indicate profoundly disabled (n = 1), mildly disabled (n = 2), borderline (n = 1), and average (n = 1) levels of intelligence. Furthermore, results indicate weaknesses in speed of information processing/sustained attention in all participants, and difficulties in planning and maintaining overview in three participants. Furthermore, parent reports of behavioral functioning primarily suggest problems in social functioning. Implications of both cognitive problems and social–emotional vulnerabilities for counseling are discussed and supplemented with suggestions for interventions.

KEYWORDS
case-series, cognition, contextual neuropsychology, neurodevelopmental disorder, SIN3A, Witteveen–Kolk syndrome

1 | INTRODUCTION

The neurodevelopmental disorder Witteveen–Kolk syndrome (WITKOS; OMIM #613406) was identified to be caused by...
heterozygous mutations in SIN3A. Since SIN3A is located in the 15q24 region, haploinsufficiency of this gene is expected to contribute substantially to the phenotype seen in patients with 15q24 microdeletion syndrome (Mefford et al., 2012; Witteveen et al., 2016). To date, 16 patients with WITKOS have been reported worldwide; 10 with intragenic SIN3A mutations—including two families with each three affected members—and six with chromosomal microdeletions encompassing SIN3A (Mefford et al., 2012; Narumi-Kishimoto et al., 2018; Witteveen et al., 2016). The resemblance between these patients includes typical facial dysmorphisms (broad and high forehead, full eyelids, depressed nose bridge, a small mouth, and down-slanted palpebral fissures) as well as short stature and microcephaly (in half of the described patients). Hypermobile joints and hearing loss have also been reported. As to brain imaging, subtle brain abnormalities, present in some patients, include cortical/corpus callosum dysgenesis, white matter abnormalities, and enlarged ventricles.

The sparsely described behavioral and cognitive features seem to be characterized by developmental delay, a mild intellectual disability (ID; present in 13/16) and behaviors that were classified as an ASD (Mefford et al., 2012; Narumi-Kishimoto et al., 2018; Witteveen et al., 2016). Besides ASD, obsessive–compulsive as well as ADHD symptoms have also been reported. Understanding the associated cognitive functions of the described psychopathology is essential in order to provide both effective treatment and counseling in daily living (Roelofs, 2019; Roelofs, Wingbermühle, Kessels, and Egger, 2019).

Until now, behavioral problems in WITKOS have not been substantiated with psychological measures, and potential associated cognitive deficits have not been studied either. To address this issue, this study aims to explore behavioral and cognitive functioning by means of extensive neuropsychological assessment in five patients with WITKOS, to provide insights and tools for an adequate syndrome specific treatment strategy.

2 | METHODS

Five participants (three males, mean chronological age 13.8 years, age range 10–23) with a pathogenic mutation in SIN3A without carrying any other known pathogenic variants were included. All participants were approached for the study by the Department of Human Genetics of the Radboud University Medical Centre (Nijmegen, The Netherlands) and they participated voluntarily. The molecular and phenotypical characteristics of three participants have previously been reported (Witteveen et al., 2016). Data of all participants were collected by both systematic analysis of their medical records and an extensive assessment of intelligence, cognition and behavioral functioning. The study was conducted according to the Declaration of Helsinki and approved by the Central Committee on Research Involving Human Subjects region Arnhem-Nijmegen (NL43187.091.13) with written informed consent obtained from all participants, or their legal representatives.

From medical records, both levels of intelligence and levels of adaptive functioning were extracted. Adaptive functioning refers to the conceptual, social and practical skills that have been learned by people in order to function in everyday life (American Association on Intellectual and Developmental Disabilities, 2019), and was mainly measured by semi structured proxy interviews (Vineland Adaptive Behavior Scales; VABS). In the VABS, different domains of functioning can be distinguished, including communication, daily functioning, and social skills. Communication comprises speech, language understanding, reading and writing. Social skills cover a more general understanding of behavior in social situations. Daily functioning skills refer to a general ability to take care of oneself (e.g., dressing up, house cleaning, use of money, and safety in traffic).

As part of the cognitive assessment, intelligence was measured by state-of the-art, age-appropriate intelligence tests (Wechsler Adult Intelligence Scale - fourth edition, WAIS-IV; Wechsler Intelligence Scale for Children - third/fifth edition, WISC-III/WISC-V; Snijders-Oomen Non-verbal intelligence test - revised, SON-R; Bayley Scales of Infant and Toddler Development - second edition, BSID-II). Furthermore, a measure of sustained (d2 sustained-attention test) attention was obtained, as well as measures of executive functions that focus on planning and organization (subtasks “Key search” and “Zoo map” of the Behavioural Assessment of the Dysexecutive Syndrome for Children). Executive functioning refers to complex control mechanisms such as planning, shifting and monitoring that enable a person to perform effective, goal-directed and self-regulating behavior (Barkley, 2012; Blesmans, van Aken, Frunt, Wingbermühle & Egger, 2019; Lezak, Howieson, Tranel & Bigler, 2012; Salthouse, 2005). As for memory functioning, learning tasks with both auditory and visual stimuli were performed (Auditory Verbal Learning Test, Rey Complex Figure Test). Regarding social cognitive functioning, measures included age-appropriate mentalization and emotion recognition tasks (Theory of Mind test Revisited; NEuroPSYchological Assessment II, NEPSY-II; Emotion Recognition Test). Visuoconstruction was measured by the Beery-Buktenica developmental test of Visual-Motor Integration - sixth edition. Psychopathology has been explored by means of several questionnaires that focus on different aspects of behavioral functioning. Due to age-differences, several questionnaires had to be used to be able to tap similar symptoms of psychopathology and behavior. Subjective measures include (by proxy) questionnaires and interviews (CBCL, Child Behavior Checklist; SDQ, Strengths and Difficulties Questionnaire; PIMRA, Psychopathology Instrument for Mentally Retarded Adults; Mini PASS-ADD, Mini Psychiatric Assessment Schedule for Adults with Developmental Disabilities). For a list of references to test manuals of all tests and questionnaires used, see “Supplementary data”. In order to enhance comparability, questionnaire subscales that seem to measure similar psychological constructs were inspected jointly. A subdivision into several domains of behavioral dysfunction was made, based on the similarities of the subscales of the questionnaires. Subdomains include “attention problems”, “anxious/depressed”, “social
problems, behavior problems, and thought problems. For an overview of the subscales that were used for each domain see footnote in Table 1. In order to detect emerging trends in this explorative study, behavior problems were classified as either “absent”, “present but subtle” or “present” for scores that were, respectively, <1 SD, 1–1.5 SD, and ≥1.5 SD from the means of norm groups.

| TABLE 1 | Cognitive and behavioral assessment |
|-----------------|---------------------------------|
| **Patient** | **Mean normative Z-score** | **n impaired (i.e., Z < −1.5)** |
| | 1 | 2 | 3 | 4 | 5 | |
| **Cognition** | | | | | | |
| Intelligence | FSIQ | −2.3<sup>a</sup> | −1.7<sup>b</sup> | 21<sup>c</sup> | −2.5<sup>d</sup> | −0.6<sup>e</sup> | 4/5 |
| | VIQ/VCI | −1.7<sup>a</sup> | NA | NA | −1.3<sup>d</sup> | −0.7<sup>e</sup> | 1/4 |
| | PIQ/PRI | −2.6<sup>a</sup> | NA | NA | −2.7<sup>d</sup> | −0.4<sup>e</sup> | 2/4 |
| | WMI | NA | NA | NA | −2.8<sup>d</sup> | −0.6<sup>e</sup> | 1/2 |
| **Attention** | PSI | NA | NA | NA | −2.0<sup>d</sup> | −0.5<sup>e</sup> | 1/2 |
| | D2 (TN) | −1.6 | −1.5 | NA | −2.0 | −2.0 | 4/4 |
| **Executive functioning** | D2 (F) | 1.1 | −1.5 | NA | 0.5 | 0.9 | 1/4 |
| | Key search | −2.0 | −0.7 | NA | −2.0 | 0.7 | 2/4 |
| **Memory** | Zoo map | −2.0 | −0.7 | NA | −2.6 | −1.6 | 3/4 |
| | Zoo map 2 | −2.4 | 0.8 | NA | −2.3 | 0.7 | 2/4 |
| | CFT Rey copy | −2.0 | −1.5 | NA | −1.3 | −1.1 | 2/4 |
| | CFT Rey recall | −2.6 | −2.6 | NA | <−1.3 | −0.8 | 2/4 |
| | RAVLT immediate recall | −0.6 | <−1.3 | NA | −1.3 | −1.1 | 0/4 |
| | RAVLT delayed recall | 1.1 | >1.4 | NA | −0.4 | −1.1 | 0/4 |
| **Social cognition** | ToM test R | −0.5 | <−2.0 | NA | −2.0 | 0.0<sup>f</sup> | 2/4 |
| | ERT | NA | −2.0 | NA | −0.8 | −1.4<sup>f</sup> | 1/3 |
| **Visuoconstruction** | Beery VMI | −0.2 | −0.7 | NA | NA | −0.7 | 0/3 |
| | Beery visual perception | −0.7 | −1.2 | NA | NA | −1.2 | 0/3 |
| | Beery motor coordination | −0.5 | −0.7 | NA | NA | −0.7 | 0/3 |

Note: +, present (≥1.5 SD); −, absent (<1 SD); ±, present but subtle (1–1.5 SD).

Abbreviations: Beery VMI, beery-buktenica developmental test of visual-motor integration; CFT Rey, Rey-Osterrieth complex figure test; D2 (TN), d2 sustained-attention test (total number of characters processed); D2 (F), d2 sustained-attention test (total number of errors); ERT, emotion recognition task; FSIQ, full scale intelligence quotient; Key Search, Zoo Map 1 and Zoo Map 2 are subtest of the behavioural assessment of the dysexecutive syndrome (for Children); NA: results not available; PIQ, performal intelligence quotient; PRI, perceptual reasoning index; PSI, processing speed index; RAVLT, rey auditory verbal learning test; ToM-test R, theory of mind test-revised; VIQ, verbal intelligence quotient; VCI, verbal comprehension index; WMI, working memory index.

<sup>a</sup>Based on WISC-III; IQ scores are 65, 74, and 61, respectively.
<sup>b</sup>Based on SON-R; IQ score is 74.
<sup>c</sup>Based on BSID-II, developmental age in months.
<sup>d</sup>Based on WAIS-IV; IQ scores are 63, 81, 60, 58, and 70, respectively.
<sup>e</sup>Based on WISC-V; IQ scores are 91, 89, 94–100, 91, and 92, respectively.
<sup>f</sup>Based on the subtests Affect Recognition and Theory of Mind in the NEPSY-II.
<sup>g</sup>Based on the subscales: Attention problems (CBCL), Hyperactivity/inattention (SDQ).
<sup>h</sup>Based on the subscales: Withdrawn/depressed (CBCL) + Anxious/depressed (CBCL), Emotional symptoms (SDQ), Affective disorder (PIMRA) + Anxiety disorder (PIMRA), Depressive disorder (Mini PASS-ADD) + Anxiety disorder (PIMRA).
<sup>i</sup>Based on the subscales: Social problems (CBCL), Peer relations (SDQ) or Autism spectrum disorder (social skills, Mini PASS-ADD).
<sup>j</sup>Based on the subscales: Rule-breaking behavior (CBCL) + Aggressive behavior (CBCL) or Conduct problems (SDQ).
<sup>k</sup>Based on the subscales: Thought problems (CBCL), Schizophrenia (PIMRA) or Psychotic disorder (Mini PASS-ADD).
3 | RESULTS

3.1 | Medical records

Demographic variables, genetic details and other relevant medical characteristics, are displayed in Table 2. The numbers in square brackets in this paragraph refer to the numbers of the respective participants, as described in Table 2.

Developmental history was characterized by delayed motor development in some participants; they walked independently at 30 (1), 18 (2), 14 (3), and 36 (4) months (for participant 5 the exact date was unknown, but motor development was delayed), and problems related to speech and language development were reported in three participants. In all participants, intelligence had been measured at several timepoints in their childhood, displaying a profound ID (3), mild ID (1, 2, 4) and below-average level of intelligence (5). With respect to adaptive functioning, documented results indicated lower levels than would be expected from the full scale intelligence quotient (FSIQ). Moreover, inter-comparison of subdomains of adaptive functioning displayed relatively weak social skills and relative strengths in communication.

In childhood between the age of 6 and 11 years, four participants had been classified with developmental disorders (ADHD [1] and ASD [2,3,4]). Behavior was described as repetitive and rigid, and the children needed an adjusted environment that was highly organized and provided sufficient structure. Enhanced sensory sensitivity for (especially auditive) stimuli was present in all participants. In adolescence and early adulthood, symptoms of depression emerged, including self-harming behaviors and suicidal thoughts/behaviors (1,4). A history of sleep problems was reported in three participants (2,3,4). Treatment of behavioral problems and psychopathology included both psychotropic drugs (methylphenidate (1), oxazepam (4)) and psychotherapy (Eye Movement Desensitization and Reprocessing for trauma as a result of a history of bullying [1]).

3.2 | Neuropsychological assessment: Cognitive and behavioral functioning

Table 1 displays the results of extensive neuropsychological assessment in adolescence or early adulthood in all participants. In participant 3, measurement of cognitive functioning was restricted to a global measurement of intelligence only, due to evident impairments in attention, motor skills, and language functioning, that hampered formal testing. When performances of the four other participants were compared with test norms (representing the general population) of the respective cognitive tests, weaknesses were found in sustained attention and speed of information processing in all participants; as reflected in high deviation scores on the d2 sustained-attention task. All participants worked slowly compared to the average score of the norm group. However, only a small number of errors were made, which may reflect a tendency to prefer accuracy above speed. Moreover, a few participants had problems in planning (1,4,5) and visual memory (1,2). Since the visual memory task that was used requires the initial reproduction of a complex geometric figure, adequate perception and visuoconstructive skills are a prerequisite to perceive the figure as a whole, instead of separate fragments. In order to perform well in this task, participants need to perceive (and remember) both individual parts of the figure, as well as maintaining an overview of the complete figure. Therefore, weak performances on this visual memory task may also reflect problems in visuoconstruction or in the maintenance of overview (executive function).

For results regarding behavioral functioning, based on several interviews and questionnaires, see Table 1. On a group level, problems were mainly seen in social interactions. Additionally, there were indications for attention (2,3,5) and internalizing (depression/anxiety) problems (1,3).

4 | DISCUSSION

In this study, behavioral and cognitive functioning of patients with WITKOS is described systematically for the first time, in a small series. Although behavioral difficulties were previously mentioned for this syndrome, descriptions of behavior were never substantiated by objective measurements.

Full scale intelligence level in the participants varied from mild ID to average intelligence, with the exception of one participant with a profound ID. Other patients with moderate to severe intellectual disability have been described before (Witteveen et al., 2016), hence it is plausible that this is part of the phenotype spectrum. This is supported by the fact that genetic testing for other variants excluded other explanations for the profound ID in this participant. This also applies to the girl with an average level of intelligence; genetic characteristics nor observations during assessment provide an evident explanation for her high level of functioning, her performance is therefore likely to represent the upper end of the phenotype spectrum. Furthermore, medical records of the described participants displayed lower levels of adaptive functioning compared to levels of intelligence, suggesting more profound limitations in daily functioning than expected.

As for specific aspects of cognitive functioning, problems in speed of information processing/sustained attention were present in all participants. Furthermore, weak performances were displayed in tests which required planning and an ability to maintain overview. These findings suggest attentional and executive problems and provide preliminary support for the hypothesis that patients with WITKOS suffer from weaknesses related to suboptimal prefrontal cortex functioning.

It could, however, not completely be ruled out that the established weak performances on attention and executive functioning tasks were related to the participants’ level of intelligence. It is in general difficult to identify specific weaknesses in domains of information processing in patients with an ID, given the fact that the norm groups of multiple cognitive measures mainly represent average intelligent individuals, and do not correct for education levels or levels of intelligence. Because most participants had an ID, a comparison with
### TABLE 2  Patient characteristics

| Demographical Details | Patient | Gender | 1 | 2 | 3 | 4 | 5 |
|-----------------------|---------|--------|---|---|---|---|---|
|                       |         |        | Age | 14 | 10 | 12 | 23 | 10 |
| Genetic details       |         |        |     |    |    |    |    |    |
| Chromosome            |         |        |    |Chr15(GRCh37): g.75702623_75682059del|Chr15(GRCh37): g.75704038dup|Chr15(GRCh37): g.75693133G>A|Chr15(GRCh37): 75694230_75694231del|
| Mutation              |         |        |    |NM_001145357.1: c.1010_1013del|NM_001145358.1: c.803dup|NM_001145358.1: c.1675C>T|NM_001145357.1: c.1488_1498del|
| Protein               |         |        |    |p.Lys337fs|p.Glu985fs|p.Leu269fs|p.Arg559*|p.Arg497fs|
| Genetic tests         |         |        |    |EYA1, DGUOK, POLG, array, karyotype, MELAS, WES (ID panel + open exome) |Karyotype, fragile X, array, WES (ID panel + open exome) |BRAF, MAP2K1, MAP2K2, array, WES (ID panel) |Karyotype, array, WES (craniofacial anomalies + ID panel) |
| Additional genetic findings | | | |Polymorphism in MELAS | |FLNA: c.7172G>A (p.[Arg2391His]) | |Gain 5q12.2 (paternally), deletion 10q21.2 (maternally) |
| Medical characteristics | Pregnancy abnormalities | | | | | | | Born at 32 weeks |
| Vision                | | | |Hypermetropia was successfully corrected with glasses | |Hypermetropia was successfully corrected with glasses | | |
| Hearing               | | | |Hearing aids |Ear tubes as of regular ears infections |Hearing aids | |Ear tubes as of regular ears infections |
| Epilepsy              | | | |Tonic dionic seizures until the age of 2 |Two incidental seizures during puberty |Started at the age of 2 with an incidence of twice a week, treated with depakine and Frisium | | |
| Brain MRI             | | | |Enlarged intra and extra-cerebral spaces |Enlarged lateral ventricles, agenesis of the corpus callosum |Bilateral hypomyelination of the insular region, enlarged gyri, lower position of the cerebellar tonsils |NA |NA |
| Other                 | | | | | |Central sleep apnea, treated with acetazolam and supplemental oxygen | | |

Abbreviations: F, female; M, male; NA, not available.
test norm groups is inherently accompanied by a high risk of overestimation of cognitive deficits. It is recommended therefore that a further study on cognitive functioning in WITKOS takes FSIQ into account when interpreting cognitive performances, for instance by including a control group with a similar level of intelligence.

Behavioral functioning as described in the medical records of the participants, seems to be best characterized by DSM classifications of ASD. Additionally, disturbances in sensory information processing, as well as repetitive and rigid behavior, are often reported. The results of the current study substantiate these findings, revealing social problems in all participants. Moreover, symptoms of depression in adolescence were described in medical records and internalizing problems were also reported to be present in some of the participants according to the results of the questionnaires. As is the case with the cognitive tasks, the norm groups for behavior questionnaires represent the overall population (with an average intelligence). Since participant 3 has a profound ID, the fact that he displayed difficulties on all subdomains of behavioral functioning, may be related to his level of intellectual functioning. The aforementioned behavioral problems in social functioning may partly be explained by the increased risk of problems in social behavior in patients with intellectual disability (Dekker, Koot, Van der Ende, and Verhulst, 2002; Peijnenborgh et al., 2017). Therefore, treatment and counseling for these behavioral problems can be optimized by taking the level of developmental functioning into account. In the same way, the slow speed of information processing will have to be taken into account in patients with WITKOS, especially in educational settings. Moreover, specialized training of social skills (e.g., emotion recognition and mentalization) as developed for individuals with ASD, or non-verbal therapies focusing on the training of recognition and regulation of emotions, may help children with WITKOS to become more engaged in more interaction with peers in order to improve their social–emotional development. From adolescence onwards, it is also important to actively monitor patients’ moods, as well as a possible tendency to withdraw from social situations.

A limitation of the current study is the small sample size and the inevitable use of a convenience sample, although it is the only study to-date that has included behavioral and cognitive measures. Strengths of the study are: the unique, systematic description of neurocognitive and behavior assessment of patients with WITKOS in adolescence/early adulthood.

In conclusion, preliminary evidence for weaknesses in speed of information processing/sustained attention and executive functioning was found in participants with WITKOS. As for behavioral functioning, social problems as well as internalizing symptoms were present, which highlight the importance of early specialized training of social skills and monitoring of social–emotional development in patients with WITKOS.

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CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

AUTHOR CONTRIBUTIONS

L.C.M.D., J.I.M.E., T.K., and E.W. designed and planned the study. L.C.V.D., A.J.M.D., A.G.B.-R., and K.V. acquired the data and performed neuropsychological assessments. T.K. and M.P.P. diagnosed and recruited the patients and contributed to the interpretation of the genetic analyses and medical records. L.C.M.D., E.W., and J.I.M.E. contributed to the interpretation of the neuropsychological data and drafted the manuscript. T.K., A.J.I.M.D., A.G.B.-R., K.V. and M.P.P. critically reviewed the manuscript. All authors read and authorized the final version of the manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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REFERENCES

American Association on Intellectual and Developmental Disabilities (2019). Definition of adaptive behavior. Retrieved from http://aaid.org/intellectual-disability/definition
Barkley, R. A. (2012). Executive functions: What they are, how they work, and why they evolved. New York: The Guilford Press.
Biesmans, K. E., van Aken, L., Frunt, E. M. J., Wingermühle, P. A. M., & Egger, J. I. M. (2019). Inhibition, shifting and updating in relation to psychometric intelligence across ability groups in the psychiatric population. Journal of Intellectual Disability Research, 63, 149–160. https://doi.org/10.1111/jir.12559
Dekker, M. C., Koot, H. M., Van der Ende, J., & Verhulst, F. C. (2002). Emotional and behavioral problems in children and adolescents with and without intellectual disability. Journal of Child Psychology and Psychiatry, 43, 1087–1098. https://doi.org/10.1111/1469-7610.00235
Lezak, M. D., Howieson, D. B., Tranel, D., & Bigler, E. D. (2012). Basic concepts. In Neuropsychological Assessment. New York: Oxford University Press Inc.
Meford, H. C., Rosenfeld, J. A., Shur, N., Slavotinek, A. M., Cox, V. A., Hennekam, R. C., ... Eichler, E. E. (2012). Further clinical and molecular delineation of the 15q24 microdeletion syndrome. Journal of Medical Genetics, 49, 110–118. https://doi.org/10.1136/jmedgenet-2011-100499
Narumi-Kishimoto, Y., Akari, N., Migita, O., Kawai, T., Okamura, K., Nakabayashi, K., ... Hata, K. (2018). Novel SIN3A mutation identified
in a Japanese patient with Witteveen–Kolk syndrome. European Journal of Medical Genetics, 62, 103547. https://doi.org/10.1016/j.ejmg.2018.09.014

Peijnenborgh, J., van Abeelen, S. A. M., Hurks, P. P. M., Laridon, A. M., Klinkenberg, S., Aldenkamp, A. P., … Hendriksen, J. G. M. (2017). Can IQ predict parent-reported behavioral and emotional problems in children with neurological deficiencies? European Journal of Paediatric Neurology, 21, 336–343. https://doi.org/10.1016/j.ejpn.2016.09.004

Roelofs, R. L. (2019). A clinical neuropsychological perspective on Noonan syndrome: From assessment to treatment (Doctoral dissertation). Retrieved from https://repository.ubn.ru.nl/bitstream/handle/2066/202963/202963.pdf?sequence=1

Roelofs, R. L., Wingbermühle, E., Kessels, R. P., & Egger, J. I. M. (2019). Social cognitive training for adults with Noonan syndrome: A feasibility study. Neuropsychiatric Disease and Treatment, 15, 611–626. https://doi.org/10.2147/NDT.S179527

Salthouse, T. A. (2005). Relations between cognitive abilities and measures of executive functioning. Neuropsychology, 19, 532–540. https://doi.org/10.1037/0894-4105.19.4.532

Witteveen, J. S., Willemsen, M. H., Dombroski, T. C., van Bakel, N. H., Nillesen, W. M., van Hulten, J. A., … Kolk, S. M. (2016). Haploinsufficiency of MeCP2-interacting transcriptional co-repressor SIN3A causes mild intellectual disability by affecting the development of cortical integrity. Nature Genetics, 48(8), 877–887. https://doi.org/10.1038/ng.3619

SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section at the end of this article.

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