Social Cognitive Development in Noonan Syndrome: Mediated by Executive Functioning?

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Abstract

Introduction A variety of impairments in social cognition is found in both children and adults with Noonan syndrome. However, because no longitudinal study has investigated the social cognitive development in Noonan syndrome, this study we focused on this aspect. **Method** Fourteen patients with a confirmed clinical diagnosis of Noonan syndrome underwent neuropsychological assessment in both childhood and adulthood. Social cognition was operationalized by measures of alexithymia, theory of mind, and emotion recognition. Patient scores were compared with those of fourteen controls, which were matched with respect to sex, age, education level, and intelligence. Moreover, social behaviour in childhood was used as predictor for social cognition in adulthood. Subsequently, executive functioning was added as a second predictor. **Results** Adult patients with Noonan syndrome did not perform significantly worse on measures of social cognition compared to controls. Additionally, no significant predictive value was found for social behaviour in childhood on social cognition in adulthood, and executive functioning had no significant effect on this relation. **Discussion** Based on the results of our study, we conclude that social cognition is not significantly worse in adult patients with Noonan syndrome when compared to controls, and social behaviour in childhood did not have a predictive value for social cognition in adulthood, neither was this relation mediated by executive functioning.

Keywords Noonan syndrome, social cognition, social behaviour, social cognitive development, alexithymia, theory of mind, emotion recognition

Introduction

Noonan syndrome is a heterogeneous developmental disorder caused by mutations in the Ras-mitogen-activated protein kinase (RAS/MAPK) signaling pathway. The RAS/MAPK pathway is an important mediator of several developmental processes (Smpokou, Tworog-Dube, Kucherlapati & Roberts, 2012). This pathway controls several cellular processes, including: (1) proliferation; whereby cells are multiplied, (2) differentiation; which is the stage where cells specialize, (3) cell survival, and (4) metabolism; a comprehensive term for all the chemical processes in the body (Fey, Matallanas, Rauch, Rukhlenko & Kholodenko, 2016). Furthermore, the RAS/MAPK signaling pathway plays a role in a variety of cognitive functions, including memory and learning (Ryu & Lee, 2016). Genetic disorders in which this signaling pathway is malfunctioning, are known as RASopathies. With a prevalence of 1:1000

to 1:2500 live births, Noonan syndrome is the most common of all RASopathies (Pierpont, Tworog-Dube & Roberts, 2015).

In approximately 75% of the cases with Noonan syndrome, mutations in one or several genes are expressed within the RAS/MAPK signaling pathway (including *PTPN11*, *SOS1*, *RAF1*, *KRAS*, *NRAS*, *SHOC2*, *RIT1*, and *CBL*). For the remaining cases, the underlying genetic etiology has not been identified (Pierpont et al., 2015). Consequently, Noonan syndrome is frequently diagnosed on clinical grounds. Clinical features of Noonan syndrome are facial and musculoskeletal features, short stature, chest deformity, and congenital heart diseases (Romano et al., 2010). The facial features are most evident in infancy. With age these facial characteristics become less apparent, but in some adults the typical features remain. Moreover, some facial characteristics are seen in both children and adults, for example the low-set and posteriorly rotated ears and the wide-spread eyes (Romano et al., 2010). Besides these bodily features the neurologic, cognitive, and behavioural aspects in Noonan syndrome are variable as well. Most of the patients have an intellectual capacity within the normal range, but approximately 10% to 40% needs special education in relation to their general cognitive abilities (Romano et al., 2010). Additionally, *SOS1* and *PTPN11* mutations are associated with no or mild cognitive impairments (Romano et al., 2010). Several factors contribute to this variation in intellectual capacity, including neurobiological risk factors due to mutations in the RAS/MAPK signaling pathway, as well as medical factors associated with Noonan syndrome (Pierpont, 2016). Even, a relationship between the severity of physical characteristics and intellectual impairments is observed (Van der Burgt et al., 1999).

When considering the more specific cognitive functions, in the literature it is found that children with Noonan syndrome have more cognitive impairments compared to adults, especially in domains of visual processing, memory, language functioning, communication, attention, motor functioning, and executive functioning (Wingbermühle, Egger, van der Burgt & Verhoeven, 2009). However, Wingbermühle, Egger, Verhoeven, van der Burgt and Kessels (2012) found in adults with Noonan syndrome a slower information processing speed than in healthy controls. In other cognitive domains, such as memory, executive functioning, and visuoconstruction, no fundamental impairments were found when cognitive functioning was objectively measured. Nevertheless, on self-report questionnaires, patients reported more problems with regard to executive functioning than controls (Wingbermühle et al., 2012). An important aspect to clarify is why children with Noonan syndrome apparently have more cognitive deficits compared to adults. Roelofs, Janssen, Wingbermühle, Kessels and Egger

(2016) examined the intellectual development in Noonan syndrome. They found that intelligence in childhood has a predictive value on intelligence in adulthood, and that adults performed significantly higher on the Full-Scale IQ and Performance IQ compared to children. Therefore, Roelofs and colleagues (2016) hypothesized that this improvement may reflect an developmental delay in executive functioning. This hypothesis follows logically since the Performance IQ is a composite index that includes tasks that tap into fluid intelligence, which is the competence to reason, problem solve, and to see patterns and relations. It is argued that fluid intelligence may be synonymous with several aspects of executive functioning (Diamond, 2013). The executive functions are a heterogeneous collection of cognitive skills, including: regulation, inhibitory control, planning, attentional flexibility, error detection and correction, and resistance to interference (Carlson, Moses & Breton, 2002). Previous studies have concluded that proteins in the RAS/MAPK signaling pathway are involved in the release of neurotransmitters in brain regions which are involved in executive functions, including the prefrontal cortex and striatum (Pierpont et al., 2015).

The specific aspects of executive functioning mentioned above, contribute to the monitoring and control of thoughts and actions (Carlson et al., 2002). Particularly, executive functioning is associated with the development of theory of mind. Premack and Woodruff (1978) introduced the term "theory of mind", and described it as "the capacity of an individual to impute mental states to himself and to others". There are several arguments for the relationship between executive functioning and theory of mind. First, they share the same developmental timetable. Second, the same prefrontal brain regions are responsible for both executive functioning, as well as for theory of mind in adults (Carlson et al, 2002). Moreover, it is important to mention that theory of mind is part of a larger concept, called social cognition. Social cognition is the skill of constructing representations of the relation between oneself and others, and to use those representations flexibly to guide social behaviour in daily life (Adolphs, 2001).

Research in children with Noonan syndrome showed that social problems are one of the most important behavioural deficits, as measured with the Child Behaviour Checklist (Alfieri et al., 2014). In line with these results, Pierpont and colleagues (2015) found that impairments in social skills were more prevalent in children with Noonan syndrome, when compared with their unaffected siblings. Only one longitudinal study in children with Noonan syndrome was performed, whereby autistic behavioural characteristics and other neurobehavioural comorbidities were studied (Garg, 2017). In addition, intelligence and

executive functioning were also included. They confirmed previous findings that intelligence is within the normal range, and found that 42% of children with Noonan syndrome had problems in executive functioning (Garg et al., 2017). However, in this study follow-up was set at 10 months, and social impairments were only investigated on a behavioural level. The latter is a debatable aspect, and was discussed in a review of Pierpont (2016), who indicated that individuals with Noonan syndrome have been described as having social problems. However, in children these characteristics have not been examined in depth. In adults with Noonan syndrome, social cognition was studied by Wingbermühle and colleagues (2012). They found that emotion recognition (i.e., the perception and labelling of emotional facial expressions) was lower in adult patients with Noonan syndrome than in healthy controls. However, the effect size was small, suggesting that patients with Noonan syndrome do not have a fundamental shortcoming in emotion recognition. Moreover, the authors suggested that there was an impairment in the experience and verbalization of *own* emotions (i.e., alexithymia) (Wingbermühle et al., 2012).

Since a variety of problems in social cognition are reported in Noonan syndrome, and no longitudinal research has been performed on social cognition in general yet, it is decided to perform the current longitudinal study. It is important to determine which variables in childhood influence social cognitive development, which makes it possible to intervene at young age. Consequently, impairments in social cognition can be reduced. First it will be examined whether social cognition is worse in patients with Noonan syndrome when compared to controls. Additionally, it will be examined whether social behaviour in children with Noonan syndrome will predict social cognitive functioning in adulthood. A behavioural measure is chosen in childhood, since no in-depth research has been performed into social cognition in childhood yet, and it is unknown whether there are any deficiencies in it. Based on the above summarized literature, it is expected that this relation is mediated by executive functioning in childhood. As such, it is hypothesized that: (1) social cognition is significantly worse in adult patients with Noonan syndrome when compared to controls, (2) social behaviour in childhood is a predictor of social cognition in adulthood, and (3) executive functions have a mediating effect on the relation between social behaviour in childhood and social cognition in adulthood.

Method

Participants

The patient group (n =14) underwent neuropsychological assessment at the Centre of Excellence for Neuropsychiatry of the Vincent van Gogh Institute for Psychiatry in Venray between 2006 and 2012. This assessment took place in context of the study of Wingbermühle and colleagues (2012). Inclusion criteria for the patient group in the current study were: (1) a confirmed clinical diagnosis of Noonan syndrome, and (2) the availability of neuropsychological assessment in both childhood (Wechsler Intelligence Scale for Children – Revised, WISC-R; Child Behavioural Checklist, CBCL) and adulthood (Wechsler Adult Intelligence Scale – III, WAIS-III; 20-item Toronto Alexithymia Scale, TAS-20; Theory of Mind-test, ToM-test; Emotion Recognition Task, ERT). Data collection in childhood had been done at the department of Pediatrics of Radboud University Medical Center in Nijmegen. The patient group was matched to a control group (n = 14), with respect to sex, age, education level, and Full-Scale IQ scores of the WAIS-III. For the adult control group, assessment took place in context of the study of Wingbermühle and colleagues (2012) as well. No data from childhood was available for the control group.

Patients and controls did not differ with respect to sex, education level and Full-Scale IQ scores (see Table 1 for an overview of the characteristics). Of the 14 included patients, there were five male (35.71%) and nine female (64.29%) subjects. Half of the patients showed a mutation in the *PTPN11* gene (50%). One patient had a mutation in the *SOS1* gene (7.14%). In four patients no mutation was found (28.57%), and in two patients the mutation analysis was not performed or completed yet (14.29%). In childhood, the average age at which the assessment took place was 10.28 (standard deviation (SD) = 3.60, range 6-16), whereas in adulthood this took place at the average age of 21.21 years (SD = 3.49, range 16-27). The mean difference between the age of childhood and adulthood assessment was 10.93 years (SD = 1.49, range 9-15). Educational level in adulthood was classified according to the classification system of Verhage (1964), ranging from category 1 (1-5 years of education) to 7 (19-20 years of education) (Bouma, Mulder, Lindeboom, & Schmand, 2012). In the patient group, the educational level ranged from category 2 (6 years of education) to 6 (7-16 years of education). In childhood, the patients scored an average Full-Scale IQ of 85.29 (SD = 13.66, range 59-110) on the WISC-R, whereas adult patients accomplished an average Full-Scale IQ of 89.71 (SD = 13.09, range 73-115) on the WAIS-III.

The control group consisted of five males (35.71%) and nine females (64.29%), with a mean age of 21.64 (SD = 3.63, range 18-30). The educational level according to the classification system of Verhage, ranged from 3 (7-8 years of education) to 6. The control group showed an average TIQ of 93.0 (SD = 8.74, range 77-105) on the WAIS-III.

Table 1
Characteristics of the participants (N = 28)

	Patients *n* (%)	Controls *n* (%)	*t*	χ^2	*p*
Sex				.000	1.000
- Male	5 (35.71)	5 (35.71)			
- Female	9 (64.29)	9 (64.29)			
Age in childhood, mean±SD (range)	10.28±3.60 (6-16)				
Age in adulthood, mean±SD (range)	21.21±3.49 (16-27)	21.64±3.63 (18-30)	.318		.753
Education				5.467	.243
- 1	0 (0)	0 (0)			
- 2	2 (14.29)	0 (0)			
- 3	4 (28.57)	1 (7.14)			
- 4	2 (14.29)	2 (14.29)			
- 5	5 (35.71)	10 (71.43)			
- 6	1 (7.14)	1 (7.14)			
- 7	0 (0)	0 (0)			
WISC-R Full-Scale IQ, mean±SD	85.29±13.66 (59-110)				
WAIS-III Full-Scale IQ, mean±SD (range)	89.71±13.09 (73-115)	93±8.74 (77-105)	.781		.442
Genetic mutation					
- PTPN11	7 (50)				
- SOS1	1 (7.14)				
- No mutation found	4 (28.57)				
- No analysis performed or completed	2 (14.29)				

WISC-R, Wechsler Intelligence Scale for Children – Revised; WAIS-III, Wechsler Adult Intelligence Scale-III

Measurement

Intelligence. Intelligence in childhood was measured with the Dutch version of the Wechsler Intelligence Scale for Children Revised (WISC-R-NL; Van Haassen et al., 1986b,c). The test consists of 12 subtests, including: Information, Picture Completion, Similarities, Picture Arrangement, Arithmetic, Block Design, Vocabulary, Object Assembly, Comprehension, Coding, Digit Span, and Mazes. Based on the standard scores of these subtests, a Full-Scale IQ was calculated. Full-Scale IQ consists of a Verbal IQ and a Performance IQ. It was found

that the reliability of the Full-Scale IQ was very high, and both congruent and criterion validity were demonstrated (Van Haassen et al., 1986c). Moreover, the subtest Mazes was used as a measure for executive functioning in the current study. With this subtest, children have to use paper and pencil to plot a path, and plan a way to get to the exit. It is not allowed to remove the pencil from the paper, neither it is allowed to get stuck in dead-end paths, therefore this subtest appeals to the process of previse and planning (Van Haassen et al., 1986b). A moderate high reliability coefficient (.73) was found for this subtest, and it had the second largest specificity of all WISC-R-NL subtests (Van Haassen et al., 1986c). In adulthood (≥16 years) intelligence was measured with the Dutch version of the Wechsler Adult Intelligence Scale-III (WAIS-III-NL; Wechsler, 2005a). This test consists of 11 subtests, including: Picture Completion, Vocabulary, Digit Symbol, Similarities, Block Design, Arithmetic, Matrix Reasoning, Digit Span, Information, Picture Arrangement, and Comprehension. Standard scores were calculated for each subtest, and a Full-Scale IQ was computed. Full-Scale IQ consists of a Verbal IQ and a Performance IQ. For the internal consistency, very high correlations were found for Full-Scale IQ, Verbal IQ and Performance IQ. Moreover, with regard to the criterion validity, very high correlations were found for Full-Scale IQ (.97) and Verbal IQ (.98), but moderate high (.75) correlations for Performance IQ (Wechsler, 2005a).

Social behaviour. As an indication for social behaviour in childhood, the subscale 'Social Behaviour' of the Child Behaviour Checklist (CBCL) was included (Verhulst, Koot, Akkerhuis & Veerman, 1990). The CBCL is part of The Achenbach System of Empirically Based Assessment (ASEBA): an integrated set of forms for assessing competencies, adaptive functioning and problems (Achenbach & Rescorla, 2001). The CBCL is a questionnaire completed by parents and others who know the children in family-like context. The CBCL consists of competence items and questions with regard to so-called syndrome scales (Achenbach & Rescorla, 2001). Since the subscale 'Social Behaviour' belongs to the competence items, the syndrome scales were not included in the current study. 'Social Behaviour' includes scores for participation in organizations, number of close friends, number of weekly contacts with friends, how well the child gets along with others, and how well the child plays and works alone (Achenbach & Rescorla, 2001). For each of these items the scores were summed together, giving the total subscale score. This total subscale score ranges from 0 to 14. In the age category of 6 to 11 years, a total subscale score of 4.5 or 4.0 is indicative for an impairment (-1.5 SD), whereas a total subscale score of 3.5 or lower is

indicative for a disorder (-2 SD). Additionally, in the age category of 12 to 18 years, a total subscale score of 5.0, 4.5 or 4.0 is indicative for an impairment, whereas a total subscale score of 3.5 or lower is indicative for a disorder (Achenbach & Rescorla, 2001). The interrater reliability and test-retest reliability of the CBCL were very high. For the internal consistency, moderate high correlations were found. Moreover, both content validity and discriminant validity were demonstrated for the CBCL (Achenbach & Rescorla, 2001).

Alexithymia. Social cognition was operationalized by measures of alexithymia, theory of mind and emotion recognition. First, the 20-item Toronto Alexithymia Scale (TAS-20), a self-report measure for alexithymia, was used (Bagby, Parker & Taylor, 1994a,b). This questionnaire is based on three different factors: (1) 'Difficulty Identify Feelings' (e.g. *'I am often confused about what emotion I am feeling'*), (2) 'Difficulty Describing Feelings' (e.g. *'It is difficult for me to find the right words for my feelings'*), and (3) 'Externally-Oriented Thinking' (e.g. *'I prefer to analyze problems rather than just describe them*') (Bagby et al., 1994a). The respondent had to choose an answer on a five points Likert scale, choosing 'option one' if they strongly disagreed with the statement, and 'option five' if they strongly agreed with the statement. Therefore, the total score ranged from 20 to 100, whereby a cutoff score of ≥ 61 was demonstrated empirically to be indicative for high alexithymia (Parker, Taylor, & Bagby, 2003). In the current study, total scores on the TAS-20 were used. Furthermore, previous research showed that the TAS-20 had a good internal consistency and test-retest reliability. Additionally, convergent, discriminant, and criterion validity of the TAS-20 were also demonstrated (Bagby et al., 1994b).

Theory of mind. In addition, the Theory of Mind-test (ToM-test) was used to measure three different stages: (1) precursors of theory of mind, (2) first order belief and false belief, and (3) second order belief (Steerneman, Meesters & Muris, 2003). Seventy-two items had to be completed as a structured interview. The ToM-test provides information on the extent to which people have social insight, social understanding, and social sensitivity (Steerneman et al., 2003). On each item, a score of zero or one could be achieved. Scores of all three stages were added together, whereby a total score (ranging from 0 to 72) was obtained. Previous research showed a good internal consistency for the entire ToM-test, as well as for the three different subscales (Steerneman et al., 2003). Additionally, the test-retest reliability and the interrater reliability were considered as satisfactory. The construct, concurrent, and discriminant validity were also demonstrated for this test (Steerneman et al., 2003).

Emotion recognition. Finally, the Emotion Recognition Task (ERT) was used. The ERT is a computer-generated paradigm for measuring the recognition of six basic facial emotional expressions: anger, disgust, fear, happiness, sadness, and surprise (Montagne, Kessels, De Haan & Perrett, 2007). During this task, the different facial emotional expressions were presented gradually from neutral (0%) to four levels of intensity (40%, 60%, 80%, 100%; Kessels, Montagne, Hendriks, Perrett & De Haan, 2014). Therefore, the task started with more difficult expressions and became later easier. After each morph, the participant was asked to make a choice between the six basic facial emotional expressions. Research that has been done into the applicability of the paradigm, have shown that the ERT can be effectively administered in different clinical groups. This was concluded due the different impairments on specific emotions which were found, varying between different clinical groups and neuropathologies (Montagne et al., 2007). First, a total score was computed for each emotion by adding the correct answers for each level of intensity. For each emotion, a minimum of 0 and a maximum score of 16 could be achieved. Secondly, total scores for each emotion were added together, resulting in a total score for the ERT, and ranging from 0 to 96. This latter ERT total score was used in the current study.

Statistical analyses

For all statistical analyses, IBM SPSS Statistics version 24 (IBM Corp, 2016) and an alpha of .05 was used. Before all analyses, pre-analyses were executed to determine that no assumption was violated (see Table 2). All assumptions were not violated, except for one. More specifically, only two outliers were found in scores of the patient group on the ToM-test. Given the clinical relevance of these scores, and they do not deviate more than 1.5 SD, it has been decided not to exclude these patients. The assumption of normally distributed data was tested with the Shapiro-Wilk test for normally distributed data ($p > .05$). Moreover, the assumption of homogeneity of variances was tested with the Levene's test for equality of variances ($p > .05$ for equal variances assumed). In case this test was significant, results of the Welch t-test were reported. Additionally, outliers were checked with a boxplot, which is important to determine because outliers and influential scores can (partially) explain a relation between variables (Field, 2005). The assumption of independent errors was tested with the Durbin-Watson test ($d = \pm 2$ for uncorrelated errors), which tests serial correlations between errors (Field, 2005).

Table 2
Test assumptions

Test	Assumptions[1]
Chi square test	Each person, item or entity contributes to only one cell of the contingency table
	The expected frequencies should be greater than 5
Independent samples t-test	Normally distributed data
	Data measured at least interval level
	Homogeneity of variance
	No outliers
	Independent scores
Multiple regression analysis	No outliers
	Non-zero variance
	No perfect multicollinearity
	Predictors are uncorrelated with external variables
	Homoscedasticity
	Independent errors
	Normally distributed errors
	Independence
	Linearity

[1] Field (2015)

First, frequencies, percentages, mean scores, and/or standard deviations were calculated for demographic variables (age, sex, educational level), type of genetic mutation, and for Full-Scale IQ scores on the WISC-R and WAIS-III. Secondly, to investigate whether there are differences in social cognitive functioning between adult patients and controls, independent samples t-tests were used. Group (patients vs. controls) was used as independent variable, whereas scores on the TAS-20, ToM-test, and ERT were used as dependent variables. Thirdly, to investigate whether social behaviour in childhood is a predictor of social cognitive functioning in adulthood, three regression analyses were executed. Scores on the 'Social Behaviour' subscale of the CBCL was used as predictor, whereas scores on the TAS-20, ToM-test, and ERT were used as dependent variables. Additionally, to investigate whether executive functioning in childhood has a mediating effect on the relation between social behaviour in childhood and social cognitive functioning in adulthood, scores on the WISC-R Mazes were added as a second predictor.

Results

Comparison of social cognition

To investigate whether there are differences in social cognitive functioning between adult patients and controls, independent samples t-tests were executed on measures of social

cognition in adulthood (see Table 3). No significant results were found for scores on the TAS-20, ToM-Test, and ERT.

Table 3
Adult performance on social cognition tasks: Patients versus Controls (N = 28)

	Patients M±SD(n)	Controls M±SD(n)	*t*	*df*	Effect Size (*d*)	*p*
TAS-20	53.50±7.98(14)	53.08±10.68(13)	0.12	25	0.05	.91
ToM-test	70.43±2.17(14)	69.79±1.76(14)	0.86	26	0.30	.40
ERT	57.62±8.85(13)	62.71±9.56(14)	-1.44	25	-0.55	.16

TAS-20, 20-item Toronto Alexithymia Scale; ToM-test, Theory of Mind-test; ERT, Emotion Recognition Task.

Table 4
Test statistics of the regression analyses (n = 14)

Predictors	B	SE (B)	95% CI for B	*B*	*t*	*p*
TAS-20 (adj. R^2 = -.07, p = .75)						
CBCL 'Social Behaviour'	.38	1.16	-2.15 to 2.91	.10	0.33	.75
ToM-test (adj. R^2 = -.08, p = .77)						
CBCL 'Social Behaviour'	-.09	0.32	-0.78 to 0.60	-.08	-0.29	.77
ERT (adj. R^2 = -.09, p = .82)						
CBCL 'Social Behaviour'	.30	1.29	-2.54 to 3.15	.07	0.23	.82
TAS-20 (adj. R^2 = -.17, p = .92)						
CBCL 'Social Behaviour'	.37	1.22	-2.33 to 3.06	.09	0.30	.77
WISC-R Mazes	.08	0.74	-1.54 to 1.70	.03	0.11	.92
ToM-test (adj. R^2 = .16, p = .06)						
CBCL 'Social Behaviour'	-.17	0.28	-0.79 to 0.45	-.15	-0.60	.56
WISC-R Mazes	.36	0.17	-0.02 to 0.73	.53	2.10	.06
ERT (adj. R^2 = -.10, p = .39)						
CBCL 'Social Behaviour'	.12	1.32	-2.82 to 3.06	.03	0.09	.93
WISC-R Mazes	.77	0.85	-1.13 to 2.66	.28	0.39	.39

CBCL, Child Behaviour Checklist; TAS-20, 20-item Toronto Alexithymia Scale; ToM-test, Theory of Mind-test; ERT, Emotion Recognition Task; WISC-R, Wechsler Intelligence Scale for Children – Revised.

Prediction of social cognition

To investigate whether social behaviour in childhood has a predictive value on social cognition in adulthood, three regression analyses were executed (see Table 4). Scores on the 'Social Behaviour' subscale of the CBCL did not have a significant predictive value in scores on the TAS-20, ToM-test, and ERT.

In addition, to examine whether executive functioning has a mediating effect on the relation between social behaviour in childhood and social cognition in adulthood, scores on the WISC-R Mazes were added as a second predictor. However, no significant predictive power was found for this covariate. Scores on the subscale 'Social Behaviour' of the CBCL and on the subtest Mazes together, explained 17% in scores on the TAS-20 (F (2, 11) = 0.06,

p = .95). Moreover, together they explained 16% in scores on the ToM-test (F (2, 11) = 2.26, p = .15), and 10% in scores on the ERT (F (2, 10) = .44, p = .66).

Discussion

In the current study, it was investigated whether adult patients with Noonan syndrome performed significantly worse on domains of social cognition, operationalized by measures of alexithymia, theory of mind, and emotion recognition. Secondly, social cognitive development was examined in a group of patients with Noonan syndrome, and it was investigated whether executive functioning had a mediating effect on this development. Social cognitive functioning was not significantly worse in patients with Noonan syndrome when compared to controls. Furthermore, no significant predictive value was found for social behaviour in childhood, on social cognition in adulthood. Additionally, executive functioning had no significant effect on this relation. These findings are not in accordance with the hypotheses.

Research in children with Noonan syndrome, showed that social problems are one of the most important behavioural deficits (Alfieri et al., 2014). However, this tendency was only observed when looking within the Noonan syndrome. When results were compared with those of other RASopathies, it was found that children with Noonan syndrome (32%) had significantly less frequent social problems compared to children with cardiofaciocutaneous syndrome (86%) and Noonan-like syndrome with loose anagen hair (67%) (Alfieri et al., 2014). Moreover, among children with Noonan syndrome, social problems were more frequently observed in children with a mutation in the *SOS1* gene than in the *PTPN11* gene (Alfieri et al., 2014). In the current study, mutations in the type of gene were disproportionately distributed (50% *PTPN11* vs. 7% *SOS1*), suggesting that there was less variation in scores on the subscale 'Social Behaviour' of the CBCL, which could be a possible explanation for the findings that it has no predictive value.

Furthermore, results of the current study are in line with those of Roelofs and colleagues (2015), who compared alexithymia, emotion perception, and social assertiveness between adult females with Noonan and Turner syndromes, and controls. With regard to the concept of alexithymia, the authors found no significant differences between patients with Noonan syndrome and controls, except for the scale Emotionalizing (i.e. the degree to which someone is emotionally aroused by emotion inducing events). Women with Noonan syndrome showed lower levels of alexithymia on this scale compared to controls (Roelofs et

al., 2015). In addition, groups did not significantly differ in accuracy of emotion recognition, except that patients with Noonan syndrome had more difficulties with recognizing angry faces (Roelofs et al., 2015). Moreover, results of the current study are partly in accordance with those of Wingbermühle and colleagues (2012), who did not found a significant difference in theory of mind between patients with Noonan syndrome and controls either. However, the authors did found a significant difference with respect to emotion recognition and alexithymia levels. Patients had more difficulties with emotion recognition than controls, but the effect size was small, suggesting that patients with Noonan syndrome do not have a fundamental shortcoming in emotion recognition (Wingbermühle et al., 2012), what fits with findings from the current study. Additionally, patients reported higher levels of alexithymia. In the study of Wingbermühle and colleagues (2012), alexithymia was measured with both the TAS-20 and the Bormond-Vorst Alexithymia Questionnaire (BVAQ). On the latter questionnaire, patients reported significant higher levels of problems within the cognitive domain of alexithymia, whereby problems in verbalizing emotions had a large part in this (Wingbermühle et al., 2012).

Additionally, in a literature review of Pierpont (2016), it is argued that no clear interpretable profile emerges from results of previous studies, with regard to intellectual strengths and weaknesses in Noonan syndrome. Nevertheless, many individuals have an intelligence profile that is disharmoniously distributed; sometimes in favor of verbal reasoning abilities, whereas sometimes in favor of nonverbal reasoning abilities (Pierpont, 2016). In the current study, it was hypothesized that a lower nonverbal reasoning ability was associated with a developmental delay in executive functioning and problems in social cognition. However, in line with findings of Wingbermühle and colleagues (2012), an alternative hypothesis is that it is not a developmental delay in executive functioning, but a lowered verbal intellectual ability that might cause higher levels of alexithymia. The latter hypothesis would explain why no mediating effect was found for executive functioning in childhood in the current study.

Another possible explanation is that possibly existing effects were not confirmed, due some limitations of the measures which were used. Firstly, the TAS-20 is a self-report questionnaire for alexithymia. Since alexithymia is defined as having problems with experiencing and verbalization of *own* emotions (Wingbermühle, 2012), it is possible that reporting about own emotions in form of a questionnaire, specifically is problematic. For explorative purposes, the correlation between scores on the two different versions (‘self’ vs.

'others') of the TAS-20 was computed. The other version was completed by a close relative of the participant. This is not an official version of this questionnaire; the Centre of Excellence for Neuropsychiatry of the Vincent van Gogh Institute for Psychiatry in Venray improved this version of the TAS-20 for clinical purposes. It appeared that there was a low correlation between both, suggesting that there was a discrepancy between the opinion of the self and the other, with regard to the concept of alexithymia. Furthermore, the internal consistency of the two versions was determined. Notable is that, in scores of the self version, two negative correlations were found between the subscales, whereas in the other version only moderate to very high positive correlations were found. These findings suggest that the internal consistency is better for the version that was completed by a close relative, and that this version of the TAS-20 might have been a better measure for alexithymia.

Secondly, the ToM-test was originally developed for children in the age category of four to 12 years. In this study, the ToM-test was used in adults nevertheless. This may mean that the test was too easy for the participants, causing the tendency whereby *all* participants achieve a maximum score, or close to the maximum: a so-called ceiling effect. In healthy controls, as well as in patient groups, these ceiling effects are frequently observed in standard measures for theory of mind (Dodell-Feder, Lincoln, Coulson & Hooker, 2013). Based on the mean scores on the ToM-test, this trend is also seen in the current study. Assessing theory of mind accurately and reliably, and in a way that is sensitive to subtle individual differences, has always been a challenge for researches (Dodell-Feder et al., 2013). Standard theory of mind tasks like the ToM-test, have been used successfully to distinguish different clinical populations. However, these standard tasks are insensitive for more subtle deficits in theory of mind (Dodell-Feder et al., 2013). Therefore, Dodell-Feder and colleagues (2013) introduced a new measure for theory of mind in adults, called the Short Story Task. In this task, participants had to read a short story, in which characters display sarcasm, non-verbal and indirect communication, higher-order emotions like guilt, and attempts to hide their intentions and feelings from one another. The authors found a substantial variation in the performance of 72 healthy participants, and no ceiling effects were found, suggesting that the Short Story Task is sensitive to individual differences in theory of mind ability (Dodell-Feder et al., 2013).

Thirdly, explorative findings that both patients and controls have more difficulty in recognizing the emotions of fear and sadness, suggests that those two specific emotions are too difficult for *all* participants: a so-called bottom effect. This is in line with results of

Montagne and colleagues (2007). Therefore, less variance in the ERT total scores could be observed. Possibly, no significant differences were found between patients and controls due to this limited variance. Another suggestion is that scores on the ERT were affected by gender. Kessels and colleagues (2014) found that females scored more accurately on the emotions of anger, fear, and sadness, as well as on the ERT total score. Among the participants in our study, there were almost twice as many females as males, suggesting that ERT total scores in our study were advantaged.

A significant strength of the current study is the longitudinal design, since no longitudinal research in Noonan syndrome has been performed on social cognition in general yet. In addition, another significant strength of the study, is that it focuses on the predictive value of variables in childhood on outcome in adulthood. By understanding these syndrome related variables, it might be possible to develop intervention strategies at a young age and consequently prevent for problems in daily living impairments in adulthood. Nevertheless, the results should also be interpreted in light of some limitations. First, for performing multiple regression analyses, many different rules of thumb have been recommended concerning sample sizes. The sample size of this study may be considered relatively small to achieve good statistical power. If the power of a study is low, the probability that an observed effect passes the required threshold (statistical significance) increases (Button et al., 2013). However, in the current study no analysis has reached statistical significance, suggesting that low statistical power has no major influence on how the results should be interpreted in this particular case. Second, the predictor which was used, was measured at a behavioural level, whereas the outcome variables were measured at a cognitive level. In the introduction it was argued that this design was chosen, because it is still unknown whether children with Noonan syndrome are actually having impairments in social cognitive functioning. However, future research has to examine this in depth.

In conclusion, the results of this study showed that social cognition is not significantly worse in adult patients with Noonan syndrome when compared to controls. Secondly, social behaviour in childhood has no predictive value on social cognition, neither is this relation mediated by executive functioning. In future, a first step would be to examine social cognitive functioning in children with Noonan syndrome in depth. Additionally, longitudinal studies whereby it is carefully considered which variables will be used, might be helpful to distinguish variables in childhood that influence social cognitive development. However, results of previous research are variable, whereby significant differences in social cognition at

test level have not always been confirmed, when adults with Noonan syndrome and controls were compared. Therefore, it would be interesting to compare two groups with Noonan syndrome and a comparable intellectual capacity, of which one group reports problems in social cognitive functioning, whereas the other group does not. In such manner, it could be possibly determined which factors contribute to subjectively experienced problems in social cognitive functioning.

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