



Social Functioning in Adolescents with 22q11.2 Deletion Syndrome:

A Developmental Perspective

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Master Thesis MSc Clinical Psychology

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April 16, 2021

5866790

Abstract

The 22q11 deletion syndrome (22q11DS) is associated with a wide variety of developmental disorders. Individuals with this birth defect present impairments in social reciprocal behaviour. However, they often do not meet the full criteria of autism spectrum disorder (ASD). The development of social functioning is an area of concern and it remains unclear how IQ is related. The aim of this longitudinal study was to give an overview of the social functioning profile in a sample of 22q11DS adolescents. The Social Responsiveness Scale – second edition (SRS-2) was used for measuring social functioning. We compared scores of social functioning on different timepoints to examine developmental trajectories.

Additionally, we compared scores between adolescents with diagnosed ASD, any other psychiatric diagnosis and without a psychiatric diagnosis and explored the role of IQ on social functioning. Social functioning seems to decline between the ages 18,67 and 22,34 years ($p = .036$). Against the expectation, reported deficits in social functioning are clinically significant in the whole sample of 22q11DS adolescents, regardless of psychiatric diagnoses. Autistic mannerism are significantly more problematic in patients with diagnosed ASD ($p = .022$) compared to the other diagnosis groups. IQ is not significantly associated with social functioning. Current results highlight the importance of early and frequent evaluation of social functioning in adolescents with 22q11DS. More research is needed to investigate the observed decline of social functioning. Furthermore, a broader investigation of social deficits related to ASD in 22q11DS individuals in clinical practice and research may facilitate treatment for all patients experiencing social functioning problems. This can increase quality of life in 22q11DS individuals and their caregivers.

Keywords: 22q11 deletion syndrome, social functioning, decline, ASD, IQ

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A Developmental Perspective

The 22q11.2 deletion syndrome is a genetic syndrome, previously referred to as velo-cardio-facial syndrome, DiGeorge syndrome and Shprintzen syndrome, that involves genetic deletions of about fifty genes on the long arm of chromosome 22 (McDonald-McGinn et al., 2015). The estimated prevalence lies around 1 in every 4000 births, making it the most common recurrent copy-number variant (CNV) associated with developmental disorders described to date (Ousley et al., 2017; Oskarsdottir et al., 2004). Common physical characteristics include cardiac and palatal abnormalities, characteristic facial features and autoimmune disease. The field has gradually broadened, as more and more behavioural phenotypes and psychiatric illness seem to be associated with the deletion syndrome. Likewise, it well serves as a research model to better understand rare birth defects and common developmental disorders (McDonald-McGinn et al., 2015).

Psychopathology

Individuals with 22q11DS are at greater risk for developing behavioural and psychiatric disorders and variable cognitive delays. In adults, high rates of psychotic disorders, especially schizophrenia have been well established (Fiksinski et al., 2018). The Full Scale Intelligence Quotient (FSIQ) of 22q11DS individuals most commonly ranges between 70 and 85 followed by mild intellectual disability (FSIQ 55-70) (De Smedt et al., 2007; Evers et al., 2009; Swillen et al., 1999; Tang et al., 2015; McDonald-McGinn et al., 2015). Moreover, high prevalence rates of developmental disorders such as attention deficit disorder (ADHD), mood and anxiety disorders, autism spectrum disorder (ASD) and other problems in social interaction have become increasingly apparent (Paylor et al., 2006).

Social Functioning

General social impairments such as maintaining social relationships are described in patients with 22q11DS across all ages, for those with and without psychiatric diagnoses (Mayo & Niendam, 2019). Typical social deficits include lower social competence skills, socio-communicative challenges, social immaturity, and difficulties with initiating social interactions. In school settings, youth with 22q11DS displayed higher rates of bullying perpetration and victimization (Fine et al., 2005; Norkett et al., 2017). Regarding social cognition, multiple studies have indicated emotion processing problems. Adolescents with 22q11DS seem to experience difficulties in recognizing anger and understanding the mental states of others (Schreiner et al., 2014; McCabe et al., 2011).

Various studies have recognized autistic traits in patients with 22q11DS (Ousley et al., 2017; Gerdes et al., 2001; Niklasson et al., 2001). Despite the high prevalence of autism spectrum disorder (ASD), a strong sense of empathy, humour and other more complex social skills (uncommon in ASD) are reported when describing social behaviour of children with 22q11DS (Angkustsiri et al., 2014 ;Vorstman et al., 2006). Moreover, professionals working with 22q11DS children report a difference in presentation of symptoms when comparing them to idiopathic autism (Eliez, 2007; Fiksinski et al., 2018; Schneider et al., 2014; Tang et al., 2015). Therefore, more research is needed to dimensionally investigate the autistic traits in 22q11DS.

Development of Social Functioning

Research on developmental trajectories of social responsiveness associated with 22q11DS is inconsistent. Little longitudinal data of childhood predictors of social functioning in adulthood is available. Some cross-sectional research indicates that adolescents experience more peer relationship problems compared to typically developing peers (Campbell et al., 2015). Additionally, youth with 22q11DS seems to display more internalizing social

behaviour (withdrawn and anxiety) when they grow older (Swillen et al., 1997; Tang, Antshel, Fremont & Kates, 2015). In contrast, other evidence describes symptoms of developmental disorders in 22q11DS like ADHD and ASD improving with age, consistent with the idiopathic population (Shattuck et al., 2007; Fiksinski et al., 2018).

Investigating the stability of cognition through development can provide important insights into underlying mechanisms of social deficits, especially in a group with high prevalence rates of psychopathology (Morrison et al., 2020). Recent studies have described a decline of cognitive abilities in patients with 22q11DS (Fiksinski et al., 2021; Vorstman et al., 2015; Morrison et al., 2020, de Smedt et al., 2007). Cognitive development in individuals with 22q11DS appears to be slower compared to typically developing peers, resulting in a developmental gap that becomes larger when growing up (Chawner et al., 2017; Swillen & McDonald-McGinn, 2015). This is in line with results of Van Den Heuvel and colleagues (2018) describing a decline in cognition and social responsiveness in primary school-aged children with 22q11DS.

Comorbidity

The current diagnostic classification system possibly does not pick up on the correlated nature of psychopathology in 22q11.2DS. Niarchou and colleagues (2017) examined psychopathology at symptom-level and found a disposition to developing any form of common psychopathologies in 22q11DS individuals. Additionally, half of individuals with 22q11DS appears to have two or more psychiatric disorders (Yi et al., 2015). An increased psychiatric comorbidity is known to be associated with a more severe disease course, differential treatment response and reduced global functioning (Arcelus & Vostanis, 2005; Yi et al., 2015). Considering that social functioning is related to well-being, a complete identification of social difficulties in individuals with 22q11DS may contribute to their quality of life (Norkett et al., 2017).

An important question remaining is whether social impairments are a part of the syndrome or can be attributed to the intellectual disability frequently present in individuals with 22q11DS. Noteworthy, in the general population behavioural problems seem to be up to four times higher for adolescents with an intellectual disability compared to peers without an intellectual disability (Einfeld & Tonge, 1996). In contrast, Kates and colleagues (2007) found that 22q11DS children score higher on the subscale Autistic Mannerism of the Social Responsiveness Scale – second edition (SRS-2), compared to peers with an intellectual disability. This suggests that restricted interests may be more common in children with 22q11DS compared to IQ-matched peers (Kates et al., 2007).

Present Study

In the current study we aim to describe the strengths and weaknesses in the social functioning profile of adolescents with 22q11DS. The first goal is to give an overview of common relevant problems in social functioning. Second, the different aspects of social functioning from eleven year of age onward are studied. Elaborating on the observed pattern of decline in childhood, we hypothesize that adolescents with 22q11DS display deficits in social skills that increase during adolescence. The third aim is to analyse whether problems in social functioning are specifically related to a having a diagnosis of ASD. We expect that participants with ASD show more problems on different domains of social functioning compared to participants with any other psychiatric diagnosis or without any established psychiatric diagnosis. Following findings Kates and colleagues (2007), we hypothesize that lower IQ is a predictor of deficits in social functioning.

Method

The current study is a longitudinal cohort study within a larger ongoing behavioural and genetic research project of patients with 22q11DS. The study has been approved by the research ethics board of the UMCU in 2002 (Dutch Central Committee on Research Involving

Human Subjects; C.C.M.O) and the used data is obtained at the department of Psychiatry at the University Medical Centre in Utrecht in The Netherlands from 2002 to 2019. Parents and participants provided written informed consent.

Participants

We included 217 participants with 22q11DS between 11.3 and 28.9 years old ($M = 18.5$, $SD = 2.8$) diagnosed with 22q11DS. All participants had a molecularly confirmed pathogenic genome variant at the 22q11.2 locus, which was determined using established genetic methods (fluorescence in situ hybridization or multiplex ligation-dependant probe amplification, McDonald-McGinn et al., 2015). Most patients with 22q11DS throughout the country are routinely monitored in the national 22q11DS outpatient clinics ('NFU acknowledged expert centres') at the UMC Utrecht or the Wilhelmina Children's Hospital (WCH). In order to be eligible to participate in this study, participants needed to be at least eleven years old. Exclusion criteria were brain trauma not related to the genomic disorder.

Instruments

Social Functioning

The Social Responsiveness Scale – second edition (SRS-2) was used for measuring social functioning. This 65 item questionnaire was filled out by parents or caregivers to define social deficits. Five subscales are included: Social Awareness (for example item 2, 'Doesn't seem to mind being out of step with or not on the "same wavelength" with others'), Social Cognition (item 10, 'Takes things too literally and doesn't get the real meaning of a conversation'), Social Communication (item 47, 'Laughs at inappropriate times'), Social Motivation (item 9, 'Seems too dependent on others for help with meeting basic needs') and Autistic Mannerisms (item 39, 'Has an unusually narrow range of interests')(Constantino & Gruber, 2012).

Respondents rate their level of agreement with each item on a four-point Likert scale, rating behaviour over the past six months. The sum of all items is calculated to provide a total score (max 195). Raw scores can be transformed into age corrected T-scores ($M = 50$, $SD = 10$). A T-score lower than 56 indicates no social difficulties associated with an ASD diagnosis. T-scores between 60 and 65 indicate mild to moderate clinically relevant deficiencies in social behaviour. Scores between 66 and 75 are considered moderate, signalling some clinically significant social deficits. T-scores 76 or higher indicate severe deficits in social functioning that interfere with interactions with others (Constantino, 2003).

Psychiatric Disorders

We used the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS) for determining the major psychiatric disorders depression, schizophrenia, ADHD as described in the DSM-5 (American Psychiatric Association, 2013). Most items are scored on a four-point-scale, a small part on a three-point-scale. It reviews the most severe current and past psychiatric symptoms, grouped into modules. If probes and scoring criteria for each presented symptom are not met, the rest of the module's questions were not asked (Kaufman et al., 1997).

For defining symptoms of autism spectrum disorder (ASD) we used the Autism Diagnostic Interview – Revised (ADI-R). This is an extensive interview about early childhood behaviours (age 4 – 5 years) in the areas of reciprocal social interaction, communication and language and patterns of behaviour, filled out by either parents, caregivers or teachers (Rutter et al., 2003). All psychiatric diagnoses were determined taking additional information from parents and school into account, with the judgement of child psychiatrists and psychologists being decisive (Rutter, Le Couteur & Lord, 2003).

Cognitive Functioning

Full Scale Intelligence Quotient (FSIQ) in children younger than 16 years old was measured using the Dutch version of the Wechsler Intelligence Scale for Children – Fifth Edition (WISC-V; Wechsler, 2014). We used the adult version of the Wechsler Adult Intelligence Scale – Fourth Edition (WAIS-IV; Wechsler, 2008) for participants over 16 years old. These intelligence tests are widely used and reviewed as a valid with a sufficient reliability (Wechsler, 2014; Wechsler, 2008; Egberink, Janssen, & Vermeulen, 2005).

Procedure

According to international guidelines for care for individuals with 22q11DS it is recommended to frequently assess cognitive and mental health, given the genetically increased risk for psychiatric problems (Fung et al., 2015). After the first assessment (T0), follow-up assessments are scheduled every two to three years (T1 and T2) as a part of routine clinical care at the psychiatry department. All individuals with 22q11DS and their caregivers were asked to participate in this longitudinal cohort study. After which both participants, parents or legal guardians provided written informed consent. Subsequently a multidisciplinary team conducted psychiatric and cognitive measurements with both children and their parents. All instruments except the ADI-R were re-administered during follow-up assessments. The total interview time with parents was around 90-120 minutes and for children around 30 minutes. Additionally patients underwent cognitive testing, which lasted two hours with a short break halfway.

Data analyses

Social Functioning

Statistical analyses were done using SPSS 25 (Statistical Package for Social Sciences version 25, IBM, 2017). Assumptions about the independence of observations, normality of the data and compound symmetry were checked and not violated. The data obtained during

the baseline measurement T0 was used to answer the first research question about the social functioning profile for the whole 22q11DS group.

Longitudinal Analyses

Second, changes over time were explored comparing Total Scores on the SRS-2 from T0 to follow-up assessments T1 and T2. Prior to performing analysis, normality of residuals, homoscedasticity, independence and linearity of the data were checked and not violated. Repeated measures ANOVA was used to compare social functioning between the different timepoints.

Psychiatric Disorders

For statistical analyses the total sample was categorized into three groups, based on psychiatric diagnoses. The first group contains all participants with an autism spectrum disorder (ASD) diagnosis. The second group contains participants with any other psychiatric diagnosis, besides ASD. The third group contains all individuals without a life-time history of psychiatric diagnosis. Assumptions about data distribution and homogeneity of variance were checked beforehand and not violated. Differences in scores on the six subscales of the SRS-2 (dependent variable) between psychiatric diagnosis groups (independent variable) were investigated, using one-way ANOVA analyses, correcting for multiple testing effects using Bonferroni correction. Lastly, simple linear regression analysis was used to investigate the role of IQ on Total Scores of the SRS-2 on T0. Assumptions were checked and not violated.

Results

Missing Data and Reliability

Participation in this study was voluntary, resulting in missing SRS-2 data ($n = 74$) on the first timepoint. Pearson's Chi-square test analyses indicated no significant difference in sex ($p = .841$) and the amount of reported ASD diagnoses ($p = .496$) between participants who filled in the SRS-2 and who did not. Independent samples t-test also revealed no significant difference in IQ between participants who have filled in the SRS-2 and who have not (p

>.524), suggesting that data is missing completely at random. Undergoing follow-up assessment was voluntary and some patients have yet to receive an invitation, causing unequal amounts of data on the three timepoints. Pearson's Chi-square test analyses indicated no significant difference in frequency of follow-up assessments (T1 and T2) after T0 between participants with ASD, any other psychiatric diagnosis or without a diagnosis ($p = .053$). When looking at standardized residuals of the analysis, it appears that participants without a psychiatric diagnosis more often undergo follow-up assessments after T0 in comparison to participants with ASD or any other psychiatric diagnosis. Furthermore, reliability analyses showed high internal consistency for all subscales of the SRS-2 ($\alpha > .677$).

Social Functioning

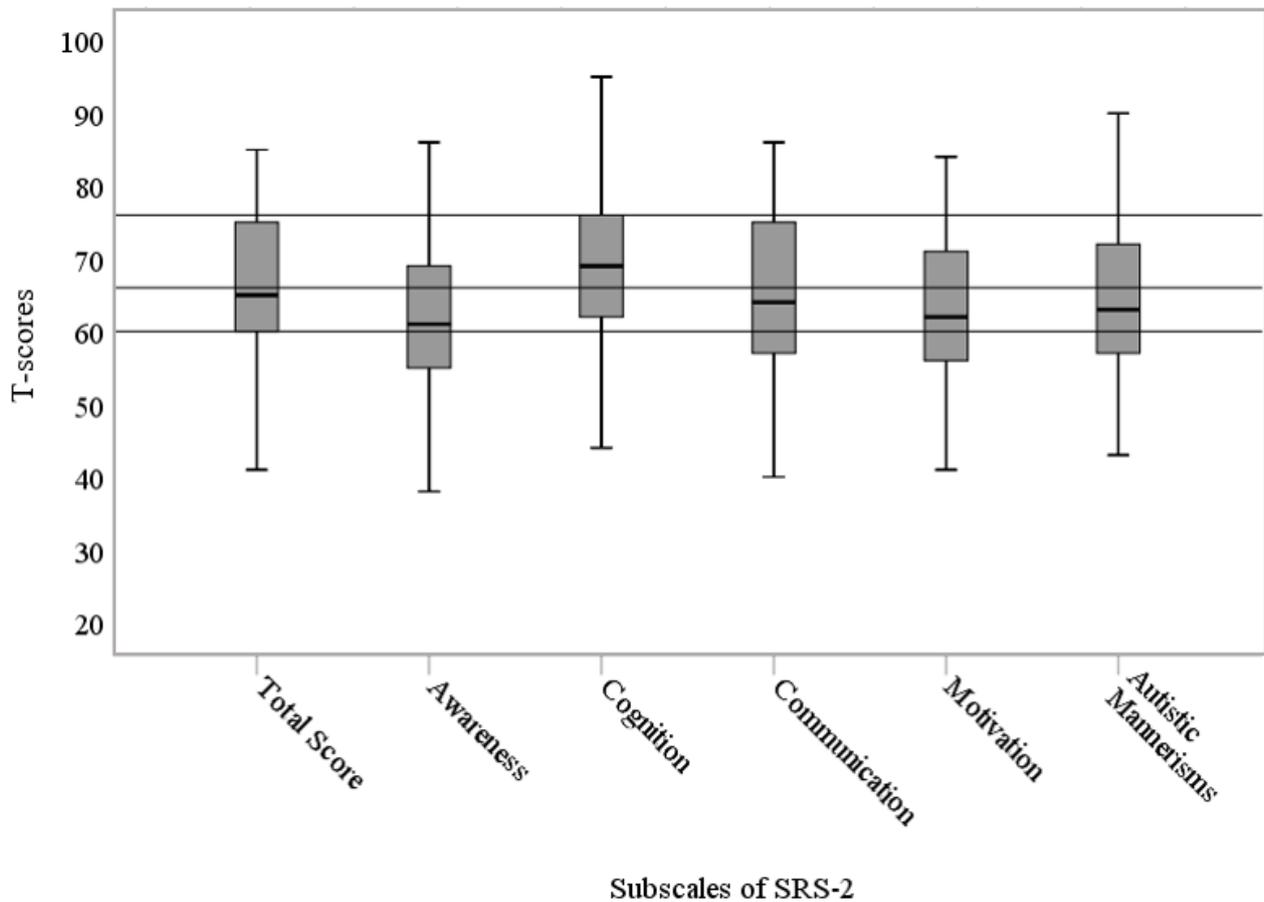
Mean T-scores of the subscales on T0 are displayed in figure 1 below and mean scores, standard deviations and sample characteristics are presented in table 1. On the Total Score subscale 67.63% of participants scored above 60, representing mild to moderate social functioning problems. Mean T-scores of the sample on all subscales fall within the range of clinically significant deficiencies in social functioning. The T-scores of the scale Social Cognition is the highest on all three timepoints, Social Motivation being the lowest on T0 and Autistic Mannerisms the lowest on T1 and T2.

Longitudinal Analysis

To examine social functioning over time, differences in scores on the three timepoints were analysed. Repeated Measures ANOVA did not indicate a statistically significant effect of time on the total T-score: $F(2, 20) = 1.18, p = .11$. Because of the small group of participants with data on all three timepoints ($n = 11$), two separated repeated measures ANOVA's have been executed comparing T-scores between the first and second measurement and the second and third measurement. The T-score of the Total Score scale did not differ significantly between the first and second timepoint ($n = 68$); $F(1, 67) = 0.07, p =$

.984. The T-score of the Total Score is significantly different between the second and third timepoint ($n = 23$); $F(1, 22) = 4.974, p = .036, \eta^2 = .184$. Total scores are significantly higher on T3 compared to T2. Table 1 below presents sex, mean age and IQ, mean scores and standard deviations of the six subscales of the SRS-2 on the three timepoints.

Figure 1
Boxplot with T-scores of subscales of the SRS-2 on T0



Note. Lines represent cut-off scores: $T > 60$ (mild), $T > 66$ (moderate) and $T > 76$ (severe).

Table 1

Number of Males and Females, Means and Standard Deviations for Age, IQ and the Means and Standard Deviations of the SRS-2 Scales on Three Timepoints for the Total Sample.

Timepoint	T0		T1		T2					
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%				
Gender										
Female	81	58.27	66	60.55	19	65.52				
Male	58	41.73	43	39.45	10	34.48				
	<i>n</i>	<i>M</i>	<i>SD</i>	<i>T > 60(%)*</i>	<i>n</i>	<i>M</i>	<i>SD</i>	<i>n</i>	<i>M</i>	<i>SD</i>
Age	132	14.52	2.23		72	18.67	2.78	24	22.34	3.60
IQ	139	64.08	12.18		88	69.15	13.72	29	68.94	12.10
Total score	139	62.94	10.06	67.63	109	63.26	9.24	29	67.26	7.83
Awareness	129	62.53	10.35	60.47	101	64.38	9.98	25	69.28	12.47
Cognition	136	67.49	11.05	77.94	108	67.38	11.10	26	70.58	9.25
Communication	133	63.73	11.30	57.89	97	64.18	10.44	25	64.12	8.63
Motivation	135	62.37	9.87	58.52	101	62.29	9.55	23	65.43	9.13
Autistic Mannerisms	130	63.18	11.38	56.92	102	61.87	10.06	24	62.71	10.34

Note. T-scores of subscales

*Percentage of participants with cut-off score for clinically significant impairment $T > 60$.

Psychiatric Disorders

Analysis of variance showed a main effect of difference in psychiatric diagnosis on the subscales Total Score, Social Communication, Social Motivation and Autistic Mannerisms ($F < 3.67, p < .045$). The main effect of psychiatric diagnosis was not significant for the subscales Social Awareness and Cognition ($F < 1.91, p > .153$). Post-hoc analyses using Bonferroni correction indicated that the only the scores on the subscale Autistic Mannerisms were significantly higher in the ASD group compared to the group with any other psychiatric diagnosis $F(2,124) = 4.62, p = .022, \eta^2 = .071$. However, on all other subscales participants with ASD scored higher compared to participants with any other or without a psychiatric diagnosis, with largest observed differences on scales Total Score, Communication and

Motivation ($p > .062$). Table 2 includes T-scores and ANOVA statistics per subscales of the three groups of participants.

Table 2

Number of Females and Males, Means and Standard Deviations for Age, ANOVA statistics and scores on SRS-2 Scales for Participants According to Psychiatric Diagnosis.

Diagnosis	ASD*		Other diagnosis**			No diagnosis		Missing		<i>F</i> ***	<i>p</i>
	<i>n</i>	%	<i>n</i>	%	<i>SD</i>	<i>n</i>	%	<i>n</i>	%		
Gender											
Female	32	51.42	14	56.67		31	66.67	2	40		
Male	30	48.48	11	43.33		15	33.33	4	60		
	<i>n</i>	<i>M</i>	<i>SD</i>	<i>n</i>	<i>M</i>	<i>SD</i>	<i>n</i>	<i>M</i>	<i>SD</i>	<i>F</i> ***	<i>p</i>
Age	90	14.61	2.16	32	27.41	3.04	58	14.07	1.85		
Total score	62	67.58	10.47	25	62.36	9.71	46	63.17	10.73	3.40	0.04
Awareness	60	63.18	11.20	22	61.55	8.30	41	61.76	9.88	0.33	0.72
Cognition	61	69.34	10.80	24	64.54	11.50	45	66.49	11.07	1.91	0.15
Communication	61	66.41	11.18	23	60.78	10.43	43	61.23	11.32	3.67	0.03
Motivation	62	64.53	9.71	23	60.61	10.15	45	60.07	9.52	3.17	0.05
Autistic Mannerisms	56	66.43	11.56	24	59.08	9.77	44	61.48	10.93	4.62	0.01

Note. T-scores of subscales

*Autism Spectrum Disorder.

** ADHD, Psychotic disorder, Depression, Anxiety, Conduct Disorder or Language Disorder.

*** *F* statistic and *p*-value of ANOVA analysis.

Cognitive Functioning

Single linear regression was used to analyse whether the Total Score of the whole sample (T0) was associated with a lower IQ. Results indicated that Total IQ did not significantly predict 'Total Score' on the SRS-2 ($F(1, 122) = 2.22, p = .139, R^2 = .137$)

Discussion

With this longitudinal study we give an overview of the social functioning profile in adolescents with 22q11DS. When describing the social functioning profile of 22q11DS adolescents, social cognition seems particularly problematic. Autistic mannerisms, repetitive or stereotypical behaviour for example, are problematic but less affected. This is consistent

with previous research indicating deficits in social skills in people with 22q11DS (Kiley-Brabeck & Sobin, 2006; Niklasson, et al., 2002; Shashi et al., 2012). Results do not support Kates and colleagues (2007), suggesting that autistic mannerisms are a relative weakness compared to other deficiencies in reciprocal social behaviour in people with 22q11DS. Current results emphasize deficiencies in reciprocal social behaviour in the whole sample of adolescents with 22q11DS.

Development of Social Functioning

Longitudinal analyses indicated a decline of social functioning between the second and third measurement (between the ages 18,67 and 22,34 years), consistent with our expectation. Results are in line with other research reporting an increase of social problems in children with 22q11DS compared to peers with an idiopathic intellectual disability (Van de Heuvel et al., 2018). The decline resembles a previously described growing into deficit trend of social functioning (Fiksinski et al., 2018; de Smedt et al., 2007, Evers et al., 2009; Swillen et al., 1999). The observed decline is in contrast with findings on ASD in the general population where adolescents report fewer symptoms compared to younger age groups (Shattuck et al., 2007).

An increase in problems over time emphasizes the importance of early and frequent evaluation of social deficits of 22q11DS adolescents in clinical practice. Repeated monitoring may allow for early detection of problems, creating the opportunity to adapt recommendations for caregivers to the social needs of 22q11DS children (Van de Heuvel, 2017). This can also support preparation for the future, for example by searching for suitable education and appropriate residential living (Norkett et al., 2017).

Further research is needed to provide a complete description of the developmental trajectory of social functioning. Understanding the development of social behaviour can promote the development of adequate interventions. This is important since rejection or low

acceptance among peers in childhood is related to a variety of negative outcomes. For example, traumatic experiences because of bullying can lead to developmental problems, elevating the risk for early onset psychotic disorders and other forms of psychopathology (Mayo & Niendam, 2017).

Psychiatric Disorders

This study shows that social functioning is significantly different between participants with ASD, participants with any other diagnosis and with no psychiatric diagnosis. However, analyses on other dimensions of social functioning shows only significantly more autistic mannerisms in participants with ASD, compared to participants with any other psychiatric diagnosis. As previously proposed by Norkett and colleagues (2017), the current evidence points to social impairments in the whole group of patients regardless of a psychiatric diagnosis. Results are also consistent with research reporting significant social and communication impairments, restrictive and repetitive behaviours, in people with 22q11DS without an ASD diagnosis (Ousley et al., 2017).

Remarkably, a large part of the patients displaying social problems has not received a diagnosis of ASD. This might be due to different needs of caregivers of children with 22q11DS when it comes to requesting help, compared to caregivers from children with ASD in the general population. Behavioural problems of patients with 22q11DS are often overlooked in the context of stressful medical care for life threatening diseases. ASD symptoms may be de-prioritized when caregivers discuss issues with professionals (Niarchou et al., 2017). However, it should be considered that an ASD diagnosis can help caregivers understand their child's 'deviating' behaviour in social settings. Moreover, a diagnosis can help in explaining the child's behaviour to the outside world, as little is known about 22q11DS in the general public (Horner, et al., 2002). This may result in more clarity on

expectations of 22q11DS individuals in social settings, preventing stress which decreases the risk of developing psychiatric disorders (Van de Heuvel, 2017).

Additionally, the Social Responsiveness Scale – second edition (SRS-2) possibly does not detect symptoms of ASD in 22q11DS individuals. Using multiple independent assessors, direct observations in classrooms or at occupational settings, alongside of interviews and questionnaires may be needed in describing the social functioning profile of 22q11DS individuals (Constantino & Gruber, 2012). These broader methods can facilitate diagnosing ASD in 22q11DS. Future research should also approach the investigation of social functioning in 22q11DS from a broader perspective. This is supported by the recommendation of Stochl and colleagues (2015), who suggest to evaluate symptoms of social impairment rather than focussing on the diagnosis of ASD. This may give a better representation of all underlying dimensions of social functioning, taking the high psychiatric comorbidity in 22q11DS into account.

Cognitive Functioning

Our results do not confirm that social impairments can be attributed to the intellectual disability frequently present in individuals with 22q11DS. A lower IQ is not significantly associated with problems in social functioning within this sample of 22q11DS adolescents. Research suggests that individuals with ASD in the general population report different social deficits at different parts of the IQ spectrum (Rommelse et al., 2015). Cognitive deficits in social cognition, executive functioning, basic processing speed, language and sensory processing appear somewhat more severe in individuals with ASD who have an IQ above average (≥ 115) compared to those with an IQ below average ($70 < IQ \leq 85$) (Rommelse et al., 2015). The below average IQ within this sample may explain the unobserved association between IQ and social functioning.

Strengths and Limitations

A strength of this study is the comparison of social functioning on different timepoints, describing social development during adolescence. Another strength is the use of the SRS-2 as an instrument for measuring multiple dimensions of social functioning; recognizing social cues, interpretation, reciprocity and motivation of social behaviour along with stereotypy and restricted interest. However, some study limitations should be noted. Firstly, the patient sample consists of participants that are under medical supervision in the UMC Utrecht. These individuals may be experiencing more health problems and social difficulties at school or in other social settings compared to 22q11DS individuals who are not under medical supervision. This makes it difficult to extrapolate data to the whole 22q11DS population.

Secondly, a substantial part of the sample did not respond to an invitation for a second or third medical re-evaluation. This is a likely cause of missing data on the three different timepoints, which negatively influenced the sample size. Additionally, systematic differences may arise between those who undergo follow-up assessment and those who do not. This can be an alternative explanation for the higher scores on the third measurement. Future research could examine social functioning over time in larger sample sizes on a regular basis from early childhood into later adulthood. This will verify whether the observed growing into deficit trajectories are consistent for the complete group of people with 22q11DS.

Lastly, report bias of caregivers may have influenced our results. The deletion syndrome is often identified at birth, making caregivers immediately aware that the development of their child is different. This can cause caregivers to integrate unusual behaviour into their conceptualization of the deletion syndrome. Thus, it becomes less likely that they will question these symptoms and report this when filling in a questionnaire, compared to parents of children without a condition identified at birth (Fine et al., 2005). This should be taken into

account when interpreting scores of social functioning on the SRS-2 filled in by caregivers of 22q11DS individuals.

Conclusion

This study emphasized the social functioning problems in all adolescents with 22q11DS. Social responsiveness problems increase significantly over time, emphasizing the importance of regular assessment. Additionally, a diagnosis of autism spectrum disorder (ASD) does not seem to fully explain social deficits within 22q11DS adolescents. This suggests that all individuals with 22q11DS are at increased risk for developing social problems. A more comprehensive study is needed to describe a detailed profile of social functioning. This will contribute to accurate assessment of ASD and promote the development of adapted recommendations for caregivers and the social environment of 22q11DS individuals. With this, more tailored guidance and treatment plans may prevent stress in individuals with 22q11DS and decrease their risk for developing psychiatric disorders which improves their quality of life.

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