The relation between autistic traits and cognitive functions: A general population study

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Samenvatting

Achtergrond: Autisme Spectrum Stoornissen (ASDs) worden geassocieerd met kwalitatieve beperkingen in sociale interactie en communicatie en rigide, repetitief en stereotiep gedrag, interesses en activiteiten. Onderzoek naar autistische trekken in de volwassen algemene populatie is minimaal.

Doel: Het onderzoeken van de relatie tussen autistische trekken en cognitieve functies. Daarnaast ook de modulerende rol van het AUTS2 gen.

Methoden: Om dit te onderzoeken in de huidige studie zijn 178 participanten gegenotypeerd en hebben ze de Social Responsiveness Scale (SRS) ingevuld. De relatie tussen de SRS score, het AUTS2 gen en de cognitieve maten worden onderzocht.

Resultaten: Significante verschillen zijn gevonden in de SRS scores tussen mannen en vrouwen. Ook zijn tussen hoog en laag scorende participanten op de SRS en tussen de AUTS2 groepen significante verschillen gevonden voor de scores op de Iowa Gambling Task (IGT). Daarnaast is er een significante interactie gevonden tussen het AUTS2 gen en de SRS op de Brixton Spatial Anticipation test. Bovendien werd er een significant resultaat gevonden bij de 'anger'-conditie van de Degraded Facial Affect Recognition Task (DAR) wanneer de SRS groepen worden vergeleken.

Conclusie: In de huidige studie is gevonden dat mannen meer autistische trekken hebben dan vrouwen. Ook zien we dat participanten met autistische trekken grotere risico's nemen. Verder blijkt dat participanten met autistische trekken slechter zijn in het identificeren van de emotie 'anger'. We hebben geen relatie gevonden tussen de SRS en het AUTS2 gen, maar vonden wel dat participanten met autistische trekken slechter presteren op de Brixton wanneer zij drager zijn van het AUTS2 gen.

Keywords: Autistische trekken, emotieherkenning, executief functioneren, volwassenen, algemene populatie

Abstract

Background: Autism Spectrum Disorders (ASDs) are associated with qualitative impairment in social interaction and communication and restricted, repetitive and stereotyped patterns of behavior, interests and activities. Research on autistic traits in the general adult population is limited.

Aim: To asses the relation between autistic traits and cognitive functions. Additionally, we will investigate the possible modulating role of the AUTS2 gene.

Methods: 178 participants were genotyped and they completed the Social Responsiveness Scale (SRS). The relation between the SRS score, the AUTS2 gene and the cognitive measures was examined.

Results: Significant differences were found in the SRS scores between males and females. Also a difference in Iowa Gambling Task (IGT) scores was observed between the low and high scoring SRS groups and between the AUTS2 groups. Furthermore, a significant difference was found on the anger-condition of the Degraded Facial Affect Recognition Task (DAR) when we compared the SRS groups. A significant result was also found when we looked at the modulating role of the AUTS2 gene on SRS groups on the Brixton.

Conclusion: In the current study we found that males have more autistic traits than females. We also found that participants with autistic traits take bigger risks. In addition, we found that participants with autistic traits are worse at identifying the emotion anger. We found no relation between the SRS and the AUTS2 gene, however we did find that participant with autistic traits perform worse on the Brixton when they carry the AUTS2 gene.

Keywords: Autistic traits, emotion recognition, executive functioning, adults, general population

Introduction

Autism spectrum disorders

Autism spectrum disorders (ASDs) are pervasive developmental disorders of the brain with a complex genetic aetiology. The ASD group includes classic autism, pervasive developmental disorders-not otherwise specified (PDD-NOS) and Asperger's disorder. The ASD construct is still evolving, but the current clinical criteria used to diagnose ASDs are those described in the Diagnostic and Statistical Manual 4th edition (DSM-IV-TR) of the American Psychiatric Association. Three symptom domains define ASDs in the DSM-IV-TR (American Psychiatric Association, 2000):

1. Qualitative impairment in social interaction;
2. Qualitative impairment in social communication;
3. Restricted, repetitive and stereotyped patterns of behavior, interests and activities.

Currently, the prevalence of ASDs is estimated around 60-70 cases per 10,000 children (Fombonne, 2009; Williams, Higgins, & Brayne, 2006; Wing & Potter, 2002). However, multiple resources provide different results, ranging from 1.7 to 181.1 cases per 10,000 children (Fombonne, 2003; Fombonne, 2005; Fombonne, 2009; Sadock & Sadock, 2007; Williams et al., 2006; Wing et al., 2002; World Health Organisation, 2003).

Autistic traits in adults in the general population

Until now, most of the research is done on children, but lately there is increasing interest in the prevalence of ASDs and autistic traits in adults. It is possible to obtain new insights on the development of autism by studying adults. Moreover, studying autistic traits in the general population might also be a good way to gain new insights.

It is not easy to study ASDs and autism in the general population, mainly because of its low prevalence, which makes screening for autism an intensive and costly procedure. However, for scientific purposes autism may be studied as a continuous trait. Studying autistic traits in adults in the general population might contribute to insights on the neurobiological base of autism. Research on ASDs and autistic traits in the general population so far has been limited. However, several studies imply that ASDs embody an assortment of traits that could be continuously distributed in the general population (Baron-Cohen, Wheelwright, Skinner, Martin, & Clubley, 2001; Constantino & Todd, 2000; Constantino & Todd, 2003; Piven, Palmer, Jacobi, Childress, & Arndt, 1997; Spiker, Lotspeich, Dimiceli, Myers, & Risch, 2002; Bolte, Westerwald, Holtmann, Freitag, & Poustka, 2011). Longitudinal research shows that autistic symptoms decrease over time. Social communication improves the most, followed by

social interactions and restricted, repetitive and stereotyped behavior symptoms (Hengeveld, Van Londen, & Van Der Gaag, 2008; Kan, Buitelaar, & Van Der Gaag, 2008; Seltzer et al., 2003; Seltzer, Shattuck, Abbeduto, & Greenberg, 2004; Matson & Horovitz, 2010).

Recent general population studies on ASDs are the studies by Constantino et al. (2009) and Robinson et al. (2011). However, there are some limitations in those studies, for example, the research population of the Constantino et al. (2009) study existed exclusively out of twin males. Robinson et al. (2011) studied the stability of autistic traits in participants from 7 to 13 years of age, and provided some interesting findings in this study. They "suggest that autistic traits are highly stable in the general population, even in individuals with the highest concentrations of autism-like behaviors" (Robinson et al. 2011).

Restricted, repetitive and stereotyped behavior

Of the three symptom domains, the restricted, repetitive and stereotyped behavior domain has received considerably less attention than the other two domains (Langen, 2011; Turner, 1999); research on this domain has been neglected (Hollander et al., 2003; Turner, 1999; Baron-Cohen, 1989a). According to Turner (1999) two types of repetitive behavior can be distinguished: lower-level and higher-level repetitive behavior. Lower-level repetitive behaviors typically feature repetition of movement, the more complex higher-level repetitive behaviors are characterized by excessive preoccupations/interests (Carcani Rathwell, Rabe Hasketh, & Santosh, 2006; Turner, 1999; Hus, Pickles, Cook Jr, Risi, & Lord, 2007; Turner, 1997; Cuccaro et al., 2003). Lam, Bodfish, & Piven (2008) state that higher-level repetitive behaviors are more exclusive to autism, compared to lower-level repetitive behaviors.

Executive functioning

ASDs are associated with deficits in executive functioning (Turner, 1999). Executive functions are involved in problem solving, response inhibition, cognitive flexibility and planning (Turner, 1999). In executive functions it is not possible to rely on routine behavior (Hill, 2004). Research by Lopez, Lincoln, Ozonoff, & Lai (2005) shows that the occurrence of repetitive behavior in adults with autism is an indication for poor performance on executive functioning tasks. Several other studies also report impaired performance on executive tasks in individuals with ASDs (Hughes, Russell, & Robbins, 1994; Ozonoff, 1997; Ozonoff & Jensen, 1999).

Neurobiological theories of ASDs emphasize functional abnormalities in the amygdala, prefrontal cortex, basal ganglia and fusiform gyrus (Baron-Cohen et al., 2000;

Schultz, Romanski, & Tsatsanis, 2000; Cody, Pelphrey, & Piven, 2002), These regions are also used for executive functioning (e.g. decision making) (O'Hearn, Asato, Ordaz, & Luna, 2008; Zelazo, Carter, Reznick, & Frye, 1997). Performance on the Iowa Gambling Task (IGT) (Bechara, Damasio, Damasio, & Anderson, 1994) may be sensitive to damage to those regions. The IGT is a decision-making task that requires participants to learn to make advantageous choices on the basis of feedback in the form of monetary gains and losses. The game is fairly complex and during the game the participant develops an idea about which stacks are good, and which are bad. Research from Bechara, Damasio, & Damasio (2000) shows that patients with lesions in the regions used for executive functioning do not develop this feeling, and they keep losing money.

Previous research has also shown that people with problems in executive functioning show impairments in tests where they have to detect and follow a rule (Anderson, Damasio, Jones, & Tranel, 1991; Burgess et al., 1997; Owen, Downes, Sahakian, Polkey, & Robbins, 1990; Ozonoff, 1995). Therefore, performance on the Brixton Spatial Anticipation Task (Burgess & Shallice, 1997) may be influences by damage to the executive functioning regions. The Brixton is a task that assesses executive functioning (e.g. self-monitoring), by testing whether participants are able to follow a rule and if they can adapt when the rule changes unexpectedly.

Emotion recognition

A common aspect of the impaired social communication observed among people with ASDs is a difficulty with face processing. The ability to process facial expressions and gain socially relevant information from them is an essential necessity for social interactions. When emotions or mental states need to be identified, the face processing difficulties become even more problematic (Baron-Cohen, 1989c; Baron-Cohen, 1989b). Pelphrey et al. (2002) report differences in face processing in adults with and without autism; adults with autism scored significantly worse at identifying anger and fear. The amygdala is the brain region involved in emotion processing. Previous research has shown that there is an amygdala dysfunction in people with autism (Baron-Cohen et al., 2000). Other studies have also shown that the amygdala structure is abnormal in autism (Sparks et al., 2002; Schumann et al. 2004). With regards to the restricted, repetitive and stereotyped behavior, previous research has shown that a smaller amygdala volume is involves in higher levels of the restricted, repetitive and stereotyped behavior (Dziobek, Fleck, Rogers, Wolf, & Convit, 2006). In the Degraded Facial Affect Recognition Task (DAR) (van 't Wout, Aleman, Kessels, Laroi, & Kahn, 2004)

participants have to label (happy, angry, neutral, fear) an emotional face they see. Performance on the DAR may be influenced by the abnormality of the amygdala, and thus extent of autistic traits in the participant.

Risk factors: Genetics, IQ and Gender

A range of risk factors has been associated with ASDs. A genetic risk factor may be particularly important in the aetiology of ASDs. Research shows that in monozygotic twins the concordance rate for ASDs is 90% and in dizygotic twins it is 10% (Muhle, Trentacoste, & Rapin, 2004; Sebat et al., 2007; Bailey et al., 1995), resulting in a heritability estimate of 80%. However, more recent research implies that susceptibility to ASD has moderate genetic heritability (Hallmayer et al., 2011). This research shows concordance rates of 77% for male and 50% in female monozygotic twins, and 31% in male and 36% in female dizygotic twins (Hallmayer et al., 2011). Efforts to map genes involved in ASDs suggest that there are up to 12 genes involved (International Molecular Genetic Study of Autism Consortium, 1998). SNP rs6943555 in the autism susceptibility candidate 2 (AUTS2) gene is located at chromosome 7q11.22, and has been identified and proposed to contribute to ASDs (Huang, Zou, Maher, Newton, & Milunsky, 2010; Schumann et al., 2011; Sultana et al., 2002).

Low IQ is a known risk factor for ASDs. A study by Nishiyama et al. (2009) reported a high genetic correlation between IQ and autistic traits. Preceding research found modest to moderate correlations between social and communication impairments and IQ (Hus, Pickles, Cook, Risi, & Lord, 2007; Spiker, Lotspeich, Dimicell, Myers, & Risch, 2002; Hoekstra, Happé, Baron-Cohen, & Ronals, 2009). Regarding restricted, repetitive and stereotyped patterns of behavior (Georgiades et al., 2007) reported a positive relationship between IQ and inflexible behavior, but results are mixed (Hus, Pickles, Cook, Risi, & Lord, 2007; Spiker, Lotspeich, Dimicell, Myers, & Risch, 2002; Hoekstra, Happé, Baron-Cohen, & Ronals, 2009).

Gender is also a known risk factor for ASDs. Currently, ASDs seem to be predominantly represented in males (Baron-Cohen, Knickmeyer, & Belmonte, 2005; Baron-Cohen, 2002; Lord, Schopler, & Revicki, 1982; Lord & Schopler, 1985). However, prior research shows an interaction between IQ and gender (Skuse, Mandy, & Scourfield, 2005). According to Volkmar, Szatmari, & Sparrow (1993) autism is more prevalent among males with a high IQ, and more prevalent in females with a low IQ.

Social Responsiveness Scale

In search of a better understanding of ASDs, researchers keep developing new questionnaires. A recently marketed questionnaire, the Social Responsiveness Scale (SRS), seems the most suitable instrument to map autistic traits in the general population. The SRS (Constantino, Gruber, & Western Psychological Services (Firm), 2007) has the important advantage of covering the different sub domains (social awareness, social cognition, social communication, social motivation and autistic mannerisms) on ASDs and it is a continuous measure. The major advantage of the SRS is that this questionnaire takes the severity of the symptoms into consideration. It acknowledges that even the mild degrees of impairment can have a severe effect; therefore it measures impairment on a quantitative scale (Constantino et al., 2007).

The present study

In order to develop a better understanding of ASDs, this study attempts to investigate autistic traits in adults in the general population. The focus of the study is the restricted, repetitive and stereotyped patterns of behavior. We plan on using the SRS (Constantino et al., 2007) to map autistic traits in the general population. Furthermore, we will use the DAR (Lang et al., 1999), which is an emotion recognition task, to measure the extent of problems with processing emotions in the participants. We suggest that the IGT (Bechara et al., 1994) may reveal useful insights into the behaviors associated with repetitive processes (responses to gains and losses) in ASDs. We propose that because of the rigidity in individuals with autistic traits, they might have difficulty switching between rules in the Brixton Spatial Anticipation Task (Burgess et al., 1997). In addition, based on previous research, we will also look at IQ and gender. Finally, we will look at susceptibility for the AUTS2 gene in the participants.

Methods

Participants

Participants for the 'Building Blocks' study are recruited through the 'Leidsche Rijn Health Project' (LRHP). This is an epidemiological cohort study conducted in a healthy population in the Leidsche Rijn district in Utrecht, which started in 2000 (Grobbee et al., 2005). LRHP aims to answer questions about the causes of illness and on factors influencing health. The general practitioner invites all new residents of the Leidsche Rijn district to participate in the LRHP, regardless of socioeconomic status, ethnic background, age or gender. After an informed consent was contained, a baseline individual health profile (IHP) is made.

For the 'Building Blocks' study, DNA was genotyped for the first 2400 participants of the research population with four Dutch ancestors, available IHP data and sufficient available DNA. Five genes are examined in this study (APOE, BDNF, COMT, DAOA, NRG1), and recently the AUTS2 gene is added to this list. Based on the genotype, participants were selected and invited to participate. Up to August 2011, 299 participants completed the assessments.

Material

Material used to test hypotheses:

Social Responsiveness Scale (SRS) (Constantino et al., 2007):

All participants completed the Dutch version of the SRS over the internet. The Dutch version is in its test phase, but is found to be appropriate for testing adults (De la Marche, Steyart, Scholte, Dorst, van Verckelaer-Onnes & Noens, 2009). The SRS measures the extent of autism spectrum symptoms that occur in a natural social setting. It consists of 65 items, which are rated on a scale of 1 (not true) to 4 (almost always true). The SRS consists of two parts, a maternal report and a spouse report. The maternal report is a self-report questionnaire; the spouse report is to be made by a person close to the participant. The SRS takes up to 20 minutes to complete.

For the analysis of the data the score of several items is reversed according to the test manual by Constantino et al. (2007) (reversed items in the maternal report are: 3, 7, 11, 12, 15, 17, 21, 22, 26, 32, 38, 40, 43, 45, 48, 52 and 55). All items are combined for an overall score, but it is also possible to score each separate subscale. The subscales are defined according to the test manual by Constantino et al. (2007): social awareness, social cognition, social communication, social motivation and autistic mannerisms.

For the present study a cut-off of 90 is chosen (Constantino et al., 2007). Therefore, participants with a t-score of 90 are identified as high-scoring participants and participants with a t-score of 89 or lower are identified as normal-scoring participants.

Wechsler Adult Intelligence Scale – Third Edition (WAIS-III) (Wechsler, 1997):

To measure the intelligence quotient (IQ) four subtests of the Wechsler Adult Intelligence Scale – Third Edition (WAIS-III) are used. The subtests used are: Digit symbol substitution, block design, arithmetic and information. Previous research has shown that this combination is the most reliable four-subtest version of estimating IQ (Aukes, 2009).

Iowa Gambling Task (IGT) (Bechara et al., 1994):

The Iowa Gambling Task is a task in which the participant is presented with four stacks of cards. The participant is asked to pick a card from one of the stacks. This is repeated a hundred times. The participant can make money or lose money by drawing cards from the stacks. The participant is provided with $2000 at the beginning of the game. Out of the four stacks, two are high-risk stacks and the other two are low-risk stacks. The high-risk stacks are stacks A and B, which provide loss in the long term. The low-risk stacks are stacks C and D, which provide gains in the long term. The goal is for the participant to maximize his winnings, without knowing which stacks are the high or low risk stacks. Therefore, decisions to choose low risk stacks C and D should increase over time as a result of the reward and punishment schedules inherent to the task (Schutter, van Bokhoven, Vanderschuren, Lochman, & Matthys, 2011). The outcome measure is calculated by dividing the hundred card selections into five sections of twenty each (Schutter et al., 2011; Bechara et al., 1994). The mean percentage choices for the high risk decks A and B are computed for each of the five sections. Choice percentage should decrease over time.

Degraded Facial Affect Recognition Task (DAR) (van 't Wout, Aleman, Kessels, Laroi, & Kahn, 2004) :

Researchers at the University Medical Centre and Experimental Psychology Department in Utrecht recently developed an emotion recognition task called the Degraded Facial Affect Recognition Task (DAR) (van 't Wout et al., 2004). The DAR is a task in which the participant has to recognize emotional faces. It is presented in the computer program Presentation® and in the form of a forced-choice task. Participants are shown 64 blurred faces, divided in 4 conditions (neutral, happiness, fear and anger) of 16 faces each. The

pictures are blurred to increase the difficulty of the task and to increase the effect of perceptual expectations and interpretation. The visual contrast of the pictures was reduced by 30% (van 't Wout et al., 2004). During the task, the participant has to indicate which emotion the face expresses; neutral, happiness, fear or anger, by clicking on the button with the relevant emotion (which is presented at the bottom of the screen). The outcome measure is the number of correct responses.

The international affective picture system (IAPS) provided the facial stimuli for the DAR. The IAPS supplies a set of normative emotional stimuli for research on emotion (Lang, Bradley, & Cuthbert, 1999). The IAPS is developed by the NIMH center for emotion and attention (CSEA) at the University of Florida (Lang et al., 1999). By using pictures from this database there is more control and it is possible to compare the results across studies that have used the same database.

Brixton Spatial Anticipation Task (Burgess et al., 1997):

In the Brixton Spatial Anticipation Task, the participant is shown a sheet with 10 numbered circles on it. One of these circles is black, according to a rule. The participant is shown one page at a time and has to predict which circle will be black on the next page. The position of the black circle will change on each page. Ever so often, the rule will change, and the participant has to adapt to this change. The Brixton Spatial Anticipation Task is used for assessing executive functioning (e.g. self-monitoring). Reponses are correct if the rule is followed correctly. On the trials where the rule changes, correct responses are those that continue to follow the rule as if the rule had not changed. The outcome measure is the number of wrong responses.

Procedure

The research of the ‘Building Blocks’ study is located at the University Medical Centre (UMC) Utrecht in the Netherlands. The ‘Building Blocks’ study is part of a bigger scientific research called the ‘Leidsche Rijn Health Project’. It investigates influences of genetics on behavior and emotion in the healthy population. The study is population based. By using a ‘forward genetics’ approach (Boks, Derks, Dolan, Kahn, & Ophoff, 2010), participants are selected on genes of which we know that they are associated with psychiatric illnesses. The genetic analyses were performed by the department ‘Complex Genetics’ of the UMC Utrecht. After selection, a letter was sent to the selected people to invite them to participate. When 2 weeks passed, we called the participants to make appointments. This

resulted in a final sample of participants. Participation in this study was voluntary. A written informed consent was secured from each of the study's participants. Subjects were able to cease participation at any time during the study. All data collected for this study are confidential. Participant's names were used for recruitment purposes only.

The tests took up 4 hours in total. The participants filled in online questionnaires (http://www.ken-uzelf.nl) at home for the first 2 hours. For the second 2 hours participants had appointments in the UMC Utrecht. Here they participated in neurocognitive assessments, a psychiatric interview, an interview for physical illnesses and venapuncture. The participants received €40,- for compensation and their travel expenses were reimbursed. Afterwards, if a participant was interested in how they performed, an informational letter was provided.

Genotyping

The genotyping of SNP rs6943555 in the AUTS2 gene was performed by a Taqman® SNP Genotyping assay (Applied Biosystems, Foster City). Differentiation between alleles was done by an Applied Biosystems 7900HT Real-Time PCR System according to the manufacturer's protocol (Applied Biosystems, Foster City. Assay order number: C__26000428_20 and C__11592758_10). The A allele of the SNP rs6943555 is the risk allele (Schumann et al., 2011).

Statistical Analyses

All analyses for this research are conducted using IBM SPSS (Statistical Package for the Social Science) version 19.0 for Mac (SPSS Inc, Chicago, Illinois, US). For all analyses a significance level of alpha = 0.05 is used.

Out of the 299 participants who completed the assessments, not all finished the Social Responsiveness Scale. Those participants who did not complete the SRS were excluded. Therefore, the final research group exists out of 178 participants. In this final research group group sizes for each separate test (IGT, DAR and Brixton) differ.

Range, mean and standard deviation for age are determined for the demographic information. For sex and education level, frequencies and percentages are determined. Also, number of participants per genotype is determined. The difference in age between the carriers of the risk gene and the non-carriers is checked through an independent sample T-test, the difference in sex distribution through a chi-squared test and the difference in education level with a Mann-Whitney U test.

Normality of the distributions was checked. An independent samples T-test was used when there was a normal distribution. When there was no normal distribution, a non-parametric test was used. In order to adjust for multiple testing, we used the Bonferroni correction to maintain the experiment-wise significance level of 5%.

An independent samples T-test was performed to compare the means and the standard deviation for the subscales and the total score on the SRS between the carriers of the risk gene and the non-carriers.

To test whether there is a difference in performance on DAR and the IGT between high and low scoring participants an independent samples T-test was used with SRS score as the between-subjects factor. The SRS was corrected for gender. The same was done for IQ and performance on the Brixton, again with SRS score as between-subjects factor in an independent sample T-test. The independent samples T-test is used here because of the different group sizes for the Brixton, the IGT, the DAR and IQ tests. To assess whether there were gender differences on SRS scores, an independent samples T-test was used to determine if the performance on the SRS between males and females differed significantly. Additionally, an independent samples T-test was conducted to research the performance on neurocognitive assessments and IQ using the score on the mannerism subscale of the SRS as a between-subjects factor.

To test whether there is a difference between carriers and non-carriers of the AUTS2 gene with respect to the neurocognitive assessments and IQ, an independent samples T-test was used with AUTS2 gene status as between-subjects factor. The independent samples T-test is used here because of the different group sizes of the Brixton, the IGT, the Dar and IQ.

To test whether there is an interaction between AUTS2 gene status and high or low scores on the SRS, an ANOVA was performed with the neurocognitive assessments as dependent variable and with AUTS2 gene and SRS score as between-subject factors. To locate the direction of any possible interactions between the AUTS2 gene and SRS we performed two univariate ANOVA's with AUTS2 gene status as independent variable.

Results

Demographic information

Table 1 presents the demographic information of the research population. The total research population existed out of 178 participants. 50 participants carried the AUTS2 risk gene and 86 did not carry the risk gene, genotype could not be determined for the remainder of the participants (42). 58.4% of the research group were female and 41.6% were male. The age range of the participants was 20-83, with a mean age of 46.42 years. Out of the participants, 87.1% had a middle or high educational level. For 4 participants the level of education was not known. The distribution of the different genotypes is shown. Of the participants, 28.3% is either carrier of the TA-allele or the AA-allele and 48.3% is carrier of the TT-allele.

Table 1. Demographic information of the study population

	All participants N = 178	**Carriers risk gene N = 50**	**Non-carriers risk gene N = 86**
Age			
Range (year)	20-83	31-83	27-78
Mean (SD)	46.42 (13.29)	49.44 (13.29)	47.31 (11.59)
N missing	0	0	0
Gender			
Male	74 (41.6%)	24 (48%)	35 (40.7%)
Female	104 (58.4%)	26 (52%)	51 (59.3%)
N missing	0 (0%)	0 (0%)	0 (0%)
Education level			
Low	19 (10.7%)	4 (8%)	11 (12.8%)
Medium	48 (27%)	14 (30%)	24 (27.9%)
High	107 (60.1%)	30 (60%)	48 (55.8%)
N missing	4 (2.2%)	1 (2%)	3 (3.5%)
Auts2			
TT	86 (48.3%)		
TA	43 (24.2%)		
AA	7 (3.9%)		
N missing	42 (23.6%)		

Age, gender and education level were compared between the participants who carry the AUTS2 risk gene and those who do not carry the AUTS2 risk gene (table 1). The age difference was not significant, $t(135) = -.981$, $p = .328$. Furthermore, there was no difference in the distribution between males and females ($\chi^2(1) = .686$, $p = .407$). In addition, there was

no significant difference in the distribution of the education level between the two groups (U = 2126.000, p = .619).

To test the effect of the AUTS2 gene on the SRS (subscales and total raw score) independent samples T-tests were performed. The results are shown in table 2. Results indicate no significant difference between carriers and non-carriers of the AUST2 gene in SRS scores.

Table 2. Mean (SD) on the SRS (subscales and total raw score) for carriers and non-carriers of AUTS2

	Carriers risk gene	**Non-carriers risk gene**	**p-value**
SRS			
Awareness subscale	13.18 (1.69)	13.26 (2.20)	.834
Communication subscale	32.22 (5.37)	33.85 (5.67)	.102
Motivation subscale	17.18 (4.21)	17.56 (4.93)	.650
Mannerism subscale	14.60 (2.43)	15.33 (3.07)	.155
Cognition subscale	17.88 (3.39)	18.08 (3.43)	.741
Total score	95.06 (14.49)	98.19 (15.56)	.249

To test the difference between males and females on the SRS score, an independent samples T-test was performed. Results are shown in table 3. Significant differences were found for the subscales awareness (t (176) = 3.496, p = .001), communication (t (176) = 2.245, p = .026) and mannerism (t (176) = 3.498, p = .001) and for the total score (t (176) = 2.210, p = .028) on the SRS. Following Bonferroni correction, the communication subscale and the total score were no longer significant.

Table 3. SRS score (mean (SD)) for males and females.

	Male	**Female**	**p-value**
SRS			
Awareness subscale	13.93 (1.99)	12.88 (1.99)	**.001***
Communication subscale	34.38 (6.00)	32.44 (5.43)	**.026**
Motivation subscale	17.95 (4.78)	17.39 (4.83)	.451
Mannerism subscale	16.11 (3.61)	14.53 (2.42)	**.001***
Cognition subscale	18.22 (3.39)	17.93 (3.47)	.588
Total score	100.58 (16.64)	95.27 (15.19)	**.028**

* Statistically significant following Bonferroni correction

To test whether participants with a high score on the SRS would have a low score on the DAR, an independent samples T-test was performed. Results are shown in table 4. For the emotions happiness, fear and neutral no significant differences were found between high and low scoring SRS individuals. In addition, there was no significant difference between the

high-score group and the low-score group in the total score on the DAR. However, for the emotion angry there was a significant difference between the two groups, t (169) = 2.796, p = .006.

To test whether participants with a high score on the SRS would have a low score on the IGT, an independent samples T-test was performed. Results are shown in table 4. A significant difference between the high-score group and the low-score group was found in block 3 (t (163) = -2,197, p = .029), block 4 (t (163) = -2,736, p = .007) and block 5 (t (163) = -2,615, p = .010). Block 3 was significant before the Bonferroni correction, but not after it.

To test whether participants with a high score on the SRS would have a low score on the Brixton Spatial Anticipation Task, again an independent samples T-test was performed. Results are shown in table 4. Results indicate no significant difference between the two SRS groups on the Brixton.

To test the difference in IQ between the two groups, an independent samples T-test was performed. Results (table 4) indicate no significant difference.

Table 4. IQ and neurocognitive assessments (mean (SD)) for normal and high scores on the SRS.

	SRS <90	**SRS >90**	**p-value**
IQ	111.37 (17.18)	107.39 (16.22)	.236
Brixton	14.37 (5.33)	15.51 (6.18)	.259
DAR			
Happy	17.44 (2.81)	17.41 (3.30)	.956
Angry	13.61 (3.21)	11.92 (3.67)	**.006***
Fear	11.19 (3.76)	12.23 (3.60)	.127
Neutral	21.63 (5.03)	22.44 (5.34)	.387
Total	49.58 (4.91)	49.00 (6.30)	.549
IGT			
Block 1	4.38 (1.73)	4.36 (1.77)	.964
Block 2	3.64 (2.01)	3.48 (2.15)	.680
Block 3	2.66 (2.07)	3.51 (2.22)	**.029**
Block 4	2.45 (2.30)	3.69 (3.00)	**.007***
Block 5	2.06 (2.14)	3.13 (2.51)	**.010***

* Statistically significant following Bonferroni correction

To study the restricted, repetitive and stereotyped patterns of behavior, interests and activities in particular, two groups were distinguished: a group with a high score on the mannerism subscale of the SRS and a group with a normal score. To test the differences on IQ and neurocognitive assessments between the two groups an independent samples T-test was

performed. Results are shown in table 5. A significant difference was found on block 2 of the IGT (t (163) = 2.763, p = 0.006) and a trend was found on the emotion fear of the DAR (t (169) = -1.697, p = 0.091). No other significant results were found.

Table 5. IQ and neurocognitive assessments (mean (SD)) for normal and high scores on the mannerism subscale of the SRS.

	Mannerism <90	**Mannerism >90**	**p-value**
IQ	109.76 (17.25)	116.17 (14.21)	.133
Brixton	14.54 (5.44)	15.44 (6.44)	.511
DAR			
Happy	17.41 (2.96)	17.61 (2.59)	.785
Angry	13.37 (3.31)	12.06 (3.86)	.120
Fear	11.26 (3.72)	12.83 (3.73)	.091
Neutral	21.85 (4.97)	21.50 (6.24)	.784
Total	49.33 (4.99)	50.39 (7.16)	.421
IGT			
Block 1	4.41 (1.73)	4.13 (1.74)	.523
Block 2	3.76 (1.99)	2.41 (2.04)	**.006***
Block 3	2.86 (2.11)	2.87 (2.35)	.983
Block 4	2.84 (2.57)	1.99 (2.09)	.168
Block 5	2.26 (2.23)	2.74 (2.56)	.386

* Statistically significant following Bonferroni correction

To test whether carriers of the risk gene scored significantly different from the non-carriers on the DAR, an independent samples T-test was performed. Results (shown in table 6) indicate no significant difference.

To test whether carriers of the risk gene would have a low score on the IGT, an independent samples T-test was performed. Results are shown in table 6. A significant difference between the carriers and non-carriers was found in block 3 (t (125) = 2.988, p = .003) and block 5 (t (125) = 2.420, p = .017). Block 5 was no longer significant following the Bonferroni correction.

To test the difference in performance of the carriers and the non-carriers of the risk gene on the Brixton Spatial Anticipation Task, an independent samples T-test was performed. Results are shown in table 6. Results indicate no significant difference.

To test the difference in IQ between the carriers and the non-carriers of the risk gene, an independent samples T-test was performed. Results are shown in table 6. Results indicate no significant difference.

Table 6. IQ and neurocognitive assessments (mean (SD)) for carriers and non-carriers of the AUTS2 risk gene.

	Carriers risk gene	Non-carriers risk gene	p-value
IQ	110.41 (17.66)	110.96 (18.86)	.880
Brixton	15.04 (5.84)	15.05 (5.67)	.995
DAR			
Happy	17.92 (3.11)	17.06 (2.88)	.114
Angry	12.88 (3.72)	13.71 (3.07)	.167
Fear	11.65 (3.16)	11.36 (3.86)	.666
Neutral	21.54 (4.72)	21.69 (4.89)	.869
Total	48.67 (4.97)	50.04 (5.10)	.137
IGT			
Block 1	4.23 (1.61)	4.51 (1.69)	.358
Block 2	3.47 (1.68)	3.68 (2.16)	.566
Block 3	2.30 (1.62)	3.47 (2.37)	**.003***
Block 4	2.78 (2.28)	2.97 (2.73)	.688
Block 5	1.84 (1.83)	2.86 (2.51)	**.017**

* Statistically significant following Bonferroni correction

To test whether carrying the AUTS2 risk gene modifies the effect of the SRS on IQ and the Neurocognitive assessments, an ANOVA was performed, with AUTS2 status and SRS group as between subject variables. Results are shown in table 7. No significant effects were found for IQ, DAR and IGT. However, there was a significant interaction effect for the AUTS2 gene and SRS score on the Brixton ($F(130, 1) = 4.898$, $p = .041$).

Because there were two levels, we do not know where the interaction effect lies. Therefore, we performed two univariate ANOVA's, which shows us that the difference between high and low scores on the SRS is significant ($F(46, 1) = 7.531$, $p = .009$) on the carrier group of the AUTS2 gene, and not significant on the non-carrier group ($F(81,1) = .159$, $p = 691$).

Table 7. Influence AUTS2 gene on the normal and high SRS scores on IQ and the neurocognitive assessments

	Carriers risk gene		Non-carriers risk gene		
	SRS <90	SRS >90	SRS <90	SRS >90	p-value
IQ	111.42 (17.78)	103.20 (16.71)	111.76 (19.02)	108.50 (18.66)	.627
Brixton	14.15 (5.52)	20.29 (5.12)	14.90 (5.63)	15.48 (5.89)	**.041**

DAR					
Happy	18.05 (3.27)	17.14 (1.86)	17.16 (2.69)	16.76 (3.45)	.724
Angry	13.24 (3.62)	10.71 (3.86)	14.16 (2.89)	12.38 (3.25)	.631
Fear	11.32 (3.28)	13.57 (1.13)	11.18 (3.84)	11.90 (3.97)	.380
Neutral	21.37 (4.77)	22.57 (4.61)	21.26 (4.81)	22.95 (5.05)	.883
Total	48.59 (4.41)	49.14 (7.97)	50.40 (4.99)	48.95 (5.38)	.411
IGT					
Block 1	4.27 (1.54)	3.97 (2.08)	4.39 (1.67)	4.83 (1.72)	.357
Block 2	3.29 (1.62)	4.44 (1.79)	3.80 (2.09)	3.36 (2.33)	.100
Block 3	2.18 (1.70)	2.92 (0.90)	3.23 (2.78)	4.11 (2.54)	.889
Block 4	2.59 (2.39)	3.84 (1.30)	2.56 (2.32)	4.06 (3.44)	.834
Block 5	1.70 (1.88)	2.63 (1.40)	2.56 (2.33)	3.68 (2.85)	.870

Discussion

In this population-based study we aimed to investigate the extent of autistic traits in the general population. The present study shows that autistic traits, as measured by the SRS in the general population, show a significant gender difference, with males scoring higher than females. Moreover, a significant difference was found in scores on the IGT between the participants with high and low SRS scores and between the carriers and non-carriers of the AUTS2 gene. No significant relation was found between the SRS and the AUTS2 gene, however the AUTS2 gene does seem to modulate the difference between high and low scoring SRS groups in performance on the Brixton.

The Social Responsiveness Scale was used to measure the extent of autistic traits for each participant. Furthermore, we incorporated the AUTS2 gene and determined who carried the risk allele and who did not carry the risk allele. Carriers of the risk gene are more susceptible for ASDs according to previous research (Huang, Zou, Maher, Newton, & Milunsky, 2010; Schumann et al., 2011; Sultana et al., 2002). In theory, participants with a high score on the SRS should be carrier of the risk allele. However, the results in current study imply that this association is non-existent in this research population. Recent research suggests an association between the AUTS2 gene and alcohol consumption, rather than autistic traits (Schumann et al., 2011), which might explain why we find no relation with the SRS. This could mean that the AUTS2 gene might not contribute to ASDs, but that it does contribute to other disorders.

Regarding IQ and gender, results show that IQ is not significantly different between the high and low scoring SRS groups and the carriers and the non-carriers of the AUTS2 gene. Nor is IQ significantly different when we look at the normal and high scorers (on the SRS) who carry the AUTS2 gene and the normal and high scorers who do not carry the AUTS2 gene. This is not in line with previous research, which shows that IQ is a known risk factor for ASDs (Nishiyama et al., 2009). In theory, a high score on the SRS implies that a person has more autistic traits, which should mean that a high scoring participant should have a lower IQ (Nishiyama et al., 2009). However, prior research on the SRS has shown that the SRS scores are unrelated to IQ (Constantino & Todd, 2003; Constantino, Przybeck, Friesen & Todd; 2000), this might explain why this study does not find significant results for IQ. In spite of the non-significance of IQ, results show that there are significant differences between males and females on the SRS. The finding of a significant gender difference is in line with previous findings (Constantino & Todd, 2003). Several preceding studies show that males are more likely to have autistic traits compared to females (Baron-Cohen, Knickmeyer, &

Belmonte, 2005; Baron-Cohen, 2002; Lord, Schopler, & Revicki, 1982; Lord & Schopler, 1985), which is in accordance with the idea that ASDs are more frequent in males than in females (Fombonne, 2003).

Three behavioural measures assessing different cognitive functions that are affected in ASDs were used, respectively the IGT, the DAR and the Brixton. Only one of these tests, the IGT, showed significant differences between high and normal scoring individuals on the SRS. That is, high-scorers on the SRS have an overall preference for the risky disadvantageous decks (IGT) compared to the normal-scorers. This result confirms our hypothesis that people who have more autistic traits perform worse on an executive functioning task compared to people who have fewer autistic traits. Also, results show that non-carriers of the risk gene perform better than carriers of the risk gene. The findings with the IGT are in accordance with previous research, which has shown that having an ASD is an indication for poor performance on executive functioning tasks (Hughes, Russell, & Robbins, 1994; Ozonoff, 1997; Ozonoff & Jensen, 1999; Lopez, Lincoln, Ozonoff, & Lai, 2005). When looking specifically at the IGT scores for the mannerism subscales of the SRS, results show that only block 2 is significantly different. These results suggest that increased risk taking in repetitive behavior does not seem to play a part in autism, and that participants who score high on the mannerism subscale of the SRS do not perform significantly worse than those participants who score within a normal range on the mannerism subscale. Based on previous research we expected more significant results on the IGT for the restricted, repetitive and stereotyped patterns of behavior, interests and activities, because previous research has shown that poor performance on executive functioning tasks is predicted by the incidence of repetitive behavior in adults with autism (Lopez, Lincoln, Ozonoff, & Lai, 2005; Hill, 2004), instead a more general difference was found on the IGT between high and normal SRS scorers.

Our results show only minor difference in performance on the other two tests, the Brixton and the DAR. Previous research has shown that people with problems with executive functioning do not perform well on tasks like the Brixton (Anderson, Damasio, Jones, & Tranel, 1991; Burgess et al., 1997; Owen, Downes, Sahakian, Polkey, & Robbins, 1990; Ozonoff, 1995). However, in the present study the high-scoring SRS group and the normal-scoring SRS group did not significantly differ in their results. Only when we looked at the modifying role of the AUTS2 gene on the effect of the SRS on the Brixton a significant result was found. This means that there is an interaction between the AUTS2 gene and the SRS when looking at performance on the Brixton. Further analysis shows that the high-scorers perform significantly worse than the normal-scorers in the carrier group of the AUTS2 gene.

This is consistent with our expectations, in which we anticipated that people with more autistic traits perform worse on an executive functioning task. Regarding the restricted, repetitive and stereotyped patterns of behavior, interests and activities we expected participants with a high score on the mannerism subscale to perform poorly on this task, however, results do not confirm this. Another well-known aspect of ASDs is the emotion recognition difficulties; several studies have shown that people with ASDs have difficulty in recognizing emotion (Baron-Cohen, 1989c; Baron-Cohen, 1989b; Pelphrey et al., 2002). However, previous research provided mixed results. Some studies have shown that people with autism have an amygdala dysfunction and emotional face-processing impairments (Baron-Cohen et al., 2000; Baron-Cohen, 1989c; Baron-Cohen, 1989b; Pelphrey et al., 2002; Pelphrey, Adolphs, & Morris, 2004). In the current study, the DAR was used to measure emotion recognition in faces. We expected that participants who scored high on the SRS scale would perform poorly on the DAR. However, the only significant result for the DAR was found in the anger-condition, which means that participants with autistic traits are worse at identifying the emotion anger. Therefore, our results only partially confirm the results from the Pelphrey et al. (2002) study. Nonetheless, other studies did not find the difference in emotion recognition between people with autism and controls (Adolphs, Sears, & Piven, 2001; Volkmar, Sparrow, Rende, & Cohen, 1989; Baron-Cohen, Wheelwright, & Jollife, 1997). Thus, our study is also partially consistent with these results. A possible explanation for this result is provided by the study of Schumann et al. (2004), which shows that the amygdala in children with autism is enlarged, but it has a normal size in adolescents with autism. It may be that, by the time adulthood is reached, participants with autistic traits are able to recognize basic emotions from facial expressions (Adolphs, Sears, & Piven, 2001; Grossman, Klin, Carter, & Volkmar, 2000).

Limitations

The current study has some limitations. For example, participants volunteered to participate in this study. Thus, they should see the importance of scientific research and be willing to invest time in participating. This may create a selection bias and the volunteer sample limits the generalizability of the results. Furthermore, the neuropsychological assessments took up to 2-3 hours, which might have had a negative effect on the motivation that was invested in performing on the IGT, DAR and Brixton, and may have discouraged some people from participating

It is possible that a selection bias occurred by selecting the research group from the Leidsche Rijn district. The average education level of the research group is high and perhaps

not in line with the average level in the general population. Therefore, generalisation to other populations is uncertain. Also, the Leidsche Rijn district is a relatively enriched environment, which may have enhanced the pattern of improved functioning over the life course (level of functional adaption was not determined in this study).

The restricted, repetitive and stereotyped behavior domain has been neglected in research on ASDs. Therefore, it is not totally clear what the function of repetitive behavior is (Lewis & Bodfish, 1998; Turner, 1999) and what the relationship between repetitive behavior and executive dysfunction is. Different studies provide mixed evidence on this relationship (Hill, 2004; Lopez et al., 2005). Furthermore, previous research has shown that autistic symptoms decrease over time (Hengeveld et al., 2008; Kan et al., 2008; Seltzer et al., 2003; Seltzer et al., 2004; Matson et al., 2010; Piven, Harper, Palmer & Arndt, 1995). Therefore, it is possible that some of the older participants may have had more problems with repetitive behavior earlier in life.

Our study relied on maternal report measurement of autistic traits, through the SRS. Reliance on the maternal report of the SRS is potentially vulnerable to rater bias. The participants may under- or overestimate their impairments. No information about ASD diagnosis was available in this study, but the research population included a lot of high scorers on the SRS. Also, the SRS focuses more on the social deficits of autism and less on the repetitive behaviors of autism.

The genetic basis of autism is unknown. In this study we used the AUTS2 gene, because it seems to be a strong contender for autism. The AUTS2 gene expresses especially in the neurons of frontal parts of the brain and research shows that it is observed in Attention Deficit Hyperactivity Disorder (ADHD), epilepsy and in alcoholism (Elia et al., 2010; Mefford et al., 2010 ;Schumann et al., 2011). The AUTS2 gene is not yet linked with autism, it is merely a candidate gene. The gene could lead to ASD susceptibility, however, this is not yet clear. Therefore, it is possible that the AUTS2 gene is not involved in autism. Regardless, the results from this study seem to imply that there is no relation between AUTS2 and ASDs.

Despite above-mentioned limitations, this study did have strengths. The research population existed out of 178 participants, which is a decent size for research. Furthermore, these participants completed several neuropsychological assessments and questionnaires, which provided comprehensive information.

Implications for future research

Future research is needed to further investigate autistic traits in the general population. The research group existed out of 178 participants, bigger sample sizes are recommended for future research. Although the current sample reflects the demographic composition of the population of the Leidsche Rijn district, it is recommended for future research to use a more heterogeneous population (it should include a broader range of people, with a greater variety in race, social status and income).

Future research may want to use a different instrument to measure autistic traits. The SRS focuses too much on the social deficits, and it might be useful to use an instrument that pays more attention to the repetitive behaviors of autism.

Also, in future research, more candidate genes should be examined. It is still not known which gene is responsible for autism. A plausible idea is that there are more genes involved in autism which interact with each other. Therefore, future research should involve more genes, and also look at the interaction between those genes.

Another important point of improvement is that in future research multiple raters of autistic behavior should be included. Different raters might provide additional information and the rater bias could be reduced.

Conclusions

The aim of the current study was to investigate the relation between autistic traits and cognitive functions in the general population. In addition, we looked at the modulating role of the AUTS2 gene. Based on the current results we would like to point out that there was no relation between the SRS and the AUTS2 gene. Therefore, we propose that the influence of the AUTS2 gene on autism is minimal and that the AUTS2 gene might contribute more to other disorders (e.g. ADHD, epilepsy and alcohol consumption). Furthermore, we found that there was a gender difference with respect to autistic traits, in which males have more autistic traits than females. Comparing the high-scoring group (on the SRS) to the normal-scoring group on executive functioning provided mixed results. On the first executive function task, the IGT, results showed overall poor performance for the high-scoring (on the SRS) participants. Results also showed that the non-carriers of the AUTS2 gene had a poorer performance on the IGT than the AUTS2 gene carriers. Only when looking at the modifying role of the AUTS2 gene on the SRS a significant difference was found for the Brixton, with high-scorers performing significantly worse than normal-scorers when they carried the AUTS2 gene. The emotional face-processing task yielded a significant result on the anger-

condition when we compared the SRS groups, with the high-scoring group identifying this emotion correctly less often than the normal-scoring group.

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