Orderly chaos

Citation for published version (APA):

Schalbroeck, R. (2021). *Orderly chaos: social defeat as a risk factor for psychosis in autism*. [Doctoral Thesis, Maastricht University]. Maastricht University. <https://doi.org/10.26481/dis.20211105rs>

Document status and date:

Published: 01/01/2021

DOI:

[10.26481/dis.20211105rs](https://doi.org/10.26481/dis.20211105rs)

Document Version:

Publisher's PDF, also known as Version of record

Please check the document version of this publication:

- A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
- The final author version and the galley proof are versions of the publication after peer review.
- The final published version features the final layout of the paper including the volume, issue and page numbers.

[Link to publication](#)

General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal.

If the publication is distributed under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license above, please follow below link for the End User Agreement:

www.umlib.nl/taverne-license

Take down policy

If you believe that this document breaches copyright please contact us at:

repository@maastrichtuniversity.nl

providing details and we will investigate your claim.

Orderly chaos: social defeat as a risk factor for psychosis in autism

Rik Schalbroeck

ISBN

978-94-6423-453-4

Cover

Willem van Genk, *Station Berlin Ost*, ca 1972, Particuliere collectie
Museum van de Geest | Outsider Art, Amsterdam

Layout and printing

ProefschriftMaken | www.proefschriftmaken.nl

Copyright

Rik Schalbroeck, 2021, The Netherlands

Orderly chaos: social defeat as a risk factor for psychosis in autism

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad van doctor aan de Universiteit Maastricht,
op gezag van de Rector Magnificus, Prof. dr. Rianne M. Letschert
volgens het besluit van het College van Decanen,
in het openbaar te verdedigen
op vrijdag 5 november 2021 om 16.00 uur

door

Rik Schalbroeck

Promotores

Prof. dr. J.P. Selten

Prof. dr. L.F. de Geus-Oei (Leids Universitair Medisch Centrum)

Prof. dr. J. Booij (Amsterdam UMC, locatie AMC)

Beoordelingscommissie

Prof. dr. B.P.F. Rutten (voorzitter)

Dr. E.M. van de Giessen (Amsterdam UMC, locatie AMC)

Prof. dr. M.C. Marcelis

Prof. dr. F.M. Mottaghy

Prof. dr. I.E.C. Sommer (UMC Groningen)

Table of contents

Chapter I	General introduction	9
Chapter II	Risk of non-affective psychotic disorder or bipolar disorder in autism spectrum disorder: a longitudinal register-based study in the Netherlands	23
Chapter III	Childhood trauma as a mediator of the association between autistic traits and psychotic experiences: evidence from the ALSPAC birth cohort	45
Chapter IV	Striatal dopamine synthesis capacity in autism spectrum disorder and its relation with social defeat: an [^{18}F]-FDOPA PET/CT study	73
Chapter V	Cerebral [^{18}F]-FDOPA uptake in autism spectrum disorder and its association with autistic traits	117
Chapter VI	The social defeat hypothesis of schizophrenia: a parsimonious explanation for multiple psychosis risk factors?	131
Chapter VII	General discussion	141
Appendices		165
	Nederlandse samenvatting	167
	Impact paragraph	175
	List of publications	179
	Dankwoord	181
	Curriculum vitae	183

Chapter I

General introduction

1. General introduction

1.1 Autism and psychosis

Autism and psychosis share a long and complex history (Evans, 2017). The term autism was initially used in 1911 by psychiatrist Eugen Bleuler to refer to a way of thinking that was detached from the external world and filled with fantasies and hallucinations, which was a symptom he often saw in patients with schizophrenia. The word was later adapted by child psychiatrists such as Leo Kanner and Hans Asperger, who used it to describe children we would now also call autistic (Kanner, 1943; Wing, 1981). However, for years, the concepts of autism and psychosis were used interchangeably, and it was not until the 1960s and 1970s that they were more definitively separated.

Nowadays, the term autism is used to refer to difficulties in social communication and interaction, restrictive and repetitive behaviours and interests, and sensory hypo- or hypersensitivity (Lai & Baron-Cohen, 2015). In 1–2% of the population, these traits merit a clinical diagnosis of autism spectrum disorder (ASD) (Maenner et al., 2020). However, a broader autism phenotype exists, as these traits are also found in varying degrees in people who do not meet ASD criteria (Le Couteur et al., 1996; Constantino et al., 2003).

Psychosis particularly refers to positive psychotic symptoms such as hallucinations and delusions (Howes & Murray, 2014), although the term is also used to describe negative (e.g., flattened affect or social withdrawal) and cognitive symptoms (e.g., memory problems). In this thesis, the word psychosis will be mainly reserved for positive psychotic symptoms. These symptoms are present in non-affective (e.g., schizophrenia) and affective (e.g., bipolar disorder with psychotic features) psychotic disorders, which are clinical diagnoses with a combined lifetime prevalence of approximately 3% (Perälä et al., 2007). Additionally, less severe psychotic symptoms such as increased suspiciousness or unusual perceptual experiences, commonly referred to as psychotic experiences, have a lifetime prevalence of approximately 5–8% in the general population and occur at even higher rates in individuals with non-psychotic mental health conditions (Linscott & Van Os, 2013; DeVylder et al., 2014; McGrath et al., 2015). For many individuals, these psychotic experiences are transient and harmless. However, in some, they are associated with, or predictive of, mental health problems such as a psychotic disorder (Fusar-Poli et al., 2020).

The Diagnostic and Statistical Manual of Mental Disorders, fifth edition (American Psychiatric Association, 2013), allows ASD and psychotic disorders such as schizophrenia to be diagnosed simultaneously. However, given the partial overlap in symptoms (e.g., social withdrawal is common in both disorders), this requires a patient to meet the criteria for both disorders and have prominent delusions or hallucinations for at least one month (or less if treated successfully).

In the past decades there has been growing interest in whether, and to what extent, ASD and psychotic disorders and their respective non-clinical expressions co-occur (Chisholm et al., 2015). Moreover, researchers have increasingly started examining what might cause this possible association between them.

1.2 The social defeat hypothesis of schizophrenia

In 2005, Selten and Cantor-Graae formulated the social defeat hypothesis of schizophrenia, which states that social defeat, defined as subordinate position or outsider status, increases the risk of schizophrenia or psychosis. In later work, social defeat has additionally been defined as the negative experience of being excluded from the majority group (i.e., social exclusion) (Selten et al., 2013; Selten et al., 2017). The social defeat hypothesis states that social defeat leads to a sensitized mesolimbic dopamine

system (i.e., enhanced dopaminergic response, e.g., to stress) and/or to an increased baseline activity of this system. The hypothesis was formulated as a parsimonious explanation for four schizophrenia risk factors, including migration, urban upbringing, low intelligence quotient (IQ), and drug abuse, and was later applied to other groups, such as lesbian, gay, or bisexual individuals, individuals with a severe hearing impairment, and individuals with a history of childhood trauma (Selten et al., 2013).

The social defeat hypothesis mainly focuses on groups rather than individuals, since individuals might not be willing to admit being socially defeated (Selten et al., 2013). Studies in groups presumed to be socially defeated have generally supported the hypothesis. For example, increased risks of psychotic experiences and/or psychotic disorders have been found in individuals exposed to bullying victimisation (Cunningham et al., 2016), sexual minorities (Gevonden et al., 2014a), and specific migrant groups such as those with a dark skin colour (Selten et al., 2020). Moreover, individuals with a history of low maternal care or childhood trauma (Pruessner et al., 2004; Oswald et al., 2014; Egerton et al., 2016), individuals with a severe hearing impairment (Gevonden et al., 2014b), and immigrants (Egerton et al., 2017), were shown to have an increased striatal dopamine synthesis capacity and/or release.

The social defeat hypothesis is not the only hypothesis to state that psychosocial adversity increases the risk of psychosis. For example, other researchers have proposed that this risk is influenced by social isolation (Hoffman, 2007) or cumulative social disadvantage (Morgan et al., 2008). The social defeat hypothesis differs from these hypotheses in two important respects. First, while the social defeat hypothesis similarly acknowledges that different types of social adversity (e.g., trauma, bullying, discrimination, isolation) can increase the risk of psychosis, it emphasizes that this risk is dependent on the extent to which these adversities increase the experience of social defeat (Selten et al., 2013). Second, the social defeat hypothesis states that social defeat influences dopamine signalling (Selten & Cantor-Graae, 2005; Selten et al., 2017), whereas other hypotheses do not propose such a link between social adversity and dopamine.

1.3 Social defeat, psychosis, and dopamine

The proposition that social defeat increases dopamine signalling is in accordance with the influential idea that excessive subcortical dopamine is associated with psychosis. This idea was most comprehensively formulated in the dopamine hypothesis of schizophrenia, which has gone through several iterations in the past decades (e.g., Meltzer & Stahl, 1976; Davis et al., 1991; Howes & Kapur, 2009).

Early versions of the dopamine hypothesis were mainly based on studies showing that dopamine receptor antagonists or dopamine agonists are effective in treating or eliciting psychotic symptoms, respectively (Meltzer & Stahl, 1976; Davis et al., 1991). The hypothesis was further supported by animal studies and by studies in patients with schizophrenia that indirectly assessed the dopamine system (e.g., its metabolites) or that conducted post-mortem analysis.

In the past decades, *in vivo* measurements of the dopamine system using single-photon emission computed tomography (SPECT) and positron emission tomography (PET) have enabled researchers to examine with increasing specificity which aspects of dopamine signalling are affected. The resulting studies have found that relative to controls, psychotic patients show a mean increase in presynaptic striatal dopamine synthesis capacity and release, and a greater interindividual variability in striatal dopamine transporter (DAT) and dopamine D_{2/3} receptor availabilities (Brugger et al., 2020; Cumming et al., 2020). For instance, presynaptic striatal dopamine synthesis capacity and/or release are increased in individuals with a psychotic disorder (Cheng et al., 2020), in individuals at a high risk of psychotic disorder (Howes

et al., 2020), and in conditions such as bipolar disorder when positive psychotic symptoms are present (Jauhar et al., 2017).

In accordance with these studies, the most recent version of the dopamine hypothesis proposes that the main locus of excessive striatal dopamine is presynaptic, emphasizing its role in positive psychotic symptoms rather than schizophrenia alone (Howes et al., 2009). These dopaminergic disruptions appear to be most pronounced for the dorsal, nigrostriatal dopamine pathway rather than the ventral, mesolimbic dopamine pathway (McCutcheon et al., 2018). However, it has been suggested that dopamine in mesolimbic striatal regions could be affected in initial stages of psychosis (Howes et al., 2020), which would be in line with the social defeat hypothesis (Selten & Cantor-Graae, 2005). This excess in presynaptic dopamine signalling has been named ‘the final common pathway’ of schizophrenia, hypothesized to result from different and/or interacting genetic and environmental risk factors (Howes & Kapur, 2009; Howes & Murray, 2014).

The description of the dopamine hypothesis given here is simplified (e.g., cortical abnormalities are also described by the hypothesis). Moreover, it has long been noted that changes in single neurotransmitter systems are unlikely to fully explain complex psychological phenomena such as psychosis (e.g., Reis, 1974), and studies have already begun integrating findings on the dopamine system with other neurotransmitter systems such as glutamate (Howes et al., 2015; McCutcheon et al., 2020). Still, it is a well-replicated finding that a substantial proportion of patients with psychotic symptoms have excessive striatal presynaptic dopamine functioning, and this finding provides a starting point for further study on psychosis aetiology and pathogenesis.

1.4 The relevance of the social defeat hypothesis to autism

Individuals with ASD are widely exposed to socially defeating experiences, such as bullying victimisation (Schroeder et al., 2014), loneliness (Bauminger et al., 2003; Mazurek, 2014), discrimination (Johnson & Joshi, 2016), and trauma (Peterson et al., 2019). These experiences are also more common in individuals with autistic traits who do not meet the criteria for an ASD (e.g., Gong et al., 2017; Rai et al., 2018; Han et al., 2019).

Given the high rates of defeating experiences in individuals with ASD or with autistic traits, the social defeat hypothesis of schizophrenia might help explain an increased risk of psychosis in these individuals. Specifically, from the hypothesis, three testable predictions can be derived. That is, first, individuals with ASD or autistic traits should be at an increased risk of developing psychosis relative to non-autistic individuals (i.e., those without ASD and/or with no or fewer autistic traits). Second, individuals with ASD or autistic traits should have an increase in striatal presynaptic dopamine functioning relative to non-autistic individuals. Third, among individuals with ASD or autistic traits, the increased risk of psychosis and the increase in dopamine functioning should be associated with social defeat. What evidence is there for these predictions?

1.5 Risk of psychosis in autistic individuals

Until recently, there was much uncertainty about the association between autism and psychosis. For instance, even in 2010, a review concluded that there was conflicting evidence regarding the frequency of schizophrenia in ASD (Skokauskas & Gallagher, 2010). In the past decade, increasingly large cross-sectional studies have been conducted, which indicate that ASD and psychotic disorders co-occur at elevated rates. For example, a large and well-cited study by Croen et al. (2015) reported that relative to non-autistic controls ($n = 15,070$), adults with ASD ($n = 1507$) had an odds ratio (OR) for

schizophrenic disorders of 22.24 (99% confidence interval [CI] 14.34–34.48) and for 'other psychoses' of 11.81 (99% CI 7.87–17.73). Furthermore, studies reported a strong relationship between subclinical autistic traits and psychotic experiences in the general population (Zhou et al., 2019; Martinez et al., 2020), increased rates of psychotic experiences in ASD (e.g., Eussen et al., 2015; Goto et al., 2015), and increased rates of ASD and autistic traits in individuals with psychotic disorders (Kincaid et al., 2017).

However, there are at least two important forms of bias which might result in an overestimation of the co-occurrence between autism and psychosis in cross-sectional studies. First, symptoms of autism and psychosis can be the same or appear similar (see Table 1), which can result in a diagnostic bias. That is, an individual might be mistakenly diagnosed with ASD as well as a psychotic disorder based on the presence of these similar symptoms (e.g., a person with schizophrenia might erroneously receive an ASD diagnosis on the basis of social withdrawal, reduced social reciprocity, and flattened affect). Similarly, studies that assess the co-occurrence of subclinical autistic traits and psychotic experiences are likely to find at least some relationship between them simply because of this overlap in symptoms.

Second, estimates of psychosis in adults with ASD might be prone to selection bias. That is, ASD is likely more often recognized in those adults with additional mental health problems, who might also be more likely to have psychotic symptoms.

These biases might be resolved by evaluating whether autistic traits were present since childhood. Psychotic symptoms in childhood are rare, and as such they are unlikely to be mistaken for autistic traits or to be a reason for the recognition of, for instance, an ASD. Childhood autistic traits can be measured with a thorough retrospective developmental assessment, but such an assessment is often difficult or impossible to conduct (and which has often not or only partly been done in empirical studies), for instance because (parental) information about the early childhood is unavailable. Alternatively, longitudinal studies can be conducted, which allow individuals with autistic traits to be followed from childhood to adulthood.

Several relatively small longitudinal studies have indeed shown that the risk of psychotic disorder is increased in ASD (Chisholm et al., 2015). Moreover, a large ($n = 9602$ ASD, $n = 90,620$ controls) Swedish population-based study reported an OR of up to 6.2 (95% CI 4.1–9.3) of non-affective psychotic disorder in individuals diagnosed with ASD before age 16, after a follow-up period of up to 11 years (Selten et al., 2015). However, at follow-up most participants were relatively young (mean age = 15.3 years old) and replication of this study is necessary.

In addition to studies examining psychotic disorders, a few longitudinal studies have shown that childhood autistic traits, ASD, and ASD polygenic risk scores are associated with psychotic experiences in adolescence (Bevan-Jones et al., 2012; Sullivan et al., 2013; Velthorst et al., 2018), although two studies reported only weak or no associations (Taylor et al., 2015; Cederlöf et al., 2016). Thus far, no studies followed individuals with childhood autistic traits beyond an age of 18 years.

In sum, there is preliminary evidence that individuals with ASD are at an increased risk of developing psychotic disorders, and mixed evidence showing that these findings extend to non-clinical expressions of the disorders.

Table 1*Similarities and differences in some characteristics of autism and psychosis.*

	Autism	Psychosis
Similarities	Reduced non-verbal communication	Flattened affect
	Reduced physical responsivity or increased (repetitive) bodily movements	Catatonic stupor or excitement
	Difficulties with and reductions in social interactions	Social withdrawal
	Language and communication difficulties	Disorganized speech
	Sensory hypersensitivity (e.g., auditory, tactile)	Hallucinations
	Strong and/or rigid interests in specific topics	Delusions
Differences	Present since childhood (although characteristics might not become apparent until later in life)	(Usually) develops in adolescence or adulthood
	Positive psychotic symptoms not considered to be part of ASD	Positive psychotic symptoms, such as hallucinations and delusions, are considered to be core characteristics of a psychotic disorder

1.6 Associations between social defeat and psychosis in autism

Assuming that the risk of psychosis is increased in autism, we can evaluate what is known about its relationship with social defeat. Thus far, no studies have examined associations between psychosis and (proxies of) social defeat in ASD samples. Moreover, the results of two longitudinal studies examining individuals with autistic traits are inconclusive. One found that the association between autistic traits and psychotic experiences remained unchanged after adjusting for experiences of bullying victimisation. However, follow-up had been to an age of 12 years only (Bevan-Jones et al., 2012). The other found that polygenic risk scores for ASD were associated with an increased risk of psychotic experiences at an age of 18 years, and that this relationship was mediated by peer problems that had developed in adolescence (Velthorst et al., 2018). This association remained statistically significant when taking into account polygenic risk scores for schizophrenia.

Overall, there is insufficient evidence to evaluate whether the risk of psychosis in individuals with ASD or autistic traits is related to social defeat.

1.7 Dopamine signalling in autism

Few PET studies examined presynaptic dopamine in ASD (Zürcher et al., 2015). A recent [^{11}C]-raclopride PET study found that striatal dopamine release in response to monetary reward was decreased in adults with ASD ($n = 10$) relative to controls ($n = 12$), but amphetamine- or stress-induced dopamine release was not examined (Zürcher et al., 2021). Two studies examined striatal dopamine synthesis capacity using 3,4-dihydroxy-6- ^{18}F -fluoro-L-phenylalanine (^{18}F -FDOPA) PET. Ernst et al. (1997) found no increase in dopamine synthesis capacity in striatal regions in autistic children ($n = 14$) relative to non-autistic peers ($n = 10$), but most ($n = 11$) autistic children were sedated using propofol which can influence dopamine concentrations (Pain et al., 2002). Nieminen-von Wendt et al. (2004) conducted a study in male adults with Asperger syndrome ($n = 8$), and obtained evidence of increased striatal

dopamine synthesis capacity relative to controls ($n = 5$). However, the number of participants was small and risk factors were not examined. No studies examined associations between presynaptic dopamine and subclinical autistic traits.

In sum, findings on striatal dopamine in autism are conflicting and based on small samples, and no associations with possible risk factors have been examined. It is not known whether social defeat increases dopamine signalling in autism.

1.8 The present thesis

The aim of this thesis is to examine whether social defeat constitutes a risk factor for psychosis in autism, as is predicted by the social defeat hypothesis of schizophrenia. To do so, we will examine individuals with clinical and non-clinical expressions of autism and psychosis. Three predictions derived from the social defeat hypothesis will be tested, namely that (1) individuals with ASD or autistic traits are at an increased risk of developing a psychotic disorder and psychotic experiences relative to non-autistic individuals, (2) individuals with ASD or autistic traits show an increase in presynaptic striatal dopaminergic functioning, operationalized as striatal dopamine synthesis capacity, relative to non-autistic individuals, and (3) these risks of psychosis and increases in dopamine synthesis capacity are associated with social defeat.

In chapters II and III, we examine the risks of psychosis in autism. In chapter II, we present a longitudinal register-based study in which the risk of non-affective psychotic disorder (NAPD) in individuals with ASD is estimated. In this study, we vary the age and sequence of ASD and NAPD diagnoses in an attempt to overcome possible biases that might influence estimates of their co-occurrence. In chapter III, we present a longitudinal birth-cohort study, which examines the association between childhood autistic traits and psychotic experiences in adolescence and young adulthood. Moreover, in the study we examine whether traumatic experiences in childhood mediate this association.

In chapter IV, we examine whether dopaminergic functioning is increased in individuals with ASD and associated with social defeat. It presents an [^{18}F]-FDOPA PET study that examines striatal presynaptic dopamine synthesis capacity in ASD and its relationship with measures of social defeat. Exploratory findings from this study are presented in Chapter V, which includes results on the association between dopamine synthesis capacity and autistic traits.

Chapter VI is not directly aimed at testing the predictions made by the social defeat hypothesis, but rather consists of a brief commentary on the hypothesis itself.

Finally, the findings are summarized and discussed in chapter VII.

2. References

- American Psychiatric Association. (2013). *Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5)*. American Psychiatric Publishing.
- Bauminger, N., Shulman, C., & Agam, G. (2003). Peer interaction and loneliness in high-functioning children with autism. *Journal of Autism and Developmental Disorders*, 33(5), 489-507.
- Bevan-Jones, R., Thapar, A., Lewis, G., & Zammit, S. (2012). The association between early autistic traits and psychotic experiences in adolescence. *Schizophrenia Research*, 135(1-3), 164-169.
- Brugger, S. P., Angelescu, I., Abi-Dargham, A., Mizrahi, R., Shahrezaei, V., & Howes, O. D. (2020). Heterogeneity of striatal dopamine function in schizophrenia: meta-analysis of variance. *Biological Psychiatry*, 87(3), 215-224.
- Cederlöf, M., Pettersson, E., Sariaslan, A., Larsson, H., Östberg, P., Kelleher, I., Långström, N., Gumpert, C. H., Lundström, S., & Lichtenstein, P. (2016). The association between childhood autistic traits and adolescent psychotic experiences is explained by general neuropsychiatric problems. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, 171(2), 153-159.
- Cheng, P. W. C., Chang, W. C., Lo, G. G., Chan, K. W. S., Lee, H. M. E., Hui, L. M. C., Suen, Y. N., Leung, Y. L. E., Yeung, K. M. P. A., & Chen, S. (2020). The role of dopamine dysregulation and evidence for the transdiagnostic nature of elevated dopamine synthesis in psychosis: a positron emission tomography (PET) study comparing schizophrenia, delusional disorder, and other psychotic disorders. *Neuropsychopharmacology*, 45(11), 1870-1876.
- Chisholm, K., Lin, A., Abu-Akel, A., & Wood, S. J. (2015). The association between autism and schizophrenia spectrum disorders: A review of eight alternate models of co-occurrence. *Neuroscience & Biobehavioral Reviews*, 55, 173-183.
- Constantino, J. N., Davis, S. A., Todd, R. D., Schindler, M. K., Gross, M. M., Brophy, S. L., Metzger, L. M., Shoushtari, C. S., Splinter, R., & Reich, W. (2003). Validation of a brief quantitative measure of autistic traits: comparison of the social responsiveness scale with the autism diagnostic interview-revised. *Journal of Autism and Developmental Disorders*, 33(4), 427-433.
- Croen, L. A., Zerbo, O., Qian, Y., Massolo, M. L., Rich, S., Sidney, S., & Kripke, C. (2015). The health status of adults on the autism spectrum. *Autism*, 19(7), 814-823.
- Cumming, P., Abi-Dargham, A., & Gründer, G. (2020). Molecular imaging of schizophrenia: neurochemical findings in a heterogeneous and evolving disorder. *Behavioural Brain Research*, 1-13.
- Cunningham, T., Hoy, K., & Shannon, C. (2016). Does childhood bullying lead to the development of psychotic symptoms? A meta-analysis and review of prospective studies. *Psychosis*, 8(1), 48-59.
- Davis, K. L., Kahn, R. S., Ko, G., & Davidson, M. (1991). Dopamine in schizophrenia: a review and reconceptualization. *The American Journal of Psychiatry*, 148(11), 1474-1486.
- DeVylder, J., Burnette, D., & Yang, L. (2014). Co-occurrence of psychotic experiences and common mental health conditions across four racially and ethnically diverse population samples. *Psychological Medicine*, 44(16), 3503-3513.
- Egerton, A., Howes, O. D., Houle, S., McKenzie, K., Valmaggia, L. R., Bagby, M. R., Tseng, H.-H., Bloomfield, M. A., Ken, M., & Bhattacharyya, S. (2017). Elevated striatal dopamine function in immigrants and their children: a risk mechanism for psychosis. *Schizophrenia Bulletin*, 43(2), 293-301.

- Egerton, A., Valmaggia, L. R., Howes, O. D., Day, F., Chaddock, C. A., Allen, P., Winton-Brown, T. T., Bloomfield, M. A., Bhattacharyya, S., & Chilcott, J. (2016). Adversity in childhood linked to elevated striatal dopamine function in adulthood. *Schizophrenia Research*, 176(2-3), 171-176.
- Ernst, M., Zametkin, A., Matochik, J., Pascualvaca, D., & Cohen, R. (1997). Low medial prefrontal dopaminergic activity in autistic children. *The Lancet*, 350(9078), 638.
- Eussen, M. L., de Bruin, E. I., Van Gool, A. R., Louwerse, A., van der Ende, J., Verheij, F., Verhulst, F. C., & Greaves-Lord, K. (2015). Formal thought disorder in autism spectrum disorder predicts future symptom severity, but not psychosis prodrome. *European Child & Adolescent Psychiatry*, 24(2), 163-172.
- Evans, B. (2017). *The metamorphosis of autism*. Manchester University Press.
- Fusar-Poli, P., de Pablo, G. S., Correll, C. U., Meyer-Lindenberg, A., Millan, M. J., Borgwardt, S., Galderisi, S., Bechdolf, A., Pfennig, A., & Kessing, L. V. (2020). Prevention of psychosis: advances in detection, prognosis, and intervention. *JAMA Psychiatry*, 77(7), 755-765.
- Gevonden, M., Seltén, J., Myin-Germeys, I., De Graaf, R., Ten Have, M., Van Dorsselaer, S., Van Os, J., & Veling, W. (2014a). Sexual minority status and psychotic symptoms: findings from the Netherlands Mental Health Survey and Incidence Studies (NEMESIS). *Psychological Medicine*, 44(2), 421-433.
- Gevonden, M., Booij, J., van den Brink, W., Heijtel, D., van Os, J., & Seltén, J.-P. (2014b). Increased release of dopamine in the striata of young adults with hearing impairment and its relevance for the social defeat hypothesis of schizophrenia. *JAMA Psychiatry*, 71(12), 1364-1372.
- Gong, J.-b., Wang, Y., Lui, S. S., Cheung, E. F., & Chan, R. C. (2017). Childhood trauma is not a confounder of the overlap between autistic and schizotypal traits: A study in a non-clinical adult sample. *Psychiatry Research*, 257, 111-117.
- Goto, A., Miyawaki, D., Kusaka, H., Okada, Y., Asada, N., Iwakura, Y., Yanagihara, E., & Inoue, K. (2015). High prevalence of non-psychotic delusions in children with high-functioning pervasive developmental disorder. *Osaka City Medical Journal*, 61(2), 73-80.
- Han, G. T., Tomarken, A. J., & Gotham, K. O. (2019). Social and nonsocial reward moderate the relation between autism symptoms and loneliness in adults with ASD, depression, and controls. *Autism Research*, 12(6), 884-896.
- Hoffman, R. E. (2007). A social deafferentation hypothesis for induction of active schizophrenia. *Schizophrenia Bulletin*, 33(5), 1066-1070.
- Howes, O., & Kapur, S. (2009). The dopamine hypothesis of schizophrenia: version III—the final common pathway. *Schizophrenia Bulletin*, 35(3), 549-562.
- Howes, O., McCutcheon, R., & Stone, J. (2015). Glutamate and dopamine in schizophrenia: an update for the 21st century. *Journal of Psychopharmacology*, 29(2), 97-115.
- Howes, O. D., Hird, E. J., Adams, R. A., Corlett, P. R., & McGuire, P. (2020). Aberrant salience, information processing and dopaminergic signalling in people at clinical high risk for psychosis. *Biological Psychiatry*, 88(4), 304-314.
- Howes, O. D., Montgomery, A. J., Asselin, M.-C., Murray, R. M., Valli, I., Tabraham, P., Bramon-Bosch, E., Valmaggia, L., Johns, L., & Broome, M. (2009). Elevated striatal dopamine function linked to prodromal signs of schizophrenia. *Archives of General Psychiatry*, 66(1), 13-20.
- Howes, O. D., & Murray, R. M. (2014). Schizophrenia: an integrated sociodevelopmental-cognitive model. *The Lancet*, 383(9929), 1677-1687.

- Jauhar, S., Nour, M. M., Veronese, M., Rogdaki, M., Bonoldi, I., Azis, M., Turkheimer, F., McGuire, P., Young, A. H., & Howes, O. D. (2017). A test of the transdiagnostic dopamine hypothesis of psychosis using positron emission tomographic imaging in bipolar affective disorder and schizophrenia. *JAMA Psychiatry*, 74(12), 1206-1213.
- Johnson, T. D., & Joshi, A. (2016). Dark clouds or silver linings? A stigma threat perspective on the implications of an autism diagnosis for workplace well-being. *Journal of Applied Psychology*, 101(3), 430-449.
- Kanner, L. (1943). Autistic disturbances of affective contact. *Nervous Child*, 2(3), 217-250.
- Kincaid, D. L., Doris, M., Shannon, C., & Mulholland, C. (2017). What is the prevalence of autism spectrum disorder and ASD traits in psychosis? A systematic review. *Psychiatry Research*, 250, 99-105.
- Lai, M.-C., & Baron-Cohen, S. (2015). Identifying the lost generation of adults with autism spectrum conditions. *The Lancet Psychiatry*, 2(11), 1013-1027.
- Le Couteur, A., Bailey, A., Goode, S., Pickles, A., Gottesman, I., Robertson, S., & Rutter, M. (1996). A broader phenotype of autism: the clinical spectrum in twins. *Journal of Child Psychology and Psychiatry*, 37(7), 785-801.
- Linscott, R., & Van Os, J. (2013). An updated and conservative systematic review and meta-analysis of epidemiological evidence on psychotic experiences in children and adults: on the pathway from proneness to persistence to dimensional expression across mental disorders. *Psychological Medicine*, 43(6), 1133-1149.
- Maenner, M. J., Shaw, K. A., & Baio, J. (2020). Prevalence of autism spectrum disorder among children aged 8 years—autism and developmental disabilities monitoring network, 11 sites, United States, 2016. *MMWR Surveillance Summaries*, 69(4), 1-12.
- Martinez, A. P., Wickham, S., Rowse, G., Milne, E., & Bentall, R. P. (2020). Robust association between autistic traits and psychotic-like experiences in the adult general population: epidemiological study from the 2007 Adult Psychiatric Morbidity Survey and replication with the 2014 APMS. *Psychological Medicine*, online ahead of print, 1-7.
- Mazurek, M. O. (2014). Loneliness, friendship, and well-being in adults with autism spectrum disorders. *Autism*, 18(3), 223-232.
- McCutcheon, R., Beck, K., Jauhar, S., & Howes, O. D. (2018). Defining the locus of dopaminergic dysfunction in schizophrenia: a meta-analysis and test of the mesolimbic hypothesis. *Schizophrenia Bulletin*, 44(6), 1301-1311.
- McCutcheon, R. A., Krystal, J. H., & Howes, O. D. (2020). Dopamine and glutamate in schizophrenia: biology, symptoms and treatment. *World Psychiatry*, 19(1), 15-33.
- McGrath, J. J., Saha, S., Al-Hamzawi, A., Alonso, J., Bromet, E. J., Bruffaerts, R., Caldas-de-Almeida, J. M., Chiu, W. T., de Jonge, P., & Fayyad, J. (2015). Psychotic experiences in the general population: a cross-national analysis based on 31 261 respondents from 18 countries. *JAMA Psychiatry*, 72(7), 697-705.
- Meltzer, H. Y., & Stahl, S. M. (1976). The dopamine hypothesis of schizophrenia: a review. *Schizophrenia Bulletin*, 2(1), 19-76.
- Morgan, C., Kirkbride, J., Hutchinson, G., Craig, T., Morgan, K., Dazzan, P., Boydell, J., Doody, G. A., Jones, P. B., & Murray, R. M. (2008). Cumulative social disadvantage, ethnicity and first-episode psychosis: a case-control study. *Psychological Medicine*, 38(12), 1701-1715.

- Nieminen-von Wendt, T. S., Metsähonkala, L., Kulomäki, T. A., Aalto, S., Autti, T. H., Vanhala, R., Eskola, O., Bergman, J., Hietala, J. A., & von Wendt, L. O. (2004). Increased presynaptic dopamine function in Asperger syndrome. *Neuroreport*, 15(5), 757-760.
- Oswald, L. M., Wand, G. S., Kuwabara, H., Wong, D. F., Zhu, S., & Brasic, J. R. (2014). History of childhood adversity is positively associated with ventral striatal dopamine responses to amphetamine. *Psychopharmacology*, 231(12), 2417-2433.
- Pain, L., Gobaille, S., Schleef, C., Aunis, D., & Oberling, P. (2002). In vivo dopamine measurements in the nucleus accumbens after nonanesthetic and anesthetic doses of propofol in rats. *Anesthesia & Analgesia*, 95(4), 915-919.
- Perälä, J., Suvisaari, J., Saarni, S. I., Kuoppasalmi, K., Isometsä, E., Pirkola, S., Partonen, T., Tuulio-Henriksson, A., Hintikka, J., & Kieseppä, T. (2007). Lifetime prevalence of psychotic and bipolar I disorders in a general population. *Archives of General Psychiatry*, 64(1), 19-28.
- Peterson, J. L., Earl, R. K., Fox, E. A., Ma, R., Haidar, G., Pepper, M., Berliner, L., Wallace, A. S., & Bernier, R. A. (2019). Trauma and autism spectrum disorder: Review, proposed treatment adaptations and future directions. *Journal of Child & Adolescent Trauma*, 12(4), 529-547.
- Pruessner, J. C., Champagne, F., Meaney, M. J., & Dagher, A. (2004). Dopamine release in response to a psychological stress in humans and its relationship to early life maternal care: a positron emission tomography study using [¹¹C] raclopride. *Journal of Neuroscience*, 24(11), 2825-2831.
- Rai, D., Culpin, I., Heuvelman, H., Magnusson, C. M., Carpenter, P., Jones, H. J., Emond, A. M., Zammit, S., Golding, J., & Pearson, R. M. (2018). Association of autistic traits with depression from childhood to age 18 years. *JAMA Psychiatry*, 75(8), 835-843.
- Reis, D. J. (1974). Consideration of some problems encountered in relating specific neurotransmitters to specific behaviors or disease. In *Catecholamines and Schizophrenia* (pp. 145-148). Elsevier.
- Schroeder, J. H., Cappadocia, M. C., Bebko, J. M., Pepler, D. J., & Weiss, J. A. (2014). Shedding light on a pervasive problem: A review of research on bullying experiences among children with autism spectrum disorders. *Journal of Autism and Developmental Disorders*, 44(7), 1520-1534.
- Selten, J.-P., Booij, J., Buwalda, B., & Meyer-Lindenberg, A. (2017). Biological mechanisms whereby social exclusion may contribute to the etiology of psychosis: a narrative review. *Schizophrenia Bulletin*, 43(2), 287-292.
- Selten, J.-P., & Cantor-Graae, E. (2005). Social defeat: risk factor for schizophrenia? *The British Journal of Psychiatry*, 187(2), 101-102.
- Selten, J.-P., Lundberg, M., Rai, D., & Magnusson, C. (2015). Risks for nonaffective psychotic disorder and bipolar disorder in young people with autism spectrum disorder: a population-based study. *JAMA Psychiatry*, 72(5), 483-489.
- Selten, J.-P., van der Ven, E., Rutten, B. P., & Cantor-Graae, E. (2013). The social defeat hypothesis of schizophrenia: an update. *Schizophrenia Bulletin*, 39(6), 1180-1186.
- Selten, J.-P., van der Ven, E., & Termorshuizen, F. (2020). Migration and psychosis: a meta-analysis of incidence studies. *Psychological Medicine*, 50(2), 303-313.
- Skokauskas, N., & Gallagher, L. (2010). Psychosis, affective disorders and anxiety in autistic spectrum disorder: prevalence and nosological considerations. *Psychopathology*, 43(1), 8-16.
- Sullivan, S., Rai, D., Golding, J., Zammit, S., & Steer, C. (2013). The association between autism spectrum disorder and psychotic experiences in the Avon longitudinal study of parents and children (ALSPAC) birth cohort. *Journal of the American Academy of Child & Adolescent Psychiatry*, 52(8), 806-814.

- Taylor, M. J., Robinson, E. B., Happé, F., Bolton, P., Freeman, D., & Ronald, A. (2015). A longitudinal twin study of the association between childhood autistic traits and psychotic experiences in adolescence. *Molecular Autism*, 6(1), 1-11.
- Velthorst, E., Froudast-Walsh, S., Stahl, E., Ruderfer, D., Ivanov, I., Buxbaum, J., Banaschewski, T., Bokde, A. L., Büchel, C., & Quinlan, E. B. (2018). Genetic risk for schizophrenia and autism, social impairment and developmental pathways to psychosis. *Translational Psychiatry*, 8(1), 1-11.
- Wing, L. (1981). Asperger's syndrome: a clinical account. *Psychological Medicine*, 11, 115-129.
- Zhou, H.-Y., Yang, H.-X., Gong, J.-B., Cheung, E. F., Gooding, D. C., Park, S., & Chan, R. C. (2019). Revisiting the overlap between autistic and schizotypal traits in the non-clinical population using meta-analysis and network analysis. *Schizophrenia Research*, 212, 6-14.
- Zürcher, N. R., Bhanot, A., McDougle, C. J., & Hooker, J. M. (2015). A systematic review of molecular imaging (PET and SPECT) in autism spectrum disorder: current state and future research opportunities. *Neuroscience & Biobehavioral Reviews*, 52, 56-73.
- Zürcher, N. R., Walsh, E. C., Phillips, R. D., Cernasov, P. M., Tseng, C.-E. J., Dharanikota, A., Smith, E., Li, Z., Kinard, J. L., & Bizzell, J. C. (2021). A simultaneous [^{11}C]raclopride positron emission tomography and functional magnetic resonance imaging investigation of striatal dopamine binding in autism. *Translational Psychiatry*, 11(1), 1-11.

Chapter II

Risk of non-affective psychotic disorder or bipolar disorder in autism spectrum disorder: a longitudinal register-based study in the Netherlands

Schalbroeck, R., Termorshuizen, F., Visser, E., van Amelsvoort, T., Selten, J. P.
Psychological Medicine (2019), 49(15), 2543-2550.

Abstract

Background: Individuals with autism spectrum disorder (ASD) appear to be at increased risk of non-affective psychotic disorder (NAPD) and bipolar disorder (BD). However, most previous studies examined the co-occurrence of ASD and NAPD or BD, ignoring possible diagnostic bias and selection bias. We used longitudinal data from Dutch psychiatric case registers to assess the risk of NAPD or BD among individuals with ASD, and compared the results to those obtained for the Dutch population in earlier studies.

Methods: Individuals with ASD ($n = 17,234$) were followed up between 16 and 35 years of age. Kaplan-Meier estimates were used to calculate the risk of NAPD or BD. We conducted separate analyses to reduce possible bias, including an analysis among individuals diagnosed with ASD before age 16 years ($n = 8337$).

Results: Of the individuals with ASD, 23.50% (95% confidence interval 21.87–25.22) were diagnosed with NAPD and 3.79% (3.06–4.69) with BD before age 35 years. The corresponding figures for the general population were 0.91% (0.63–1.28) and 0.13% (0.08–0.20). Risk estimates were substantially lower, but still higher than general population estimates, when we restricted our analyses to individuals diagnosed with ASD before age 16, with 1.87% (1.33–2.61) being diagnosed with NAPD and 0.57% (0.21–1.53) with BD before age 25 years. The corresponding figures for the general population were 0.63% (0.44–0.86) and 0.08% (0.05–0.12).

Conclusions: Individuals with ASD are at increased risk of NAPD or BD. This is likely not the result of diagnostic or selection bias.

1. Introduction

Recent years have seen a growing interest in the long-term prognosis of individuals with autism spectrum disorder (ASD), and in particular their risk of developing non-affective psychotic disorder (NAPD) or bipolar disorder (BD). However, risk estimates vary greatly. Two reviews reported a range of prevalence figures of NAPD in individuals with ASD from 0% to over 34% (Skokauskas & Gallagher, 2010; Chisholm et al., 2015). Another review reported a prevalence of BD in individuals with ASD of up to 9% (Vannucchi et al., 2014), but the authors also noted a general lack of investigations.

Most of these studies examined the co-occurrence of ASD and NAPD or BD, but this can result in diagnostic and/or selection bias. Since some signs typical of ASD, such as social withdrawal, are also common in NAPD and BD, some clinicians might erroneously diagnose ASD based on the assumption that these difficulties were present since early childhood. Selection bias may occur if individuals with previously unrecognized ASD are diagnosed with ASD after they have been diagnosed with NAPD or BD.

These sources of bias are less likely in studies in which young individuals with ASD are followed over time, because NAPD and BD generally do not develop until late adolescence or adulthood. However, earlier studies with such a design had small sample sizes, with few including more than 100 (and no more than 200) individuals with some form of autism (Volkmar & Cohen, 1991; Billstedt et al., 2005; Cederlund et al., 2008; Hutton et al., 2008; Mouridsen et al., 2008). A Swedish population-based study included individuals registered with ASD before 16 years of age over an 11-year period ($n = 9062$) and calculated their odds of developing NAPD or BD within that period (Selten et al., 2015). Compared with non-ASD peers, individuals with ASD had a higher risk of developing NAPD or BD (adjusted odds ratio 4.6 and 4.3, respectively); however, the study did not take into account the sequence of diagnoses in time. Overall, more large longitudinal studies examining the risk of NAPD and BD are needed, especially studies that consider the sequence of diagnoses in time (ASD preferably before NAPD or BD) and the age at which ASD is diagnosed.

The current study investigated the risk that individuals with ASD aged 16–35 years would develop NAPD or BD, using longitudinal data from Dutch psychiatric case registers (PCRs). Several analyses were conducted to minimize the possible contribution of diagnostic and selection bias. We compared the risk estimates with those for the Dutch population reported in earlier studies. Additionally, we assessed potential risk factors for NAPD or BD in individuals with ASD.

2. Methods

2.1 Psychiatric case registers

Data were retrieved from two PCRs in the Netherlands (PCR Northern-Netherlands and PCR Middle-Netherlands), which received anonymized diagnostic and demographic information on all patients attending inpatient/outpatient facilities for mental healthcare in a specified geographical area. We extracted data collected between 2000 and 2012 by PCR Northern-Netherlands and between 1999 and 2015 by PCR Middle-Netherlands. Data for each patient included information on Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV diagnoses (diagnosis and date of diagnosis), sex, date of birth, country of birth, and country of birth of each parent. Informed consent was not obtained from individual patients, as Dutch privacy law permits the use of anonymous data for medical research.

2.2 Cases

The initial extraction included all individuals registered with a DSM-IV diagnosis of ASD (codes 299.xx) during the above-mentioned periods ($n = 39,434$). Individuals with ASD were excluded if information on their date of birth, date of first PCR registration, date of ASD diagnosis, or date of NAPD or BD diagnosis (if made) was missing ($n = 195$), or if the date of the ASD, NAPD, or BD diagnosis had been registered retroactively ($n = 4855$), that is, if the diagnosis had been made before 2000 (PCR Northern-Netherlands), before 1999 (PCR Middle-Netherlands), or before the first PCR registration. Furthermore, as we were interested in the risk of NAPD and BD in individuals aged 16–35 years, we excluded individuals diagnosed with NAPD or BD at or before 16 years of age ($n = 129$), who were younger than 16 years when the PCR closed ($n = 12,785$), or who had been diagnosed with ASD when aged 36 or older ($n = 4236$). In total, 17,234 individuals with ASD were included in the analyses.

2.3 Outcomes

The outcome of interest was a diagnosis of NAPD or BD made between 16 and 35 years of age. NAPD was defined as a DSM-IV diagnosis of schizophrenia, schizophreniform disorder, or schizoaffective disorder (codes 295.x), delusional disorder (code 297.1), or psychotic disorder not otherwise specified (NOS) or brief psychotic disorder (codes 298.x). BD was defined as a DSM-IV diagnosis of bipolar I disorder (codes 296.0x, 296.4x, 296.5x, 296.6x, or 296.7), bipolar II disorder (code 296.89), or BD NOS (296.80). If individuals were diagnosed with both NAPD and BD ($n = 42$), we assumed that the last diagnosis reflected a valid revision of the previous one. In these cases, only the last diagnosis was used in the analyses but the date of the previous diagnosis was used as an estimate of the age at onset. Two individuals were simultaneously diagnosed with NAPD and BD and were only included in the NAPD analyses. General population estimates of the cumulative incidence of NAPD were obtained from a 2-year first-contact study conducted in The Hague, the Netherlands, in the period 1997–1999 (Selten et al., 2001).

General population estimates of the cumulative incidence of BD were obtained from a population-based cohort study conducted in the Netherlands in the period 1996–2007 (Kroon et al., 2013). Incidence rates for different age groups (for NAPD 15–19, 20–24, 25–29, 30–34 years; for BD 15–24, 25–34 years) by sex were provided by the researchers involved in these studies and were used to estimate the cumulative incidence.

2.4 Statistical analyses

2.4.1 Risk of NAPD or BD

The risk of NAPD among individuals with ASD was calculated using Kaplan-Meier survival estimates, which reflect the proportion of individuals with ASD who had not been diagnosed with NAPD at a certain age. Individuals were followed up until they were 36 years old, until NAPD or BD was diagnosed, or until the PCR closed, whichever came first. Kaplan-Meier estimates for men and women separately, and their comparison with general population estimates, are reported in Supplementary Table 1.

In the first analysis, we estimated the risk of a first diagnosis of NAPD between ages 16 and 36 among all individuals diagnosed with ASD before 36 years of age. Here we did not consider the sequence in which diagnoses were made or the age at which ASD was diagnosed. Consequently, we expected a greater likelihood of diagnostic bias (i.e., signs of NAPD being mistakenly diagnosed as ASD) and selection bias (i.e., individuals being recognized and/or registered with ASD due to the development of NAPD). The follow-up started at the age of first contact with mental healthcare services for any DSM-IV diagnosis or at age 16, whichever came later.

In the second analysis, we excluded individuals who were diagnosed with ASD after they had been diagnosed with NAPD, or who were diagnosed with ASD and NAPD simultaneously. By restricting the analysis to individuals still at risk of being diagnosed with NAPD at the time they were diagnosed with ASD, we expected that the influence of diagnostic and selection bias would be reduced. Follow-up started at age 16 or at the age of ASD diagnosis, whichever came later.

In the third analysis, we further restricted the analysis to individuals diagnosed with ASD before 16 years of age. We expected selection or diagnostic bias to play a minor role if ASD was diagnosed at an early age. Of note, individuals diagnosed with NAPD or BD before 16 years of age had already been excluded.

In the fourth analysis, we restricted the analysis to individuals diagnosed with ASD after (or at) 16 years of age. In these cases, a diagnosis of NAPD shortly after ASD was diagnosed may indicate that ASD was only diagnosed because of the development of NAPD. Therefore, we also conducted a fifth analysis from which we excluded individuals diagnosed with NAPD within 1 year of the ASD diagnosis.

The risk of BD among individuals with ASD was calculated using the same analyses described for NAPD, but with a diagnosis of BD as the outcome of interest.

For general population risk estimates, we calculated the cumulative incidence of NAPD or BD by subtracting the survivor function $S(t) = \{\exp[-H(t)]\}$ from 1, in which S denotes the probability that a member of the general population did not receive a diagnosis of NAPD or BD up to t years, and H represents the cumulative hazard function (Cleves et al., 2010). This formula was equated to $S(t) = \exp\{-\Sigma(\text{incidence}(t) \cdot \Delta t)\}$, in which we implemented the NAPD and BD incidence rates for different age groups, as provided by Selten et al. (2001) and Kroon et al. (2013). The 95% confidence interval (CI) of the cumulative incidence for the general population was compared with the 95% CIs of the cumulative incidence for individuals with ASD (1 minus Kaplan-Meier estimate) to examine whether they significantly differed. For the general population estimates, CIs were calculated assuming a Poisson distribution of the number of NAPD/BD cases (Rothman, 2015). For the comparison of the cumulative incidence, relative risks (RRs) are also provided.

2.4.2 Risk factors for NAPD or BD

Cox regression analyses were used to identify potential risk factors for the development of NAPD or BD. For these analyses, we used information from individuals diagnosed with ASD before age 16 years and from those diagnosed with ASD after (or at) this age, provided that NAPD or BD was

diagnosed at least 1 year after ASD was diagnosed. We expected that the contribution of diagnostic or selection bias to the risk estimates would be small in these individuals.

The following potential risk factors were evaluated: sex, intellectual disability (ID; DSM-IV codes 317, 318.x, 319) present before or at the moment of the ASD diagnosis, migrant status based on parental country of birth (non-migrant if both parents were Dutch, migrant if at least one of the parents had been born abroad, or other if this information was unknown), ASD subtype [autistic disorder v. pervasive developmental disorder-not otherwise specified (PDD-NOS) or Asperger's syndrome], and age at ASD diagnosis (four age groups: 0–7, 8–15, 16–25, 26–35 years). Owing to the limited data available for the Cox regression analyses for BD, migrant status was not included, and the age at ASD diagnosis was split into three groups (0–15, 16–25, 26–35 years). An alpha of 0.05 was used to examine whether a variable violated the proportional hazard assumption and to evaluate whether a variable was significantly related to an increased or decreased risk of NAPD or BD.

2.5 Missing data

Information about sex was missing for six individuals with ASD (0.03%). Data for these individuals were omitted from Kaplan-Meier estimates by sex and from the Cox regression analyses. Migrant status could not be ascertained in 3019 individuals (17.5%). As described above, in the Cox regression analyses the migrant status of these individuals was coded as 'other'.

2.6 Software

Data were prepared with SPSS version 22.0 (IBM). STATA version 13.1 (StataCorp) was used to calculate Kaplan-Meier survival estimates (using the `sts list` and `sts graph` commands) and for Cox regression analyses and corresponding proportional hazards tests (using the `stcox` and `estat phtest` commands).

Table 1*Characteristics of individuals with autism spectrum disorder registered in Dutch psychiatric case registers.*

Characteristic	ASD diagnosed first ²				
	1. Whole ASD sample ¹	2. Total	3. ASD < 16 ³	4. ASD ≥ 16 ⁴	5. ASD ≥ 16, NAPD/BD not in first year ⁵
No. ASD cases	17,234	16,715	8337	8378	8197
Male sex ⁶	76.07%	75.98%	78.77%	73.20%	72.99%
Autistic disorder	10.49%	10.25%	7.51%	12.97%	12.79%
Migrant	4.07%	3.95%	4.31%	3.60%	3.49%
ID ⁷	10.51%	10.45%	8.36%	12.53%	12.49%
Age start follow-up, mean (SD)	18.55 (4.51)	19.17 (5.02)	16.00 (0.00)	22.32 (5.52)	22.30 (5.52)
Age end follow-up, mean (SD)	23.15 (5.60)	23.09 (5.61)	19.45 (2.38)	26.72 (5.55)	26.79 (5.53)
Total observation time in years	79,333	65,641	28,784	36,857	36,824
No. cases with NAPD	845	381	68	313	154
Male sex ⁶	80.81%	81.32%	74.63%	82.75%	82.47%
Autistic disorder	17.75%	16.54%	8.8%	18.21%	12.34%
Migrant	7.69%	7.87%	11.76%	7.03%	5.19%
ID ⁷	13.02%	13.12%	13.24%	13.10%	11.69%
No. cases with BD	116	61	13	48	26
Male sex ⁶	65.52%	62.30%	46.15%	66.67%	53.85%
Autistic disorder	12.93%	11.48%	7.69%	12.5%	19.23%
Migrant	6.03%	3.28%	0.00%	4.17%	0.00%
ID ⁷	11.21%	13.11%	15.38%	12.5%	11.54%

ASD, autism spectrum disorder; NAPD, non-affective psychotic disorder; BD, bipolar disorder; ID, intellectual disability; SD, standard deviation.

¹ All ASD cases, without age or diagnostic restrictions.² Restricted to ASD cases still at risk of a first diagnosis of NAPD or BD at the time of the ASD diagnosis.³ Restricted to cases diagnosed with ASD before age 16.⁴ Restricted to cases diagnosed with ASD after (or at) age 16.⁵ Restricted to cases diagnosed with ASD after (or at) age 16, in which an NAPD or BD diagnosis was not made within the first year after the ASD diagnosis.⁶ Calculated over total number of cases. Information about sex was missing for $n=6$.⁷ Diagnosed before or simultaneously with ASD.

3. Results

3.1 Risk of NAPD or BD

Table 1 gives an overview of the characteristics of the individuals with ASD included in each analysis. Figure 1 shows the estimated risk of NAPD or BD in each analysis, which are compared with general population estimates in Table 2.

The results of the first analysis, which did not take into account the age at ASD diagnosis or sequence of diagnoses, showed that an estimated 24.36% (95% CI 22.68–26.14) of individuals with ASD were diagnosed with NAPD and an estimated 4.00% (95% CI 3.23–4.95) were diagnosed with BD before 36 years of age.

For the second analysis, we excluded 464 of 845 individuals with NAPD (54.91%) and 55 of 116 individuals with BD (47.41%), as these diagnoses had been made before or simultaneously with an ASD diagnosis. Of the remaining individuals with ASD, 13.27% (95% CI 11.80–14.91) were diagnosed with NAPD and 2.39% (95% CI 1.77–3.24) were diagnosed with BD before 36 years of age.

In the third analysis, we restricted to individuals diagnosed with ASD before 16 years of age. These individuals could not be followed up until 36 years of age because the PCRs were not operational long enough, but an estimated 1.87% (95% CI 1.33–2.61) were diagnosed with NAPD and 0.57% (95% CI 0.21–1.53) with BD before 25 years of age.

We restricted the fourth analysis to individuals diagnosed with ASD at or after 16 years of age. The results showed that an estimated 16.46% (95% CI 14.37–18.82) were diagnosed with NAPD and an estimated 2.61% (95% CI 1.93–3.52) with BD before 36 years of age. In total, 159 of 313 of individuals diagnosed with NAPD (50.80%) and 22 of 48 individuals diagnosed with BD (45.83%) had been diagnosed within 1 year of the ASD diagnosis. After exclusion of these individuals in the fifth analysis, an estimated 7.90% (95% CI 6.70–9.31) of individuals were diagnosed with NAPD and an estimated 1.35% (95% CI 0.89–2.04) were diagnosed with BD before 36 years of age.

Overall, 623 of 845 NAPD diagnoses (73.72%) and 77 of 116 BD diagnoses (66.38%) were made before, simultaneously with, or within 1 year of the ASD diagnosis.

In general, the risks of NAPD and BD were higher in individuals with ASD than in the general population (with non-overlapping 95% CIs), irrespective of the restrictions that we applied to the analysis. These differences were not explained by sex, as both men and women with ASD had a higher risk of developing NAPD or BD than did men and women without ASD. As shown in Supplementary Table 1, risk estimates for NAPD and BD among men diagnosed with ASD before 16 years of age were an exception to this. The risk estimates were larger than the risk estimates among men in the general population, but the 95% CIs were partially overlapping.

Figure 1

The Kaplan-Meier survival estimates per analysis showing the estimated proportion of individuals with autism spectrum disorder (ASD) registered in Dutch psychiatric case registers remaining without a diagnosis of non-affective psychotic disorder (NAPD) (left panel) or bipolar disorder (BD) (right panel) with increasing age. Note that the scale on the y-axis differs for the two figures. The large increase in risk of NAPD after age 26 years in individuals who were diagnosed with ASD before age 16 is the result of a small number of remaining cases.

Table 2

Estimated cumulative incidence (%) and associated 95% confidence intervals (in brackets) of non-affective psychotic disorder and bipolar disorder as reported for the Dutch general population and for individuals with autism spectrum disorder registered in Dutch psychiatric case registers.

Age interval	General population ^{1,2}	ASD diagnosed first ⁴				5. ASD ≥ 16, NAPPD/BD not in first year ⁷			
		1. Whole ASD sample ³	2. Total	3. ASD < 16 ⁵	4. ASD ≥ 16 ⁶	RR	RR	RR	RR
		%	%	%	%				
NAPPD									
15-19 ⁸	0.27% (0.18-0.40)	2.38% (2.08-2.73)*	8.81 (1.41-2.00)*	6.22 (0.74-1.30)*	0.98% (2.96-6.82)*	3.63	4.51%	16.70	0.60% (0.36-0.99)
15-24	0.63% (0.44-0.86)	7.79% (7.12-8.53)*	12.37 (3.92-5.10)*	7.10 (1.33-2.61)*	1.87% (6.32-10.19)*	2.97	8.03%	12.75	2.55% (2.02-3.20)*
15-29	0.81% (0.57-1.12)	15.80% (14.62-17.07)*	19.51 (7.73-9.89)*	10.80	11.45%		11.45%	14.14	5.40% (4.52-6.45)*
15-34	0.91% (0.63-1.28)	23.50% (21.87-25.22)*	25.82 (11.37-14.38)*	14.05	16.20% (14.12-18.55)*		16.20%	17.80	7.60% (6.44-8.96)*
15-35		24.36% (22.68-26.14)	13.27% (11.80-14.91)		16.46% (14.37-18.82)		16.46%		7.90% (6.70-9.31)
BD									
15-19 ⁸		0.24% (0.15-0.37)	0.20% (0.12-0.33)	0.16% (0.08-0.32)	0.32% (0.14-0.74)		0.32%		0.12% (0.04-0.39)
15-24	0.08% (0.05-0.12)	1.19% (0.92-1.53)*	14.88 (0.59-1.16)*	10.38 (0.21-1.53)*	1.03% (0.69-1.53)*	7.13	1.03%	12.88	0.51% (0.30-0.86)*
15-29		2.29% (1.83-2.87)	1.57% (1.15-2.15)		1.79% (1.29-2.47)		1.79%		0.91% (0.59-1.41)
15-34	0.13% (0.08-0.20)	3.79% (3.06-4.69)*	29.15 (1.69-3.1)*	17.62	2.50% (1.85-3.39)*		2.50%	19.23	1.35% (0.89-2.04)*
15-35		4.00% (3.23-4.95)	2.39% (1.77-3.24)		2.61% (1.93-3.52)		2.61%		1.35% (0.89-2.04)

CIs, confidence intervals; NAPPD, non-affective psychotic disorder; BD, bipolar disorder; ASD, autism spectrum disorder; RR, relative risk.

^{1,2} Retrieved from Selten et al. (2001; NAPPD) and Kroon et al. (2013; BD).

³ All ASD cases, without age or diagnostic restrictions.

⁴ Restricted to ASD cases still at risk of a first diagnosis of NAPPD or BD at the time of the ASD diagnosis.

⁵ Restricted to cases diagnosed with ASD before age 16.

⁶ Restricted to cases diagnosed with ASD after (or at) age 16.

⁷ Restricted to cases diagnosed with ASD after (or at) age 16, in which an NAPPD or BD diagnosis was not made within the first year after the ASD diagnosis.

⁸ Individuals from the general population were included from age 15 onwards. ASD cases were included from age 16 onwards.

* 95% CIs not overlapping with (known) general population estimates.

3.2 Risk factors for NAPD or BD

We then examined potential risk factors for NAPD. The proportional hazards assumption was violated for the variable sex ($\chi^2 = 6.94, p = 0.008$), but not for other variables (all p -values > 0.05). Inspection of the data showed that the risk of NAPD among men and women with ASD was similar between 16 and 25 years of age, but diverged between 26 and 35 years of age. For this reason, we added a term for the interaction between time (follow-up during ages 16–25 v. 26–35) and sex to the analysis.

We initially conducted univariable analyses and subsequently added all variables to a multivariable model (see Table 3). Univariable analyses showed that men with ASD had a higher risk of NAPD than women with ASD, but only during the follow-up between age 26 and age 35 years. This risk remained increased in the multivariable model. Univariable analyses also showed an increased risk of NAPD among migrants than among native Dutch individuals ($p = 0.04$). In the multivariable model, this relative risk was of borderline statistical significance ($p = 0.07$). We found no other significant univariable or multivariable results (all p -values > 0.05).

In the analysis of risk factors for BD, none of the variables violated the proportional hazards assumption (all p -values > 0.05). Univariable analyses showed that men with ASD had a lower risk of BD than did women with ASD. This finding remained significant in the multivariable analysis. No other variables were significantly related to risk of BD (all p -values > 0.05).

Table 3

Cox regression analyses examining potential risk factors for NAPD or BD among individuals with autism spectrum disorder registered in Dutch psychiatric case registers (n = 16,528).

Variable	ASD < 16 or ASD ≥ 16 without NAPD/BD diagnosis in first year ¹			
	Univariable analyses		Multivariable analyses	
	HR (95% CI)	p-value	HR (95% CI)	p-value
NAPD²				
Sex				
Female (follow-up during ages 16-25 years)	Reference		Reference	
Male (follow-up during ages 16-25 years)	1.03 (0.71–1.50)	0.87	1.05 (0.72–1.52)	0.81
Female (follow-up during ages 26-35 years)	Reference		Reference	
Male (follow-up during ages 26-35 years)	2.43 (1.16–5.10)	0.02*	2.46 (1.17–5.16)	0.02*
Migrant status				
Dutch	Reference		Reference	
Migrant	1.72 (1.03–2.88)	0.04*	1.64 (0.97–2.78)	0.07
Unknown	0.88 (0.62–1.24)	0.47	0.87 (0.62–1.24)	0.45
ID				
No comorbid ID	Reference		Reference	
Comorbid ID	1.17 (0.78–1.76)	0.44	1.20 (0.80–1.81)	0.38
ASD subtype				
Asperger's syndrome/PDD-NOS	Reference		Reference	
Autistic disorder	1.03 (0.68–1.57)	0.89	1.01 (0.66–1.55)	0.96
Age ASD diagnosis				
0-7	Reference		Reference	
8-15	1.71 (0.24–12.43)	0.60	1.64 (0.23–11.92)	0.63
16-25	1.95 (0.26–14.39)	0.51	1.88 (0.25–13.89)	0.54
26-35	1.57 (0.20–12.62)	0.67	1.56 (0.19–12.52)	0.68
BD³				
Sex				
Female	Reference		Reference	
Male	0.33 (0.18–0.63)	0.001**	0.34 (0.18–0.63)	0.001**
ID				
No comorbid ID	Reference		Reference	
Comorbid ID	1.27 (0.50–3.26)	0.62	1.07 (0.41–2.77)	0.90
ASD subtype				
Asperger's syndrome/PDD-NOS	Reference		Reference	
Autistic disorder	1.53 (0.63–3.67)	0.35	1.52 (0.62–3.71)	0.36
Age ASD diagnosis				
0-15	Reference		Reference	
16-25	1.05 (0.44–2.47)	0.92	0.97 (0.41–2.28)	0.94
26-35	1.63 (0.32–8.36)	0.56	1.42 (0.28–7.29)	0.68

NAPD, non-affective psychotic disorder; BD, bipolar disorder; ASD, autism spectrum disorder; HR, hazard ratio; CI, confidence interval; ID, intellectual disability.

¹ Analyses were restricted to cases diagnosed with ASD before age 16 and cases diagnosed with ASD after (or at) age 16 who remained without NAPD and BD diagnoses for at least one year.

² 221 cases diagnosed with NAPD.

³ 39 cases diagnosed with BD.

* $p < 0.05$.

** $p < 0.001$.

4. Discussion

The results of the current study show that men and women with ASD are at increased risk of developing NAPD or BD. Men had a relatively higher risk of developing NAPD and women a relatively higher risk of developing BD.

It is difficult to estimate the contribution of bias to the variability in risk reported in earlier studies. However, this study confirms and extends those earlier findings by showing that the increased risks persist after adjusting for potential diagnostic and selection bias. That is, when we restricted our analyses to individuals already diagnosed with ASD before age 16, approximately 1.87% were diagnosed with NAPD and 0.57% with BD by 25 years of age (Table 2, analysis 3). We obtained similar results when we restricted our analyses to individuals diagnosed with ASD after 16 years of age who were not diagnosed with NAPD or BD within a year of the ASD diagnosis (Table 2, analysis 5). Of these individuals, 2.55% were diagnosed with NAPD and 0.51% with BD by 25 years of age, which increased up to 7.90% and 1.35% by 36 years of age, respectively.

Strikingly, we found that 74% of NAPD diagnoses and 66% of BD diagnoses were made before, simultaneously with, or within 1 year of the ASD diagnosis. An earlier study that followed up children diagnosed with ASD also reported that a subsequent diagnosis of schizophrenia spectrum disorder was most often made within a year (Maibing et al., 2015). How can these observations be explained? One possibility is that these individuals had had a milder form of autism since childhood that was only recognized by healthcare services when their mental health deteriorated. Alternatively, some clinicians may have forgotten that autism-like signs and symptoms are part of NAPD and assume too readily that these have been present since early childhood. This interpretation fits with the observation of Kendler (2016) that some clinicians equate ‘schizophrenia’ with its DSM criteria only. It is less clear whether such confusion exists between ASD and BD, although signs such as irritability and being overly talkative appear in both disorders and may result in similar confusion.

The sex difference in the risk of developing NAPD or BD warrants further investigation, as previous studies show mixed results (Stahlberg et al., 2004; Billstedt et al., 2005; Hofvander et al., 2009; Croen et al., 2015; Lugnegård et al., 2015). The same applies to the finding that the risk of NAPD was high among migrants with ASD. We found no relation between risk of NAPD or BD and DSM-IV subtypes of ASD or age at ASD diagnosis. Furthermore, we did not replicate the finding of Selten et al. (2015), who reported that individuals with ASD and ID had a lower risk of developing NAPD and BD than peers without such disability.

The current study has several strengths. To the best of our knowledge, it is the largest to study the risk of NAPD or BD in individuals with ASD. Furthermore, we conducted longitudinal analyses and took steps to avoid diagnostic and selection bias. However, the study also has a number of limitations. First, general population risk estimates were retrieved from previous studies, which collected data in partially non-overlapping periods and geographical areas. The study of Selten et al. (2001) was conducted in The Hague, which is a large city in the Netherlands, whereas our data were partially collected in more rural, northern parts of the Netherlands. Since the risk of psychosis is reported to be higher in urban areas (e.g., van Os et al., 2001), the relative risk of NAPD in individuals with ASD may have been underestimated. As Kroon et al. (2013) excluded individuals with BD and co-morbid ID, the relative risk of BD among individuals with ASD may have been overestimated. A second limitation is that misdiagnosis cannot entirely be excluded as an explanation for some findings, as we did not have information about the diagnostic process. In this respect, the availability of extensive diagnostic information can be seen as a

strength of some of the previous smaller studies (e.g., Stahlberg et al., 2004; Billstedt et al., 2005; Joshi et al., 2013; Lugenård et al., 2015).

There is still much uncertainty about why individuals with ASD have an increased risk of NAPD and BD (Padgett et al., 2010; Chisholm et al., 2015). Understanding the mechanisms underlying the increased risk will be an important next step for the prevention and treatment of these disorders in individuals with ASD. Shared risk factors, such as genetic overlap between ASD, NAPD, and BD (Carroll & Owen, 2009; Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013), may increase the risk of all three disorders. Individuals with ASD may also be exposed to environmental risk factors, such as an urban upbringing (Lauritsen et al., 2014), or psychosocial factors, such as social exclusion or childhood trauma (Cappadocia et al., 2012; Kerns et al., 2015), that increase the risk of developing NAPD and/or BD (Read et al., 2005; Laursen et al., 2007; Van Dam et al., 2012; Selten et al., 2013; Cunningham et al., 2016). Additionally, it may be worthwhile to consider the possibility that there are different risk factors for distinct, DSM-independent, autism subtypes (Chisholm et al., 2015).

In conclusion, the current study showed that individuals with ASD are at increased risk of developing NAPD or BD. These results are likely not the result of diagnostic or selection bias. Future research should examine the mechanisms underlying these increased risks.

5. Acknowledgements

We are thankful to Janneke Giele for her assistance with the PCR data, and to Hjalmar Bos for his help with data preparation and literature search. Furthermore, we wish to thank Jojanneke Kroon for her substantial help in providing data about the incidence of BD in the general population.

6. References

- Billstedt, E., Gillberg, C., & Gillberg, C. (2005). Autism after adolescence: population-based 13-to 22-year follow-up study of 120 individuals with autism diagnosed in childhood. *Journal of Autism and Developmental Disorders*, 35(3), 351-360.
- Cappadocia, M. C., Weiss, J. A., & Pepler, D. (2012). Bullying experiences among children and youth with autism spectrum disorders. *Journal of Autism and Developmental Disorders*, 42(2), 266-277.
- Carroll, L. S., & Owen, M. J. (2009). Genetic overlap between autism, schizophrenia and bipolar disorder. *Genome Medicine*, 1(10), 1-7.
- Cederlund, M., Hagberg, B., Billstedt, E., Gillberg, I. C., & Gillberg, C. (2008). Asperger syndrome and autism: A comparative longitudinal follow-up study more than 5 years after original diagnosis. *Journal of Autism and Developmental Disorders*, 38(1), 72-85.
- Chisholm, K., Lin, A., Abu-Akel, A., & Wood, S. J. (2015). The association between autism and schizophrenia spectrum disorders: A review of eight alternate models of co-occurrence. *Neuroscience & Biobehavioral Reviews*, 55, 173-183.
- Cleves, M., Gutierrez, R., Gould, W., & Marchenko, Y. (2010). *An introduction to survival analysis using Stata (2nd ed.)*. Stata press.
- Croen, L. A., Zerbo, O., Qian, Y., Massolo, M. L., Rich, S., Sidney, S., & Kripke, C. (2015). The health status of adults on the autism spectrum. *Autism*, 19(7), 814-823.
- Cross-Disorder Group of the Psychiatric Genomics Consortium (2013). Identification of risk loci with shared effects on five major psychiatric disorders: a genome-wide analysis. *The Lancet*, 381(9875), 1371-1379.
- Cunningham, T., Hoy, K., & Shannon, C. (2016). Does childhood bullying lead to the development of psychotic symptoms? A meta-analysis and review of prospective studies. *Psychosis*, 8(1), 48-59.
- Hofvander, B., Delorme, R., Chaste, P., Nydén, A., Wentz, E., Ståhlberg, O., Herbrecht, E., Stopin, A., Anckarsäter, H., & Gillberg, C. (2009). Psychiatric and psychosocial problems in adults with normal-intelligence autism spectrum disorders. *BMC Psychiatry*, 9, 35.
- Hutton, J., Goode, S., Murphy, M., Le Couteur, A., & Rutter, M. (2008). New-onset psychiatric disorders in individuals with autism. *Autism*, 12(4), 373-390.
- Joshi, G., Wozniak, J., Petty, C., Martelon, M. K., Fried, R., Bolfek, A., Kotte, A., Stevens, J., Furtak, S. L., & Bourgeois, M. (2013). Psychiatric comorbidity and functioning in a clinically referred population of adults with autism spectrum disorders: a comparative study. *Journal of Autism and Developmental Disorders*, 43(6), 1314-1325.
- Kendler, K. S. (2016). Phenomenology of schizophrenia and the representativeness of modern diagnostic criteria. *JAMA Psychiatry*, 73(10), 1082-1092.
- Kerns, C. M., Newschaffer, C. J., & Berkowitz, S. J. (2015). Traumatic childhood events and autism spectrum disorder. *Journal of Autism and Developmental Disorders*, 45(11), 3475-3486.
- Kroon, J. S., Wohlfarth, T. D., Dieleman, J., Sutterland, A. L., Storosum, J. G., Denys, D., de Haan, L., & Sturkenboom, M. C. (2013). Incidence rates and risk factors of bipolar disorder in the general population: a population-based cohort study. *Bipolar Disorders*, 15(3), 306-313.
- Lauritsen, M. B., Astrup, A., Pedersen, C. B., Obel, C., Schendel, D. E., Schieve, L., Yeargin-Allsopp, M., & Parner, E. T. (2014). Urbanicity and autism spectrum disorders. *Journal of Autism and Developmental Disorders*, 44(2), 394-404.
- Laursen, T. M., Munk-Olsen, T., Nordentoft, M., & Bo Mortensen, P. (2007). A comparison of selected risk factors for unipolar depressive disorder, bipolar affective disorder, schizoaffective disorder,

- and schizophrenia from a Danish population-based cohort. *The Journal of Clinical Psychiatry*, 68(11), 1673-1681.
- Lugnegård, T., Hallerbäck, M. U., & Gillberg, C. (2015). Asperger syndrome and schizophrenia: Overlap of self-reported autistic traits using the Autism-spectrum Quotient (AQ). *Nordic Journal of Psychiatry*, 69(4), 268-274.
- Maibing, C. F., Pedersen, C. B., Benros, M. E., Mortensen, P. B., Dalsgaard, S., & Nordentoft, M. (2015). Risk of schizophrenia increases after all child and adolescent psychiatric disorders: a nationwide study. *Schizophrenia Bulletin*, 41(4), 963-970.
- Mouridsen, S., Rich, B., & Isager, T. (2008). Psychiatric disorders in adults diagnosed as children with atypical autism. A case control study. *Journal of Neural Transmission*, 115(1), 135-138.
- Padgett, F. E., Miltsiou, E., & Tiffin, P. A. (2010). The co-occurrence of nonaffective psychosis and the pervasive developmental disorders: a systematic review. *Journal of Intellectual and Developmental Disability*, 35(3), 187-198.
- Read, J., van Os, J., Morrison, A. P., & Ross, C. A. (2005). Childhood trauma, psychosis and schizophrenia: a literature review with theoretical and clinical implications. *Acta Psychiatrica Scandinavica*, 112(5), 330-350.
- Rothman, K. J. (2015). *Episheet: spreadsheets for the analysis of epidemiologic data*. Retrieved 19 April from <http://www.krothman.org/episheet>
- Selten, J.-P., Lundberg, M., Rai, D., & Magnusson, C. (2015). Risks for nonaffective psychotic disorder and bipolar disorder in young people with autism spectrum disorder: a population-based study. *JAMA Psychiatry*, 72(5), 483-489.
- Selten, J.-P., van der Ven, E., Rutten, B. P., & Cantor-Graae, E. (2013). The social defeat hypothesis of schizophrenia: an update. *Schizophrenia Bulletin*, 39(6), 1180-1186.
- Selten, J.-P., Veen, N., Feller, W., Blom, J. D., Schols, D., Camoenie, W., Oolders, J., Van der Velden, M., Hoek, H., & Rivero, V. V. (2001). Incidence of psychotic disorders in immigrant groups to The Netherlands. *The British Journal of Psychiatry*, 178(4), 367-372.
- Skokauskas, N., & Gallagher, L. (2010). Psychosis, affective disorders and anxiety in autistic spectrum disorder: prevalence and nosological considerations. *Psychopathology*, 43(1), 8-16.
- Stahlberg, O., Soderstrom, H., Rastam, M., & Gillberg, C. (2004). Bipolar disorder, schizophrenia, and other psychotic disorders in adults with childhood onset AD/HD and/or autism spectrum disorders. *Journal of Neural Transmission*, 111(7), 891-902.
- Van Dam, D., Van Der Ven, E., Velthorst, E., Selten, J., Morgan, C., & De Haan, L. (2012). association with psychosis in non-clinical and clinical samples: a review and meta-analysis. *Psychological Medicine*, 42(12), 2463-2474
- van Os, J., Hanssen, M., Bijl, R. V., & Vollebergh, W. (2001). Prevalence of psychotic disorder and community level of psychotic symptoms: an urban-rural comparison. *Archives of General Psychiatry*, 58(7), 663-668.
- Vannucchi, G., Masi, G., Toni, C., Dell'Osso, L., Marazziti, D., & Perugi, G. (2014). Clinical features, developmental course, and psychiatric comorbidity of adult autism spectrum disorders. *CNS Spectrums*, 19(2), 157-164.
- Volkmar, F. R., & Cohen, D. J. (1991). Comorbid association of autism and schizophrenia. *The American Journal of Psychiatry*, 148(12), 1705-1707.

Appendix to chapter II

Supplementary information

Supplementary Table 1

Estimated cumulative incidences (%) and associated 95% CIs (in brackets) of NAPD and BD by sex, as reported for the Dutch general population and among individuals with autism spectrum disorder registered in the Dutch psychiatric case registers.

Age interval	General population ^{1,2}		ASD diagnosed first ⁴									
			1. Whole ASD sample ³		2. Total		3. ASD < 16 ⁵		4. ASD ≥ 16 ⁶		5. ASD ≥ 16, NAPD/BD not in first year ⁷	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
NAPD												
15-19 ⁸	0.48% (0.31-0.71)	0.06% (0.02-0.17)	2.32% (1.98-2.72)*	2.53% (1.93-3.31)*	1.56% (1.27-1.91)*	2.02% (1.45-2.82)*	0.85% (0.60-1.19)	1.40% (0.83-2.36)*	5.67% (3.61-8.85)*	3.75% (2.31-6.07)*	0.48% (0.25-0.93)	0.91% (0.41-2.01)*
15-24	1.02% (0.69-1.46)	0.24% (0.11-0.47)	8.26% (7.46-9.14)*	6.41% (5.25-7.82)*	4.56% (3.93-5.29)*	4.18% (3.17-5.50)*	1.74% (1.18-2.54)	2.26% (1.13-4.50)*	9.34% (7.08-12.26)*	6.30% (4.50-8.78)*	2.63% (2.03-3.40)*	2.32% (1.42-3.77)*
15-29	1.25% (0.84-1.81)	0.37% (0.18-0.70)	17.32% (15.90-18.86)*	11.36% (9.47-13.59)*	9.4% (8.18-10.78)*	6.82% (5.17-8.96)*			13.88% (11.44-16.78)*	8.92% (6.71-11.82)*	5.75% (4.72-7.00)*	4.4% (2.94-6.55)*
15-34	1.37% (0.90-2.01)	0.45% (0.21-0.87)	25.43% (23.51-27.47)*	17.71% (14.89-20.99)*	14.26% (12.52-16.21)*	8.21% (6.20-10.83)*			18.5% (15.85-21.53)*	10.29% (7.80-13.50)*	8.42% (7.02-10.09)*	5.1% (3.44-7.54)*
15-35			26.34% (24.36-28.45)	18.39% (15.46-21.80)	14.87% (13.08-16.89)	8.21% (6.20-10.83)			19.09% (16.41-22.14)	10.29% (7.80-13.50)*	8.82% (7.36-10.54)	5.1% (3.44-7.54)
BD												
15-19 ⁸			0.15% (0.08-0.29)	0.52% (0.29-0.94)	0.10% (0.05-0.23)	0.52% (0.27-1.01)	0.13% (0.05-0.32)	0.28% (0.11-0.76)	0.08% (0.01-0.56)	0.99% (0.39-2.49)	0% (0.00-0.00)	0.46% (0.15-1.43)
15-24	0.07% (0.03-0.13)	0.08% (0.04-0.15)	1.16% (0.85-1.57)*	1.33% (0.86-2.04)*	0.76% (0.50-1.15)*	1.09% (0.64-1.84)*	0.48% (0.11-2.06)	0.93% (0.40-2.16)*	0.89% (0.56-1.42)*	1.41% (0.68-2.91)*	0.37% (0.19-0.74)*	0.88% (0.39-1.95)*

15-29	2.21% (1.68- 2.9)	2.59% (1.73- 3.87)	1.32% (0.89- 1.97)	2.36% (1.43- 3.87)	1.47% (0.98- 2.2)	2.70% (1.58- 4.62)	0.63% (0.34- 1.16)	1.71% (0.91- 3.19)
15-34	0.13% (0.06- 0.24)	0.12% (0.06- 0.23)	5.21% (3.60- 7.49)*	3.10% (1.88- 5.09)*	2.18% (1.49- 3.17)*	3.44% (2.06- 5.73)*	0.97% (0.55- 1.71)*	2.45% (1.34- 4.46)*
15-35	3.60% (2.76- 4.68)	5.21% (3.60- 7.49)	2.17% (1.49- 3.17)	3.10% (1.88- 5.09)	2.32% (1.60- 3.36)	3.44% (2.06- 5.73)	0.97% (0.55- 1.71)	2.45% (1.34- 4.46)

CI, confidence interval; NAPP, non-affective psychotic disorder; BD, bipolar disorder; ASD, autism spectrum disorder.
^{1,2} Retrieved from Selten *et al.* (2001; NAPP) and Kroon *et al.* (2013; BD).
³ All ASD cases, without age or diagnostic restrictions.
⁴ Restricted to ASD cases still at risk of a first diagnosis of NAPP or BD at the time of the ASD diagnosis.
⁵ Restricted to cases diagnosed with ASD before age 16.
⁶ Restricted to cases diagnosed with ASD after (or at) age 16.
⁷ Restricted to cases diagnosed with ASD after (or at) age 16, in which an NAPP or BD diagnosis was not made within the first year after the ASD diagnosis.
⁸ Individuals from the general population were included from age 15 onwards. ASD cases were included from age 16 onwards.
* 95% CIs not overlapping with (known) general population estimates.

Chapter III

Childhood trauma as a mediator of the association between autistic traits and psychotic experiences: evidence from the ALSPAC birth cohort

Dardani, C.*, Schalbroeck, R. *, Jones, H., Hammerton, G., Croft, J., Madley-Dowd, P., Sullivan, S., Zammit, S., Seltén, J. P., & Rai, D.

* Joint first authors

Manuscript submitted

Abstract

Introduction: There is increasing evidence that autistic traits are associated with psychotic experiences. However, the mechanisms underlying such associations are still unknown. In this longitudinal birth cohort study, we examine the relationship between childhood autistic traits and psychotic experiences in adolescence and young adulthood, and the influence of childhood trauma on this association.

Methods: We analysed data from the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort. We used four dichotomized measures of autistic traits (social communication difficulties at age 7 years, repetitive behaviour at age 5 years, sociability at age 3 years, and coherence at age 9 years). Psychotic experiences were assessed at ages 18 and 24 years using the semi-structured Psychosis-Like Symptoms interview. Traumatic experiences between ages 5 to 11 years were assessed with questionnaires and interviews administered to children and parents. Additional information about childhood trauma was obtained retrospectively when the child was 22 years old.

Results: The maximum sample with complete data was 3410 for the autistic traits-psychotic experiences analyses and 3327 for the mediation analyses. Social communication difficulties were associated with psychotic experiences (odds ratio [OR] = 1.43, 95% confidence interval [CI] 1.01–2.02), including those that were distressing and/or frequent (OR = 1.60, 95% CI 1.02–2.52). Childhood trauma mediated approximately 40% of this association. Other autistic traits showed no consistent relationship with psychotic experiences. Results were similar when we adjusted for covariates or schizophrenia PRS.

Discussion: Childhood social communication difficulties are associated with psychotic experiences by age 24. This association is mediated by childhood traumatic experiences and not confounded by a genetic liability to schizophrenia. The experience of trauma may be an important, potentially modifiable pathway between autistic features and later onset of psychotic psychopathology where interventions could be targeted.

1. Introduction

Individuals with an autism spectrum disorder (ASD) are at an increased risk of developing a psychotic disorder (Lai et al., 2019). Moreover, an increasing number of studies indicate that throughout the population, subclinical psychotic experiences are more common in individuals with autistic traits. This association between autistic traits and psychotic experiences has been observed in several cross-sectional studies (Zhou et al., 2019; Martinez et al., 2020) and in studies in which children with autistic traits were followed up to a maximum of age 18 years (Bevan-Jones et al., 2012; Sullivan et al., 2013; Taylor et al., 2015; Cederlöf et al., 2016). Although psychotic experiences can be transient and harmless, they are associated with distress and other poor mental health outcomes (Demirkaya et al., 2016; van der Linden et al., 2020), including the development of psychotic disorder (Foss-Feig et al., 2019).

The association between autism and psychosis might partly stem from a genetic overlap (Chisholm et al., 2015). For instance, several rare genetic variants are associated with both ASD and psychotic disorder (Muhle et al., 2018), genome-wide association studies (GWASs) have shown a genetic correlation between ASD and schizophrenia (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2019), and polygenic risk scores (PRS) for ASD are associated with an increased odds of psychotic experiences (Legge et al., 2019). However, the risk of psychosis in autism is likely also influenced by environmental factors (Chisholm et al., 2015).

One of the most reported environmental risk factors for psychotic experiences and psychotic disorder is a history of childhood trauma (Varese et al., 2012; Croft et al., 2019). Individuals with ASD and with subthreshold autistic traits might be more exposed and vulnerable to childhood traumatic experiences, for example because they have reduced access to social support and because socio-communicative differences make victimization more likely (Humphrey & Symes, 2010; Sevelever et al., 2013; Kerns et al., 2015; Novin et al., 2019). Indeed, there is evidence that childhood maltreatment and/or bullying victimization is associated with ASD (Schroeder et al., 2014; McDonnell et al., 2019), autistic traits (Gong et al., 2017; Rai et al., 2018), and PRS for ASD (Warrier & Baron-Cohen, 2019).

Few studies have examined whether childhood trauma influences the risk of psychotic experiences in individuals with autistic traits. One study in college students ($n = 2469$) found that self-reports of trauma did not account for the association between autistic and schizotypal traits (Gong et al., 2017), but its cross-sectional design precludes directional and causal inferences. A longitudinal study reported that bullying victimization did not mediate the relationship between childhood autistic traits and psychotic experiences (Bevan-Jones et al., 2012). However, the follow up was only until age 12 years and other traumatic experiences were not assessed. In sum, it remains unclear whether and to what extent trauma mediates the association between autistic traits and psychotic experiences.

Using a population-based birth cohort, we further examined the association between childhood autistic traits and psychotic experiences in young adulthood, and the influence of childhood trauma on this association. We examined (1) whether autistic traits assessed between ages 3 and 9 were associated with psychotic experiences measured at ages 18 and 24, (2) the extent to which this association was mediated by trauma experienced between ages 5 and 11, and (3) the possible confounding effects of several child and family factors and PRS for schizophrenia.

2. Methods

2.1 Participants

We used data from the Avon Longitudinal Study of Parents and Children (ALSPAC), a population-based cohort study of children born from 14,541 pregnant mothers residing in the former county of Avon, United Kingdom, with an expected delivery date between 1 April 1991 and 31 December 1992. Of these pregnancies, there was a total of 14,676 fetuses, resulting in 14,062 live births and 13,988 children who were alive at 1 year of age. When the oldest children were approximately 7 years of age, eligible samples who did not join the study initially were contacted, and additional participants were recruited. This resulted in a total of 15,454 pregnancies and 15,589 fetuses, of which 14,901 were alive at 1 year of age. Depending on the analysis conducted, we restricted our sample to participants with complete data on autistic traits, traumatic experiences, psychotic experiences, covariates, and/or schizophrenia PRS.

Further information on the ALSPAC cohort is available on the ALSPAC website (<http://www.bristol.ac.uk/alspac>) and in previous publications (Boyd et al., 2013; Fraser et al., 2013). In addition, the study website contains details of all the data that is available through a fully searchable data dictionary and variable search tool (<http://www.bristol.ac.uk/alspac/researchers/our-data/>). Part of the data were collected using REDCap (Harris et al., 2009; Harris et al., 2019). Ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees. Informed consent for the use of data collected via questionnaires and clinics was obtained from participants following the recommendations of the ALSPAC Ethics and Law Committee at the time.

2.2 Measures

Autistic traits

We used four measures of autistic traits, which were predictive of ASD in the ALSPAC cohort (Steer et al., 2010). These included social communication difficulties assessed with the Social Communication Disorder Checklist (SCDC) at age 7 years (Skuse et al., 2005), communicative coherence assessed with a subscale of the Children's Communication Checklist at age 9 years (Bishop, 1998), sociability assessed with a subscale of the Emotionality, Activity and Sociability Temperament Scale at age 3 years (Buss & Plomin, 2014), and repetitive behaviour assessed with measures obtained from the Development and Well-Being Assessment at age 5 years (Goodman et al., 2000). Participants who had scores within the approximately highest 10% on a measure were classified as being 'case positive' for the autistic trait (Guyatt et al., 2015).

Psychotic experiences

Positive psychotic experiences were assessed at ages 18 and 24 using the semi-structured Psychosis-Like Symptoms interview (PLIKSi), administered by trained psychologists and scored according to criteria predefined by the World Health Organization (1994). The PLIKSi consists of 12 core questions covering hallucinations, delusions, and thought interference. Participants were asked about experiences that had occurred since age 12 years. Psychotic experiences were considered present if, at ages 18 and/or 24 years, one or more of the experiences was rated by the interviewer as suspected or definitely present, and if this was not attributable to falling asleep or waking up, fever, or substance use. We additionally examined psychotic experiences that had been distressing and/or frequent, since these experiences appear to be more clinically-relevant and predictive of psychotic disorder (Sullivan et al., 2020).

In sensitivity analyses we excluded reports of tactile hallucinations, since we expected that these experiences might be difficult to distinguish from the heightened tactile perception often seen in autism (Robertson & Baron-Cohen, 2017).

Childhood trauma

The measures of childhood trauma and their associations with psychotic experiences have previously been described in detail elsewhere (Croft et al., 2019). In brief, we assessed childhood trauma in participants using questionnaires and interviews about domestic violence (presence of regular acts of physical violence taking place in the home), physical abuse (physical harm to the participant from caregivers or other adults), emotional abuse (emotional cruelty to the participant from caregivers or other adults), emotional neglect (caregivers not taking an interest in the participant's life), sexual abuse (adults or older children forcing the participant into sexual activity, including attempts to do so), and bullying victimization (regular name-calling, blackmail, or assault by peers).

We restricted our analyses to traumatic experiences between ages 5 and 11 to reduce the overlap with measures of autistic traits and psychotic experiences. Multiple assessments of trauma were completed by the participant and/or their caregivers when the participant was age 5 to 11 and retrospectively when the participant was age 22. The assessments when the participant was 22 years old were particularly used to supplement data on sexual abuse, which had mostly been based on parental report prior to this age. Each type of trauma was coded as present or not, and a single trauma variable was created representing exposure to any type of trauma (Croft et al., 2019).

Covariates

We adjusted for covariates that were previously shown to be associated with autistic traits, traumatic events, and/or psychotic experiences, as well as attrition in the ALSPAC cohort (Fraser et al., 2013; Maclean et al., 2017; Rai et al., 2018). These included child sex (male/female), parity (≤ 1 child versus ≥ 2 children), major financial problems in the family (yes/no), maternal highest educational attainment, maternal age (at delivery), maternal Crown-Crisp anxiety scores (Crown & Crisp, 1966) (18 weeks gestation), maternal depression measured with the Edinburgh Postnatal Depression Scale (Cox et al., 1987) (EPDS; 18 weeks gestation scores ≥ 13), and child IQ scores at age 8 assessed with the Wechsler Intelligence Scale for Children third edition (Wechsler et al., 1992) (WISC-III).

Polygenic risk scores

For each genotyped ALSPAC child, we calculated PRS for schizophrenia using the results of the Schizophrenia Working Group of the Psychiatric Genomics Consortium schizophrenia GWAS (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014) as our discovery sample. PRS were based on single nucleotide polymorphisms associated with schizophrenia diagnosis. In our analyses adjusting for SCZ PRS, we used scores corresponding to a 0.05 p -value threshold, as it has been found to optimally capture schizophrenia liability across different samples.

We additionally calculated PRS for ASD for each genotypes ALSPAC child using results of the ASD GWAS (Grove et al., 2019), and explored its association with autism and psychosis variables. PRS were based on single nucleotide polymorphisms associated with ASD diagnosis at 13 p -value thresholds (0.5 to 5×10^{-08}). In supplementary analyses, we examined association between ASD PRS and autism and psychosis variables across these different thresholds.

2.3 Statistical analyses

Statistical analyses were conducted in STATA/MP version 15. We compared individuals with and without autistic traits on covariate data, traumatic experiences, and psychotic experiences using Pearson χ^2 -test and independent-samples *t*-tests. We conducted logistic regression analyses to examine associations between autistic traits and psychotic experiences, with and without adjusting for covariates or schizophrenia PRS.

Mediation analysis were performed using the g-formula package in STATA (Daniel et al., 2011). We used the parametric g-formula using Monte Carlo simulations to estimate the natural direct effect (NDE) of autistic traits on psychotic experiences, and the natural indirect effect (NIE) that was mediated via traumatic experiences between ages 5 to 11. An interaction between autistic traits and trauma was not included in the mediation models. We performed unadjusted as well as adjusted models for covariates or schizophrenia PRS. A schematic depiction of the mediation analyses is provided in Figure 1. We estimated log odds ratios (logOR), which we exponentiated to derive odds ratios (OR). Corresponding 95% confidence intervals (CIs) were estimated using the standard errors from 1000 non-parametric bootstrap resamples. The proportion mediated was calculated as: $[(OR_{NDE} * (OR_{NIE} - 1)) / (OR_{NDE} * OR_{NIE} - 1)] * 100$ (VanderWeele & Vansteelandt, 2010).

Figure 1
Schematic depiction of the mediation analyses.

Table 1
Characteristics of individuals with and without autistic traits.¹

Variable	Social communication difficulties (<i>n</i> = 5107)			Repetitive behaviour (<i>n</i> = 5128)			Sociability (<i>n</i> = 5435)			Coherence (<i>n</i> = 5087)		
	No	Yes	<i>p</i> -value ²	No	Yes	<i>p</i> -value ²	No	Yes	<i>p</i> -value ²	No	Yes	<i>p</i> -value ²
No. (%)	4646 (90.97)	461 (9.03)	N/A	4815 (93.90)	313 (6.10)	N/A	4835 (88.96)	600 (11.04)	N/A	4637 (91.15)	450 (8.85)	N/A
Male sex, No. (%)	2258 (48.60)	298 (64.64)	<0.001	2378 (49.39)	194 (61.98)	<0.001	2380 (49.22)	354 (59.00)	<0.001	2251 (48.54)	284 (63.11)	<0.001
Parity (≤1 child), No. (%)	3889 (83.71)	367 (79.61)	0.02	4012 (83.32)	259 (82.75)	0.79	4025 (83.25)	491 (81.83)	0.38	3874 (83.55)	369 (82.00)	0.40
Maternal educational attainment (university degree), No. (%)	575 (12.38)	91 (19.74)	<0.001	837 (17.38)	59 (18.85)	0.51	835 (17.27)	91 (15.17)	0.20	826 (17.81)	75 (16.67)	0.54
Major financial problems (present), No. (%)	550 (12.18)	88 (19.78)	<0.001	614 (12.75)	48 (15.34)	0.19	642 (13.28)	79 (13.17)	0.94	591 (12.75)	63 (14.00)	0.45
Maternal depression during pregnancy (EPDS ≥= 12), No. (%)	590 (12.70)	102 (22.13)	<0.001	628 (13.04)	60 (19.17)	0.002	649 (13.42)	88 (14.67)	0.40	604 (13.03)	90 (20.00)	<0.001
Mother's age at delivery, mean (SD)	29.55 (4.39)	29.21 (4.58)	0.11	29.52 (4.38)	29.38 (4.50)	0.60	29.43 (4.43)	29.24 (4.28)	0.33	29.51 (4.41)	29.53 (4.35)	0.92
Maternal anxiety during pregnancy, mean (SD)	4.48 (3.28)	5.40 (3.68)	<0.001	4.50 (3.33)	5.71 (3.37)	<0.001	4.55 (3.34)	4.57 (3.36)	0.92	4.51 (3.32)	5.17 (3.56)	<0.001
Total IQ score (WISC-III), mean (SD)	106.18 (15.87)	99.57 (19.08)	<0.001	105.70 (16.19)	101.83 (18.37)	<0.001	105.23 (16.48)	103.43 (15.82)	0.01	106.51 (15.84)	96.09 (17.93)	<0.001

SD, standard deviation; EPDS, Edinburgh Postnatal Depression Scale; IQ, Intelligence Quotient; WISC-III, Wechsler Intelligence Scale for Children third edition.
¹ Characteristics are shown for observations with complete data on exposure and covariates.
² The *p*-values for No. (%) and mean (SD) are based on Pearson χ^2 test and independent-samples *t*-test, respectively.

3. Results

3.1 Sample characteristics

Table 1 shows the characteristics of the samples with and without autistic traits. The maximum available sample size was 3537 in the analyses examining the relationship between autistic traits and psychotic experiences, and 3327 in the mediation analyses.

ASD PRS were associated with an ASD diagnosis and social communication difficulties at multiple p -value thresholds and inconsistently associated with sociability (see Supplement 1). We found no strong associations between ASD PRS and repetitive behaviour, coherence, or psychotic experiences (see Supplements 1 and 2).

3.2 Autistic traits and psychotic experiences

Social communication difficulties were associated with psychotic experiences, and in particular with those that were distressing and/or frequent (see Table 2). These associations remained of similar magnitude after we adjusted for covariates, although the 95% CIs crossed one. Adjusting for schizophrenia PRS and/or restricting to psychotic experiences without tactile hallucinations had little influence on the outcomes (see Supplements 3 and 4).

We found less or inconsistent evidence to suggest an association between repetitive behaviour, coherence, and sociability with any psychotic experiences measure (although the point estimates for coherence and sociability were raised). Therefore, we continued the mediation analyses with social communication difficulties only.

Table 2
Psychotic experiences in individuals with and without childhood autistic traits.¹

Exposure	No.	Psychotic experiences at age 18/24				Psychotic experiences at age 18/24, distressing and/or frequent			
		Unadjusted		Adjusted ²		Unadjusted		Adjusted ²	
		OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Social communication difficulties	3385	1.43 (1.01–2.02)	0.04	1.33 (0.93–1.90)	0.11	1.60 (1.02–2.52)	0.04	1.54 (0.97–2.45)	0.07
Repetitive behaviour	3398	0.98 (0.63–1.53)	0.93	0.94 (0.59–1.47)	0.77	1.17 (0.65–2.09)	0.60	1.14 (0.64–2.06)	0.65
Sociability	3537	1.27 (0.94–1.72)	0.12	1.27 (0.93–1.72)	0.13	1.31 (0.87–1.98)	0.20	1.33 (0.88–2.02)	0.18
Coherence	3410	1.08 (0.75–1.54)	0.69	1.00 (0.69–1.45)	0.99	1.45 (0.92–2.28)	0.11	1.37 (0.85–2.19)	0.19

OR, odds ratio; CI, confidence interval.

¹ Estimates based on observations with complete data on exposure, outcome, and covariates.

² Adjusted for the following covariates: child sex, parity, major financial problems, maternal highest educational attainment, maternal anxiety, maternal depression, and child IQ.

3.3 Mediation analysis with social communication difficulties

The results of the mediation analyses are shown in Table 3. There was strong evidence of an association between social communication difficulties and traumatic experiences at ages 5 to 11 (of note, we also found associations between traumatic experiences and repetitive behaviours and coherence, but not sociability; see Supplement 5). In the adjusted analysis, we found that 39.2% of the association between social communication difficulties and psychotic experiences, and 35.0% of its association with distressing and/or frequent psychotic experiences, was mediated by traumatic experiences. After adjusting for traumatic experiences, there was no evidence of a direct effect between social communication difficulties and psychotic experiences.

Results of the mediation analyses were comparable when we adjusted for schizophrenia PRS (see Supplement 3) or examined psychotic experiences but excluded tactile hallucinations (see Supplement 4).

Table 3

Results of the mediation analyses for the relationship between childhood social communication difficulties and psychotic experience (n = 3327).¹

Estimate	Unadjusted		Adjusted ²	
	OR (95% CI)	p	OR (95% CI)	p
<i>Outcome: psychotic experiences at ages 18/24</i>				
Natural direct effect	1.27 (0.89–1.81)	0.19	1.22 (0.85–1.74)	0.28
Natural indirect effect	1.15 (1.08–1.22)	<0.001	1.11 (1.05–1.18)	<0.001
Total effect	1.45 (1.02–2.08)	0.04	1.36 (0.95–1.94)	0.09
Proportion mediated	41.2%		39.2%	
<i>Outcome: psychotic experiences at ages 18/24, distressing and/or frequent</i>				
Natural direct effect	1.38 (0.86–2.21)	0.18	1.37 (0.85–2.20)	0.19
Natural indirect effect	1.18 (1.08–1.28)	<0.001	1.15 (1.06–1.24)	<0.001
Total effect	1.62 (1.01–2.59)	0.04	1.57 (0.98–2.50)	0.06
Proportion mediated	39.1%		35.0%	

OR, odds ratio; CI, confidence interval.

¹ Estimates based on observations with complete data on exposure, mediator, outcome, and covariates.

² Adjusted for the following covariates: child sex, parity, major financial problems, maternal highest educational attainment, maternal anxiety, maternal depression, and child IQ.

4. Discussion

In this longitudinal population-based birth cohort study, we examined the association between autistic traits and psychotic experiences, and the influence of childhood trauma thereon. We found that social communication difficulties at age 7 years were associated with psychotic experiences at ages 18 and 24 years, but observed less evidence for associations with measures of repetitive behaviour, coherence, or sociability. The relationship between social communication difficulties and psychotic experiences was substantially mediated by traumatic experiences in early childhood, and not strongly influenced by confounding variables or schizophrenia PRS.

Our longitudinal study is the first to show a relationship between childhood autistic traits and psychotic experiences up to age 24 years, and thereby extends previous reports that utilized the same ALSPAC cohort. Although the association between ASD and psychotic disorder has not been examined in ALSPAC, two studies found that psychotic experiences at age 12 years were more common in children with ASD or autistic traits (Bevan-Jones et al., 2012; Sullivan et al., 2013). In other cohorts, there have also been partially contrasting findings. One study found only weak associations between autistic traits assessed between ages 8–16 years and psychotic experiences at age 16 years (Taylor et al., 2015), whereas another similarly reported weak correlations between autistic traits at ages 9 or 12 years and psychotic experiences at ages 15 or 18 years (Cederlöf et al., 2016). Importantly, the studies conducted thus far have used varying operationalizations and measures of subclinical autistic traits and psychotic experiences, which could account for some of these discrepant results. For example, we found strongest evidence for an association between social communication difficulties and psychotic experiences, whereas this class of autistic traits was omitted or combined with other traits in previous work (Taylor et al., 2015).

Our results showed no or inconsistent evidence for relationships between measures of repetitive behaviours, sociability, or coherence and psychotic experiences. In contrast, previous studies of the ALSPAC cohort did observe associations between measures of repetitive behaviours and coherence with psychotic experiences at age 12 (Sullivan et al., 2013). To some extent, the negative findings in our main analyses might be the result of a low statistical power. Another possibility is that children with social communication difficulties are especially prone to developing psychotic experiences, for instance because they encounter more problems in social relationships than individuals exhibiting repetitive behaviours.

Among children with social communication difficulties, point estimates for the occurrence of distressing and/or frequent psychotic experiences were particularly high. Notably, three previous studies have also shown that individuals with ASD reported more distress when experiencing psychotic symptoms than non-autistic peers (Milne et al., 2017; Jutla et al., 2020; van der Linden et al., 2020). These distressing and/or frequent psychotic experiences appear to be most strongly related to negative mental health consequences, such as the development of psychotic disorder (Sullivan et al., 2020). Still, thus far there has been surprisingly little work examining how these psychotic experiences can be best identified and addressed in individuals with autistic traits, and more work is necessary in this respect.

We found that experiences of interpersonal trauma in childhood mediated a substantial proportion of the relationship between social communication difficulties and psychotic experiences. This mediation effect was not strongly influenced by schizophrenia PRS. These findings are consistent with the idea that a shared genetic liability between autism and psychosis is not solely responsible for their association, but rather that this association is also influenced by environmental risk factors. The experience of trauma in childhood is a well-established risk factor for psychosis (Varese et al., 2012; Alameda et al., 2020). However, despite reports of elevated rates of trauma in individuals with ASD or autistic traits (Roberts et

al., 2015; McDonnell et al., 2019), studies of its mental health consequences are lacking (Hoover, 2015). Our findings indicate that trauma may be an important, potentially modifiable pathway between autistic features and later onset of psychotic experiences, and more work is necessary to examine how (the consequences of) trauma can best be prevented, identified, or treated in autistic individuals. Additionally, elucidating the mechanisms through which these traumatic experiences lead to psychosis, building on work in non-autistic populations (Selten et al., 2013; Alameda et al., 2020; Bloomfield et al., 2021), can be an important avenue for future research.

Strengths of our study include its longitudinal design and long-term follow-up in a representative, population-based cohort. A limitation of the study is that the measures of autistic traits partially overlapped with the age at exposure to trauma. To some extent, early traumatic experiences might have exacerbated autistic traits such as difficulties in social communication. However, social communication difficulties were associated with an ASD diagnosis and ASD PRS in the ALSPAC cohort (Steer et al., 2010; Rai et al., 2018), indicating that they are unlikely to be the sole result of trauma. A second limitation is that 95% CIs in some analyses crossed one and that estimates of effects became statistically non-significant, in particular if we would have taken into account multiple testing. We expect that this is mainly the result of a lower statistical power, as a relatively small sample had complete data on all measures of interest. Moreover, even if 95% CIs were wide, point estimates of the effects remained increased, and multiple imputation of missing data resulted in narrower CIs (data not shown). Nevertheless, replication studies are necessary to confirm our findings.

In conclusion, social communication difficulties in childhood are associated with psychotic experiences until young adulthood. This association is substantially mediated by experiences of childhood trauma, and not the result of an overlap with schizophrenia genetic liability. Childhood trauma constitutes a potentially modifiable environmental risk factor for psychosis in autistic individuals that warrants further attention in research and clinical practice.

5. References

- Alameda, L., Rodriguez, V., Carr, E., Aas, M., Trotta, G., Marino, P., Vorontsova, N., Herane-Vives, A., Gadelrab, R., & Spinazzola, E. (2020). A systematic review on mediators between adversity and psychosis: potential targets for treatment. *Psychological Medicine*, 50(12), 1966-1976.
- Bevan-Jones, R., Thapar, A., Lewis, G., & Zammit, S. (2012). The association between early autistic traits and psychotic experiences in adolescence. *Schizophrenia Research*, 135(1-3), 164-169.
- Bishop, D. V. (1998). Development of the Children's Communication Checklist (CCC): A method for assessing qualitative aspects of communicative impairment in children. *The Journal of Child Psychology and Psychiatry and Allied Disciplines*, 39(6), 879-891.
- Bloomfield, M. A., Chang, T., Woodl, M. J., Lyons, L. M., Cheng, Z., Bauer-Staeb, C., Hobbs, C., Bracke, S., Kennerley, H., & Isham, L. (2021). Psychological processes mediating the association between developmental trauma and specific psychotic symptoms in adults: a systematic review and meta-analysis. *World Psychiatry*, 20(1), 107-123.
- Boyd, A., Golding, J., Macleod, J., Lawlor, D. A., Fraser, A., Henderson, J., Molloy, L., Ness, A., Ring, S., & Davey Smith, G. (2013). Cohort profile: the 'children of the 90s'—the index offspring of the Avon Longitudinal Study of Parents and Children. *International Journal of Epidemiology*, 42(1), 111-127.
- Buss, A. H., & Plomin, R. (2014). *Temperament (PLE: Emotion): Early developing personality traits*. Psychology Press.
- Cederlöf, M., Pettersson, E., Sariaslan, A., Larsson, H., Östberg, P., Kelleher, I., Långström, N., Gumpert, C. H., Lundström, S., & Lichtenstein, P. (2016). The association between childhood autistic traits and adolescent psychotic experiences is explained by general neuropsychiatric problems. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, 171(2), 153-159.
- Chisholm, K., Lin, A., Abu-Akel, A., & Wood, S. J. (2015). The association between autism and schizophrenia spectrum disorders: A review of eight alternate models of co-occurrence. *Neuroscience & Biobehavioral Reviews*, 55, 173-183.
- Cox, J., Holden, J., & Sagovsky, R. (1987). Edinburgh postnatal depression scale (EPDS). *The British Journal of Psychiatry*, 150, 782-786.
- Croft, J., Heron, J., Teufel, C., Cannon, M., Wolke, D., Thompson, A., Houtepen, L., & Zammit, S. (2019). Association of trauma type, age of exposure, and frequency in childhood and adolescence with psychotic experiences in early adulthood. *JAMA Psychiatry*, 76(1), 79-86.
- Cross-Disorder Group of the Psychiatric Genomics Consortium (2019). Genomic relationships, novel loci, and pleiotropic mechanisms across eight psychiatric disorders. *Cell*, 179(7), 1469-1482.
- Crown, S., & Crisp, A. (1966). A short clinical diagnostic self-rating scale for psychoneurotic patients: The Middlesex Hospital Questionnaire (MHQ). *The British Journal of Psychiatry*, 112(490), 917-923.
- Daniel, R. M., De Stavola, B. L., & Cousens, S. N. (2011). gformula: Estimating causal effects in the presence of time-varying confounding or mediation using the g-computation formula. *The Stata Journal*, 11(4), 479-517.
- Demirkaya, S. K., Tutkunkardaş, M. D., & Mukaddes, N. M. (2016). Assessment of suicidality in children and adolescents with diagnosis of high functioning autism spectrum disorder in a Turkish clinical sample. *Neuropsychiatric Disease and Treatment*, 12, 2921-2926.
- Foss-Feig, J. H., Velthorst, E., Smith, L., Reichenberg, A., Addington, J., Cadenhead, K. S., Cornblatt, B. A., Matalon, D. H., McGlashan, T. H., & Perkins, D. O. (2019). Clinical profiles and conversion

- rates among young individuals with autism spectrum disorder who present to clinical high risk for psychosis services. *Journal of the American Academy of Child & Adolescent Psychiatry*, 58(6), 582-588.
- Fraser, A., Macdonald-Wallis, C., Tilling, K., Boyd, A., Golding, J., Davey Smith, G., Henderson, J., Macleod, J., Molloy, L., & Ness, A. (2013). Cohort profile: the Avon Longitudinal Study of Parents and Children: ALSPAC mothers cohort. *International Journal of Epidemiology*, 42(1), 97-110.
- Gong, J.-B., Wang, Y., Lui, S. S., Cheung, E. F., & Chan, R. C. (2017). Childhood trauma is not a confounder of the overlap between autistic and schizotypal traits: A study in a non-clinical adult sample. *Psychiatry Research*, 257, 111-117.
- Goodman, R., Ford, T., Richards, H., Gatward, R., & Meltzer, H. (2000). The development and well-being assessment: Description and initial validation of an integrated assessment of child and adolescent psychopathology. *Journal of Child Psychology and Psychiatry*, 41(5), 645-655.
- Grove, J., Ripke, S., Als, T. D., Mattheisen, M., Walters, R. K., Won, H., Pallesen, J., Agerbo, E., Andreassen, O. A., & Anney, R. (2019). Identification of common genetic risk variants for autism spectrum disorder. *Nature Genetics*, 51(3), 431-444.
- Guyatt, A. L., Heron, J., Knight, B. L. C., Golding, J., & Rai, D. (2015). Digit ratio and autism spectrum disorders in the Avon Longitudinal Study of Parents and Children: a birth cohort study. *BMJ Open*, 5(8), 1-8.
- Harris, P. A., Taylor, R., Minor, B. L., Elliott, V., Fernandez, M., O'Neal, L., McLeod, L., Delacqua, G., Delacqua, F., & Kirby, J. (2019). The REDCap consortium: Building an international community of software platform partners. *Journal of Biomedical Informatics*, 95, 103208.
- Harris, P. A., Taylor, R., Thielke, R., Payne, J., Gonzalez, N., & Conde, J. G. (2009). Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. *Journal of Biomedical Informatics*, 42(2), 377-381.
- Hoover, D. W. (2015). The effects of psychological trauma on children with autism spectrum disorders: a research review. *Review Journal of Autism and Developmental Disorders*, 2(3), 287-299.
- Humphrey, N., & Symes, W. (2010). Responses to bullying and use of social support among pupils with autism spectrum disorders (ASDs) in mainstream schools: A qualitative study. *Journal of Research in Special Educational Needs*, 10(2), 82-90.
- Jutla, A., Donohue, M. R., Veenstra-VanderWeele, J., & Foss-Feig, J. H. (2020). Reported autism diagnosis strongly predicts psychotic-like experiences in the Adolescent Brain Cognitive Development cohort. *medRxiv*, 2020.2002.2007.20021170.
- Kerns, C. M., Newschaffer, C. J., & Berkowitz, S. J. (2015). Traumatic childhood events and autism spectrum disorder. *Journal of Autism and Developmental Disorders*, 45(11), 3475-3486.
- Lai, M.-C., Kassee, C., Besney, R., Bonato, S., Hull, L., Mandy, W., Szatmari, P., & Ameis, S. H. (2019). Prevalence of co-occurring mental health diagnoses in the autism population: a systematic review and meta-analysis. *The Lancet Psychiatry*, 6(10), 819-829.
- Legge, S. E., Jones, H. J., Kendall, K. M., Pardiñas, A. F., Menzies, G., Bracher-Smith, M., Escott-Price, V., Rees, E., Davis, K. A., & Hotopf, M. (2019). Association of genetic liability to psychotic experiences with neuropsychotic disorders and traits. *JAMA Psychiatry*, 76(12), 1256-1265.
- Maclean, M. J., Sims, S., Bower, C., Leonard, H., Stanley, F. J., & O'Donnell, M. (2017). Maltreatment risk among children with disabilities. *Pediatrics*, 139(4), e20161817.

- Martinez, A. P., Wickham, S., Rowse, G., Milne, E., & Bentall, R. P. (2020). Robust association between autistic traits and psychotic-like experiences in the adult general population: epidemiological study from the 2007 Adult Psychiatric Morbidity Survey and replication with the 2014 APMS. *Psychological Medicine*, online ahead of print, 1-7.
- McDonnell, C. G., Boan, A. D., Bradley, C. C., Seay, K. D., Charles, J. M., & Carpenter, L. A. (2019). Child maltreatment in autism spectrum disorder and intellectual disability: results from a population-based sample. *Journal of Child Psychology and Psychiatry*, 60(5), 576-584.
- Milne, E., Dickinson, A., & Smith, R. (2017). Adults with autism spectrum conditions experience increased levels of anomalous perception. *PLoS ONE*, 12(5), e0177804.
- Muhle, R. A., Reed, H. E., Stratigos, K. A., & Veenstra-VanderWeele, J. (2018). The emerging clinical neuroscience of autism spectrum disorder: a review. *JAMA Psychiatry*, 75(5), 514-523.
- Novin, S., Broekhof, E., & Rieffe, C. (2019). Bidirectional relationships between bullying, victimization and emotion experience in boys with and without autism. *Autism*, 23(3), 796-800.
- Rai, D., Culpin, I., Heuvelman, H., Magnusson, C. M., Carpenter, P., Jones, H. J., Emond, A. M., Zammit, S., Golding, J., & Pearson, R. M. (2018). Association of autistic traits with depression from childhood to age 18 years. *JAMA Psychiatry*, 75(8), 835-843.
- Roberts, A. L., Koenen, K. C., Lyall, K., Robinson, E. B., & Weisskopf, M. G. (2015). Association of autistic traits in adulthood with childhood abuse, interpersonal victimization, and posttraumatic stress. *Child Abuse & Neglect*, 45, 135-142.
- Robertson, C. E., & Baron-Cohen, S. (2017). Sensory perception in autism. *Nature Reviews Neuroscience*, 18(11), 671-684.
- Schizophrenia Working Group of the Psychiatric Genomics Consortium (2014). Biological insights from 108 schizophrenia-associated genetic loci. *Nature*, 511(7510), 421-427.
- Schroeder, J. H., Cappadocia, M. C., Bebko, J. M., Pepler, D. J., & Weiss, J. A. (2014). Shedding light on a pervasive problem: A review of research on bullying experiences among children with autism spectrum disorders. *Journal of Autism and Developmental Disorders*, 44(7), 1520-1534.
- Selten, J.-P., van der Ven, E., Rutten, B. P., & Cantor-Graae, E. (2013). The social defeat hypothesis of schizophrenia: an update. *Schizophrenia Bulletin*, 39(6), 1180-1186.
- Sevlever, M., Roth, M. E., & Gillis, J. M. (2013). Sexual abuse and offending in autism spectrum disorders. *Sexuality and Disability*, 31(2), 189-200.
- Skuse, D. H., Mandy, W. P., & Scourfield, J. (2005). Measuring autistic traits: heritability, reliability and validity of the Social and Communication Disorders Checklist. *The British Journal of Psychiatry*, 187(6), 568-572.
- Steer, C. D., Golding, J., & Bolton, P. F. (2010). Traits contributing to the autistic spectrum. *PLoS ONE*, 5(9), e12633.
- Sullivan, S., Rai, D., Golding, J., Zammit, S., & Steer, C. (2013). The association between autism spectrum disorder and psychotic experiences in the Avon longitudinal study of parents and children (ALSPAC) birth cohort. *Journal of the American Academy of Child & Adolescent Psychiatry*, 52(8), 806-814.
- Sullivan, S. A., Kounali, D., Cannon, M., David, A. S., Fletcher, P. C., Holmans, P., Jones, H., Jones, P. B., Linden, D. E., & Lewis, G. (2020). A population-based cohort study examining the incidence and impact of psychotic experiences from childhood to adulthood, and prediction of psychotic disorder. *American Journal of Psychiatry*, 177(4), 308-317.

- Taylor, M. J., Robinson, E. B., Happé, F., Bolton, P., Freeman, D., & Ronald, A. (2015). A longitudinal twin study of the association between childhood autistic traits and psychotic experiences in adolescence. *Molecular Autism*, 6(1), 1-11.
- van der Linden, K., Simons, C., van Amelsvoort, T., & Marcelis, M. (2020). Lifetime and momentary psychotic experiences in adult males and females with an autism spectrum disorder. *Frontiers in Psychiatry*, 11, 1-11.
- VanderWeele, T. J., & Vansteelandt, S. (2010). Odds ratios for mediation analysis for a dichotomous outcome. *American Journal of Epidemiology*, 172(12), 1339-1348.
- Varese, F., Smeets, F., Drukker, M., Lieveise, R., Lataster, T., Viechtbauer, W., Read, J., van Os, J., & Bentall, R. P. (2012). Childhood adversities increase the risk of psychosis: a meta-analysis of patient-control, prospective-and cross-sectional cohort studies. *Schizophrenia Bulletin*, 38(4), 661-671.
- Warrier, V., & Baron-Cohen, S. (2019). Childhood trauma, life-time self-harm, and suicidal behaviour and ideation are associated with polygenic scores for autism. *Molecular Psychiatry*, 1-15.
- Wechsler, D., Golombok, S., & Rust, J. (1992). *Wechsler Intelligence Scale for Children (WISC-III UK)*. The Psychological Corporation.
- World Health Organization (1994). *Schedules for Clinical Assessment in Neuropsychiatry*. American Psychiatric Press.
- Zhou, H.-Y., Yang, H.-X., Gong, J.-B., Cheung, E. F., Gooding, D. C., Park, S., & Chan, R. C. (2019). Revisiting the overlap between autistic and schizotypal traits in the non-clinical population using meta-analysis and network analysis. *Schizophrenia Research*, 212, 6-14.

Appendix to chapter III

Supplementary information

Supplement 1: Associations between polygenic risk scores (PRS) for autism spectrum disorder (ASD) and measures of autistic traits.

Supplementary Figure 1.1

Association between ASD PRS and ASD diagnosis (sample $n = 7509$; ASD diagnosis $n = 80$).

Supplementary Figure 1.2

Association between ASD PRS and measures of social communication difficulties (sample $n = 5444$; social communication difficulties $n = 519$).

Supplementary Figure 1.3

Association between ASD PRS and measures of repetitive behaviour (sample $n = 5550$; repetitive behaviours $n = 381$).

Supplementary Figure 1.4

Association between ASD PRS and measures of sociability (sample $n = 6170$; sociability $n = 714$).

Supplementary Figure 1.5

Association between ASD PRS and measures of coherence (sample $n = 5563$; coherence $n = 551$).

Supplement 2: Associations between polygenic risk scores (PRS) for autism spectrum disorder (ASD) and psychotic experiences.

Supplementary Figure 2.1
Association between ASD PRS and psychotic experiences (sample n = 4015; psychotic experiences n = 511).

Supplementary Figure 2.2
Association between ASD PRS and distressing and/or frequent psychotic experiences (sample n = 4015; psychotic experiences n = 258).

Supplementary Figure 2.3

Association between ASD PRS and psychotic experiences, excluding tactile hallucinations (sample n = 4015; psychotic experiences n = 465).

Supplementary Figure 2.4

Association between ASD PRS and distressing and/or frequent psychotic experiences, excluding tactile hallucinations (sample n = 4015; psychotic experiences n = 245).

Supplement 3: Association between autistic traits and psychotic experiences, adjusted for schizophrenia polygenic risk scores.**Supplementary Table 3.1***Associations between autistic traits and psychotic experiences, adjusted for schizophrenia polygenic risk scores.¹*

Exposure	No.	Including tactile hallucinations						Excluding tactile hallucinations					
		Psychotic experiences at age 18/24			Psychotic experiences at age 18/24, distressing and/or frequent			Psychotic experiences at age 18/24			Psychotic experiences at age 18/24, distressing and/or frequent		
		Unadjusted	Adjusted ²	Adjusted ²	Unadjusted	Adjusted ²	Adjusted ²	Unadjusted	Adjusted ²	Adjusted ²	Unadjusted	Adjusted ²	Adjusted ²
		OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Social communication difficulties	3299	1.47 (1.04–2.08)	0.03	1.47 (1.04–2.08)	0.03	1.68 (1.07–2.62)	0.02	1.45 (1.01–2.08)	0.05	1.45 (1.01–2.09)	0.05	1.59 (1.00–2.53)	0.05
		0.80 (0.50–1.29)	0.37	0.81 (0.50–1.29)	0.37	1.00 (0.55–1.82)	0.98	0.85 (0.52–1.39)	0.52	0.86 (0.53–1.39)	0.53	0.96 (0.51–1.79)	0.91
Repetitive behaviour	3293	1.13 (0.83–1.54)	0.45	1.13 (0.83–1.54)	0.45	1.18 (0.78–1.79)	0.44	1.09 (0.79–1.51)	0.60	1.09 (0.79–1.51)	0.60	1.03 (0.66–1.61)	0.90
		0.80 (0.50–1.29)	0.37	0.81 (0.50–1.29)	0.37	1.00 (0.55–1.82)	0.98	0.85 (0.52–1.39)	0.52	0.86 (0.53–1.39)	0.53	0.96 (0.51–1.79)	0.91
Sociability	3493	1.13 (0.83–1.54)	0.45	1.13 (0.83–1.54)	0.45	1.18 (0.78–1.79)	0.44	1.09 (0.79–1.51)	0.60	1.09 (0.79–1.51)	0.60	1.03 (0.66–1.61)	0.90
		0.80 (0.50–1.29)	0.37	0.81 (0.50–1.29)	0.37	1.00 (0.55–1.82)	0.98	0.85 (0.52–1.39)	0.52	0.86 (0.53–1.39)	0.53	0.96 (0.51–1.79)	0.91
Coherence	3444	1.12 (0.79–1.59)	0.51	1.12 (0.79–1.59)	0.51	1.43 (0.92–2.21)	0.11	1.23 (0.87–1.75)	0.24	1.24 (0.87–1.76)	0.24	1.52 (0.98–2.35)	0.06
		0.79 (0.50–1.29)	0.37	0.81 (0.50–1.29)	0.37	1.00 (0.55–1.82)	0.98	0.85 (0.52–1.39)	0.52	0.86 (0.53–1.39)	0.53	0.96 (0.51–1.79)	0.91

OR, odds ratio; CI, confidence interval.

¹ Estimates based on observations with complete data on exposure, outcome, and schizophrenia polygenic risk scores.² Adjusted for schizophrenia polygenic risk scores.

Supplementary Table 3.2

Mediation analyses examining the relationships between childhood social communication difficulties and psychotic experiences, adjusted for schizophrenia polygenic risk scores (n = 3195).¹

Estimate	Unadjusted		Adjusted for schizophrenia PRS	
	OR (95% CI)	p	OR (95% CI)	p
<i>Outcome: psychotic experiences at ages 18/24</i>				
Natural direct effect	1.28 (0.90–1.82)	0.16	1.28 (0.90–1.82)	0.16
Natural indirect effect	1.14 (1.08–1.21)	<0.001	1.14 (1.08–1.21)	<0.001
Total effect	1.46 (1.03–2.08)	0.04	1.46 (1.03–2.08)	0.03
Proportion mediated	39.2%		39.0%	
<i>Outcome: psychotic experiences at ages 18/24, distressing and/or frequent</i>				
Natural direct effect	1.40 (0.88–2.25)	0.16	1.42 (0.89–2.27)	0.15
Natural indirect effect	1.16 (1.08–1.25)	<0.001	1.16 (1.08–1.25)	<0.001
Total effect	1.63 (1.02–2.62)	0.04	1.65 (1.03–2.64)	0.04
Proportion mediated	36.1%		35.7%	
<i>Outcome: psychotic experiences at ages 18/24, excluding tactile hallucinations</i>				
Natural direct effect	1.24 (0.86–1.80)	0.24	1.25 (0.87–1.80)	0.23
Natural indirect effect	1.15 (1.08–1.22)	<0.001	1.15 (1.08–1.22)	<0.001
Total effect	1.43 (0.99–2.08)	0.06	1.44 (0.99–2.09)	0.06
Proportion mediated	43.3%		42.8%	
<i>Outcome: psychotic experiences at ages 18/24, distressing and/or frequent, excluding tactile hallucinations</i>				
Natural direct effect	1.33 (0.82–2.17)	0.25	1.34 (0.82–2.19)	0.24
Natural indirect effect	1.16 (1.08–1.25)	<0.001	1.16 (1.08–1.25)	<0.001
Total effect	1.55 (0.94–2.53)	0.08	1.56 (0.95–2.56)	0.08
Proportion mediated	39.6%		39.0%	

PRS, polygenic risk scores; OR, odds ratio; CI, confidence interval.

¹ Estimates based on observations with complete data on exposure, mediator, outcome, and schizophrenia polygenic risk scores.

Supplement 4: Association between autistic traits and psychotic experiences, excluding tactile hallucinations

Supplementary Table 4.1

Psychotic experiences in individuals with and without childhood autistic traits.¹

Exposure	No.	Psychotic experiences at age 18/24, excluding tactile hallucinations				Psychotic experiences at age 18/24, distressing and/or frequent, excluding tactile hallucinations			
		Unadjusted		Adjusted for covariates ²		Unadjusted		Adjusted for covariates ²	
		OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Social communication difficulties	3385	1.48 (1.04–2.11)	0.03	1.36 (0.94–1.95)	0.10	1.69 (1.07–2.67)	0.02	1.61 (1.01–2.56)	0.05
Repetitive behaviour	3398	0.97 (0.61–1.55)	0.91	0.92 (0.57–1.47)	0.72	1.13 (0.62–2.06)	0.70	1.09 (0.59–2.01)	0.78
Sociability	3537	1.25 (0.91–1.71)	0.16	1.24 (0.90–1.71)	0.18	1.20 (0.78–1.86)	0.40	1.22 (0.79–1.88)	0.38
Coherence	3410	1.15 (0.8–1.66)	0.46	1.04 (0.71–1.52)	0.84	1.54 (0.98–2.42)	0.06	1.43 (0.89–2.29)	0.14

OR, odds ratio; CI, confidence interval.

¹ Estimates based on observations with complete data on exposure, outcome, and covariates.

² Adjusted for the following covariates: child sex, parity, major financial problems, maternal highest educational attainment, maternal anxiety, maternal depression, and child IQ.

Supplementary Table 4.2

Results of the mediation analyses for the relationship between childhood social communication difficulties and psychotic experiences, excluding tactile hallucinations (n = 3327).¹

Estimate	Unadjusted		Adjusted for covariates ²	
	OR (95% CI)	p	OR (95% CI)	p
<i>Outcome: psychotic experiences at ages 18/24, excluding tactile hallucinations</i>				
Natural direct effect	1.32 (0.92–1.91)	0.14	1.25 (0.87-1.80)	0.24
Natural indirect effect	1.14 (1.07–1.22)	<0.001	1.11 (1.04-1.17)	0.001
Total effect	1.51 (1.05–2.17)	0.03	1.38 (0.96-1.98)	0.08
Proportion mediated	36.4%		34.8%	
<i>Outcome: psychotic experiences at ages 18/24, distressing and/or frequent, excluding tactile hallucinations</i>				
Natural direct effect	1.45 (0.90–2.34)	0.12	1.43 (0.89-2.30)	0.14
Natural indirect effect	1.18 (1.08–1.29)	<0.001	1.15 (1.06-1.24)	<0.001
Total effect	1.72 (1.07–2.75)	0.02	1.64 (1.03-2.62)	0.04
Proportion mediated	36.6%		33.0%	

OR, odds ratio; CI, confidence interval.

¹ Estimates based on observations with complete data on exposure, mediator, outcome, and covariates.

² Adjusted for the following covariates: child sex, parity, major financial problems, maternal highest educational attainment, maternal anxiety, maternal depression, and child IQ.

Supplement 5: Associations between autistic traits and childhood traumatic experiences

Supplementary Table 5.1
Associations between autistic traits and childhood trauma.¹

Exposure	Trauma between ages 5-11				
	Unadjusted			Adjusted for covariates ²	
	No.	OR (95% CI)	<i>p</i>	OR (95% CI)	<i>p</i>
Social communication difficulties	4960	2.54 (2.08–3.10)	<0.001	2.20 (1.79–2.70)	<0.001
Repetitive behaviour	5037	1.57 (1.25–1.98)	<0.001	1.35 (1.07–1.71)	0.01
Sociability	5211	0.97 (0.82–1.16)	0.76	0.93 (0.77–1.11)	0.41
Coherence	4947	1.83 (1.50–2.22)	<0.001	1.56 (1.28–1.92)	<0.001

OR, odds ratio; CI, confidence interval.
¹ Estimates based on observations with complete data on exposure, covariates, and childhood trauma.
² Adjusted for the following covariates: child sex, parity, major financial problems, maternal highest educational attainment, maternal anxiety, maternal depression, and child IQ.

A large, stylized graphic of the letters 'TV' in a bold, sans-serif font. The letters are filled with a complex collage of historical and cultural images. The 'T' features a ship on the left and a city street on the right. The 'V' is filled with a dense pattern of small, repeating images, possibly a crowd or a cityscape. The overall style is reminiscent of mid-20th-century graphic design.

Chapter IV

Striatal dopamine synthesis capacity in autism spectrum disorder and its relation with social defeat: an [^{18}F]-FDOPA PET/CT study

Schalbroeck, R., van Velden, F. H. P., de Geus-Oei, L. F., Yaqub, M., van
Amelsvoort, T., Booij, J., & Selten, J. P.
Translational Psychiatry (2021), 11(1), 1-10.

Abstract

Alterations in dopamine signalling have been implied in autism spectrum disorder (ASD), and these could be associated with the risk of developing a psychotic disorder in ASD adults. Negative social experiences and feelings of social defeat might result in an increase in dopamine functioning. However, few studies examined dopamine functioning *in vivo* in ASD. Here we examine whether striatal dopamine synthesis capacity is increased in ASD and associated with social defeat. Forty-four unmedicated, non-psychotic adults diagnosed with ASD and 22 matched controls, aged 18 to 30 years, completed a dynamic 3,4-dihydroxy-6- ^{18}F -fluoro-L-phenylalanine positron emission tomography/computed tomography (^{18}F)-FDOPA PET/CT) scan to measure presynaptic dopamine synthesis capacity in the striatum. We considered unwanted loneliness, ascertained using the UCLA Loneliness Scale, as primary measure of social defeat. We found no statistically significant difference in striatal dopamine synthesis capacity between ASD and controls ($F_{1,60} = 0.026, p = 0.87$). In ASD, striatal dopamine synthesis capacity was not significantly associated with loneliness ($\beta = 0.01, p = 0.96$). Secondary analyses showed comparable results when examining the associative, limbic, and sensorimotor sub-regions of the striatum (all p -values > 0.05). Results were similar before and after adjusting for age, sex, smoking-status, and PET/CT-scanner-type. In conclusion, in unmedicated, non-psychotic adults with ASD, striatal dopamine synthesis capacity is not increased and not associated with social defeat.

1. Introduction

Adults with autism spectrum disorder (ASD) are at an increased risk of developing a psychotic disorder (Lai et al., 2019). However, risk factors and neurobiological alterations associated with this risk remain poorly understood (Chisholm et al., 2015).

A well-replicated finding of neurotransmitter functioning in psychosis has been that of increased presynaptic dopamine functioning. *In vivo* molecular imaging studies using positron emission tomography (PET) or single-photon emission computed tomography (SPECT) have consistently shown that psychosis is strongly related to increased presynaptic dopamine synthesis capacity and endogenous dopamine release in the striatum (McCutcheon et al., 2018). This increase in presynaptic dopamine functioning has also been reported in individuals at-risk of psychotic disorder (Howes et al., 2009; Egerton et al., 2013) and in individuals with a non-psychotic disorder when psychotic symptoms are present (Jauhar et al., 2017).

Several researchers have suggested that alterations in dopamine functioning exist in ASD (Marotta et al., 2020). For instance, this has been implied in theoretical work (Pavā, 2017), gene studies (Staal et al., 2015), and studies examining dopamine-modulating medication (Oswald & Sonenklar, 2007; Buck et al., 2014). However, molecular imaging studies, in particular of presynaptic dopamine, are lacking (Zürcher et al., 2015). No studies examined striatal dopamine release, and only two studies used 3,4-dihydroxy-6- ^{18}F -fluoro-L-phenylalanine (^{18}F -FDOPA) PET to measure dopamine synthesis capacity. The first found no significant increase in striatal dopamine synthesis capacity in autistic children ($n = 14$) relative to non-autistic peers ($n = 10$), but most ($n = 11$) autistic children were sedated using propofol which can influence dopamine concentrations (Ernst et al., 1997; Pain et al., 2002). The second obtained evidence of increased striatal dopamine synthesis capacity in adults with Asperger syndrome ($n = 8$) relative to controls ($n = 5$), but the number of participants was small and the influence of possible risk factors was not examined (Nieminen-von Wendt et al., 2004).

Evidence indicates that psychosocial stress can influence dopamine functioning (Mizrahi, 2016). According to the social defeat hypothesis of schizophrenia, the long-term subjective experience of outsider status or subordinate position leads to increased baseline activity and/or sensitization of the brain dopamine system (Selten & Cantor-Graae, 2005; Selten et al., 2013; Selten et al., 2017). In line with this hypothesis, increased presynaptic dopamine functioning has been reported in non-psychotic groups presumed to be more socially defeated, such as immigrants, individuals with severe hearing impairment, and individuals with a history of childhood trauma (Gevonden et al., 2014; Oswald et al., 2014; Egerton et al., 2016; Egerton et al., 2017). Whether social defeat also increases presynaptic dopamine functioning in individuals with ASD, who are widely exposed to defeating experiences such as loneliness (Bauminger et al., 2003), bullying victimization (Sterzing et al., 2012; Schroeder et al., 2014), and discrimination (Johnson & Joshi, 2016), remains unknown.

Here we examine striatal presynaptic dopamine synthesis capacity, measured with ^{18}F -FDOPA PET/computed tomography (PET/CT), in non-psychotic adults with ASD and controls aged 18 to 30 years. We expect (hypothesis 1a) that striatal dopamine synthesis capacity is increased in ASD relative to controls. Furthermore, we expect (hypothesis 1b) that in ASD, striatal dopamine synthesis capacity is positively associated with loneliness, as an approximate measure of social defeat. As secondary outcomes, we expect (hypothesis 2a) that adults with ASD report more social defeat than controls, and (hypothesis 2b) that striatal dopamine synthesis capacity is positively related to other measures of social defeat (besides loneliness) and to subclinical psychotic symptoms. Finally, we expect (hypothesis 3) the strongest associations with dopamine synthesis capacity in the associative striatum (with reference to

hypotheses 1a-b and 2b), since the largest striatal dopaminergic disruptions in psychosis have been reported in this sub-region (McCutcheon et al., 2018).

2. Materials and Methods

2.1 Participants

ASD and control participants were Dutch adults aged 18-30 years, recruited via online social media and poster advertisements. Adults with ASD were also recruited at mental healthcare institutes, ASD housing services, university counselling services, and ASD-related websites. All of these adults had previously been diagnosed with an ASD by a registered mental health clinician, and the first author confirmed this diagnosis using the Autism Diagnostic Observation Schedule-2 (ADOS-2) module 4 (Lord et al., 2012; Hus & Lord, 2014). The ASD and control samples consisted of 45 and 24 participants, respectively, which were frequency-matched on age, sex, and smoking-status (yes/no).

Exclusion criteria (explained in detail in Supplement 1) included a lifetime diagnosis of psychotic or bipolar disorder assessed by self-report, psychotic symptoms indicative of psychotic disorder assessed with the Comprehensive Assessment of At-Risk Mental States (CAARMS; Yung et al., 2005; Ising et al., 2012), IQ lower than 85 assessed with the Dutch Adult Reading Test (Schmand et al., 1991), or a history of alcohol- or drug abuse or dependence assessed with the Composite International Diagnostic Interview (CIDI) v2.1 (Ter Smitten et al., 1998). Additional exclusion criteria included self-reported or suspected neurological disorder, brain damage, history of meningitis, fragile X syndrome, Rett syndrome, 22q11 deletion syndrome, metal objects in or around the body, participation in a scientific examination where radiation was used in the past year, and (in females) lactation or pregnancy (confirmed with a urinary pregnancy test). Current and/or recent medication or illicit drug use, assessed through self-report, was also prohibited. A urinary test on the day of the PET/CT-scan had to be negative for opiates, cocaine, cannabis, and amphetamines.

2.2 Sample size calculations

Sample size calculations were conducted using G*Power v3.1 (Faul et al., 2007; Faul et al., 2009), on the basis of a two-tailed alpha of 0.05 and analysis within the general linear model. The necessary sample size to examine group differences in striatal dopamine synthesis capacity was calculated using a study that compared dopamine synthesis capacity in striatal regions of adults with Asperger syndrome and controls (Nieminen-von Wendt et al., 2004). If results from our study would have been similar to the smallest effect and the largest standard deviation (*SD*) of dopamine synthesis capacity values of that study (difference in means = 0.34, *SD* = 0.35), we would need between 19 and 24 participants assuming a power of 0.80 to 0.90. Therefore, we included 24 controls.

The necessary sample size to examine the relationship between striatal dopamine synthesis capacity and loneliness in ASD was based on a study that examined the relationship between dopamine functioning and reports of childhood trauma in healthy volunteers (Oswald et al., 2014). Assuming a similar effect size of approximately $r = 0.4$ and a power of 0.80, we would need 45 participants. Therefore, the ASD sample included 45 participants.

2.3 Design and procedures

Participants were assessed on three separate testing days, during which they were screened for in- and exclusion criteria, underwent a magnetic resonance imaging (MRI) scan (see below), and completed measures of social defeat and an [^{18}F]-FDOPA PET/CT-scan. All participants signed informed consent prior to the start of the study. The study was approved by the medical ethics committee of Leiden University Medical Center (reference NL54244.058.15), and pre-registered within the Netherlands Trial Register (registration number NL6207, <https://www.trialregister.nl/trial/6207>).

2.4 Measures of social defeat and psychotic symptoms

Measures of social defeat and psychosis are described in Supplement 2. In brief, we assessed loneliness using the UCLA Loneliness Scale (Russell, 1996) and used this as the primary measure of social defeat since it reflects a lack of social participation as well as the negative experience of this, in line with the definition of social defeat (Selten et al., 2013).

As secondary measures of social defeat we assessed experiences of being ostracized using the Ostracism Experience Scale (OES; Gilman et al., 2013), bullying victimisation (yes/no) and its total duration before age 17 using a modified version of the Olweus Bullying Interview (Olweus, 1996), social network size using the Lubben Social Network Scale (LSNS; Lubben et al., 2006), and childhood trauma before age 17 using the Childhood Trauma Questionnaire (CTQ; Bernstein et al., 2003; Thomsb et al., 2009). Moreover, we assessed the desire for social acceptance and belonging using the Need to Belong Scale (NBS; Leary et al., 2013), and the perceived availability of social support using the Interpersonal Support Evaluation List (ISEL; Cohen et al., 1985). We calculated the interaction between the NBS and ISEL and used this as a predictor variable in the analyses to examine whether a discrepancy between them was related to the outcomes.

We assessed self-reported psychotic symptoms using the Prodromal Questionnaire-16 (PQ-16; Loewy et al., 2011; Ising et al., 2012). The PQ-16 was added to the project when data collection had already been started and was therefore completed by a subset of 48 participants ($n = 31$ ASD, $n = 17$ controls). Furthermore, we assessed depressed mood and anxiety using the Beck's Depression Inventory-II (BDI-II; Beck et al., 1996) and State-Trait Anxiety Inventory-Trait subscale (STAI-T; Spielberger, 1983), which we used in exploratory analyses.

2.5 MRI and PET/CT acquisition

A structural T1-weighted MRI (3D fast field echo sequence) was obtained for each participant on a 3T Ingenia MR scanner (Philips Healthcare, Best, The Netherlands). Due to a necessary replacement of the PET/CT-scanner at the hospital in which this study was conducted, PET/CT data were collected on two different PET/CT systems, i.e., a Biograph Horizon with TrueV option (Siemens Healthineers, Erlangen, Germany) or Vereos (Philips Healthcare, Best, The Netherlands). Both systems received EARL PET/CT accreditation. Reconstruction settings were harmonized using acquisitions of a Hoffman 3D brain phantom (Boellaard et al., 2018) (data not shown). Participants were asked to refrain from smoking and from eating or drinking (except water) three and six hours, respectively, prior to the PET/CT-scan. One hour before the scan, participants consumed 150 mg carbidopa and 400 mg entacapone to reduce the formation of radiolabelled [^{18}F]-FDOPA metabolites (Hoffman et al., 1992; Sawle et al., 1994). Immediately prior to the PET acquisition, a low-dose CT-scan of the brain (110/120 kVp, 35 mAs) was acquired for attenuation correction purposes. Subsequently, 150 MBq [^{18}F]-FDOPA was administered intravenously as a bolus, which was followed by a 90-minute dynamic PET acquisition. Head movement was minimised with a headrest and head strap, and participants were monitored throughout the PET acquisition so that any discomfort could be observed and addressed. Data were collected in list mode and histogrammed into 25 timeframes (5x1, 3x2, 3x3, and 14x5 minute(s)). PET data were reconstructed iteratively with resolution modelling and 2-mm full-width-at-half-maximum Gaussian smoothing filter with a voxel size of $2 \times 2 \times 2 \text{ mm}^3$.

2.6 Image processing

Image processing was conducted by researchers who were blind to ASD status. The MRI- and PET-images (except for the first two frames) were rigidly co-registered to a single PET-frame acquired 7 minutes post-injection using Vinci (v4.83; Max Planck Institute for Neurological Research, Cologne, Germany; Vollmar et al., 2004; MPI for Metabolism Research, 2020), based on mutual information (Čížek et al., 2004), to spatially align the images and compensate for minor head motion. Head movement was quantified by taking the square root of the sum of movement in millimetres squared in x, y, and z directions from the last PET frame relative to the reference frame. Prior to pharmacokinetic analysis, volumes of interest (cerebellum and striatum) were generated automatically using PVElab (v2.3; Neurobiology Research Unit, Copenhagen, Denmark; Quarantelli et al., 2004; Svarer et al., 2005) based on a maximum probability atlas (Hammers et al., 2003). In addition, SPM12 (Wellcome Centre for Human Neuroimaging, London, UK) was used to segment the MRI image into grey (GM) and white matter (WM). Subsequently, the GM cerebellum was used as a reference region to calculate the influx constant k_i^{cer} (min^{-1} ; from here on labelled as k_i^{cer}) as a measure of dopamine synthesis capacity using reference Patlak graphical analysis (Patlak & Blasberg, 1985) as implemented in PPET (Amsterdam UMC, Amsterdam, The Netherlands; Boellaard et al., 2006). PET frames acquired between minutes 25 and 90 were used for linear fit, resulting in a whole-brain parametric image. From this parametric image, k_i^{cer} for the GM striatum was extracted.

The functional striatal sub-regions (associative, limbic, and sensorimotor), defined in the Oxford-GSK-Imanova brain atlas (Tziortzi et al., 2014), and a standard Montreal Neurological Imaging (MNI) brain template were extracted from FSLeys v0.3 in FSL (v6.0; Analysis Group, Oxford, United Kingdom; Jenkinson et al., 2012; McCarthy, 2020). Using Vinci, the MNI-template was warped to match the participant MRI using a non-linear affine transformation. The resulting transformation matrix was applied to the striatal sub-regions, thereby warping them from standard- to subject-space. From the parametric image, we extracted GM k_i^{cer} values for voxels with at least 60% probability of belonging to the functional striatal sub-regions (Avram et al., 2019).

We conducted several additional analyses to ensure the validity of the methods that we used (reported in Supplement 3). First, we calculated a whole-striatum k_i^{cer} value obtained from the three sub-regions weighted by their respective volumes and compared this to the k_i^{cer} value for the striatum obtained from the maximum probability atlas. Second, we repeated our main analyses with k_i^{cer} values extracted from the combined GM and WM tissue, since previous studies examining dopamine synthesis capacity did not always separate these tissues. Third, in the analyses with the striatal sub-regions, we additionally investigated a stricter threshold of at least 90% probability. Fourth, we compared the mean standardized uptake values (SUV) in GM cerebellum in ASD and controls, to examine whether non-specific uptake of [^{18}F]-FDOPA differed between groups. Finally, we repeated the main analyses for the two PET/CT-scanners separately.

2.7 Statistical analyses

Statistical analyses were conducted using SPSS v26. A two-tailed alpha of $\alpha = 0.05$ was used to evaluate statistical significance. Statistical test assumptions were adequately met, unless stated otherwise. We had few missing data on the measures of social defeat (less than 0.25% of total responses on any questionnaire). Since imputation of these missing data did not change the outcomes of the study, we report the results without these data imputed.

For the primary analyses, we compared the striatal k_i^{cer} between ASD and controls using ANCOVA. We examined the relationship between striatal k_i^{cer} and loneliness within ASD by conducting linear regression analysis. Analyses were adjusted for age, sex, smoking-status, and scanner-type (i.e., Biograph Horizon or Vereos) (for unadjusted results, see Supplementary Table 3).

In the secondary analyses (see also Supplement 4), group differences in social defeat were examined using independent samples t -tests or χ^2 -tests. We report these results without adjusting for covariates, but regression analyses adjusted for age, sex, and smoking-status are reported in Supplementary Table 4. The measures of childhood trauma and total bullying duration violated assumptions of normality and equality of variances, which we resolved by computing bootstrapped p -values (Rietveld & van Hout, 2015; Dwivedi et al., 2017). Furthermore, we conducted regression analyses to examine relationships between measures of social defeat (besides loneliness) and striatal k_i^{cer} . Finally, we conducted the previously-described analyses using the k_i^{cer} in the three striatal sub-regions (rather than whole striatum) as dependent variables.

3. Results

3.1 Participants

Forty-five adults with ASD and 24 controls completed the study. For technical reasons, we were unable to use the data of three participants ($n = 1$ ASD, $n = 2$ controls). Thus, the final sample included 44 adults with ASD and 22 controls. Table 1 shows the characteristics of the two samples. Average head movement was comparable in ASD and controls. We included 3 participants with substantial head movement (> 5 mm; 1 control and 2 ASD participants), as we excluded deviating frames during parametric analysis and the k_i^{cer} values of these participants fell within the range of values of the other participants. Moreover, excluding them did not alter the results.

Table 1

Sample characteristics of adults with autism spectrum disorder (ASD) and controls.

Variable	ASD ($n = 44$)	Controls ($n = 22$)
Male, No. (%)	28 (64%)	14 (64%)
Age in years, mean (SD)	23.74 (2.64)	23.47 (2.48)
Smoker, No. (%)	2 (5%)	1 (5%)
Scanned on Vereos PET/CT-scanner, No. (%)	31 (70%)	13 (59%)
IQ, mean (SD)	103.75 (5.19)	105.05 (4.90)
Approximate injected [^{18}F]-FDOPA dose in MBq, mean (SD)	161.55 (7.26)	157.24 (8.57)
Head movement in millimetres, mean (SD)	2.44 (2.78)	2.54 (1.67)

SD, standard deviation; IQ, intelligence quotient; MBq, megabecquerel.

3.2 Dopamine synthesis capacity in ASD and controls

Figure 1 shows the dopamine synthesis capacity in the striatum of adults with ASD and controls. In contrast to hypothesis 1a, we found no significant differences in dopamine synthesis capacity in ASD ($M = 0.0145$, $SD = 0.0023$) and controls ($M = 0.0143$, $SD = 0.0024$) in the striatum after adjusting for covariates ($F_{1,60} = 0.026$, $p = 0.87$). Moreover, as shown in Figure 2, secondary analyses showed no significant group differences in dopamine synthesis capacity in the associative (ASD: $M = 0.0155$, $SD = 0.0024$; controls: $M = 0.0155$, $SD = 0.0027$; $F_{1,60} = 0.003$, $p = 0.96$), limbic (ASD: $M = 0.0152$, $SD = 0.0026$; controls: $M = 0.0151$, $SD = 0.0028$; $F_{1,60} = 0.000$, $p > 0.99$), or sensorimotor (ASD: $M = 0.0165$, $SD = 0.030$; controls: $M = 0.0166$, $SD = 0.0032$; $F_{1,60} = 0.011$, $p = 0.92$) striatal sub-regions after adjusting for covariates.

Figure 1
Boxplots showing the median, quartiles, and range of presynaptic dopamine synthesis capacity ($k_i^{ser} \text{ min}^{-1}$) in the striatum in adults with autism spectrum disorder (ASD) and controls.

Figure 2
Boxplots showing the median, quartiles, and range of presynaptic dopamine synthesis capacity ($k_i^{ser} \text{ min}^{-1}$) in the (A) associative, (B) limbic, and (C) sensorimotor sub-regions of the striatum in adults with autism spectrum disorder (ASD) and controls.

3.3 Association between loneliness and dopamine synthesis capacity in ASD

In contrast to hypothesis 1b, among adults with ASD there was no statistically significant association between loneliness and dopamine synthesis capacity in the striatum after adjusting for covariates ($\beta = 0.01$, $p = 0.96$) (see Figure 3). Furthermore, secondary analyses showed no significant associations between loneliness and dopamine synthesis capacity in the associative ($\beta = -0.03$, $p = 0.87$), limbic ($\beta = -0.01$, $p = 0.93$), or sensorimotor ($\beta = 0.01$, $p = 0.97$) striatal sub-regions after adjusting for covariates.

Figure 3

Scatterplot of the unadjusted relationship between total scores on the UCLA Loneliness Scale and presynaptic dopamine synthesis capacity ($k_{\text{t}}^{\text{cer}}$ min⁻¹) in the striatum in adults with autism spectrum disorder.

3.4 Secondary analyses with social defeat

Adults with ASD reported more loneliness, more experiences of being ostracized, more and longer-lasting episodes of bullying victimization, smaller social networks, and more traumatic experiences in childhood than controls (see Table 2). Both samples reported a similar need to belong, but adults with ASD reported a lower availability of interpersonal support.

The relations between the secondary measures of social defeat and striatal dopamine synthesis capacity in adults with ASD are shown in Supplementary Table 5. We found no significant association between the measures of social defeat with dopamine synthesis capacity in the striatum or any of its sub-regions after adjusting for covariates. A possible exception to this was childhood trauma (see Supplementary Figure 2), which did show a significant positive association with striatal dopamine synthesis capacity ($\beta = 0.32$, $p = 0.05$). However, this association was largely driven by one outlier (after excluding, $\beta = 0.20$, $p = 0.25$) and became non-significant after adjusting the p -value for multiple testing.

Notably, contrary to our expectations, exploratory post-hoc analyses in controls showed a significant negative association between childhood trauma and striatal dopamine synthesis capacity (Supplementary Table 6 and Supplementary Figure 3). On the other hand, the relationship between social

support and dopamine synthesis capacity was negative in controls with a high need to belong (but positive in those with a low need to belong; Supplementary Figure 4).

Table 2

Measures of social defeat in adults with autism spectrum disorder (ASD) and controls.

Variable	ASD (<i>n</i> = 44)	Controls (<i>n</i> = 22)	<i>p</i> -value
UCLA Loneliness Scale, mean (SD)	44.66 (8.65)	32.14 (5.77)	$p < 0.001^1$
OES, mean (SD)	29.73 (5.76)	21.86 (4.35)	$p < 0.001^1$
Bullied (yes/no), No. (%)	36 (82%)	11 (50%)	$p = 0.01^2$
Bullying total duration in months, mean (SD)	48.57 (40.57)	11.32 (18.63)	$p < 0.001^{1,3,4}$
LSNS, mean (SD)	15.89 (5.34)	21.36 (3.13)	$p < 0.001^{1,3}$
CTQ, mean (SD)	38.70 (12.29)	30.32 (4.65)	$p < 0.001^{1,3,4}$
NBS, mean (SD)	31.36 (6.43)	31.45 (4.62)	$p = 0.95^{1,3}$
ISEL, mean (SD)	119.25 (16.13)	137.45 (7.79)	$p < 0.001^{1,3}$

SD, standard deviation; OES, Ostracism Experience Scale; LSNS, Lubben Social Network Scale; CTQ, Childhood Trauma questionnaire; NBS, Need to Belong Scale; ISEL, Interpersonal Support Evaluation List.

¹ Independent-samples *t*-test.

² χ^2 -test.

³ Equal variances not assumed.

⁴ Estimated with 10 000 bootstrapping samples.

3.5 Associations with symptoms

Adults with ASD ($M = 3.13$, $SD = 1.93$) reported more psychotic symptoms on the PQ-16 than controls ($M = 1.06$, $SD = 0.97$). However, these symptoms were not significantly associated with dopamine synthesis capacity in the striatum in ASD ($\beta = -0.05$, $p = 0.81$) or in controls ($\beta = -0.26$, $p = 0.30$) after adjusting for covariates. Results were also non-significant for the striatal sub-regions (see Supplementary Table 7).

Exploratory analyses showed no statistically significant associations between dopamine synthesis capacity and depressed mood or anxiety (see Supplementary Table 8).

3.6 Sensitivity analyses

As shown in Supplement 3, k_i^{cer} values somewhat differed depending on the image processing procedure and/or PET/CT-scanner that was used, but the results of the analyses were comparable and conclusions remained unchanged. Non-specific uptake of [^{18}F]-FDOPA in the cerebellum was similar in ASD and controls.

4. Discussion

We used PET/CT to examine striatal dopamine synthesis capacity in unmedicated, non-psychotic adults with ASD and its association with measures of social defeat. Contrary to our expectations, adults with ASD did not have a greater presynaptic dopamine synthesis capacity in the striatum or any of its sub-regions relative to controls. Furthermore, among adults with ASD we found no significant association between striatal dopamine synthesis capacity and loneliness or other measures of social defeat.

Our findings do not support previous ideas about the involvement of presynaptic dopamine signalling in ASD (Pavál, 2017). However, dopamine synthesis capacity is only one aspect of dopamine signalling and other studies in ASD have found local alterations in dopamine transporter binding (Nakamura et al., 2010) and dopamine receptor density (Kubota et al., 2020). Moreover, it is well-established that ASD is heterogeneous (Motttron & Bzdok, 2020), and as a result, deviations in dopamine synthesis might be present only in a subgroup of individuals. ASD adults with a low IQ, who used medication, and/or who had substantial psychotic symptoms were excluded from our study, and it would be interesting to examine whether abnormalities in dopamine synthesis capacity are present among them. Future studies can further elucidate whether alterations in dopamine functioning are involved in ASD.

The social defeat hypothesis of schizophrenia, which predicts that non-psychotic adults with ASD show an increase in dopamine synthesis capacity and that this capacity is associated with measures of social defeat (Selten et al., 2013), was not supported. This might be explained as follows. First, the social defeat hypothesis might be incorrect. However, studies that examined striatal dopamine synthesis capacity and/or release in immigrants (Egerton et al., 2017), individuals with severe hearing impairment (Gevonden et al., 2014), and individuals exposed to childhood trauma (Oswald et al., 2014; Egerton et al., 2016) supported this hypothesis. Furthermore, experiments reported increased dopamine release in the nucleus accumbens of (sub)chronically defeated rodents (Hammels et al., 2015). In contrast, in line with post-hoc analyses with reference to childhood trauma in our control group, two recent studies observed negative associations between different types of social adversity and dopamine synthesis capacity (Bloomfield et al., 2019) or amphetamine-induced striatal dopamine release (Dahoun et al., 2019). One possibility is that social defeat only increases dopamine functioning in certain individuals and that, for example, individuals with ASD respond neurochemically different to defeat than other risk groups. Nevertheless, given the high rates of social defeat in adults with ASD and the absence of a relationship with presynaptic dopamine, one can conclude from this study that social defeat per se does not *necessarily* upregulate dopamine synthesis capacity.

Second, dopamine sensitization might have been demonstrated if presynaptic dopamine release had been examined, for instance after a challenge with amphetamine. Since knowledge about the relationship between presynaptic dopamine synthesis capacity and amphetamine-induced dopamine release is limited, it is difficult to predict the outcome of this challenge (Abi-Dargham et al., 2009). To the best of our knowledge, presynaptic dopamine release has not yet been examined in ASD and it might be worthwhile to do so. It should be performed with great care, however, since inducing dopamine release might precipitate psychotic symptoms.

This study has several strengths. First, this is by far the largest PET/CT-study to examine dopamine synthesis capacity in ASD and the first to examine an association with possible risk factors. Given the (for PET/CT studies) large, *a priori* determined sample size, it is highly unlikely that the negative findings are due to a lack of statistical power. Second, we had strict inclusion measures, which might limit the generalizability of the findings to the entire ASD population but does reduce the influence of external factors such as (dopaminergic) medication use. Third, in addition to our main analysis with

loneliness, we used multiple measures to assess social defeat, which consistently showed an absence of relation with striatal dopamine functioning.

The study also has several limitations. First, the study was cross-sectional. To understand how dopaminergic abnormalities arise, longitudinal studies are necessary. Second, we relied on self-report measures of social defeat, which may be prone to several types of bias. Third, PET/CT-scans were acquired on two different PET/CT systems. However, reconstruction parameters for the two scanners were harmonized as much as possible and scanner-type was added as a covariate to the analyses. Moreover, conclusions did not change when we conducted the main analyses for the two PET/CT-scanners separately.

In conclusion, non-psychotic, unmedicated adults with ASD do not show a significant increase in striatal dopamine synthesis capacity, and this capacity is not associated with measures of social defeat.

5. Acknowledgments

We would like to thank Jacqueline Aanholt-Bijlemeer, Ina Boot, Neanke Bouwman, Robert Bovenkerk, Johan van Brecht, Michael Bruijns, Paul de Bruin, Mark van Buchem, Petra Dibbets-Schneider, Demi Jansen, Jordi Vonk-van Oosten, and Patrick van der Zwet for facilitating the MRI- and PET/CT-scans. Furthermore, we would like to express our gratitude to Daniëlle Bos, Carlijn Clemens, Truda Driesen, Deborah Op 't Eijnde, Erik Giltay, Jori Henke, and Jessie Kosterman for their assistance with conducting this study. We would also like to thank Ronald Boellaard, Patricia Cambraia Lopes, Elsmarieke van de Giessen, Sandeep Golla, Claus Svarer, and Charlotte van der Vos for their support with PET/CT data processing, and Fabian Termorshuizen for his support with the statistical analyses. Finally, we would like to thank JADOS (in particular Elles van Woerkum and Paul Stoffer), Anna Souverijn, Marcel Melchers, Els van der Ven, Villa Abel, PAS Nederland, Leviaan, aspergersyndroom.nl, outsiders.net, RIAN Autismenetwerk, and the Dutch Association for Autism (*Nederlandse Vereniging voor Autisme*) for their help with recruiting study participants. The study was funded in part by Stichting J.M.C. Kapteinfonds.

6. References

- Abi-Dargham, A., van de Giessen, E., Slifstein, M., Kegeles, L. S., & Laruelle, M. (2009). Baseline and amphetamine-stimulated dopamine activity are related in drug-naïve schizophrenic subjects. *Biological Psychiatry*, 65(12), 1091-1093.
- Avram, M., Brandl, F., Cabello, J., Leucht, C., Scherr, M., Mustafa, M., Leucht, S., Ziegler, S., & Sorg, C. (2019). Reduced striatal dopamine synthesis capacity in patients with schizophrenia during remission of positive symptoms. *Brain*, 142(6), 1813-1826.
- Bauminger, N., Shulman, C., & Agam, G. (2003). Peer interaction and loneliness in high-functioning children with autism. *Journal of Autism and Developmental Disorders*, 33(5), 489-507.
- Beck, A. T., Steer, R. A., & Brown, G. K. (1996). *Beck Depression Inventory (2nd ed.)*. The Psychological Corporation.
- Bernstein, D. P., Stein, J. A., Newcomb, M. D., Walker, E., Pogge, D., Ahluvalia, T., Stokes, J., Handelsman, L., Medrano, M., & Desmond, D. (2003). Development and validation of a brief screening version of the Childhood Trauma Questionnaire. *Child Abuse & Neglect*, 27(2), 169-190.
- Bloomfield, M. A., McCutcheon, R. A., Kempton, M., Freeman, T. P., & Howes, O. (2019). The effects of psychosocial stress on dopaminergic function and the acute stress response. *eLife*, 8, e46797.
- Boellaard, R., Golla, S., Kaleep, A., Lubberink, M., Van Velden, F., Bettinardi, V., Yaqub, M., Sera, T., Rijnsdorp, S., & Lammertsma, A. (2018). Feasibility of brain PET/CT harmonization-a multicenter, multivendor pilot study. *Journal of Nuclear Medicine*, 59(supplement 1), 286-286.
- Boellaard, R., Yaqub, M., Lubberink, M., & Lammertsma, A. (2006). PPET: a software tool for kinetic and parametric analyses of dynamic PET studies. *Neuroimage*(31), T62.
- Buck, T. R., Viskochil, J., Farley, M., Coon, H., McMahon, W. M., Morgan, J., & Bilder, D. A. (2014). Psychiatric comorbidity and medication use in adults with autism spectrum disorder. *Journal of Autism and Developmental Disorders*, 44(12), 3063-3071.
- Chisholm, K., Lin, A., Abu-Akel, A., & Wood, S. J. (2015). The association between autism and schizophrenia spectrum disorders: A review of eight alternate models of co-occurrence. *Neuroscience & Biobehavioral Reviews*, 55, 173-183.
- Čížek, J., Herholz, K., Vollmar, S., Schrader, R., Klein, J., & Heiss, W.-D. (2004). Fast and robust registration of PET and MR images of human brain. *Neuroimage*, 22(1), 434-442.
- Cohen, S., Mermelstein, R., Kamarck, T., & Hoberman, H. M. (1985). Measuring the functional components of social support. In *Social support: Theory, research and applications* (pp. 73-94). Springer.
- Dahoun, T., Nour, M. M., McCutcheon, R. A., Adams, R. A., Bloomfield, M. A., & Howes, O. D. (2019). The relationship between childhood trauma, dopamine release and dexamphetamine-induced positive psychotic symptoms: a [¹¹C]-(+)-PHNO PET study. *Translational Psychiatry*, 9(1), 1-12.
- Dwivedi, A. K., Mallawaarachchi, I., & Alvarado, L. A. (2017). Analysis of small sample size studies using nonparametric bootstrap test with pooled resampling method. *Statistics in Medicine*, 36(14), 2187-2205.
- Egerton, A., Chaddock, C. A., Winton-Brown, T. T., Bloomfield, M. A., Bhattacharyya, S., Allen, P., McGuire, P. K., & Howes, O. D. (2013). Presynaptic striatal dopamine dysfunction in people at ultra-high risk for psychosis: findings in a second cohort. *Biological Psychiatry*, 74(2), 106-112.
- Egerton, A., Howes, O. D., Houle, S., McKenzie, K., Valmaggia, L. R., Bagby, M. R., Tseng, H.-H., Bloomfield, M. A., Kenk, M., & Bhattacharyya, S. (2017). Elevated striatal dopamine function in

- immigrants and their children: a risk mechanism for psychosis. *Schizophrenia Bulletin*, 43(2), 293-301.
- Egerton, A., Valmaggia, L. R., Howes, O. D., Day, F., Chaddock, C. A., Allen, P., Winton-Brown, T. T., Bloomfield, M. A., Bhattacharyya, S., & Chilcott, J. (2016). Adversity in childhood linked to elevated striatal dopamine function in adulthood. *Schizophrenia Research*, 176(2-3), 171-176.
- Ernst, M., Zametkin, A., Matochik, J., Pascualvaca, D., & Cohen, R. (1997). Low medial prefrontal dopaminergic activity in autistic children. *The Lancet*, 350(9078), 638.
- Faul, F., Erdfelder, E., Buchner, A., & Lang, A.-G. (2009). Statistical power analyses using G* Power 3.1: Tests for correlation and regression analyses. *Behavior Research Methods*, 41(4), 1149-1160.
- Faul, F., Erdfelder, E., Lang, A.-G., & Buchner, A. (2007). G* Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behavior Research Methods*, 39(2), 175-191.
- Gevonden, M., Booij, J., van den Brink, W., Heijtel, D., van Os, J., & Selten, J.-P. (2014). Increased release of dopamine in the striata of young adults with hearing impairment and its relevance for the social defeat hypothesis of schizophrenia. *JAMA Psychiatry*, 71(12), 1364-1372.
- Gilman, R., Carter-Sowell, A., DeWall, C. N., Adams, R. E., & Carboni, I. (2013). Validation of the ostracism experience scale for adolescents. *Psychological Assessment*, 25(2), 319.
- Hammels, C., Pishva, E., De Vry, J., van den Hove, D. L., Prickaerts, J., van Winkel, R., Selten, J.-P., Lesch, K.-P., Daskalakis, N. P., & Steinbusch, H. W. (2015). Defeat stress in rodents: from behavior to molecules. *Neuroscience & Biobehavioral Reviews*, 59, 111-140.
- Hammers, A., Allom, R., Koeppe, M. J., Free, S. L., Myers, R., Lemieux, L., Mitchell, T. N., Brooks, D. J., & Duncan, J. S. (2003). Three-dimensional maximum probability atlas of the human brain, with particular reference to the temporal lobe. *Human Brain Mapping*, 19(4), 224-247.
- Hoffman, J. M., Melega, W. P., Hawk, T. C., Grafton, S. C., Luxen, A., Mahoney, D. K., Barrio, J. R., Huang, S.-C., Mazziotta, J. C., & Phelps, M. E. (1992). The effects of carbidopa administration on 6-[¹⁸F] fluoro-L-dopa kinetics in positron emission tomography. *Journal of Nuclear Medicine*, 33(8), 1472-1477.
- Howes, O. D., Montgomery, A. J., Asselin, M.-C., Murray, R. M., Valli, I., Tabraham, P., Bramon-Bosch, E., Valmaggia, L., Johns, L., & Broome, M. (2009). Elevated striatal dopamine function linked to prodromal signs of schizophrenia. *Archives of General Psychiatry*, 66(1), 13-20.
- Hus, V., & Lord, C. (2014). The autism diagnostic observation schedule, module 4: revised algorithm and standardized severity scores. *Journal of Autism and Developmental Disorders*, 44(8), 1996-2012.
- Ising, H. K., Veling, W., Loewy, R. L., Rietveld, M. W., Rietdijk, J., Dragt, S., Klaassen, R. M., Nieman, D. H., Wunderink, L., & Linszen, D. H. (2012). The validity of the 16-item version of the Prodromal Questionnaire (PQ-16) to screen for ultra high risk of developing psychosis in the general help-seeking population. *Schizophrenia Bulletin*, 38(6), 1288-1296.
- Jauhar, S., Nour, M. M., Veronese, M., Rogdaki, M., Bonoldi, I., Azis, M., Turkheimer, F., McGuire, P., Young, A. H., & Howes, O. D. (2017). A test of the transdiagnostic dopamine hypothesis of psychosis using positron emission tomographic imaging in bipolar affective disorder and schizophrenia. *JAMA Psychiatry*, 74(12), 1206-1213.
- Jenkinson, M., Beckmann, C. F., Behrens, T. E., Woolrich, M. W., & Smith, S. M. (2012). FSL. *Neuroimage*, 62(2), 782-790.

- Johnson, T. D., & Joshi, A. (2016). Dark clouds or silver linings? A stigma threat perspective on the implications of an autism diagnosis for workplace well-being. *Journal of Applied Psychology*, 101(3), 430-449.
- Kubota, M., Fujino, J., Tei, S., Takahata, K., Matsuoka, K., Tagai, K., Sano, Y., Yamamoto, Y., Shimada, H., & Takado, Y. (2020). Binding of Dopamine D1 Receptor and Noradrenaline Transporter in Individuals with Autism Spectrum Disorder: A PET Study. *Cerebral Cortex*, 30(12), 6458-6468.
- Lai, M.-C., Kasse, C., Besney, R., Bonato, S., Hull, L., Mandy, W., Szatmari, P., & Ameis, S. H. (2019). Prevalence of co-occurring mental health diagnoses in the autism population: a systematic review and meta-analysis. *The Lancet Psychiatry*, 6(10), 819-829.
- Leary, M. R., Kelly, K. M., Cottrell, C. A., & Schreindorfer, L. S. (2013). Construct validity of the need to belong scale: Mapping the nomological network. *Journal of Personality Assessment*, 95(6), 610-624.
- Loewy, R. L., Pearson, R., Vinogradov, S., Bearden, C. E., & Cannon, T. D. (2011). Psychosis risk screening with the Prodromal Questionnaire—brief version (PQ-B). *Schizophrenia Research*, 129(1), 42-46.
- Lord, C., Rutter, M., Dilavore, P. C., Risi, S., Gotham, K., & Bishop, S. L. (2012). *Autism Diagnostic Observation Schedule – second edition*. Western Psychological Services.
- Lubben, J., Blozik, E., Gillmann, G., Iliffe, S., von Renteln Kruse, W., Beck, J. C., & Stuck, A. E. (2006). Performance of an abbreviated version of the Lubben Social Network Scale among three European community-dwelling older adult populations. *The Gerontologist*, 46(4), 503-513.
- Marotta, R., Risoleo, M. C., Messina, G., Parisi, L., Carotenuto, M., Vetri, L., & Roccella, M. (2020). The Neurochemistry of Autism. *Brain Sciences*, 10(3), 163.
- McCarthy, P. (2020). *FSLeys*. <https://users.fmrib.ox.ac.uk/~paulmc/fsleys/userdoc/latest/>
- McCutcheon, R., Beck, K., Jauhar, S., & Howes, O. D. (2018). Defining the locus of dopaminergic dysfunction in schizophrenia: a meta-analysis and test of the mesolimbic hypothesis. *Schizophrenia Bulletin*, 44(6), 1301-1311.
- Mizrahi, R. (2016). Social stress and psychosis risk: common neurochemical substrates? *Neuropsychopharmacology*, 41(3), 666-674.
- Mottron, L., & Bzdok, D. (2020). Autism spectrum heterogeneity: fact or artifact? *Molecular Psychiatry*, 1-8.
- MPI for Metabolism Research. (2020). *VINCI*. <http://vinci.sf.mpg.de/>
- Nakamura, K., Sekine, Y., Ouchi, Y., Tsujii, M., Yoshikawa, E., Futatsubashi, M., Tsuchiya, K. J., Sugihara, G., Iwata, Y., & Suzuki, K. (2010). Brain serotonin and dopamine transporter bindings in adults with high-functioning autism. *Archives of General Psychiatry*, 67(1), 59-68.
- Nieminen-von Wendt, T. S., Metsähonkala, L., Kulomäki, T. A., Aalto, S., Autti, T. H., Vanhala, R., Eskola, O., Bergman, J., Hietala, J. A., & von Wendt, L. O. (2004). Increased presynaptic dopamine function in Asperger syndrome. *Neuroreport*, 15(5), 757-760.
- Olweus, D. (1996). Revised Olweus Bully/Victim Questionnaire. *British Journal of Educational Psychology*.
- Oswald, D. P., & Sonenklar, N. A. (2007). Medication use among children with autism spectrum disorders. *Journal of Child and Adolescent Psychopharmacology*, 17(3), 348-355.
- Oswald, L. M., Wand, G. S., Kuwabara, H., Wong, D. F., Zhu, S., & Brasic, J. R. (2014). History of childhood adversity is positively associated with ventral striatal dopamine responses to amphetamine. *Psychopharmacology*, 231(12), 2417-2433.

- Pain, L., Gobaille, S., Schleef, C., Aunis, D., & Oberling, P. (2002). In vivo dopamine measurements in the nucleus accumbens after nonanesthetic and anesthetic doses of propofol in rats. *Anesthesia & Analgesia*, 95(4), 915-919.
- Patlak, C. S., & Blasberg, R. G. (1985). Graphical evaluation of blood-to-brain transfer constants from multiple-time uptake data. Generalizations. *Journal of Cerebral Blood Flow & Metabolism*, 5(4), 584-590.
- Pavál, D. (2017). A dopamine hypothesis of autism spectrum disorder. *Developmental Neuroscience*, 39(5), 355-360.
- Quarantelli, M., Berkouk, K., Prinster, A., Landeau, B., Svarer, C., Balkay, L., Alfano, B., Brunetti, A., Baron, J.-C., & Salvatore, M. (2004). Integrated software for the analysis of brain PET/SPECT studies with partial-volume-effect correction. *Journal of Nuclear Medicine*, 45(2), 192-201.
- Rietveld, T., & van Hout, R. (2015). The t test and beyond: Recommendations for testing the central tendencies of two independent samples in research on speech, language and hearing pathology. *Journal of Communication Disorders*, 58, 158-168.
- Russell, D. W. (1996). UCLA Loneliness Scale (Version 3): Reliability, validity, and factor structure. *Journal of Personality Assessment*, 66(1), 20-40.
- Sawle, G., Burn, D., Morrish, P., Lammertsma, A., Snow, B., Luthra, S., Osman, S., & Brooks, D. (1994). The effect of entacapone (OR-611) on brain [^{18}F]-6-L-fluorodopa metabolism: Implications for levodopa therapy of Parkinson's disease. *Neurology*, 44(7), 1292-1292.
- Schmand, B., Bakker, D., Saan, R., & Louman, J. (1991). The Dutch Reading Test for Adults: a measure of premorbid intelligence level. *Tijdschrift voor Gerontologie en Geriatrie*, 22(1), 15-19.
- Schroeder, J. H., Cappadocia, M. C., Bebko, J. M., Pepler, D. J., & Weiss, J. A. (2014). Shedding light on a pervasive problem: A review of research on bullying experiences among children with autism spectrum disorders. *Journal of Autism and Developmental Disorders*, 44(7), 1520-1534.
- Selten, J.-P., Booi, J., Buwalda, B., & Meyer-Lindenberg, A. (2017). Biological mechanisms whereby social exclusion may contribute to the etiology of psychosis: a narrative review. *Schizophrenia Bulletin*, 43(2), 287-292.
- Selten, J.-P., & Cantor-Graae, E. (2005). Social defeat: risk factor for schizophrenia? *The British Journal of Psychiatry*, 187(2), 101-102.
- Selten, J.-P., van der Ven, E., Rutten, B. P., & Cantor-Graae, E. (2013). The social defeat hypothesis of schizophrenia: an update. *Schizophrenia Bulletin*, 39(6), 1180-1186.
- Spielberger, C. D. (1983). *Manual for the State-Trait Anxiety Inventory (Form Y)*. Consulting Psychologists Press.
- Staal, W. G., Langen, M., Van Dijk, S., Mensen, V. T., & Durston, S. (2015). DRD3 gene and striatum in autism spectrum disorder. *The British Journal of Psychiatry*, 206(5), 431-432.
- Sterzing, P. R., Shattuck, P. T., Narendorf, S. C., Wagner, M., & Cooper, B. P. (2012). Bullying involvement and autism spectrum disorders: prevalence and correlates of bullying involvement among adolescents with an autism spectrum disorder. *Archives of Pediatrics & Adolescent Medicine*, 166(11), 1058-1064.
- Svarer, C., Madsen, K., Hasselbalch, S. G., Pinborg, L. H., Haugbøl, S., Frøkjær, V. G., Holm, S., Paulson, O. B., & Knudsen, G. M. (2005). MR-based automatic delineation of volumes of interest in human brain PET images using probability maps. *Neuroimage*, 24(4), 969-979.

- Ter Smitten, R., Smeets, R., & Van den Brink, W. (1998). *Composite International Diagnostic Interview version 2.1: Dutch translation and adaptation*. WHO-CIDI Training en Referentie Centrum voor het Nederlands taalgebied, Psychiatrisch Centrum AMC.
- Thombs, B. D., Bernstein, D. P., Lobbestael, J., & Arntz, A. (2009). A validation study of the Dutch Childhood Trauma Questionnaire-Short Form: factor structure, reliability, and known-groups validity. *Child Abuse & Neglect*, 33, 518-523.
- Tziortzi, A. C., Haber, S. N., Searle, G. E., Tsoumpas, C., Long, C. J., Shotbolt, P., Douaud, G., Jbabdi, S., Behrens, T. E., & Rabiner, E. A. (2014). Connectivity-based functional analysis of dopamine release in the striatum using diffusion-weighted MRI and positron emission tomography. *Cerebral Cortex*, 24(5), 1165-1177.
- Vollmar, S., Čížek, J., Sué, M., Klein, J., Jacobs, A., & Herholz, K. (2004). VINCI - Volume Imaging in Neurological Research, Co-Registration and ROIs included. In K. Kremer & V. Macho (Eds.), *Forschung und Wissenschaftliches Rechnen 2003*. GWDG.
- Yung, A. R., Yung, A. R., Pan Yuen, H., McGorry, P. D., Phillips, L. J., Kelly, D., Dell'olio, M., Francey, S. M., Cosgrave, E. M., & Killackey, E. (2005). Mapping the onset of psychosis: the comprehensive assessment of at-risk mental states. *Australian & New Zealand Journal of Psychiatry*, 39(11-12), 964-971.
- Zürcher, N. R., Bhanot, A., McDougale, C. J., & Hooker, J. M. (2015). A systematic review of molecular imaging (PET and SPECT) in autism spectrum disorder: current state and future research opportunities. *Neuroscience & Biobehavioral Reviews*, 52, 56-73.

Appendix to chapter IV

Supplementary information

Supplement 1. Full list of in- and exclusion criteria

Inclusion criteria

1. DSM-5 diagnosis of autism spectrum disorder (ASD; only for the ASD sample).
2. Age: 18–30 years.

Exclusion criteria

1. DSM-5 diagnosis of ASD (controls only).
2. Autism spectrum disorder due to a known organic disorder (“Syndromal ASD”, e.g., due to Fragile X syndrome, Klinefelter syndrome, 22q11 deletion syndrome).
3. Neurological disorder (e.g., epilepsy) or evidence of brain damage.
4. History of meningitis.
5. IQ < 85.
6. Non-affective psychotic disorder or bipolar disorder (DSM-5: 297.1, 298.8, 295.40, 295.90, 295.70, 292.9, 291.9, 293.81, 293.82, 293.89, 298.9, 296.89, 303.13, 293.83, 296.89, 296.80, 296.4x, 296.5x, 296.7).
7. Social exclusion due to other causes than ASD, such as visible ethnic minority status, serious physical disability, serious visual or hearing impairment, at discretion of the researcher.

Exclusion criteria related to alcohol, soft/hard-drugs, medicinal drugs:

1. Current use of drugs (XTC, cocaine, etc.). Use of cannabis was allowed, but should have been stopped at least one month before the study. Cannabis abuse earlier in life was not allowed.
2. Alcohol- or drug abuse or dependence (DSM-5).
3. Use of an antipsychotic (ever) if prescribed for a psychotic disorder, as a former psychotic disorder is an exclusion criterion. Occasionally, antipsychotics are prescribed against e.g., anxiety or aggression. In these cases:
 - a. Incidental former use of antipsychotic was allowed, if the last use had been more than a year ago.
 - b. Regular former use of antipsychotic was allowed, if the last use had been more than two years ago.
 - c. Antipsychotic formerly administered as depot medication was allowed, if the last injection had been more than two years ago.
4. Use of the antipsychotic quetiapine (ever), if prescribed in relation to a psychotic disorder. However, quetiapine is often prescribed against sleep difficulties and has a low affinity to dopamine receptors (Kapur et al., 2000). In these cases:
 - a. Consumption was allowed if previously consumed in a low dose ($\leq 50\text{mg}$), but last use had been more than 3 months ago.
 - b. Consumption was allowed if previously consumed in a high dose ($> 50\text{mg}$), but last use had been more than 6 months ago.
5. Use of medication usually prescribed for attention-deficit/hyperactivity disorder (ADHD) (e.g., methylphenidate). Individuals who had stopped using these drugs for at least one year could participate in the study.
6. Use of benzodiazepine or promethazine, unless last use had been more than 1 month ago.
7. Use of other psychotropic drugs. Individuals who had stopped using the drugs for at least 3 months could participate in the study.

Exclusion criteria directly related to MRI- and PET/CT-scanning:

8. Smoking during the period of three hours prior to the PET/CT-scan and eating or drinking (except water) during the period of six hours prior to the PET/CT-scan.
9. Participation in a scientific examination where radiation was used, in the last year before participation.
10. Positive urine drug screen on the day of the PET/CT-scan. Participants were tested on cannabis, amphetamine, cocaine, and opiates.
11. In women: positive pregnancy test on the day of the PET/CT-scan and/or lactation.
12. Metal objects in or around the body.

Note that we did not ask participants to change their behaviour in order to participate in this study. For example, we did not ask them to stop using medication for a month so that they could participate. Instead, if participants did not comply with the in- or exclusion criteria, we excluded them from current and future participation.

Supplement 2. Description of measures**Primary outcome**

UCLA Loneliness Scale: We used the UCLA Loneliness Scale to measure loneliness (Russell, 1996). We selected this questionnaire as the primary measure of social defeat, since it reflects a lack of social participation as well as the subjective negative experience of this, in line with the definition and previous studies of social defeat (Selten et al., 2013; Gevonden et al., 2014). The questionnaire consists of 20 items (e.g., “How often do you feel that you lack companionship?”), which are scored between 1 (Never) and 4 (Always). After reverse-coding, total scores range from 20 to 80, with higher scores indicating more feelings of loneliness.

Secondary outcomes

In addition to measuring loneliness, we assessed other measures of social defeat. Furthermore, we assessed the presence of psychotic symptoms. The following instruments were used:

Ostracism Experience Scale (OES): The OES (Gilman et al., 2013) measures the extent to which participants feel excluded or ignored (i.e., ostracized). The questionnaire consists of 11 items (e.g., “In general, others ignore me during conversation”), which are scored between 1 (Never) and 5 (Always). Total scores range from 11 to 55, with higher scores indicating more experiences of being ostracized.

Bullying Interview: We conducted a semi-structured interview based on the definition of bullying proposed by Olweus (Olweus, 1996), to assess whether participants had been the victim of bullying prior to age 17. This definition was given as follows: “We say a child is being bullied when another child, or several other children say mean and hurtful things or make fun of him or her or call him or her mean and hurtful names; completely ignore or exclude him or her from their group of friends or leave him or her out of things on purpose; hit, kick, push, shove around, or lock him or her inside a room; tell lies or spread false rumours about him or her or send mean notes and try to make other children dislike him or her; and other hurtful things like that. When we talk about bullying, these things happen repeatedly, and it is difficult for the child being bullied to defend himself or herself. We also call it bullying, when a child is teased repeatedly in a mean and hurtful way. But we don’t call it bullying when the teasing is done in a friendly and playful way. Also, it is not bullying when two children of about equal strength or power argue or fight.”. After giving this definition, we asked questions about the frequency (i.e., number of bullying episodes), chronicity (i.e., duration of each bullying episode), severity, and age of bullying victimization. We used a binarized outcome of bullying victimization (bullied yes/no), as well as the total duration in months of the bullying episode(s).

Lubben Social Network Scale (LSNS): The 6-item LSNS assesses social network size (Lubben et al., 2006). The questionnaire asks about the number of family and friends that participants regularly engage with or can engage with if they need help or support (e.g., “How many relatives do you see or hear from at least once a month?”). Scores range from 6 to 36. Higher scores indicate the availability of a greater social network.

Childhood Trauma Questionnaire (CTQ): The 24-item version of the CTQ is a retrospective self-report questionnaire that assesses childhood maltreatment occurring before age 17 (Bernstein et al., 2003). Items contain questions about five domains of maltreatment (physical, emotional, and sexual abuse, and physical and emotional neglect; e.g., “When I was growing up, I thought that my parents wished I had never been born.”), which are scored between 1 (Never true) and 5 (Very often true). All subscales consist of five items, except for the sexual abuse subscale from which one item was removed in Dutch validation

studies (Thombs et al., 2009; Spinhoven et al., 2014). In this study total scores (between 24 and 120) were used, with greater scores indicating more experiences of childhood trauma.

Need to Belong Scale (NBS): The NBS assesses the need for social acceptance and belonging (Leary et al., 2013). The questionnaire consists of 10 items (e.g., "I want other people to accept me."), which are scored between 1 (Not at all) and 5 (Extremely). After reverse-coding, total scores range from 10 to 50, with higher scores indicating a greater need to belong.

Interpersonal Support Evaluation List (ISEL): The ISEL measures the extent to which participants perceive that social support is available (Cohen et al., 1985). The questionnaire consists of 40 items (e.g., "If I decide one afternoon that I would like to go to a movie that evening, I could easily find someone to go with me."), which are scored between 1 and 4. Total scores range from 40 to 160. Higher scores indicate a greater availability of social support.

Comprehensive Assessment of At-Risk Mental States (CAARMS). The CAARMS is a semi-structured interview, which assesses the presence of positive psychotic symptoms (Yung et al., 2005; Ising et al., 2012). The interview is most often used to classify participants as being at a clinically high risk of developing a psychotic disorder. This classification is made in case of past-year reduced social functioning, combined with the presence of attenuated psychotic symptoms or the presence of a psychotic disorder in first-degree relatives.

Prodromal Questionnaire-16 (PQ-16): The PQ-16 was used to assess self-reported psychotic symptoms (Loewy et al., 2011; Ising et al., 2012). The questionnaire consists of 16 items (e.g., "I have heard things other people can't hear like voices of people whispering or talking"), which are dichotomously scored (False=0 or True=1). Total scores range from 0 to 16.

Supplement 3. Control analyses

Here we show the results of additional analyses that we conducted to compare our calculations of striatal k_i^{cer} values to other methods. Supplementary Table 1 shows the whole-striatum k_i^{cer} values calculated with different methods. In Supplementary Table 2 we show that these values are highly correlated. In Supplement 3.1 we show that the conclusions of the main findings remain the same, regardless of which method is used. In Supplement 3.2, we show that the k_i^{cer} values obtained from striatal sub-regions calculated with a strict 90% threshold, give the same results as those with a 60% threshold. In Supplementary Figure 1, we show that mean standardized uptake values (SUV), corrected for body weight, in cerebellar grey matter are similar in ASD and controls. Finally, in Supplement 3.3, we show that the results are similar when analysed for the two PET/CT scanners separately.

Supplementary Table 1

Presynaptic dopamine synthesis capacity (k_i^{cer}) for the whole striatum, calculated with different methods.

Whole striatum k_i^{cer} calculated from	Sample	GM (mean [SD], range)	GM+WM (mean [SD], range)
Probabilistic atlas ¹	ASD	0.0145 (0.0023) ³ , 0.0105–0.0199	0.0135 (0.0020), 0.0098–0.0179
	Controls	0.0143 (0.0024) ³ , 0.0100–0.0186	0.0134 (0.0023), 0.0093–0.0173
	ASD	0.0155 (0.0024), 0.0110–0.0214	0.0153 (0.0024), 0.0109–0.0210
	Controls	0.0155 (0.0027), 0.0102–0.0204	0.0153 (0.0027), 0.0102–0.0204
Combined striatal sub-regions from FSL ² (60% threshold)	ASD	0.0167 (0.0027), 0.0119–0.0238	0.0167 (0.0027), 0.0118–0.0237
	Controls	0.0167 (0.0029), 0.0112–0.0224	0.0167 (0.0029), 0.0112–0.0224
	ASD	0.0167 (0.0027), 0.0119–0.0238	0.0167 (0.0027), 0.0118–0.0237
	Controls	0.0167 (0.0029), 0.0112–0.0224	0.0167 (0.0029), 0.0112–0.0224

GM, grey matter; WM, white matter; SD, standard deviation; ASD, autism spectrum disorder.

¹ See: Hammers et al. (2003)

² See: Tziortzi et al. (2014), Jenkinson et al. (2012), McCarthy (2020)

³ As reported in the main article.

Supplementary Table 2

Pearson correlations between k_i^{cer} values for the whole striatum in the entire sample (ASD+controls), calculated with different methods.

Whole striatum k_i^{cer} calculated from:	Probabilistic atlas¹ (GM)	Probabilistic atlas¹ (GM+WM)	Combined striatal sub-regions² (60%; GM)	Combined striatal sub-regions² (60%; GM+WM)	Combined striatal sub-regions² (90%; GM)	Combined striatal sub-regions² (90%; GM+WM)
Probabilistic atlas ¹ (GM)	1					
Probabilistic atlas ¹ (GM+WM)	0.986	1				
Combined striatal sub-regions ² (60%; GM)	0.969	0.953	1			
Combined striatal sub-regions ² (60%; GM+WM)	0.966	0.955	0.998	1		
Combined striatal sub-regions ² (90%; GM)	0.962	0.944	0.996	0.995	1	
Combined striatal sub-regions ² (90%; GM+WM)	0.960	0.945	0.995	0.996	0.999	1

ASD, autism spectrum disorder; GM, grey matter; WM, white matter.

¹ See: Hammers et al. (2003)

² See: Tziortzi et al. (2014), Jenkinson et al. (2012), McCarthy (2020)

Supplement 3.1. Main analyses with alternative calculations of whole-striatum k_i^{cer}

Regardless of the method used to calculate the whole-striatum k_i^{cer} , the k_i^{cer} did not differ between adults with ASD and controls (lowest $p=0.91$). Moreover, none of the k_i^{cer} values were associated with loneliness in adults with ASD (lowest $p=0.24$).

Supplement 3.2. k_i^{cer} in striatal sub-regions with 90% threshold

When we used a stricter 90% threshold to calculate the k_i^{cer} values in the striatal sub-regions, we still found no significant difference in k_i^{cer} values in the associative, limbic, or sensorimotor striatum between adults with ASD and controls (lowest $p=0.77$) and none of these values were associated with loneliness in adults with ASD (lowest $p=0.21$).

Supplementary Figure 1
Mean standardized uptake values (SUV) of [^{18}F]-FDOPA in grey matter cerebellum in minutes post-injection in adults with autism spectrum disorder (ASD) and controls.

Supplement 3.3. Results of the main analyses for the two PET/CT scanners separately.

When we restricted the analyses to data collected on the Siemens Biograph Horizon, we found no statistically significant difference in whole-striatal k_i^{cer} between ASD ($n = 13$, $M = 0.0143$, $SD = 0.0026$) and controls ($n = 9$, $M = 0.0139$, $SD = 0.0026$) ($F_{1,20} = 0.09$, $p = 0.77$; adjusted for age, sex, smoking: $F_{1,17} = 0.46$, $p = 0.51$). On average, the whole-striatal k_i^{cer} collected on the Philips Vereos was somewhat higher in ASD ($n = 31$, $M = 0.0146$, $SD = 0.0022$) and in controls ($n = 13$, $M = 0.0146$, $SD = 0.0024$), but on this scanner we also found no significant group differences ($F_{1,42} = 0.001$, $p = 0.97$; adjusted for age, sex, smoking: $F_{1,39} = 0.08$, $p = 0.77$).

Furthermore, we found no association between loneliness and whole-striatum k_i^{cer} in ASD when only looking at data collected on the Siemens Biograph Horizon ($n = 13$; $\beta = 0.03$, $p = 0.92$; adjusted for age, sex, smoking: $\beta = 0.24$, $p = 0.34$) or Philips Vereos ($n = 31$; $\beta = -0.13$, $p = 0.48$; adjusted for age, sex, smoking: $\beta = -0.15$, $p = 0.47$).

Supplement 4. Secondary analyses

On the next pages we show the results of several secondary analyses. We first show the difference in striatal k_i^{cer} between ASD and controls, and the association between striatal k_i^{cer} and loneliness in ASD, without adjusting for covariates (Supplementary Table 3). Next, we report the differences in measures of social defeat between ASD and controls after adjusting for age, sex, and smoking status, using (logistic) regression analyses (Supplementary Table 4). We then show associations between striatal k_i^{cer} and other measures of social defeat in ASD (Supplementary Table 5; Supplementary Figure 2) and controls (Supplementary Table 6; Supplementary Figures 3 and 4). We then show associations between measures of psychosis (Supplementary Table 7) and depression and anxiety (Supplementary Table 8) and striatal k_i^{cer} in ASD and controls.

Supplementary Table 3

Striatal k_i^{cer} in adults with autism spectrum disorder (ASD) and controls and its association with loneliness in ASD, without adjusting for covariates.

Analysis	Test statistic
Difference in k_i^{cer} between ASD and controls	
Whole-striatum k_i^{cer}	$F_{1,64}=0.069, p=0.79$
Associative striatum k_i^{cer}	$F_{1,64}=0.000, p>0.99$
Limbic striatum k_i^{cer}	$F_{1,64}=0.026, p=0.87$
Sensorimotor striatum k_i^{cer}	$F_{1,64}=0.000, p=0.99$
Association between k_i^{cer} and loneliness in ASD	
Whole-striatum k_i^{cer}	$\beta=-0.09, p=0.55$
Associative striatum k_i^{cer}	$\beta=-0.16, p=0.31$
Limbic striatum k_i^{cer}	$\beta=-0.14, p=0.37$
Sensorimotor striatum k_i^{cer}	$\beta=-0.10, p=0.50$

Supplementary Table 4
Differences in measures of social defeat between adults with autism spectrum disorder and controls after adjusting for age, sex, and smoking-status (yes/no).

Variable	Standardized beta, <i>p</i> -value
UCLA Loneliness Scale	$\beta=0.60, p<0.001^1$
OES	$\beta=0.57, p<0.001^1$
Bullied (yes/no)	OR=4.5, $p=0.01^2$
Bullying total duration in months	$\beta=0.46, p<0.001^1$
LSNS	$\beta=-0.48, p<0.001^1$
CTQ	$\beta=0.36, p=0.003^1$
NBS	$\beta=0.003, p=0.98^1$
ISEL	$\beta=-0.52, p<0.001^1$

OES, Ostracism Experience Scale; LSNS, Lubben Social Network Scale; CTQ, Childhood Trauma Questionnaire; NBS, Need to Belong Scale; ISEL, Interpersonal Support Evaluation List; OR, odds ratio.

¹ Multivariable linear regression analysis.

² Multivariable logistic regression analysis.

Supplementary Table 5

Associations between measures of social defeat and striatal k_i^{cer} in adults with autism spectrum disorder (ASD), before and after adjusting for covariates.

Variable	Covariates ¹	Striatal region (k_i^{cer})			
		Whole striatum	Associative striatum	Limbic striatum	Sensorimotor striatum
OES	Non-adjusted	$\beta=-0.19, p=0.23$	$\beta=-0.24, p=0.12$	$\beta=-0.25, p=0.11$	$\beta=-0.13, p=0.41$
	Adjusted	$\beta=-0.12, p=0.51$	$\beta=-0.12, p=0.48$	$\beta=-0.16, p=0.34$	$\beta=0.01, p=0.94$
Bullied (yes/no)	Non-adjusted	$\beta=-0.16, p=0.30$	$\beta=-0.20, p=0.19$	$\beta=-0.16, p=0.30$	$\beta=-0.22, p=0.14$
	Adjusted	$\beta=-0.12, p=0.46$	$\beta=-0.13, p=0.40$	$\beta=-0.10, p=0.52$	$\beta=-0.16, p=0.30$
Bullying total duration in months	Non-adjusted	$\beta=-0.15, p=0.32$	$\beta=-0.11, p=0.49$	$\beta=-0.16, p=0.29$	$\beta=-0.05, p=0.77$
	Adjusted	$\beta=-0.18, p=0.26$	$\beta=-0.14, p=0.37$	$\beta=-0.17, p=0.27$	$\beta=-0.10, p=0.50$
LSNS	Non-adjusted	$\beta=-0.25, p=0.11$	$\beta=-0.19, p=0.21$	$\beta=-0.15, p=0.34$	$\beta=-0.20, p=0.20$
	Adjusted	$\beta=-0.31, p=0.05$	$\beta=-0.24, p=0.12$	$\beta=-0.23, p=0.14$	$\beta=-0.20, p=0.19$
CTQ	Non-adjusted	$\beta=0.31, p=0.04^*$	$\beta=0.33, p=0.03^*$	$\beta=0.31, p=0.04^*$	$\beta=0.27, p=0.07$
	Adjusted	$\beta=0.32, p=0.05^*$	$\beta=0.31, p=0.05$	$\beta=0.35, p=0.03^*$	$\beta=0.17, p=0.27$
NBS*ISEL ²	Non-adjusted	$\beta=0.18, p=0.30$	$\beta=0.12, p=0.51$	$\beta=0.21, p=0.23$	$\beta=-0.04, p=0.83$
	Adjusted	$\beta=0.18, p=0.35$	$\beta=0.08, p=0.66$	$\beta=0.14, p=0.46$	$\beta=-0.03, p=0.88$

OES, Ostracism Experience Scale; LSNS, Lubben Social Network Scale; CTQ, Childhood Trauma Questionnaire; NBS, Need to Belong Scale; ISEL, Interpersonal Support Evaluation List; NBS*ISEL, interaction between the two variables.

¹ Covariates: age, sex, smoking-status (yes/no), PET/CT-scanner type (Biograph Horizon or Vereos)

² Variables were centred prior to calculating their interaction effect.

* $p < 0.05$

Supplementary Figure 2

Unadjusted scatterplot of the relationship between total scores on the Childhood Trauma Questionnaire (CTQ) and presynaptic dopamine synthesis capacity (k_i^{cer}) in the whole striatum in adults with autism spectrum disorder.

Supplementary Table 6

Associations between measures of social defeat and striatal k_i^{cer} in controls, before and after adjusting for covariates.

Variable	Covariates ¹	Striatal region (k_i^{cer})			
		Whole striatum	Associative striatum	Limbic striatum	Sensorimotor striatum
UCLA Loneliness Scale	Non-adjusted	$\beta=-0.25$, $p=0.26$	$\beta=-0.28$, $p=0.21$	$\beta=-0.27$, $p=0.22$	$\beta=-0.19$, $p=0.39$
	Adjusted	$\beta=-0.35$, $p=0.14$	$\beta=-0.30$, $p=0.19$	$\beta=-0.39$, $p=0.10$	$\beta=-0.11$, $p=0.60$
OES	Non-adjusted	$\beta=-0.22$, $p=0.32$	$\beta=-0.20$, $p=0.38$	$\beta=-0.24$, $p=0.28$	$\beta=-0.07$, $p=0.76$
	Adjusted	$\beta=-0.29$, $p=0.19$	$\beta=-0.28$, $p=0.19$	$\beta=-0.30$, $p=0.18$	$\beta=-0.13$, $p=0.49$
Bullied (yes/no)	Non-adjusted	$\beta=-0.11$, $p=0.64$	$\beta=-0.01$, $p=0.97$	$\beta=-0.12$, $p=0.60$	$\beta=0.11$, $p=0.61$
	Adjusted	$\beta=-0.10$, $p=0.72$	$\beta=-0.14$, $p=0.62$	$\beta=-0.07$, $p=0.80$	$\beta=-0.15$, $p=0.54$
Bullying total duration in months	Non-adjusted	$\beta=-0.31$, $p=0.16$	$\beta=-0.31$, $p=0.17$	$\beta=-0.32$, $p=0.15$	$\beta=-0.27$, $p=0.23$
	Adjusted	$\beta=-0.20$, $p=0.41$	$\beta=-0.24$, $p=0.29$	$\beta=-0.21$, $p=0.39$	$\beta=-0.28$, $p=0.16$
LSNS	Non-adjusted	$\beta=0.16$, $p=0.49$	$\beta=0.16$, $p=0.48$	$\beta=0.15$, $p=0.49$	$\beta=0.17$, $p=0.45$
	Adjusted	$\beta=0.17$, $p=0.45$	$\beta=0.19$, $p=0.36$	$\beta=0.16$, $p=0.49$	$\beta=0.23$, $p=0.22$
CTQ	Non-adjusted	$\beta=-0.38$, $p=0.08$	$\beta=-0.36$, $p=0.10$	$\beta=-0.37$, $p=0.09$	$\beta=-0.27$, $p=0.23$
	Adjusted	$\beta=-0.51$, $p=0.03^*$	$\beta=-0.50$, $p=0.03^*$	$\beta=-0.48$, $p=0.05$	$\beta=-0.41$, $p=0.04^*$
NBS*ISEL ²	Non-adjusted	$\beta=-0.48$, $p=0.26$	$\beta=-0.47$, $p=0.26$	$\beta=-0.49$, $p=0.23$	$\beta=-0.26$, $p=0.54$
	Adjusted	$\beta=-0.93$, $p=0.03^*$	$\beta=-0.94$, $p=0.02^*$	$\beta=-0.87$, $p=0.05$	$\beta=-0.78$, $p=0.03^*$

OES, Ostracism Experience Scale; LSNS, Lubben Social Network Scale; CTQ, Childhood Trauma Questionnaire; NBS, Need to Belong Scale; ISEL, Interpersonal Support Evaluation List.

¹ Covariates: age, sex, smoking-status (yes/no), PET/CT-scanner type (Vereos or Biograph Horizon)

² Variables were centred prior to calculating their interaction effect.

* $p < 0.05$

Supplementary Figure 3
Unadjusted scatterplot of the relationship between total scores on the Childhood Trauma Questionnaire (CTQ) and presynaptic dopamine synthesis capacity (k_i^{cer}) in the whole striatum in controls.

Supplementary Figure 4

Unadjusted scatterplot of the relationship between scores on the Interpersonal Support Evaluation List (ISEL) and presynaptic dopamine synthesis capacity ($k_{i^{cer}}$) in controls with lowest ($n=7$), medium ($n=8$), and highest ($n=7$) scores on the Need to Belong Scale (NBS).

Supplementary Table 7
Associations between striatal k_i^{cer} and measures of psychosis.

Analysis	Covariates ¹	Striatal region (k_i^{cer})			
		Whole striatum	Associative	Limbic	Sensorimotor
PQ-16 in ASD ⁵	Non-adjusted	$\beta=-0.12, p=0.51$	$\beta=-0.17, p=0.37$	$\beta=-0.04, p=0.82$	$\beta=-0.17, p=0.35$
	Adjusted	$\beta=-0.05, p=0.81^7$	$\beta=-0.10, p=0.61$	$\beta=0.01, p=0.95$	$\beta=-0.10, p=0.62$
PQ-16 in controls ⁶	Non-adjusted	$\beta=-0.36, p=0.16$	$\beta=-0.27, p=0.29$	$\beta=-0.34, p=0.18$	$\beta=-0.05, p=0.86$
	Adjusted	$\beta=-0.26, p=0.30^7$	$\beta=-0.21, p=0.38$	$\beta=-0.22, p=0.40$	$\beta=-0.09, p=0.69$

ASD, autism spectrum disorder; CHR, clinical high risk; PQ-16, Prodromal Questionnaire-16.

¹ Covariates: age, sex, smoking-status (yes/no), PET/CT-scanner type (Vereos or Biograph Horizon)

² $n=3$ (all ASD)

³ $n=41$

⁴ $n=24$

⁵ $n=31$

⁶ $n=17$

⁷ As reported in the main article.

Supplementary Table 8*Associations between striatal k_i^{cer} and measures of depressed mood and anxiety.*

Analysis	Covariates ¹	Striatal region (k_i^{cer})			
		Whole striatum	Associative	Limbic	Sensorimotor
BDI-II in ASD	Non-adjusted	$\beta=-0.17, p=0.27$	$\beta=-0.20, p=0.19$	$\beta=-0.11, p=0.46$	$\beta=-0.26, p=0.09$
	Adjusted	$\beta=-0.11, p=0.51$	$\beta=-0.12, p=0.46$	$\beta=-0.04, p=0.81$	$\beta=-0.19, p=0.22$
BDI-II in controls	Non-adjusted	$\beta=-0.02, p=0.93$	$\beta=-0.05, p=0.82$	$\beta=0.00, p=1.00$	$\beta=-0.04, p=0.85$
	Adjusted	$\beta=0.01, p=0.97$	$\beta=0.05, p=0.83$	$\beta=0.00, p=0.99$	$\beta=0.15, p=0.45$
STAI-T in ASD	Non-adjusted	$\beta=0.12, p=0.46$	$\beta=0.10, p=0.54$	$\beta=0.20, p=0.18$	$\beta=-0.04, p=0.80$
	Adjusted	$\beta=0.13, p=0.40$	$\beta=0.12, p=0.43$	$\beta=0.23, p=0.13$	$\beta=-0.02, p=0.87$
STAI-T in controls	Non-adjusted	$\beta=-0.14, p=0.52$	$\beta=-0.10, p=0.67$	$\beta=-0.20, p=0.38$	$\beta=0.03, p=0.88$
	Adjusted	$\beta=-0.20, p=0.37$	$\beta=-0.15, p=0.47$	$\beta=-0.24, p=0.28$	$\beta=-0.02, p=0.93$

ASD, autism spectrum disorder; CHR, clinical high risk; BDI-II, Beck's Depression Inventory-II; STAI-T, State-Trait Anxiety Inventory-Trait subscale.

¹ Covariates: age, sex, smoking-status (yes/no), PET/CT-scanner type (Vereos or Biograph Horizon)

Supplementary References

- Bernstein, D. P., Stein, J. A., Newcomb, M. D., Walker, E., Pogge, D., Ahluvalia, T., Stokes, J., Handelsman, L., Medrano, M., & Desmond, D. (2003). Development and validation of a brief screening version of the Childhood Trauma Questionnaire. *Child Abuse & Neglect*, 27(2), 169-190.
- Cohen, S., Mermelstein, R., Kamarck, T., & Hoberman, H. M. (1985). Measuring the functional components of social support. In *Social support: Theory, research and applications* (pp. 73-94). Springer.
- Gevonden, M., Booij, J., van den Brink, W., Heijtel, D., van Os, J., & Selten, J.-P. (2014). Increased release of dopamine in the striata of young adults with hearing impairment and its relevance for the social defeat hypothesis of schizophrenia. *JAMA Psychiatry*, 71(12), 1364-1372.
- Gilman, R., Carter-Sowell, A., DeWall, C. N., Adams, R. E., & Carboni, I. (2013). Validation of the ostracism experience scale for adolescents. *Psychological Assessment*, 25(2), 319.
- Hammers, A., Allom, R., Koepp, M. J., Free, S. L., Myers, R., Lemieux, L., Mitchell, T. N., Brooks, D. J., & Duncan, J. S. (2003). Three-dimensional maximum probability atlas of the human brain, with particular reference to the temporal lobe. *Human Brain Mapping*, 19(4), 224-247.
- Ising, H. K., Veling, W., Loewy, R. L., Rietveld, M. W., Rietdijk, J., Dragt, S., Klaassen, R. M., Nieman, D. H., Wunderink, L., & Linszen, D. H. (2012). The validity of the 16-item version of the Prodromal Questionnaire (PQ-16) to screen for ultra high risk of developing psychosis in the general help-seeking population. *Schizophrenia Bulletin*, 38(6), 1288-1296.
- Jenkinson, M., Beckmann, C. F., Behrens, T. E., Woolrich, M. W., & Smith, S. M. (2012). Fsl. *Neuroimage*, 62(2), 782-790.
- Kapur, S., Zipursky, R., Jones, C., Shammi, C., Remington, G., & Seeman, P. (2000). A positron emission tomography study of quetiapine in schizophrenia: a preliminary finding of an antipsychotic effect with only transiently high dopamine D2 receptor occupancy. *Archives of General Psychiatry*, 57(6), 553-559.
- Leary, M. R., Kelly, K. M., Cottrell, C. A., & Schreindorfer, L. S. (2013). Construct validity of the need to belong scale: Mapping the nomological network. *Journal of Personality Assessment*, 95(6), 610-624.
- Loewy, R. L., Pearson, R., Vinogradov, S., Bearden, C. E., & Cannon, T. D. (2011). Psychosis risk screening with the Prodromal Questionnaire—brief version (PQ-B). *Schizophrenia Research*, 129(1), 42-46.
- Lubben, J., Blozik, E., Gillmann, G., Iliffe, S., von Renteln Kruse, W., Beck, J. C., & Stuck, A. E. (2006). Performance of an abbreviated version of the Lubben Social Network Scale among three European community-dwelling older adult populations. *The Gerontologist*, 46(4), 503-513.
- McCarthy, P. (2020). *FSLeys*. <https://users.fmrib.ox.ac.uk/~paulmc/fsleyes/userdoc/latest>
- Olweus, D. (1996). Revised Olweus Bully/Victim Questionnaire. *British Journal of Educational Psychology*.
- Russell, D. W. (1996). UCLA Loneliness Scale (Version 3): Reliability, validity, and factor structure. *Journal of Personality Assessment*, 66(1), 20-40.
- Selten, J.-P., van der Ven, E., Rutten, B. P., & Cantor-Graae, E. (2013). The social defeat hypothesis of schizophrenia: an update. *Schizophrenia Bulletin*, 39(6), 1180-1186.

- Spinhoven, P., Penninx, B. W., Hickendorff, M., van Hemert, A. M., Bernstein, D. P., & Elzinga, B. M. (2014). Childhood Trauma Questionnaire: factor structure, measurement invariance, and validity across emotional disorders. *Psychological Assessment*, 26(3), 717-729.
- Thombs, B. D., Bernstein, D. P., Lobbetael, J., & Arntz, A. (2009). A validation study of the Dutch Childhood Trauma Questionnaire-Short Form: factor structure, reliability, and known-groups validity. *Child Abuse & Neglect*, 33, 518-523.
- Tziortzi, A. C., Haber, S. N., Searle, G. E., Tsoumpas, C., Long, C. J., Shotbolt, P., Douaud, G., Jbabdi, S., Behrens, T. E., & Rabiner, E. A. (2014). Connectivity-based functional analysis of dopamine release in the striatum using diffusion-weighted MRI and positron emission tomography. *Cerebral Cortex*, 24(5), 1165-1177.
- Yung, A. R., Yung, A. R., Pan Yuen, H., McGorry, P. D., Phillips, L. J., Kelly, D., Dell'olio, M., Francey, S. M., Cosgrave, E. M., & Killackey, E. (2005). Mapping the onset of psychosis: the comprehensive assessment of at-risk mental states. *Australian & New Zealand Journal of Psychiatry*, 39(11-12), 964-971.

Chapter V

Cerebral [^{18}F]-FDOPA uptake in autism spectrum disorder and its association with autistic traits

Schalbroeck, R., de Geus-Oei, L. F., Selten, J. P., Yaqub, M., Schrantee, A., van Amelsvoort, T., Booij, J., & van Velden, F. H. P.

Manuscript submitted

Abstract

Dopaminergic functioning is believed to be related to autistic traits. We conducted an exploratory 3,4-dihydroxy-6-[^{18}F]-fluoro-L-phenylalanine positron emission tomography/computed tomography ([^{18}F]-FDOPA PET/CT) study to examine cerebral [^{18}F]-FDOPA influx constant (k_i^{cer} min^{-1}), reflecting predominantly striatal dopamine synthesis capacity and a mixed monoaminergic innervation in extrastriatal neurons, in adults diagnosed with autism spectrum disorder (ASD). Unmedicated, non-psychotic adults with ASD ($n = 44$) and controls ($n = 22$) aged 18 to 30 years completed a dynamic [^{18}F]-FDOPA PET/CT scan. Autistic traits were assessed with the Autism Spectrum Quotient (AQ). Region-of-interest and voxel-based analyses showed no statistically significant differences in k_i^{cer} values between adults with ASD and controls. However, in adults with ASD, but not in controls, k_i^{cer} values in the whole striatum, putamen, and nucleus accumbens were significantly, negatively associated with AQ attention to detail subscale scores. No other significant associations in striatal or extra-striatal regions were observed. In conclusion, among adults with ASD, specific autistic traits may be associated with reduced striatal dopamine synthesis capacity. Our findings contribute to a better understanding of neurotransmission in ASD, and may help guide future best-practice treatment guidelines.

1. Introduction

Atypical functioning of dopaminergic and other monoaminergic systems has long been hypothesized to contribute to autism spectrum disorder (ASD) traits (e.g., Damasio & Maurer, 1978). For instance, according to the dopamine hypothesis of ASD (Pavál, 2017), alterations in the midbrain dopaminergic system are associated with clinical and subclinical autistic traits related to difficulties in social interaction and communication and stereotyped behaviours. However, there is a lack of studies assessing monoaminergic functioning *in vivo* in ASD (Zürcher et al., 2015).

Two positron emission tomography/computed tomography (PET/CT) studies have used 3,4-dihydroxy-6-[^{18}F]-fluoro-L-phenylalanine ([^{18}F]-FDOPA) to assess presynaptic dopamine synthesis capacity in ASD. One found that [^{18}F]-FDOPA uptake was decreased in the anterior medial prefrontal cortex in (mostly-sedated) autistic children ($n = 14$) relative to typically-developing controls ($n = 10$) (Ernst et al., 1997). The other found that [^{18}F]-FDOPA uptake was increased in frontal and striatal regions in adults with Asperger syndrome ($n = 8$) relative to controls ($n = 5$) (Nieminen-von Wendt et al., 2004). However, in both studies, sample sizes were small, and associations with measures of autistic traits were not examined.

The social defeat hypothesis of schizophrenia posits that a subordinate or outsider position leads to an increased baseline activity or sensitization of the mesolimbic dopamine system and thereby to an increased risk of schizophrenia (Selten et al., 2017). Since ASD is a risk factor for schizophrenia (Lai et al., 2019), we conducted a large [^{18}F]-FDOPA PET/CT study and tested the pre-registered hypothesis of increased striatal dopamine synthesis capacity in non-psychotic individuals with ASD (Schalbroeck et al., 2021). Contrary to our hypothesis, the results indicated no differences in striatal [^{18}F]-FDOPA uptake between individuals with ASD ($n = 44$) and controls ($n = 22$), and no association between this uptake and social defeat.

Here we extend our previous study with exploratory region-of-interest (ROI) and voxel-based analyses, in which we compare cerebral [^{18}F]-FDOPA uptake between adults with ASD and controls, and examine its association with self-reported autistic traits.

2. Methods

2.1 Participants and procedures

Full procedures are described in our previous publication (Schalbroeck et al., 2021). We recruited unmedicated Dutch participants aged 18 to 30 years. Those with ASD had received their diagnosis from a registered mental health clinician, and this diagnosis was confirmed by the first author using the Autism Diagnostic Observation Schedule-2 (ADOS-2) module 4 (Lord et al., 2012; Hus & Lord, 2014). We included 44 participants with ASD and 22 controls (frequency-matched on age, sex, and smoking-status). All participants provided informed consent. The study was approved by the medical ethics committee of the Leiden University Medical Center (reference NL54244.058.15).

2.2 Autism Spectrum Quotient

The Autism Spectrum Quotient (AQ) is a 50-item self-report questionnaire that assesses the presence of autistic traits (Baron-Cohen et al., 2001). Items are scored between 1 (definitely agree) and 4 (definitely disagree). After reverse-scoring, higher total scores reflect the presence of more autistic traits. Additionally, in line with the original validation of the Dutch AQ (Hoekstra et al., 2008), we calculated scores on the “social interaction” and “attention to detail” subscales. Higher scores on these subscales indicate greater difficulties in social interactions, and a greater attention to, and interests in, patterns and details, respectively. The AQ was completed by both samples.

2.3 MRI and PET/CT acquisition and processing

Details of magnetic resonance imaging (MRI) and PET/CT-acquisitions and initial processing steps have been described previously (Schalbroeck et al., 2021). In short, a structural T1-weighted MRI-scan was obtained on a 3T Ingenia (Philips Healthcare, Best, The Netherlands). A 90-minute dynamic PET-scan was obtained on a Biograph Horizon with TrueV option (Siemens Healthineers, Erlangen, Germany) or Vereos (Philips Healthcare, Best, The Netherlands) directly after the administration of approximately 150 MBq [^{18}F]-FDOPA. A low-dose CT-scan (110/120 kVp, 35 mAs) was acquired for attenuation-correction purposes. Participants consumed 150 mg carbidopa and 400 mg entacapone one hour before starting the PET/CT-scan.

We used [^{18}F]-FDOPA uptake in grey matter (GM) cerebellum as a reference to calculate the influx constant k_i^{cer} (min^{-1} ; from here on labelled as k_i^{cer}) throughout the brain using reference Patlak graphical analysis (Patlak & Blasberg, 1985). ROIs were automatically identified from the co-registered MRI-scan using PVELab (v2.3; Neurobiology Research Unit, Copenhagen, Denmark; Quarantelli et al., 2004; Svarer et al., 2005), using a maximum probability atlas (Hammers et al., 2003). ROIs included the combined left- and right-hemisphere GM of the whole striatum and three striatal anatomical sub-regions (putamen, nucleus accumbens, and caudate nucleus), which were selected on the basis of their putative role in ASD (Pavál, 2017), and/or their proven reliability in terms of imaging [^{18}F]-FDOPA uptake (Egerton et al., 2010).

In addition to the ROI analysis, the parametric image of each participant was transformed to standard-space to facilitate voxel-based comparisons. To do so, we first normalized the participant’s co-registered MRI-scan using SPM12 (Institute of Neurology, London, UK). The resulting transformation matrix was applied to the parametric image, which was then smoothed using an 8 mm full-width-at-half-maximum (FWHM) Gaussian filter (Egerton et al., 2010).

2.4 Statistical analysis

With reference to the ROI method, we used multiple linear regression analysis to compare regional k_i^{cer} values between ASD and controls and to assess the associations of k_i^{cer} with AQ total and subscale scores. We adjusted for four confounders, i.e., age, sex, smoker status (yes/no), and scanner-type (Vereos/Biograph Horizon). A two-tailed p -value of 0.05 was used to evaluate statistical significance.

As for the voxel-based comparisons, an independent samples t -test was used to examine group differences in k_i^{cer} , and multiple linear regression analysis was used to examine associations between k_i^{cer} and AQ scores. Confounders included age, sex, smoker status, and scanner-type. A family-wise error (FWE) rate of $\alpha = 0.05$ was used to evaluate statistical significance. We conducted several additional control analyses. First, we repeated our analyses restricting to voxels with a k_i^{cer} above 0.001, effectively excluding voxels showing little specific [^{18}F]-FDOPA uptake and thereby reducing the number of FWE-adjustments. Second, we repeated our analyses with unsmoothed data and after smoothing with a 4 mm FWHM Gaussian filter. Third, we conducted the analyses for the two PET/CT scanners separately.

3. Results

3.1 Sample characteristics

Sample characteristics are reported in Table 1. Participants with ASD had significantly higher AQ total scores ($t_{64} = 8.74, p < 0.001$), as well as social interaction ($t_{64} = 8.34, p < 0.001$) and attention to detail ($t_{64} = 5.55, p < 0.001$) subscale scores.

Table 1

Sample characteristics of adults with autism spectrum disorder (ASD) and controls.

Variable	ASD ($n = 44$)	Controls ($n = 22$)
Male, No. (%)	28 (64%)	14 (64%)
Age in years, mean (SD)	23.74 (2.64)	23.47 (2.48)
IQ, mean (SD)	103.75 (5.19)	105.05 (4.90)
Smoker, No. (%)	2 (5%)	1 (5%)
Scanned on Vereos PET/CT-scanner, No. (%)	31 (70%)	13 (59%)
Approximate injected [^{18}F]-FDOPA dose in MBq, mean (SD)	161.55 (7.26)	157.24 (8.57)
AQ total score, mean (SD)	132.41 (20.05)	91.73 (12.01)
AQ social interaction subscale, mean (SD)	105.25 (17.65)	71.27 (10.22)
AQ attention to detail subscale, mean (SD)	27.16 (4.94)	20.45 (4.19)

SD, standard deviation; IQ, intelligence quotient; MBq, megabecquerel; AQ, Autism Spectrum Quotient.

3.2 ROI analyses

Table 2 shows the k_i^{cer} values in striatal ROIs and their associations with AQ total and subscale scores. We found no significant differences in striatal k_i^{cer} values between ASD and controls. Moreover, within the control sample, and within the combined ASD and control sample, we found no significant associations between AQ scores and striatal k_i^{cer} values. In contrast, in the ASD sample, k_i^{cer} values in the whole striatum, putamen, and nucleus accumbens were significantly negatively associated with AQ attention to detail subscale scores. These associations remained negative when we examined the results without adjusting for confounders or for the two PET/CT scanners separately, although they became statistically non-significant. No other statistically significant associations were observed.

Table 2*Striatal [^{18}F]-FDOPA uptake (k_i^{cer} min $^{-1}$) in adults with ASD and controls, and its association with self-reported autistic traits.*

ROI	Association between k_i^{cer} value and AQ scores											
	k_i^{cer} , mean (SD)			ASD			Controls			Combined sample		
	ASD	Controls	p-value	Total	Social	Detail	Total	Social	Detail	Total	Social	Detail
Whole	0.0145	0.0143	0.87 ¹	$\beta = -0.04$, $p = 0.81$	$\beta = 0.04$, $p = 0.80$	$\beta = -0.35$, $p = 0.04^*$	$\beta = 0.08$, $p = 0.74$	$\beta = 0.08$, $p = 0.74$	$\beta = 0.03$, $p = 0.90$	$\beta = 0.02$, $p = 0.87$	$\beta = 0.06$, $p = 0.65$	$\beta = -0.14$, $p = 0.28$
striatum	(0.0023) ¹	(0.0024) ¹										
Putamen	0.0157	0.0153	0.61	$\beta = 0.03$, $p = 0.86$	$\beta = 0.12$, $p = 0.46$	$\beta = -0.36$, $p = 0.04^*$	$\beta = 0.10$, $p = 0.67$	$\beta = 0.06$, $p = 0.80$	$\beta = 0.13$, $p = 0.56$	$\beta = 0.10$, $p = 0.43$	$\beta = 0.14$, $p = 0.28$	$\beta = -0.08$, $p = 0.52$
NAcc	(0.0025)	(0.0026)										
	0.0114	0.0108	0.38	$\beta = -0.09$, $p = 0.58$	$\beta = 0.00$, $p = 0.99$	$\beta = -0.43$, $p = 0.01^*$	$\beta = 0.13$, $p = 0.59$	$\beta = 0.14$, $p = 0.57$	$\beta = 0.04$, $p = 0.85$	$\beta = 0.09$, $p = 0.49$	$\beta = 0.12$, $p = 0.33$	$\beta = -0.10$, $p = 0.45$
Caudate	(0.0024)	(0.0024)										
	0.0135	0.0137	0.69	$\beta = -0.12$, $p = 0.48$	$\beta = -0.06$, $p = 0.72$	$\beta = -0.29$, $p = 0.09$	$\beta = 0.05$, $p = 0.84$	$\beta = 0.10$, $p = 0.69$	$\beta = -0.09$, $p = 0.72$	$\beta = -0.09$, $p = 0.48$	$\beta = -0.05$, $p = 0.66$	$\beta = -0.19$, $p = 0.12$
nucleus	(0.0022)	(0.0025)										
ASD, autism spectrum disorder; AQ, Autism Spectrum Quotient; SD, standard deviation; ROI, region-of-interest; Total, AQ total scores; Social, AQ social interaction subscale scores; Detail, AQ attention to detail subscale scores; NAcc, nucleus accumbens.												

ASD, autism spectrum disorder; AQ, Autism Spectrum Quotient; SD, standard deviation; ROI, region-of-interest; Total, AQ total scores; Social, AQ social interaction subscale scores; Detail, AQ attention to detail subscale scores; NAcc, nucleus accumbens.

Analyses adjusted for age, sex, smoking status, and PET/CT scanner type.

¹ As reported in Schalbroeck et al. (2021).

* $p < 0.05$

3.3 Voxel-based comparisons

Figure 1 shows the average whole-brain k_i^{cer} for ASD and control participants. We found no statistically significant differences in k_i^{cer} between ASD and controls. Moreover, in the separate and combined samples, k_i^{cer} values showed no significant associations with AQ total or subscale scores in any of the individual voxels. Results were similar regardless of whether we did or did not adjust for confounders, used a threshold of $k_i^{cer} > 0.001$, used unsmoothed data, smoothed with a 4 mm FWHM Gaussian filter, or examined the results for the two PET/CT scanners separately.

Figure 1

Axial (left), coronal (middle), and sagittal (right) view of the mean cerebral [^{18}F]-FDOPA uptake ($k_i^{cer} \text{ min}^{-1}$) in (A) adults with autism spectrum disorder ($n = 44$), and (B) controls ($n = 22$). Unadjusted, unsmoothed data are shown.

A

B

4. Discussion

In this exploratory study, we found no significant differences in striatal and extrastriatal [^{18}F]-FDOPA uptake in unmedicated adults with ASD relative to controls. In the ASD sample, but not in the control or combined samples, AQ attention to detail subscale scores significantly negatively correlated with dopamine synthesis capacity in the whole striatum, putamen, and nucleus accumbens. No other significant associations were found.

The results of our exploratory analyses confirm our previous ROI analysis, in which we found no differences in [^{18}F]-FDOPA uptake in the striatum and its functional sub-regions (i.e., associative, limbic, and sensorimotor striatum) between ASD and controls (Schalbroeck et al., 2021). We extend these findings by showing that [^{18}F]-FDOPA uptake does not differ in anatomical sub-regions of the striatum (i.e., putamen, nucleus accumbens, and caudate nucleus) nor in extrastriatal brain regions. In the striatum, [^{18}F]-FDOPA is decarboxylated to fluorodopamine through amino acid decarboxylase (AADC) and stored in vesicles within presynaptic terminals (Moore et al., 2003). Although it is well-established that striatal [^{18}F]-FDOPA uptake represents dopamine synthesis capacity, the radiotracer is taken up and stored by all AADC-containing, monoaminergic neurons (Brown et al., 1999). On the one hand, this can be considered a limitation of the method, since to some extent it remains unknown what [^{18}F]-FDOPA uptake in extrastriatal regions reflects (Egerton et al., 2010). On the other hand, since we observed no significant difference in uptake in the whole brain, this might indicate that for instance also serotonergic functioning in the raphe nuclei may be unaltered in ASD (Pavese et al., 2012).

Our findings partially differ from the study by Ernst et al. (1997), who reported decreased [^{18}F]-FDOPA uptake in the anterior medial prefrontal cortex in autistic children ($n = 14$), and from the study by Nieminen-von Wendt et al. (2004), who found increased [^{18}F]-FDOPA uptake in striatal and frontal regions in adults with Asperger syndrome ($n = 8$). Future studies can assess whether the differences in samples in terms of factors such as age, ASD diagnosis, and symptom severity might have contributed to these partially discrepant findings.

Although we found no group differences in [^{18}F]-FDOPA uptake, we did find significant negative associations between AQ attention to detail subscale scores and dopamine synthesis capacity in striatal ROIs among adults with ASD. Notably, a recent study showed that in individuals with ASD ($n = 18$), but not in controls ($n = 20$), striatal dopamine D_1 receptor binding was negatively associated with the same AQ attention to detail subscale (Kubota et al., 2020). This finding might be accounted for by either increased endogenous dopamine or by the expression of fewer D_1 receptors. This latter explanation seems more plausible since the authors note that the assessment of D_1 receptor binding is unlikely to be strongly influenced by the availability of endogenous dopamine. Our findings of no increased striatal dopamine synthesis capacity in ASD, and another recent study reporting decreased striatal dopamine release in response to monetary reward in adults with ASD ($n = 10$) compared to controls ($n = 12$) (Zürcher et al., 2021), also support this interpretation, as these suggest that endogenous synaptic dopamine may be not higher in ASD. Together, these findings can then be interpreted as indicating that a reduction in striatal dopamine signalling is associated with attentional processes relevant to ASD, which accords with previous theoretical and empirical work on the role of striatal dopamine in ASD (Damasio & Maurer, 1978; Fuccillo, 2016; Pavál, 2017).

Still, striatal dopamine might be related to attentional processing in ASD in different ways. For example, striatal dopamine could be involved in the direction of attention to salient information (Kapur et al., 2005; Cools & D'Esposito, 2011; Fuccillo, 2016), but our findings might also reflect alterations secondary to perturbations in other neurotransmitter systems. Future studies, combining molecular

imaging methods with objective assessments of cognitive functioning would be useful in this respect. Of note, there has been a relative scarcity of molecular imaging studies in ASD (Zürcher et al., 2015), and future (preferably longitudinal) assessments of different aspects of the dopamine and other neurotransmitter systems would help elucidate the role of these systems in ASD. Such assessments might also increase our knowledge on why certain medications might (not) work in autistic individuals, which, given their high prescription rates (Wong et al., 2014), seems useful and necessary.

Strengths of the present study are its large sample size and the completion of additional analyses to ensure the robustness of our findings. Note that, as reported previously (Schalbroeck et al., 2021), the mean cerebellar standardized uptake values were comparable for ASD and controls and therefore possible differences in non-specific uptake of [^{18}F]-FDOPA can be excluded.

A limitation of the study is the exclusion of participants such as those with a low IQ or with psychotic symptoms, as we do not know how our findings generalize to those populations. Moreover, autistic traits were assessed by self-report only. Furthermore, the study was exploratory, and as a consequence, we did not conduct *a priori* sample size calculations for the present study purposes.

In conclusion, our exploratory findings indicate that [^{18}F]-FDOPA uptake in the brain does not significantly differ between adults with ASD and controls, but do show that striatal dopamine synthesis capacity is negatively associated with scores on the AQ attention to detail subscale in ASD.

5. References

- Baron-Cohen, S., Wheelwright, S., Skinner, R., Martin, J., & Clubley, E. (2001). The autism-spectrum quotient (AQ): Evidence from asperger syndrome/high-functioning autism, males and females, scientists and mathematicians. *Journal of Autism and Developmental Disorders*, 31(1), 5-17.
- Brown, W. D., Taylor, M., Roberts, A. D., Oakes, T. R., Schueller, M., Holden, J. E., Malischke, L., DeJesus, O. T., & Nickles, R. J. (1999). FluoroDOPA PET shows the nondopaminergic as well as dopaminergic destinations of levodopa. *Neurology*, 53(6), 1212-1253.
- Cools, R., & D'Esposito, M. (2011). Inverted-U-shaped dopamine actions on human working memory and cognitive control. *Biological Psychiatry*, 69(12), e113-e125.
- Damasio, A. R., & Maurer, R. G. (1978). A neurological model for childhood autism. *Archives of Neurology*, 35(12), 777-786.
- Egerton, A., Denjaha, A., McGuire, P., Mehta, M. A., & Howes, O. D. (2010). The test-retest reliability of 18F-DOPA PET in assessing striatal and extrastriatal presynaptic dopaminergic function. *Neuroimage*, 50(2), 524-531.
- Ernst, M., Zametkin, A., Matochik, J., Pascualvaca, D., & Cohen, R. (1997). Low medial prefrontal dopaminergic activity in autistic children. *The Lancet*, 350(9078), 638.
- Fuccillo, M. V. (2016). Striatal circuits as a common node for autism pathophysiology. *Frontiers in Neuroscience*, 10, 1-19.
- Hammers, A., Allom, R., Koeppe, M. J., Free, S. L., Myers, R., Lemieux, L., Mitchell, T. N., Brooks, D. J., & Duncan, J. S. (2003). Three-dimensional maximum probability atlas of the human brain, with particular reference to the temporal lobe. *Human Brain Mapping*, 19(4), 224-247.
- Hoekstra, R. A., Bartels, M., Cath, D. C., & Boomsma, D. I. (2008). Factor structure, reliability and criterion validity of the Autism-Spectrum Quotient (AQ): a study in Dutch population and patient groups. *Journal of Autism and Developmental Disorders*, 38(8), 1555-1566.
- Hus, V., & Lord, C. (2014). The autism diagnostic observation schedule, module 4: revised algorithm and standardized severity scores. *Journal of Autism and Developmental Disorders*, 44(8), 1996-2012.
- Kapur, S., Mizrahi, R., & Li, M. (2005). From dopamine to salience to psychosis—linking biology, pharmacology and phenomenology of psychosis. *Schizophrenia Research*, 79(1), 59-68.
- Kubota, M., Fujino, J., Tei, S., Takahata, K., Matsuoka, K., Tagai, K., Sano, Y., Yamamoto, Y., Shimada, H., & Takado, Y. (2020). Binding of Dopamine D₁ Receptor and Noradrenaline Transporter in Individuals with Autism Spectrum Disorder: A PET Study. *Cerebral Cortex*, 30(12), 6458-6468.
- Lai, M.-C., Kassee, C., Besney, R., Bonato, S., Hull, L., Mandy, W., Szatmari, P., & Ameis, S. H. (2019). Prevalence of co-occurring mental health diagnoses in the autism population: a systematic review and meta-analysis. *The Lancet Psychiatry*, 6(10), 819-829.
- Lord, C., Petkova, E., Hus, V., Gan, W., Lu, F., Martin, D. M., Ousley, O., Guy, L., Bernier, R., & Gerds, J. (2012). A multisite study of the clinical diagnosis of different autism spectrum disorders. *Archives of General Psychiatry*, 69(3), 306-313.
- Moore, R. Y., Whone, A. L., McGowan, S., & Brooks, D. J. (2003). Monoamine neuron innervation of the normal human brain: an ^{18}F -DOPA PET study. *Brain Research*, 982(2), 137-145.
- Nieminen-von Wendt, T. S., Metsähonkala, L., Kulomäki, T. A., Aalto, S., Autti, T. H., Vanhala, R., Eskola, O., Bergman, J., Hietala, J. A., & von Wendt, L. O. (2004). Increased presynaptic dopamine function in Asperger syndrome. *Neuroreport*, 15(5), 757-760.

- Patlak, C. S., & Blasberg, R. G. (1985). Graphical evaluation of blood-to-brain transfer constants from multiple-time uptake data. Generalizations. *Journal of Cerebral Blood Flow & Metabolism*, 5(4), 584-590.
- Pavál, D. (2017). A dopamine hypothesis of autism spectrum disorder. *Developmental Neuroscience*, 39(5), 355-360.
- Pavese, N., Simpson, B., Metta, V., Ramlackhansingh, A., Chaudhuri, K. R., & Brooks, D. J. (2012). [^{18}F]FDOPA uptake in the raphe nuclei complex reflects serotonin transporter availability. A combined [^{18}F]FDOPA and [^{11}C]DASB PET study in Parkinson's disease. *Neuroimage*, 59(2), 1080-1084.
- Quarantelli, M., Berkouk, K., Prinster, A., Landeau, B., Svarer, C., Balkay, L., Alfano, B., Brunetti, A., Baron, J.-C., & Salvatore, M. (2004). Integrated software for the analysis of brain PET/SPECT studies with partial-volume-effect correction. *Journal of Nuclear Medicine*, 45(2), 192-201.
- Schalbroeck, R., van Velden, F. H. P., de Geus-Oei, L.-F., Yaqub, M., van Amelsvoort, T., Booij, J., & Seltén, J.-P. (2021). Striatal dopamine synthesis capacity in autism spectrum disorder and its relation with social defeat: an [^{18}F]-FDOPA PET/CT study. *Translational Psychiatry*, 11, 1-10.
- Seltén, J.-P., Booij, J., Buwalda, B., & Meyer-Lindenberg, A. (2017). Biological mechanisms whereby social exclusion may contribute to the etiology of psychosis: a narrative review. *Schizophrenia Bulletin*, 43(2), 287-292.
- Svarer, C., Madsen, K., Hasselbalch, S. G., Pinborg, L. H., Haugbøl, S., Frøkjær, V. G., Holm, S., Paulson, O. B., & Knudsen, G. M. (2005). MR-based automatic delineation of volumes of interest in human brain PET images using probability maps. *Neuroimage*, 24(4), 969-979.
- Wong, A. Y., Hsia, Y., Chan, E. W., Murphy, D. G., Simonoff, E., Buitelaar, J. K., & Wong, I. C. (2014). The variation of psychopharmacological prescription rates for people with autism spectrum disorder (ASD) in 30 countries. *Autism Research*, 7(5), 543-554.
- Zürcher, N. R., Bhanot, A., McDougale, C. J., & Hooker, J. M. (2015). A systematic review of molecular imaging (PET and SPECT) in autism spectrum disorder: current state and future research opportunities. *Neuroscience & Biobehavioral Reviews*, 52, 56-73.
- Zürcher, N. R., Walsh, E. C., Phillips, R. D., Cernasov, P. M., Tseng, C.-E. J., Dharanikota, A., Smith, E., Li, Z., Kinard, J. L., & Bizzell, J. C. (2021). A simultaneous [^{11}C]raclopride positron emission tomography and functional magnetic resonance imaging investigation of striatal dopamine binding in autism. *Translational Psychiatry*, 11(1), 1-11.

[illegible]

Chapter VI

The social defeat hypothesis of schizophrenia: a parsimonious explanation for multiple psychosis risk factors?

Schalbroeck, R.

Psychological Medicine (2020), online ahead of print, 1-2.

1. Correspondence

In their recent meta-analysis, Selten, van der Ven, and Termorshuizen (2020) report an increased risk of psychotic disorder in first- and second-generation migrants, and show that this risk is associated with skin colour and region of origin and destination. The authors argue that the social defeat hypothesis of schizophrenia offers an explanation for these findings. However, this hypothesis has limitations related to the definition and measurement of social defeat, which hinder its use as a scientific explanation for the risks of psychosis in migrants and other groups.

The social defeat hypothesis states that the negative experience of being excluded from the majority group (i.e., social exclusion) leads to a sensitized mesolimbic dopamine system and/or increased baseline activity of this system and thereby to an increased risk of schizophrenia or psychosis (Selten et al., 2013). The hypothesis originally aimed to provide a parsimonious explanation for four psychosis risk factors, including migration, low intelligence quotient (IQ), illicit drug use, and urban upbringing (Selten & Cantor-Graae, 2005), and was later also applied to groups such as individuals with autism spectrum disorder (ASD) and lesbian, gay, and bisexual individuals.

At first glance, it might seem defensible that social defeat is a common risk factor between these groups. However, since social defeat has been defined inconsistently, it is difficult to evaluate whether it truly is associated with the risk of psychosis in these individuals. That is, social defeat is defined in some publications (including the present meta-analysis) as social exclusion (e.g., Selten et al., 2013; Selten et al., 2020), and in other publications as subordinate position or outsider status (e.g., Selten et al., 2017; Selten & Cantor-Graae, 2005). Although these constructs can be related, their interchangeable use is unjustified since they are not equivalent (e.g., in contrast, a person can be in a subordinate position within a majority group).

As a result, it is unclear whether the hypothesis proposes that subordinate position, outsider status, social exclusion, or some combination of them accounts for the observed risks of psychosis in migrants and other groups (this issue is complicated even further when definitions from animal and depression research are taken into account, which define defeat in terms of losing and/or a sense of failed struggle; Gilbert et al., 2002). This lack of uniform definition of defeat also demonstrably results in conflicting interpretations of the hypothesis. For example, social defeat was operationalized in one study as loneliness as this resembled the subjective experience of social exclusion (Gevonden et al., 2014), and in another as low social rank, which was contrasted with loneliness (Jaya et al., 2017).

A second limitation of the hypothesis is that the authors argue that defeat can be difficult to measure because people do not want to admit having this experience (e.g., Selten et al., 2013). This statement is problematic for several reasons. First, it is unclear what people do not want to admit since social defeat has not been defined uniformly. Second, one can question whether this statement is true, as other studies did, for instance, measure experiences of outsider status and reduced value (van Nierop et al., 2014). Third, this statement limits the hypothesis' falsifiability, as it provides researchers with an excuse in the case of null-findings, allowing them to claim that they found no relationship between reports of social defeat and psychosis because their subjects did not want to admit feeling defeated.

Several solutions to the problem of immeasurability have been proposed. First, the authors state that the hypothesis can be tested by examining risks of psychosis and/or dopaminergic functioning in groups presumed to be socially defeated (Selten et al., 2013; Selten et al., 2020). However, often it is nearly impossible to unequivocally establish whether (or to what extent) a group is socially defeated, since the experience of defeat is subjective and does not necessarily vary in proportion to exposure to social adversity (Selten & Cantor-Graae, 2005). For example, one researcher might argue that individuals

with ASD experience more social adversity and thus feel more defeated, whereas another might argue the opposite by stating that these individuals do not care about or notice their social adversity. Subsequent empirical observations then still cannot test the hypothesis. Moreover, groups presumed to be socially defeated usually share exposure to other factors, such as threat and negative affect, which could alternatively underlie observed risks of psychosis.

Second, it has been suggested that alternative measurements (e.g., of certain cognitive schemas or self-esteem) can be used to (indirectly) assess social defeat (Selten et al., 2013). However, these measurements (and/or complex interactions between them) might be associated with the development of psychosis even if they are unrelated to social defeat, and such unique contributions are likely underestimated or missed if they are solely interpreted as being indicative of social defeat.

In the past 15 years the social defeat hypothesis of schizophrenia has provided an intuitive and influential explanation for the role of the social environment in the development of psychosis. It has had demonstrable predictive power and seems to grasp some aspect of the social world that is important for understanding the development of psychosis. However, its use as a scientific hypothesis is hindered by the unclear definition and presumed immeasurability of social defeat. As a result, at this time it cannot be convincingly argued that the social defeat hypothesis provides a parsimonious explanation for the risk of psychosis in migrants and other groups.

2. References

- Gevonden, M., Booij, J., van den Brink, W., Heijtel, D., van Os, J., & Selten, J. P. (2014). Increased release of dopamine in the striata of young adults with hearing impairment and its relevance for the social defeat hypothesis of schizophrenia. *JAMA Psychiatry*, 71(12), 1364–1372.
- Gilbert, P., Allan, S., Brough, S., Melley, S., & Miles, J. (2002). Relationship of anhedonia and anxiety to social rank, defeat and entrapment. *Journal of Affective Disorders*, 71(1–3), 141–151.
- Jaya, E. S., Ascone, L., & Lincoln, T. M. (2017). Social adversity and psychosis: The mediating role of cognitive vulnerability. *Schizophrenia Bulletin*, 43(3), 557–565.
- Selten, J. P., Booij, J., Buwalda, B., & Meyer-Lindenberg, A. (2017). Biological mechanisms whereby social exclusion may contribute to the etiology of psychosis: A narrative review. *Schizophrenia Bulletin*, 43(2), 287–292.
- Selten, J. P., & Cantor-Graae, E. (2005). Social defeat: Risk factor for schizophrenia? *The British Journal of Psychiatry*, 187(2), 101–102.
- Selten, J. P., van der Ven, E., Rutten, B. P., & Cantor-Graae, E. (2013). The social defeat hypothesis of schizophrenia: An update. *Schizophrenia Bulletin*, 39(6), 1180–1186.
- Selten, J. P., van der Ven, E., & Termorshuizen, F. (2020). Migration and psychosis: A meta-analysis of incidence studies. *Psychological Medicine*, 50(2), 303–313.
- van Nierop, M., van Os, J., Gunther, N., van Zelst, C., De Graaf, R., Ten Have, M., van Dorsselaer, S., Bak, M., Myin-Germeys, I., Viechtbauer, W., van Os, J., & van Winkel, R. (2014). Does social defeat mediate the association between childhood trauma and psychosis? Evidence from the NEMESIS-2 study. *Acta Psychiatrica Scandinavica*, 129(6), 467–476.

Appendix to chapter VI

The social defeat hypothesis of schizophrenia is more topical than ever. Reply to Schalbroeck.

Selten, J. P.

Psychological Medicine (2021), online ahead of print, 1-2.

1. Correspondence

We thank Mr. Schalbroeck for his interesting and well-written letter in which he raises two points: (i) the authors of the social defeat hypothesis defined the concept of defeat inconsistently; (ii) since social defeat is difficult to measure, the hypothesis is of limited scientific value (Schalbroeck, 2020).

Firstly, we prefer the original definition of social defeat: the long-term experience of a subordinate position or outsider status (Selten & Cantor-Graae, 2005). In 2013 we defined social defeat as “the negative experience of being excluded from the majority group” to make clear that we refer to an unwanted position, not to the outsider status of individuals such as expats or avant-garde artists (Selten et al., 2013). However, we think that the experience of a subordinate position, with the accompanying lack of autonomy, is important too.

Secondly, with reference to the measurement of social defeat, we would like to distinguish between the measurement of (i) outcomes that often indicate the experience of social defeat (such as a low level of education, single status, unemployment, low income and poor housing) and (ii) the experience of social defeat itself. While the measurement of these outcomes is not particularly difficult, that of the experience of social defeat itself constitutes a problem. One can ask persons to evaluate their status, but some persons will not admit to others that they are unsuccessful. They may even not admit it to themselves. Scales to measure self-esteem, for example, do not indicate a lower global self-esteem among ethnic minority youth in western countries (Verkuyten, 1993).

The social defeat hypothesis is an interpretation of a pattern of epidemiological findings. Researchers who question the value of a hypothesis based on an interpretation may be misled by the dominance of neuroscience and its emphasis of measurement. Interpretation is vital to a discipline like psychiatry, which combines neuroscience with social science.

According to the most influential philosopher of science, the utility of a hypothesis is not determined by measurability, but by falsifiability (Popper, 1963). We developed falsifiable hypotheses (e.g., increased psychosis risk for individuals with a non-heterosexual orientation or for those with an autism spectrum disorder; increased amphetamine-induced dopamine release in the striatum of persons with hearing impairment), which survived the pertinent tests and yielded valuable information to the field (e.g., Gevonden et al., 2014a; Gevonden et al., 2014b; Selten et al., 2015). On the basis of our theory one can develop more falsifiable hypotheses, such as increased psychosis risks for Aboriginal populations in Australia, New Zealand and Canada, and for individuals with a gender identity disorder. One could criticize the hypothesis for not enabling us to predict the outcome for an individual, but such hypotheses are scarce in psychiatry.

Mr. Schalbroeck questions the possibility to establish whether a group is differentially exposed and provides the example of autism, but most persons with this disorder do feel the need for social participation. As for groups of people with a black skin colour, low IQ, hearing impairment, autism or a non-heterosexual orientation, their diminished access to mainstream society is beyond any reasonable doubt. One could argue that this method entails the risk of an ecological fallacy, which would be the case if, for instance, successful migrants were found to be at an equal risk as non-successful migrants, but the available evidence does not support this interpretation. Morgan et al. (2008) demonstrated for African-Caribbeans a clear linear relationship between the number of outcomes that reflect social defeat and the risk of psychosis.

In 2005 we were unaware of a theory developed by the epidemiologist Marmot, who proposed that persons lower in the hierarchy are more likely to be affected by a wide range of diseases, a

phenomenon he coined status syndrome (Marmot, 2005). He argued that key factors related to a person's position in the hierarchy include a subjective sense of control over one's life (autonomy) and the opportunity for social participation. The resemblance between the social defeat hypothesis and Marmot's status syndrome is striking. Both theories are based on the idea that man is a social animal that does not endure subjugation or social exclusion. According to Marmot low status leads to increased activity of the sympatho-adreno-medullary axis and the hypothalamic-pituitary-adrenal axis (HPA-axis), which leads in turn to metabolic changes and reduced immunity. While his theory does not pretend to explain why a person develops a particular disorder, the social defeat hypothesis posits that dopamine dysregulation in response to social defeat may lead to schizophrenia. Given the influence of the HPA-axis on dopaminergic pathways, one could hypothesize that an increased sensitivity of these pathways (in particular the nigrostriatal pathway) to stimulation by glucocorticoids may contribute to the vulnerability to schizophrenia.

In order to avoid any misunderstanding we would like to point out that a "parsimonious explanation for several psychosis risk factors" is not equivalent to "the experience of social defeat explains everything". As we already observed in 2005, social defeat is not always followed by the development of a psychiatric disorder and is also a risk factor for depression and addiction. Other factors, including genetic vulnerability, would determine the nature of the outcome (Selten & Cantor-Graae, 2005).

Finally, since defeating experiences have probably more impact in societies with a higher level of socio-economic inequality, the social defeat hypothesis is more topical than ever.

2. References

- Gevonden, M. J., Selten, J. P., Myin-Germeys, I., de Graaf, R., Ten Have, M., van Dorsselaer, S., van Os, J., & Veling, W. (2014a). Sexual minority status and psychotic symptoms: findings from the Netherlands Mental Health Survey and Incidence Studies (NEMESIS). *Psychological Medicine*, 44(2), 421-433.
- Gevonden, M. J., Booij, J., van den Brink, W., Heijtel, D., van Os, J., Selten, J. P. (2014b). Increased release of dopamine in the striata of young adults with hearing impairment and its relevance for the social defeat hypothesis of schizophrenia. *JAMA Psychiatry*, 71(12), 1364-1372.
- Marmot, M. (2005). *The status syndrome. How social standing affects our health and longevity*. Holt & Co.
- Morgan C., Kirkride J., Hutchinson G., Craig T., Morgan K., Dazzan P., Boydell, J., Doody, G. A., Jones, P. B., Murray, R. M., Leff, J., & Fearon, P. (2008). Cumulative social disadvantage, ethnicity and first-episode psychosis: a case-control study. *Psychological Medicine*, 38(12), 1701-1715.
- Popper, K. R. (1963). *Conjectures and refutations. The growth of scientific knowledge*. Routledge.
- Schalbroeck, R. (2020). The social defeat hypothesis of schizophrenia: a parsimonious explanation for multiple psychosis risk factors? *Psychological Medicine*, online ahead of print, 1-2.
- Selten, J. P., Cantor-Graae, E. (2005). Social defeat: risk factor for schizophrenia? *The British Journal of Psychiatry*, 187, 101-102.
- Selten, J. P., van der Ven, E., Rutten, B., Cantor-Graae, E. (2013). The social defeat hypothesis of schizophrenia: an update. *Schizophrenia Bulletin*, 39(6), 1180-1186.
- Selten, J. P., Lundberg, M., Rai, D., Magnusson, C. (2015). Risk of non-affective psychotic disorder or bipolar disorder for young people diagnosed with autism spectrum disorder. A population-based study. *JAMA Psychiatry*, 72(5), 483-489.
- Verkuyten, M. (1994). Self-esteem among ethnic minority youth in Europe. *Social Indicators Research* 32, 21-47.

vi

Chapter VII

General discussion

1. General discussion

1.1 An orderly chaos

The cover of this thesis depicts a painting by Willem van Genk, a Dutch artist who lived from 1927 to 2005 (Walda, 2019). Van Genk was diagnosed with schizophrenia, likely also met the criteria for what is now called an autism spectrum disorder (ASD), and was generally considered to be an outsider. His autistic and schizophrenic traits are reflected in his works of art, which on the one hand show a high degree of order, eye to detail, and repetitiveness, and on the other hand are chaotic, overwhelming, and filled with delusional messages. However, Van Genk's autistic and schizophrenic traits were not only a source of inspiration, but also a source of distress, and at multiple times he was admitted to the psychiatric hospital Parnassia in The Hague. His story illustrates how a person with autistic traits might be prone to developing psychotic symptoms, and according to the social defeat hypothesis of schizophrenia, his experiences as an outsider undoubtedly contributed to the development of these symptoms.

The aim of this thesis was to examine whether social defeat constitutes a risk factor for psychosis in autism. In this chapter, I will first summarize and discuss the empirical findings presented in this thesis. In particular, I will evaluate the extent to which these findings support the three predictions derived from the social defeat hypothesis, namely (1) that individuals with ASD or autistic traits are at an increased risk of developing a psychotic disorder and psychotic experiences relative to non-autistic individuals, (2) that individuals with ASD or autistic traits show an increase in striatal dopamine synthesis capacity relative to non-autistic individuals, and (3) that these risks of psychosis and increases in dopamine synthesis capacity are associated with social defeat. In the second part of this chapter, I will discuss the social defeat hypothesis itself. Finally, I will describe clinical implications and give recommendations for future research.

1.2 Risk of psychosis in autistic individuals

1.2.1 Does bias explain the risk of psychosis in autism?

We first examined whether risks of psychosis were increased in individuals with ASD or autistic traits, and thereby attempted to take into account the possible contributions of misdiagnosis and selection bias. Misdiagnosis could result from an overlap in symptoms between autism and psychosis, such as reduced social contact or difficulties with speech. These overlapping symptoms can have different developmental origins (e.g., Dossetor, 2007; Bechi et al., 2020), but if information about childhood development is limited or unavailable, then, for instance, a patient with a psychotic disorder might erroneously be diagnosed with ASD. Likewise, cross-sectional assessments of subclinical autism and psychosis features likely correlate at least in part because they ask about the same phenomena. Selection bias could result from psychotic symptoms in individuals with an as-of-yet undiagnosed ASD increasing the probability of ASD being detected.

In chapter II, we analysed data from Dutch psychiatric case registers, and found that individuals with ASD had a highly increased risk of developing a non-affective psychotic disorder (NAPD) in late adolescence and young adulthood compared to previously-reported general population estimates (relative risk [RR] = 25.82 before age 35). However, most NAPD diagnoses (74%) were made in the years before, simultaneously with, or shortly after the ASD diagnosis. This observation, which has also been made in two smaller longitudinal studies (Nylander et al., 2013; Maibing et al., 2015), could indicate that the presence of one condition indeed makes it more likely for the other to also be observed.

Nevertheless, when we restricted our analyses to individuals diagnosed with ASD before the age of 16 years (RR = 2.97 before age 25 years), or to individuals who had not been diagnosed with NAPD

until at least one year after receiving an ASD diagnosis ($RR = 8.35$ before age 35 years), risks of NAPD remained significantly increased. In other words, individuals diagnosed with ASD at a point in time when misdiagnosis or selection bias due to NAPD was unlikely, still showed a greater risk of developing an NAPD in later years than non-autistic peers.

In chapter III, we examined the association between autistic traits and psychotic experiences using data from the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort, an ongoing population-based cohort of children born in 1991 and 1992 in the former county of Avon, United Kingdom. We showed that children with social communication difficulties (relative to those without such difficulties or with less severe difficulties), but not with other autistic traits, were more likely to report psychotic experiences in young adulthood (odds ratio = 1.43, 95% confidence interval [CI] 1.01–2.02). These longitudinal results, observed in a population sample that was not selected on the basis of any clinical criteria, again indicate that misdiagnosis and selection bias unlikely account for the observed relationship between autistic traits and psychotic experiences.

There are now multiple longitudinal studies showing similar associations between childhood ASD or autistic traits and subsequent psychotic disorder or psychotic experiences (e.g., Bevan-Jones et al., 2012; Sullivan et al., 2013; Maibing et al., 2015; Selten et al., 2015). There are also some partially contrasting findings. Taylor et al. (2015) found only small and partially non-significant correlations between autistic traits at ages 8 to 16 years and psychotic experiences at the age of 16 years. Similarly, Cederlöf et al. (2016) reported a significant but weak association between autistic traits at ages 9 or 12 years and psychotic experiences at ages 15 or 18 years. Importantly, the studies conducted thus far have used varying operationalizations and measures of subclinical autistic traits and psychotic experiences. This methodological heterogeneity could account for some of the discrepancies in the results. For instance, in our study of the ALSPAC cohort, we found most evidence for an association between social communication difficulties and psychotic experiences, whereas this class of autistic traits was omitted in the study by Taylor et al. (2015).

In sum, our findings support the social defeat hypothesis, as children with ASD or autistic traits had an increased risk of developing a psychotic disorder or psychotic experiences later in life compared to non-autistic peers.

1.2.2 Social defeat as a risk factor for psychosis in autism

If psychosis is more prevalent in autism, then is this the result, at least in part, of the experience of social defeat? Alternatively, one might argue that such a relationship is explained by, for instance, a previously-reported small but significant genetic association between ASD and schizophrenia (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2019). In chapter III, we attempted to answer this question. We found that a substantial proportion of the relationship between social communication difficulties and psychotic experiences was mediated by childhood trauma (approximately 40%), even after adjusting for polygenic risk scores for schizophrenia.

We defined childhood trauma as exposure to physical or emotional abuse or neglect, sexual abuse, or bullying victimization. These traumatic experiences are among the best-established social risk factors for psychosis (Varese et al., 2012; Croft et al., 2019), and our study is the first longitudinal study to show similar associations in individuals with autistic traits. One previous longitudinal study within the ALSPAC birth cohort reported that the association between childhood autistic traits and psychotic experiences at age 12 was not changed by adjusting for bullying victimization at age 8 years (Bevan-Jones et al., 2012). However, the study did not conduct formal mediation analysis, and besides bullying

victimization, other traumatic experiences were not considered. Another longitudinal study did not assess traumatic experiences, but did find that peer problems that had developed in adolescence (i.e., being disliked by peers, having no friends, being alone) mediated the association between ASD polygenic risk and psychotic experiences at age 18 years, independently of schizophrenia polygenic risk (Velthorst et al., 2018).

Importantly, the authors of the social defeat hypothesis state that childhood trauma can result in the experience of social defeat, but do not state that they are equivalent (Selten et al., 2013). Besides social defeat, other psychological mechanisms might explain the link between trauma and psychosis. These include, for instance, negative affect, negative cognitive schemas, and dissociation (Alameda et al., 2020; Bloomfield et al., 2021). The mechanisms linking trauma to psychosis in autism will need to be elucidated in future work. For now, since exposure to abuse, neglect and/or bullying likely induces feelings of defeat such as experiences of being an outsider (van Nierop et al., 2014), we can cautiously consider the findings presented here to be compatible with the social defeat hypothesis.

1.3 Striatal dopamine synthesis capacity in ASD

In chapters IV and V, we used 3,4-dihydroxy-6- ^{18}F -fluoro-L-phenylalanine positron emission tomography (^{18}F -FDOPA PET) to examine striatal dopamine synthesis capacity in ASD. The results of these studies show that striatal dopamine synthesis capacity is not increased in ASD relative to matched controls, and is not in a positive direction associated with autistic traits or measures of social defeat. Here I first discuss these findings relative to other dopamine PET and single-photon emission computed tomography (SPECT) studies in ASD samples, and then examine the implications of our findings for the social defeat hypothesis of schizophrenia.

1.3.1 Molecular imaging studies of dopamine in ASD

Abnormalities in striatal dopamine function have been implied in ASD for decades. For example, Damasio and Maurer (1978) already hypothesized that dopamine deficiencies causally contribute to childhood autism. The more recently posited dopamine hypothesis of ASD similarly emphasized the role of nigrostriatal and mesolimbic dopamine pathways in the emergence of autistic traits in clinical and non-clinical samples (Pavál, 2017).

Early studies, for example those examining the dopamine metabolite homovanillic acid in blood plasma or urine, indeed showed some (albeit inconsistent) evidence for a role of dopaminergic alterations in ASD (McDougle et al., 2005). However, such indirect measures do not capture the complexity of the dopamine system, which consists of a wide range of biological processes such as dopamine synthesis, dopamine release, and expression of different classes of dopamine receptors. Additionally, the expression and functions of these dopaminergic processes are dependent on the brain regions in which they are present (e.g., Nieoullon, 2002), and this anatomical specificity cannot be studied with indirect, peripheral measures. The introduction of molecular imaging techniques such as SPECT and PET has allowed scientists to examine with more anatomical and functional specificity the various aspects of the brain dopamine system in living humans (Booij & van Amelsvoort, 2012). However, few studies used these techniques in ASD samples (Zürcher et al., 2015). In this thesis, we conducted the largest ^{18}F -FDOPA PET study in ASD thus far, to examine striatal presynaptic dopamine synthesis capacity.

Our finding of no significant increase in striatal dopamine synthesis capacity in adults with ASD partially contrasts with earlier ^{18}F -FDOPA PET studies in ASD samples. Ernst et al. (1997) found reduced medial prefrontal, but not striatal, ^{18}F -FDOPA uptake in autistic children ($n = 14$) relative to

non-autistic controls ($n = 10$). Nieminen-von Wendt et al. (2004) reported an increased frontal and striatal [^{18}F]-FDOPA uptake in adults with Asperger syndrome ($n = 8$) relative to non-autistic peers ($n = 5$).

One possibility is that these previous findings are the result of chance, and in this respect, our 3- to 5-fold increase in sample size is an improvement. Moreover, we applied more sophisticated and objective methods to quantify dopamine synthesis capacity, which might have contributed to some of the differences between studies. For instance, we conducted dynamic (rather than static) PET scans and automatically (rather than manually, which is observer-dependent and less reliable) generated regions of interest based on structural magnetic resonance imaging (MRI). Alternatively, these differences might be related to the specific characteristics of the samples studied. For example, although Nieminen-von Wendt et al. (2004) also examined medication-free, healthy (i.e., without comorbid conditions), young adult participants, these participants were all diagnosed with Asperger syndrome. We did not exclude such individuals from our study, but did additionally include a broader range of individuals diagnosed with an ASD, such as those originally diagnosed with pervasive developmental disorder-not otherwise specified (PDD-NOS) or autistic disorder. Asperger syndrome has been integrated into ASD for a good reason as it does not appear to be a subtype that can be reliably identified (Lord et al., 2012a). However, the heterogeneous nature of the ASD diagnosis has been noted, and the incorporation of a diverse set of clinical features into a single diagnostic classification might decrease the probability that group differences between individuals meeting this classification and controls are observed (Motttron & Bzdok, 2020). Future work could assess whether certain individuals with ASD, such as those with different ages, varying symptom severities, particular comorbidities, lower intelligence quotients (IQs), and/or certain genetic variations (e.g., catechol-*O*-methyl transferase (COMT) polymorphisms; Wu et al., 2012), do show alterations in dopamine synthesis capacity.

In addition to examining striatal [^{18}F]-FDOPA uptake, which is a well-established measure of dopamine synthesis capacity, we conducted voxel-wise comparisons to examine extra-striatal [^{18}F]-FDOPA uptake. In contrast to the studies by Ernst et al. (1997) and Nieminen-von Wendt et al. (2004), we did not find differences in extra-striatal [^{18}F]-FDOPA uptake between ASD and controls. Again, as mentioned above, there can be different explanations for these discrepant findings. However, it should also be noted that the test-retest reliability and signal-to-noise ratio of [^{18}F]-FDOPA uptake are lower in extra-striatal regions (particularly on the individual voxel level) than in the striatum (Egerton et al., 2010). Moreover, extra-striatal [^{18}F]-FDOPA uptake likely reflects a mixture of monoamine function rather than dopamine synthesis capacity alone (Brown et al., 1999), making it less suitable for the study of dopamine function.

Besides its large sample size and improvements in methodology, our study makes another important addition to the two previous [^{18}F]-FDOPA PET studies. That is, we examined potential factors associated with striatal dopamine synthesis capacity, such as social defeat and autistic traits. We believe that it is important to include such measures in future research, as this can help elucidate how dopamine abnormalities arise and/or correlate with certain phenotypes. For instance, it is informative to know whether dopamine signalling correlates with core autism features, or whether they solely arise in the presence of conditions such as psychosis. A further study of the role of dopamine in ASD would not only advance our scientific knowledge, but also has the potential to contribute to best-practice treatment guidelines. Currently, prescription rates of dopamine receptor agonists and antagonists to individuals with ASD are high (Wong et al., 2014), yet there is only limited empirical evidence from neurochemical studies that justifies their use.

In our study, despite observing no group differences in striatal dopamine synthesis capacity between ASD and controls, we did find in the ASD sample, that this capacity was negatively associated with the attention to detail subscale of the Autism Spectrum Quotient (AQ; Baron-Cohen et al., 2001). Intriguingly, a recent PET study by Kubota et al. (2020) studied dopamine D₁ receptor binding using the radiotracer [¹¹C]-SCH23390. They found no significant difference in striatal D₁ receptor binding between adults with ASD ($n = 18$) and controls ($n = 20$), but did show that this binding was negatively associated with AQ attention to detail scores among those with ASD. Although this latter finding might be related to either increased endogenous dopamine or to the expression of fewer D₁ receptors, the authors refer to animal studies showing that the assessment of dopamine D₁ receptor availability with this particular tracer is unlikely to be strongly influenced by the availability of endogenous dopamine (Abi-Dargham et al., 1999; Chou et al., 1999). Our findings of no increased striatal dopamine synthesis capacity in ASD, and another recent study reporting decreased striatal dopamine release in response to monetary reward in adults with ASD ($n = 10$) compared to controls ($n = 12$) (Zürcher et al., 2021), lend further support to this interpretation, as these results suggest that endogenous synaptic dopamine is not increased in ASD.

Together, these findings then imply that within ASD samples, intra-individual variations in dopamine signalling contribute to particular autistic symptoms, in such a manner that reduced signalling is associated with greater symptom load. This interpretation corresponds well to the previously observed associations between autistic traits and striatal functioning assessed with functional magnetic resonance imaging (e.g., Fuccillo, 2016), as well as the theoretically and empirically implied roles of striatal dopamine in attention and salience processing (Kapur et al., 2005; Cools & D'Esposito, 2011). Nevertheless, the AQ is a coarse instrument. For example, the attention to detail subscale not only assesses attentional processes, but also asks about personal interests. Further work with more objective quantifications of behaviour and cognition is necessary.

Finally, the observed correlation between dopamine signalling and autistic traits as of yet does not sufficiently explain the underlying mechanisms of their relationship. Future studies that assess multiple neurotransmitter systems and link their activity to particular behavioural and cognitive functions will be necessary to elucidate such mechanisms. For instance, multi-tracer PET studies, combined PET-magnetic resonance spectroscopy (MRS) studies, and/or pharmacological studies can be used to assess how (manipulations of) different ASD-relevant neurotransmitters, such dopamine, serotonin, gamma-aminobutyric acid (GABA), and glutamate (e.g., Pardo & Eberhart, 2007; Foss-Feig et al., 2017), relate to specific ASD traits.

1.3.2 Implications for the social defeat hypothesis of schizophrenia

Since we found no increase in striatal dopamine synthesis capacity in ASD, and no positive association between this capacity and autistic traits, the social defeat hypothesis was not supported. The social defeat hypothesis is partly based on animal studies showing increased mesocorticolimbic dopamine release in socially defeated rodents (Tidey & Miczek, 1996; Hammels et al., 2015). Several SPECT and PET studies in humans (see Table 1 for an overview) have been in accordance with the hypothesis, since these have shown that striatal dopamine synthesis capacity and/or release is increased in individuals exposed to low maternal care or trauma in childhood (Pruessner et al., 2004; Oswald et al., 2014; Egerton et al., 2016), in individuals with severe hearing impairment (Gevonden et al., 2014), and in immigrants (Egerton et al., 2017). More recently, two studies did not support the hypothesis, as they found a decrease in striatal dopamine synthesis capacity in individuals exposed to psychosocial adversity in child- and adulthood (Bloomfield et al., 2019), and a negative association between childhood trauma and ventral

striatal dopamine release in healthy volunteers (Dahoun et al., 2019). Multiple explanations for these findings are possible.

First, social defeat might not increase striatal dopamine synthesis or release, but rather contribute to the development of psychosis through other pathways. For instance, the experience of social defeat might result in certain maladaptive cognitive schemas, which place an individual at a greater vulnerability to developing psychotic symptoms when disruptions in striatal dopamine signalling emerge (Howes & Murray, 2014; Howes & Nour, 2016). In accordance with this suggestion, Dahoun et al. (2019) showed that the interaction between childhood trauma and ventral striatal dopamine release was positively associated with dexamphetamine-induced psychotic symptoms, whereas no independent associations were observed. However, this explanation insufficiently accounts for the findings of increased dopamine synthesis capacity and/or release in individuals who experienced childhood adversities, individuals with severe hearing impairment, and immigrants.

Second, variations in factors such as the age at exposure, chronicity, frequency, intensity, and type of social stressor, as well as prior and later experiences in life such as the availability of social support and exposure to other stressful events, might influence whether, to what extent, and in what direction dopamine signalling is disrupted (e.g., Oswald et al., 2014; Holly & Miczek, 2016; Bloomfield et al., 2019). The idea that such factors modulate the effects of social stress on dopamine signalling is supported by animal studies, which have shown, for instance, that repeated, brief exposure versus chronic exposure to social defeat stress can have opposite effects on dopamine concentrations in the nucleus accumbens (Miczek et al., 2011). These findings might help explain why mixed results have been observed in human studies thus far, as these examined individuals exposed to different adversities in varying circumstances. In addition, as reported in Table 1, studies have sometimes examined associations between social adversity and dopamine function in different striatal sub-regions, which is relevant since prior work has shown divergent associations of dopamine functioning in anatomical and functional striatal sub-regions with psychosis (e.g., McCutcheon et al., 2018).

Third, social defeat might lead to an increase in dopamine signalling only in certain susceptible individuals, such as those with a high genetic vulnerability (Selten & Cantor-Graae, 2005; Selten et al., 2016). Indeed, Kasanova et al. (2016) reported that associations between childhood trauma and dopamine release in the medial prefrontal cortex differed between healthy individuals and patients with NAPD. Moreover, Egerton et al. (2016) studied a combined sample of individuals at-risk of psychotic disorder and healthy volunteers, and found that the observed association between childhood trauma and striatal dopamine synthesis capacity might have been largely driven by the former group. However, this preliminary suggestion of the existence of subgroups in which defeat leads to certain neurobiological outcomes should be considered with some caution, as it has the potential of limiting the hypothesis' falsifiability. One can always state that no effect of defeat on dopamine functioning was found because some unknown moderator was not taken into account. Still, thus far, not much work has been conducted to assess how dopamine signalling might be affected by the interaction between social defeat and other risk factors, and there are several obvious candidate moderators (e.g., polygenic risk for schizophrenia) that could be explored.

Finally, it is important to highlight once more that the dopamine system is multi-faceted, and that in addition to dopamine synthesis capacity, its signalling depends on, for instance, dopamine release, dopamine transporter (DAT) expression, the expression of various dopamine receptors, and the breakdown of dopamine by enzymes such as monoamine oxidase (MAO) and COMT (Finberg, 2019). The social defeat hypothesis notes that defeat might lead to an increased baseline activity of, as well as

sensitized, dopamine system (Selten & Cantor-Graae, 2005). In the latter case, we would expect defeat to lead to increased dopamine responsivity to certain stressors. As noted, a recent small PET study found that striatal dopamine release in response to monetary reward was decreased in adults with ASD relative to controls (Zürcher et al., 2021). However, amphetamine- or stress-induced striatal dopamine release has not yet been assessed in ASD (Zürcher et al., 2015). In addition, reduced availability of DAT and/or increased dopamine receptor expression can lead to increased dopamine signalling, even if dopamine synthesis and release are normal. Thus far, findings on DAT binding in ASD have been mixed (Makkonen et al., 2008; Nakamura et al., 2010), and with exception of the previously-described study by Kubota et al. (2020), studies of dopamine receptor expression in ASD are lacking. Future SPECT or PET studies, in which a variety of radiotracers are used within the same persons, might be necessary to fully elucidate how dopamine signalling may be altered and affected by social defeat in ASD.

In conclusion, the relationship between social defeat and dopamine dysregulation may not be as straightforward as it was initially posited. Groups considered to be socially defeated, such as individuals exposed to trauma or adults with ASD, do not necessarily show an increase in dopamine synthesis capacity or release. The possible explanations presented here are speculative, and not mutually exclusive. Only fairly recently have studies begun examining associations between different social stressors and different types of dopamine responsiveness in humans, and more work is necessary. In particular, prospective longitudinal studies need to be conducted to establish how social stress influences dopamine signalling. These studies could, for example, examine dopamine signalling in migrants at varying points in time after migration (Selten et al., 2016) or in adults with ASD after they transition from school to working life. To conduct these studies, multi-centre PET collaborations will likely be necessary, as a large number of participants will need to be tested to achieve sufficient statistical power to compare defeated versus non-defeated individuals.

Table 1
SPECT and PET studies of striatal dopamine synthesis capacity and/or release relevant to the social defeat hypothesis of schizophrenia.

Reference	Exposure	Radiotracer	Aspect of dopamine signalling	Findings
Pruessner et al. (2004)	Early life maternal care	[¹¹ C]-raclopride	Stress-induced striatal dopamine release	Stress resulted in dopamine release in the VS in healthy adults with low ($n = 5$), but not with high ($n = 5$), maternal care.
Oswald et al. (2014)	Childhood trauma	[¹¹ C]-raclopride	Amphetamine-induced striatal dopamine release	Childhood trauma was associated with increased dopamine release in the VS in healthy adults ($n = 28$).
Egerton et al. (2016)	Childhood trauma	[¹⁸ F]-FDOPA	Striatal dopamine synthesis capacity	Childhood trauma was associated with increased dopamine synthesis capacity in the WS, AS, and SS in a mixed sample of healthy adults ($n = 20$) and adults at-risk of psychotic disorder ($n = 47$).
Dahoun et al. (2019)	Childhood trauma	[¹¹ C]-(+)-PHNO	Dexamphetamine-induced striatal dopamine release	Childhood trauma was associated with decreased dopamine release in the VS in healthy adults ($n = 24$).
Bloomfield et al. (2019)	Cumulative exposure to psychosocial adversity in child- and adulthood	[¹⁸ F]-FDOPA	Striatal dopamine synthesis capacity	Dopamine synthesis capacity in the WS, AS, and LS was significantly lower in adults exposed to high ($n = 17$) versus low ($n = 17$) cumulative psychosocial adversity.
Gevonden et al. (2014)	Hearing impairment	[¹²³ I]-IBZM	Dexamphetamine-induced striatal dopamine release	Dopamine release in the WS was greater in adults with severe hearing impairment ($n = 19$) than in healthy controls ($n = 19$), but not associated with reports of social exclusion.
Egerton et al. (2017)	Immigration	[¹¹ C]-(+)-PHNO	Stress-induced striatal dopamine release	Dopamine release in the WS, AS, LS, and SS was greater in Canadian immigrants ($n = 25$) than in non-immigrants ($n = 31$).
		[¹⁸ F]-FDOPA	Striatal dopamine synthesis capacity	Dopamine synthesis capacity in the WS, AS, and SS was greater in UK immigrants ($n = 32$) than in non-immigrants ($n = 44$).

WS, whole striatum; VS, ventral striatum; AS, associative striatum; LS, limbic striatum; SS, sensorimotor striatum.

1.4 The social defeat hypothesis of schizophrenia

Thus far, we have shown that individuals with ASD are at increased risk of developing psychotic disorders, and that children with social communication difficulties show higher rates of psychotic experiences in adolescence and early adulthood, relative to non-autistic peers. We have also shown that individuals with ASD do not have a greater striatal dopamine synthesis capacity than non-autistic controls, and that this capacity is not in positive directions related to measures of social defeat or autistic traits. As such, it appears that the studies presented in this thesis show mixed support for the social defeat hypothesis of schizophrenia. However, conceptual issues of the hypothesis need to be discussed, as these could hinder the interpretation of the empirical findings presented above.

In chapter VI of this thesis, I argued that the social defeat hypothesis has limitations related to the definition and measurement of social defeat. Selten (2021) replied to my commentary, and his reaction has been included as an appendix to the chapter. Below I further discuss my commentary and Selten's reply.

1.4.1 The definition of social defeat

In my commentary, I described that multiple, non-overlapping definitions of social defeat exist, and that as a result, there have been divergent operationalisations of social defeat in animal studies and in studies of psychosis and depression in humans (e.g., Björkqvist, 2001; Gilbert et al., 2002; Gevonden et al., 2014; Jaya et al., 2017; Termorshuizen et al., 2020). Of course, the authors of the social defeat hypothesis of schizophrenia are not responsible for how others define social defeat, and conceptualizations of defeat in other fields might be less relevant to the development of psychosis. However, it is important to keep in mind that these different definitions are used, and that findings from one field of research might not easily translate to the other.

With regard to the definition used by the authors of the social defeat hypothesis of schizophrenia, Selten (2021) notes that the description of outsider status as the negative experience of being excluded from the majority group was mainly given to emphasize that an outsider position needs to be evaluated as negative. This elucidates the definition of social defeat and once more emphasizes that the hypothesis does not concern, for instance, expats or avant-garde artists. Although I agree with Selten's suggestions, in my opinion, the hypothesis should further strive to a single definition of social defeat that is shared by multiple researchers. Subordinate position and outsider status often influence each other, but they are not the same experience and can occur independently. I believe that a single definition of social defeat would further clarify which individuals can be expected to show an increased risk of psychosis and why.

1.4.2 Measuring social defeat

The second limitation that I described was related to the proposed difficulties surrounding measurements of social defeat (e.g., Selten et al., 2013). In his reply, Selten (2021) argues that a hypothesis' utility is determined by its falsifiability rather than its measurability, and that the social defeat hypothesis enabled researchers to discover risks of psychosis (and dopaminergic dysregulation) in groups presumed to be socially defeated. I agree with Selten that the social defeat hypothesis has been successful in these respects, and that it provides novel information relative to other work (e.g., as discussed in the General introduction, section 1.2, and in Selten et al., 2013). Moreover, in many cases, it is evident whether certain findings support the hypothesis or not. Few would contest that the hypothesis would be falsified if we were to find *lower* risks of psychotic disorder in individuals with a black skin colour who migrated to Europe.

However, in other groups, it can be less clear which findings corroborate or falsify the hypothesis. I gave ASD as an example. One researcher might conclude from the social defeat hypothesis that individuals with ASD are at an increased risk of psychosis, since these individuals are exposed to social adversity and have less access to social support. Another researcher might interpret the hypothesis differently, stating that it predicts no increased risk of psychosis in ASD as these individuals do not interpret adversity or a lack of support as defeating. This researcher might refer to, for instance, theories that presume a diminished social motivation in ASD (Chevallier et al., 2012). The contradicting inferences made by these two researchers would both logically follow from the social defeat hypothesis, and as a result, empirical observations on the risk of psychosis in ASD would not test the hypothesis.

Another issue with interpreting group-level epidemiological findings is that groups can have other factors in common besides social defeat, such as exposure to threat and feelings of negative affect. When testing the social defeat hypothesis, we are interested in finding out whether social defeat, and not whether these other factors, contributed to the risk of psychosis, which cannot readily be ascertained.

The proposal to use measures of social adversity as proxies for social defeat (e.g., self-esteem, loneliness; Selten et al., 2013) does not fully resolve measurement issues, as we are unsure how such alternative measures relate to the experience of defeat. Moreover, interpreting measures of social adversity as indicative of social defeat could have the unwanted effect that the complexity of their role in the development of psychosis is underestimated.

Direct measurements of social defeat do appear to offer some solution. Depending on how defeat is defined, I expect that it can be measured on a group-level basis, as previous studies appear to have obtained valid results with assessments of, for instance, subjective appraisals of social status (e.g., Singh-Manoux et al., 2003; Jaya et al., 2017). However, there could indeed be certain groups in which self-report assessments of social defeat would show unlikely results. For instance, Selten refers to work in ethnic minority youth, which surprisingly does not show self-reports of lower self-esteem (Verkuyten, 1994). In such cases, it might be unwise to consider the social defeat hypothesis falsified if a single negative finding is observed. Alternatively, researchers could then attempt to measure social defeat using information available from other sources. For example, studies on friendships in schools supplement self-report assessments with peer-reports, teacher-reports, and playground observations (e.g., Kasari et al., 2011). Such an approach might also be used to more objectively quantify exclusion or social standing in society, at school, at work, in groups of friends, or in a family. Still, the subjective nature of the experience of defeat remains a problem for measurement that is not easily solved. Consider a handsome man, 30 years old, with an average level of education, who works as a sports instructor. If he has a working-class background, he may feel proud. When his brothers and sisters are medical specialists, his situation is very different. The challenge is to develop an instrument that measures these aspects of experience and that can be administered within an acceptable amount of time.

In conclusion, the social defeat hypothesis of schizophrenia appears to capture aspects of the social world that are relevant to the development of psychosis. Despite its scientific merit, if researchers want to test the hypothesis, then there needs to be agreement on what social defeat encompasses and on how it can be ascertained whether certain individuals feel socially defeated. Currently, the absence of reliable and valid instruments to measure the experience of social defeat can lead to difficulties in interpreting whether empirical findings support or falsify the hypothesis. It is a highly complex endeavour to tackle these issues, but one that might eventually lead to a further improvement of the hypothesis' scientific utility.

1.5 Clinical implications

Although this thesis is mainly concerned with questions about the aetiology and pathogenesis of psychosis in autism, several clinical implications are evident.

The relationship between autism and psychosis has been a historically contentious topic, and the validity of their co-occurrence has often been questioned (Evans, 2017). From this thesis, two conclusions may be drawn. First, similarities in symptoms can be expected to contribute to erroneous diagnoses of co-occurring ASD and psychotic disorder. Clinicians treating patients with a psychotic disorder should refrain from making an additional diagnosis of ASD in the absence of information on the development in childhood. Second, bias does not explain their co-occurrence entirely. Rather, individuals with autistic traits or ASD show greater risks of psychotic experiences and psychotic disorder than non-autistic peers. In clinical practice, clinicians should systematically ask autistic individuals about any psychotic experiences they might have.

This latter recommendation is especially relevant in light of our finding that point estimates for distressing and/or frequent psychotic experiences were particularly high in children with social communication difficulties. Similarly, three studies showed that psychotic experiences in ASD were associated with higher rates of distress than in non-autistic peers (Milne et al., 2017; Jutla et al., 2020; van der Linden et al., 2020). Furthermore, psychotic experiences in individuals with ASD or autistic traits are associated with a range of negative outcomes, such as depressed mood, self-harm, suicidality, reduced social functioning, and risk of psychotic disorder (Demirkaya et al., 2016; Uptegrove et al., 2018; Foss-Feig et al., 2019; Jokiranta-Olkonemi et al., 2020; Kølves et al., 2021). In other words, individuals with ASD or autistic traits not only show higher rates of psychotic symptoms, but are also more likely to suffer from them, warranting sufficient attention in clinical practice.

If psychosis occurs in ASD, then ideally, evidence-based treatments should be used, but as of yet no randomized controlled trials have been conducted. Observational work indicates that treatments for psychosis might be less effective in ASD, as one study showed that antipsychotic treatments failed more often in children with psychotic disorders with ASD relative to those without ASD (adjusted hazard ratio = 1.99, 95% CI 1.19-3.31; Downs et al., 2017). Early studies do suggest that effective treatment strategies might involve stress reduction (van der Linden et al., 2020) and the strengthening of emotion regulation capabilities (Larson et al., 2017; Larson et al., 2020). Moreover, in light of our findings of a relationship between trauma and psychotic experiences in individuals with autistic traits, it might be beneficial to identify prior traumatic experiences and to treat its consequences (van den Berg et al., 2015).

Finally, the social defeat hypothesis offers important clues as to how psychosis in ASD might be prevented. That is, we cannot expect the risk of psychosis to decrease in individuals with ASD as long as they keep having difficulties with finding and maintaining jobs (NU.nl, 2020, August 4), have to obtain their driving license through unnecessarily complicated and expensive procedures (Nieuwsuur, 2019, November 11), are denied proper education (Trouw, 2016, June 13), have to go through harmful treatments such as Complete Elimination of Autistic Spectrum Expression (CEASE) therapy (De Monitor, 2020, September 21), and in many other ways remain seen as subordinate people and keep getting forcibly driven to the rim of society. Meaningful change will only come when society becomes more inclusive to autistic individuals.

1.6 Recommendations for future research

Future studies need to further examine how psychotic symptoms might best be assessed in ASD. Semi-structured interviews can be used to validly identify psychotic symptoms in ASD (Wilson et al.,

2020), but self-report questionnaires, which might be interpreted differently by individuals with ASD (e.g., more literally), are still more often used in research and clinical practice. Moreover, more work is necessary to ensure that autistic traits can be validly assessed in psychotic individuals, as commonly-used instruments such as the AQ and the Autism Diagnostic Observation Schedule-2 (Lord et al., 2012b), do not differentiate between features with an early versus late onset.

We found no increase in striatal dopamine synthesis in ASD, but we did not assess ASD individuals with substantial psychotic symptoms (e.g., those diagnosed with a psychotic disorder). Studies of individuals with psychotic disorders (e.g., Cheng et al., 2020), individuals with non-psychotic disorders in which psychotic symptoms are present (Jauhar et al., 2017), and individuals with schizophrenia during remission of positive symptoms (Avram et al., 2019), indicate that increased striatal dopamine synthesis capacity and dopamine release are particularly associated with the presence of positive psychotic symptoms. This might explain why we found no increase of dopamine synthesis capacity in an ASD sample reporting few psychotic symptoms. Additionally, the participants that we studied had a relatively high IQ, few comorbidities, and did not use medication. Our ASD sample did report higher rates of social defeat than controls on all the measures that we administered, and based on the social defeat hypothesis, an increase in dopamine synthesis capacity would have still been expected. Nevertheless, future studies need to examine whether striatal dopamine synthesis capacity is increased in autistic individuals with psychotic symptoms, and/or in those with other features of interest (e.g., with certain comorbidities, varying symptom severities, medication use, low IQ).

In continuation of the study by Downs et al. (2017), it might also prove useful to further examine whether ASD adults with psychotic symptoms are more treatment-resistant to dopamine receptor-targeting antipsychotic medications. Some studies show that indeed, in treatment-resistant psychotic patients, autistic traits are more prevalent (Sheitman et al., 2004; Nakata et al., 2020). If there is an association between treatment-resistant psychosis and ASD, then PET studies might be used to further unravel the neurobiological underpinnings of treatment response in ASD. For instance, we could compare striatal dopamine synthesis capacity between psychotic individuals with and without an ASD prior to administration of antipsychotic medication, and examine whether this capacity predicts subsequent treatment response. Currently, similar studies are already being done in (non-autistic) psychotic patients, and these indicate that those responding worse to dopamine receptor-targeting antipsychotics show a lower striatal dopamine synthesis capacity (e.g., Veronese et al., 2020).

Finally, further work on the social defeat hypothesis can be conducted. The hypothesis could be tested with longitudinal studies of dopamine signalling and by imaging other aspects of the dopamine system, such as amphetamine- or stress-induced dopamine release in ASD. Moreover, studies could examine whether variations in factors such as age at onset and duration of social defeat differentially affect dopamine dysregulation and/or psychosis risk, and examine how social defeat interacts with other social stressors and non-social factors to determine subsequent outcomes. The use of validated instruments measuring social defeat would strengthen the conclusions drawn from such studies.

1.7 Strengths and limitations

The present thesis has several general strengths and limitations besides those already mentioned in each chapter. A first strength is that we used several advanced multimodality functional and molecular imaging techniques, such as structural T1-weighted MRI combined with dynamic PET/CT imaging performing pharmacokinetic analyses, and a variety of study designs, such as two (independent) cohort studies, to examine the predictions derived from the social defeat hypothesis. Second, our two

investigations of the relationships between measures of autism and psychosis were longitudinal, which allowed us to consider the age and sequence at which these measures were administered. Third, the studies presented here are among the largest conducted thus far in their respective disciplines. For example, the PET study is currently the largest [^{18}F]-FDOPA study in individuals with ASD ($n = 44$), substantially larger than two previous investigations of 8 and 14 individuals with an ASD, respectively.

A limitation of this thesis is the relatively little influence that we had on which and how certain data were collected, particularly in the two longitudinal studies. For example, data in psychiatric case registers are collected in clinical practice, and we do not know whether valid diagnoses were made in each case. A second limitation is the use of self-report measures of autistic traits and psychotic experiences in our PET study. Finally, our PET study was cross-sectional, whereas longitudinal studies would provide additional information on how dopamine abnormalities might develop.

1.8 Conclusion

In this thesis we examined whether the social defeat hypothesis of schizophrenia provides an explanation for the risk of psychosis in autism. In accordance with the hypothesis, we found that individuals with ASD are at a greater risk of developing an NAPD, and that this is likely not the result of a diagnostic or selection bias. Additionally, we found that individuals with childhood social communication difficulties were more likely to report psychotic experiences at ages 18 and 24. This association was substantially mediated by exposure to childhood trauma, and not strongly influenced by a genetic liability to schizophrenia. Contrary to our predictions, we found no increase in striatal dopamine synthesis capacity in young adults with an ASD diagnosis, and this capacity was not associated in a positive direction with measures of social defeat or autistic traits. Although the social defeat hypothesis of schizophrenia has proven scientific merit, future work could focus on improving the definition and measurability of social defeat, and further examine its relationship with dopamine dysregulation and psychosis.

2. References

- Abi-Dargham, A., Simpson, N., Kegeles, L., Parsey, R., Hwang, D. R., Anjilvel, S., Zea-Ponce, Y., Lombardo, I., Van Heertum, R., & Mann, J. J. (1999). PET studies of binding competition between endogenous dopamine and the D1 radiotracer [^{11}C]NNC 756. *Synapse*, 32(2), 93-109.
- Alameda, L., Rodriguez, V., Carr, E., Aas, M., Trotta, G., Marino, P., Vorontsova, N., Herane-Vives, A., Gadelrab, R., & Spinazzola, E. (2020). A systematic review on mediators between adversity and psychosis: potential targets for treatment. *Psychological Medicine*, 50(12), 1966-1976.
- Avram, M., Brandl, F., Cabello, J., Leucht, C., Scherr, M., Mustafa, M., Leucht, S., Ziegler, S., & Sorg, C. (2019). Reduced striatal dopamine synthesis capacity in patients with schizophrenia during remission of positive symptoms. *Brain*, 142(6), 1813-1826.
- Baron-Cohen, S., Wheelwright, S., Skinner, R., Martin, J., & Clubley, E. (2001). The autism-spectrum quotient (AQ): Evidence from asperger syndrome/high-functioning autism, males and females, scientists and mathematicians. *Journal of Autism and Developmental Disorders*, 31(1), 5-17.
- Bechi, M., Agostoni, G., Buonocore, M., Bosinelli, F., Spangaro, M., Bianchi, L., Cocchi, F., Guglielmino, C., Cavallaro, R., & Bosia, M. (2020). The Influence of Premorbid Adjustment and Autistic Traits on Social Cognitive Dysfunction in Schizophrenia. *Journal of the International Neuropsychological Society*, 26(3), 276-285.
- Bevan-Jones, R., Thapar, A., Lewis, G., & Zammit, S. (2012). The association between early autistic traits and psychotic experiences in adolescence. *Schizophrenia Research*, 135(1-3), 164-169.
- Bezemer, M. (2016, June 13). School schrijft kind met autisme te vroeg af. *Trouw*.
<https://www.trouw.nl/nieuws/school-schrijft-kind-met-autisme-te-vroeg-af-be1bdaa8/>
- Björkqvist, K. (2001). Social defeat as a stressor in humans. *Physiology & Behavior*, 73(3), 435-442.
- Bloomfield, M. A., Chang, T., Woodl, M. J., Lyons, L. M., Cheng, Z., Bauer-Staeb, C., Hobbs, C., Bracke, S., Kennerley, H., & Isham, L. (2021). Psychological processes mediating the association between developmental trauma and specific psychotic symptoms in adults: a systematic review and meta-analysis. *World Psychiatry*, 20(1), 107-123.
- Bloomfield, M. A., McCutcheon, R. A., Kempton, M., Freeman, T. P., & Howes, O. (2019). The effects of psychosocial stress on dopaminergic function and the acute stress response. *eLife*, 8, e46797.
- Booij, J., & van Amelsvoort, T. (2012). *Imaging as tool to investigate psychoses and antipsychotics* (Vol. 212). Springer-Verlag.
- Brown, W. D., Taylor, M., Roberts, A. D., Oakes, T. R., Schueller, M., Holden, J. E., Malischke, L., DeJesus, O. T., & Nickles, R. J. (1999). FluoroDOPA PET shows the nondopaminergic as well as dopaminergic destinations of levodopa. *Neurology*, 53(6), 1212-1253.
- Cederlöf, M., Pettersson, E., Sariaslan, A., Larsson, H., Östberg, P., Kelleher, I., Långström, N., Gumpert, C. H., Lundström, S., & Lichtenstein, P. (2016). The association between childhood autistic traits and adolescent psychotic experiences is explained by general neuropsychiatric problems. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, 171(2), 153-159.
- Cheng, P. W. C., Chang, W. C., Lo, G. G., Chan, K. W. S., Lee, H. M. E., Hui, L. M. C., Suen, Y. N., Leung, Y. L. E., Yeung, K. M. P. A., & Chen, S. (2020). The role of dopamine dysregulation and evidence for the transdiagnostic nature of elevated dopamine synthesis in psychosis: a positron emission tomography (PET) study comparing schizophrenia, delusional disorder, and other psychotic disorders. *Neuropsychopharmacology*, 45(11), 1870-1876.
- Chevallier, C., Kohls, G., Troiani, V., Brodtkin, E. S., & Schultz, R. T. (2012). The social motivation theory of autism. *Trends in Cognitive Sciences*, 16(4), 231-239.

- Chou, Y.-H., Karlsson, P., Halldin, C., Olsson, H., & Farde, L. (1999). A PET study of D1-like dopamine receptor ligand binding. *Psychopharmacology*, 146(2), 220-227.
- Cools, R., & D'Esposito, M. (2011). Inverted-U-shaped dopamine actions on human working memory and cognitive control. *Biological Psychiatry*, 69(12), e113-e125.
- Croft, J., Heron, J., Teufel, C., Cannon, M., Wolke, D., Thompson, A., Houtepen, L., & Zammit, S. (2019). Association of trauma type, age of exposure, and frequency in childhood and adolescence with psychotic experiences in early adulthood. *JAMA Psychiatry*, 76(1), 79-86.
- Cross-Disorder Group of the Psychiatric Genomics Consortium (2019). Genomic relationships, novel loci, and pleiotropic mechanisms across eight psychiatric disorders. *Cell*, 179(7), 1469-1482. e1411.
- Dahoun, T., Nour, M. M., McCutcheon, R. A., Adams, R. A., Bloomfield, M. A., & Howes, O. D. (2019). The relationship between childhood trauma, dopamine release and dexamphetamine-induced positive psychotic symptoms: a [¹¹C]-(+)-PHNO PET study. *Translational Psychiatry*, 9(1), 1-12.
- Damasio, A. R., & Maurer, R. G. (1978). A neurological model for childhood autism. *Archives of Neurology*, 35(12), 777-786.
- De Monitor (2020, September 21). *Autisme*. <https://pointer.kro-ncrv.nl/autisme>
- Demirkaya, S. K., Tutkunkardaş, M. D., & Mukaddes, N. M. (2016). Assessment of suicidality in children and adolescents with diagnosis of high functioning autism spectrum disorder in a Turkish clinical sample. *Neuropsychiatric Disease and Treatment*, 12, 2921.
- Dossetor, D. R. (2007). 'All That Glitters Is Not Gold': Misdiagnosis of Psychosis in Pervasive Developmental Disorders—A Case Series. *Clinical Child Psychology and Psychiatry*, 12(4), 537-548.
- Downs, J. M., Lechler, S., Dean, H., Sears, N., Patel, R., Shetty, H., Simonoff, E., Hotopf, M., Ford, T. J., & Diaz-Caneja, C. M. (2017). The association between co-morbid autism spectrum disorders and antipsychotic treatment failure in early-onset psychosis: a historical cohort study using electronic health records. *The Journal of Clinical Psychiatry*, 78(9), e1233.
- Egerton, A., Demjaha, A., McGuire, P., Mehta, M. A., & Howes, O. D. (2010). The test–retest reliability of 18F-DOPA PET in assessing striatal and extrastriatal presynaptic dopaminergic function. *Neuroimage*, 50(2), 524-531.
- Egerton, A., Howes, O. D., Houle, S., McKenzie, K., Valmaggia, L. R., Bagby, M. R., Tseng, H.-H., Bloomfield, M. A., Kenk, M., & Bhattacharyya, S. (2017). Elevated striatal dopamine function in immigrants and their children: a risk mechanism for psychosis. *Schizophrenia Bulletin*, 43(2), 293-301.
- Egerton, A., Valmaggia, L. R., Howes, O. D., Day, F., Chaddock, C. A., Allen, P., Winton-Brown, T. T., Bloomfield, M. A., Bhattacharyya, S., & Chilcott, J. (2016). Adversity in childhood linked to elevated striatal dopamine function in adulthood. *Schizophrenia Research*, 176(2-3), 171-176.
- Ernst, M., Zametkin, A., Matochik, J., Pascualvaca, D., & Cohen, R. (1997). Low medial prefrontal dopaminergic activity in autistic children. *The Lancet*, 350(9078), 638.
- Evans, B. (2017). *The metamorphosis of autism*. Manchester University Press.
- Finberg, J. P. (2019). Inhibitors of MAO-B and COMT: Their effects on brain dopamine levels and uses in Parkinson's disease. *Journal of Neural Transmission*, 126(4), 433-448.
- Foss-Feig, J. H., Adkinson, B. D., Ji, J. L., Yang, G., Srihari, V. H., McPartland, J. C., Krystal, J. H., Murray, J. D., & Anticevic, A. (2017). Searching for cross-diagnostic convergence: neural

- mechanisms governing excitation and inhibition balance in schizophrenia and autism spectrum disorders. *Biological Psychiatry*, 81(10), 848-861.
- Foss-Feig, J. H., Velthorst, E., Smith, L., Reichenberg, A., Addington, J., Cadenhead, K. S., Cornblatt, B. A., Mathalon, D. H., McGlashan, T. H., & Perkins, D. O. (2019). Clinical profiles and conversion rates among young individuals with autism spectrum disorder who present to clinical high risk for psychosis services. *Journal of the American Academy of Child & Adolescent Psychiatry*, 58(6), 582-588.
- Fucciillo, M. V. (2016). Striatal circuits as a common node for autism pathophysiology. *Frontiers in Neuroscience*, 10, 1-19.
- Gevonden, M., Booij, J., van den Brink, W., Heijtel, D., van Os, J., & Selten, J.-P. (2014). Increased release of dopamine in the striata of young adults with hearing impairment and its relevance for the social defeat hypothesis of schizophrenia. *JAMA Psychiatry*, 71(12), 1364-1372.
- Gilbert, P., Allan, S., Brough, S., Melley, S., & Miles, J. (2002). Relationship of anhedonia and anxiety to social rank, defeat and entrapment. *Journal of Affective Disorders*, 71(1-3), 141-151.
- Hammels, C., Pishva, E., De Vry, J., van den Hove, D. L., Prickaerts, J., van Winkel, R., Selten, J.-P., Lesch, K.-P., Daskalakis, N. P., & Steinbusch, H. W. (2015). Defeat stress in rodents: from behavior to molecules. *Neuroscience & Biobehavioral Reviews*, 59, 111-140.
- Holly, E. N., & Miczek, K. A. (2016). Ventral tegmental area dopamine revisited: effects of acute and repeated stress. *Psychopharmacology*, 233(2), 163-186.
- Howes, O. D., & Murray, R. M. (2014). Schizophrenia: an integrated sociodevelopmental-cognitive model. *The Lancet*, 383(9929), 1677-1687.
- Howes, O. D., & Nour, M. M. (2016). Dopamine and the aberrant salience hypothesis of schizophrenia. *World Psychiatry*, 15(1), 3-4.
- Jauhar, S., Nour, M. M., Veronese, M., Rogdaki, M., Bonoldi, I., Azis, M., Turkheimer, F., McGuire, P., Young, A. H., & Howes, O. D. (2017). A test of the transdiagnostic dopamine hypothesis of psychosis using positron emission tomographic imaging in bipolar affective disorder and schizophrenia. *JAMA Psychiatry*, 74(12), 1206-1213.
- Jaya, E. S., Ascone, L., & Lincoln, T. M. (2017). Social adversity and psychosis: the mediating role of cognitive vulnerability. *Schizophrenia Bulletin*, 43(3), 557-565.
- Jokiranta-Olkonien, E., Gyllenberg, D., Sucksdorff, D., Suominen, A., Kronström, K., Chudal, R., & Sourander, A. (2020). Risk for premature mortality and intentional self-harm in autism spectrum disorders. *Journal of Autism and Developmental Disorders*, 1-11.
- Jutla, A., Donohue, M. R., Veenstra-VanderWeele, J., & Foss-Feig, J. H. (2020). Reported autism diagnosis strongly predicts psychotic-like experiences in the Adolescent Brain Cognitive Development cohort. *medRxiv*, 2020.2002.2007.20021170. <https://doi.org/10.1101/2020.02.07.20021170>
- Kapur, S., Mizrahi, R., & Li, M. (2005). From dopamine to salience to psychosis—linking biology, pharmacology and phenomenology of psychosis. *Schizophrenia Research*, 79(1), 59-68.
- Kasanova, Z., Hernaus, D., Vaessen, T., Van Amelsvoort, T., Winz, O., Heinzl, A., Pruessner, J., Mottaghy, F. M., Collip, D., & Myin-Germeys, I. (2016). Early-life stress affects stress-related prefrontal dopamine activity in healthy adults, but not in individuals with psychotic disorder. *PLoS One*, 11(3), e0150746.

- Kasari, C., Locke, J., Gulsrud, A., & Rotheram-Fuller, E. (2011). Social networks and friendships at school: Comparing children with and without ASD. *Journal of Autism and Developmental Disorders*, 41(5), 533-544.
- Kölves, K., Fitzgerald, C., Nordentoft, M., Wood, S. J., & Erlangsen, A. (2021). Assessment of Suicidal Behaviors Among Individuals With Autism Spectrum Disorder in Denmark. *JAMA Network Open*, 4(1), e2033565-e2033565.
- Kubota, M., Fujino, J., Tei, S., Takahata, K., Matsuoka, K., Tagai, K., Sano, Y., Yamamoto, Y., Shimada, H., & Takado, Y. (2020). Binding of Dopamine D1 Receptor and Noradrenaline Transporter in Individuals with Autism Spectrum Disorder: A PET Study. *Cerebral Cortex*, 30(12), 6458-6468.
- Lai, M.-C., Kasse, C., Besney, R., Bonato, S., Hull, L., Mandy, W., Szatmari, P., & Ameis, S. H. (2019). Prevalence of co-occurring mental health diagnoses in the autism population: a systematic review and meta-analysis. *The Lancet Psychiatry*, 6(10), 819-829.
- Larson, F. V., Wagner, A. P., Chisholm, K., Reniers, R. L., & Wood, S. J. (2020). Adding a dimension to the dichotomy: affective processes are implicated in the relationship between autistic and schizotypal traits. *Frontiers in Psychiatry*, 11, 1-12.
- Larson, F. V., Wagner, A. P., Jones, P. B., Tantam, D., Lai, M.-C., Baron-Cohen, S., & Holland, A. J. (2017). Psychosis in autism: comparison of the features of both conditions in a dually affected cohort. *The British Journal of Psychiatry*, 210(4), 269-275.
- Lord, C., Petkova, E., Hus, V., Gan, W., Lu, F., Martin, D. M., Ousley, O., Guy, L., Bernier, R., & Gerdt, J. (2012a). A multisite study of the clinical diagnosis of different autism spectrum disorders. *Archives of General Psychiatry*, 69(3), 306-313.
- Lord, C., Rutter, M., Dilavore, P. C., Risi, S., Gotham, K., & Bishop, S. L. (2012b). *Autism Diagnostic Observation Schedule – second edition*. Western Psychological Services.
- Maibing, C. F., Pedersen, C. B., Benros, M. E., Mortensen, P. B., Dalsgaard, S., & Nordentoft, M. (2015). Risk of schizophrenia increases after all child and adolescent psychiatric disorders: a nationwide study. *Schizophrenia Bulletin*, 41(4), 963-970.
- Makkinen, I., Riikonen, R., Kokki, H., Airaksinen, M. M., & Kuikka, J. T. (2008). Serotonin and dopamine transporter binding in children with autism determined by SPECT. *Developmental Medicine & Child Neurology*, 50(8), 593-597.
- McCutcheon, R., Beck, K., Jauhar, S., & Howes, O. D. (2018). Defining the locus of dopaminergic dysfunction in schizophrenia: a meta-analysis and test of the mesolimbic hypothesis. *Schizophrenia Bulletin*, 44(6), 1301-1311.
- McDougle, C. J., Erickson, C. A., Stigler, K. A., & Posey, D. J. (2005). Neurochemistry in the pathophysiology of autism. *The Journal of Clinical Psychiatry*, 66(suppl 10), 9-18.
- Miczek, K. A., Nikulina, E. M., Shimamoto, A., & Covington, H. E. (2011). Escalated or suppressed cocaine reward, tegmental BDNF, and accumbal dopamine caused by episodic versus continuous social stress in rats. *Journal of Neuroscience*, 31(27), 9848-9857.
- Milne, E., Dickinson, A., & Smith, R. (2017). Adults with autism spectrum conditions experience increased levels of anomalous perception. *PLoS ONE*, 12(5), 1-12.
- Morgan, C., Kirkbride, J., Hutchinson, G., Craig, T., Morgan, K., Dazzan, P., Boydell, J., Doody, G. A., Jones, P. B., & Murray, R. M. (2008). Cumulative social disadvantage, ethnicity and first-episode psychosis: a case-control study. *Psychological Medicine*, 38(12), 1701-1715.
- Mottron, L., & Bzdok, D. (2020). Autism spectrum heterogeneity: fact or artifact? *Molecular Psychiatry*, 25, 3178-3185.

- Nakamura, K., Sekine, Y., Ouchi, Y., Tsujii, M., Yoshikawa, E., Futatsubashi, M., Tsuchiya, K. J., Sugihara, G., Iwata, Y., & Suzuki, K. (2010). Brain serotonin and dopamine transporter bindings in adults with high-functioning autism. *Archives of General Psychiatry*, 67(1), 59-68.
- Nakata, Y., Kanahara, N., Kimura, A., Niitsu, T., Komatsu, H., Oda, Y., Ishikawa, M., Hasegawa, T., Kamata, Y., & Yamauchi, A. (2020). Autistic traits and cognitive profiles of treatment-resistant schizophrenia. *Schizophrenia Research: Cognition*, 22, 100186.
- Nieminen-von Wendt, T. S., Metsähonkala, L., Kulomäki, T. A., Aalto, S., Autti, T. H., Vanhala, R., Eskola, O., Bergman, J., Hietala, J. A., & von Wendt, L. O. (2004). Increased presynaptic dopamine function in Asperger syndrome. *Neuroreport*, 15(5), 757-760.
- Nieoullon, A. (2002). Dopamine and the regulation of cognition and attention. *Progress in Neurobiology*, 67(1), 53-83.
- Nylander, L., Holmqvist, M., Gustafson, L., & Gillberg, C. (2013). Attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) in adult psychiatry. A 20-year register study. *Nordic Journal of Psychiatry*, 67(5), 344-350.
- Oostra, L. (2020, August 4). Eerlijk over psychische klachten: 'Ontslag kwam door mijn openheid'. *NU.nl*. <https://www.nu.nl/werk/6068327/eerlijk-over-psychische-klachten-ontslag-kwam-door-mijn-openheid.html>
- Oswald, L. M., Wand, G. S., Kuwabara, H., Wong, D. F., Zhu, S., & Brasic, J. R. (2014). History of childhood adversity is positively associated with ventral striatal dopamine responses to amphetamine. *Psychopharmacology*, 231(12), 2417-2433.
- Pardo, C. A., & Eberhart, C. G. (2007). The neurobiology of autism. *Brain Pathology*, 17(4), 434-447.
- Pavál, D. (2017). A dopamine hypothesis of autism spectrum disorder. *Developmental Neuroscience*, 39(5), 355-360.
- Pruessner, J. C., Champagne, F., Meaney, M. J., & Dagher, A. (2004). Dopamine release in response to a psychological stress in humans and its relationship to early life maternal care: a positron emission tomography study using [¹¹C]raclopride. *Journal of Neuroscience*, 24(11), 2825-2831.
- Selten, J.-P. (2021). The social defeat hypothesis of schizophrenia is more topical than ever. Reply to Schalbroeck. *Psychological Medicine*, online ahead of print, 1-2.
- Selten, J.-P., & Cantor-Graae, E. (2005). Social defeat: risk factor for schizophrenia? *The British Journal of Psychiatry*, 187(2), 101-102.
- Selten, J.-P., Lundberg, M., Rai, D., & Magnusson, C. (2015). Risks for nonaffective psychotic disorder and bipolar disorder in young people with autism spectrum disorder: a population-based study. *JAMA Psychiatry*, 72(5), 483-489.
- Selten, J.-P., van der Ven, E., Rutten, B. P., & Cantor-Graae, E. (2013). The social defeat hypothesis of schizophrenia: an update. *Schizophrenia Bulletin*, 39(6), 1180-1186.
- Selten, J.-P., van Os, J., & Cantor-Graae, E. (2016). The social defeat hypothesis of schizophrenia: issues of measurement and reverse causality. *World Psychiatry*, 15(3), 294-295.
- Sheitman, B. B., Kraus, J. E., Bodfish, J. W., & Carmel, H. (2004). Are the negative symptoms of schizophrenia consistent with an autistic spectrum illness? *Schizophrenia Research*, 69, 119-120.
- Singh-Manoux, A., Adler, N. E., & Marmot, M. G. (2003). Subjective social status: its determinants and its association with measures of ill-health in the Whitehall II study. *Social Science & Medicine*, 56(6), 1321-1333.
- Sullivan, S., Rai, D., Golding, J., Zammit, S., & Steer, C. (2013). The association between autism spectrum disorder and psychotic experiences in the Avon longitudinal study of parents and

- children (ALSPAC) birth cohort. *Journal of the American Academy of Child & Adolescent Psychiatry*, 52(8), 806-814.
- Taylor, M. J., Robinson, E. B., Happé, F., Bolton, P., Freeman, D., & Ronald, A. (2015). A longitudinal twin study of the association between childhood autistic traits and psychotic experiences in adolescence. *Molecular Autism*, 6(1), 1-11.
- Termorshuizen, F., van der Ven, E., Tarricone, I., Jongsma, H. E., Gayer-Anderson, C., Lasalvia, A., Tosato, S., Quattrone, D., La Cascia, C., Szöke, A., Beradi, D., Llorca, P.-M., de Haan, L., Velthorst, E., Bernardo, M., Sanjuán, J., Arrojo, M., Murray, R. M., Rutten, B. P., Jones, P. B., van Os, J., Kirkbride, J. B., Morgan, C., & Selten, J.-P. (2020). The incidence of psychotic disorders among migrants and minority ethnic groups in Europe: findings from the multinational EU-GEI study. *Psychological Medicine*, online ahead of print, 1-10.
- Tidey, J. W., & Miczek, K. A. (1996). Social defeat stress selectively alters mesocorticolimbic dopamine release: an in vivo microdialysis study. *Brain Research*, 721(1-2), 140-149.
- Upthegrove, R., Abu-Akel, A., Chisholm, K., Lin, A., Zahid, S., Pelton, M., Apperly, I., Hansen, P. C., & Wood, S. J. (2018). Autism and psychosis: clinical implications for depression and suicide. *Schizophrenia Research*, 195, 80-85.
- van den Berg, D. P., de Bont, P. A., van der Vleugel, B. M., de Roos, C., de Jongh, A., Van Minnen, A., & van der Gaag, M. (2015). Prolonged exposure vs eye movement desensitization and reprocessing vs waiting list for posttraumatic stress disorder in patients with a psychotic disorder: a randomized clinical trial. *JAMA Psychiatry*, 72(3), 259-267.
- van der Linden, K., Simons, C., van Amelsvoort, T., & Marcelis, M. (2020). Lifetime and Momentary Psychotic Experiences in Adult Males and Females With an Autism Spectrum Disorder. *Frontiers in Psychiatry*, 11, 766.
- van Hest, R. (2019, November 11). Autismevereniging doet aangifte: 200 euro voor kwartiertje rijkeuring. *Nieuwsuur*. <https://nos.nl/nieuwsuur/artikel/2309462-autismevereniging-doet-aangifte-200-euro-voor-kwartiertje-rijkeuring.html>
- van Nierop, M., Van Os, J., Gunther, N., Van Zelst, C., De Graaf, R., Ten Have, M., Van Dorsselaer, S., Bak, M., Myin-Germeys, I., & van Winkel, R. (2014). Does social defeat mediate the association between childhood trauma and psychosis? Evidence from the NEMESIS-2 S study. *Acta Psychiatrica Scandinavica*, 129(6), 467-476.
- Varese, F., Smeets, F., Drukker, M., Lieveerse, R., Lataster, T., Viechtbauer, W., Read, J., van Os, J., & Bentall, R. P. (2012). Childhood adversities increase the risk of psychosis: a meta-analysis of patient-control, prospective-and cross-sectional cohort studies. *Schizophrenia Bulletin*, 38(4), 661-671.
- Velthorst, E., Froudust-Walsh, S., Stahl, E., Ruderfer, D., Ivanov, I., Buxbaum, J., Banaschewski, T., Bokde, A. L., Büchel, C., & Quinlan, E. B. (2018). Genetic risk for schizophrenia and autism, social impairment and developmental pathways to psychosis. *Translational Psychiatry*, 8(1), 1-11.
- Verkuyten, M. (1994). Self-esteem among ethnic minority youth in Western countries. *Social Indicators Research*, 32(1), 21-47.
- Veronese, M., Santangelo, B., Jauhar, S., D'Ambrosio, E., Demjaha, A., Salimbeni, H., Huajie, J., McCrone, P., Turkheimer, F., & Howes, O. (2020). A potential biomarker for treatment stratification in psychosis: evaluation of an [¹⁸F] FDOPA PET imaging approach. *Neuropsychopharmacology*, 46, 1122-1132.

- Walda, D. (2019). *Koning der stations: Bizarre episoden uit het leven van Willem van Genk Nederlands beroemdste outsider-kunstenaar*. De Schalm.
- Wilson, C. S., Anthony, L., Kenworthy, L., Fleischman, R., Demro, C., Andorko, N., Chelsea Armour, A., & Schiffman, J. (2020). Feasibility of psychosis risk assessment for adolescents diagnosed with autism. *Autism*, 24(4), 834-850.
- Wong, A. Y., Hsia, Y., Chan, E. W., Murphy, D. G., Simonoff, E., Buitelaar, J. K., & Wong, I. C. (2014). The variation of psychopharmacological prescription rates for people with autism spectrum disorder (ASD) in 30 countries. *Autism Research*, 7(5), 543-554.
- Wu, K., O'Keeffe, D., Politis, M., O'Keeffe, G. C., Robbins, T. W., Bose, S. K., Brooks, D. J., Piccini, P., & Barker, R. A. (2012). The catechol-O-methyltransferase Val(158)Met polymorphism modulates fronto-cortical dopamine turnover in early Parkinson's disease: a PET study. *Brain*, 135(8), 2449-2457.
- Zürcher, N. R., Bhanot, A., McDougale, C. J., & Hooker, J. M. (2015). A systematic review of molecular imaging (PET and SPECT) in autism spectrum disorder: current state and future research opportunities. *Neuroscience & Biobehavioral Reviews*, 52, 56-73.
- Zürcher, N. R., Walsh, E. C., Phillips, R. D., Cernasov, P. M., Tseng, C.-E. J., Dharanikota, A., Smith, E., Li, Z., Kinard, J. L., & Bizzell, J. C. (2021). A simultaneous [¹¹C]raclopride positron emission tomography and functional magnetic resonance imaging investigation of striatal dopamine binding in autism. *Translational Psychiatry*, 11(1), 1-11.

Appendices

Nederlandse samenvatting

Impact paragraph

List of publications

Dankwoord

Curriculum vitae

Nederlandse samenvatting

1. Autisme en psychose

In de afgelopen decennia zijn de begrippen autisme en psychose veelvuldig door elkaar heen gebruikt (Evans, 2017). Zo refereerde de Zwitserse psychiater Eugen Bleuler in 1911 met het woord autisme naar een manier van fantasierijk denken die volledig was gericht op de eigen innerlijke wereld, los van de externe werkelijkheid, welke volgens hem een kenmerkend symptoom was van schizofrenie. Pas in de jaren zestig en zeventig van de vorige eeuw werden de begrippen autisme en psychose meer van elkaar gescheiden.

Tegenwoordig verwijst de term autisme voornamelijk naar moeilijkheden in de sociale interactie en communicatie, beperkt, repetitief gedrag en interesses en sensorische onder- of overgevoeligheid. In een deel van de bevolking zijn deze eigenschappen sterk aanwezig en wordt het functioneren erdoor belemmerd. In deze gevallen kan er een diagnose autismespectrumstoornis (ASS) worden gesteld, welke een prevalentie heeft van 1–2% (Maenner et al., 2020). Daarnaast komen kenmerken van autisme tevens in uiteenlopende mate voor bij mensen die niet aan alle criteria van een ASS-diagnose voldoen (Le Couteur et al., 1996; Constantino et al., 2003).

De term psychose verwijst tegenwoordig voornamelijk naar positieve psychotische symptomen, zoals hallucinaties en waanideeën. Deze symptomen komen voor bij niet-affectieve en affectieve psychotische stoornissen, zoals schizofrenie spectrumstoornissen en bipolaire stoornissen met psychotische kenmerken, die bij ongeveer 3% van de bevolking worden gediagnosticeerd (Perälä et al., 2007). Echter, in minder ernstige mate komen psychotische ervaringen, zoals sterk wantrouwend zijn of ongewone waarnemingen hebben, voor bij ongeveer 5–8% van de algemene bevolking (Linscott & Van Os, 2013; McGrath et al., 2015).

De *social defeat*-hypothese stelt dat het risico op psychose verhoogd is bij mensen die langdurig worden blootgesteld aan een ondergeschikte positie of een (ongewenste) status van buitenstaander (Selten & Cantor-Graae, 2005; Selten et al., 2013). Volgens de hypothese leidt *social defeat* tot psychose, doordat het de activiteit of responsiviteit van dopaminerge systemen in het brein verhoogt (Selten et al., 2017).

De *social defeat*-hypothese is oorspronkelijk opgesteld om een verklaring te bieden voor bekende risicofactoren voor psychose, waaronder migratie, een lage intelligentie, opgroeien in een stedelijke omgeving en drugsgebruik (Selten & Cantor-Graae, 2005). Vervolgens is de hypothese tevens gerelateerd aan risicofactoren als het ervaren van trauma in de kindertijd en het hebben van een ernstige gehoorbeperking (Selten et al., 2013). In overeenstemming met de hypothese vonden studies een hogere striatale dopamine afgifte en/of dopaminesynthesecapaciteit bij migranten (Egerton et al., 2017), mensen met een ernstige gehoorbeperking (Gevonden et al., 2014) en mensen die zijn blootgesteld aan meer traumatische ervaringen in de kindertijd (Oswald et al., 2014; Egerton et al., 2016).

Personen met ASS of met kenmerken van autisme maken vaker negatieve sociale gebeurtenissen mee dan leeftijdsgenoten zonder kenmerken van autisme. Zo worden zij vaker gepest en gediscrimineerd (Schroeder et al., 2014; Johnson & Joshi, 2016), ervaren zij minder sociale steun (Humphrey & Symes, 2010) en voelen zij zich vaker eenzaam (Bauminger et al., 2003; Mazurek, 2014). Vanuit de *social defeat*-hypothese is het aannemelijk dat mensen met ASS of met kenmerken van autisme een verhoogd risico op psychose hebben, net als een daaraan gerelateerde verhoogde activiteit in het dopaminerge systeem.

Hoewel schattingen van prevalentiecijfers sterk uiteenlopen, lijken psychotische stoornissen vaker voor te komen bij personen met ASS dan in de algemene bevolking (Chisholm et al., 2015). Daarnaast heeft onderzoek in de algemene bevolking aangetoond dat mensen met meer subklinische

kenmerken van autisme, meer psychotische ervaringen rapporteren (Zhou et al., 2019; Martinez et al., 2020). Echter, deze resultaten zijn voornamelijk gebaseerd op cross-sectioneel onderzoek. Hierbij wordt op één moment, meestal bij volwassenen, gekeken of kenmerken van autisme en psychose samengaan. Een belangrijk nadeel van dit soort onderzoek is dat deze kenmerken deels hetzelfde zijn. Zo zijn zowel bij ASS als bij psychose stoornissen in het contact, katatonie, sociale teruggetrokkenheid en afvlakkingen in het affect te zien. Deze overlap in symptomen zou eraan bij kunnen dragen dat de twee stoornissen onterecht tegelijk gediagnosticeerd worden, waardoor schattingen van het samengaan van deze diagnoses te hoog zijn. Daarnaast is het mogelijk dat juist diegenen die op latere leeftijd worden gediagnosticeerd met ASS in aanraking zijn gekomen met de geestelijke gezondheidszorg als gevolg van andere gezondheidsklachten. Deze zogenaamde selectiebias van mensen met meer gezondheidsklachten, zoals psychose, kan er wederom toe leiden dat het risico op psychose bij ASS overschat wordt. Meer onderzoek naar de relatie tussen autisme en psychose, waarin misdiagnose en selectiebias worden ondervangen, is dus noodzakelijk.

Om de aanmaak en/of afgifte van de neurotransmitter dopamine in het brein te meten, kan gebruik worden gemaakt van *positron emission tomography* (PET). Met deze beeldvormende techniek kunnen specifieke aspecten van neurotransmittersystemen in kaart worden gebracht bij levende participanten. Een recente studie die gebruik maakte van [¹¹C]-raclopride PET vond dat de striatale dopamine afgifte in reactie op beloning verlaagd was bij volwassenen met ASS ($n = 10$) ten opzichte van controles ($n = 12$) (Zürcher et al., 2021). Amfetamine- of stress-geïnduceerde striatale dopamine afgifte is nog niet onderzocht (Zürcher et al., 2015). Slechts twee studies onderzochten de striatale dopaminesynthesecapaciteit bij ASS met [¹⁸F]-FDOPA PET, maar de steekproefgroottes waren erg klein ($n = 14$ en $n = 8$ personen met ASS), de resultaten waren tegenstrijdig en eventuele risicofactoren werden niet onderzocht (Ernst et al., 1997; Nieminen-von Wendt et al., 2004).

In dit proefschrift hebben wij drie voorspellingen van de *social defeat*-hypothese over de relatie tussen autisme en psychose getoetst. Dit waren de voorspellingen (1) dat personen met ASS of met kenmerken van autisme verhoogde risico's hebben op het ontwikkelen van psychoses ten opzichte van personen zonder ASS of kenmerken van autisme, (2) dat personen met ASS een hogere striatale dopaminesynthesecapaciteit hebben, zoals gemeten met [¹⁸F]-FDOPA PET, dan personen zonder ASS of kenmerken van autisme en (3) dat het risico op psychose en de striatale dopaminesynthesecapaciteit samenhangen met ervaringen van *social defeat*.

2. Resultaten en discussie

2.1 Risico op psychose

In hoofdstuk II gebruikten wij informatie uit de psychiatrische casusregisters Midden-Nederland en Noord-Nederland om het verband tussen ASS en niet-affectieve psychotische stoornissen te onderzoeken. In hoofdstuk III bekeken wij de relatie tussen kenmerken van autisme en psychotische ervaringen met data van de Avon Longitudinal Study of Parents and Children (ALSPAC), een cohortstudie van personen die in 1991 en 1992 zijn geboren in de voormalige provincie Avon in het Verenigd Koninkrijk. Een aanname die wij binnen deze twee longitudinale studies deden, was dat ASS of kenmerken van autisme die op vroege leeftijd al aanwezig waren waarschijnlijk niet sterk beïnvloed zouden worden door de aanwezigheid van psychotische symptomen, die vaak pas ontstaan op latere leeftijd. Door rekening te houden met de leeftijd waarop kenmerken van autisme aanwezig waren, verwachtten wij de kans op misdiagnose of selectiebias te verkleinen.

In hoofdstuk II lieten wij zien dat personen met ASS een substantieel hoger risico hebben op het ontwikkelen van een niet-affectieve psychotische stoornis dan personen uit de algemene bevolking (relatief risico [RR] = 25.82 voor het 35^e levensjaar). In totaal waren 74% van de niet-affectieve psychotische stoornissen eerder dan of vrijwel tegelijk met de ASS-diagnose vastgesteld, wat een indicatie kan zijn voor misdiagnose of selectiebias. Echter, het risico op niet-affectieve psychotische stoornissen bleef sterk verhoogd onder personen die al vóór hun 16^e levensjaar gediagnosticeerd waren met ASS (RR = 2.97 vóór het 25^e levensjaar) en onder personen die op latere leeftijd een ASS-diagnose hadden ontvangen en op dat moment (of in het daaropvolgende jaar) nog niet waren gediagnosticeerd met een niet-affectieve psychotische stoornis (RR = 8.35 vóór het 35^e levensjaar).

In hoofdstuk III vonden wij dat kinderen met moeilijkheden in de sociale communicatie meer psychotische ervaringen rapporteerden op leeftijden van 18 tot 24 jaar (odds ratio = 1.43, 95% betrouwbaarheidsinterval 1.01–2.02). Traumatische ervaringen in de kindertijd, waaronder blootstelling aan fysiek en emotioneel misbruik of verwaarlozing, seksueel misbruik en/of pesten, medieerden een groot deel van dit verband. Bovendien hield dit verband niet sterk samen met polygene risicoscores voor schizofrenie.

Bovenstaande bevindingen ondersteunen de *social defeat*-hypothese. Dat wil zeggen, mensen met ASS of kenmerken van autisme hebben een respectievelijk hoger risico op niet-affectieve psychotische stoornissen en psychotische ervaringen. Misdiagnose of selectiebias lijken deze risico's niet te verklaren, aangezien een vroege ASS-diagnose en vroege kenmerken van autisme samenhangen met een daaropvolgend hoger risico op psychose. Verder lijkt het verband tussen kenmerken van autisme en psychotische ervaringen samen te hangen met traumatische ervaringen in de kindertijd. Daarnaast wordt dit verband niet sterk beïnvloed door het hebben van een genetische gevoeligheid voor schizofrenie.

2.2 Striatale dopaminesynthesecapaciteit

In hoofdstukken IV en V gebruikten wij [¹⁸F]-FDOPA PET om de relatie tussen autisme en striatale dopaminesynthesecapaciteit te onderzoeken. De resultaten lieten zien dat mensen met ASS of met kenmerken van autisme geen verhoging hebben in striatale dopaminesynthesecapaciteit ten opzichte van personen zonder ASS of kenmerken van autisme. Daarnaast hing deze capaciteit in beide groepen niet samen met zelf-gerapporteerde ervaringen van *social defeat*, zoals eenzaamheid en de ervaring te worden buitengesloten (ostracisme). Deze bevindingen lijken de *social defeat*-hypothese dus te weerspreken.

Onze resultaten komen niet overeen met meerdere studies die wel een verband vonden tussen striatale dopaminesynthesecapaciteit en/of dopamine afgifte en indicatoren voor *social defeat*, waaronder studies naar traumatische ervaringen in de jeugd, ernstige gehoorbeperking en migratie (Pruessner et al., 2004; Gevonden et al., 2014; Oswald et al., 2014; Egerton et al., 2016; Egerton et al., 2017). Echter, twee recentere onderzoeken vonden ook geen verhoging in dopamine synthesecapaciteit en dopamine afgifte bij personen blootgesteld aan traumatische ervaringen in de jeugd en/of volwassenheid (Bloomfield et al., 2019; Dahoun et al., 2019).

Er zijn meerdere potentiële verklaringen voor deze uiteenlopende bevindingen. Zo is het mogelijk dat verschillende populaties anders reageren op *social defeat* en/of dat het uitmaakt onder welke omstandigheden *social defeat* wordt ervaren. Toekomstig onderzoek is noodzakelijk om de relatie tussen *social defeat* en activiteit van de neurotransmitter dopamine verder te verhelderen. Zo zou de responsiviteit van het dopaminerge systeem na blootstelling aan psychosociale stress en/of amfetamine bij personen met ASS kunnen worden onderzocht.

In exploratieve analyses binnen de groep personen met ASS vonden wij wel een negatief verband tussen striatale dopaminesynthesecapaciteit en scores op de subschaal ‘aandacht voor detail’ van de Autism Spectrum Quotient (AQ; Baron-Cohen et al., 2001). Kubota et al. (2020) toonden recentelijk ook aan dat de beschikbaarheid van striatale dopamine D₁ receptoren negatief samenhangt met dezelfde AQ subschaal scores. Bij personen met ASS hangt een verminderde activatie van het dopaminerge systeem dus mogelijk samen met de aanwezigheid van bepaalde kenmerken van autisme.

2.3 Een beschouwing van de *social defeat*-hypothese

Hoofdstuk VI bestaat uit een korte beschouwing van de *social defeat*-hypothese. In het hoofdstuk beargumenteerde ik dat er onder onderzoekers geen consensus is over het begrip *social defeat*. Verschillende onderzoekers definiëren *social defeat* op dit moment als lage sociale status, buitenstaander positie, sociale uitsluiting, verliezen van een confrontatie en/of het niet kunnen behalen van bepaalde doelen (Björkqvist, 2001; Gilbert et al., 2002; Selten & Cantor-Graae, 2005). Verder gaf ik aan dat een veronderstelde moeilijke meetbaarheid van *social defeat* eraan bijdraagt dat de hypothese lastig te toetsen is. Een reactie van Selten (2021) op mijn beschouwing resulteerde in een verdere discussie over dit onderwerp, waarin ik concludeerde dat consensus over het begrip *social defeat* en een verbeterde meetbaarheid van *social defeat* kan leiden tot een verdere bijdrage van de *social defeat*-hypothese aan het begrip over de ontwikkeling van psychoses.

3. Conclusie

In de afgelopen jaren heeft de *social defeat*-hypothese meerdere succesvolle voorspellingen gedaan over het risico op psychose bij bepaalde groepen, wat heeft geleid tot nieuwe inzichten en ontdekkingen. De bevindingen in dit proefschrift laten gemengd bewijs zien voor de hypothese. Hoewel de risico's op psychotische stoornissen en psychotische ervaringen bij respectievelijk personen met ASS en personen met kenmerken van autisme verhoogd zijn en deze risico's samenhangen met blootstelling aan negatieve sociale gebeurtenissen, vonden we bij personen met ASS geen verhoging in striatale dopaminesynthesecapaciteit. Verder hing deze capaciteit niet samen met proxies voor *social defeat* of met de aanwezigheid van meer kenmerken van autisme. Gezien het belang van de rol van de sociale omgeving in preventie van psychose is verder onderzoek naar de rol van *social defeat* in het risico op psychose noodzakelijk.

4. Referenties

- Baron-Cohen, S., Wheelwright, S., Skinner, R., Martin, J., & Clubley, E. (2001). The autism-spectrum quotient (AQ): Evidence from asperger syndrome/high-functioning autism, males and females, scientists and mathematicians. *Journal of Autism and Developmental Disorders*, 31(1), 5-17.
- Bauminger, N., Shulman, C., & Agam, G. (2003). Peer interaction and loneliness in high-functioning children with autism. *Journal of Autism and Developmental Disorders*, 33(5), 489-507.
- Björkqvist, K. (2001). Social defeat as a stressor in humans. *Physiology & Behavior*, 73(3), 435-442.
- Bloomfield, M. A., McCutcheon, R. A., Kempton, M., Freeman, T. P., & Howes, O. (2019). The effects of psychosocial stress on dopaminergic function and the acute stress response. *eLife*, 8, e46797.
- Chisholm, K., Lin, A., Abu-Akel, A., & Wood, S. J. (2015). The association between autism and schizophrenia spectrum disorders: A review of eight alternate models of co-occurrence. *Neuroscience & Biobehavioral Reviews*, 55, 173-183.
- Constantino, J. N., Davis, S. A., Todd, R. D., Schindler, M. K., Gross, M. M., Brophy, S. L., Metzger, L. M., Shoushtari, C. S., Splinter, R., & Reich, W. (2003). Validation of a brief quantitative measure of autistic traits: comparison of the social responsiveness scale with the autism diagnostic interview-revised. *Journal of Autism and Developmental Disorders*, 33(4), 427-433.
- Dahoun, T., Nour, M. M., McCutcheon, R. A., Adams, R. A., Bloomfield, M. A., & Howes, O. D. (2019). The relationship between childhood trauma, dopamine release and dexamphetamine-induced positive psychotic symptoms: a [¹¹C]-(+)-PHNO PET study. *Translational Psychiatry*, 9(1), 1-12.
- Egerton, A., Howes, O. D., Houle, S., McKenzie, K., Valmaggia, L. R., Bagby, M. R., Tseng, H. -H., Bloomfield, M. A., Kenk, M., & Bhattacharyya, S. (2017). Elevated striatal dopamine function in immigrants and their children: a risk mechanism for psychosis. *Schizophrenia Bulletin*, 43(2), 293-301.
- Egerton, A., Valmaggia, L. R., Howes, O. D., Day, F., Chaddock, C. A., Allen, P., Winton-Brown, T. T., Bloomfield, M. A., Bhattacharyya, S., & Chilcott, J. (2016). Adversity in childhood linked to elevated striatal dopamine function in adulthood. *Schizophrenia Research*, 176(2-3), 171-176.
- Ernst, M., Zametkin, A., Matochik, J., Pascualvaca, D., & Cohen, R. (1997). Low medial prefrontal dopaminergic activity in autistic children. *The Lancet*, 350(9078), 638.
- Evans, B. (2017). *The metamorphosis of autism*. Manchester University Press.
- Gevonden, M., Booij, J., van den Brink, W., Heijtel, D., van Os, J., & Selten, J.-P. (2014). Increased release of dopamine in the striata of young adults with hearing impairment and its relevance for the social defeat hypothesis of schizophrenia. *JAMA Psychiatry*, 71(12), 1364-1372.
- Gilbert, P., Allan, S., Brough, S., Melley, S., & Miles, J. (2002). Relationship of anhedonia and anxiety to social rank, defeat and entrapment. *Journal of Affective Disorders*, 71(1-3), 141-151.
- Humphrey, N., & Symes, W. (2010). Responses to bullying and use of social support among pupils with autism spectrum disorders (ASDs) in mainstream schools: A qualitative study. *Journal of Research in Special Educational Needs*, 10(2), 82-90.
- Johnson, T. D., & Joshi, A. (2016). Dark clouds or silver linings? A stigma threat perspective on the implications of an autism diagnosis for workplace well-being. *Journal of Applied Psychology*, 101(3), 430-449.
- Kubota, M., Fujino, J., Tei, S., Takahata, K., Matsuoka, K., Tagai, K., Sano, Y., Yamamoto, Y., Shimada, H., & Takado, Y. (2020). Binding of Dopamine D₁ Receptor and Noradrenaline Transporter in Individuals with Autism Spectrum Disorder: A PET Study. *Cerebral Cortex*, 30(12), 6458-6468.

- Le Couteur, A., Bailey, A., Goode, S., Pickles, A., Gottesman, I., Robertson, S., & Rutter, M. (1996). A broader phenotype of autism: the clinical spectrum in twins. *Journal of Child Psychology and Psychiatry*, 37(7), 785-801.
- Linscott, R., & Van Os, J. (2013). An updated and conservative systematic review and meta-analysis of epidemiological evidence on psychotic experiences in children and adults: on the pathway from proneness to persistence to dimensional expression across mental disorders. *Psychological Medicine*, 43(6), 1133-1149.
- Maenner, M. J., Shaw, K. A., & Baio, J. (2020). Prevalence of autism spectrum disorder among children aged 8 years—autism and developmental disabilities monitoring network, 11 sites, United States, 2016. *MMWR Surveillance Summaries*, 69(4), 1-12.
- Martinez, A. P., Wickham, S., Rowse, G., Milne, E., & Bentall, R. P. (2020). Robust association between autistic traits and psychotic-like experiences in the adult general population: epidemiological study from the 2007 Adult Psychiatric Morbidity Survey and replication with the 2014 APMS. *Psychological Medicine*, online ahead of print, 1-7.
- Mazurek, M. O. (2014). Loneliness, friendship, and well-being in adults with autism spectrum disorders. *Autism*, 18(3), 223-232.
- McGrath, J. J., Saha, S., Al-Hamzawi, A., Alonso, J., Bromet, E. J., Bruffaerts, R., Caldas-de-Almeida, J. M., Chiu, W. T., de Jonge, P., & Fayyad, J. (2015). Psychotic experiences in the general population: a cross-national analysis based on 31 261 respondents from 18 countries. *JAMA Psychiatry*, 72(7), 697-705.
- Nieminen-von Wendt, T. S., Metsähonkala, L., Kulomäki, T. A., Aalto, S., Autti, T. H., Vanhala, R., Eskola, O., Bergman, J., Hietala, J. A., & von Wendt, L. O. (2004). Increased presynaptic dopamine function in Asperger syndrome. *Neuroreport*, 15(5), 757-760.
- Oswald, L. M., Wand, G. S., Kuwabara, H., Wong, D. F., Zhu, S., & Brasic, J. R. (2014). History of childhood adversity is positively associated with ventral striatal dopamine responses to amphetamine. *Psychopharmacology*, 231(12), 2417-2433.
- Perälä, J., Suvisaari, J., Saarni, S. I., Kuoppasalmi, K., Isometsä, E., Pirkola, S., Partonen, T., Tuulio-Henriksson, A., Hintikka, J., & Kiesepää, T. (2007). Lifetime prevalence of psychotic and bipolar I disorders in a general population. *Archives of General Psychiatry*, 64(1), 19-28.
- Pruessner, J. C., Champagne, F., Meaney, M. J., & Dagher, A. (2004). Dopamine release in response to a psychological stress in humans and its relationship to early life maternal care: a positron emission tomography study using [¹¹C] raclopride. *Journal of Neuroscience*, 24(11), 2825-2831.
- Schroeder, J. H., Cappadocia, M. C., Bebko, J. M., Pepler, D. J., & Weiss, J. A. (2014). Shedding light on a pervasive problem: A review of research on bullying experiences among children with autism spectrum disorders. *Journal of Autism and Developmental Disorders*, 44(7), 1520-1534.
- Selten, J.-P. (2021). The social defeat hypothesis of schizophrenia is more topical than ever. Reply to Schalbroeck. *Psychological Medicine*, online ahead of print, 1-2.
- Selten, J.-P., Booij, J., Buwalda, B., & Meyer-Lindenberg, A. (2017). Biological mechanisms whereby social exclusion may contribute to the etiology of psychosis: a narrative review. *Schizophrenia Bulletin*, 43(2), 287-292.
- Selten, J.-P., & Cantor-Graae, E. (2005). Social defeat: risk factor for schizophrenia? *The British Journal of Psychiatry*, 187(2), 101-102.
- Selten, J.-P., van der Ven, E., Rutten, B. P., & Cantor-Graae, E. (2013). The social defeat hypothesis of schizophrenia: an update. *Schizophrenia Bulletin*, 39(6), 1180-1186.

- Zhou, H.-Y., Yang, H.-X., Gong, J.-B., Cheung, E. F., Gooding, D. C., Park, S., & Chan, R. C. (2019). Revisiting the overlap between autistic and schizotypal traits in the non-clinical population using meta-analysis and network analysis. *Schizophrenia Research*, 212, 6-14.
- Zürcher, N. R., Bhanot, A., McDougle, C. J., & Hooker, J. M. (2015). A systematic review of molecular imaging (PET and SPECT) in autism spectrum disorder: current state and future research opportunities. *Neuroscience & Biobehavioral Reviews*, 52, 56-73.
- Zürcher, N. R., Walsh, E. C., Phillips, R. D., Cernasov, P. M., Tseng, C.-E. J., Dharanikota, A., Smith, E., Li, Z., Kinard, J. L., & Bizzell, J. C. (2021). A simultaneous [¹¹C]raclopride positron emission tomography and functional magnetic resonance imaging investigation of striatal dopamine binding in autism. *Translational Psychiatry*, 11(1), 1-11.

Impact paragraph

1. Impact

Curiosity is the main driver of scientific enquiry. Inherent to research is that the direct societal or clinical relevance of a study can be unclear, that findings prove to be useless, or that the impact of a study becomes evident only in the long-term. Still, researchers should at least consider the short-term relevance of their own research, and evaluate what the impact of their studies might be. In this final chapter, I address the (potential) impact of this thesis on science and clinical practice.

The main purpose of this thesis was to examine whether social defeat contributes to the risk of psychosis in autism. We found that individuals with ASD were at a higher risk of non-affective psychotic disorder than individuals from the general population. Moreover, children with social communication difficulties were at a greater risk of psychotic experiences than individuals without such difficulties, and this association was substantially mediated by experiences of childhood trauma. We did not find a difference in dopamine synthesis capacity between individuals with ASD and controls, and this capacity was not associated with social defeat or autistic traits.

In terms of scientific relevance, this thesis makes several novel contributions to previous literature. Former studies of the link between autism and psychosis had mostly been cross-sectional, and we extend these previous findings by, in chapters II and III, conducting longitudinal studies, which confirmed the existence of associations between childhood autism and psychosis later in life. The durations of follow-up in these studies are among the longest available thus far. For instance, we are the first to examine the relationship between childhood autistic traits and psychotic experiences measured until age 24 years. In addition, in this thesis, we have conducted some of the first studies of potential risk factors for psychosis in autism. For example, in chapter II we found that migrants with ASD were at an even greater risk of non-affective psychotic disorder than non-migrants with ASD, and in chapter III, we found that childhood trauma substantially mediated the association between autistic traits and psychotic experiences.

Our large [^{18}F]-FDOPA PET study of dopamine synthesis capacity in ASD, reported in chapters IV and V, makes another important addition to the literature. This study is currently the largest investigation of dopamine signalling that has been conducted in individuals with ASD (Zürcher et al., 2015), and includes several methodological improvements relative to prior studies on dopamine synthesis capacity in ASD, such as the use of dynamic (rather than static) PET scans, and the use of automatic (rather than manual) generation of regions of interest based on structural MRI.

We expected to find a significant difference in dopamine synthesis capacity between adults with ASD and non-autistic peers, but surprisingly we did not observe this. Moreover, other PET studies have now reported findings that are consistent as well as inconsistent with the social defeat hypothesis, and even studies that examined exposure to the same stressor (e.g., childhood trauma) have sometimes shown opposite results (Egerton et al., 2016; Dahoun et al., 2019). It is clear that much more work is necessary to unravel how the social environment and dopamine signalling interact. Additionally, a question that remains is whether a study of stress- or amphetamine-induced dopamine release might have been more sensitive to detect changes in dopamine signalling in ASD individuals exposed to social defeat.

It is surprising that so few molecular imaging studies have been conducted in ASD, especially since there have been such strong ideas about the role of disruptions in dopamine signalling in ASD and its concurrent health conditions. Future studies could assess whether certain individuals with ASD, such as those with different ages, varying symptom severities, particular comorbidities, lower intelligence

quotients (IQs), and/or certain genetic variations, do show alterations in dopamine signalling. Those studies would not only increase our understanding of ASD and its comorbidities, but could potentially also help improve best-practice treatment guidelines. For instance, the imaging of the dopamine system in groups such as autistic individuals with psychotic symptoms might help guide treatment decisions on which types of antipsychotic medications are likely to be most effective.

In this thesis, I did not only present empirical work that tested the social defeat hypothesis, but also commented on the hypothesis itself. This has resulted in a correspondence with Jean-Paul Selten in the journal *Psychological Medicine* (Schalbroeck, 2020; Selten, 2021), which can be read in chapter VI. I hope that this thesis will stimulate researchers to further think critically about the role of social risk factors in the development of psychosis, and expect that elucidating their roles will be crucial to making progress in prevention and treatment of psychosis.

Thus far, the findings reported in this thesis have been well-received in academia. Most findings have been published in peer-reviewed scientific journals, and we have disseminated the findings at several scientific conferences, such as the European Conference on Schizophrenia Research (ECSR), the Schizophrenia International Research Society (SIRS) conference, and the International Society for Autism Research (INSAR) conference.

In terms of clinical relevance, first and foremost, I hope that this thesis will help individuals with ASD receive better mental health support. My PhD research has enabled me to talk to many young adults with ASD, and a comment that I heard on multiple occasions was that, even though these individuals had received years of mental health support, no one had really ever asked them about psychotic experiences. Still, often these individuals reported that the psychotic experiences that they had were distressing, and indicated that they would have loved to receive information on how to deal with them. Of course, we need not pathologize all psychotic-like experiences, as they can be part of normal human functioning. Nevertheless, even among those individuals with ASD that reported benign psychotic experiences, I noticed that there was curiosity to learn more about them, and that they were happy to finally discuss them with someone without being judged for it.

This thesis can help increase attention to the occurrence of psychosis in autistic individuals, and stimulate mental healthcare professionals to focus more on this topic in their work. Thus far, it has been my personal experience that many mental healthcare professionals expect that psychosis hardly occurs in autistic individuals or that they disregard the seriousness of these experiences. I hope that clinicians will regularly ask autistic individuals about these experiences in clinical practice, even if it is just to provide support, normalize the experiences, and to give people the opportunity to talk about them without being stigmatized. We have no problems asking people about feelings of depression or anxiety, and I hope that the same will be true for psychotic experiences in the future.

With regard to treatment, in recent years there has been increased attention to the treatment of trauma in psychotic patients, which appears to be effective in reducing psychotic symptoms and improving well-being (van den Berg et al., 2015). The findings from this thesis indicate that a similar approach might prove useful in autistic individuals as well.

As a researcher, I will try my best to disseminate the findings of this thesis among mental health professionals, and have for example done so by presenting at the spring conference of the Dutch Psychiatric Association and at the Dutch Autism Conference, and by publishing on this topic in the *Wetenschappelijk Tijdschrift Autisme* (Schalbroeck & Selten, 2020), a trade journal for autism professionals.

Finally, this thesis highlights once again that, as a society, we should aim to improve the social circumstances for marginalized and discriminated groups, such as migrants, individuals with a severe hearing impairment, LGBTQ+ individuals, and autistic individuals.

2. References

- Dahoun, T., Nour, M. M., McCutcheon, R. A., Adams, R. A., Bloomfield, M. A., & Howes, O. D. (2019). The relationship between childhood trauma, dopamine release and dexamphetamine-induced positive psychotic symptoms: a [^{11}C](+)-PHNO PET study. *Translational Psychiatry*, 9(1), 1-12.
- Egerton, A., Valmaggia, L. R., Howes, O. D., Day, F., Chaddock, C. A., Allen, P., Winton-Brown, T. T., Bloomfield, M. A., Bhattacharyya, S., & Chilcott, J. (2016). Adversity in childhood linked to elevated striatal dopamine function in adulthood. *Schizophrenia Research*, 176(2-3), 171-176.
- Schalbroeck, R. (2020). The social defeat hypothesis of schizophrenia: a parsimonious explanation for multiple psychosis risk factors? *Psychological Medicine*, online ahead of print, 1-2.
- Schalbroeck, R., & Selten, J.-P. (2020). Psychose bij personen met een autismespectrumstoornis. *Wetenschappelijk Tijdschrift Autisme*, 1(19), 58-64.
- Selten, J.-P. (2021). The social defeat hypothesis of schizophrenia is more topical than ever. Reply to Schalbroeck. *Psychological Medicine*, online ahead of print, 1-2.
- van den Berg, D. P., de Bont, P. A., van der Vleugel, B. M., de Roos, C., de Jongh, A., Van Minnen, A., & van der Gaag, M. (2015). Prolonged exposure vs eye movement desensitization and reprocessing vs waiting list for posttraumatic stress disorder in patients with a psychotic disorder: a randomized clinical trial. *JAMA Psychiatry*, 72(3), 259-267.
- Wong, A. Y., Hsia, Y., Chan, E. W., Murphy, D. G., Simonoff, E., Buitelaar, J. K., & Wong, I. C. (2014). The variation of psychopharmacological prescription rates for people with autism spectrum disorder (ASD) in 30 countries. *Autism Research*, 7(5), 543-554.
- Zürcher, N. R., Bhanot, A., McDougle, C. J., & Hooker, J. M. (2015). A systematic review of molecular imaging (PET and SPECT) in autism spectrum disorder: current state and future research opportunities. *Neuroscience & Biobehavioral Reviews*, 52, 56-73.

List of publications

Peer-reviewed journal articles

- Naughton, F., Hopewell, S., Lathia, N., Schalbroeck, R., Brown, C., Mascolo, C., McEwen, A., & Sutton, S. (2016). The feasibility of a context sensing smoking cessation smartphone application (Q Sense): a mixed methods study. *JMIR mHealth and uHealth*, 4(3), e106.
- van Son, D., Schalbroeck, R., Angelidis, A., van der Wee, N., van der Does, W., & Putman, P. (2018). Acute effects of caffeine on threat-selective attention: moderation by anxiety and EEG theta/beta ratio. *Biological Psychology*, 136, 100-110.
- Schalbroeck, R., Termorshuizen, F., Visser, E., van Amelsvoort, T., & Selten, J. P. (2019). Risk of non-affective psychotic disorder or bipolar disorder in autism spectrum disorder: a longitudinal register-based study in the Netherlands. *Psychological Medicine*, 49(15), 2543-2550.
- Schalbroeck, R. (2020). The social defeat hypothesis of schizophrenia: a parsimonious explanation for multiple psychosis risk factors? *Psychological Medicine*, 1-2.
- Schalbroeck, R., van Velden, F. H. P., de Geus-Oei, L.F., Yaqub, M., van Amelsvoort, T., Booij, J., & Selten, J. P. (2021). Striatal dopamine synthesis capacity in autism spectrum disorder and its relation with social defeat: an [¹⁸F]-FDOPA PET/CT study. *Translational Psychiatry*, 11, 1-10.

Trade journal article

- Schalbroeck, R., & Selten, J. P. (2020). Psychose bij personen met een autismespectrumstoornis. *Wetenschappelijk Tijdschrift Autisme*, 19(1), 58-64.

Dankwoord

In december 2016 startte ik met mijn promotieonderzoek. Ik werd promovendus aan Maastricht University, kwam te werken bij GGZ Rivierduinen, deed mijn onderzoek grotendeels bij het LUMC en werkte samen met het AMC. Hoewel het af en toe lastig was om deze complexe constructie aan buitenstaanders uit te leggen, stelde deze mij in staat om bij een verscheidenheid aan instellingen mensen te leren kennen. Deze mensen waren niet alleen belangrijk voor mijn onderzoek, maar hebben er ook aan bijgedragen dat ik erg van mijn promotietraject heb kunnen genieten. Ik wil iedereen die direct of indirect bij mijn promotietraject betrokken is geweest dan ook hartelijk bedanken.

In het bijzonder gaat mijn dank uit naar de leden van mijn promotieteam: Prof. Jean-Paul Selten, Prof. Lioe-Fee de Geus-Oei en Prof. Jan Booij.

Jean-Paul, ik heb je leren kennen als een bevoegen en betrokken wetenschapper met een enorme kennis van de menselijke geest. We waren het niet altijd over alles eens, maar zoals je vaak zei, is dat inherent aan wetenschappelijk onderzoek. Ik wil je bedanken voor het vertrouwen dat je mij hebt geboden en voor de vele lessen die je mij hebt geleerd. Onze gesprekken over Ajax, de etentjes in restaurants en bij jou thuis en de gezamenlijke congresbezoeken zal ik erg gaan missen.

Lioe-Fee, ik wil je bedanken dat je altijd voor me klaar stond. Niet alleen was je in staat om binnen *no-time* iets op het LUMC geregeld te krijgen, maar je hebt er ook aan bijgedragen dat ik als buitenstaander (om maar even in *social defeat*-termen te blijven!) met open armen werd ontvangen binnen de sectie Nucleaire Geneeskunde. Daarnaast was je nooit te beroerd om mee te helpen met de organisatie van een gezellige afdelingsborrel. Bedankt voor de leuke tijd binnen het LUMC.

Jan, wat was het fijn om ook jou als promotor te hebben. Bedankt voor je positiviteit en je bereidheid om op elk moment van de dag een mailtje met een vraag over striatale dopamine te beantwoorden. Je aanstekelijke enthousiasme over wetenschappelijk onderzoek is inspirerend en je kennis jaloersmakend.

Naast mijn promotoren kan ik ook Fabian Termorshuizen en Floris van Velden niet genoeg bedanken. Fabian, bedankt voor al je hulp bij het oplossen van de meest uiteenlopende statistische problemen, maar bovenal voor de gezelligheid die je binnen de onderzoeksgroep bracht met je verhalen over varkens, opera, zwemmen en het Statenkwartier. Floris, ook jou wil ik bedanken voor al je hulp. Ondanks je volle agenda wist je altijd tijd voor me te maken, zodat we onder het genot van een kopje koffie onze hersens konden pijnigen over de analyses van [^{18}F]-FDOPA PET/CT (hoewel we een groot deel van onze afspraken ook vulden met praten over hardlopen en reizen!). Bedankt voor je steun en je aanhoudende optimisme als het een en ander weer eens dreigde mis te gaan.

Als psycholoog is het doen van onderzoek met *positron emission tomography* (PET) onwennig, uitdagend en spannend. Zonder de hulp van vele medewerkers van GGZ Rivierduinen, het LUMC, Maastricht University, het VUmc en King's College London was dit mij niet gelukt. Bedankt hiervoor.

Binnen GGZ Rivierduinen wil ik in het bijzonder Wilma Hartwijk, Els van der Ven en de onderzoeksassistenten bedanken. Wilma, bedankt dat je altijd beschikbaar was als er iets geregeld moest worden en voor de gezelligheid tijdens de kerstborrels. Els, dank je voor je enthousiasme en voor je bereidheid om over van alles en nog wat mee te denken (zelfs vanuit een speeltuin in New York!). Jessie Kosterman, Carlijn Clemens en Daniëlle Bos, mijn dank is groot voor het belangrijke werk dat jullie als onderzoeksassistenten hebben geleverd en voor de gezelligheid die jullie binnen de onderzoeksgroep hebben gebracht.

Ook bedank ik mijn collega's van het LUMC die betrokken waren bij het maken van de PET/CT-scans en MRI-scans (en altijd zin hadden in een feestje!): Jacqueline Aanholt-Bijlemeer, Ina Boot, Neanke Bouwman, Robert Bovenkerk, Johan van Brecht, Michael Bruijns, Petra Dibbets-Schneider, Willem Grootjans, Demi Jansen, Joeri Kuil, Dennis Robbemon, Jordi Vonk-van Oosten, Patrick van der Zwet en alle medewerkers van het secretariaat Nucleaire Geneeskunde.

Alle coauteurs die een bijdrage hebben geleverd aan de verschillende publicaties wil ik bedanken voor het meedenken, de hulp bij de analyses en het meeschrijven. In het bijzonder wil ik Prof. Therese van Amelsvoort bedanken, die bij een groot deel van de publicaties betrokken is geweest en altijd bereid was om te brainstormen over nieuw onderzoek.

Mijn dank gaat verder uit naar de leden van de beoordelingscommissie voor het lezen en beoordelen van mijn proefschrift: Prof. Bart Rutten, Prof. Iris Sommer, Dr. Elsmarieke van de Giessen, Prof. Felix Mottaghy en Prof. Machteld Marcelis.

Daarnaast bedank ik de instellingen die een bijdrage hebben geleverd aan mijn promotieonderzoek. Allereerst bedank ik GGZ Rivierduinen voor het bieden van de mogelijkheid om te promoveren binnen een klinische setting. De samenwerking tussen academische en klinische instellingen is essentieel voor vooruitgang en ik hoop dat deze traditie binnen GGZ Rivierduinen voortgezet zal worden. Verder bedank ik de vele instanties en personen die onderzoek naar autisme faciliteren en mij onder andere geholpen hebben bij het werven van deelnemers met autisme: JADOS (in het bijzonder Elles van Woerkum en Paul Stoffer), Marcel Melchers van de Universiteit Leiden, Villa Abel, PAS Nederland, Leviaan, aspergersyndroom.nl, autsider.net, RIAN Autismenetwerk en de Nederlandse Vereniging voor Autismen.

Uiteraard bedank ik ook alle proefpersonen met en zonder autisme die vaak met veel enthousiasme aan het wetenschappelijk onderzoek deelnamen. Zonder klagen lagen zij 90 minuten stil voor het maken van een PET/CT-scan en beantwoordden zij uitgebreide vragenlijsten over uiteenlopende onderwerpen als pesten, eenzaamheid en psychose. Bedankt dat jullie mij een inkijk in jullie leven hebben gegeven en mij daarmee veel hebben geleerd.

Mijn mede-promovendi, Jonas, Yvonne en Carmen, wil ik bedanken voor de gezellige jaren die we met elkaar hebben doorgebracht. Jonas, bedankt voor de leuke en interessante gesprekken over mentaliseren, reizen en Japanse whisky. Ook het schnitzels eten en biertjes drinken in Berlijn en het met-iets-te-veel-wijn-op filosoferen over van alles en nog wat in Florence zal ik niet gauw vergeten. Yvonne, onze wandelingen tijdens de lunch hielden me nog een beetje in conditie, bedankt daarvoor! Ook bedankt voor al je steun (o.a. tijdens de turbulente vlucht naar Berlijn!) en voor de gezelligheid door de jaren heen. Carmen, jongste aanwinst van de onderzoekslijn en PET-buddy; helaas gooide het coronavirus enigszins roet in het eten waardoor leuke dingen, zoals congresbezoeken, niet door konden gaan. Desondanks hebben we een gezellige tijd gehad binnen Rivierduinen. Ik heb er het volste vertrouwen in dat ook jij je PET-onderzoek mooi zal afronden!

Bas, Boaz, Eveline, Femke, Joran, Merel, Petri, Renaldo, Robin, Renata, Roland, Ryan, Saskia en alle aanhang, dank jullie wel voor onze vriendschap, jullie steun en jullie geduld als ik weer eens de behoefte had om over dopamine te praten. Paranimfen Chester en Jeffrey, bedankt voor de vele (quasi-)filosofische discussies en voor het helpen herinneren dat er meer is in het leven dan PET-scanners.

Paul, Connie, Bas, Aleks, Menno, Manisha, Jace, Hans, Lidy, Martijn, Amber, oma Hennie, oma Mies, Henk en de rest van de familie, bedankt dat jullie altijd voor me klaar staan en mij aanmoedigen.

Manouk, mijn proefschrift draag ik op aan jou. Dankjewel voor je onvoorwaardelijke steun, vertrouwen en liefde.

Curriculum vitae

Rik Schalbroeck was born on January 15, 1992 in The Hague, The Netherlands. After completing high school at the Alfrink College Zoetermeer, he obtained his bachelor's degree in Psychology at Leiden University. At the same university, he completed his research master's in Psychology, with a specialization in Clinical and Health Psychology (cum laude). In December 2016, he started as an external PhD candidate at GGZ Rivierduinen and Maastricht University, School for Mental Health and Neuroscience, under supervision of Prof. Dr. Jean-Paul Selten, Prof. Dr. Lioe-Fee de Geus-Oei, and Prof. Dr. Jan Booij. He is currently a postdoctoral researcher at the University of Cambridge, Autism Research Centre.