Orderly chaos

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

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