A diagnostic Venn diagram; a conceptual review on overlapping diagnoses between schizophrenia spectrum disorders and autism spectrum disorders and state-of-the-art approaches on how to tackle them

Author: Emily I. Michail, BSc
Student number: s4901118
Track: N
Date: 11.07.2023
Research Group: Behavioral Neurosciences
Supervisor: Prof. Dr. Martien J.H. Kas

Table of contents

A diagnostic Venn diagram; a conceptual review on overlapping diagnoses between schizophrenia spectrum disorders and autism spectrum disorders and state-of-the-art approaches on how to tackle them

Emily I. Michail[1] | Supervision: Prof. Dr. Martien J.H. Kas[1]

[1]Department of Behavioural and Cognitive Neurosciences, Faculty of Science and Engineering, University of Groningen

Abstract

Through the years the field of psychiatry has strived to update diagnostic tools and research approaches to cater to one of the most challenging practices: understanding the human brain. In recent years attention has been directed to the concept of overlapping diagnoses and comorbidity, which calls for diagnostic and treatment approaches that oftentimes answer to a patient-specific set of symptoms (Jutla et al., 2022). The agreed list of symptoms is exhaustive, and considering the vast possibilities of combinations, the utilization of predefined clusters of criteria has made accurate diagnosis and personalized treatment a major challenge (Michelini et al., 2021). Modern tools strive to introduce continuum-based methods that approach disorders as points on a spectrum, rather than a predefined set of textbook symptoms (Michelini et al., 2021). In the present review, the example of schizophrenia spectrum disorders and autism spectrum disorders, is used to demonstrate such a case of disorders that are cited in literature as to having, to an extent, overlapping phenotypes and shared molecular patterns (Jutla et al., 2021). The question of whether these two spectrums can be merged into one diverse continuum will be addressed through a careful revision of existing literature. Furthermore, state-of-the-art attempts of new diagnostic and research tools are discussed in the context of the two aforementioned disorders (Morris-Rosendahl & Crocq, 2020).

Keywords: autism spectrum disorders; schizophrenia spectrum disorders; comorbidity; RDoC; continuum-based classification in psychiatry.

Introduction

The term 'spectrum' is defined as a broad range of classified points arranged on a scale; a term that has been coined in psychiatry, and is used to group a variety of clinical manifestations into a broader and comprehensive category of a psychiatric disorder (American Psychological Association, APA). In a similar realm, the term comorbidity is used to describe the presence of two or more clinical conditions simultaneously, a phenomenon often present in psychiatric patients (APA). In recent years, the interplay between various conditions and disorders has raised the question on whether these two terms can be used interchangeably, or rather whether the comorbidity between certain disorders could in fact be the result of them residing as points on a common spectrum, instead of a simple co-existence brought about by other factors. As many disorders seem to manifest in the form of similar symptoms, it has become increasingly tempting to speculate that some of them may be part of a much larger spectrum within which subcategories and classifications can come forth and display phenotypes that traditional psychiatric classification treats as separate disorders (Cuthbert, 2020). Overlapping diagnoses is a common phenomenon that makes these speculations even more interesting, but would also make diagnoses and treatment approaches all the more challenging. This is because spectrum-based approaches allow for an endlessly broad range of personalized diagnoses to take place and defy traditional one-size-fits-all treatment approaches (Michelini et al., 2021). Within this enigmatic niche of psychiatry, the intricate relationship between autism spectrum disorders (ASD) and schizophrenia spectrum disorders (SSD) has recently sparked interest due to a fascinating tapestry of overlapping symptoms, and possibly revealing many more common features than what was previously thought (Jutla et al., 2021). Despite this recent rise of interest, ASD and SSD 'go way back', as the term "autism" was firstly used in 1911 by Eugene Bleuler to describe a profound withdrawal from the outside world, a symptom observed in schizophrenia patients. Later, in the 1940s, "autism" was additionally considered a possible early-onset form of schizophrenia observed in children. It was not until 1972 when Michael Rutter brought forth the idea that autism and schizophrenia were in fact different disorders and should be treated as such; his view prevailed and still remains the widely understood diagnostic nosological norm. Despite ASD and SSD's distinct clinical profiles, further described below, recent literature has presented with evidence of overlap between the two, not just on a phenotypical

level but also on a molecular and cerebral level (Jutla et al., 2021). Furthermore, this overlap has often been brought up in discussion, as autism diagnosis in childhood was found to be a strong predictor of psychosis, and SSD alone is three to six times more common in patients with ASD in comparisons to control counterparts. Recent meta-analyses and reviews (Cochran et al., 2013; Fernandes et al., 2018; Hossain et al., 2020; Jutla et al., 2021) have presented results which reveal that the comorbidity of ASD and SSD is more frequent than what would be expected by chance; this elucidates the important of understanding their converging clinical features and distinctive nuances in search of appropriate diagnostic, predictive, and treatment tools. For that, modern classification tools such as the Research Domain Criteria (RDoC) project introduced by the National Institue of Mental Health (NIMH) can be utilized. The RDoC emphasizes on functional dimensions that range from normal to abnormal and provides a platform that strays away from symptom-based diagnostic categories, thus providing space for the concept of overlapping diagnoses to be studied with a less-than-biased approach (Cuthbert, 2020). Taking all of the above into consideration the question that arises is whether ASD and SSD commonalities are enough to justify regarding them part of a much wider, common, and interchangeable spectrum? And if this is true, how can modern classification tools such as the RDoC be utilized to better understand and research these disorders on a spectrum basis?

Hypothesis

"ASD and SSD share enough overlapping features,
to render them appropriate candidates
for classification on a wider shared spectrum."

Understanding Schizophrenia Spectrum Disorders

In order to assess converging areas of ASD and SSD, it is important to first understand their unique phenotypical and genotypical characteristics. Schizophrenia in itself is quite diverse and the clinical symptoms can vary between individuals. According to the Diagnostical and Statistical Manual 5 (DSM-V), the list of symptoms that correspond to schizophrenia include positive symptoms such as hallucinations, delusions (bizarre or non-bizarre), disorganized speech, and grossly disorganized or catatonic behaviour, as well as negative symptoms (affective flattening, alogia or avolition). An individual must satisfy at least two of five main symptoms for a continuous period over at least six months in order to receive a diagnosis. Further, the schizophrenia spectrum disorder includes diagnoses of schizoaffective disorder, schizophreniform disorder, brief psychotic disorder, and delusional disorder. Despite many commonalities in terms of cognitive, perceptional, and sociofunctional symptom manifestations, all of these disorders exhibit varying levels of symptom presentation, and duration, rightfully justifying their presence on a spectrum. *Schizoaffective disorder* is present in individuals displaying a combination of mood disorder symptoms (often surfacing as a manic or depressive episode) and psychotic symptoms commonly seen in schizophrenia, such as delusions, hallucinations, and disorganized speech, while *schizophreniform disorder* is provided as a diagnosis for individuals who evidently display schizophrenia-related psychotic symptoms, but for duration lower than six months; this aspect also deems this diagnosis as "good prognosis schizophrenia". Similarly, *brief psychotic disorder* is characterized by a very brief duration; individuals experience a sudden onset of psychotic behaviour that lasts less than one month followed by complete remission. Future relapses are possible, and in order to receive diagnosis individuals must display at least one of the following symptoms: delusions, hallucinations, or disorganized speech. It ought to be noted that these symptoms must not be attributed to any other disorder, or be result of a drug, medication, or other medical condition. Further, *delusional disorder* is a diagnosis given to individuals who have one or more non-bizarre delusional thoughts that could be possible in real-life, but are false/untrue. It is important to note that the delusions stay true to the individual for a duration of time but do not impair their functionality in any way. In such scenarios, the individual's cultural and/or religious beliefs merit consideration before a diagnosis is given, and the delusions must not come as a result of drug, medication, or any other medical condition. It is apparent that clinical manifestations of schizophrenia and related disorders are diverse and although classic diagnostic tools have proved relatively reliable, many aspects of its psychopathological dimensions still remain elusive (Tandon et al., 2013). In order to better understand and define such a heterogenous disorder, research must take into consideration a number of variables such as observable symptoms and behavior, alterations in perception and cognition, quantifiable biomarkers, genetic and environmental risk factors, and comorbidity (Jutla et al., 2021); the latter being particularly interesting in the convergent relationship between SSD and ASD.

Understanding Autism Spectrum Disorders

The term ASD is used to describe a wide array of neurodevelopmental disorders characterized by early-onset, and that typically include impairments of social-communication abilities, and behaviours of repetitive and/or stereotypical nature (Cochran et al., 2013). The level of impairment sets the individual at varying points on the ASD spectrum and also defines their level of functionality (e.g. high-functioning) (Wiggins et al.,

2019). The manifestation of symptoms heavily varies amongst individuals, and over the years traditional classification and diagnostic tools have frequently been updated to more accurately describe the vast heterogeneity of ASD. Subtypes and categories are arbitrary and have continuously been challenged as research in the field progressed. During the update from DSM-4 to DSM-5, defined subtypes (e.g. Asperger's disorder) were dropped because they were still not able to cover the remarkable heterogeneity of cases (Wiggins et al., 2019). Instead, the latest version ASD no longer includes subtypes but is represented as a disorder with varying levels of functionality. In order to gain a diagnosis, an individual must satisfy all three social criteria (deficits in social-emotional reciprocity, deficits in nonverbal communicative behaviors, and deficits in developing, understanding, and maintaining relationships), as well as two out of four behavioral criteria (repetitive speech or motor movements, insistence on sameness, restricted interests, or unusual response to sensory input). Notably, Cochran et al. (2013) reports that several of these symptom domains can often be misinterpreted as psychotic symptomatology; these include illogical thinking, incoherence, poor speech, and inappropriate and/or blunted affect. This is consistent with past research that supports the co-occurrence of ASD with other psychiatric disorders (Hossain et al., 2020). Notably, it is estimated that almost 70% of individuals with ASD experience at least one comorbid psychiatric disorder (Hossain et al., 2020). These can include anxiety disorder, depression, bipolar disorder, attention-deficit/hyperactivity disorder, disruptive / impulse-control / conduct disorders, and schizophrenia spectrum disorders (Hossain et al., 2020).

ASD and SSD comorbidity

Interestingly, the comorbidity between ASD and a second diagnosis is more prevalent in youth (Hossain et al., 2020); this further supported by previous literature that suggests that children and young adolescents diagnosed with ASD are at higher risk for developing SSD (Sullivan et al., 2013; Jutla et al., 2021). Specifically, in their 2021 study, Jutla and colleagues report that parent-reported ASD diagnosis was a strong predictor of psychotic symptoms in middle childhood. It should be noted that the comorbidity of ASD and SSD has direct implications when it comes to treatment. Downs et al. (2017) suggests that youth with ASD that are experiencing emerging psychotic symptoms, report poorer responses to initial antipsychotic medication. In such cases, identifying the co-occurrence early on can help make better calculated decisions on the appropriate treatment suited for each individual's unique set of symptoms and thus, avoid possible physical side effects and/or mental strains warranted by sudden remedication (Jutla et al., 2021). In order to do so, further transdiagnostic research would need to take place, and at the moment, the number of studies touching upon this topic, remains modest. However, recent conceptual reviews and meta-analyses have made attempts to illustrate the overlap of ASD and SSD seen through their clinical presentation (Jutla et al., 2021). Below, several of these points of convergence are summarized and discussed.

Clinical symptoms

As aforementioned, symptom manifestations in both ASD and SSD are grossly heterogeneous amongst individuals and whilst both disorder spectrums are characterized by unique symptomatology, several symptom clusters seem to overlap. Some of these include social communication deficits, diminished emotional affect, social withdrawal, lowered cognitive processing speed, impaired language ability, sensory sensitivities, and abnormal perception, amongst others (Cochran et al., 2013) (Fig 1). These are mostly in line with what is defined as negative symptoms in schizophrenia, which are notably also more commonly the first to appear in patients (Correll & Schooler, 2020). Nonetheless, the two also present with several symptoms that have not been reported in existent literature to overlap, for example positive psychotic symptoms (hallucinations, paranoia, delusions) in SSD, and repetitive routines and particular special interests in ASD (Neff, 2022). It is tempting to suggest that in the context of a shared spectrum between ASD and SSD different subtypes and/or clinical cases can be distinguished from each other on the basis of their most prevalent symptoms. In such a case, a diagnosis could include a set of symptoms shared between the two traiditonal diagnoses and also be complemented by possible co-occuring symptoms more specific to one or the other (ASD or SSD). This option allows the professional to not rule out one or the either diagnosis, but rather have them complement each other. This becomes particularly relevant when condidering a study carried out by Larson and colleagues (2017), in which they compared adults with ASD and co-occuring psychosis to ASD-only and psychosis-only groups. They found that participants of the ASD+psychosis group were the most likely to have a diagnosis of "psychosis, not otherwise specified" than a certain diagnosis of schizophrenia, on the premise of not meeting schizophrenia's duration criteria. Moreover, participants of this group were also significantly less likely to present symptoms related to particular special interests and repetitive behaviours, pointing towards a possible subtype of ASD characterized by more affective symptoms, similar to negative schizophrenia symptoms (Larson et al, 2017). These findings represent an example of a context in which schizophrenia-related psychosis may arise in ASD and reflect a unique

diagnosis subtype residing on a potential shared autism-schizophrenia spectrum.

Cognition

Another area in which ASD and SSD significantly converge is cognitive impairments (Jutla et al., 2021). Both ASD and SSD seem to share abnormalities in three pillars of cognition, namely social cognition (e.g. emotion processing), language ability, and non-social cognition (e.g. executive function, and processing speed) (Jutla et al., 2021). The former two have been illustrated in literature as to having similar clinical presentation across both ASD and SSD (Sasson et al., 2011), whilst the latter is subject to some discrepancies between the two disorders. In ASD, non-social cognition seems to be correlated, possibly de novo, to the individual's intellectual ability, but in SSD decline of non-social cognitive abilities seems to worsen as the course of illness progresses (Jutla et al., 2021). Although studies in this area are scarce, it would be interesting to explore whether individuals with an ASD diagnosis and a co-occurrence of SSD (e.g. psychosis not otherwise specified subtype) show a faster rate of non-social cognitive decline in comparison to non-ASD diagnosed counterparts. Such investigations can provide with valuable input about the susceptibility of current ASD-diagnosed patients to potential psychotic symptoms. Further, understanding how to recognize potential overlapping cognitive markers can help prevent psychotic episodes or the possibility of comorbidity in such patient groups. However, it ought to be noted that the use of cognitive markers is ambivalent, as they can be influenced by co-founding or otherwise uncontrolled factors such as intelligence (Hirosawa et al., 2020). This is where other factors, such as molecular and genetic biomarkers come into play in order to illustrate converging pathways that transcend simple behavioral symptom comparisons.

Genetic risk variants

In the scope of molecular and genetic biomarkers, research suggests that patients diagnosed for SSD present with rare coding variants in genes associated with neurodevelopmental disorders, and more so with ASD and intellectual disability (Rees et al., 2021). In their 2021 analytical study, Rees and colleagues showed that in shared risk genes de novo variants of SSD and ASD were of the same functional category and that de novo variants seen in ASD (and other neurodevelopmental disorders) not only were enriched in schizophrenia, but were also known to be pathogenic for syndromic disorders. Furthermore, a genome-wide study by Cross-Disorder Group of the Psychiatric Genomics Consortium showed statistically significant genetic correlation between ASD and SSD (Devlin et al., 2013). A prime example is the duplication of chromosome 16p11.2, identified in both ASD and SSD at very similar rates (~0.28% of cases, and ~0.3% of cases, respectively) (Walsh & Bracken, 2011; Marshall et al., 2017). Moreover, literature indicates that ASD-diagnosed individuals harbouring this mutation seem to have an increased risk for SSD, which supports the presence of a possible psychosis-prone ASD subtype (Jutla & Turner et al., 2020). These findings suggest that ASD and SSD have shared molecular aetiology, that oftentimes may also give rise to various subtypes of these disorders.

Inflammation

Recently, the presence of central nervous system (CNS) inflammation has been linked to the pathogenesis of several disorders (Feng et al., 2021). It has been suggested that inflammation may also be revelant in the development of ASD and SSD, although studies tackling the topic are limited. Separate examination of ASD and SSD individuals showed that both groups exhibit increased microglial activation in multiple identical brain regions, including the frontal and temporal lobe grey matter (Suzuki et al., 2013 & Bloomfield et al., 2015 as cited in Jutla et al., 2021). However, microglial activation in ASD was also present in the cerebellum and the brainstem; this was not true for SSD (Bloomfield et al., 2015), which could point to a possible point of divergence, and/or a pattern of differentiating regional inflammation-based ASD-SSD subtypes.

Brain structure

Another area of interest, is cortical structure. Albeit current literature yielding mixed results when it comes to possible convergence between ASD and SSD in this regard, a recent meta-analysis (Cauda et al., 2017 as cited in Jutla et al., 2021) has highlighted the relevance of the anterior insula (AI). They used individuals with an ASD, SSD, or obsessive compulsive disorder (OCD) diagnosis, and demonstrated that participants fell into one of two broad clusters of regional volume changes. The cluster more relevant to SSD patients seemed to present decreases in AI, medial prefrontal cortex (mPFC), and thalamic volume. The second cluster was more relevant to individuals with OCD and displayed volume decrease in the parietal, temporal, and occipital lobes. What was particularly interesting is that individuals with ASD were distributed evenly across the two groups. This further supports not only the heterogeneity of ASD, but also a significant area of overlap with SSD. Notably, the AI is widely accepted as the anchoring region of the salience network (SN) (Menon, 2015). The SN is a large-scale network that includes several cortical and subcortical structures (AI, dorsal anterior cingulated cortex, amygdala, ventral striatum, and substantia nigra). Through these structures, the SN carries out various complex brain functions such as communication, social behavior, and

self-awareness all through the utility of sensory, emotional, and cognitive information (Menon, 2015). Because of this, SN dysfunction has been linked to both ASD and SSD, as it's been observed to predict severity level of repetitive behaviors in ASD, and severity of positive symptomatology in SSD (Uddin et al., 2013 & Krishnadas et al., 2014 as cited in Jutla et al., 2021). These insights provide information on possible underlying structural similarities and/or aetiology, between the two, as well as areas of divergence through which subtypes can be identified. In addition to the known similar behavioural and cognitive clinical picture of ASD and SSD, these findings further support the hypothesis that the two may lie on a continuum that fosters a co-occuring relationship in some clinical populations.

Transdiagnostic research tools

The present essay does not provide an exhaustive list of overlapping variables between ASD and SSD. However several papers have been published that provide further insight to categories such as brain structure, genetic risk variants, neural networks, environmental risk factors, and other areas in which the two show notable overlap (Cochran et al., 2013; Hossain et al., 2020; Morris-Rosendahl & Crocq, 2020; Jutla et al., 2021). Nonetheless, several key aspects have been summarized and discussed. A number of arguments have been provided which supports the initial hypothesis that ASD and SSD may possibly co-reside on a continuous spectrum with several subtypes of clinical manifestations. Albeit the small number of studies and reviews available on the topic, additional research needs to be done in order to further uncover the relationship between ASD and SSD as components of a spectrum. For that, traditional diagnostic tools and classifications may not offer an appropriate and reliable point of reference. Instead, researchers should opt to utilize transdiagnostic approaches that intrinsically provide a platform onto which co-occurrence of diagnoses can be studied, such as the RDoC.

Research Domain Criteria (RDoC)

The RDoC is a translational framework for psychopathology research. The project was initiated by the NIMH with the purpose of providing a research platform that could circumvent issues arising from the use of symptom-based diagnostic classifications (Cuthbert, 2020). This framework takes into consideration a number of factors such as observable behavior and neurobiological measures in order to present psychopathology through multiple dimensions. Further, it aims to serve as a tool in translating data of behavioral and neuroscientific nature into psychopathology (Cuthbert, 2020). Because of this, it could prove useful in sorting possible ASD-SSD co-occurrence subtypes onto a comprehensive spectrum, by taking into consideration their overlapping features across several biological and behavioral variables. By applying this integrative approach, an extensive list of subtypes/biotypes of a proposed ASD-SSD spectrum could be generated. Utilizing those biotypes, researchers can then divert their studies to better defined clusters of individuals, the comparability across studies would be increased, and more informed conclusions could be drawn. It should be noted that the RDoC seeks to act as a research framework to complement diagnostic systems towards the development of precision medicine and personalized treatment, as well as facilitate accurate diagnostic assessment and/or prevention (Cuthbert, 2020; Morris-Rosendahl & Crocq, 2020). This is particularly relevant to the case of ASD and SSD as their comorbidity has be shown to instigate treatment failure of first-episode psychosis (FEP) in individuals with ASD (Downs et al., 2017). Specifically, Downs et al. (2017) showed that a co-occuring ASD diagnosis sandbagged two different antipsychotic treatments for FEP. Even when controlling for possible confounding factors, such as age, gender, intellectual disability, and psychosis severity, this effect persisted, pointing towards evidence that the presence of an ASD diagnosis during FEP needs to be accounted for when choosing the appropriate medication. Applying a spectrum-based approach in this case, could render two different biotypes; 1) FEP with previous ASD diagnosis, 2) FEP without previous ASD diagnosis. Based on the results presented by Downs and colleagues (2017), these two biogroups would require different medication approaches, carefully curated to suit the needs of the individual and their unique diagnosis.

Modeling the spectrum

When it comes to studying this relationship between ASD and SSD the RDoC can prove to be a useful tool by mitigating problems arising from traditional reductionistic diagnostic approaches. However, when it comes to modeling the proposed spectrum, the task becomes much harder and complex considering the continuously growing body of data on the topic. Albeit the promising data presented in the discussed literature, Jutla et al. (2021) argue that little consistency exists across studies and that different methodological approaches render comparisons difficult. Moreover, the replicability of most available studies has yet to be challenged. Further, the term spectrum itself may be deceiving, as ASD and SSD seem to generate subtypes of their own in the context of co-occurrence, so it is perhaps more appropriate to visualize the spectrum as an extensive Venn-diagram or a constellation of subtype clusters, leaning towards one "side" of a spectrum, or the other, based on their unique features, molecular underpinnings, and clinical presentations.

Conclusions

The present essay sought to provide evidence from previous studies, conceptual reviews, and meta-analyses, to explore the idea of ASD and SSD co-residing on a common spectrum. Although the data discussed support the original hypothesis, it should be noted that the literature presented is not exhaustive. Many other overlapping variables, such as environmental risk factors and neuroimaging biomarkers were not discussed. These would add dimension to the argument and possibly unveil information to further support the hypothesis, or oppose it. Furthermore, the RDoC framework was introduced as a tool of transdiagnostic research and a simple example illustrating its utility was presented. Nonetheless, it is important to highlight that the RDoC has not been introduced as a diagnostic manual to replace traditional classification, but rather a tool to complement it. In the example provided above, the widely accepted terminology of ASD and SSD is used to convey a possible way the RDoC can be introduced in the study of elusive subtypes of traditional diagnoses. The summarized data seemed to suggest that ASD and SSD may indeed be adequate candidates of disorders that can be modeled on a single extensive spectrum. Further, it was discussed that co-occurrence may not only result in overlapping phenotypes, but may also meddle with medicinal treatment approaches. Understanding the implications brought about by ASD and SSD commonalities may allow for better, personalized treatment approaches, help identify markers for prevention, and help professionals make more informed decisions when it comes to giving a diagnosis.

However, as many aspects of this relationship still remain elusive it is not with certainty that we can claim a shared ASD-SSD spectrum yet. Furthermore, existent literature on comorbidity between the two with other disorders not discussed here, such as OCD and attention deficit hyperactivity disorder (ADHD), raises the question on whether other diagnostic pairs may converge on a larger, more significant scale, than the two presented in the present essay (Hossain et al., 2020). Is an ASD-ADHD or an SSD-OCD spectrum more relevant? Or should we opt for an even broader spectrum network that allows the co-occurrence of all to be studied simultaneously? This challenges the ambiguity of spectrum-based approaches that stray away from traditional classifications systems, as the lack of clearly defined boundaries between diagnoses can give rise to other issues. These may include the inability of professionals to narrow down treatment approaches, or communicating diagnoses between patients and other clinicians. In the search for answers more questions arise; this is why additional research, as well as study replication, is required in order to unveil more sophisticated and reliable data regarding the relationship between ASD and SSD, their comorbidity patterns, and how co-occurrence can have an effect on disorder progression and treatment efficiency.

Fig.1 *Venn-diagram of convergent and divergent features between ASD and SSD*

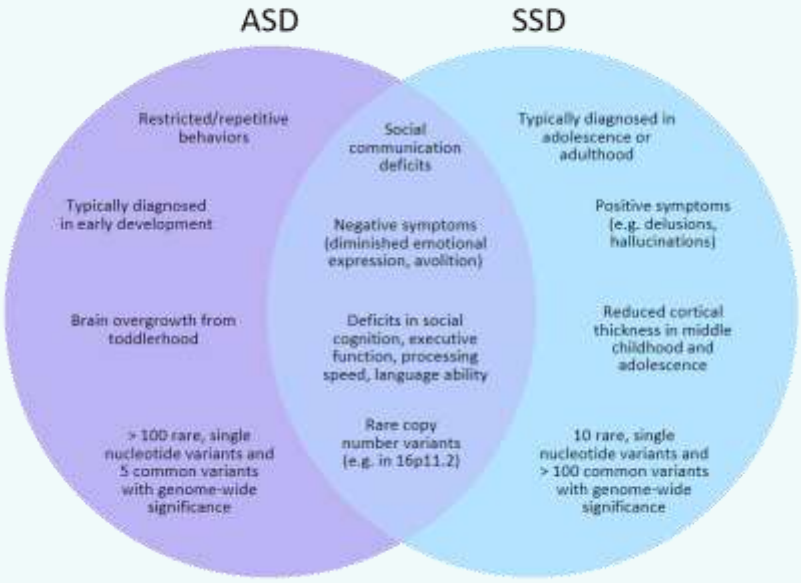

Fig.1 *Adapted from Jutla et al. (2021)*. Autism spectrum disorders (ASD) and schizophrenia spectrum disorders (SSD) exhibit both unique phenotypical manifestations, as well as overlapping features across many different variables such as behavior, symptoms, genetic risk factors. Examples from several of those domains are depicted.

References

Bloomfield, P. S., Selvaraj, S., Veronese, M., Rizzo, G., Bertoldo, A., Owen, D. R., ... & Howes, O. D. (2016). Microglial activity in people at ultra high risk of psychosis and in schizophrenia: an [11C] PBR28 PET brain imaging study. American Journal of Psychiatry, 173(1), 44-52.

Cochran, D. M., Dvir, Y., & Frazier, J. A. (2013). "Autism-plus" spectrum disorders: intersection with psychosis and the schizophrenia spectrum. *Child and Adolescent Psychiatric Clinics*, *22*(4), 609-627.

Correll, C. U., & Schooler, N. R. (2020). Negative symptoms in schizophrenia: a review and clinical guide for recognition, assessment, and treatment. *Neuropsychiatric disease and treatment*, 519-534.

Cuthbert, B. N. (2022). The role of RDoC in future classification of mental disorders. *Dialogues in Clinical Neuroscience*.

Devlin, B., Kelsoe, J. R., Sklar, P., Daly, M. J., O'Donovan, M. C., Craddock, N., ... & Wray, N. R. (2013). Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs. *Nature genetics*, *45*(9), 984-994.

Downs, J. M., Lechler, S., Dean, H., Sears, N., Patel, R., Shetty, H., ... & Pina-Camacho, L. (2017). The association between comorbid 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), 1411.

Feng, T., Tripathi, A., & Pillai, A. (2020). Inflammatory pathways in psychiatric disorders: the case of schizophrenia and depression. *Current behavioral neuroscience reports*, *7*, 128-138.

Fernandes, J. M., Cajão, R., Lopes, R., Jerónimo, R., & Barahona-Corrêa, J. B. (2018). Social cognition in schizophrenia and autism spectrum disorders: a systematic review and meta-analysis of direct comparisons. *Frontiers in psychiatry*, *9*, 504.

Hirosawa, T., Kontani, K., Fukai, M., Kameya, M., Soma, D., Hino, S., ... & Kikuchi, M. (2020). Different associations between intelligence and social cognition in children with and without autism spectrum disorders. PLoS One, 15(8), e0235380.

Hossain, M. M., Khan, N., Sultana, A., Ma, P., McKyer, E. L. J., Ahmed, H. U., & Purohit, N. (2020). Prevalence of comorbid psychiatric disorders among people with autism spectrum disorder: An umbrella review of systematic reviews and meta-analyses. *Psychiatry research*, *287*, 112922.

Jutla, A., Foss-Feig, J., & Veenstra-VanderWeele, J. (2022). Autism spectrum disorder and schizophrenia: An updated conceptual review. *Autism Research*, *15*(3), 384-412.

Jutla, A., Turner, J. B., Green Snyder, L., Chung, W. K., & Veenstra-VanderWeele, J. (2020). Psychotic symptoms in 16p11. 2 copy-number variant carriers. *Autism Research*, *13*(2), 187-198.

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.

Marshall, C. R., Howrigan, D. P., Merico, D., Thiruvahindrapuram, B., Wu, W., Greer, D. S., ... & Kähler, A. K. (2017). CNV and Schizophrenia Working Groups of the Psychiatric Genomics Consortium. Contribution of copy number variants to schizophrenia from a genome-wide study of 41,321 subjects. *Nat Genet*, *49*(1), 27-35.

Menon, V. (2015). Salience network. *Brain mapping*, *2*, 597-611.

Michelini, G., Palumbo, I. M., DeYoung, C. G., Latzman, R. D., & Kotov, R. (2021). Linking RDoC and HiTOP: A new interface for advancing psychiatric nosology and neuroscience. *Clinical psychology review*, *86*, 102025.

Morris-Rosendahl, D. J., & Crocq, M. A. (2022). Neurodevelopmental disorders—the history and future of a diagnostic concept. *Dialogues in clinical neuroscience*.

National Institute of Mental Health (n.d.). U.S. Department of Health and Human Services, National Institutes of Health

Neff, M. A. (2022). Schizophrenia or Autism: A brief history of schizophrenia and autism and how to spot the difference — Insights of a Neurodivergent Clinician. Insights of a Neurodivergent Clinician. https://neurodivergentinsights.com/misdiagnosis-monday/shizophrenia-vs-autism

Rees, E., Creeth, H. D., Hwu, H. G., Chen, W. J., Tsuang, M., Glatt, S. J., ... & O'Donovan, M. C. (2021). Schizophrenia, autism spectrum disorders and developmental disorders share specific disruptive coding mutations. *Nature communications*, *12*(1), 5353.

Sasson, N. J., Pinkham, A. E., Carpenter, K. L., & Belger, A. (2011). The benefit of directly comparing autism and schizophrenia for revealing mechanisms of social cognitive impairment. Journal of neurodevelopmental disorders, 3(2), 87-100.

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.

Tandon, R., Gaebel, W., Barch, D. M., Bustillo, J., Gur, R. E., Heckers, S., ... & Carpenter, W. (2013). Definition and description of

The Diagnostic and Statistical Manual of Mental Disorders (5th ed.; DSM–5; American Psychiatric Association, 2013

Walsh, K. M., & Bracken, M. B. (2011). Copy number variation in the dosage-sensitive 16p11. 2 interval accounts for only a small proportion of autism incidence: a systematic review and meta-analysis. *Genetics in Medicine*, *13*(5), 377-384.