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Autism spectrum disorder and schizophrenia: an updated conceptual review

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Abstract

Autism spectrum disorder (ASD) and schizophrenia (SCZ) are separate disorders, with distinct clinical profiles and natural histories. ASD, typically diagnosed in childhood, is characterized by restricted or repetitive interests or behaviors and impaired social communication, and it tends to have a stable course. SCZ, typically diagnosed in adolescence or adulthood, is characterized by hallucinations and delusions, and tends to be associated with declining function. However, youth with ASD are three to six times more likely to develop SCZ than their neurotypical counterparts, and increasingly, research has shown that ASD and SCZ converge at several levels. We conducted a systematic review of studies since 2013 relevant to understanding this convergence, and present here a narrative synthesis of key findings, which we have organized into four broad categories: symptoms and behavior, perception and cognition, biomarkers, and genetic and environmental risk. We then discuss opportunities for future research into the phenomenology and neurobiology of overlap between ASD and SCZ. Understanding this overlap will allow for researchers, and eventually clinicians, to understand the factors that may make a child with ASD vulnerable to developing SCZ.

Lay Summary:

Autism spectrum disorder and schizophrenia are distinct diagnoses, but people with autism and people with schizophrena share several characteristics. We review recent studies that have examined these areas of overlap, and discuss the kinds of studies we will need to better understand how these disorders are related. Understanding this will be important to help us identify which autistic children are at risk of developing schizophrenia.

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Keywords

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Introduction

Autism spectrum disorder (ASD) and schizophrenia (SCZ) have a strong historic connection. In 1911, Eugen Bleuler coined the term “autism” to describe the apparent withdrawal from the outside world that he observed in schizophrenia patients (Kuhn & Cahn, 2004). By the 1940s, Leo Kanner had reappropriated “autism” to describe a childhood behavioral disorder that he speculated could be an early-onset form of schizophrenia (Kanner, 1949). Over time, Michael Rutter (1972) argued that autism was a disorder in its own right, independent of schizophrenia, and this has remained the prevailing nosological view (B. J. Crespi, 2010).

ASD and SCZ have divergent clinical profiles and natural histories (American Psychiatric Association, 2013). ASD, typically diagnosed in childhood and characterized by a stable or improving longitudinal course (Anderson, Liang, & Lord, 2014; Fein et al., 2013; Lord et al., 2006) is defined by impaired social communication and restricted or repetitive behaviors. SCZ, in contrast, is typically diagnosed in late adolescence or early adulthood. and is characterized by a progressive course (Andreasen, 2010), often with persistent long-term impairment (Fett et al., 2020; Velthorst et al., 2017). It is defined by “psychosis,” as reflected by delusional beliefs, perceptual disturbances, or disorganized thought. Psychosis may precede the onset of frank SCZ, and can also be associated with other conditions, such as bipolar disorder.

Despite their clear differences, ASD and SCZ do share some qualities and have increasingly been shown to converge at certain levels. People with ASD and SCZ show similarly impaired performance on neurocognitive measures of social cognition, demonstrate similar abnormalities of functional connectivity in large-scale brain networks, and share some neuroanatomical findings. The disorders also share genetic liability, with several loci implicated in both. Finally, ASD and SCZ co-occur much more frequently than would be expected by chance. One meta-analysis of studies examining adults with ASD found that “SCZ spectrum disorders” (which include SCZ and its antecedents, delusional disorder, schizoaffective disorder, and brief psychotic disorder) had a pooled prevalence of 12% in ASD (Lugo Marín et al., 2018). Two other meta-analyses have found that SCZ alone is three to six times more common in people with ASD than in controls (Lai et al., 2019; Z. Zheng, Zheng, & Zou, 2018).

The overlap between ASD and SCZ is particularly relevant when considering which youth with ASD are at risk of developing SCZ. Our group, in a study of the large U.S. Adolescent Brain Cognitive Development cohort, found that a parent-reported autism diagnosis was a strong predictor of psychotic symptoms in middle childhood (Jutla, Donohue, Veenstra-VanderWeele, & Foss-Feig, 2021). Work in the Avon Longitudinal Study of Parents and Children has found the same relationship in early adolescence(S. Sullivan, Rai, Golding, Zammit, & Steer, 2013). In contrast, older adolescents and young adults with ASD at

clinical high risk of psychosis appear to convert to SCZ at similar rates to the neurotypical population (Foss-Feig et al., 2019; Sunwoo et al., 2019).

At the individual level, the co-occurrence of ASD and psychosis or SCZ has concrete implications for treatment. In children and adolescents with emerging psychosis, co-occurring ASD is associated with poorer response to an initial medication (Downs et al., 2017), indicating a possible need for the clinician to be more willing to switch medications early in this population. In adolescents and adults with SCZ, co-occurring ASD could warrrant emphasizing treatments to mitigate deficits in social functioning, including cognitive remediation (Eack et al., 2018) and community-based (Foss-Feig, Lurie, & Hubert, 2020) interventions. In some cases, an individual with one diagnosis who receives the other could even may even have improved access to care. In the United States, for example, most states have separate bureaucracies, providing separate services, for people with developmental disabilities such as ASD and those with mental health diagnoses such as SCZ (Pinals, Hovermale, Mauch, & Anacker, 2021). The overlap between ASD and SCZ thus has clear clinical importance.

Some areas of convergence between ASD and SCZ have been reviewed previously (de Lacy & King, 2013), particularly, similarities in molecular mechanisms and cerebral development. We have thus chosen in this paper to focus on research published over the past eight years, and to emphasize clinical findings in groups of human patients.

In preparing this review, we outlined a systematic approach to identifying appropriate papers. However, as we began reviewing the literature, we realized that it would be most helpful to take a conceptual approach rather than to try to comprehensively survey what turned out to be quite a sparse and wide literature. This review therefore intends to provide an updated conceptual review of the relationship between ASD and SCZ, as well as a framework for future research. For the purpose of the current review, we recognize that the literature primarily looks at ASD and SCZ, but we sought to also include studies of psychosis regardless of SCZ diagnosis.**

Methods

Eligibility criteria, information sources, and search strategy

Our study sought to include both SCZ and psychosis. We realize that these are not necessarily the same. However, many papers are framed in a way that looks at SCZ rather than psychosis or psychotic symptoms.

We decided *a priori* that any data-driven, clinical paper that examined characteristics of ASD in SCZ, examined characteristics of SCZ in ASD, or compared ASD and SCZ directly, would be eligible. We drew on two sources: the Web of Science Core Collection and MEDLINE. We searched both databases on 2/18/2021 for journal articles published in English since 2013, the year the last major systematic review of psychosis and autism was published. The Web of Science Core Collection search was for titles containing “autis* AND (schizophreni* OR psychosis OR psychotic).” The MEDLINE search was for the MeSH headings “Autism Spectrum Disorder (AND Psychotic Disorders OR

Schizophrenia).” We then merged results from both database searches and deduplicated the pooled results.

Study selection

We screened abstracts (in a first pass) and full-text papers (in a second pass) to exclude papers that were purely theoretical, papers that described traits in non-psychiatric populations, and papers that only described data from animal or cell models or from postmortem tissue.

Manual addition of relevant papers not identified by search

If papers from our search results contained references to relevant papers published after 2013 that our search did not identify, we included these. We also continuously monitored for relevant new papers published after 2/18/2021 via Stork (storkapp.me), which searched across Web of Science and MEDLINE for the keyword string “autism AND psychosis” and sent us a daily alert listing newly indexed papers.

Data collection process

We sorted each result into one of four categories: symptoms and behavior, perception and cognition, biomarkers, and genetics. For each result, we noted the study’s design, the characteristics and age range of its participants, and its notable findings.

Results

Our search (Figure 1) identified 675 records (318 from Web of Science Core Collection, 269 from MEDLINE, 3 published following our search, and 85 cited within other articles), with 579 remaining after automated deduplication, and 286 remaining after manual screening of abstracts to remove records that were not relevant or usable. After manually screening the full text of these 286 records, we excluded an additional 201 papers.

Of the 85 papers remaining, we classified 25 as describing symptoms or behavior, 19 as describing perception or cognition, 30 as describing biomarkers, and 39 as describing genetic or environmental risk. We present here a qualitative synthesis of the key results from these papers.

Symptoms and behavior

A psychiatric diagnosis is based on current observed or reported symptoms taken in the context of longitudinal history. In differentiating ASD from SCZ, the similarities between these disorders at the level of cross-sectional symptoms can make them particularly difficult to separate. A childhood developmental history is usually - but not universally - helpful.

Popular measures used to identify autism traits or establish an autism diagnosis, such as the Autism Quotient (AQ), which does not include longitudinal history from collateral informants, or the Autism Diagnostic Observation Schedule (ADOS), do not consistently separate ASD from SCZ in adults (Fusar-Poli et al., 2020; Lugnegard, Hallerback, & Gillberg, 2015; Maddox et al., 2017). A large proportion of young adults with SCZ also

meet DSM symptom criteria for ASD, based on structured diagnostic interviews with them and their parents (Unenge Hallerbäck, Lugnegård, & Gillberg, 2012). Many individuals with ASD would also meet symptom criteria for SCZ without DSM-5 Criterion F, which specifically requires prominent hallucinations or delusions if the patient has ASD (American Psychiatric Association, 2013; Bastiaansen et al., 2011; de Bildt, Sytema, Meffert, & Bastiaansen, 2016; Z. Zheng et al., 2018).

The largest apparent area of symptom overlap between ASD and SCZ is the similarity between the social communication deficits associated with ASD (Criterion A, deficits in social-emotional reciprocity, deficits in nonverbal communicative behaviors used for social interaction, and deficits in developing, maintaining, and understanding relationships) and the “negative symptoms” commonly observed in SCZ (Criterion A.5, diminished emotional expression, avolition, alogia, anhedonia, and asociality) (American Psychiatric Association, 2013). Although social deficits are required for an ASD diagnosis, negative symptoms are not required for SCZ but do represent a core aspect of the disorder (Marder & Galderisi, 2017). In direct comparisons, ratings of social communication and negative symptoms have been shown to correlate in adults with SCZ (Sheitman, Kraus, Bodfish, & Carmel, 2004) and in youth with ASD (Gadow, 2013).

In the context of this symptom overlap, clinicians and investigators can differentiate ASD from SCZ by focusing on disorder-specific features of each. For example, the “positive symptoms,” which include delusions, hallucinations, and formal thought disorder (FTD) (Criteria A.1 - A.3)(American Psychiatric Association, 2013), are typical of SCZ. In the case of FTD, however, there are caveats, as the existence of FTD is typically inferred from “disorganized speech,” which can be difficult to assess in an individual with ASD, where speech at baseline may be unusual or stereotyped relative to neurotypical peers. Thus, assessment of FTD should be based upon comparison with an individual’s baseline speech, and delusions and hallucinations should be emphasized in the diagnosis of SCZ in ASD. In ASD, restricted or repetitive behaviors (Criterion B) are required and can be used to differentiate from SCZ (American Psychiatric Association, 2013; Trevisan et al., 2020). Developmental history, as noted above, can also help differentiate between these diagnoses because ASD must be present “in the early developmental period” (Criterion C, DSM-5) (American Psychiatric Association, 2013); whereas SCZ has no developmental specification.

Examinations of SCZ symptoms in ASD—Several studies (Table 1) have examined the correlates and predictors of SCZ symptoms in ASD. Two have examined FTD, as operationalized by idioscyncratic language use, and together suggest that FTD exists in ASD even at a young age and may be an indicator of cognition or disorder severity.

In a cross-sectional study, Ziermans and colleagues (2017) compared FTD and cognition between youth aged 9 to 19 with high-functioning ASD and controls. Although they found greater levels of FTD in the ASD group overall, they did not find that a particular type of FTD was characteristic of ASD. They did note that FTD severity correlated negatively with verbal working memory in the ASD group only, potentially linking FTD with executive functioning in ASD youth.

Eussen and colleagues (2015) assessed younger children with ASD, aged 5 to 12, for early signs of FTD. Then, seven years later, they assessed for prodromal psychosis and ASD severity. Early FTD at initial assessment was surprisingly common, present in about twenty percent of the sample. Neither illogical thinking nor loose associations predicted prodromal symptoms. However, illogical thinking predicted ASD severity at follow-up, even after adjusting for ASD severity at initial assessment. Although this study's longitudinal design is a key strength, its generalizability may be limited by the age of its participants. Children at time of follow-up assessment ranged from 12 to 20 years old and may have been too young for psychotic symptoms to manifest. The substantial presence of FTD at initial assessment may also highlight some of the inherent difficulties in assessing for FTD in the ASD population, as FTD may be difficult to distinguish from idiosyncratic language as a function of ASD.

Another study that may corroborate the notion of FTD as an indicator of ASD severity focused on the "multiple complex developmental disorder" (MCDD) cluster of symptoms. MCDD includes FTD and various anxiety symptoms and has been thought to increase risk of psychotic behavior in ASD youth. Kyriakopoulos and colleagues (2015) investigated these symptoms in a unique cohort of children and adolescents with ASD who had been admitted to a specialized inpatient unit for severe behavioral problems. A latent class analysis identified a distinct group of participants with FTD, disorganized behavior, idiosyncratic fears, and paranoid ideas. Members of this group had longer hospitalizations, suggesting greater overall impairment. Hallucinations, which are characteristic of SCZ but unusual in ASD, were more common in this group, lending validity to the idea that the MCDD symptom cluster may be associated with psychosis in ASD.

Gadow and colleagues (2017), using a different but complementary approach, investigated an index of ASD severity – specifically, a history of regression in early life – as a potential predictor of parent- and teacher-reported SCZ symptoms in ASD youth aged 6 to 18. Among youth whose parents reported regression between 18 and 36 months, "strange behavior" and avolition were more likely to be present and more likely to be impairing, even after adjustment for IQ; although these symptoms are not specific to SCZ.

Most studies of SCZ symptoms in ASD over the past eight years have primarily focused on children or adolescents, rather than adults. However, one study of adults with ASD with and without intellectual disability (ID) examined co-occurring psychiatric symptoms, including psychosis, using the Diagnostic Assessment Measure for the Severely Handicapped-II (Cervantes & Matson, 2015). The measure's SCZ item "mood seems totally unrelated to what is going on around him/her" was endorsed significantly more often in the ASD with ID group, perhaps highlighting the complexities that co-occurring intellectual disability and accompanying communication difficulties introduce when attempting to identify psychotic symptoms in ASD, and raising the possibility that, in the ASD with ID population, psychosis could be related to mood disturbance instead of or in addition to SCZ.

Another study, by van der Linden and colleagues (2020), examined lifetime and transient subclinical psychotic-like experiences (rather than SCZ per se) in adults with and without ASD. Participants reported lifetime and transient psychotic experiences by filling out a

rating scale and reported their level of event-related stress by keeping a daily diary over ten days. Although rates of lifetime experiences were similar across groups, members of the ASD group were more likely to report transient psychotic-like experiences, such as “I feel suspicious,” “I can’t get these thoughts out of my head,” “My thoughts are influenced by others,” and “I hear voices others don’t.” Furthermore, these transient experiences were more likely to be associated with event-related stress in the ASD group.

Studies of ASD symptoms in SCZ—Behavioral studies have also approached the overlap from the opposite direction, examining ASD symptoms in populations with psychosis, whether frank SCZ or first-episode psychosis (FEP). Similar to studies of FTD in the ASD population, studies have suggested that the presence of an ASD diagnosis or substantial ASD traits in FEP or SCZ are a marker of the severity of the primary psychotic disorder.

At a diagnostic level, Downs and colleagues (2017) examined the longitudinal electronic health records of youth aged 10 to 17 with FEP. Clinician documentation of a co-occurring ASD diagnosis at any time over a five-year period from the time of initial FEP referral was associated with failing treatment with at least two different antipsychotic medications over the five-year interval. This association persisted after adjusting for numerous potential confounders, including gender, age, intellectual disability, and severity of psychosis. This association with treatment failure could suggest that FEP in ASD is more complex than FEP in the neurotypical population and highlights the importance of studying FEP in this population.

Consistent with this, Strålin & Hetta (2019) found that, among a group of 2091 youth or young adults (aged 17 to 25) hospitalized for FEP in Sweden, five percent had a co-occurring ASD diagnosis at the time of hospitalization. Such a diagnosis predicted continued prescription of medication for psychosis two years after hospitalization. Interestingly, a diagnosis of delusional disorder at time of hospitalization was more likely among those with ASD.

At a trait level, Upthegrove and colleagues (2017) found in a cross-sectional study that both severity of ASD traits and severity of psychotic symptoms were associated with greater risk of depressive symptoms in FEP. In a mediation analysis, they found that ASD traits specifically increased the likelihood of suicidal behavior via increased ratings of hopelessness. Chisholm and colleagues (2019) further found that more autistic traits cross-sectionally predicted greater severity of psychosis, poorer functioning, and lower quality of life in FEP.

Zheng and colleagues (2020) found that, at baseline, more ASD traits among FEP patients were associated with a greater likelihood of having “psychosis, not otherwise specified,” “mood disorder with psychotic features,” or “brief psychotic disorder” diagnoses, rather than a schizophrenia diagnosis. At one year follow-up, more ASD traits in the same FEP group predicted lesss improvement in severity of psychotic symptoms or level of functioning.

Two more studies of ASD symptoms in SCZ elegantly highlight the bidirectional symptom overlap between ASD and SCZ. Kästner and colleagues (2015) derived a measure of ASD symptom severity by taking select items from the well-known Positive and Negative Syndrome Scale (PANSS) used for SCZ and administering them to a validation sample of people with ASD. They then verified that the items correlated well with that sample's Autism Diagnostic Observation Schedule (ADOS) ratings. The derived measure, coined the PAUSS (PANSS Autism Severity Scale), was then used by Deste and colleagues (2018) to characterize ASD symptoms in an SCZ sample. The PAUSS identified a subgroup of participants with significant ASD features, defined by a PAUSS score greater than 30. Executive function, particularly working memory and processing speed, was relatively more impaired in this subgroup.

Subsequent cross-sectional studies have applied the PAUSS to adults with SCZ, and found that a higher PAUSS score was associated with greater impairment in social cognition (Deste, Vita, Penn, et al., 2020; Vita et al., 2020), social relationships (Deste, Vita, Nibbio, et al., 2020), and self-reported everyday functioning (Harvey et al., 2019).

Direct comparisons of behavior between ASD and SCZ—Surprisingly few published studies have directly compared behavior across ASD and SCZ.

In one such study, Larson and colleagues (2017) compared a group of adults with ASD and co-occurring psychosis to ASD-only and psychosis-only groups. Compared with the psychosis-only group, participants with ASD and psychosis were more likely to have a diagnosis of "psychosis, not otherwise specified" than schizophrenia, most often because they did not meet schizophrenia's duration criterion. Those with ASD and co-occurring psychosis also had significantly fewer restricted interests and repetitive behaviors, and more affective symptoms, than the ASD-only group. These findings may reflect the unique contexts in which psychosis may arise in ASD. The association with affective symptoms is particularly interesting, as it may suggest that at least some psychosis in ASD is a function of a mood disorder rather than SCZ per se.

Taking a different, task-based approach, Morrison and colleagues (2017) compared social skills among ASD, SCZ, and neurotypical adults using a role-playing exercise. Each participant was tasked with "getting to know a new neighbor" during a conversation with a researcher that was videotaped and coded. Overall social skills were impaired in both disorders relative to the neurotypical group, but the ASD group was more impaired than the SCZ group. The characteristics of each group's social interactions also diverged in fundamental ways. ASD participants were less socially involved, asking fewer questions of their new neighbor. In contrast, SCZ participants were more socially engaged, despite having more blunted affective expressiveness than their ASD counterparts. IQ was also associated with level of social skill in SCZ but not ASD. This may be consistent with social impairment being fundamental to ASD and therefore independent of intellectual ability.

Perception and cognition

Perception—ASD and SCZ both include deficits in perceiving and integrating sensory information (Noel, Stevenson, & Wallace, 2018). However, relatively few studies have tested

the two groups in parallel using the same paradigms (Table 2). Findings from small studies suggest that social difficulties in ASD and SCZ may emerge from quite different patterns of sensory processing.

Haigh and colleagues (2016) compared fMRI response amplitudes to sensory stimuli between ASD, SCZ and controls. Participants were exposed to each of three sensory modalities – visual, auditory, and somatosensory – while performing an irrelevant one-back task designed to control for differences in attention level. Results indicated that although sensory responses in both ASD and SCZ differed from those in controls, the nature of the difference differed by disorder. Sensory responses among ASD participants did not differ from controls in strength, but instead were more variable across trials. In SCZ participants, however, the opposite was the case, with smaller, but consistent, response amplitudes.

Minchino and colleagues (2016) examined mu rhythm suppression, which is thought to be an index of mirror neuron system function, during the perception of biological motion. Their sample comprised adolescents and young adults across four groups: ASD, early psychosis with negative symptoms, early psychosis without negative symptoms, and controls. They found a significant difference in mu suppression among the four groups, with significant pairwise differences between ASD and controls and between psychosis with negative symptoms and controls. Notably, they did not find significant differences between ASD and either early psychosis group; although the difference between ASD and psychosis without negative symptoms approached significance. The small sample sizes, particularly of the early psychosis group without negative symptoms, limit this study's interpretability.

Finally, Noel and colleagues (2020) compared spatial multisensory processing – the ability to integrate tactile and visual input to evaluate what is occurring in the environment around one's body – between ASD, SCZ, and a control group. They did so using a paradigm in which each participant reacted to a tactile stimulus in the presence or absence of a simultaneous visual stimulus that appeared to move towards or away from the participant. The time to react to this multisensory stimulus was used to define a participant's "peripersonal space," which delineates the area surrounding the participant inside of which stimuli are perceived as physically relevant. They found that peripersonal space was significantly smaller and more sharply delineated in ASD participants than in SCZ or control participants. This is consistent with previous work suggesting a smaller peripersonal space in ASD patients than controls. It is also broadly consistent with the idea that multisensory processing differs between ASD and SCZ, though the lack of an effect of SCZ on peripersonal space warrants further exploration.

Cognition—Cognition has social, nonsocial, and language-related components. Social cognition includes two closely-related processes: theory of mind (ToM, also considered mentalization), which can be broadly described as the ability to make inferences about the intentions or beliefs of others; and emotion processing, which is the ability to recognize the emotional states of others based on facial expressions or tone of voice. Impaired social cognition is well known as a characteristic of ASD, but increasingly it is recognized in SCZ as well (Sasson, Pinkham, Carpenter, & Belger, 2011). Just as in ASD, impaired social cognition in SCZ is persistent (Green et al., 2012) and a key determinant of functional

outcome (Fett et al., 2011). Nonsocial cognition includes executive function, processing speed, and abstract thought. In ASD, nonsocial cognition is variably impaired, depending upon cognitive domain and degree of intellectual disability. In SCZ, impaired nonsocial cognition is observed as the illness course progresses. Lastly, language ability represents a component of cognition that can be both social and nonsocial and shows abnormalities in both disorders.

Studies of social cognition: Classically, ASD has been thought to be characterized by an underactive theory of mind (ToM) mechanism ("hypo-mentalization" (Baron-Cohen, Leslie, & Frith, 1985)), leading to difficulties reading others' intentions, as reflected by reduced performance on ToM tasks. Extending this idea, it has been suggested that the similarly poor performance on ToM tasks in SCZ is driven by the opposite problem: an overactive ToM (B. Crespi & Badcock, 2008; Gray, Jenkins, Heberlein, & Wegner, 2011). Overactive ToM ("hyper-mentalization") could explain the paranoid tendency of some with schizophrenia to jump to unusual conclusions about others' intentions, or to ascribe human-like intentionality to objects or natural forces.

Emotion processing, sometimes alternately referred to as "affective theory of mind," involves emotion recognition, face processing, and prosody recognition, and may represent a lower-level, earlier-developing process than ToM (Sasson et al., 2011). Emotion processing is generally impaired in both SCZ and ASD (Samaey, van der Donck, van Winkel, & Boets, 2020), but comparisons between the disorders reveal potential differences. For example, individuals with ASD and SCZ both have difficulty recognizing complex facial emotions (Sachse et al., 2014). However, accuracy of emotion recognition in SCZ, but not ASD, is related to intelligence (Sasson, Pinkham, Weittenhiller, Faso, & Simpson, 2016). Additionally, deficits in emotion recognition in SCZ, but not ASD, are strongly related to psychosocial functioning (Tobe et al., 2016).

In a recent systematic review and meta-analysis, Oliver and colleagues (2020) assessed the results of 36 studies that directly compared social cognition between SCZ and ASD. Informed by both earlier meta-analytic findings (Chung, Barch, & Strube, 2014; Fernandes, Cajão, Lopes, Jerónimo, & Barahona-Corrêa, 2018) and the earlier symptom onset typical in ASD, they hypothesized that emotion processing, as an early-developing process, would be relatively more impaired in ASD than in SCZ, but that ToM impairment across groups would be similar. Instead, they found a similar degree of impairment in both groups, with no statistically significant between-group differences in either ToM or emotion processing.

Their review highlights that interest in social cognition across ASD and SCZ has increased in recent years. However, their results also highlight some of the literature's limitations. Studies to date have been small, with either the ASD or SCZ group containing fewer than 25 participants in 22 of the 36 studies. Studies also largely focused on male participants, and measured social cognition using a variety of measures.

Only two of these 36 studies that focused on social cognition also collected clinical measures of ASD and SCZ symptoms from both groups (Hyatt et al., 2020; Martinez et al., 2017). This represents an opportunity for future studies to extend our understanding of

social cognitive impairment across ASD and SCZ by assessing how clinical measures relate to performance. Given the heterogeneity of both disorders, assessing symptom domains as spectra may allow a clearer understanding of the relationships between performance on tests of social cognition and degree of impairment in ASD and SCZ symptom domains.

Studies of nonsocial cognition

Executive function: Executive function (EF), or cognitive control, refers to a broad array of top-down mechanisms that drive behavior. Important EF domains include working memory, response inhibition, cognitive flexibility, attention, and planning (Diamond, 2013). Impaired EF is not required to make a SCZ diagnosis, but is thought to be an important driver of negative symptoms (Dibben, Rice, Laws, & McKenna, 2009; Marder & Galderisi, 2017).

Likewise, ASD is characterized by a broad and generalized impairment in EF that appears to be consistent across EF domains (E. A. Demetriou et al., 2018). Direct comparisons of EF in ASD and SCZ have showed a similar degree of impairment in both disorders relative to typically developing controls(Mance Calisir, Atbasoglu, Devrimci Ozguven, & Olmez, 2018) and to individuals with social anxiety (Eleni A. Demetriou et al., 2018; Pepper et al., 2018), an alternative control group. Relative to each other, SCZ shows greater impairment in EF than ASD (Kuo & Eack, 2020).

Within ASD, impaired response inhibition, a particular form of EF impairment, appeared in one small study to be associated with self-reported “schizotypal” disorganized thoughts (Barneveld, Sonneville, Rijn, Engeland, & Swaab, 2013). This finding is interesting in light of a report of greater impairment in auditory response inhibition in SCZ compared to ASD in a population of males aged 11 to 16 but similar impairment in visual response inhibition across both disorders (Shi et al., 2020). Response inhibition may be a potential avenue for future exploration with regard to SCZ vulnerability within ASD.

Processing speed—Comparisons of processing speed across ASD, SCZ and control groups have shown impaired processing speed in SCZ (de Boer, Spek, & Lobbestael, 2014; Eack et al., 2013; Marinopoulou, Lugnegard, Hallerback, Gillberg, & Billstedt, 2016), with the majority of studies also finding a similar degree of impairment in ASD (Eack et al., 2013; Kuo & Eack, 2020; Marinopoulou et al., 2016).

Studies of language ability: Although direct comparisons of language ability across ASD and SCZ are limited, one study found a differential ability to reason by analogy across ASD, SCZ and typically developing individuals. Both ASD and SCZ participants showed impairment, but this was particularly pronounced in SCZ, suggesting an avenue for further research (Krawczyk et al., 2014). One recent proof-of-concept study has suggested that automated language analysis of transcribed speech could, in the future, play a clinical role in differentiating ASD from SCZ (Wawer, Chojnicka, Okruszek, & Sarzynska-Wawer, 2021).

Biomarkers

Researchers have leveraged several methodologies to study neurobiological indicators of disease presence or severity in ASD and SCZ. These include neuroimaging, electrophysiology, and the study of peripheral blood markers.

Neuroimaging biomarkers—In a 2013 review, Baribeau & Anagnostou (2013) compared neuroimaging findings in ASD and SCZ. Although they emphasized that heterogeneity across studies and a lack of prospective longitudinal data limited their ability to draw firm conclusions, they noted that some evidence appeared to support generalized patterns of brain growth that are divergent. Where ASD is characterized by subtle brain overgrowth in a subgroup beginning in toddlerhood, (Raznahan et al., 2013) SCZ is characterized by reduced cortical thickness in middle childhood and adolescence (Gogtay et al., 2004; Greenstein et al., 2006). Patterns of connectivity are less consistent, as although ASD has frequently been associated with impaired long-range connectivity but increased local connectivity (Just, Keller, Malave, Kana, & Varma, 2012), whereas SCZ is associated with the opposite pattern (A.F. Alexander-Bloch et al., 2013; A. Alexander-Bloch et al., 2010); although other findings challenge these reports (L. Uddin, Supekar, & Menon, 2013; White, Moeller, Schmidt, Pardo, & Olman, 2011).

Several studies since have compared changes in brain structure and function across ASD and SCZ. These studies have tended either to use a whole-brain approach or to have an *a priori* focus on key large-scale networks with hypothetical relevance to both disorders. These include the default mode network (DMN), salience network (SN), and “social brain.”

The DMN is thought to be involved in self-reflection, and includes the medial prefrontal cortex (mPFC), posterior cingulate cortex (PCC), precuneus, and lateral parietal cortex (Raichle, 2015). The SN includes the anterior cingulate cortex (ACC) and anterior insula (AI), and is thought to be involved in identifying the relative importance of environmental or internal stimuli (Menon, 2011).

The “social brain” is not a network per se, but comprises a number of brain regions involved in aspects of social cognition, including ToM and facial affect recognition. These regions, some of which overlap with the DMN and SN, include the amygdala, AI, temporoparietal junction (TPJ), orbitofrontal cortex (OFC), mPFC, ACC, superior temporal gyrus, superior temporal sulcus (STS), PCC, and fusiform gyrus.(Adolphs, 2008; Barlati et al., 2020; Blakemore, 2008; Kennedy & Adolphs, 2012).

Comparisons of brain structure between ASD and SCZ: Comparisons of brain structure between ASD and SCZ have yielded mixed findings but do indicate specific anatomical regions where ASD and SCZ are associated with changes in local gray or white matter volumes. As differences in findings across neuroimaging studies can sometimes be a function of participant age, we have noted below whether each reported study below included children, adolescents, or adults. For additional detail, see Table 3 for age means and standard deviations by group for each study.

Katz and colleagues, in a study of adults, (2016) compared high-functioning ASD, SCZ, and control participant groups** using voxel-based morphometry (VBM). ASD participants showed an increase in PFC gray matter volume relative to controls, whereas SCZ participants showed a decrease.

Consistent with this, another morphometric comparison in adults of high-functioning ASD, SCZ and controls, conducted by Mitelman and colleagues (2017) found a pattern of divergence between ASD and SCZ. In the frontal, temporal, parietal, and occipital lobes, as well as in the cingulate gyrus, gray matter volumes were increased in ASD participants but decreased in SCZ participants. However, white matter volumes in these same areas were decreased in ASD participants but increased in SCZ participants.

VBM findings comparing ASD to first-episode psychosis are somewhat divergent, perhaps suggesting differences between early and chronic psychosis. Parellada and colleagues, (2017), observed volume decreases in the insula (including the AI and the posterior insula) in children and adolescents with both ASD and first-episode psychosis relative to controls. Diaz-Caneja and colleagues (2018), building on that initial VBM analysis, demonstrated that these volume decreases were, in both disorders, largely explained by localized decreases in cortical surface area and thickness.

A meta-analysis of VBM data from adult studies of ASD, SCZ and OCD by Cauda and colleagues (2017) supports the apparent relevance of the AI. Using a data-driven machine-learning approach, they found that participants, regardless of their diagnosis, fell into one of two broad clusters defined by patterns of regional volume alterations. The first cluster, relatively specific for SCZ, was characterized by decreases in AI, mPFC, and thalamic volume. The second cluster, more specific for OCD, was characterized by decreases in parietal, temporal and occipital lobe volumes. Notably, participants with ASD were distributed evenly across the two groups, perhaps highlighting the heterogeneity of ASD.

Tractography findings are somewhat less consistent. In their study described above, Katz and colleagues (2016) also compared groups using diffusion-weighted imaging (DWI). They found that ASD and SCZ participants both a shared decrease in white matter integrity (as reflected by decreased fractional anisotropy, or FA) relative to controls in the left inferior fronto-occipital fasiculus. In contrast with this, a DWI study of adults by Haigh and colleagues (2019) found no significant differences in FA across ASD, SCZ or controls. However, they did find greater radial and mean diffusivity throughout the brain in the SCZ group compared to both the ASD and control groups, indicating a potential subtle abnormality in myelination that may be relatively specific to SCZ, but not ASD.

Comparisons of brain function between ASD and SCZ: The results from direct comparisons of brain function between ASD and SCZ are relatively varied, and replication of most findings has not yet occurred.

Ciaramidaro and colleagues (2015) compared functional connectivity in the mPFC and STS between ASD, SCZ and control participants in adolescents and adults as they completed

two tasks: a ToM task that required inferring communicative intent between people, and a control task that required inferring physical causality between inanimate objects. ASD and SCZ groups performed worse on both tasks than the control group, with the ASD group showing reduced accuracy and the SCZ group showing increased reaction times. During the ToM task, the ASD group, but not the SCZ group, showed decreased connectivity between the right STS and mPFC relative to the control group. Conversely, during the control task, the SCZ group, but not the ASD group, showed increased connectivity between those same regions. In another study of functional connectivity during a ToM task, Hyatt and colleagues (2020) similarly found that both adults with ASD and those with SCZ showed group-level differences from controls in the connectivity between the mPFC and TPJ.

A study of visual perspective-taking, which is closely related to ToM, was conducted in adults by Eack and colleagues (2017). Although ASD and SCZ groups had similarly impaired accuracy on the perspective-taking task relative to controls, the apparent neural correlates of this impairment differed. Where ASD participants showed greater connectivity than controls between the left OFC and bilateral mPFC, and between the left OFC and left TPJ, SCZ participants showed reduced connectivity between the right OFC and right mPFC, and between the left OFC and right TPJ.

The marked differences in connectivity patterns between ASD and SCZ groups in both of these studies, despite similar impairments during task performance, suggest that impairments in ToM and visual perspective-taking in ASD and SCZ that at face value seem similar could be the result of different underlying neural deficits.

Results are somewhat inconclusive regarding differences in connectivity between ASD and SCZ during facial affect recognition. Ciaramidaro and colleagues (2018) compared brain activation during facial affect recognition in adults among ASD, SCZ, and control groups. ASD and SCZ participants performed worse than controls during implicit facial recognition, explicit facial recognition, and a control object recognition task, indicating nonspecific impairment interpreting sensory stimuli in both disorders. On a neural level, ASD and SCZ participants differed from controls during the implicit facial affect recognition task only, with both groups showing reduced activation in the amygdala and the fusiform gyrus compared to controls. These findings alone could indicate that despite areas of apparent divergence, at least some of the neural underpinnings of social cognitive deficits in ASD and SCZ are shared.

However, a functional near infrared spectroscopy study (fNIRS) of facial affect recognition in adults had different results, with ASD showing decreased activation in the left frontotemporal region relative not only to controls but also to SCZ (Hirata et al., 2018). And, an fMRI study of facial affect recognition in adults (Martínez et al., 2019) found differential activation patterns between ASD and SCZ participants within the pulvinar nuclei of the thalamus, with increased activation in SCZ, and decreased activation in ASD, relative to controls. Differences in methodology, or in regions of the brain examined, could partially explain these discrepancies.

Resting-state fMRI studies of ASD and SCZ have compared connectivity in large-scale brain networks, finding patterns of convergence and divergence in the DMN and SN.

The DMN appears to be dysfunctional in both ASD (Padmanabhan, Lynch, Schaer, & Menon, 2017) and psychotic disorders (M.-L. Hu et al., 2017). In a review that compared DMN findings from studies of adolescents with ASD to findings from studies of adolescents with early-onset psychosis, Nair and colleagues (2020) observed that DMN dysfunction was, across both groups of studies, consistently associated with greater severity of social impairment as measured by symptom rating scales. However, the nature of the dysfunction differed by group. In ASD, under-connectivity within the DMN (intra-network connectivity) was more often reported, whereas psychosis was more often characterized by a mixture of over- and under-connectivity. In both ASD and psychosis, patterns of connectivity between the DMN and other large-scale networks (inter-network connectivity) were mixed.

SN dysfunction has been observed to predict severity of restricted and repetitive behaviors in children with ASD (L. QUddin et al., 2013), as well as positive symptom severity in adults with SCZ (Krishnadas et al., 2014). Chen and colleagues (2017) trained two separate models to differentiate a sample of control adolescents from 1) adolescents with ASD and 2) adolescents with first-episode psychosis based on patterns of functional connectivity. Atypical connections involving the SN and DMN were the most important contributors to classification in both models, with atypical connectivity within the SN more important in ASD, and atypical connectivity between the SN and DMN more important in SCZ.

In a similar approach, Mastrovito and colleagues (2018) also trained two separate models to differentiate adult controls from adults with ASD and adults with SCZ. However, they then used the most important distinguishing features for each group to train a third model differentiating ASD from SCZ. They confirmed that both ASD and SCZ showed the most changes in connectivity relative to controls in the SN and DMN. DMN connectivity in particular was the main characteristic differentiating ASD from SCZ. Specifically, ASD was characterized by increased connectivity within the DMN and reduced connectivity between the DMN and language networks; whereas SCZ was characterized by decreased connectivity within the DMN and increased connectivity between the DMN and novel language networks.

Rabany and colleagues (2019) identified another potential dimension of difference among ASD, SCZ and control groups of adults by using a novel “dynamic” approach to resting-state connectivity that focuses on the stability of measured connectivity across the duration of the scan, rather than making the traditional simplifying assumption that connectivity is static across the resting state. Relative to controls, participants with both ASD and SCZ tended to spend relatively more time during a resting-state scan in a state of weak intra-network connectivity. SCZ, but not ASD, participants further showed fewer transitions between weakly and strongly-connected states, consistent with a tendency to be “stuck” in a weakly-connected state.

Although most investigations of brain function in ASD and SCZ have used fMRI, one notable study (Mitelman et al., 2017) used positron emission tomography (PET) to compare

cortical and subcortical resting-state glucose metabolism across ASD, SCZ and control groups of adults. Relative to controls, ASD and SCZ participants had similar metabolic changes in several brain regions. Both showed decreased metabolism in areas including the amygdala and the ventral posteromedial nucleus of the thalamus (involved in sensory processing). Both also showed increased metabolism in the hippocampus, the pulvinar nuclei of the thalamus and parts of the occipital cortex, as well as the tail of the caudate, putamen, and globus pallidus. Divergent changes, with increased metabolism in SCZ but decreased metabolism in ASD, were noted in the primary motor and somatosensory cortices. In addition, ASD was associated with increased metabolism in the anterior cingulate cortex relative to both controls and SCZ.

Inflammatory markers—Numerous studies indicate that inflammation, both within the central nervous system and in the peripheral blood, seems to play a role in ASD and SCZ (Prata, Santos, Almeida, Coelho, & Barbosa, 2017). However, specific and reproducible markers that would differentiate people with either disorder from controls have not yet been identified, and no studies have yet directly compared these disorders with each other. Thus, we highlight here some relevant findings that suggest possibilities for future investigations of transdiagnostic overlap.

Central inflammation: Recent PET studies have separately found increased activation of microglia, which mediate the central nervous system's immune response, in both ASD and SCZ. Suzuki and colleagues (2013) found that, compared to controls, people with ASD showed increased microglial activation in multiple brain regions, as reflected by increased regional binding potentials of a radiotracer for activated microglia. Regions with increased microglial activation included the cerebellum, brainstem, and anterior cingulate, as well as the frontal lobe, temporal lobe, and parietal lobe.

In a study of people with SCZ and others at clinical high risk of psychosis, Selvaraj and colleagues (2015), in a study of people with SCZ and people at clinical high risk of psychosis, found increased microglial activation in both groups relative to controls. In both groups, the increase in activation was identified in total, frontal lobe, and temporal lobe grey matter. Although the primary outcome measure in this study was total rather than regional radiotracer binding potential, secondary regional analyses showed no differences from controls in the cerebellum or brainstem in either group, which may suggest that these changes could be specific to ASD.

These *in vivo* findings are consistent with evidence from previous studies of increased microglial density in postmortem brain tissue from ASD and SCZ patients (Prata et al., 2017). They potentially suggest that differences in microglial activation patterns could be a way to differentiate ASD from SCZ, or to identify the emergence of psychosis in ASD patients.

Peripheral inflammation: Studies also have investigated the peripheral blood levels of several pro-inflammatory cytokines in ASD and SCZ. Most cytokines have been studied in either ASD or SCZ, but not both. Two – interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-alpha) – have been examined across disorders (Prata et al., 2017). In ASD,

a recent study by Yang and colleagues (2015) reported significant elevations in IL-6 and TNF-alpha in a group of ASD youth relative to controls. IL-6 elevation also has been reported in adults with SCZ (Borovcanin et al., 2017; Frydecka et al., 2015). Moreover, in one longitudinal study, IL-6 elevation at age nine appeared to predict emerging psychotic symptoms at age eighteen (Khandaker, Pearson, Zammit, Lewis, & Jones, 2014), suggesting IL-6 may be elevated in youth at risk for SCZ. TNF-alpha also seems to be elevated in young adults with first episode psychosis (Upthegrove, Manzanares-Teson, & Barnes, 2014). In chronic schizophrenia, TNF-alpha findings are inconsistent, with reports of both increases and decreases in the literature (Momtazmanesh, Zare-Shahabadi, & Rezaei, 2019).

Genetic and environmental risk

Overlap in genetic risk, as reflected by extensive cross-disorder heritability, is broadly seen across multiple developmental and psychiatric conditions. In narrower terms, however, certain risk variants may contribute to the risk of specific phenotypic presentations, including those of ASD, SCZ, or their combination. Advances in molecular genetics have allowed both common and rare variants to be directly assessed and tested for contribution to these risks.

Cross-disorder heritability—ASD and SCZ are individually highly heritable. For ASD as a diagnosis, twin studies reveal an estimated heritability that ranges from 64–91% (Tick, Bolton, Happé, Rutter, & Rijsdijk, 2016) and is consistent both with estimates from prior family studies (M. Rutter, 2000) and studies of ASD traits (Robinson et al., 2011). SCZ twin and family studies show comparable heritability estimates that range from 73–90% (P. F. Sullivan, Kendler, & Neale, 2003).

At a diagnostic level, epidemiological studies in Scandinavian and Finnish populations suggest that SCZ in a parent (Daniels et al., 2008; Jokiranta et al., 2013; Larsson et al., 2005; P. F. Sullivan et al., 2012) or sibling (P. F. Sullivan et al., 2012) increases ASD risk. At a trait level, one longitudinal study examined the association between parent-reported childhood autistic traits and later parent and child-reported psychotic traits across twin pairs. Independently, as might be expected, autistic traits and negative symptoms of psychosis (both parent- and self-reported) were each strongly correlated across twins. Cross-trait correlations were weak, yet notably higher for monozygotic than dizygotic twins, indicating genetic factors play a role in co-occurrence of ASD and SCZ traits (Taylor et al., 2015).

Common risk variants—Five common variants with genome-wide significance for ASD have been identified(Autism Spectrum Disorder Working Group of the Psychiatric Genomics Consortium et al., 2019). In contrast, over a hundred common variants have been associated with SCZ (Ripke et al., 2014). Future genome-wide association studies of ASD, with larger sample sizes, are likely to reduce this gap. At present, however, no loci overlap between these disorders.

Statistical approaches to common variation can complement individual locus findings by looking at the simultaneous effect of multiple variants. A landmark study by the Cross-Disorder Group of the Psychiatric Genomics Consortium (Lee et al., 2013) took such an approach by estimating genome-wide similarities between five major psychiatric disorders.

They found statistically significant genetic correlation between multiple disorders, including ASD and schizophrenia.

Polygenic risk scores sum individual variants associated with a disorder into a linear predictor that corresponds to the overall contribution of common variation across multiple polymorphisms, most of which are not individually statistically significant. The score can then be calculated in individuals with a different disorder as a way of estimating cross-disorder polygenic risk. Vorstman and colleagues (2013) applied the polygenic risk score from a 2009 genome-wide association study of schizophrenia to a modest cohort of ASD probands, along with familial controls. Their finding that this schizophrenia score did not differ between ASD cases and controls suggested that the common risk variants it included did not meaningfully contribute to autism risk. Larger sample sizes are needed to better understand whether there is any overlap between polygenic risk scores in the two disorders.

Rare risk variants

Copy number variants: A key finding that followed the sequencing of the human genome was the discovery of extensive “copy number variation” in the population. A “copy number variant” (CNV) is a segment of genetic material that is prone to be duplicated, deleted, or rearranged, typically based upon flanking repeat regions. Although some CNVs are common and not associated with a phenotype (Iafrate et al., 2004), a growing number of specific, rare CNVs have been implicated in neuropsychiatric disease. Several studies have examined their associations with both ASD and SCZ (Table 4).

Duplication of chromosome 16p11.2 is one of the most common genetic findings in ASD (approximately 0.28% of cases) (Walsh & Bracken, 2011) and has been identified at a similar rate in schizophrenia (approximately 0.30%) (Marshall et al., 2017). About 26% of youth with 16p11.2 duplication meet ASD criteria (Niarchou et al., 2019). While people with 16p11.2 duplication also appear to be at increased risk of SCZ, it is not yet possible to estimate the percentage. Preliminary evidence indicates that an ASD diagnosis may predict psychotic symptoms in this population (Jutla, Turner, Snyder, Chung, & Veenstra-VanderWeele, 2020). 16p11.2 duplication-associated ASD may therefore model a psychosis-prone ASD subtype. More broadly, the phenotypic characteristics of people with 16p11.2 duplication may also indicate areas of potential commonality between ASD and SCZ, including intellectual impairment (Snyder et al., 2016) and difficulties with pragmatic language (Kim et al., 2020).

22q11.2 deletion is present in approximately 0.05% of ASD (Zarrei, MacDonald, Merico, & Scherer, 2015) and approximately 0.24% of schizophrenia (Marshall et al., 2017). Among people with 22q11.2 deletion, about 21% of youth have ASD, and about 5% of youth, but approximately 32% of adults, have schizophrenia, reflecting the epidemiology of schizophrenia onset (Schneider et al., 2014). Notably, childhood ASD in this population does not appear to predict psychosis in adulthood (Fiksinski et al., 2017; Vorstman, Breetvelt, Thode, Chow, & Bassett, 2013), suggesting that the pathologies here are divergent. The 22q11.2 deletion phenotype is characterized by a two-standard deviation IQ decrement compared to first degree family members (Swillen & McDonald-McGinn,

2015), as well as impairments in social communication (Fiksinski et al., 2018) and patterns of restricted interests that are independent of ASD diagnosis (Kates et al., 2007).

3q29 deletion is present in 0.05% of ASD (Zarrei et al., 2015) and 0.08% of schizophrenia (Marshall et al., 2017). 29% of people with 3q29 deletion report an ASD diagnosis(Pollak et al., 2019), and 16% may develop schizophrenia (J. G. Mulle, 2015; Saha, Chant, Welham, & McGrath, 2005). Psychotic symptoms in this population have not yet been well characterized, though a notable case has been described of an individual with 3q29 deletion and ASD who developed apparent psychosis at age five (Sagar et al., 2013).

Several other CNVs have been noted in both ASD and schizophrenia, but less is known about them. These include 1q21.1 deletion and duplication (Bernier et al., 2016), 7q11.23 duplication (Jennifer Gladys Mulle et al., 2014; Sanders et al., 2011), 17q12 deletion (Moreno-De-Luca et al., 2010), 15q13.3 deletion (Lowther et al., 2015), 2p16.3 deletion (Viñas-Jornet et al., 2014), and 16p21.32 duplication (Larson, Arrand, Tantam, Jones, & Holland, 2018). Recent and ongoing work that makes comparisons across disorders in patients with these and other CNVs has begun to identify shared biological pathways common to autism and schizophrenia, including those that involve genomic integrity, lipid metabolism, protein phosphorylation, and the oxidative stress response (Kato et al., 2020; Kushima et al., 2018).

Variants in individual genes: In contrast to genome wide association studies of common variants, where research in SCZ is well ahead of ASD, whole exome sequencing studies have achieved much larger sample sizes in ASD than in SCZ. This has allowed identification of a small but increasing number of genes in both ASD and schizophrenia, with over 100 rare variants identified to date identified in ASD (Satterstrom et al., 2020) and 10 in SCZ (Legge et al., 2021).

For example, single nucleotide variants in *CACNA1C*, which codes for the alpha-1C subunit of voltage-gated calcium channels (Bhat et al., 2012), have repeatedly been associated with several psychiatric disorders, including ASD, SCZ, and bipolar disorder (Moon, Haan, Wilkinson, Thomas, & Hall, 2018), as well as the rare genetic disorder Timothy syndrome (Bader et al., 2011), the phenotype of which includes an autism-like behavioral presentation. Similarly, variants in *GRIN2B*, which codes for the NR2B subunit of N-methyl-D-aspartate (NMDA) receptors (Freunscht et al., 2013), have also been associated with ASD, SCZ and other psychiatric disorders(Freunscht et al., 2013). Emerging evidence suggests that other single nucleotide variants, including *DAB1* (Nawa et al., 2020), *YWHAZ* (Torrico et al., 2020), and *NRXN1* (Z. Hu, Xiao, Zhang, & Li, 2019 10 (Epub 2019 May 28); Ishizuka et al., 2020), may also be associated with both ASD and SCZ.

Environmental risk factors—Environmental risk factors for SCZ have been extensively studied. In a recent review of meta-analyses, Belbasis and colleagues (Belbasis et al., 2018) surveyed 41 reported risk factors and found the strongest evidence for cannabis use, adverse childhood experiences, and a history of obstetric complications (a very broad category that includes complications of pregnancy, such as preeclampsia or diabetes; abnormalities in fetal growth or development, such as low birth weight or congenital malformations; and

complications of delivery, including asphyxiation or uterine atony). Evidence was less strong for other commonly-cited schizophrenia risk factors, including perinatal infection, advanced paternal age, childhood traumatic brain injury, and urbanicity, indicating a need for future research.

A review of meta-analyses of ASD risk factors by Modabbernia and colleagues (2017) similarly surveyed approximately 100 reported ASD risk factors and found the strongest evidence for advanced parental age (both paternal and maternal) and a history of birth complications. Evidence for pregnancy-related factors, including perinatal infection, was less conclusive.

The association of advanced paternal age with both disorders is potentially consistent with an increased likelihood of de novo mutations in the sperm of older men, or by parents with unmeasured, subthreshold SCZ or ASD traits tending to find partners later in life.

Birth complications and perinatal infection represent relatively broad categories, but their overall association with both SCZ and ASD is consistent with the idea that these are neurodevelopmental conditions with origins early in life. Perinatal infection in particular is consistent with recent work in both humans and animals demonstrating that maternal immune activation during pregnancy can disrupt neurodevelopment (Guma, Plitrnan, & Chakravarty, 2019), though future prospective epidemiological work will need to quantify the robustness of this risk factor.

Discussion

This review sought to provide a conceptual summary of the past eight years of research regarding the overlap between ASD and SCZ. We found that although many studies have, in a broad sense, approached this overlap, little consistency exists across studies, and differences in methodology make results not easily comparable. Thus, while important work has been done, few findings have been replicated.

We also noted that not many studies have made direct comparisons between ASD and SCZ, and even fewer have examined patients in whom ASD and SCZ co-occur. We also identified some notable patterns in the literature within each broad category we identified (Figure 2). One overarching theme may relate to the age of individuals who are included in studies focused ASD versus studies focused on psychosis. In particular, we noted that although several studies have examined features of ASD in adults with SCZ, relatively fewer have taken the converse approach of examining SCZ symptoms in adults with ASD. Although some older studies, as reviewed by de Lacy and King [-de Lacy & King (2013), have explored SCZ in ASD adults, such studies will continue to be important going forward, particularly as ASD has increasingly been recognized in adulthood as diagnostic criteria have changed (Nicolaidis, 2018).

Another important theme is heterogeneity, including cohort effects from study to study as well as differences in inclusion criteria or methodology. Comparative studies of cognition or perception, for example, often exclude individuals with intellectual disability and do not always covary for overall non-verbal IQ. Most comparative studies have also typically

treated ASD and SCZ populations as independent groups in statistical comparisons and have rarely evaluated ASD or SCZ symptoms as quantitative domains, despite the recognition that symptoms in both disorders exist on a spectrum. These are complicated and pervasive problems that are certainly not unique to investigations of ASD and SCZ. One area in which researchers might be able to improve the interpretability of future studies would be to collect rating scale data regarding SCZ symptoms in their ASD participants or ASD symptoms in their SCZ participants. However, given that these trait measures are often elevated across both disorders, it will be important to develop and apply new measures that are better able to differentiate the two disorders (Trevisan et al., 2020).

The problem of heterogeneity may be even more significant for studies probing the underlying biology, especially given the many differences in methodology across neuroimaging studies. Here, one potential path forward is consortia that pool data from many participants that have been collected and processed in a standardized way. For example, we were recently able to explore the relationships between ASD diagnosis, psychotic symptoms, and resting-state connectivity within the large Adolescent Brain Cognitive Development (ABCD) dataset (Jutla et al., 2021; Jutla, Foss-Feig, Donohue, & Veenstra-VanderWeele, 2020). At the genetic level, such large-scale projects will also be helpful, particularly given the very large sample sizes required to identify statistical significance.

We can hope that future work investigating the intersection between ASD and SCZ will be able to move from description to prediction. For example, some early work has demonstrated that, in principle, machine learning approaches may be able to to separate ASD from SCZ cases based on clinical characteristics (Foss-Feig et al., 2019), electrophysiology (Foss-Feig et al., 2021), functional neuroimaging (Yassin et al., 2020; Yoshihara et al., 2020) or exome sequencing data (Sardaar et al., 2020). Longitudinal studies of individuals with specific genetic variants (22q11.2 deletion, 16p11.2 duplication, 3q29 deletion, or *CHD8* as examples) may also lead to prediction based upon cognitive profile, prodromal symptoms, or biological markers. Longitudinal work in youth with 22q11.2 deletion, for example, has highlighted that anxiety and attention difficulties in childhood may predict psychosis in adolescence within this population.

Our review has some important limitations. Although our literature search was systematic, it was not exhaustive. Our Web of Science Core Collection search was via keywords, but our MEDLINE search was via MeSH headings. We used these divergent search strategies to complement each other and capture a broad cross-section of papers, but it may be that a different search approach would have uncovered additional literature. Our aim, however, was not to identify every study ever published about ASD and SCZ, but rather to identify sufficient studies to provide a conceptual overview.

We considered this approach reasonable given the state of the literature. However, it necessarily introduced an element of subjectivity into our review, given that our summary of study findings was qualitative and not based on a set procedure of extracting data, assessing for risk of bias, and synthesizing results. Although we did not attempt to quantitatively assess the quality of evidence given the breadth and heterogeneity of the studies, we did

identify four recent meta-analyses that examined individual aspects of the ASD/SCZ overlap (Baribeau & Anagnostou, 2013; Fernandes et al., 2018; Oliver et al., 2020; Prata et al., 2017).

We sought to anchor our review in the literature and did not focus on theoretical models or implications of why ASD and SCZ overlap, which has been reviewed by other groups (Chisholm, Lin, Abu-Akel, & Wood, 2015; Foss-Feig et al., 2017). We also note that our review, although broad, did not include a few topics that are less central to the observed overlap between ASD and SCZ or simply do not have enough data to merit discussion. For example, we did not discuss trait-level associations, choosing to focus only on papers where at least one group under investigation comprised clinical patients. We did not discuss treatment, as very little data exist in this area. Finally, although psychosis often precedes SCZ and is considered that disorder's hallmark, it is not exclusive to SCZ. Prominent psychosis may occur in the context of other diagnoses such as bipolar disorder. How bipolar psychosis intersects with ASD is an important question, but is not one we were able to discuss, as our literature search only identified papers that framed psychosis in terms of SCZ. It is, however, worth noting that three papers we reviewed suggested a potential role in mood factors accompanying psychosis in ASD, highlighting the need for future research (Cervantes & Matson, 2015; Larson et al., 2017; Upthegrove et al., 2017).

In writing this review we were struck by the difficulty, in many cases, of truly summarizing results in a conceptual way rather than enumerating them. This lack of conceptual unity is a limitation of the literature in this area. We would like to highlight this as an opportunity for future work regarding the phenomenology and the neurobiological origins of overlap between ASD and SCZ. One of the major needs regarding the ASD/SCZ overlap is to have replication of research to identify consistent themes that tie findings together. In particular, as we move toward a more sophisticated understanding of the cognitive neuroscience of ASD (Constantino & Charman, 2016), difficulties with central coherence and abstract thinking need to be evaluated in relation to the formal thought disorder that is associated with SCZ. Further, schizophrenia's developmental origins begin earlier in life than once imagined, necessitating a comparison between premorbid profiles in SCZ and features of ASD and other developmental disorders (Insel, 2010). Finally, improved understanding of genetic and environmental risk factors provides opportunities to probe changes in brain development and emerging cognitive and perceptual differences that precede frank psychosis, particularly in individuals with ASD.

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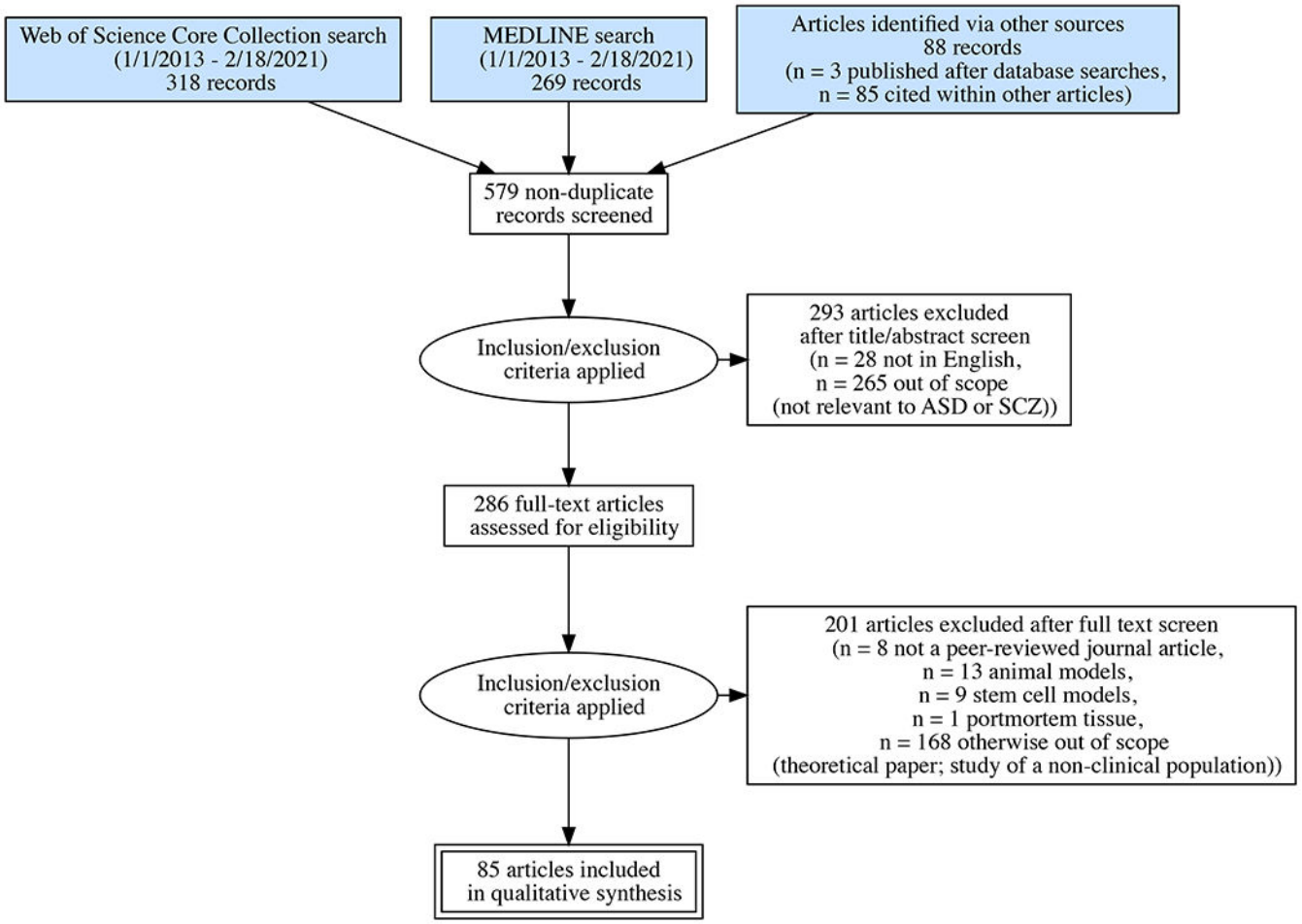

Figure 1:
PRISMA flow diagram for literature search.

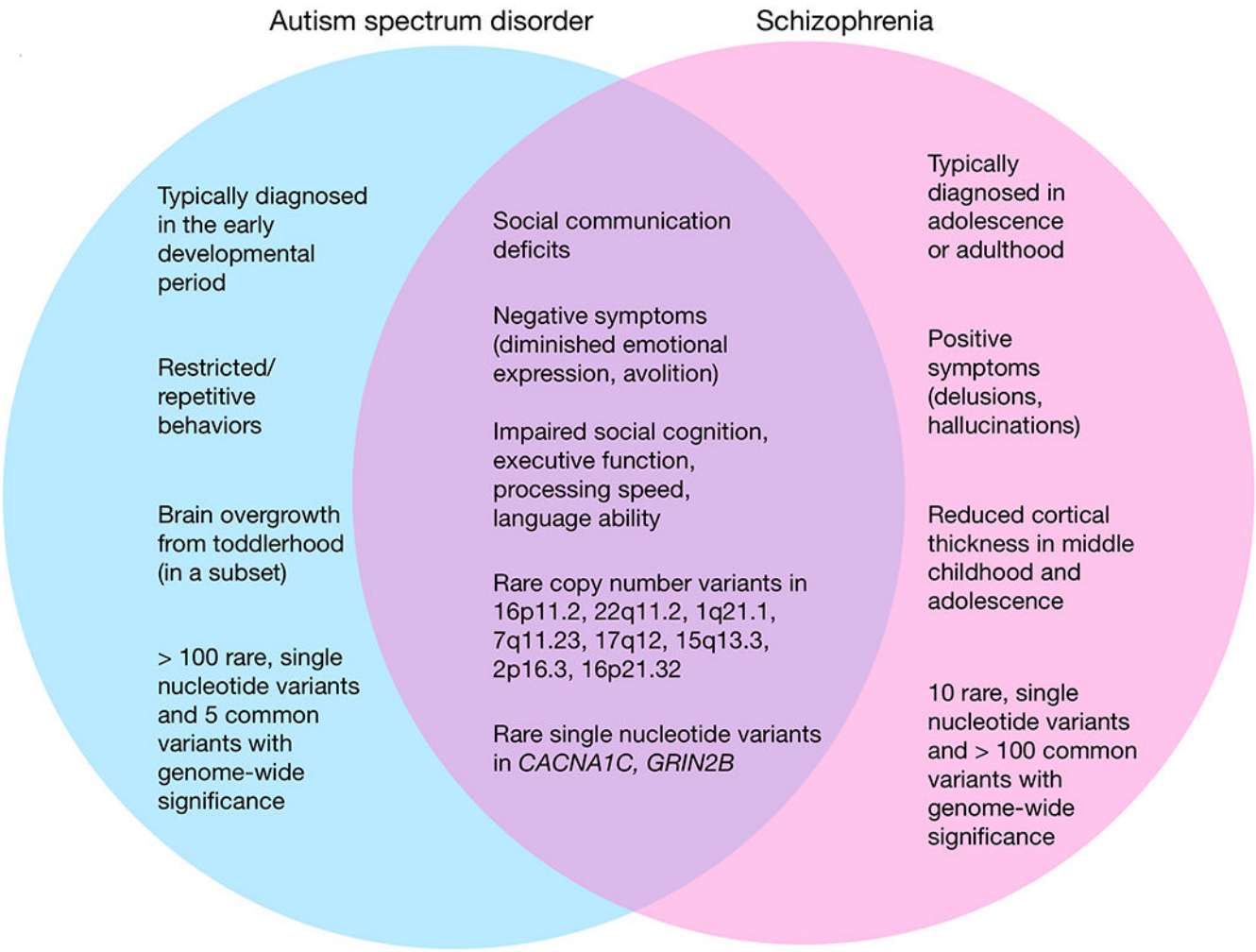

Figure 2:
Convergent and divergent features across autism spectrum disorder and schizophrenia.

Table 1:

Studies of symptoms and behavior

Authors	Year	Study design	Group(s) Studied	*n*	Age *M*	*SD*	Sex (% Male)	Key findings
Cervantes & Matson	2015	Cross-sectional	ID with ASD	149	49.0	11.0	52.0	ID with ASD group: psychosis (with a mood component) more common
			ID without ASD	158			49.4	
Chisholm et al	2019	Cross-sectional	FEP with <32 on AQ	79	25.5	5.0	67.1	AQ ≥ 32 group: increased severity of psychosis, greater impairment in informant-reported everyday functioning, and decreased quality of life
			FEP with ≥32 on AQ	8	25.9	6.8	75.0	
Deste et al	2018	Cross-sectional	SCZ with ≤30 on PAUSS	42	40.1	11.4	73.8	PAUSS score > 30 group: impaired executive function (particularly working memory and processing speed)
			SCZ with >30 on PAUSS	33	44.1	12.6	72.7	
Deste et al	2020	Cross-sectional	SCZ	361	41.7	12.0	67.6	Higher PAUSS score associated with greater impairment in social cognition
Deste et al	2020	Cross-sectional	SCZ	361	41.7	12.0	67.6	Higher PAUSS score associated with poorer informant-reported social functioning
Downs et al	2017	Longitudinal	FEP	638	15.6	1.9	51.1	29.0% of the 124 participants who developed multiple treatment failure within five years had ASD
Eussen et al	2015	Longitudinal	ASD	91	8.8	1.8	90.1	FTD at time of enrollment predicted greater severity of ASD seven years later
Fusar-Poli et al	2020	Cross-sectional	ASD	35	26.2	6.6	63.0	No significant difference in self-reported autistic traits between ASD and psychotic disorder groups
			Psychotic disorder	64	39.1	14.5	60.9	
			Nonclinical control	198	34.0	12.0	48.5	
Gadow et al	2017	Cross-sectional	ASD with regression history	48	10.8	3.1	79.0	Nonspecific SCZ-like symptoms (“strange behavior,” avolition) more common in the group with a history of regression
			ASD without regression history	136	10.7	3.5	79.0	
Harvey et al	2019	Cross-sectional	SCZ	177	40.5	11.5	54.0	Higher PAUSS score associated with greater impairment in self-reported everyday functioning
Kästner et al	2015	Cross-sectional	ASD	165	32.2	11.0	65.5	All individual PAUSS items correlated significantly with ADOS-2 score

Authors	Year	Study design	Group(s) Studied	*n*	Age *M*	*SD*	Sex (% Male)	Key findings
Kyriakopoulos et al	2015	Cross-sectional	Hospitalized with ASD	84	11.1	1.6	75.0	Latent class analysis identified a subgroup (n = 41, age 11.3±1.7, 10% female) with FTD, disorganized behavior, idiosyncratic fears, and paranoid ideas
Larson et al	2017	Cross-sectional	ASD with psychosis	75	27.7	7.6	84.0	ASD with psychosis group was more likely than psychosis only group to have a "psychosis, not otherwise specified" diagnosis, and had fewer restricted interests and repetitive behaviors, and more affective symptoms, than ASD without psychosis group
			ASD without psychosis	69	27.8	7.6	46.0	
			Psychosis only	568	30.8	Not reported	58.6	
Lugnegard et al	2015	Cross-sectional	SCZ	36	29.1	4.2	63.9	SCZ and Asperger syndrome: associated with more autistic traits (as measured by the AQ)
			Asperger syndrome	51	27.1	4.1	47.1	
			Control	49	28.6	9.2	38.8	
Maddox et al	2017	Cross-sectional	Psychiatric clinic population	75	47.8	12.2	62.7	Of the 57 participants in this community sample who had a lifetime history of psychosis, 37% scored above the ASD clinical cutoff on the ADOS-2
Morrison et al	2017	Cross-sectional	ASD	54	25.7	7.2	87.0	Social skills were impaired in ASD and SCZ groups relative to the control group, but impairment was greater in ASD, and the nature of the impairment differed: ASD participants were less socially involved/curious. SCZ participants were more socially engaged, but less affectively expressive
			SCZ	54	28.7	10.1	87.0	
			Control	56	26.9	9.2	88.0	
Strålin & Hetta	2019	Longitudinal	Hospitalized with FEP	2091	*M, SD* not reported; median 21.2, IQR 19.2 - 23.1		64.0	105 members of the cohort (5.0%) had an ASD diagnosis at time of hospitalization; ASD at hospitalization predicted continued prescription of medication for psychosis two years later
Upthegrove et al	2017	Cross-sectional	FEP	99	25.6	5.0	67.7	Increased AQ score and increased severity of positive symptoms of psychosis were associated with increased depression, hopelessness, and suicidal thoughts
van der Linden et al	2020	Cross-sectional	ASD	50	41.1	12.9	52.0	Similar rates of lifetime psychotic-like experiences across groups, but members of the ASD group were more likely to report current transient psychotic-like symptoms, and these symptoms were more likely to be associated with event-related stress
			Control	51	35.5	12.2	51.0	
Vita et al	2020	Cross-sectional	SCZ with ≥30 on PAUSS	185	41.5	0.8	73.0	SCZ with PAUSS ≥30 ("autistic schizophrenia") and SCZ with PAUSS >10 and <30 ("moderate autism symptoms") both had poorer social cognition than SCZ with PAUSS ≤ 10 group ("nonautistic schizophrenia")
			SCZ with PAUSS >10 and <30	679	40.2	0.4	69.3	
			SCZ with PAUSS ≤10	56	35.3	1.4	62.5	

Authors	Year	Study design	Group(s) Studied	*n*	Age *M*	*SD*	Sex (% Male)	Key findings
Zheng et al	2020	Longitudinal	FEP	180	28.5	5.5	52.8	More ASD traits (as rated both by self-report and by clinic staff) were associated with greater likelihood of a “psychosis, not otherwise specified”, “mood disorder with psychotic features” or “brief psychotic disorder” diagnosis than SCZ; at one-year follow-up, more ASD traits predicted greater severity of psychotic symptoms and poorer level of functioning
Ziermans et al	2020	Cross-sectional	ASD	50	12.2	2.2	82.0	ASD: Associated with more FTD, and FTD severity correlated negatively with verbal working memory in the ASD group but not in the control group
			Control	56	12.4	3.0	84.0	

ASD: autism spectrum disorder; ID: intellectual disability; FEP = first episode psychosis; AQ = Autism Quotient; PAUSS = PANSS Autism Severity Scale; FTD = formal thought disorder; ADOS = Autism Diagnostic Observation Schedule

Table 2:

Studies of perception and cognition

Authors	Year	Domain(s) studied	Group(s)	n	Age M	SD	Sex (% Male)	Key findings
Barneveld et al	2013	Executive function	ASD	29	14.7	2.1	72.4	In ASD, ↓ response inhibition (as measured by an attention-shifting task) was associated with self-reported schizotypal symptoms
			Control	40	15.2	2.5	80.0	
de Boer et al	2014	Processing speed	ASD	114	37.4	10.6	80.7	SCZ: ↓ processing speed
			SCZ	27	41.5	9.3	77.8	
			Control	30	37.3	11.0	70.0	
Demetriou et al	2018	Executive function	ASD	60	24.1	7.3	63.3	ASD and early psychosis: ↓ cognitive flexibility and attention
			Early psychosis	58	21.8	4.1	63.8	
			Social anxiety disorder	76	22.1	5.6	53.9	
			Control	59	24.9	5.3	52.5	
Eack et al	2013	Cognition (multiple domains)	ASD	43	24.9	5.8	88.4	No significant differences in processing speed, executive function (attention, working memory, planning) or social cognition between ASD and SCZ. Relative to controls, processing speed and social cognition were the most impaired in both
			SCZ	47	35.0	12.5	72.3	
			Control	24	26.3	5.5	66.7	
Haigh et al	2016	Perception	ASD	15	26.6	6.1	80	Participants were exposed to each of three sensory modalities (visual, auditory, and somatosensory) and their fMRI response amplitudes were compared. Sensory responses in ASD were less consistent than controls, varying across trials, but did not differ in strength of response. In contrast, responses in SCZ were as consistent as those in controls, but response amplitudes were weaker
			SCZ	15	25.8	4.6	66.7	
			Control	15	27.0	Not reported	73.3	
Krawczyk et al	2014	Language ability	ASD	15	21.7	4.4	73.3	Differential ability to reason by analogy across groups, with SCZ showing marked and generalized impairment relative to controls, and ASD showing moderate impairment relative to controls with some evidence of a particular difficulty with reasoning about non-living objects
			SCZ	13	30.0	5.7	53.8	
			Control	15	23.4	4.0	40.0	
Mance Calisir et al	2018	Executive function	ASD	32	33.9	9.4	53.1	ASD and SCZ: ↓ executive function
			SCZ	17	24.6	3.2	47.1	
			Control	23	27.4	4.1	56.5	

Authors	Year	Domain(s) studied	Group(s)	n	Age M	SD	Sex (% Male)	Key findings
Marinopoulou et al	2016	Cognition (multiple domains)	Asperger syndrome	50	27.7	3.9	50.0	Asperger syndrome and SCZ: ↓ working memory and processing speed (relative to norms)
			SCZ	33	29.1	4.3	54.55	
Minichino et al	2016	Perception	ASD	16	15.0	1.3	81.3	Mu rhythm suppression in response to biological motion (thought to index mirror neuron system activation) was reduced in ASD and early psychosis relative to controls but not each other. In a four-group analysis with the early psychosis group subdivided into early psychosis with (n = 15) and without (n = 5) negative symptoms , there was a suggestive finding regarding a difference (p = 0.08) between ASD and early psychosis without negative symptoms
			Early psychosis	20	19.1	4.3	80.0	
			Control	17	19.7	6.5	53.0	
Noel et al	2020	Perception	ASD	26	25.7	6.1	53.8	Peripersonal space (the radius surrounding an individual inside of which stimuli are perceived as physically relevant) was smaller and more sharply delineated in the ASD than in SCZ or control groups
			SCZ	22	45.1	10.0	59.1	
			Control	36	33.6	11.2	63.9	
Pepper et al	2018	Social cognition	ASD	53	23.9	7.4	66.0	ASD and early psychosis: ↓ performance on emotion recognition and social cognition tasks
			Early psychosis	51	21.8	4.4	70.6	
			Social anxiety disorder	64	22.7	6.0	53.1	
			Control	31	24.8	6.1	61.3	
Sachse et al	2014	Social cognition	ASD	22	20.9	5.6	81.8	ASD and SCZ both showed deficits in facial emotion recognition, with impaired facial identity recognition in ASD and impaired visual perception in SCZ; however, when directly compared to each other, there were no differences between ASD and SCZ in terms of facial identity recognition or visual perception
			SCZ	19	25.5	4.9	73.7	
			Control	20	20.1	3.8	85.0	
Sasson et al	2016	Social cognition	ASD	21	23.4	4.4	85.7	Both ASD and SCZ showed deficits in facial emotion recognition, but higher IQ correlated with greater accuracy of emotion recognition in SCZ but not in ASD or in controls
			SCZ	44	35.3	10.6	61.4	
			Control	39	35.9	9.3	59.0	
Shi et al	2020	Executive function	ASD	23	12.2	2.0	100	Greater impairment in auditory response inhibition in SCZ compared to ASD or controls, but similar impairment in visual response inhibition in SCZ and ASD compared to controls
			SCZ	23	14.2	1.1	100	
			Control	32	12.8	1.3	100	
Tobe et al	2016	Social cognition	ASD	19	39.4	12.5	89.5	SCZ: ↓ visual and auditory emotion recognition ASD: ↓ visual but not auditory emotion recognition
			SCZ	92	37.8	10.4	85.9	
			Control	73	36.0	11.8	61.6	

ASD: autism spectrum disorder; SCZ: schizophrenia; EF: executive function

Table 3:

Neuroimaging studies

Authors	Year	Modality	Groups	n	Age *M*	SD	Sex (% Male)	Key findings
Cauda et al	2017	Structural magnetic resonance imaging	ASD	1719	17.4	10.3	81.0	SCZ: ppredominantly in a cluster characterized by ↓ AI, mPFC and thalamic volume
			SCZ	5236	31.0	9.9	59.5	OCD: predominantly in a cluster characterized by ↓ parietal, temporal and occipital lobe volumes
			OCD	1738	26.4	9.8	53.3	ASD: evenly distributed across clusters
Chen et al	2017	Resting-state functional magnetic resonance imaging	ASD	22	13.1	3.1	68.2	ASD: ↑ connectivity within DMN but ↓ DMN—language networks connectivity
			ASD control	24	12.9	2.9	70.8	
			FEP	35	15.6	1.8	57.1	SCZ: ↓ connectivity within DMN but ↑ DMN—language networks connectivity
			FEP control	31	15.4	1.6	41.9	
Ciaramidaro et al	2018	Task-based functional magnetic resonance imaging	ASD	33	18.8	5.0	94.0	During facial affect recognition: ↓ amygdala and fusiform gyrus activation in ASD and SCZ
			SCZ	20	24.7	5.0	70.0	
			Control	25	19.7	3.5	84.0	
Ciaramidaro et al	2015	Task-based functional magnetic resonance imaging	ASD	23	18.7	4.8	91.3	During a theory-of-mind task (communicative intent between people): STS—mPFC connecitivty ↓ in ASD
			SCZ	18	25.7	4.5	77.8	
			Control	23	20.2	3.7	82.6	During a control task (causality between inanimate objects): STS—mPFC connectivity ↑ in SCZ
Diaz-Caneja et al	2018	Structural magnetic resonance imaging	ASD	30	13.3	2.0	93.3	ASD and FEP: ↓ insular volume largely explained by localized decreases in cortical surface area and thickness
			FEP	29	14.1	1.0	62.1	
			Control	26	13.1	2.4	96.2	
Eack et al	2017	Task-based functional magnetic resonance imaging	ASD	33	23.9	6.1	91.0	During visual perspective-taking: OFC—mPFC and OFC—TPJ connectivity ↑ in ASD but ↓ in SCZ
			SCZ	36	26.3	6.8	61.1	
			Control	37	25.4	4.7	78.3	
Haigh et al	2019	Diffusion-weighted imaging	ASD	25	28.9	7.0	84.0	SCZ: ↑ radial and mean diffusivity throughout the brain
			SCZ	15	25.8	4.6	66.7	
			Control	19	26.0	Not reported	73.7	

Authors	Year	Modality	Groups	n	Age *M*	SD	Sex (% Male)	Key findings
Hirata et al	2018	Functional infrared spectroscopy	ASD	13	M and *SD* not reported; median 30.0, IQR 23.3 - 38.5		92.3	During facial affect recognition: ↓ left frontotemporal activation in ASD
			SCZ	15	*M* and *SD* not reported; median 36.0, IQR 29.0 - 47.0		80.0	
			Control	18	*M* and *SD* not reported; Median 34.5, IQR 28.0 - 38.5		72.2	
Hyatt et al	2020	Task-based functional magnetic resonance imaging	ASD	30	21.7	3.4	86.7	ASD and SCZ: ↑ mPFC—TPJ connectivity
			SCZ	30	26.0	3.5	63.3	
			Control	30	24.2	3.6	73.3	
Katz et al	2016	Structural magnetic resonance imaging	ASD	23	26.7	6.5	100	↑ PFC volume in ASD ↓ PFC volume in SCZ vs. controls
			SCZ	24	31.2	8.2	100	
			Control	32	29.8	9.2	100	
Martinez et al	2019	Task-based functional magnetic resonance imaging	ASD	20	28.9	7.7	80.0	During facial affect recognition: ↓ thalamic activation in ASD but ↑ thalamic activation in SCZ
			SCZ	19	37.2	10.2	78.9	
			Control	17	34.0	9.8	76.5	
Mastrovito et al	2018	Resting-state functional magnetic resonance imaging	ASD	37	26.3	7.4	100	ASD: ↑ connectivity within the DMN, but ↓ connectivity between the DMN and language networks
			ASD control	27	25.4	6.3	100	
			SCZ	72	38.2	13.9	80.6	SCZ: ↓ connectivity within the DMN, but ↑ connectivity between the DMN and language networks
			SCZ control	74	35.8	11.6	68.9	
Mitelman et al	2017	Structural magnetic resonance imaging	ASD	20	28.4	6.5	85.0	ASD: ↑ gray matter but ↓ white matter in frontal, temporal, parietal, and occipital lobes, and cingulate gyrus
			SCZ	49	42.7	12.3	85.7	
			Control	39	33.7	10.8	74.4	SCZ: ↓ gray matter but ↑ white matter in frontal, temporal, parietal, and occipital lobes, and cingulate gyrus
Mitelman et al	2017	Positron emission tomography	ASD	25	31.5	11.6	84.0	ASD: ↓ metabolism in primary motor and somatosensory cortices and ↑ metabolism in anterior cingulate
			SCZ	41	40.0	18.0	78.0	
			Control	55	33.4	12.9	52.7	SCZ: ↑ metabolism in primary motor and somatosensory cortices
Parellada et al	2017	Structural magnetic resonance imaging	ASD	30	13.3	2.0	93.3	ASD and FEP: ↓ insular volume
			FEP	29	14.1	1.0	62.1	

Authors	Year	Modality	Groups	n	Age *M*	SD	Sex (% Male)	Key findings
			Control	26	13.1	2.4	96.2	
Rabany et al	2019	Dynamic resting-state functional magnetic resonance imaging	ASD	32	23.5	0.7	87.5	ASD: ↑ time in weakly-connected state, but normative number of transitions between states
			SCZ	33	24.8	0.5	75.8	
			Control	34	23.7	0.6	67.6	SCZ: ↑ time in weakly-connected state, and fewer transitions between weakly and strongly connected states

ASD: autism spectrum disorder; SCZ: schizophrenia; OCD: obsessive-compulsive disorder; FEP: first episode psychosis; DMN: default mode network; STS: superior temporal sulcus; mPFC: medial prefrontal cortex; OFC: orbitofrontal cortex

Table 4:

Studies of copy number variation

Authors	Year	Study design	Group(s)	n	Age M	SD	Sex (% Male)	Key findings
Fiksinski et al	2017	Longitudinal	22q11.2 deletion with ASD	52	14.1	1.8	46.2	No statistically significant difference between participants with ASD who developed psychosis (n = 9, 17.3%) and those without ASD who developed psychosis (n = 10, 27.0%)
			22q11.2 deletion without ASD	37	14.5	2.0	32.4	
Jutla et al	2020	Cross-sectional	16p11.2 duplication	109	19.8	17.5	46.5	ASD diagnosis is associated with psychotic symptoms in in people with 16p11.2 duplication or deletion, with the association stronger in those with the duplication
			16p11.2 deletion	131	10.9	10.4	51.9	
			Control	306	29.4	15.9	42.5	
Larson et al	2018	Cross-sectional	ASD with psychosis	116	M and SD not reported; range 6-55		76.7	Identified 27 large, previously unreported CNVs within the sample, as well as 49 rare CNVs (present in less than 1.5% of the general population)
Niarchou et al	2019	Cross-sectional	16p11.2 duplication	114	8.6	Not reported	57.0	No difference between duplication and deletion in prevalence of ASD, but greater prevalence of psychotic symptoms in duplication than in deletion
			16p11.2 duplication control	32	9.4	Not reported	56.3	
			16p11.2 deletion	217	9.0	Not reported	58.1	
			16p11.2 deletion control	77	9.8	Not reported	46.8	
Pollak et al	2019	Cross-sectional	3q29 deletion	93	10.0	8.6	58.1	27 participants had diagnoses of ASD and 4 had diagnoses of schizophrenia.
Vorstman	2013	Retrospective	22q11.2 deletion with psychosis	36	5.9 (retrospective reference age)	2.0	47.2	Parents' retrospective ratings of autism symptoms in childhood did not differ between groups with and without psychosis
			22q11.2 deletion without psychosis	41	6.4 (retrospective reference age)	2.0	53.7	

ASD: autism spectrum disorder; CNV: copy number variation