The association between autism and schizophrenia spectrum disorders:

A review of eight alternate models of co-occurrence

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Abstract

Although now believed to be two distinct disorders, autism spectrum disorders (ASD) and schizophrenia spectrum disorders (SSD) share multiple phenotypic similarities and risk factors, and have been reported to co-occur at elevated rates. In this narrative review, we give a brief overview of the phenomenological, genetic, environmental, and imaging evidence for the overlap between ASD and SSD, highlighting similarities and areas of distinction. We examine eight possible alternate models of explanation for the association and comorbidity between the disorders, and set out a research agenda to test these models. Understanding how and why these disorders co-occur has important implications for diagnosis, treatment, and prognosis, as well as for developing fundamental aetiological models of the disorders.

Keywords

Autism, psychosis, schizophrenia, Aspergers's, comorbidity, model, diagnosis

Main text

1. Introduction

SSD and ASD are currently conceptualised as separate illnesses. Schizophrenia spectrum disorders (SSD), as defined by the DSM-5, include schizophrenia, other psychotic disorders, and schizotypal personality disorder. They involve delusions, hallucinations, disorganized thinking, disorganized behaviour, and negative symptoms. Autism-spectrum disorders (ASD), included by the DSM-5 under neurodevelopmental disorders, are diagnosed when deficits of social communication and interaction are accompanied by markedly repetitive patterns of behaviour, interests, or activities. ASD traits are present in the early developmental period and may be with or without an accompanying intellectual or language impairment. This however, has not always been the case. Definitions of ASD and SSD have undergone many revisions (with much of the research cited in this review using DSM-IV or earlier definitions). Bleuler (1950) believed that autism was a central feature of schizophrenia, while others viewed it as the childhood onset of the disorder (Bender, 1947). In fact, the term autism was used interchangeably with schizophrenia until the 1970s, when Rutter (1972) and Kolvin (1971) proposed that they were distinct disorders. The nosologic separation between ASD and SSD may initially appear justified. SSD has a typical adolescent onset with prominent positive psychotic symptoms, while ASD is characterised by deficits in social interaction, communication and behaviour that begin within the first few years of life (American Psychiatric Association, 1994). Despite apparent differences, SSD and ASD share multiple phenotypic similarities and risk factors (Hamlyn, Duhig, McGrath, & Scott, 2013; Spek & Wouters, 2010), have both been conceptualised as neurodevelopmental rather than neurodegenerative disorders (Goldstein, Minshew, Allen, & Seaton, 2002), and have been reported to co-occur at elevated rates (Mouridsen, Rich, & Isager, 2008; Rapoport, Chavez, Greenstein, Addington, & Gogtay, 2009; Solomon et al., 2011; Stahlberg, Soderstrom, Rastam, & Gillberg, 2004). Systematic research on their co-occurrence has been limited, although emerging genetic and neuroanatomical evidence has led to increasing recognition of the overlap between the conditions (Carroll & Owen, 2009; Cheung et al., 2010).

In this paper we briefly review the phenomenological, genetic, environmental, and imaging evidence for the overlap between ASD and SSD, in order to highlight similarities and areas of distinction between the disorders. We then examine alternative models of explanation for the association between the disorders, and set out a research agenda to test these models. Understanding how and why these disorders co-occur has important implications for diagnosis, treatment, and prognosis, as well as for developing a fundamental understanding of the aetiologies of these disorders.

2. Phenomenology, diagnoses and overlapping traits

2.1 Co-occurrence at the diagnostic level

Although there have been reports that SSD and ASD do not co-occur at elevated rates (Volkmar & Cohen, 1991), the majority of research suggests that the disorders co-occur at a higher rate than would be expected in the general population. A brief literature search (database: Web of Science, search terms: Autism AND psychosis AND diagnosis, conducted March 2015) reveals 14 papers published in the past 10 years, which investigate diagnostic rates of ASD in individuals with SSD, or vice versa. Of these, 9 investigate rates of SSD in ASD populations, and five rates of ASD in those diagnosed with SSD.

In populations with ASD, rates of comorbid SSD have been variably reported from 0% - 34.8%. A similar pattern emerges when considering ASD in SSD populations where reported rates vary from 3.6% - 60% (see table 1). Childhood-onset schizophrenia (COS) in particular has been linked to ASD, with estimates that 30-50% of cases are preceded by a diagnosis of a Pervasive Developmental Disorder (Rapoport et al., 2009). A systematic review by Padgett et al. (2010) found that in individuals with SSD, rates of pervasive developmental disorders, including ASD, were estimated at 18-56%, but noted that all of the studies highlighted by their search reported research conducted with populations less than 18 years old, despite their search not being intentionally limited to this age range. In adult SSD populations less is known about the prevalence of ASD.

Table 1: Rates of co-occurrence between ASD and SSD

Authors	n	% co-occurrence
SSD in ASD populations		
Eaves and Ho (2008)	48 young adults with ASD	0%
Lugnegard, Hallerback, and Gillberg (2011)	54 young adults with Asperger syndrome	3.7%
Mouridsen, Rich, and Isager (2008)	118 individuals diagnosed as children with infantile autism	6.6%
Billstedt, Gillberg, and Gillberg (2005)	120 individuals with autism diagnosed in childhood	7%
Hofvander et al. (2009)	122 adults with normal intelligence ASDs	12%
Stahlberg et al. (2004)	129 adults diagnosed with ASD	14.8%
Joshi et al. (2010)	217 children and adolescents meeting diagnostic criteria for an ASD	20%
Bakken et al. (2010)	62 adults with autism and intellectual disability	25.1%
Mouridsen et al. (2008)	89 individuals with atypical autism	34.8%
ASD in SSD populations		
Davidson, Greenwood, Stansfield, and Wright (2014)	197 adults attending an early intervention in psychosis service	3.6%
Sporn et al. (2004)	75 children with COS	3.9%
Solomon et al. (2011)	16 individuals with first episode of psychosis	19%
Waris, Lindberg, Kettunen, and Tani (2013)	18 adolescents with early onset schizophrenia	44%
Hallerback, Lugnegard, and Gillberg (2012)	46 adults with a diagnoses of schizophrenic psychotic disorders	50-60%

As ASD and SSD both occur in around 1% of the population (Brugha et al., 2011; Kendler, Gallagher, Abelson, & Kessler, 1996; Centers for Disease Control and Prevention, 2012; van Os, Hanssen, Bijl, & Vollebergh, 2001), studies with fewer than 100 participants are unlikely to be truly representative. Of the 14 papers mentioned 6 had samples of over 100 participants (Billstedt et al., 2005; Davidson et al., 2014; Hofvander et al., 2009; Joshi et al., 2010; Mouridsen et al., 2008; Stahlberg et al., 2004). These papers found a mean incidence of 12.8% of SSD in ASD populations, with only one study reporting on ASD in SSD with a sample of over 100 (Davidson et al., 2014) and finding an incidence

rate of 3.6%. Large population studies are needed to ascertain true diagnostic comorbidities in ASD and SSD.

2.2 Co-occurrence at the trait level

SSD and ASD are both hypothesised to exist on extended phenotypic continua (Folstein & Rutter, 1977; van Os, Hanssen, Bijl, & Ravelli, 2000), and it is therefore important to consider not only co-occurrence at the diagnostic level, but also to investigate evidence of overlap in traits. A descriptive overlap exists in the traits that make up the diagnostic criteria for ASD and SSD. Both disorders include deficits in social interaction and communication as primary symptoms; the lack of emotional reciprocity in ASD can be compared to blunted affect (a lack of emotional response) in SSD; the delay or lack of speech development in ASD parallels alogia (poverty of speech) in SSD; and catatonic features are observed in both diagnoses. It is perhaps unsurprising that much research has found co-occurrence of traits such as these (e.g. Brüne, 2005; Spek & Wouters, 2010). Similarities are also found in traits that *relate to*, but are not *part of* the diagnostic criteria. Theory of mind and mentalizing impairments are hypothesised to be central to both disorders (Baron-Cohen, Leslie, & Frith, 1985; Bora, Yucel, & Pantelis, 2009; Brüne, 2005; Chung, Barch, & Strube, 2013). Similarly, Eack et al. (2013) report that those with ASD and SSD experience similar deficits in their neurocognitive and social-cognitive functioning.

What is more striking is that traits which, according to diagnostic criteria, should be found in only one of the disorders are often found in the other as well. For example, positive psychotic experiences are not mentioned in diagnostic criteria for ASD. Yet there is some evidence that these experiences may occur at elevated rates in ASD populations (Barneveld et al., 2011; Bevan Jones, Thapar, Lewis, & Zammit, 2012). Indeed, Konstantareas and Hewitt (2001) reported that 35% of their ASD sample displayed one or more positive symptom. Similarly, core ASD features such as circumscribed interests, resistance to change, and abnormal response to stimuli are not part of the diagnostic criteria for SSD but are often found in SSD populations (Esterberg, Trotman, Brasfield, Compton, & Walker, 2008).

Conversely, other authors report traits which do differentiate between the disorders. Intellectual disability, for example, is more common in ASD than SSD (Baio, 2010; Cooper, 1997; Morgan, Leonard, Bourke, & Jablensky, 2008). Similarly, although both disorders show a higher male to female ratio in individuals diagnosed, the male-female ratio appears to be considerably higher in ASD than SSD (Ochoa, Usall, Cobo, Labad, & Kulkarni, 2012; Wing, 1981b). Level of communication deficits may also differentiate between ASD and SSD. In a study comparing individuals at risk for psychosis, those with a first episode of psychosis, individuals with autism and healthy controls, Solomon and colleagues (2011) found that although 20% of those in the high risk or first episode psychosis groups met diagnostic criteria for ASD as assessed by parental report, there were a number of traits which distinguished between the different diagnostic categories. Atypical developmental trajectories in communication and social behaviours, as well as structural and pragmatic language, were found in the ASD group to a much greater extent than the SSD and control groups. Similarly, when comparing individuals with ASD and SSD, Spek and Wouters (2010) demonstrated that individuals with ASD reported more impairment with social skills, attention switching, and communication than those with SSD.

There is also longitudinal evidence for an overlap between ASD and SSD at the trait level. Evidence from two large cohort studies has confirmed that the presence of psychotic experiences at age 12 is associated with ASD traits earlier in life (Bevan Jones et al., 2012; Sullivan, Rai, Golding, Zammit, & Steer, 2013). Likewise, children who have received a diagnosis of ASD are more likely to report experiencing symptoms of psychosis during adolescence and adulthood (Joshi et al., 2013; Sullivan et al., 2013). Childhood deficits documented in those who later develop SSD mimic ASD traits; there is substantial evidence of early deficits in motor development (e.g. Fish, Marcus, Hans, Auerbach, & Perdue, 1992), cognition (e.g. Cannon et al., 2002), socialisation (e.g. Cannon et al., 2002; Jones, Rodgers, Murray, & Marmot, 1994) and communication (e.g. Bearden et al., 2000), many years before the expression of frank positive psychotic symptoms. These have recently been confirmed meta-analytically (Dickson, Laurens, Cullen, & Hodgins, 2011). Whether these traits reflect aspects of

ASD which were undiagnosed or did not reach clinical significance, or instead reflect the status of SSD as a neurodevelopmental disorder remains to be determined.

Other research suggests, however, that ASD traits may not be predictive of the development of SSD. Esterberg et al. (2008) found that within their sample of adolescents with schizotypal personality disorder (SPD), adolescents with other personality disorders, and those with no personality disorder, childhood and current ASD features were predictive of schizotypal and 'prodromal' symptoms, but were *not* found to be predictive of the development of psychotic illness (although it needs to be noted that Esterberg et al.'s follow up was for just 3 years which may not be long enough for a conclusive evaluation of transition to frank psychosis). Research in the 22q11.2 deletion syndrome population has also suggested that ASD traits are not predictive of the development of SSD. A study from Vorstman and colleagues (2013) investigated childhood ASD traits in 78 patients with 22q11.2 deletion syndrome, 36 of who had developed psychotic disorder. High levels of ASD traits were reported to have occurred during childhood in their population, but were *not* predictive of the development of SSD. Higher rates of ASD traits had a stronger association with the *non-psychotic* individuals with the deletion, suggesting that, in the case of 22q11.2 deletion syndrome, the disorders share a genetic vulnerability but are distinct in their expression of this vulnerability.

2.3 Section summary

ASD and SSD appear to co-occur diagnostically at a higher frequency than would be expected by chance. A trait overlap between the disorders exists both cross-sectionally and longitudinally. Overlap at the trait level, rather than diagnostically, is an important consideration, not only from an aetiological perspective, but also from a clinical one. For example, sub-threshold ASD traits may be important for tailoring psychosocial intervention for individuals with SSD.

3. Overlapping risk factors

3.1 Genetic evidence

Genetic evidence also highlights points of similarity and distinction between the disorders. The phenotypic similarities between SSD and ASD are mirrored by many overlapping genetic mechanisms. ASD and SSD rates of heritability are both estimated to be high at around 50-80%, (Cardno & Gottesman, 2000; Freitag, 2006; Sandin et al., 2014). What is particularly interesting is the fact that as well as showing high levels of heritability *within* each disorder, there is evidence of relatively high levels of heritability *between* the disorders. There is an increased risk for ASD in the offspring of parents with SSD (Larsson et al., 2005; Sullivan et al., 2012), higher levels of ASD traits among the siblings of children with COS (Sporn et al., 2004), and an increased rate of SSD in the parents of children with ASD than in parents of controls (Daniels et al., 2008).

This is consistent with studies investigating copy number variants (CNVs; variations of DNA sequence in the genome) in SSD and ASD. Particular CNVs are implicated in both ASD and SSD, and specific rare alleles have been found to occur in both disorders (e.g. Lionel et al., 2013; McCarthy et al., 2009; Moreno-De-Luca et al., 2010; Vorstman et al., 2013; Weiss et al., 2008). The high number of shared CNV deletions and duplications, including NRXN1, CNTNAP2, 22q11.2, 1q21.1 and 15q13.3, led Carroll and Owens (2009) to conclude in their review that genetic evidence challenges the assumption that ASD and SSD are completely unrelated disorders. The nature of this association is a matter of controversy, however, particularly in light of evidence suggesting that both disorders are diametrically related (Crespi, Stead, & Elliot, 2010). Crespi and colleagues propose this based on evidence that genetic risk factors in both disorders behave in a pleiotropic manner such that deletion of a part of the chromosome predisposes the individual to developing one disorder and duplication predisposes the other disorder. They also cite evidence showing that specific risk variants lead to up-regulation of growth-signalling pathways in ASD and down regulation of growth-signalling pathways in SSD.

A particularly compelling example of overlapping genetic vulnerability comes from the high rates of ASD and SSD seen in individuals with 22q11.2 deletion syndrome. In the largest study to date, investigators examined psychiatric morbidity in 1402 individuals with the syndrome (Schneider et al.,

2014). SSDs were found in 1.97% of children aged 6-12, 10.12% of adolescents age 13-17, 23.53% of emerging adults aged 18-25, 41.33% of young adults age 26-35, and 41.73% of mature adults aged 36 or above. Similarly high rates of ASD were also found, with rates varying across the life span of 12.77% for children, to 26.54% for adolescents, to 16.10% for adults.

There is also evidence of genetic differentiation between the disorders. Whilst CNVs appear to be enriched in individuals with ASD and SSD, common risk alleles have not generally been found to be shared between the disorders. Using genome-wide genotype data from the Cross-Disorder Group of the Psychiatric Genomics Consortium (2013), only a low genetic correlation was found between ASD and SSD. This compares to strong to moderate correlations between schizophrenia and bipolar disorder, schizophrenia and major depressive disorder, bipolar disorder and major depressive disorder, and attention-deficit/hyperactivity disorder and major depressive disorder. Similarly, using a schizophrenia-derived polygenic score which covered common risk alleles, Vorstman et al. (2013) found no evidence for shared common genetic risk variants between ASD and SSD. The authors hypothesise that this suggests that common risk variants may play a limited role in ASD when compared to SSD, particularly when considering the lack of confirmed genome-wide association study results in ASD (Devlin, Melhem, & Roeder, 2011).

3.2 Environmental factors

As well as sharing genetic risk factors, SSD and ASD also share a remarkable number of environmental risk factors (Hamlyn et al., 2013). Many of these relate to obstetric complications (Atladottir et al., 2010; Brown et al., 2004; Cannon, Jones, & Murray, 2002; Gardener, Spiegelman, & Buka, 2009; Larsson et al., 2005). Cannon et al.'s (2002) meta-analysis found that antepartum haemorrhage, gestational diabetes, rhesus incompatibility, preeclampsia, low birth weight, congenital malformations, reduced head circumference, uterine atony, asphyxia, and emergency caesarean section were all associated with increased risk of developing schizophrenia. Similar results have been confirmed meta-analytically for ASD, with gestational diabetes, maternal bleeding during pregnancy, maternal medication use during pregnancy and psychiatric medication use during pregnancy all

highlighted as increasing risk of ASD (Gardener et al., 2009). Paternal age has also been identified as a potential risk factor both ASD and SSD, (particularly paternal age of >50; Gardener et al., 2009; McGrath et al., 2014; Miller et al., 2011). Again these results have been confirmed meta-analytically for both disorders, with Miller et al. (2011) reporting increased risk of SSD in offspring of fathers over 29 years of age, and Hultman, Sandin, Levine, Lichtenstein, and Reichenberg (2011) observing increased risk of ASD in offspring of fathers aged 30 or more. In both analyses, the highest risk was for offspring of fathers aged 50 or more.

Other potential shared environmental risk factors have been more tentatively suggested. Urbanicity has been relatively robustly linked to the development of SSD (Marcelis, Navarro-Mateu, Murray, Selten, & van Os, 1998; Mortensen et al., 1999). Although an association between urbanicity during pregnancy and infanthood and the development of ASD has been observed (Lauritsen et al., 2014; Lauritsen, Pedersen, & Mortensen, 2005; Li, Sjöstedt, Sundquist, Zöller, & Sundquist, 2014), at least some of this observation may be explained by variations in access to diagnostic and medical services. Lauritsen et al. (2014) for example, utilising a Danish register-based cohort of more than 800,000 children, found an increased risk of ASD in children who moved to higher levels of urbanicity in early childhood, as well as an earlier age of diagnosis in urban areas. These findings indirectly suggest that availability of diagnostic services may be at least partially responsible for the increased incidence of ASD observed in urban areas. The nutrition of the mother during pregnancy, in particular low prenatal vitamin D, has also been tentatively identified as a risk factor in both ASD (Cannell, 2008; Grant & Soles, 2009; Kočovská, Fernell, Billstedt, Minnis, & Gillberg, 2012) and SSD (McGrath, Burne, Féron, Mackay-Sim, & Eyles, 2010; McGrath et al., 2010).

As with underlying genetic risk factors, there are also environmental risks which appear to be specific to one disorder or the other. For example, risk for SSD appears to be increased in first and second generation migrants (Cantor-Graae & Selten, 2005), whereas migrant status appears to be a risk for ASD specifically with regards to parental migration (Dealberto, 2011; Gardener et al., 2009; Magnusson et al., 2012). Similarly, prenatal famine has been linked to a two-fold increase in SSD but

has not currently been linked to ASD (Hoek et al., 1996; Roseboom, Painter, van Abeelen, Veenendaal, & de Rooij, 2011).

3.3 Section summary

Similar underlying risks exist between ASD and SSD, in terms of heritability and genetics, and in terms of environmental risk. On the other hand, there also appear to be areas of differentiation, with certain risk factors unique to one disorder but not the other.

4. Brain structure and functioning

Neuroimaging evidence presents a similar picture to phenomenological, genetic, and environmental risk factor research, with many similarities apparent between the disorders, but also some differences. In terms of similarities, both individuals with ASD and those with SSD have been found via meta-analysis to show reduced grey matter volume in limbic-striato-thalamic circuitry, predominantly on the right, including the insula, posterior cingulate and parahippocampal gyrus (Cheung et al., 2010). In their review comparing individuals with ASD to those with COS, Baribeau and Anagnostou (2013) suggest there may be similarities in exaggerated volume loss during adolescence. They also note similarities in volume loss in prefrontal areas including the middle frontal gyrus, volume loss in the temporal-parietal junction, and volume gains in the caudate.

Reduced fractional anisotropy values (reflecting altered white matter integrity) have also been found in both disorders (Mueller, Keeser, Reiser, Teipel, & Meindl, 2012). In ASD, implicated areas include the corpus callosum, the right corticospinal tract, the internal capsule, the left and right pedunculi cerebri, and the cingulate gyrus (Bloemen et al., 2010; Brito et al., 2009). Within SSD, implicated areas are the left frontal deep white matter including the frontal lobe, thalamus, and cingulate gyrus, and the left temporal deep white matter including the frontal lobe, insula, hippocampus-amygdala complex, and temporal and occipital lobes (Ellison-Wright & Bullmore, 2009). Comparisons between COS and ASD reveal that both disorders show volume loss in the corpus callosum and cingulum, as

well as reduced white matter integrity in the superior longitudinal fasciculus (Baribeau & Anagnostou, 2013).

Functional imaging analyses have focused on social cognition as a primary feature of both disorders. A meta-analysis has shown that brain regions thought to be part of a social cognition network show hypoactivation in both ASD and SSD in response to social stimuli, most consistently seen in the medial prefrontal cortex and superior temporal sulcus (Sugranyes, Kyriakopoulos, Corrigall, Taylor, & Frangou, 2011). Similarly, a review from Abdi and Sharma (2004) found reductions in blood flow to the fusiform gyrus and abnormal amygdala activation during emotional perception tasks in both ASD and SSD.

Neurochemical abnormalities such as dopamine disruption have also been observed in both disorders (Hérault et al., 1993; Muck-Seler et al., 2004; Stone, Morrison, & Pilowsky, 2007; Cartier, 2015). Within SSD dopamine disruption has been identified as a central feature of the disorder (Howes & Kapur, 2009; Winton-Brown, Fusar-Poli, Ungless, & Howes, 2014). Research into the dopamine system in ASD is more limited. In a study which compared 8 adults with Asperger syndrome to 5 healthy controls using positron emission tomography (PET), Nieminen-von Wendt et al. (2004) found increased FDOPA influx (Ki) values in the striatum of the ASD group. Similarly, in another PET study which compared 20 individuals with ASD with control participants, an over-functioning of dopaminergic systems in the orbitofrontal cortex was suggested by a higher level of dopamine transporter bindings in the ASD group when compared to controls (Nakamura et al., 2010).

There are also potential areas of distinction between the disorders. These include increased cerebral ventricles volume and a reduction in overall brain volume found in individuals with SSD but not ASD (Shenton, Dickey, Frumin, & McCarley, 2001; Toal et al., 2009), as well as decreased white matter integrity, again found in individuals diagnosed with SSD but not ASD (Davis et al., 2003; Hao et al., 2006; Toal et al., 2009). In the only structural MRI study to date (to the authors knowledge) to directly compare ASD and SSD, Radeloff et al. (Radeloff et al., 2014) found no global grey matter or white matter differences between individuals with ASD, SSD, or controls. Participants with ASD

however, were found to have smaller grey matter volume in the left anterior insular when compared to those with SSD. In contrast to this, a positive correlation was observed between insular grey matter volume and hallucinatory behaviour in the SSD group. A meta-analysis from Cheung et al. (2010), which aimed to quantify structural similarities between ASD and SSD, found that abnormalities in the right and left superior and medial frontal gyrus, right and left cingulate, left insula, caudate, temporal gyrus and amygdala were specific to SSD, and abnormalities in the left putamen appeared specific to ASD. In their review comparing COS with ASD, Baribeau and Anagnostou (2013) report opposing patterns between the two conditions, with cortical surface area and volume showing patterns of overgrowth in early ASD but reduced thickness in individuals with COS. Similarly, they report a pattern of diametric results demonstrated in fMRI studies, with those diagnosed with COS showing increased long range connectivity with reduced short-range connectivity, compared to research suggesting that those diagnosed with ASD may display the reverse pattern (e.g. Courchesne & Pierce, 2005; Just, Keller, Malave, Kana, & Varma, 2012).

Other research, particularly studies investigating social deficits, has found opposing patterns of activation during fMRI. A recent study from Ciaramidaro et al. (2014), which directly compared individuals with ASD and SSD on different types of intentionality, found that activation between the right posterior superior temporal sulcus and the ventral medial prefrontal cortex was abnormal in both groups, with an increased connectivity found in those with SSD and a decreased connectivity in those with ASD. The increased connectivity in SSD was found during the control condition ('physical intentionality', e.g. a balloon is blown by a gust of wind), and the decreased connectivity in ASD was found during the experimental intention condition. The authors argue that this is consistent with the hypo-hyper-intentionality hypothesis (Abu-Akel & Bailey, 2000; Crespi & Badcock, 2008) that individuals with SSD over-attribute intentions to others and physical events, whereas those with ASD often fail to attribute intentions to others. This hypothesis parallels evidence from EEG studies which find reduced Mu suppression (used as marker for mirror neuron activity) in ASD participants taking part in socio-emotional tasks (Oberman et al., 2005) and increased Mu suppression in those with SSD (McCormick et al., 2012).

A particularly interesting investigation of brain anatomy in individuals who had ASD compared to those with comorbid ASD and SSD found that the primary differences in those with comorbid ASD and SSD (compared to those with ASD alone) related to reductions in grey matter in the right insular cortex, the cerebellum, the fusiform gyrus and the lingual gyri (Toal et al., 2009). Toal et al. (2009) note that their participants with comorbid ASD and SSD did not display the same changes usually found in populations who have developed SSD such as an increased volume of cerebral ventricles with a reduction in total brain volume (Shenton et al., 2001). They suggest that their comorbid population appear to share more anatomical similarities with individuals in Ultra High Risk for psychosis (UHR) groups, rather than those with frank SSD, and point out that the cerebellum and fusiform gyrus (which showed reductions in their comorbid population) have been implicated in UHR individuals (alongside left parahippocampal gyrus, and the orbitofrontal and cingulate cortex; e.g. Job, Whalley, Johnstone, & Lawrie, 2005; Pantelis et al., 2003). Toal et al. suggest that these anatomical differences may hint that for some individuals, ASD represents a different pathway into SSD.

5. Models of association

Levels of co-occurrence and association within psychiatric disorders have long been considered contentious (Krueger & Markon, 2006). A differentiation can be made between the co-occurrence of two unrelated disorders, anorexia and hearing impairment for example, and disorders which correlate or co-occur above the level of chance, such as depression and anxiety disorders, or morbid obesity and heart failure. Many explanations of co-occurrence or association between disorders/diseases have been proposed (Crespi & Badcock, 2008; Kraemer, 1995; Krueger & Markon, 2006). These can be summarised as follows:

1. The ‘multiformity’ model
2. The ‘increased vulnerability’ model
3. The ‘chance’ or ‘spurious association’ model
4. The ‘stages’ model
5. The ‘associated liabilities’ model

6. The ‘independence’ model
7. The ‘diametrical’ model
8. The ‘multiple overlapping aetiologies’ model

Below we provide a brief description of these models followed by an evaluation of their fit in explaining the nature of the co-occurrence between ASD and SSD in lieu of current evidence.

5.1 *The multiformity model*

The multiformity model was one of four models (alongside *the associated liabilities model, increased vulnerability model*, and *the independence model*) proposed by Krueger and Markon (2006) as a potential bivariate model for understanding associations between two psychopathologies. The model suggests that two disorders which appear to co-occur may represent different *manifestations* of the same underlying disorder, with the underlying liability expressing itself in a number of ways.

In the case of SSD and ASD *the multiformity model* would predict that although ASD and SSD have different expressions, they are in fact caused by the same underlying disorder. Interestingly, *the multiformity model* therefore entails that what are currently conceptualised as two separate disorders are in fact one, potentially leading round full circle to Bleuler’s original conception of the disorders.

5.2 *The increased vulnerability model*

The increased vulnerability model (termed *the causation model* by Krueger & Markon, 2006) theorises that one disorder may predispose another disorder, for example, in the way that obesity predisposes heart disease. Applied to ASD and SSD, *the increased vulnerability model* hypothesises that individuals who experience ASD will show an increased vulnerability developing a SSD, *but* that the disorders remain separate, with areas of distinction able to be made between them.

5.3 The chance model

The chance model, discussed by Kraemer (1995), and termed *the spurious association model* by Krueger and Markon (2006), refers to disorders co-occurring due to chance, or due to external variables (such as misdiagnosis) which could lead to the appearance of co-occurrence. Other authors (e.g. Bishop, 2010) discuss 'phenomimicry', where the causal pathway for one disorder may lead to traits which mimic or resemble the other disorder. This similarity would be superficial, and not reflective of a deeper association between the disorders, but might nonetheless lead to higher levels of misdiagnosed comorbidity.

5.4 The stages model

The stages model postulates that two disorders which appear to co-occur are different stages of the same disorder. For example, the first stage of syphilis involves small, painless sores which disappear a few weeks before the disease progresses into its later stages which include more serious symptoms. When applied to ASD and SSD, the stages model suggests that ASD (whether at the diagnostic or trait level) may develop into SSD at a later stage. As with *the multiformity model*, if correct, *the stages model* also suggests that ASD and SSD are in fact one disorder rather than two.

5.5 The associated liabilities model

The associated liabilities model suggests that two disorders are related by shared risk factors, but are ultimately distinct. In the case of ASD and SSD it predicts that the disorders are separate but will share underlying genetic or environmental risks.

5.6 The independence model

The independence model proposes that when two disorders co-occur, the 'comorbid disorders' constitute a third independent disorder, which is distinct from the two disorders it is thought to be formed from. For example, rather than conceptualise people who experience periods of depression and periods of mania as experiencing two separate disorders, they are considered to experience a third disorder which encapsulates both of these: bipolar disorder. In the case of ASD and SSD, *the*

independence model would hypothesise that individuals who experience both an ASD and a SSD are actually experiencing a third, unique disorder.

5.7 The diametrical model

The diametrical model refers to disorders that emanate from reciprocal alterations to a common risk factor or factors. These disorders such as Beckwith-Wiedemann syndrome (involving overgrowth) versus Silver-Russell syndrome (involving undergrowth) or Prader-Willi versus Angelman syndromes present opposing profiles that result from either the deletion or duplications of a suite of common imprinted genes (see review by Crespi & Badcock, 2008). Having both ASD and SSD thus may be a consequence of carrying shared risk factors such as pleiotropic CNVs that confer risk for both disorders. When the disorders do co-occur, the diametrical model predicts that behaviour would be diametrically modulated towards normality by co-occurring phenotypic traits that are disorder-specific.

5.8 The multiple overlapping aetiologies model

The multiple overlapping aetiologies model applies to disorders which show a high level of clinical heterogeneity and which have multiple aetiological pathways. When disorders like this co-occur, *the multiple overlapping aetiologies model* suggests that this is because the disorders may share *some* aetiological pathways, whilst other causal pathways remain specific to one disorder or the other. *The multiple overlapping aetiologies model* applied to ASD and SSD would suggest that ASD and SSD both consist of multiple clinical syndromes, and that some of these clinical syndromes share aetiological pathways.

6. Evaluation of the co-occurrence and comorbidity of disorders

Of the eight models presented there is only limited evidence for *the chance, stages, independence,* and *multiformity models.* The evidence for the association between ASD and SSD is relatively robust and multifaceted, suggests strongly that the disorders co-occur at elevated rates, and thus precludes the

possibility that the disorders co-occur due to chance (*the chance model*). Given the evidence provided, *the stages model* also seems unlikely. The finding that there are genes which appear to differentiate between the disorders (e.g. EN2, reeln, 5-HTT, SLC6A4, AVPR1A in ASD and NRG1, Neuregulin, DTNBP1, dysbindin, DAOA, D-serine, DARPP-32, GRM3, RGS4 for SSD, see Wang, Jeffries, & Wang, 2015) suggests strongly that ASD is not a first stage of SSD. Similarly, although there are high transition rates in some groups (COS and Multiple Complex Developmental Disorder), most individuals with ASD do not develop SSD and not all of those with SSD experience autism traits. Counterintuitively, as different areas of the brain are implicated in each disorder (for example, lower putamen volumes and grey matter volume in the left anterior insular in ASD compared to SSD, and overgrowth versus undergrowth of cortical surface area in ASD compared to COS; Baribeau & Anagnostou, 2013; Cheung et al., 2010; Radeloff et al., 2014) in order for the disorder to 'progress' from the ASD stage to the SSD stage, as hypothesised by *the stages model*, certain neuroanatomical areas would have to spontaneously improve, making this model extremely unlikely.

There is limited evidence for *the independence model*. Retrospective research has identified two subgroups within SSD populations; a larger group with relatively little behavioural impairment throughout childhood, and a smaller group which displays early behavioural abnormalities (Corcoran et al., 2003; Rossi, Pollice, Daneluzzo, Marinangeli, & Stratta, 2000). This latter group has been found to have early onset SSD, greater impairment, a more chronic course of illness, and to display more negative symptoms (Myin-Germeys & van Os, 2007; Rossi et al., 2000), and has been suggested as a potential subgroup with a stronger association with ASD (Konstantareas & Hewitt, 2001). Adding support to this suggestion is a study by Goldstein et al. (2002) who classified participants with SSD psychometrically, based on neurocognitive performance, and compared the resulting four SSD subgroups to that of the ASD group. The cognitive profile of ASD was similar to only one SSD group which was characterised by deficits in complex information processing, but intact language and spatial ability. *The independence model* however, would predict just three distinct profiles of disorder; 'pure' ASD, 'pure' SSD, and a third disorder with symptoms of both ASD and SSD. As ASD and

SSD are both highly heterogeneous these kind of clear-cut profiles (as opposed to the multiple profiles predicted by *the multiple overlapping aetiologies model*) seem unlikely.

There is also only very limited evidence for *the multiformity model*, which suggests that the two disorders are different expressions of the same underlying disorder. The high number of individuals with 22q11.2 deletion syndrome who develop ASD and SSD suggests that 22q11.2 deletion syndrome *may* be an example of such an underlying disorder, of which ASD and SSD are two different expressions. On the other hand, individuals with 22q11.2 deletion may develop either ASD or SSD, or both ASD and SSD, but they can also develop neither. This suggests that 22q11.2 deletion syndrome is a vulnerability marker, rather than the underlying disorder itself; only through interaction with other factors (genetic or environmental) will a disorder develop. 22q11.2 deletion syndrome may therefore fit better with *the associated liabilities* or *the multiple overlapping aetiologies model*. The *multiformity model* also fails to explain co-occurrence of ASD and SSD in individuals without specific genetic conditions such as 22q11.2 deletion syndrome. Different brain areas, different environmental risk factors, and different genes are implicated in ASD and SSD, as well as different phenomenology such as age of onset, which Padgett et al. (2010) suggest makes the *multiformity model* extremely unlikely (although see Wang et al. (2015) for an opposing argument). A debate is needed on how many differentiating factors are needed before the underlying risk is considered to lead to an increased chance of developing two possible *disorders*, rather than considered to lead to two different *expressions* of the same disorder.

Evidence is stronger for the *increased vulnerability*, *diametrical*, *associated liabilities*, and *multiple overlapping aetiologies* models. Esterberg et al. (2008) found that although childhood ASD traits were not predictive of transition, they *were* predictive of UHR status, giving support for *the increased vulnerability model's* hypothesis that one disorder may predispose the other. Similarly, longitudinal evidence that psychotic like experiences at age 12 are associated with ASD traits in childhood (Bevan Jones et al., 2012; Sullivan et al., 2013), children diagnosed with ASD are more likely to experience symptoms of psychosis later in life (Joshi et al., 2013; Sullivan et al., 2013), those who develop SSD

often first experience childhood deficits which mimic ASD traits (Dickson et al., 2011) and children diagnosed with ASD are more likely to develop psychosis later in life than their non-diagnosed siblings (Selton, 2015) lends further endorsement to the model. Further support comes from Toal et al.'s (2009) hypothesis that due to the anatomical similarities between individuals with ASD and individuals with SSD, relatively small additional abnormalities or insults to the brain may be required for individuals with ASD to transition to SSD. Taken together, these findings suggest that, at least for a subset of individuals, ASD may represent a pathway into SSD.

Comparative studies lend strong support to *the diametrical model* suggesting that ASD and SSD are associated with opposing genetic relationships as well as opposing effects on observed behaviour and cognition. Central to this model is that ASD and SSD represent the extremes of a social cognition continuum (Abu-Akel & Bailey, 2000; Crespi & Badcock, 2008), wherein ASD is associated with underdeveloped social cognition and SSD (at least in the paranoid type) with a high level of dysfunctional hyper-mentalising, deviating in opposite directions from normality. Recent comparative genomic studies demonstrate that both disorders are associated with genetic risk factors in a pleiotropic manner (Crespi et al., 2010), such that deletion of CNVs predispose the individual to developing one disorder and duplication predisposing the other. Also commensurate with this model are studies showing that ASD and SSD are diametrically opposed in local versus global processing (Russell-Smith et al., 2010), convergent versus divergent thinking (Nettle, 2006), as well as in under- versus over-mentalising (for a review see Frith, 2004). Toal et al's (2009) hypothesis that their comorbid ASD and SSD population had anatomical changes which were more similar to UHR populations than SSD populations also gives some support to *the diametrical model*, which would argue that individuals who experience both SSD and ASD will benefit from the diametrical nature of the disorders. That is, the ASD will cause a deficit in one direction and the SSD in the opposite direction, meaning that those with both SSD and ASD will experience fewer deficits than those with just one of the disorders, although this remains to be more thoroughly investigated.

It seems evident that the disorders do share a high number of shared genetic and environmental risk factors as suggested by *the associated liabilities model*. Evidence from neuroimaging also lends support to this model, although to date, clear evidence is somewhat lacking as to whether the differences seen are neurodevelopmental (present before symptom onset) or neuroprogressive (only develop later: see Olabi et al., 2011 for a meta-analysis of progressive brain changes in SSD). There is also strong evidence for *the multiple overlapping aetiologies model*. While similar in some ways to *the independence model*, *the multiple overlapping aetiologies model* takes into account the highly heterogeneous nature of both disorders. This allows for two distinct disorder profiles to exist, albeit with considerable overlap in some areas. An example of this can be seen in Goldstein et al.'s (2002) four neurocognitive performance profiles of individuals with SSD, only one of which had a similar cognitive profile to those with ASD. Within ASD research the hypothesis that there may be many causal pathways is well acknowledged, with many authors proposing that the idea of 'the autisms' may be a more constructive way to conceptualise ASD than a concept of one unified disorder (Geschwind & Levitt, 2007; Whitehouse & Stanley, 2013). The idea of 'the schizophrenias' may also be a useful construct, with a recent genome-wide association study suggesting that there may be several 'schizophrenias' with genetically distinct causes. Arnedo et al. (2015) found 42 interacting single-nucleotide polymorphism (SNPs) clusters which resulted in several distinct clinical syndromes, all of which met diagnostic criteria for schizophrenia. Cicchetti and Rogosch (1996) discuss multifinality, where the same genotypic network can result in varying clinical outcomes, and equifinality, where different genotypic networks lead to the same clinical outcome. Both multifinality and equifinality are found within complex disorders. It is possible that both may be occurring within ASD and SSD.

6.1 The possibility of subgroups

It is important to note that these models of association are not mutually exclusive. Neither SSD nor ASD are known for their homogenous populations. The *multiple overlapping aetiologies model* hypothesises that subgroups exist within each disorder with diverse developmental pathways, and it is

entirely possible that that different models may apply to different subgroups. It seems likely, for example, that the high number of shared environmental and genetic risk factors does account for at least some of the co-occurrence of the disorders, making *the associated liabilities model* a strong candidate for explaining the co-occurrence. This doesn't preclude the possibility however, that other models may also come into play. For example, certain profiles of disorders, including COS (Padgett et al., 2010), and Multiple Complex Developmental Disorder (Sprong et al., 2008), have been suggested to have a stronger association, suggesting that co-occurrence within these specific subgroups may be accounted for by an additional model, such as *the increased vulnerability model*. This means that *the multiple overlapping aetiologies model, associated liabilities model, and increased vulnerability model* may all co-exist and enhance the co-occurrence of the disorders.

Caution is needed however, as even *within* these subgroups there are additional subgroups, with Rapoport et al. (2009) reporting that rare CNVs are found to a much greater extent in COS participants who have experienced developmental disturbances prior to onset. It is important that the disorders are not simply fractured into smaller and smaller categories as splintering the diagnoses into small and highly specific descriptions may reduce their usefulness. An alternative to this comes from a conceptual version of *the multiple overlapping aetiologies model* wherein Craddock & Owen (2010) hypothesise that the disorders exist on a continua of psychiatric syndromes, which range from a high neurodevelopmental contribution to the illness on one end, to a high degree of affective pathology on the other. Within this model, the clinical classifications of SSD and ASD are adjacent, but dimensionally there is substantial overlap between them, reflecting the shared traits, genetic contributions and other risk factors. This compliments the suggestion that some subgroups may have a stronger neurodevelopmental component (Jones et al., 1994; Jones, Rantakallio, Hartikainen, Isohanni, & Sipila, 1998).

7. Suggestions for future research

Presently no one model can currently be seen as being the 'best fit' for explaining the co-occurrence of ASD and SSD, and further research is therefore needed to establish this. It is important that future

research takes into account the strong evidence for the existence of different subgroups within both disorders. Additionally, subgroups should ideally be defined by multivariate data, rather than pre-specified. Hypotheses need to be investigated for each subgroup individually, as not all models will necessarily apply to all subgroups and heterogeneity may confound true associations. When investigating subgroups it is important to ideally consider evidence on multiple levels, phenotypic as well as genotypic (Arnedo et al., 2015), or to psychometrically identify endophenotypic markers (Goldstein et al., 2002). Similarly, it is important that the dimensional nature of both disorders is taken into account when investigating the association between them. Of the 8 models discussed there is most evidence for *the diametrical model, the associated liabilities model, the multiple overlapping aetiologies model,* and *the increased vulnerability model*. Suggestions for future research investigating these models are provided below.

7.1 *The diametrical model*

The primary prediction of *the diametrical model* is that the two disorders are diametrically opposed. This means that in clinical populations those with co-occurring ASD and SSD, instead of experiencing higher levels of deficit (where the combination of having both disorders creates an additive affect), will experience lower levels of deficit as the diametrical nature of the disorders will ameliorate any difficulties. For example, in the general population, individuals with high traits of ASD and SSD (high/high individuals) do better on social and/or cognitive measures compared to those who have a high level of traits in only one of the disorders (high/low or low/high individuals; Abu-Akel, Wood. Hansen & Apperly, 2014). Research is needed which directly compares individuals with co-morbid ASD and SSD with those who only meet diagnostic criteria for one of the disorders in terms of their phenotypic expression, brain structure and functioning, and genetic architecture. Much of the evidence for the diametrical model comes from comparing individuals with ASD and individuals with paranoid type SSD. Further research is needed to see if the diametrical model may apply to other SSD subtypes.

7.2 *The associated liabilities model*

There are many examples of shared underlying risk or liability between the disorders. *The associated liabilities model* however, is in many ways the polar opposite of *the diametric model*. It may be that the two models are both correct, but for different sub-populations. Research into populations which provide some evidence for *the associated liabilities model*, such as those with 22q11.2 deletion syndrome, will enable a closer evaluation of this model. Phenotypic behaviours in individuals with 22q11.2 deletion syndrome who develop both ASD and SSD (high/high individuals) can help to shed some light on which of these models may be correct. If those with co-morbid ASD and SSD experience the same or additional deficit compared to those with only one disorder then *the associated liabilities model* is supported. Conversely, if deficit is ameliorated in high/high individuals then *the diametrical model* gains support.

7.3 *The multiple overlapping aetiologies model*

The multiple overlapping aetiologies model predicts that there are lots of different subtypes of SSD and ASD, some of which will share aetiologies. Some of these pathways may be diametrically opposed and others due to associated liability or increased vulnerability, so *the multiple overlapping aetiologies model* is not necessarily at odds with the other models of co-occurrence. Research has begun to characterise the phenotypic and genotypic architecture of SSD (e.g. Arnedo et al., 2015), finding multiple 'schizophrenias'. The next step for investigating the co-occurrence of ASD and SSD should be to characterise the phenotypic and genotypic architecture of these disorders together, evaluating endophenotypic markers for both disorders. If characterised in this way, *the multiple overlapping aetiologies model* predicts that some of these disorders will share multiple pathways or markers, whilst others will remain distinct.

7.4 *The increased vulnerability model*

Although clearly not the case in all SSD populations, evidence is suggestive that ASD may represent a pathway into SSD for certain subgroups, including those with COS, Multiple Complex Developmental Disorder, and deficit schizophrenia populations. In contrast to *the associated*

liabilities model, *the increased vulnerability model* hypothesises that it is not the *shared liability* which makes individuals vulnerable to developing both ASD and SSD, but the actual development of ASD itself (or high trait level of ASD) which increases vulnerability for SSD. If this is the case it would be expected that in individuals with known underlying liabilities, SSD should be more common in those who first develop ASD than those who do not. One way to investigate this could be to utilise the finding that the offspring of parents with SSD are at an increased risk of ASD (Larsson et al., 2005; Sullivan et al., 2012). *The increased vulnerability model* would predict that the offspring of parents with SSD who are diagnosed with ASD are at a much higher risk of developing a SSD when older than offspring who are typically developing in childhood. This type of research could be feasible with large population cohorts such as the Swedish or Danish population registers. In addition, *the increased vulnerability model* would predict that those who have ASD and go on to develop SSD would experience either the same or additional deficits compared to those with only ASD *or* SSD, rather than experiencing an ameliorating effect of developing the additional disorder (as predicted by the *diametrical disorder*).

7.5 Limitations of proposed studies

Whilst the proposed studies would provide an excellent starting point to begin investigating potential models underlying the co-occurrence of ASD and SSD, it is important that their limitations are also recognised. Particularly salient is the possibility of models co-existing with each other. If this is the case (and it seems entirely likely that it is) then research such as that proposed above may not be able to definitively identify one particular model whilst ruling out all other models. It is important that future research account for this possibility and, if a particular model seems likely, that investigators attempts to define exactly *what* the model applies to, be it a particular subgroup of individuals (as may be the case with *the increased vulnerability model*) or to certain types of symptoms (as is possible with *the diametric model*). It is also important that research differentiate between traits of ASD, which should remain stable, and early or prodromal signs of SSD, which are unlikely to be stable (i.e. may develop after 2 years of age and may worsen over time, or go into remission).

A further complication comes from the co-occurrence of both ASD and SSD with other disorders. Bi-polar disorder for example, for which there is evidence of an overlap with SSD (Möller, 2003), also co-occurs above chance level with ASD, with rates ranging from 6% to 21.4% (Vannucchi, 2014). If considering the co-occurrence of multiple disorders, rather than just two disorders, the complexity of the issue multiplies significantly.

8. Conclusions

It is becoming increasingly evident that it is necessary to prospectively investigate the co-occurrence of, and commonalities between SSD and ASD at the trait level using multi-factorial data from large samples. Undiagnosed co-occurring disorders may result in individuals not receiving appropriate services, benefits, or treatment, and given the similarities between disorders, misdiagnosis is possible (Davidson et al., 2014; Wing, 1981a). It is important that future research account for the heterogeneity of both disorders, and examine evidence on multiple levels to identify endophenotypic markers, as well as taking the dimensional nature of the disorders into consideration. Together, these approaches can provide an important conceptual framework for understanding the association between ASD and SSD. This in turn may lead towards the development of a fundamental understanding of the two disorders.

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References

Abdi, Z., & Sharma, T. (2004). Social cognition and its neural correlates in schizophrenia and autism. *CNS spectrums, 9*, 335-343.

Abu-Akel, A., & Bailey, A. L. (2000). Letter. *Psychological Medicine, 30*(03), 735-738. doi: doi:null

Abu-Akel, A., Wood, S., Hansen, P., & Apperly, I. 2014. Perspective-taking abilities in the balance between autism tendencies and psychosis proneness. Schizophrenia Research, 153 (Suppl. 1): 289.

Arnedo, J., Svrakic, D. M., del Val, C., Romero-Zaliz, R., Hernández-Cuervo, H., Fanous, A. H., . . . Cloninger, C. R. (2015). Uncovering the Hidden Risk Architecture of the Schizophrenias: Confirmation in Three Independent Genome-Wide Association Studies. *American Journal of Psychiatry*. 1;172(2):139-53.

Association, A. P. (1994). *DSM-IV: Diagnositic and Statistical Manual of Mental Disorders.* (4th ed.). Washington, DC: The Association.

Atladottir, H. O., Thorsen, P., Ostergaard, L., Schendel, D. E., Lemcke, S., Abdallah, M., & Parner, E. T. (2010). Maternal Infection Requiring Hospitalization During Pregnancy and Autism Spectrum Disorders. *Journal of autism and developmental disorders, 40*(12), 1423-1430. doi: 10.1007/s10803-010-1006-y

Baio, J. (2010). Prevalence of Autism Spectrum Disorder Among Children Aged 8 Years — Autism and Developmental Disabilities Monitoring Network, 11 Sites, United States. *Centers for Disease Control and Prevention*.

Bakken, T. L., Helverschou, S. B., Eilertsen, D. E., Heggelund, T., Myrbakk, E., & Martinsen, H. (2010). Psychiatric disorders in adolescents and adults with autism and intellectual disability: A representative study in one county in Norway. *Research in Developmental Disabilities, 31*(6), 1669-1677. doi: 10.1016/j.ridd.2010.04.009

Baribeau, D. A., & Anagnostou, E. (2013). A comparison of neuroimaging findings in childhood onset schizophrenia and autism spectrum disorder: a review of the literature. *Frontiers in psychiatry, 4*.

Barneveld, P. S., Pieterse, J., de Sonneville, L., van Rijn, S., Lahuis, B., van Engeland, H., & Swaab, H. (2011). Overlap of autistic and schizotypal traits in adolescents with Autism Spectrum Disorders. *Schizophrenia Research, 126*(1-3), 231-236.

Baron-Cohen, S., Leslie, A. M., & Frith, U. (1985). Does the autistic child have a "theory of mind"? *Cognition, 21*(1), 37-46.

Bearden, C. E., Rosso, I. M., Hollister, J. M., Sanchez, L. E., Hadley, T., & Cannon, T. D. (2000). A prospective cohort study of childhood behavioral deviance and language abnormalities as predictors of adult schizophrenia. *Schizophrenia Bulletin, 26*(2), 395-410.

Bender, L. (1947). Childhood schizophrenia. *American Journal of Orthopsychiatry, 17*(1), 40-56.

Bevan Jones, R., Thapar, A., Lewis, G., & Zammit, S. (2012). The association between early autistic traits and psychotic experiences in adolescence. *Schizophrenia Research, 135*, 164-169.

Billstedt, E., Gillberg, C., & Gillberg, C. (2005). Autism after adolescence: Population-based 13- to 22-year follow-up study of 120 individuals with autism diagnosed in childhood. *Journal of Autism and Developmental Disorders, 35*(3), 351-360. doi: 10.1007/s10803-005-3302-5

Bishop, D. (2010). Overlaps between autism and language impairment: phenomimicry or shared etiology? *Behavior genetics, 40*(5), 618-629.

Bleuler, E. (1950). Dementia praecox or the group of schizophrenias.

Bloemen, O. J., Deeley, Q., Sundram, F., Daly, E. M., Barker, G. J., Jones, D. K., . . . Murphy, K. C. (2010). White matter integrity in Asperger syndrome: a preliminary diffusion tensor magnetic resonance imaging study in adults. *Autism Research, 3*(5), 203-213.

Bora, E., Yucel, M., & Pantelis, C. (2009). Theory of mind impairment in schizophrenia: meta-analysis. *Schizophrenia Research, 109*(1), 1-9.

Brito, A. R., Vasconcelos, M. M., Domingues, R. C., da Cruz Jr, H., Celso, L., Rodrigues, L. d. S., . . . Calçada, C. A. B. P. (2009). Diffusion Tensor Imaging Findings in School-Aged Autistic Children. *Journal of Neuroimaging, 19*(4), 337-343.

Brown, A. S., Begg, M. D., Gravenstein, S., Schaefer, C. A., Wyatt, R. J., Bresnahan, M., . . . Susser, E. S. (2004). Serologic-evidence of prenatal influenza in the etiology of schizophrenia. *Archives of general psychiatry, 61*(8), 774-780. doi: 10.1001/archpsyc.61.8.774

Brugha, T. S., McManus, S., Bankart, J., Scott, F., Purdon, S., Smith, J., . . . Meltzer, H. (2011). Epidemiology of autism spectrum disorders in adults in the community in England. *Archives of general psychiatry, 68*(5), 459-465.

Brüne, M. (2005). "Theory of mind" in schizophrenia: A review of the literature. *Schizophrenia Bulletin, 31*(1), 21-42.

Cannell, J. J. (2008). Autism and vitamin D. *Medical Hypotheses, 70*(4), 750-759. doi: 10.1016/j.mehy.2007.08.016

Cannon, M., Caspi, A., Moffitt, T. E., Harrington, H., Taylor, A., Murray, R. M., & Poulton, R. (2002). Evidence for early-childhood, pan-developmental impairment specific to schizophreniform disorder: results from a longitudinal birth cohort. *Archives of general psychiatry, 59*(5), 449-456.

Cannon, M., Jones, P. B., & Murray, R. M. (2002). Obstetric complications and schizophrenia: Historical and meta-analytic review. *American Journal of Psychiatry, 159*(7), 1080-1092. doi: 10.1176/appi.ajp.159.7.1080

Cantor-Graae, E., & Selten, J. P. (2005). Schizophrenia and migration: A meta-analysis and review. *American Journal of Psychiatry, 162*(1), 12-24. doi: 10.1176/appi.ajp.162.1.12

Cardno, A. G., & Gottesman, I. I. (2000). Twin studies of schizophrenia: from bow-and-arrow concordances to star wars Mx and functional genomics. *American journal of medical genetics, 97*(1), 12-17.

Carroll, L. S., & Owen, M. J. (2009). Genetic overlap between autism, schizophrenia and bipolar disorder. *Genome Med, 1*(10), 102.

Cartier, E., Hamilton, P.J., Belovich, A.N., Shekar, A., Campbell, N.G., et al. (2015). Rare autism-associated variants implicate syntaxin 1 (STX1 R26Q) phosphorylation and the dopamine transporter (hDAT R51W) in dopamine neurotransmission and behaviors. *EBioMedicine* 2: 135-46

Cheung, C., Yu, K., Fung, G., Leung, M., Wong, C., Li, Q., . . . McAlonan, G. (2010). Autistic disorders and schizophrenia: related or remote? An anatomical likelihood estimation. *PLoS One, 5*(8), e12233.

Chung, Y. S., Barch, D., & Strube, M. (2013). A meta-analysis of mentalizing impairments in adults with schizophrenia and autism spectrum disorder. *Schizophrenia Bulletin*, sbt048.

Ciaramidaro, A., Bölte, S., Schlitt, S., Hainz, D., Poustka, F., Weber, B., . . . Walter, H. (2014). Schizophrenia and Autism as Contrasting Minds: Neural Evidence for the Hypo-Hyper-Intentionality Hypothesis. *Schizophrenia Bulletin*, sbu124.

Cicchetti, D., & Rogosch, F. A. (1996). Equifinality and multifinality in developmental psychopathology. *Development and Psychopathology, 8*(04), 597-600.

Consortium, C.-D. G. o. t. P. G. (2013). Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs. *Nature genetics, 45*(9), 984-994.

Cooper, S. A. (1997). Psychiatry of elderly compared to younger adults with intellectual disabilities. *Journal of Applied Research in Intellectual Disabilities, 10*(4), 303-311.

Corcoran, C., Davidson, L., Sills-Shahar, R., Nickou, C., Malaspina, D., Miller, T., & McGlashan, T. (2003). A qualitative research study of the evolution of symptoms in individuals identified as prodromal to psychosis. *Psychiatric quarterly, 74*(4), 313-332.

Courchesne, E., & Pierce, K. (2005). Why the frontal cortex in autism might be talking only to itself: local over-connectivity but long-distance disconnection. *Current opinion in neurobiology, 15*(2), 225-230.

Craddock, N., & Owen, M. J. (2010). The Kraepelinian dichotomy–going, going... but still not gone. *The British Journal of Psychiatry, 196*(2), 92-95.

Crespi, B., & Badcock, C. (2008). Psychosis and autism as diametrical disorders of the social brain. *Behavioral and Brain Sciences, 31*(03), 241-261.

Crespi, B., Stead, P., & Elliot, M. (2010). Comparative genomics of autism and schizophrenia. *Proceedings of the National Academy of Sciences, 107*(suppl 1), 1736-1741.

Daniels, J. L., Forssen, U., Hultman, C. M., Cnattingius, S., Savitz, D. A., Feychting, M., & Sparen, P. (2008). Parental psychiatric disorders associated with autism spectrum disorders in the offspring. *Pediatrics, 121*(5), e1357-e1362.

Davidson, C., Greenwood, N., Stansfield, A., & Wright, S. (2014). Prevalence of Asperger syndrome among patients of an Early Intervention in Psychosis team. *Early Intervention in Psychiatry, 8*(2), 138-146. doi: 10.1111/eip.12039

Davis, K. L., Stewart, D. G., Friedman, J. I., Buchsbaum, M., Harvey, P. D., Hof, P. R., . . . Haroutunian, V. (2003). White matter changes in schizophrenia: evidence for myelin-related dysfunction. *Archives of general psychiatry, 60*(5), 443.

Dealberto, M. J. (2011). Prevalence of autism according to maternal immigrant status and ethnic origin. *Acta Psychiatrica Scandinavica, 123*(5), 339-348. doi: 10.1111/j.1600-0447.2010.01662.x

Devlin, B., Melhem, N., & Roeder, K. (2011). Do common variants play a role in risk for autism? Evidence and theoretical musings. *Brain research, 1380*, 78-84.

Dickson, H., Laurens, K., Cullen, A., & Hodgins, S. (2011). Meta-analyses of cognitive and motor function in youth aged 16 years and younger who subsequently develop schizophrenia. *Psychological Medicine, 1*(1), 1-13.

Eack, S. M., Bahorik, A. L., McKnight, S. A., Hogarty, S. S., Greenwald, D. P., Newhill, C. E., . . . Minshew, N. J. (2013). Commonalities in social and non-social cognitive impairments in adults with autism spectrum disorder and schizophrenia. *Schizophrenia Research, 148*(1), 24-28.

Eaves, L. C., & Ho, H. H. (2008). Young adult outcome of autism spectrum disorders. *Journal of Autism and Developmental Disorders, 38*(4), 739-747. doi: 10.1007/s10803-007-0441-x

Ellison-Wright, I., & Bullmore, E. (2009). Meta-analysis of diffusion tensor imaging studies in schizophrenia. *Schizophrenia Research, 108*(1), 3-10.

Esterberg, M. L., Trotman, H. D., Brasfield, J. L., Compton, M. T., & Walker, E. F. (2008). Childhood and current autistic features in adolescents with schizotypal personality disorder. *Schizophrenia Research, 104*(1), 265-273.

Fish, B., Marcus, J., Hans, S., Auerbach, J., & Perdue, S. (1992). Infants at risk for schizophrenia: sequelae of a genetic neurointergrative defect. *Archives of general psychiatry, 49*, 221-235.

Folstein, S., & Rutter, M. (1977). Infantile autism: a genetic study of 21 twin pairs. *Journal of Child Psychology and Psychiatry, 18*(4), 297-321.

Freitag, C. M. (2006). The genetics of autistic disorders and its clinical relevance: a review of the literature. *Molecular psychiatry, 12*(1), 2-22.

Gardener, H., Spiegelman, D., & Buka, S. L. (2009). Prenatal risk factors for autism: comprehensive meta-analysis. *British Journal of Psychiatry, 195*(1), 7-14. doi: 10.1192/bjp.bp.108.051672

Geschwind, D. H., & Levitt, P. (2007). Autism spectrum disorders: developmental disconnection syndromes. *Current opinion in neurobiology, 17*(1), 103-111.

Goldstein, G., Minshew, N. J., Allen, D. N., & Seaton, B. E. (2002). High-functioning autism and schizophrenia: a comparison of an early and late onset neurodevelopmental disorder. *Archives of Clinical Neuropsychology, 17*(5), 461-475.

Grant, W. B., & Soles, C. M. (2009). Epidemiologic evidence for supporting the role of maternal vitamin D deficiency as a risk factor for the development of infantile autism. *Dermato-endocrinology, 1*(4), 223-228.

Hallerback, M. U., Lugnegard, T., & Gillberg, C. (2012). Is autism spectrum disorder common in schizophrenia? *Psychiatry Research, 198*(1), 12-17. doi: 10.1016/j.psychres.2012.01.016

Hamlyn, J., Duhig, M., McGrath, J., & Scott, J. (2013). Modifiable risk factors for schizophrenia and autism - Shared risk factors impacting on brain development. *Neurobiology of Disease, 53*, 3-9. doi: 10.1016/j.nbd.2012.10.023

Hao, Y., Liu, Z., Jiang, T., Gong, G., Liu, H., Tan, L., . . . Zhang, Z. (2006). White matter integrity of the whole brain is disrupted in first-episode schizophrenia. *Neuroreport, 17*(1), 23-26.

Hérault, J., Martineau, J., Perrot-Beaugerie, A., Jouve, J., Tournade, H., Barthelemy, C., . . . Muh, J.-P. (1993). Investigation of whole blood and urine monoamines in autism. *European Child & Adolescent Psychiatry, 2*(4), 211-220.

Hoek, H. W., Susser, E., Buck, K. A., Lumey, L. H., Lin, S. P., & Gorman, J. M. (1996). Schizoid personality disorder after prenatal exposure to famine. *American Journal of Psychiatry, 153*(12), 1637-1639.

Hofvander, B., Delorme, R., Chaste, P., Nyden, A., Wentz, E., Stahlberg, O., . . . Leboyer, M. (2009). Psychiatric and psychosocial problems in adults with normal-intelligence autism spectrum disorders. *Bmc Psychiatry, 9*. doi: 10.1186/1471-244x-9-35

Howes, O. D., & Kapur, S. (2009). The dopamine hypothesis of schizophrenia: version III—the final common pathway. *Schizophrenia Bulletin, 35*(3), 549-562.

Hultman, C., Sandin, S., Levine, S., Lichtenstein, P., & Reichenberg, A. (2011). Advancing paternal age and risk of autism: new evidence from a population-based study and a meta-analysis of epidemiological studies. *Molecular psychiatry, 16*(12), 1203-1212.

Job, D. E., Whalley, H. C., Johnstone, E. C., & Lawrie, S. M. (2005). Grey matter changes over time in high risk subjects developing schizophrenia. *Neuroimage, 25*(4), 1023-1030.

Jones, P., Rodgers, B., Murray, R., & Marmot, M. (1994). Child developmental risk factors for adult schizophrenia in the British 1946 birth cohort. *The Lancet, 344*(8934), 1398-1402.

Jones, P. B., Rantakallio, P., Hartikainen, A.-L., Isohanni, M., & Sipila, P. (1998). Schizophrenia as a long-term outcome of pregnancy, delivery, and perinatal complications: a 28-year follow-up of the 1966 north Finland general population birth cohort. *American Journal of Psychiatry, 155*(3), 355-364.

Joshi, G., Petty, C., Wozniak, J., Henin, A., Fried, R., Galdo, M., . . . Biederman, J. (2010). The Heavy Burden of Psychiatric Comorbidity in Youth with Autism Spectrum Disorders: A Large Comparative Study of a Psychiatrically Referred Population. *Journal of Autism and Developmental Disorders, 40*(11), 1361-1370. doi: 10.1007/s10803-010-0996-9

Joshi, G., Wozniak, J., Petty, C., Martelon, M. K., Fried, R., Bolfek, A., . . . Bourgeois, M. (2013). Psychiatric comorbidity and functioning in a clinically referred population of adults with autism spectrum disorders: a comparative study. *Journal of autism and developmental disorders, 43*(6), 1314-1325.

Just, M. A., Keller, T. A., Malave, V. L., Kana, R. K., & Varma, S. (2012). Autism as a neural systems disorder: a theory of frontal-posterior underconnectivity. *Neuroscience & Biobehavioral Reviews, 36*(4), 1292-1313.

Kendler, K. S., Gallagher, T. J., Abelson, J. M., & Kessler, R. C. (1996). Lifetime prevalence, demographic risk factors, and diagnostic validity of nonaffective psychosis as assessed in a US community sample: the National Comorbidity Survey. *Archives of general psychiatry, 53*(11), 1022-1031.

Kočovská, E., Fernell, E., Billstedt, E., Minnis, H., & Gillberg, C. (2012). Vitamin D and autism: clinical review. *Research in Developmental Disabilities, 33*(5), 1541-1550.

Kolvin, I. (1971). Studies in the childhood psychoses: I. Diagnostic criteria and classification. *British Journal of Psychiatry, 118*(545), 381-384.

Konstantareas, M. M., & Hewitt, T. (2001). Autistic disorder and schizophrenia: diagnostic overlaps. *Journal of autism and developmental disorders, 31*(1), 19-28.

Kraemer, H. C. (1995). Statistical issues in assessing comorbidity. *Statistics in Medicine, 14*(8), 721-733.

Krueger, R. F., & Markon, K. E. (2006). Reinterpreting comorbidity: A model-based approach to understanding and classifying psychopathology. *Annual review of clinical psychology, 2*, 111.

Larsson, H. J., Eaton, W. W., Madsen, K. M., Vestergaard, M., Olesen, A. V., Agerbo, E., . . . Mortensen, P. B. (2005). Risk factors for autism: perinatal factors, parental psychiatric history, and socioeconomic status. *American Journal of Epidemiology, 161*(10), 916-925.

Lauritsen, M. B., Astrup, A., Pedersen, C. B., Obel, C., Schendel, D. E., Schieve, L., . . . Parner, E. T. (2014). Urbanicity and autism spectrum disorders. *Journal of Autism and Developmental Disorders, 44*(2), 394-404.

Lauritsen, M. B., Pedersen, C. B., & Mortensen, P. B. (2005). Effects of familial risk factors and place of birth on the risk of autism: A nationwide register-based study. *Journal of Child Psychology and Psychiatry, 46*(9), 963-971. doi: 10.1111/j.1469-7610.2004.00391.x

Li, X., Sjöstedt, C., Sundquist, K., Zöller, B., & Sundquist, J. (2014). Neighborhood deprivation and childhood autism: A nationwide study from Sweden. *Journal of psychiatric research, 53*, 187-192.

Lionel, A. C., Vaags, A. K., Sato, D., Gazzellone, M. J., Mitchell, E. B., Chen, H. Y., . . . Thiruvahindrapuram, B. (2013). Rare exonic deletions implicate the synaptic organizer Gephyrin (GPHN) in risk for autism, schizophrenia and seizures. *Human molecular genetics, 22*(10), 2055-2066.

Lugnegard, T., Hallerback, M. U., & Gillberg, C. (2011). Psychiatric comorbidity in young adults with a clinical diagnosis of Asperger syndrome. *Research in Developmental Disabilities, 32*(5), 1910-1917. doi: 10.1016/j.ridd.2011.03.025

Magnusson, C., Rai, D., Goodman, A., Lundberg, M., Idring, S., Svensson, A., . . . Dalman, C. (2012). Migration and autism spectrum disorder: population-based study. *The British Journal of Psychiatry, 201*(2), 109-115.

Marcelis, M., Navarro-Mateu, F., Murray, R., Selten, J. P., & van Os, J. (1998). Urbanization and psychosis: a study of 1942-1978 birth cohorts in The Netherlands. *Psychological Medicine, 28*(4), 871-879. doi: 10.1017/s0033291798006898

McCarthy, S. E., Makarov, V., Kirov, G., Addington, A. M., McClellan, J., Yoon, S., . . . Krastoshevsky, O. (2009). Microduplications of 16p11. 2 are associated with schizophrenia. *Nature genetics, 41*(11), 1223-1227.

McCormick, L. M., Brumm, M. C., Beadle, J. N., Paradiso, S., Yamada, T., & Andreasen, N. (2012). Mirror neuron function, psychosis, and empathy in schizophrenia. *Psychiatry Research: Neuroimaging, 201*(3), 233-239.

McGrath, J. J., Burne, T. H., Féron, F., Mackay-Sim, A., & Eyles, D. W. (2010). Developmental vitamin D deficiency and risk of schizophrenia: a 10-year update. *Schizophrenia Bulletin*, sbq101.

McGrath, J. J., Eyles, D. W., Pedersen, C. B., Anderson, C., Ko, P., Burne, T. H., . . . Mortensen, P. B. (2010). Neonatal Vitamin D Status and Risk of Schizophrenia A Population-Based Case-Control Study. *Archives of general psychiatry, 67*(9), 889-894.

McGrath, J. J., Petersen, L., Agerbo, E., Mors, O., Mortensen, P., & Pedersen, C. (2014). A comprehensive assessment of parental age and psychiatric disorders. *JAMA Psychiatry, 71*(3), 301-309. doi: 10.1001/jamapsychiatry.2013.4081

Miller, B., Messias, E., Miettunen, J., Alaraeisaenen, A., Jaervelin, M.-R., Koponen, H., . . . Kirkpatrick, B. (2011). Meta-analysis of Paternal Age and Schizophrenia Risk in Male Versus Female Offspring. *Schizophrenia Bulletin, 37*(5), 1039-1047. doi: 10.1093/schbul/sbq011

Möller, H. J. (2003). Bipolar disorder and schizophrenia: distinct illnesses or a continuum?. The Journal of clinical psychiatry, (64 Suppl 6), 23-7.

Moreno-De-Luca, D., Mulle, J. G., Kaminsky, E. B., Sanders, S. J., Myers, S. M., Adam, M. P., . . . Weik, L. (2010). Deletion 17q12 is a recurrent copy number variant that confers high risk of autism and schizophrenia. *The American Journal of Human Genetics, 87*(5), 618-630.

Morgan, V. A., Leonard, H., Bourke, J., & Jablensky, A. (2008). Intellectual disability co-occurring with schizophrenia and other psychiatric illness: population-based study. *The British Journal of Psychiatry, 193*(5), 364-372.

Mortensen, P. B., Pedersen, C. B., Westergaard, T., Wohlfahrt, J., Ewald, H., Mors, O., . . . Melbye, M. (1999). Effects of family history and place and season of birth on the risk of schizophrenia. *New England Journal of Medicine, 340*(8), 603-608. doi: 10.1056/nejm199902253400803

Mouridsen, S., Rich, B., & Isager, T. (2008). Psychiatric disorders in adults diagnosed as children with atypical autism. A case control study. *Journal of Neural Transmission, 115*(1), 135-138.

Mouridsen, S. E., Rich, B., & Isager, T. (2008). Epilepsy and other neurological diseases in the parents of children with infantile autism. A case control study. *Child Psychiatry & Human Development, 39*(1), 1-8. doi: 10.1007/s10578-007-0062-9

Muck-Seler, D., Pivac, N., Mustapic, M., Crncevic, Z., Jakovljevic, M., & Sagud, M. (2004). Platelet serotonin and plasma prolactin and cortisol in healthy, depressed and schizophrenic women. *Psychiatry Research, 127*(3), 217-226.

Mueller, S., Keeser, D., Reiser, M., Teipel, S., & Meindl, T. (2012). Functional and structural MR imaging in neuropsychiatric disorders, part 2: application in schizophrenia and autism. *American journal of neuroradiology, 33*(11), 2033-2037.
Myin-Germeys, I., & van Os, J. (2007). Stress-reactivity in psychosis: evidence for an affective pathway to psychosis. *Clinical Psychology Review, 27*(4), 409-424.
Nakamura, K., Sekine, Y., Ouchi, Y., Tsujii, M., Yoshikawa, E., Futatsubashi, M., . . . Suzuki, K. (2010). Brain serotonin and dopamine transporter bindings in adults with high-functioning autism. *Archives of General Psychiatry, 67*(1), 59-68.
Nieminen-von Wendt, T. S., Metsähonkala, L., Kulomäki, T. A., Aalto, S., Autti, T. H., Vanhala, R., . . . von Wendt, L. O. (2004). Increased presynaptic dopamine function in Asperger syndrome. *Neuroreport, 15*(5), 757-760.
Oberman, L. M., Hubbard, E. M., McCleery, J. P., Altschuler, E. L., Ramachandran, V. S., & Pineda, J. A. (2005). EEG evidence for mirror neuron dysfunction in autism spectrum disorders. *Cognitive Brain Research, 24*(2), 190-198.
Ochoa, S., Usall, J., Cobo, J., Labad, X., & Kulkarni, J. (2012). Gender differences in schizophrenia and first-episode psychosis: a comprehensive literature review. *Schizophrenia research and treatment, 2012*.
Olabi, B., Ellison-Wright, I., McIntosh, A. M., Wood, S. J., Bullmore, E., & Lawrie, S. M. (2011). Are there progressive brain changes in schizophrenia? A meta-analysis of structural magnetic resonance imaging studies. *Biological psychiatry, 70*(1), 88-96.
Padgett, F. E., Miltsiou, E., & Tiffin, P. A. (2010). The co-occurrence of nonaffective psychosis and the pervasive developmental disorders: A systematic review. *Journal of Intellectual and Developmental Disability, 35*(3), 187-198.
Pantelis, C., Velakoulis, D., McGorry, P., Wood, S., Suckling, J., Phillips, L., . . . McGuire, P. (2003). Neuroanatomical abnormalities before and after onset of psychosis: a cross-sectional and longitudinal MRI comparison. *The Lancet, 361*(9354), 281.
Prevention, C. f. D. C. a. (2012). Prevalence of Autism Spectrum Disorders - autism and developmental disabilities monotoring network, 14 sites, United States, 2008. *MMWR Surveill Summ*(61(3)), 19.
Radeloff, D., Ciaramidaro, A., Siniatchkin, M., Hainz, D., Schlitt, S., Weber, B., . . . Freitag, C. M. (2014). Structural Alterations of the Social Brain: A Comparison between Schizophrenia and Autism. *Plos One, 9*(9), e106539.
Rapoport, J., Chavez, A., Greenstein, D., Addington, A., & Gogtay, N. (2009). Autism spectrum disorders and childhood-onset schizophrenia: clinical and biological contributions to a relation revisited. *Journal of the American Academy of Child & Adolescent Psychiatry, 48*(1), 10-18.
Roseboom, T. J., Painter, R. C., van Abeelen, A. F. M., Veenendaal, M. V. E., & de Rooij, S. R. (2011). Hungry in the womb: What are the consequences? Lessons from the Dutch famine. *Maturitas, 70*(2), 141-145. doi: 10.1016/j.maturitas.2011.06.017
Rossi, A., Pollice, R., Daneluzzo, E., Marinangeli, M., & Stratta, P. (2000). Behavioral neurodevelopment abnormalities and schizophrenic disorder: a retrospective evaluation with the Childhood Behavior Checklist (CBCL). *Schizophrenia Research, 44*(2), 121-128.
Rutter, M. (1972). Childhood schizophrenia reconsidered. *Journal of autism and developmental disorders, 2*(3), 315-337.
Sandin, S., Lichtenstein, P., Kuja-Halkola, R., Larsson, H., Hultman, C. M., & Reichenberg, A. (2014). The familial risk of autism. *JAMA, 311*(17), 1770-1777.
Schneider, M., Debbané, M., Bassett, A. S., Chow, E. W., Fung, W. L. A., van den Bree, M. B., . . . Kates, W. R. (2014). Psychiatric Disorders From Childhood to Adulthood in 22q11. 2 Deletion Syndrome: Results From the International Consortium on Brain and Behavior in 22q11. 2 Deletion Syndrome. *American Journal of Psychiatry, 171*(6), 627-639.
Selton, J. P. L., M. Rai, D. Magnusson. (2015). Risks for Nonaffective Psychotic Disorder and Bipolar Disorder in Young People With Autism Spectrum Disorder: A Population-Based Study. *Jama Psychiatry*.
Shenton, M. E., Dickey, C. C., Frumin, M., & McCarley, R. W. (2001). A review of MRI findings in schizophrenia. *Schizophrenia Research, 49*(1), 1-52.

Solomon, M., Olsen, E., Niendam, T., Ragland, J. D., Yoon, J., Minzenberg, M., & Carter, C. S. (2011). From lumping to splitting and back again: Atypical social and language development in individuals with clinical-high-risk for psychosis, first episode schizophrenia, and autism spectrum disorders. *Schizophrenia Research, 131*(1-3), 146-151.

Spek, A. A., & Wouters, S. G. M. (2010). Autism and schizophrenia in high functioning adults: Behavioral differences and overlap. *Research in Autism Spectrum Disorders, 4*(4), 709-717. doi: 10.1016/j.rasd.2010.01.009

Sporn, A. L., Addington, A. M., Gogtay, N., Ordoñez, A. E., Gornick, M., Clasen, L., . . . Lenane, M. (2004). Pervasive developmental disorder and childhood-onset schizophrenia: comorbid disorder or a phenotypic variant of a very early onset illness? *Biological psychiatry, 55*(10), 989-994.

Sprong, M., Becker, H., Schothorst, P., Swaab, H., Ziermans, T., Dingemans, P., . . . van Engeland, H. (2008). Pathways to psychosis: A comparison of the pervasive developmental disorder subtype Multiple Complex Developmental Disorder and the. *Schizophrenia Research, 99*(1-3), 38-47.

Stahlberg, O., Soderstrom, H., Rastam, M., & Gillberg, C. (2004). Bipolar disorder, schizophrenia, and other psychotic disorders in adults with childhood onset AD/HD and/or autism spectrum disorders. *Journal of Neural Transmission, 111*(7), 891-902.

Stone, J. M., Morrison, P. D., & Pilowsky, L. S. (2007). Review: Glutamate and dopamine dysregulation in schizophrenia—a synthesis and selective review. *Journal of Psychopharmacology, 21*(4), 440-452.

Sugranyes, G., Kyriakopoulos, M., Corrigall, R., Taylor, E., & Frangou, S. (2011). Autism spectrum disorders and schizophrenia: meta-analysis of the neural correlates of social cognition. *PLoS One, 6*(10), e25322.

Sullivan, P. F., Magnusson, C., Reichenberg, A., Boman, M., Dalman, C., Davidson, M., . . . Långström, N. (2012). Family History of Schizophrenia and Bipolar Disorder as Risk Factors for AutismFamily History of Psychosis as Risk Factor for ASD. *Archives of general psychiatry, 69*(11), 1099-1103.

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. e802.

Toal, F., Bloemen, O. J. N., Deeley, Q., Tunstall, N., Daly, E. M., Page, L., . . . Murphy, D. G. M. (2009). Psychosis and autism: magnetic resonance imaging study of brain anatomy. *The British Journal of Psychiatry, 194*(5), 418-425.

van Os, J., Hanssen, M., Bijl, R. V., & Ravelli, A. (2000). Strauss (1969) revisited: a psychosis continuum in the general population? *Schizophrenia Research, 45*(1), 11-20.

van Os, J., Hanssen, M., Bijl, R. V., & Vollebergh, W. (2001). Prevalence of psychotic disorder and community level of psychotic symptoms: an urban–rural comparison. *Archives of general psychiatry, 58*, 663– 668.

Vannucchi, G., Masi, G., Toni, C., Dell, L., Erfurth, A., & Perugi, G. (2014). Bipolar disorder in adults with Asperger′ s Syndrome: A systematic review.Journal of affective disorders, 168, 151-160.

Volkmar, F. R., & Cohen, D. J. (1991). Comorbid association of autism and schizophrenia. *The American Journal of Psychiatry*.

Vorstman, J. A., Anney, R. J., Derks, E. M., Gallagher, L., Gill, M., de Jonge, M. V., . . . Ophoff, R. A. (2013). No evidence that common genetic risk variation is shared between schizophrenia and autism. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics, 162*(1), 55-60.

Vorstman, J. A. S., Breetvelt, E. J., Thode, K. I., Chow, E. W. C., & Bassett, A. S. (2013). Expression of autism spectrum and schizophrenia in patients with a 22q11.2 deletion. *Schizophrenia Research, 143*(1), 55-59. doi: 10.1016/j.schres.2012.10.010

Wang, H. G., Jeffries, J. J., & Wang, T. F. (2015). Genetic and Developmental Perspective of Language Abnormality in Autism and Schizophrenia One Disease Occurring at Different Ages in Humans? *The Neuroscientist*, 1073858415572078.

Waris, P., Lindberg, N., Kettunen, K., & Tani, P. (2013). The relationship between Asperger's syndrome and schizophrenia in adolescence. *European Child & Adolescent Psychiatry, 22*(4), 217-223. doi: 10.1007/s00787-012-0338-x

Weiss, L. A., Shen, Y., Korn, J. M., Arking, D. E., Miller, D. T., Fossdal, R., . . . Green, T. (2008). Association between microdeletion and microduplication at 16p11. 2 and autism. *New England Journal of Medicine, 358*(7), 667-675.

Whitehouse, A. J., & Stanley, F. J. (2013). Is autism one or multiple disorders. *Med. J. Aust, 28*, 302-303.

Wing, L. (1981a). Asperger's syndrome: a clinical account. *Psychological Medicine*.

Wing, L. (1981b). Sex ratios in early childhood autism and related conditions. *Psychiatry Research, 5*(2), 129-137.

Winton-Brown, T. T., Fusar-Poli, P., Ungless, M. A., & Howes, O. D. (2014). Dopaminergic basis of salience dysregulation in psychosis. *Trends in neurosciences, 37*(2), 85-94.