Autism and schizophrenia: Are they on the same spectrum?

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Special topic

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Introduction

With the recent publication of the DSM-5 (American Psychiatric Association, 2013) and the current process of revision of the ICD-10 (World Health Organization, 1992), the diagnostic criteria and characteristics of several mental disorders have been reconsidered and overlaps have been examined. As new evidence of commonalities and differences between illnesses becomes available, the boundaries around the different conditions are discussed and redrawn. Despite the utility of classifying patterns of symptoms for diagnostic and treatment purposes (Bourgeois, 1995), the process of identifying categories of separate disorders is not a straightforward exercise. Mercier (1980) has expressed:

The more and more numerous the cases of insanity that I have had to deal with, the more strongly the fact has impressed itself upon me that it is fruitless to endeavor to draw up an elaborate scheme of classes, orders, and genera, into which cases of insanity are to be grouped. No such divisions exist in nature, and to create them would be a highly artificial proceeding, and one that would not accurately represent the facts. (p. 284)

Thus, as evident by the different editions of the DSM, throughout the years new labels and classifications have been created for disorders that were once thought to have common causes and symptoms, and vice versa, conditions that were believed to be separate proved to overlap (King & Lord, 2010). For instance, recent research suggested an interrelation between schizophrenia and autism spectrum disorder (Gadow, 2012).
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Autism is a neurodevelopmental disorder characterised mainly by impairments in social interaction and communication, and restricted or repetitive behaviour (Unenge Hallerback, Lugnegard, & Gillberg, 2012), with onset generally before three years of age (Volkmar & Pauls, 2003). Schizophrenia is a psychotic disorder involving a constellation of positive (e.g., delusions, hallucinations, disorganised speech, disorganised or catatonic behaviour) and negative symptoms (e.g., affective flattening, alogia and avolition) associated with an impairment in social or occupational functioning (American Psychiatric Association, 2000), with onset generally in late adolescence or early adulthood (Sheitman, Bilder, Alvir, & Lieberman, 1995). The term 'autism', from the Greek 'autos' meaning 'self', was coined by the Swiss psychiatrist Bleuler in 1911 to indicate one of the fundamental (as opposed to accessory, in terms of diagnostic specificity, i.e., pathognomonic), but secondary (as opposed to primary, in terms of pathogenesis), symptoms of schizophrenia, specifically a disengagement from reality and a "predominance of the inner life" (Bleuler, 1911, p. 63; Parnas & Bovet, 1991; Tordjman et al., 2007). According to Bleuler, autism was caused by the loosening of associations and splitting ('Spaltung') typical of schizophrenia, which allowed a person to ignore the external world and focus on an inner, more effortless life (Parnas & Bovet, 1991). Later, he expanded the meaning of the term to indicate any irrational thinking, abandoning the specificity to schizophrenia.

With the adoption of the term 'autism' by post-war psychoanalysts, who used it to indicate a very early developmental stage or a defense mechanism caused by narcissistic failure, and with the various uses of the concept by clinical psychiatry in the following years, the term became too imprecise and undefinable for the field of psychiatry and was temporarily abandoned (Parnas & Bovet, 1991). However, in 1943 the American psychiatrist Kanner revived the term to classify symptoms that he noted in eleven children previously diagnosed
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with 'childhood schizophrenia', which included impairments in the use of language, especially in relation to interpersonal communication, and an insistence on repetitive behaviours and interests (King & Lord, 2010; Tordjman et al., 2007). The following year, similar characteristics were observed in approximately 200 children by Asperger (1944), who again chose the term 'autism' to classify them. Despite the emergence in the 1940s of autism as a separate diagnosis, Cappon's (1953) review of childhood schizophrenia and autism showed a clear overlap and for several years the two disorders were diagnosed interchangeably (or together), considered as belonging to a common spectrum and differing only in degree, or, by some clinicians, not distinguished at all (Eisenberg & Kanner, 1958; King & Lord, 2010). It was only in the 1970s that Rutter (1972) more clearly separated the two conditions, and proposed that the term 'childhood schizophrenia' should be retired. Moreover, this position was supported by suggestions that despite sharing some of the negative symptoms of schizophrenia, autism did not involve positive symptoms such as hallucinations and delusions (Rumsey, Andreasen, & Rapaport, 1986). Thus, a separate classification of autism was included in the DSM-III (American Psychiatric Association, 1980).

Since the 1970s, autism and schizophrenia have been considered two separate disorders. Specifically, according to the DSM-IV-TR the current diagnostic criteria for autistic disorder include the presence of six or more symptoms, including at least two impairments in social interaction (i.e., impaired use of nonverbal behaviour such as eye contact, facial expressions, body posture and gestures, failure to develop interpersonal relationships, lack of spontaneity in pursuing interests or activities with others, and lack of reciprocity), at least one impairment in communication (i.e., delayed or lack of use of spoken language -or when speech is adequate, impaired ability to initiate or preserve a conversation- stereotyped use of language and lack of make-believe or social imitative play appropriate to age), and at least one
symptom indicating repetitive and stereotyped behaviours and interests (i.e., anxious preoccupation with restricted patterns of interest, inflexible adherence to routines or rituals, repetitive motor mannerism and preoccupation with parts of objects). Moreover, the onset of disturbances should be prior to three years of age and abnormalities should not be better explained by Rett's disorder or childhood disintegrative disorder (American Psychiatric Association, 2000).

On the other hand, criteria for the diagnosis of schizophrenia involve the presence of two or more characteristic symptoms (i.e., delusions, hallucinations, disorganised speech, grossly disorganised or catatonic behaviour and negative symptoms), each for a significant amount of time within a one-month period; a significant (i.e., compared to levels achieved before the onset) impairment in social or occupational functioning (e.g., in areas such as work, interpersonal relationships and maintenance of personal health); the duration of disturbances for at least six months, including at least one month of active-phase symptoms (i.e., two of the five characteristic symptoms described above) and periods of prodromal or residual symptoms; and the exclusion of schizoaffective and mood disorder diagnoses and of physiological effects of a psychotropic substance or a general medical condition. Moreover, currently a co-diagnosis of schizophrenia and autistic disorder (or pervasive developmental disorder) is possible, but only if delusions and hallucinations are also present for at least one month (American Psychiatric Association, 2000).

However, with recent studies providing new evidence of the clinical and genetic overlap between the two disorders (Rapoport, Chavez, Greenstein, Addington, & Gogtay, 2009), and given the significant implications of similarities between the two conditions for research on causes, prevention and treatment approaches (King & Lord, 2010), there is a need for a review
of the commonalities and, if appropriate, a revision of the boundaries between the autism and schizophrenia and an integration of the research examining the pathogenesis and psychopathology of the two disorders.

Evidence of commonalities and differences

Although schizophrenia and autism are currently considered two separate disorders, it is apparent from the diagnostic criteria provided in the DSM-IV-TR that they share some clinical features (see Figure 1). For instance, the lack of spoken language and impairments in social interactions characteristic of autistic disorder are comparable to some of the negative symptoms of schizophrenia (Dvir & Frazier, 2011). Moreover, even in verbal individuals with autism symptoms such as incoherence, flattened affect and poverty of speech resemble some of the DSM-IV-TR criteria for schizophrenia (Cohen, Volkmar, & Paul, 1986). Furthermore, there is a role for positive schizophrenia symptoms in autism, such as paranoia and delusional thinking. For instance, forms of thought disorder and paranoia may appear in individuals with autism in anxiety-provoking situations, for instance, when being asked to shift set (i.e., change topic of conversation or activity; Berney, 2000). Additionally, a study of the DSM-III criteria revealed that in 20% of 50 cases of autism, parents suggested that their child's preoccupation with inner life interfered with reality, which can be compared to delusional thinking (Volkmar, Cohen, & Paul, 1986).
This report will investigate whether these clinical observations are supported by evidence of similar genetic, cognitive and biopsychological abnormalities in the two disorders. The purpose is to analyse whether commonalities are sufficient to justify the hypothesis that autism might be the childhood equivalent of schizophrenia or vice versa, that schizophrenia might simply be a grown-up autism; and that differences might be due to the two disorders presenting at different stages in life.

Comorbidity

Decades ago both Kraepelin and Bleuler observed that the onset of schizophrenia is often preceded by childhood premorbid abnormalities (Marenco and Weinberger, 2000). Since then, studies have investigated whether those neurodevelopmental impairments could be associated with autism, and thus whether autism in childhood is common before the onset of schizophrenia, and whether diagnoses of the two disorders overlap. For instance, earlier
studies suggested that 12% to 50% of individuals with autism develop psychosis at some point in their lives (Szatmari, Bartolucci, Bremner, Bond, & Rich, 1989; Tantam, 1988; Wing, 1981), although Volkmar and Cohen (1991) examined case records of people with autism and suggested that the prevalence of schizophrenia among them was comparable to that among the general population. More recently, Unenge Hallerback et al. (2012) used the Diagnostic Interview for Social and Communication Disorders, eleventh version (DISCO-11) to interview relatives of individuals with schizophrenia and found that 50% of people with schizophrenic psychosis also met the criteria for autistic disorder, and that the rate was 60% in the specific case of paranoid type schizophrenia.

Similarly, Gadow (2012) reported that children with autism spectrum disorder (ASD) presented more numerous and more severe schizophrenic symptoms than children in the control group. Konstantareas and Hewitt (2001) found that seven out of fourteen men with autistic disorder also had schizophrenia according to the Structured Clinical Interview (SCID) and Mouridsen, Rich and Isager (2008) reported that 35% of 89 children with ASD met a schizophrenia spectrum diagnosis. Moreover, childhood-onset schizophrenia (i.e., with onset prior to thirteen years of age) was found to be comorbid with ASD in 30% to 50% of cases (Sporn et al., 2004; Rapoport et al., 2009). In general, it was suggested that the Autism Diagnostic Observation Schedule is not reliable in distinguishing the two disorders and birth cohorts typically reveal similar developmental patterns (Bastiaansen et al. 2011; Lacy & King, 2013; Reaven, Hepburn, & Ross, 2008).

**Genetic overlap**

Twin studies, adoption studies, and studies of first, second and third degree relatives of probands with schizophrenia have left little doubt about the importance of genetic factors for
the development of the disorder, and modern meta-analyses suggest approximately 80% heredity (Sullivan et al., 2003), although the pattern of inheritance is associated with complex multigenic interactions rather than a single gene (Cardno & Gottesman, 2000; Gottesman & Shields, 1982; Miller, 2008). Similarly, twin and adoption studies have consistently shown the high heritability of ASD, where manner of inheritance is again likely factorial rather than Mendelian (Bailey et al., 1995; Le Couteur et al., 1996; Risch et al., 1999; Szatmari et al., 2007). Moreover, family history data suggest that genetic factors that influence the two disorders might be interrelated (Ghaziuddin, 2005). For instance, a diagnosis of schizophrenia in first degree relatives of probands was found to be associated with an increased risk for autism in samples from Sweden, Stockholm and Israel (Sullivan et al., 2012).

Specifically, studies involving copy number variants (CNVs) and other rare alleles have suggested a role for mutations in neurologins and neurexins in the development of both autism (Rapoport et al., 2009), and schizophrenia (Dvir & Frazier, 2011; Owen, O'Donovan, Thapar, & Craddock 2011). As neurexins are believed to be fundamental for excitatory and inhibitory synaptogenesis, abnormalities in this family of genes explain hypotheses proposing the role of an imbalance in excitatory and inhibitory transmission and neurodevelopmental insult in the causality of both autism and schizophrenia (Carroll & Owen, 2009; Dvir & Frazier, 2011). More particularly, Neurexin-1 is a susceptibility gene for both disorders and is believed to influence cognitive functions and brain structures that are abnormal in both autism and schizophrenia (Voineskos et al., 2011), and deletions found to correlate with both conditions include CNVs 22q11.2, 1q21.1, and 15q13.3 (Carroll & Owen, 2009). Moreover, genomewide association studies (GWAS) have tested several single-nucleotide polymorphisms (SNPs) to investigate associations between various disorders, and researchers have suggested candidate genes shared by autism and schizophrenia, including RELN, DISC1, MHC, NTNG1 and
SHANK3 (see Guilmatre et al., 2009; King & Lord, 2010; Lacy & King, 2013; Mefford & Eichler, 2009; Rodriguez-Murillo, Gogos, & Karayiorgou, 2012; Stefansson et al., 2009).

Additionally, contactin-associated protein-2 (CNTNAP2) is a single gene associated with risk of both disorders and it is fundamental in the development of the cerebral cortex, suggesting the possibility of a shared neurodevelopmental vulnerability or pathogenic mechanisms (Burbach & van der Zwaag, 2009). Moreover, a deletion between two cadherin genes (CDH12 and CDH18) has been identified in both disorders (Gross, Grimm, Meyer, & Lesch, 2003; Wang et al., 2009) and might therefore constitute a common pathway. Although Crespi and Crofts (2012) suggest that the amount of strongly statistically significant overlap between the CNV loci of the two disorders is limited, according to Lacy and King's (2013) review, when considered together GWAS and CNV studies solidly challenge the current choice to differentiate between autism and schizophrenia.

Social deficits and theory of mind

Autism and schizophrenia share an impairment in social development. With regards to schizophrenia, social deficits were considered a fundamental feature of the disorder since its formulation (Kraepelin, 1919; Bleuler, 1950), which is reflected in the DSM-IV-TR diagnostic criteria (Criterion B; American Psychiatric Association, 2000) and supported by extensive research comparing individuals with schizophrenia to controls (e.g., Argyle, 1981; Lindsay, 1982; Longabaugh et al., 1966). For instance, Mueser, Bellack, Douglas and Morrison (1990) reported that 50% of people with schizophrenia presented consistent impairments in social interaction during a one-year period, and social isolation is consistently reported in schizophrenia, although it is not clear whether this is due to an actual trait or to rejection by others caused by abnormal behaviours (Friedlander, 1946; Tordjman et al., 2007). Similarly,
social withdrawal has been associated with autism since since Kanner's (1943) conceptualisation of the disorder, and impairments in social interaction constitute one of the three fundamental autistic traits (American Psychiatric Association, 2000).

Despite social deficits being present in both autism and schizophrenia, the causes of these impairments and how they manifest themselves has been suggested by some researchers to differentiate the two disorders. For instance, Sasson, Pinkham, Carpenter and Belger (2011) suggested that while social withdrawal in schizophrenia is often due to the attribution of negative intentions to others due to delusions, withdrawal in autism is more likely due to social cynicism that developed as a consequence of people's reactions to the condition. Moreover, Crespi and Badcock (2008) proposed that traits related to social development, such as eye contact, social cognition, language and social behaviours, manifest themselves as diametrically opposite phenotypes in the two disorders, where social cognition is underdeveloped in ASD and hyper-developed in schizophrenia.

Moreover, in relation to abnormalities in the development of social skills, theory of mind deficits (i.e., impaired ability to recognise others as possessing thoughts, beliefs and desires) were suggested to be characteristic of autism by Baron-Cohen, Leslie and Frith in 1985. This was supported by several studies comparing people with ASD to controls or to individuals with other developmental disabilities (Colle, Baron-Cohen, & Hill, 2007; Tager-Flusberg, 1999; Williams & Happe, 2010). More recently, several studies have provided significant evidence of an association between theory of mind and schizophrenia as well (Burns, 2006; Fett et al., 2011; Lysaker et al., 2011; Mehl et al., 2010). As theory of mind impairments have been suggested to involve abnormalities in mirror neurons (Williams et al., 2001) and the medial prefrontal cortex (Castelli, Happe, Frith, & Frith, 2000), studies have analysed these structures in both autism and schizophrenia using functional imaging. Transcranial Magnetic
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Stimulation (TMS) and Electroencephalography (EEG) have found mirror neurons to be deficient in both disorders (Bernier et al., 2007; Bertrand et al., 2008; Enticott et al., 2008; Happe et al., 1996; Oberman et al., 2005; Park et al., 2009; Rizzolatti & Fabbri-Destro, 2010; Russell et al., 2000).

**Sensory perception**

Both autism and schizophrenia are characterised by abnormalities of sensory perception, especially concerning visual and auditory perception (Dahlgren & Gillberg, 1989; Miller, 2008; O'Neill & Jones, 1997), and some of these deficits are shared by both disorders. For instance, there is evidence of auditory impairments in autism consisting of both hypersensitivity to sound and/or under-responsiveness to sound (Ben-Sasson et al., 2008; Grandin & Scariano, 1986; Liss, Saulnier, Kinsbourne, & Kinsbourne, 2006; Yaguchi, 2009), which are similar to characteristics of schizophrenia such as heightened sensitivity to sound (Cutting & Dunne, 1989; Tregellas, Smucny, Eichman, & Rojas, 2012) and slower reaction times in auditory tests (especially related to right hemisphere function; Miller, 2008).

In terms of visual perception, individuals with autism present impairments in the integration of visual information which leads to a fragmentation of the visual world (Bertone, Mottron, & Faubert, 2004; Frith, 1989). Interestingly, deficient neuro-integrative perceptual processing and visuo-perceptual fragmentation have also been observed in schizophrenia (Arieti, 1966; Bertone et al., 2004).

**Motor function**

Autism and schizophrenia share abnormalities in eye movement and lateralisation of motor control. Miller (2008) suggests that "the best-known normal aspect of cerebral
asymmetry in the domain of motor control is handedness" (p. 35), and there is evidence of significant increases in anomalous handedness (i.e., left-handedness) compared to the general population in both ASD and schizophrenia (Lewin, Kohen, & Mathew, 1993; Miller, 2008; Sommer et al., 2001). Moreover, eye tracking abnormalities, such as deficient smooth pursuit and saccadic eye movements, and abnormally short and unsteady visual fixation were found in both disorders (Klin, Jones, Schultz, Volkmar, & Cohen, 2002a; Levin et al., 1981; Miller, 2008; Pelphrey et al., 2002; Rommelsea et al., 2008; Ross et al., 1988; Ross et al., 1996).

Finally, lateralised tests suggest that right-hemisphere processing is impaired in autism, which, as left-hemisphere functioning remains intact, leads to a loss of the normal asymmetry between the two hemispheres (Orekhova et al., 2009). These characteristics are also present in individuals with schizophrenia, which led Miller (2008) to coin the slogan "two left hemispheres" (p. 30) to describe the decreased lateralisation associated with the disorder.

Cognitive processes

Cognitive deficits have been reported in both schizophrenia and autism (Alaghband-Rad, McKenna, & Gordon, 1995; Asarnow, Tompson, & Goldstein, 1994; Baum & Walker, 1995), including impairments in attention, memory and learning (Tordjman et al., 2007). Older clinical evidence (e.g., Crumpton, 1963; Yacorzinski, 1941) and more recent experimental designs using tests such as the Wisconsin Card Sort Task and the Stroop test have consistently revealed a 'persistence of set' in individuals with schizophrenia (i.e., difficulties in shifting attention; Braff et al., 1991; Fey, 1951; Miller, 2008).

Similarly, narrower-than-normal attentional focus and problems with disengaging and shifting attention have been repeatedly observed in people with ASD (Akshoomoff & Courchesne, 1992; Courchesne et al., 1994; Townsend, Courchesne, & Egaas, 1996;
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Wainwright-Sharp & Bryson, 1993; Wainwright & Bryson, 1996). Moreover, the two disorders share social cognitive deficits (Sasson et al., 2007) such as impairments in the recognition of facial emotions (Celani, Battacchi, & Arcidiacono, 1999; Kohler & Brennan, 2004), and in the interpretation of social cues (Archer, Hay, & Young, 1994; Klin, Jones, Schultz, Volkmar, & Cohen, 2002b), particularly when tests involve a high level of social cognitive skills such as for complex social judgements (Craig, Hatton, Craig, & Bentall, 2004; Pilowsky, Yirmiya, Argelle, & Mozes, 2000).

Correlated with social cognitive dysfunction, the amygdala, which has a fundamental role in threat detection, affect recognition (especially fear) and social appraisal, has been reported to be abnormally inactive in both disorders, although structurally it seems to be abnormally small in schizophrenia (Joyal et al., 2003; Wright et al., 2000) and abnormally large in autism (Sasson et al., 2007). Accordingly, abnormalities in face processing, including a tendency to focus less on eyes and more on less salient features (e.g., ears), have been observed in both disorders (Klin et al., 2002a; Klin et al., 2002b; Pelphrey et al., 2002; Phillips & David, 1997; Williams, Loughland, Gordon, & Davidson, 1999; Watson, 2013).

Moreover, cognitive impairments typically associated with schizophrenia such as deficient executive skills, abstract reasoning, problem-solving and goal-directed behaviour have also been consistently reported in individuals with autism (Goldstein, Minshew, Allen, & Seaton, 2001; Ozonoff, 1995), and the two disorders also share short-term and working memory deficits (Barendse et al., 2013; Carolyn & Bryson, 1972; Miller, 2008).

**Language**

Autism and schizophrenia share impairments in communication and language (Tordjman et al., 2007). A critical feature of autism, which has been supported by substantial evidence, is
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an impairment in pragmatic language, involving problems with non-literal language (e.g., irony and metaphors) and semantic integration (Dennis, Lazenby, & Lockyer, 2001; Happe?, 1993; Martin & McDonald, 2004; Pijnacker, Geurts, van Lambalgen, Buitelaar, & Hagoort, 2010; Vulchanova, Talcott, Vulchanov, & Stankova, 2012). Similarly, several studies suggested that individuals with schizophrenia have difficulties comprehending metaphorical use of language and proverbs (Brownell, Potter, Michelow, & Gardner, 1984; Chapman, 1960; Epelbaum, Bonis, & de Gineste, 1992), and interpreting and integrating abstract meanings ('concretism'; Miller, 2008).

**Electrophysiology**

Several studies used event related potentials (ERPs) to investigate the neural sources of the impairments associated with schizophrenia and autism. In terms of auditory processing in autism, ERP components that reflect pre-attentive auditory detection such as the P1 and N2 in infants and P1-N1-P2 complex in adults (Jeste & Nelson, 2009), were found to be abnormal in latency and amplitude (Bruneau, Roux, Adrien, & Barthelemy, 1999; Buchwald et al. 1992; Courchesne, Courchesne, Hicks, & Lincoln, 1985; Courchesne, Lincoln, Kilman, & Galambos, 1985; Grillon, Courchesne, & Akshoomoff, 1989; Ornitz et al. 1972; Small, DeMyer, & Milstein, 1971). Although the nature of the abnormalities was not entirely consistent, shorter latencies and smaller amplitudes were the most common finding (Novick, Vaughan, Kurtzberg, & Simson, 1980; Martineau, Garreau, Barthelemy, & Lelord, 1984; Oades, Walker, Geffen, & Stern, 1988; Ferri et al., 2003), suggesting an abnormal speed and magnitude of pre-attentional detection of sound (Jeste & Nelson, 2009). A similar tendency was found in schizophrenia, where deficits in pre-attentional auditory processing were demonstrated by abnormal N1 and mismatch negativity (MMN; Milovan, Baribeau, Roth, &
Moreover, studies focusing on the P300 component (including the P3a, triggered by task-irrelevant novel stimuli, and the P3b, elicited by target, salient novel stimuli), which is dependent on attention and thus associated with higher-level cognitive processing, revealed smaller P300 amplitudes and longer latencies in both autism (Ciesielski, Courchesne, & Elmasian, 1990; Courchesne, Kilman, Galambos, & Lincoln, 1984; Courchesne et al., 1985a, 1985b; Jeste & Nelson, 2009; Lincoln, Courchesne, Harms, & Allen 1993) and schizophrenia (Bramon et al., 2004; Jeon & Polich, 2003; Miller, 2008), suggesting that fewer attentional resources are invested into cognitive processing of stimuli in individuals with both disorders. Similarly, studies using visual stimuli suggested smaller than normal P300, N1 and Nc amplitudes, suggesting deficits in visual processing and visual selective attention, in both autism (Ciesielski et al., 1990; Courchesne et al., 1985a, 1985b, 1989; Kemner et al., 1994; Orekhova et al., 2009; Verbaten et al., 1991) and schizophrenia (Adler et al., 1992; Boutros et al., 1997, 2004; Brown et al., 2000; Miller, 2008; Ogura et al., 1991). However, other studies have found normal P3b amplitudes or larger than normal parietal P3b (while central and occipital P3b were smaller) in patients with autism (Jeste & Nelson, 2009; Kemner et al., 1999).

Additionally, ERP components that are specific to face processing, such as the N290 and P400 in infancy and the N170 later in life, and that therefore may have implications for social cognitive deficits, were found to present smaller amplitudes and slower latencies in children with autism (Dawson et al., 2002a, 2002b; O’Connor, Hamm, & Kirk, 2007; Hileman, Henderson, Mundy, Newell, & Jaime, 2011) and in adults with schizophrenia (Caharel et al., 2007; Campanella, Montedoro, Strel, Verbanck, & Rosier, 2006; Herrmann, Ellgring, & Fallgatter, 2004; Johnston, Stojano, Devir, Schall, 2005; Onitsuka et al., 2006; Streit, Wolwer,
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Brinkmeyer, & Gaebel, 2001; Turetsky et al., 2007), and in both cases the deficits are specific
to the differentiation of faces, rather than of objects.

In terms of speech processing, reduced or absent N400 components have been reported
both in children and adults with ASD (Dunn, Vaughan, Kreuzer, & Kurtzberg, 1999;
Strandburg et al., 1993) and in schizophrenia (Grillon, Ameli, & Glazer, 1991; Kumar &
Debruille, 2004), suggesting a neural basis for deficits in the semantic interpretation of
language and for delays in information processing in both disorders. With regards to
distracting stimuli, individuals with autism showed abnormally high amplitudes and increased
latencies in early components triggered by novel distracters (e.g., P100 and N100), as well as
increased latencies in late components (e.g., P2a, N200, P3a), indicating over-processing of
information necessary for the differentiation of salient and unimportant stimuli (Sokhadze et
al., 2009). Similarly, ERP studies involving individuals with schizophrenia showed an
increased distractibility and an abnormal allocation of attention between task-relevant and
task-irrelevant stimuli (Cortinas et al., 2008; Grillon, Courchesne, Ameli, Geyer, & Braff,
1990).

**Brain morphology**

Studies of brain morphology have revealed some similarities between schizophrenia and
autism. For instance, there is evidence of disruption to all the stages of embryologic cerebral
development in both disorders, including migration and lamination errors (Lacy & King,
2013). Moreover, the development of brain size follows similar patterns in ASD and
schizophrenia, with head circumference being often normal or slightly smaller at birth, despite
ventricle volumes being larger than normal in infants (Gilmore et al., 2010; Hazlett et al.,
2005; Kunugi et al., 1996), and an accelerated brain growth and macrocephaly in the first
years of life (Chawarska et al., 2011; Hazlett et al., 2005; Rapoport et al., 2009). In adolescence, individuals with both disorders present atrophy, ventricular enlargement, cortical thinning and a normalisation of head size (Courchesne et al., 2007; Lacy & King, 2013; Miller, 2008; Voets et al., 2008; Ward et al., 1996).

White matter abnormalities such as reduced myelination are also found in both disorders (Hardan, Libove, Keshavan, Melhem, & Minshew, 2009; Miller, 2008), as well as abnormalities in the cerebellum (Mittleman, Goldowitz, Heck, & Blaha, 2008), although cerebellar size seems to be increased in autism and reduced in schizophrenia (Okugawa, 2013; Piven, Saliba, Bailey, & Arndt, 1997). Moreover, Cheung and colleagues (2010) suggested that the two disorders present structural similarities such as a loss of grey matter in the right parahippocampal gyrus, posterior cingulate, putamen, clastrum and left thalamus, although some areas of grey matter loss specific to each disorder were also identified. Additionally, Toal and colleagues (2009) found that individuals with ASD, when compared to controls had structural abnormalities that are also associated with schizophrenia, leading them to the hypothesis of autism as an 'entry-point' into schizophrenia, where children with autism may only necessitate minor additional developmental brain abnormalities to develop the positive symptoms of schizophrenia.

Other biological features

Additional biological characteristics were found to be shared by schizophrenia and autism. For instance, the two disorders share an abnormal stress response, especially in terms of hypothalomo-pituitary-adrenal axis response to psychosocial stress, which is related to problems adapting to novel situations and abnormal behavioural responses to stress in both disorders (Jacobson & Ackerman, 1990; Jansen et al., 1998; Tordjman et al., 1997). Issues
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with adaptation to unfamiliar situations and abnormal stress response might be mediators in
the observed relationship between immigration and both autism (Bolton, McDonald, Curtis, Kelly, & Gallagher, 2013) and schizophrenia (Ampadu, 2011). Moreover, reduced behavioural
pain reactivity was noted in both schizophrenia and ASD, although it is not clear whether this
is due to an endogenous analgesia due to increased endorphins or simply to an abnormal
expression of pain related to cognitive impairments (Guieu et al., 1994; Todjman et al., 1999).
Furthermore, there is a role for the promoter polymorphism of the serotonin transporter gene
in both disorders, as this influences the severity of social and communication impairments in
autism and the severity of positive symptoms in schizophrenia (Malhotra et al., 1998;

Additionally, there is evidence from peripheral biomarker studies of a dysregulation of
innate and adaptive immune systems in both disorders, although immune dysfunction seems
to be chronic in autism and specific to acute episodes in schizophrenia (Michel, Schmidt, &
Mirnics, 2012). Abnormalities in glutaminergic pathways are also present in both autism and
schizophrenia, and specifically a reduction in NMDA-receptor function (Carlson, 2012; Gai et
al., 2012; Gandal et al., 2012; Tsai & Coyle, 2002), as well as alterations in GABA
neurotransmission (Blatt, 2010; Blatt & Fatemi, 2011; Lewis, Pierri, Volk, Melchitzky, &
Woo, 1999). However, biological differences between autism and schizophrenia have also
been emphasised, for instance it was suggested that autism presents a general pattern of
overgrowth and upregulation of pathways due to malfunctioning negative regulators, while
schizophrenia more often involves undergrowth and reduced pathway activation (Crespi &
Badcock, 2008; Crespi, Stead, Elliot, & Stearns, 2010).
Discussion

In summary, despite the current diagnostic differentiation between schizophrenia and autism, these disorders both involve cerebral specialisation errors arising during the embryonic period (Lacy & King, 2013), and they share several features, including genetic factors, cognitive and perceptual deficits, impaired social behaviour and communication skills, and some cerebral morphological characteristics. However, differences also exist between schizophrenia and autism, such as age of onset (i.e., autism is commonly diagnosed before three years of age and onset of schizophrenia is generally in adolescence or young adulthood), stereotyped and repetitive motor mannerism being more closely associated with autism and positive symptoms being more common in schizophrenia, although clinical and empirical evidence suggests a presence of paranoia in autism comparable to those of schizophrenia (Pinkham et al., 2012; Tordjman et al., 2007), and ASD being more commonly associated with an upregulation of pathways while schizophrenia generally presents reduced pathway activation (Crespi et al., 2010). In light of the ambiguity of these results, a complete discussion of whether the current differentiation between autism and schizophrenia is appropriate should include a consideration of the hypothesised aetiology and most common and successful treatment approaches.

The most commonly suggested cause of schizophrenia is illustrated by the dopamine hypothesis, which, based on observations on the antipsychotic effects of certain dopamine antagonists and the ability of dopamine agonists such as cocaine, amphetamine and Parkinson's medication to elicit psychosis, attributes schizophrenic symptoms to a hyperactivity of dopaminergic neurons in the mesolimbic and mesocortical pathways (Matthysse, 1974). However, this hypothesis has some limitations, such as negative symptoms
not responding to antipsychotic medication that targets dopamine levels and hallucinogenic drugs that act on serotonin and glutaminergic transmission producing psychosis-like symptoms (Miller, 2008; Moncrieff, 2009). Thus, other mechanisms have been suggested, including the glutamate hypothesis, which proposes a role for dysfunctional NMDA glutamate receptors, leading to abnormal glutamatergic neurotransmission which also influences the modulation of dopamine transmission, thus explaining both positive and negative symptoms (Coyle, 2006; Olney & Farber, 1995; Miller, 2008). Research has also emphasised the role of other neurotransmitters, such as GABA (Benes & Berretta, 2001), serotonin (Meltzer, 1989) and nicotinic acetylcholine (Freedman, Adams, & Leonard, 2000). Moreover, Miller (1996) formulated the 'central hypothesis', suggesting that behind schizophrenic symptoms there is a loss of rapidly-conducting cortico-cortical axons, and that as these axons are mainly responsible for the functional properties of the right cerebral hemisphere, deficits in schizophrenia primarily involve right hemisphere-preferred functions (Miller, 2008). Moreover, as rapidly conducting axons are involved in long distance interactions (Miller, 2008), this hypothesis explains the connectivity deficits associated with schizophrenia.

The aetiology of autism is still largely unknown, but several hypotheses and models have been proposed, mainly focusing on neurodevelopmental disruptions that lead to functional and structural cerebral impairments (Watts, 2008). Suggested disruptions include errors in cortical neural migration in the first few months of gestation (Magdaleno et al., 2002; Watts, 2008), abnormal dendritic morphology and assembly of synapses (Minshew & Williams, 2007; Pickett & London, 2005), abnormal immune functioning due, for instance, to reduced antibodies and natural killer cells (Cohly & Panja, 2005; Kern & Jones, 2006), altered calcium signalling (Casanova, 2007) and mirror neuron dysfunction (Watts, 2008; Williams et al., 2001). Moreover, one of the most accepted theories emphasises defective neural wiring due to
an excessive number of neurons, which lead to overactive short-distance fibers obstructing long distance interactions, thus hindering neural connectivity (Courchesne et al., 2007; Watts, 2008) and interfering with integration across different cortical regions (Just et al., 2007).

This theory is reminiscent of the central hypothesis for schizophrenia, which also emphasises the hindering of cortico-cortical interactions due to a loss of long-distance fibers (Miller, 2008). Additionally, deficient brain connectivity in autism, and specifically long-distance under-connectivity, has been explained in a meta-analysis with alterations in the superior longitudinal fasciculus, uncinate fasciculus and corpus callosum (Aoki, Abe, Nippashi, & Yamasue, 2013). Similarly, one of the features of schizophrenia that is accounted for by the central hypothesis is an impairment in interhemispheric coordination, which seems to indicate deficits in callosal transmission (Miller, 2008). However, evidence of callosal abnormalities in schizophrenia is inconsistent and needs further exploration (Innocenti, Ansermet, & Parnas, 2002). Furthermore, aforementioned neurotransmitters commonly associated with schizophrenia were also found to have a role in autism's pathophysiology, including glutamate (Dykens, Sutcliffe, & Levitt, 2004; Gandal et al., 2012; Schmitz & Rezaie, 2008), GABA (Chugani, 2010; Watts, 2008), serotonin (Azmitia, Singh, Hou, & Wegiel, 2011; Chugani, 2010) and dopamine (McCracken et al., 2002; McDougle et al., 2005; Nakasato et al., 2007). Finally, inflammatory responses due to prenatal exposure to infection have been implicated in the pathogenesis of both disorders (Meyer, Feldon, & Dammann, 2011).

With regards to treatment, behavioural interventions proved to be the most successful approach to treating autism (Eikeseth, 2007; Lovaas, 1987; Sallows & Graupner, 2005), while antipsychotic medications are the preferred and most efficacious approach for schizophrenia, where behavioural or cognitive behavioural therapy is mainly used with antipsychotic-
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resistant patients (Brabban, Tai, & Turkington, 2009). However, there is substantial evidence that antipsychotics that were originally developed for schizophrenia, such as risperidone and aripiprazole, effectively reduce behavioural deficits in autism (King & Lord, 2010; Lacy & King, 2013), and glutamatergic drugs have been recently investigated to treat both disorders (Karam et al., 2010; King & Bostic, 2006). Thus, differences in the preferred treatment approaches might simply reflect differences in age of onset.

A review of the causes and treatments for autism and schizophrenia thus reveals, as did the above review of features and deficits, several commonalities between autism and schizophrenia. Although some differences are also present, it is possible that these are not fundamental, but rather due to the different time of onset or severity (King & Lord, 2010; Lacy & King, 2013). In this sense, it is possible that the two disorders share a common pathogenesis, and that the different times of onset and/or different degrees of severity lead to different developmental processes and thus a different phenotypic expression. Alternatively, autism and schizophrenia might share abnormalities at the cellular level, but involve different patterns of activation and axonal pathways.

**Conclusion**

In conclusion, autism and schizophrenia have several commonalities, including genetic features, cognitive, motor and perceptual impairments, problems with social behaviour and communication skills, and some functional and morphological cerebral characteristics. Moreover, there is evidence of treatment approaches that are successful with both disorders, and some aspects of the suggested aetiology are similar. Thus, it is possible that schizophrenia and autism share a common pathogenesis, and that differences between them are due to
distinct times of onset and severity. As unifying the two disorders into one spectrum would be beneficial in terms of the wealth of research available on the two conditions, where findings on one disorder could inform and enhance the understanding of the other, future research should focus on exploring and potentially confirming this association.
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