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Do Apparent Overlaps between Schizophrenia and Autistic Spectrum Disorders Reflect Superficial Similarities or Etiological Commonalities?

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Abstract

Study Background—Schizophrenia and autism are both neurodevelopmental disorders that were once considered to be the same disorder expressed in different developmental periods. Although they were separated diagnostically about 40 years ago, they share several clinical and possibly, etiological features. This paper reviews overlaps in four domains of function to consider the issue of whether these similarities are sporadic and likely to represent superficial similarities, or whether the disorders are more likely to share some features in common.

Methods—Representative areas of function were reviewed and compared for aspects of cognition (nonverbal reasoning, memory and language), social function (orienting/joint attention, eye contact and theory of mind), brain function (structural differences) and genetics. To facilitate comparisons with schizophrenia, a focus on high functioning autism/Asperger's disorder was utilized, particularly in the sections on cognition and social function.

Results—Significant similarities (and differences) characterized comparisons in each domain.

Conclusions—Disturbed function in similar clinical (in cognition and social function), neurobiological (brain volumes) and genetic (e.g., involvement of the same genes or chromosomal locations) domains in autism and schizophrenia supports the hypothesis that while they are distinct disorders, they are not entirely unique. Additional studies of similarities and differences between them may thus shed light on common etiological mechanisms and hopefully, facilitate the development of novel treatment targets.

Keywords

Autistic spectrum disorder; cognition; social cognition; schizophrenia spectrum disorder

Autism and schizophrenia are among many psychiatric and neurological disorders that share overlapping clinical features and involve widespread psychiatric and cognitive impairments. Other examples include different dementing disorders, which often produce similar clinical symptoms in their later stages, and disorders involving psychosis, such as schizophrenia and bipolar I disorder with psychotic features. The situation is complicated somewhat by a reliance on clinical symptoms to make diagnoses in psychiatry [1], but are complicated even more so by the nature of the disorders themselves. Many psychiatric (and other medical)

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disorders and normal functions have multiple causes, and many causal factors may be sufficient, often in combination with other causal factors, to contribute to the development or maintenance of a disorder.[2,3]

The multi-factorial and complex nature of autism and schizophrenia adds to the difficulty of establishing their etiologies. Nevertheless, the importance of identifying etiological factors is often an essential step in the development of new treatment strategies. While there are several potential paradigms that might be utilized to progress towards this goal, one is to assess the potential importance of overlapping symptoms in these syndromes. This approach can help determine whether observed similarities reflect common etiological factors, such as a continuum between schizophrenic and autistic spectrums, or whether they more likely reflect superficial similarities, (such as problems in attention that may result from any number of disparate causes).

In this paper, we focus on apparent overlaps between schizophrenia and autism spectrum disorders, which both reflect common, clinically significant spectrums. Until these disorders came to be viewed as distinct in the 1970s, they were viewed as different phases of the same problem, with autism manifesting as an earlier phase of schizophrenia.[4,5] Although they are viewed separately now, they do intersect along several dimensions, including, for example, problems with social interaction and emotion, verbal and nonverbal communication, and odd or inflexible behavior. It is not clear, however, whether these and other shared clinical features reflect common underlying etiological factors. Moreover, the question is complicated by heterogeneity of symptoms, differences in age of onset, environmental factors and responses to treatment. In the interests of maximizing clarity and also emphasizing cognition, we will focus somewhat on adolescents and adults whose overall cognitive abilities are above IQs of 70 (i.e., above DSM-IV ranges required for diagnoses of mental retardation). For the autism spectrum disorders, this mainly includes a composite group of individuals who are commonly diagnosed with high-functioning autism/Asperger syndrome (HFA/AS). Reviews of the schizophrenia spectrum will focus on schizophrenia itself, but will also include other DSM-IV disorders such as schizoaffective disorder (depressed type) and schizotypal personality disorder, where appropriate. The aim of this paper is not to argue for or against existing theories in either schizophrenia or autism, but to explore representative evidence about the nature of overlaps between them. Evidence for common etiological components, if present, may then provide an impetus for the development of research strategies aimed at clarifying etiology further and at developing/validating clinical interventions.

The remainder of the paper is organized into five sections. Representative overlaps between schizophrenia and HFA/AS will be reviewed briefly in four dimensions, including: 1/ cognition, 2/ social functioning, 3/ structural brain abnormalities, and 4/ genetics. We conclude by considering implications for etiology, clinical interventions and future research.

What Evidence is There For Overlap?

Cognition

Cognitive processes are essential for individuals to interact with the world and other people in a meaningful way. Overall, cognitive deficits are generally milder in high functioning autism (i.e., HFA/AS) than they are in schizophrenia,[6] and more related to social function.[7,8] They are, however, significant clinically, and form the basis of some cognitive theories of autism.[9] Representative examples of cognitive deficits will be considered for schizophrenia and HFA/AS in three domains, including (1) nonverbal reasoning, (2) memory, and (3) language. These cognitive abilities are all important for social interaction, communication,

and adaptive behavior, and are impaired in both spectra in various dimensions and to varying degrees.

Nonverbal reasoning—Nonverbal reasoning is instrumental for abstracting the essence of situations, and for assigning meaning to them. It is often measured by neuropsychological tasks that involve perceiving, organizing, integrating, and associating information in the service of goal-directed behavior. In most people, this chain of events happens more or less automatically. In people with HFA/AS, this chain of events may happen more deliberately, abnormally, or not at all. This observation contributes to cognitive theories of autism that focus on tendencies towards local rather than global processing of information.[10] Similarly, organizing and integrating information is often impaired in schizophrenia, as demonstrated, for example, by difficulties in emotion perception in schizophrenia spectrum illness.[11,12] Individuals with schizophrenia report normal emotional experiences in the presence of emotionally evocative stimuli, but are often less expressive and less likely to maintain those emotional reactions in the absence of the stimuli.[13] As with schizophrenia, emotion perception is impaired in HFA/AS in some ways,[14] but not others. Quintin et al showed recently, for example, that HFA/AS subjects perceived emotions in music normally when verbal IQ was controlled.[15] Wallace et al demonstrated impaired facial emotion perception in HFA/AS individuals who were matched to healthy controls on age, gender and IQ, but these differences were minimized for most emotions when facial expressions increased in intensity.[16]

Salience is another mediating factor in nonverbal reasoning. There is an intrinsic and bi-directional relationship between what we attend to and what is judged to be relevant. Individuals with schizophrenia often base their actions on misinformation due to idiosyncratic meaning attached to a particular stimulus, as reflected in loose associations, over- or under-inclusive thinking and paranoia.[17,18] Individuals with HFA/AS show particular deficits in salience to social stimuli, particularly in situations that involve distracters or the need to switch attention rapidly between different sensory modalities, objects or locations.[19,21] Both groups often fail to suppress information that is important, but not salient.

Memory—Deficits in declarative memory performance are well-established in patients with schizophrenia, but involve problems with encoding (i.e., learning) more than they involve problems with memory storage.[6,22,23] These deficits are not only related to other cognitive abnormalities (e.g., executive function and attention), but are linked to hippocampal abnormalities and to clinical symptoms that cause functional impairment. There are fewer published studies on declarative memory in HFA/AS than there is in schizophrenia spectrum disorders, but some conclusions may be drawn. Individuals with HFA/AS often show normal free recall, cued recall and recognition,[24] particularly for item-specific material that is subject to rote memorization. Individuals with HFA/AS show poorer recall, however, as interference increases, contextual relatedness increases, and particularly when social contextual information increases.[24–28] Similarly, adults with HFA/AS have poorer autobiographical memories,[29,30] which partly reflects difficulties in taking first-person perspectives.[28] Notably, learning/encoding problems in autism and in schizophrenia are both more prominent than are problems in recognition, which emphasizes their vulnerability to problems in executive function (e.g. in learning, retrieval, organization and resistance to distraction) and attention. Thus, despite differences (e.g., memory performance impairments in schizophrenia are broader and more robust than they are in HFA/AS), they show significant similarities as well.

These similarities may be particularly significant with respect to relational and contextual memory, which involves the ability to associate and remember names with faces, the

locations of objects or people, and the order in which events occur. Some researchers attribute declarative memory deficits in HFA/AS to problems with processing relational and contextual information.[31] Similar deficits have been observed in individuals with schizophrenia, using associative inference and transitive inference paradigms.[32,33] Almost 20 years ago, DeLong[34] postulated that autism was a developmental syndrome of hippocampal dysfunction, based on evidence that the hippocampus is involved in constructing meaning and integrating new experiences with old ones. Recent research indicates that the connection between relational and contextual memory deficits and hippocampal dysfunction in HFA/AS has to do with preferential use of item-specific information, rather than with associative learning.[25]

Procedural memory deficits in individuals with HFA/AS are sometimes captured diagnostically as DSM-IV developmental coordination disorder or as a nonverbal learning disorder (which is often diagnosed under DSM-IV cognitive disorder, not otherwise specified), with evidence of poorer memories for self-performed actions than controls.[35] These examples of impaired autonoetic awareness (i.e., remembering what is involved in episodic memory experiences) seem closely related to hippocampal-dependent relational and contextual memory impairment.

Semantic memory deficits observed in schizophrenia and HFA/AS are variable. One meta-analysis of 91 studies found an uneven profile of impairment in individuals with schizophrenia on semantic tasks involving naming, word-picture matching, verbal fluency, priming, and categorization[36]. There was a large effect size for naming and verbal fluency, medium effect size for word-picture matching and association and small effect sizes for priming and categorization. The conclusion was that there was a link between thought disorder and semantic memory impairments on tests of naming and verbal fluency, though on other tests the evidence was equivocal. These findings are consistent with observations of wide semantic boundaries and generation of atypical exemplars in schizophrenia.[37] By contrast, a PubMed search using key words “semantic memory autism asperger” resulted in only 7 articles published between 1998 and 2009. The articles examined recognition memory, self-other memory, semantic association, dream content analysis, and using context and pragmatic language. Thus, the variability in semantic memory deficits seen in schizophrenia and HFA/AS relates not only to thought disorder, but also to language, which will be explored next.

Language

Language abnormalities play a prominent role in schizophrenia and HFA/AS. People with schizophrenia and HFA/AS have trouble with coherent communication—that is, with packaging and conveying information in a meaningful way. But there are subtle differences in how this incoherence manifests itself. In schizophrenia, it may take the form of neologisms or loose associations that are characteristic of thought disorder. Communication difficulties that result from thought disorder in schizophrenia are at least partially attributable to neuropsychological deficits (e.g., in attention/working memory, immediate memory, organizational sequencing and conceptual sequencing).[38] Subjects with HFA/AS often show problems with language,[39] which may include awkward timing, phrasing or transitions during conversations and problems with pragmatic and prosodic skills, among other abnormalities, though these individuals (i.e., with IQs in the average range) also tend to show generally intact formal language capacity.[40] One recent study compared subjects who were 11–20 years old who met criteria for a clinical high risk (for psychosis) group (CHR), a first episode psychosis group (FEP), an autistic spectrum disorders (ASD) group and a typically developing individuals group (TYP).[41] Each of the three clinical groups showed deficits in social function and atypical development of language. Notably, the ASD (i.e., HFA/AS subjects) subjects showed greater grammatical and pragmatic language

symptoms (e.g., delayed echolalia, pedantic speech, and problems understanding humor, irony and sarcasm) than the other groups.

One way to assess language functioning is to administer tests of reading comprehension or narrative writing. Individuals with schizophrenia are able to read single words (decoding) but take longer to complete reading comprehension tests and obtain lower scores.[42–44] With schizophrenia, poor comprehension or writing relates to fundamental problems with attention and working memory, processing speed, and extracting and organizing salient information. With HFA/AS, poor comprehension or writing often occurs as a result of failure to integrate or assemble complex information to derive or produce a meaningful whole.

Another way to measure a person's ability to access and use language to demonstrate knowledge is to administer a verbal fluency test. Both semantic and phonemic fluency are impaired in schizophrenia and HFA/AS, and may be associated particularly with deficits in semantic processing. For example, one study found that deficits in semantic fluency but not phonologic fluency differentiated a group of 66 young patients at high risk for psychosis from 67 other psychiatric, help-seeking controls.[45] Another study reported a unique connection between action (verb) fluency and odd speech in schizophrenia, rather than a general impairment in language or executive demands that are common to fluency tasks.[46] Citing research that verbs influence causal attributions that are central to interpersonal communication, they also linked action-word fluency deficits to deficits in social interaction.

In summary, many individuals with either HFA/AS or schizophrenia show communication difficulties. Some of these problems are related to thought disorder in both spectra, but differ somewhat between disorders, with HFA/AS showing a somewhat broader and extensive set of communication difficulties, on average.

Social functioning

Deficits in social function are among the defining features of autism,[39,47] and are among the core features of schizophrenia.[48,49] At least one recent study that compared subjects with HFA/AS with subjects with schizophrenia on a range of social cognition measures showed that they performed similar to each other, but worse than controls on most measures [50] (but see also [51]). As reviewed above, both groups are affected adversely by cognitive deficits. This section reviews overlap in several key areas related to social function, including orienting/joint attention, gaze and eye contact, and theory of mind.

Orienting, joint attention and visual processing style—Joint attention is a kind of social orienting that occurs when one person turns to look in the same direction that they see another person looking. It usually emerges reliably between the ages of 1–2,[52,53] and it is one of the foundations of social interaction because shared attention is directed to objects of mutual interest. As such, it assumes knowledge of others' interests and helps to develop both 'theory of mind' (described below) and language. Abilities to identify emotions or other aspects of mental state emerge between the ages of 3–4.[53] Joint attention involves at least two well-researched phenomena: 1/ facial and emotion recognition, and 2/ visual processing style. Both of these phenomena influence social functioning by driving salient aspects of (particularly novel) social situations.

Individuals with HFA/AS do not attend well to social aspects of the environment (though they may attend as well as controls to non-social stimuli [19]), follow other people's gaze spontaneously or make normal eye contact.[53] In experimental settings using cueing tasks and eye movement (saccade) recordings, however, they can show normal overt orienting responses in response to explicit eye gaze cues and to arrow cues.[54] One implication of these

findings is that cueing, as a form of rule-based or causal relationship, can be employed to improve social functioning. Under implicit cueing conditions, individuals with HFA/AS show impaired ability to integrate emotion (fear) with gaze direction, which is opposite the effect seen in schizophrenia.

Further, individuals with schizophrenia show impairments in recognizing facial affect (particularly fear) and in making social judgments based on facial features,[55,56] but intact ability to experience emotions. In both HFA/AS and schizophrenia, there is difficulty modifying behavior based on implicit facial emotional information. In HFA/AS, miscuing occurs when a facial emotion is not automatically taken as a cue,[57] or when it is taken as cue but is avoided [58]. People with schizophrenia show some difficulties that are similar to those in HFA/AS. In one study, they did not differ from controls in gaze discrimination performance, but as subjects decided when faces (i.e., facial stimuli) were making eye contact, different brain regions were activated between groups when the stimuli were rotated from a head-on view.[59] Interestingly, results of studies that examined gaze discrimination in schizophrenia are mixed.[60–62] Miscuing in schizophrenia is also more likely to occur when a facial emotion/intention is perceived in error. This can occur as a function of several factors, including levels of positive psychiatric symptoms. Pinkham et al showed, for example, that when subjects with schizophrenia were divided into groups with and without active paranoid ideation at the time of the test, that the groups did not differ in overall task accuracy.[63] The paranoid subjects, however, showed more errors than the non-paranoid subjects, in labeling neutral faces as angry.

Rondan and Deruelle[64] examined visual processing style in adults with HFA/AS and controls. Both HFA/AS participants and controls showed a preference for matching targets according to global features on a task involving hierarchical stimuli (i.e., they matched small squares arranged in the shape of a circle to little circles arranged in the shape of a circle, instead of to small squares arranged in a square). Compared to controls, HFA/AS participants showed a preference for details over configuration, however, on a task involving inter-elemental spatial relationships (i.e., they matched geometric shapes arranged in the shape of a face to the same constituent shapes arranged in the shape of a face with different spatial proportions, instead of to different constituent shapes in the shape of a face with the same spatial proportions). Whereas HFA/AS involves problems with static aspects of visual processing (e.g., perceiving details rather than configurations), schizophrenia also involves problems with more dynamic aspects of visual processing. For example, individuals with schizophrenia show eye tracking dysfunction in a variety of ways, including trouble maintaining visual pursuit of predictably moving targets.[65,66] Despite differences in temporal aspects of visual processing between HFA/AS and schizophrenia, there are overlapping deficits in relying on discrete details or moments instead of relational information or continuity of information to regulate behavior.

Eye contact—Eye contact is an important aspect of gaze and social behavior in many species,[53] that is also among the foundations of communications and social interaction in humans.[53,67,68] Eye contact helps modulate gaze, orientation and joint attention, and helps to activate and modulate brain regions involved in social function.[67,68] Cues from eye contact often inform social perception and influence how we act or modify our actions (i.e., adapt) in given social situations.

Individuals with HFA/AS show well-documented deficits in related areas, such as gaze monitoring and joint attention, as noted above.[39] Based on eye-tracking data, individuals with autism spectrum disorders showed atypical reflexive gaze by actively avoiding eye contact or failing to orient to the eyes.[58] This effect was seen regardless of whether faces had happy, fearful, or neutral expressions, and predicted performance on an emotion

recognition task. These findings suggest that avoiding eye contact may be a cause, as well as a result of deficits in emotional facial recognition. Moreover, children with HFA/AS process eye contact more poorly than typically developing children, when shown pictures of faces.[67,69] Typically developing children performed better when the faces were shown in upright positions than when they were shown in inverted positions. Children with autistic spectrum disorders performed best when the faces were presented in full frontal views, regardless of whether they were presented in upright or inverted positions. The autistic children did not perform as well when facial orientations were turned somewhat, suggesting that compared to typically developing children, they processed the facial information abnormally, such as on the basis of bilateral symmetry.

As noted in the previous section, individuals with schizophrenia also process eye contact information differently than controls, even when they show similar levels of discrimination, behaviorally. Implicit processing of social cues in individuals with schizophrenia was assessed by asking them to classify words by pressing “left” or “right” while facial expressions with eye gaze averted to the left or right flashed in the background.[70] Interestingly, participants were slower to classify words that were incongruent to the direction of eye gaze than words that were congruent, but this effect was observed only for expressions of fear. A similar effect of fear in capturing attention has also been seen among individuals with schizophrenia.

Theory of Mind (ToM)—ToM is a construct that accounts for others having beliefs, wants, plans, or intentions that are distinct from ours. It also includes an understanding of irony, metaphors and *faux pas*, as examples of ways of understanding the meaning or intent of others’ statements beyond the literal, concrete meaning of the words. But any construct of ‘Other’ presumes first a concept of ‘Self’. Although the concept of ToM is multidimensional and complex, there is compelling evidence that aspects of it are impaired in HFA/AS and in schizophrenia.[53,71–73] Taken as a cognitive mechanism, ToM operates in a relational context, which as we have seen is often impaired in schizophrenia and HFA/AS.

In individuals with clinically stable, first-episode schizophrenia, there may be only a moderate influence of cognitive deficits on ToM, and impaired ToM may exist independent of clinical state, alexithymia, and capacity for empathy.[74] Further, there is evidence of a negative correlation between social anxiety and perspective taking, as well as a positive correlation between empathy and ToM in patients with first-episode psychosis relative to patients with chronic schizophrenia.[75] Thus, it may be that the effects of targeting cognitive impairment and ToM for remediation may not vary as a function of clinical severity, whereas enlisting empathy to increase ToM may be more effective earlier than later in the clinical course of schizophrenia.

First-order ToM involves having knowledge of another mind state. Second-order ToM involves appreciating that another person holds a different belief, and factoring this other belief (both *that* there is another belief, as well as *what* this belief is) into his or her own sense of reality (meaning-making). Stratta and colleagues (2010) found that 12–13% of schizophrenia patients scored correctly on second-order ToM but not first-order ToM. It is interesting to speculate about the clinical features of individuals with schizophrenia who display intact second-order but impaired first-order ToM. For example, it is possible that this discrepancy contributes to ontological instability.[76]

Consistent with the role of the hippocampus in integrating autonoetic awareness with episodic and procedural memory (above), autobiographical memory has been linked with ToM abilities in individuals with HFA/AS.[77] Contrary to evidence of deficits in facial emotion recognition, however, a recent study found no differences in performance on the

Eyes Test between individuals with HFA, AS, and controls.[78] This may provide clues for targeting and designing approaches for intervention; for example, matching cognitive abilities (e.g., memory) to salient details of social communication (e.g., inferring mental states from eyes instead of the whole face).

Although ToM can be can be dissociated partially from several related functions, such as cognition and clinical state,[74] it is probably a composite construct that involves a family of abilities that includes joint attention, eye contact, emotion processing, perceptual recognition abilities, empathy, cognitive abilities (e.g., memory, executive functions) and language, among others.[79] Moreover, ToM develops in accordance with a variety of environmental experiences, such as parenting, education, training and social interaction. While the focus of this review involves autism and schizophrenia, deficits in other neurodevelopmental disorders, such as attention deficit/hyperactivity disorder (ADHD) and acquired brain disorders (e.g., traumatic brain injuries), particularly involving the non-dominant hemisphere, are also associated with impairments in ToM.[80–82] The multifactorial nature of ToM contributes to variability in patterns of impairment in different disorders, as shown in a recent study that compared individuals with childhood schizophrenia with children who had autism and with normally developing children.[83] Children with schizophrenia were impaired in ‘false-belief’ tasks, but they showed better understanding of deception than did the children with autism (and the normally developing children). The children with autism showed a broader range of ToM impairments generally than did the children with schizophrenia.

Findings such as these raise the point that the breadth and severity of ToM deficits in schizophrenia often varies between studies.[71] State dependence is a moderator variable that might explain some of this variability, as patients with higher positive symptoms, such as paranoia and delusions, often show greater ToM deficits than patients with lower levels of such symptoms.[71,84] A recent meta-analysis confirmed this view, in part by showing that ‘remitted’ patients showed lower levels of ToM deficits than non-remitted patients.[85] The effect sizes of ToM deficits remained large, however, in remitted patients (Cohen’s $d = 0.80$, versus 1.21 in non-remitted patients).

Brain

The nature and extent of abnormal brain function in schizophrenia and HFA/AS are areas of intense interest and study. Here we emphasize a few representative areas of overlap in brain volumes that may underlie similarities in clinical, cognitive or social dysfunctions. Developmental features of HFA/AS and schizophrenia are especially relevant at this level, as is the passage of time as an organizing principle of adaptation.

Numerous structural and functional brain abnormalities occur in both schizophrenia and autism, although results vary between and within disorders, at least partly as a function of methodological differences between studies.[59,67,86–91] A meta-analysis of structural MRI studies in autism showed, for example, increased volumes in total brain, both hemispheres, the cerebellum and the caudate.[87] Toal et al also found increased volume in the right caudate, and in more restricted clusters in the brainstem, right middle frontal gyrus, precentral and postcentral gyri (that extended bilaterally to the cingulate gyrus, among other areas).[88] Cheung et al, using a modification of Anatomical Likelihood estimation (ALE), did not show global differences in gray matter between subjects with autistic spectrum disorders and controls in most studies,[86] but they did show lower gray matter volumes in several striato-limbic regions that are also lower in schizophrenia.[86,92] These included the right parahippocampal gyrus, the posterior cingulate, the putamen, the left insula and the left thalamus. Somewhat in contrast to HFA/AS, schizophrenia is associated more with lowered volume than with increased volume, especially in whole brain and in hippocampus.[89,93]

Differences in cerebellar[86–88] and amygdala[87,90,91] volumes are reported in some studies, but not others, within schizophrenia and autism spectrum disorders. These differences are influenced by both methodological and other variables (e.g., younger ages were associated with larger amygdala volumes; see [87]).

The question of hippocampal volume abnormalities is less clear in HFA/AS than it is in schizophrenia. Increased bilateral hippocampal volumes were reported in children with HFA,[94] whereas differences in adults are more equivocal.[87,95,96] By contrast, decreased hippocampal volume is characteristic of schizophrenia, with no apparent effect of duration of illness.[89,93] Nevertheless, decreased volumes in the parahippocamal gyri in both disorders implicate both the hippocampal formation and the medial temporal lobe more generally in their neuropathologies. It should be emphasized that the hippocampus is also a part of a broader system involving the social environment. Structural abnormalities early in development—such as altered hippocampal volumes—should correspond to abnormal development of other brain structures and related processes. This is borne out to some degree by evidence of association cortex and white matter abnormalities in HFA/AS, and by research that defines HFA/AS and schizophrenia as disorders of integration and connectivity.[97,98] In schizophrenia, smaller hippocampal volumes co-exist with problems discriminating relevant from irrelevant information or discerning figure and ground relationships, as demonstrated by research on thalamic lateral inhibition and sensory gating paradigms, respectively.[99,100] One study found decreased gray matter volume in the right insula in adults with pervasive developmental disorders versus controls, and that gray matter volume correlated negatively with Autism Spectrum Quotient scores.[101] Other studies involving HFA/AS relate social and cognitive deficits to inefficient connectivity in the mirror neuron system and between limbic and prefrontal areas in HFA/AS.[102,103]

Genetics

Like many complex psychiatric disorders and normal mental abilities, schizophrenia and autism result from genetic etiological components that interact with environmental factors to facilitate either optimal or disordered function.[104] Evidence for a genetic influence in schizophrenia is compelling at this point,[3,105] based on both behavioral genetic and molecular biologic studies.[106–109] One recent review of twin studies showed, for example, that variance attributable to heritability was about 84%, and that if one sibling developed the disorder, the risk to the other sibling would increase about 12-fold.[106] Although linkage studies have had little success in identifying genes that contribute to the development of schizophrenia,[105] association studies have identified many genes involved in neuronal signaling or other aspects of brain structure and function whose dysfunction might contribute to schizophrenia.[109] Several of these genes may be related to either the diagnostic category of schizophrenia, or to quantitative endophenotypes for schizophrenia. A recent study from the Consortium on the Genetics of Schizophrenia (COGS), for example, examined 12 heritable endophenotypes[110] in relation to 1594 single nucleotide polymorphisms (SNP) identified from 94 genes.[111] The 47 strongest SNP-endophenotype combinations exceeded the number of significant findings expected to occur by chance alone.

Other paradigms have also shed light on genetic mechanisms involved in schizophrenia. These include recent work showing, for example, differences in gene expression between subjects with schizophrenia, bipolar disorder and controls,[112] gene splicing[113] and abnormalities in genomic copy number variants (CNVs).[108]

Like schizophrenia, autism (including HFA/AS) has a significant genetic component. In their review of twin studies, Glatt et al reported a heritability estimate of 93% for autism, with a relative risk of 22 for siblings if one twin develops autism (i.e. they are 22 times more

likely to develop autism than are individuals drawn from the general population). Similar to the notion of a schizophrenia spectrum in which non-psychotic relatives show milder features of schizophrenia,[114] non-autistic relatives of individuals with autism often show milder features of autism.[115] Moreover, numerous candidate genes have been proposed to contribute to the disorder,[116] and many CNVs have been reported.[117]

Although family studies of schizophrenia and of autism show consistently elevated rates of disorders presumed to lie in the schizophrenia and autistic spectrums respectively, it is notable that diagnostic overlap also occurs. In one study, for example, half of a group of individuals with autism (not restricted to HFA/AS) also met DSM-IV diagnostic criteria for schizophrenia, disorganized type.[118] In another study, 20% of subjects in a clinical high risk group for psychosis and a first episode psychosis group met diagnostic criteria for an autistic spectrum disorder.[41] A few studies showed that parental diagnoses of schizophrenia were associated with elevated rates of autism in offspring.[119,120]

Moreover, certain co-morbid medical conditions are elevated in both disorders, such as amyotrophic lateral sclerosis (ALS) and several bleeding disorders (e.g., Gaucher's disease), and may be related to similar chromosomal regions.[121] Interestingly, overlapping genetic mechanisms do not necessarily produce the same phenotypic effects. Crespi and Thiselton showed evidence, for example, that alleles at DRB1 influence risk for rheumatoid arthritis, schizophrenia and autism in a pleiotropic manner.[122] Alleles at DRB1*04 increased risk for arthritis and autism but decreased it for schizophrenia, while alleles at DRB1*13 alleles reduce the risk for arthritis and autism, but increase it for schizophrenia. Deletions in the 22q11.2 region (also known as velocardiofacial syndrome) is a well-known example of a CNV that confers risk for both autism and for schizophrenia.[117] Copy number variants at other chromosomal locations, such as 16p11.2, are also associated with schizophrenia, autism and other disorders.[123–125] Similarly, CNVs that were associated with another neurodevelopmental disorder, ADHD, were reported in both autism and schizophrenia at the same chromosomal loci.[126] In addition to chromosomal locations, several candidate genes have been implicated in both disorders, such as disrupted in schizophrenia (DISC1),[127,128] contactin-associated protein-2 (CNTNAP2)[117] and others.[129]

Summary

This review focused on several substantive areas of overlap between schizophrenia and autism, with an emphasis on HFA/AS. Representative examples involving cognitive deficits, social dysfunction, brain abnormalities and genetics show significant areas of correspondence between these two conditions, and the spectra they represent. It should be noted that while the sections on cognition and social function focused on HFA/AS, the sections on brain function and genetics did not maintain that distinction to the same degree, but showed similar levels of correspondence with schizophrenia. Moreover, the areas selected for review, though important functionally or etiologically, are only a subset of domains in which the two conditions might overlap. Other proposed areas of overlap are related to clinical symptoms (including paranoia and psychosis), abnormal information processing (as shown by 'sensory gating' problems), minor physical anomalies (such as neurological 'soft signs) and vitamin D deficiency during pregnancy, for example.[86]

Forty years after schizophrenia and autism separated diagnostically into distinct disorders, however, the purpose of these comparisons is not to conflate them again. Despite apparent similarities at several levels of analysis, they remain distinct entities, with important differences in clinical phenotypes, age of onset, neurobiological mediation and treatment. Each of the domains reviewed in this paper showed significant differences in addition to the similarities. Nevertheless, the similarities in phenotypes (cognition, social function and brain

structure) and genotypes (overlapping genes and genetic mechanisms) support hypotheses that these disorders are not entirely unique, either.[86,108,117] Moreover, the overlap between schizophrenia and autism may be part of a broader set of overlaps between these neurodevelopmental disorders and others, such as ADHD, bipolar disorder and intellectual disability.[108,126] In this view, common pleiotropic risk alleles and rarer risk alleles, together with protective genetic factors and other environmental and biological factors can produce a number of different, heterogeneous disorders that may share certain features in common, but differ along other dimensions.

Both the etiological and the functional significance of these areas of overlap are uncertain at this time. If several major dimensions of function share pathological and possibly etiological similarities, however, then the study of these concordances may shed additional light on the nature of both disorders. Among the questions future research may help to resolve are which problems are more etiological, and which are more resultant. We proposed that psychosis, for example, despite its disruptive effects in schizophrenia, was more likely a non-specific consequence of earlier, etiological factors.[130]

The resolution of such issues, in turn, may facilitate the development of novel treatment targets, or suggest approaches that are known to be useful for one disorder, for use with the other disorder. Antipsychotic medications, for example, which have long been first-line treatments for schizophrenia, have been utilized more recently in other psychiatric conditions, including autism.[131] The administration of oxytocin to subjects with either schizophrenia or with autism, shows preliminary promise of improving social cognition, mood problems and psychotic symptoms in both autism and schizophrenia.[132–134] In this instance, positive effects in any of these clinically significant domains in either the schizophrenia or autism spectra is likely to encourage investigation of these problems in the other spectra. Similarly, non-pharmacological treatments such as cognitive enhancement therapy, which is a promising intervention for cognitive problems in schizophrenia,[135,136] may have applications for autism as well. More generally, the growing range of apparent similarities between autism and schizophrenia raises the potentially significant possibility that etiological overlaps of their spectra may extend to productive overlaps in therapeutic intervention strategies.

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