

NEURODEVELOPMENTAL DISORDERS WITH COMORBID AFFECTIVE DISORDERS SOMETIMES
PRODUCE PSYCHIATRIC CONDITIONS TRADITIONALLY DIAGNOSED AS SCHIZOPHRENIA

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Abstract

The knowledge in psychiatric genetics, neuroanatomy, functional neuroanatomy, neuropsychology, neuropsychopharmacology and clinical psychiatry, has immensely increased in the last decades. Here, the psychiatric conditions schizophrenia, affective disorders and autism spectrum disorder are discussed. Reported findings in relevant literature and our clinical experience in adult psychiatry in line with these findings, are subjects of this article. Disorders that in the last 100 years typically have been described as schizophrenia might today be better viewed as neurodevelopmental disorders (NDD:s), particularly autism spectrum disorder, combined with affective disorders. Also in affective disorders, without any signs and symptoms typical of a diagnosis of schizophrenia, NDD:s are very common, albeit generally less severe. The ensuing view on schizophrenia and on affective disorders respectively has very important and far reaching conceptual and clinical implications.

Key words: schizophrenia, neurodevelopmental disorders, autism spectrum disorder, ADHD, affective disorders, depression, bipolar disorder, manic symptoms, mixed episodes

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Introduction

Over the years, there have been many opinions on how schizophrenia should be diagnosed and separated from other psychiatric disorders with psychotic symptoms. Various diagnostic criteria have been used over time. The criteria have varied from strict and tight to very wide, and hence the prevalence has varied up to four times (Cooper 1972).

Emil Kraepelin was the first who defined and demarcated schizophrenia in 1896, when he described dementia praecox (Decker 2007). Kraepelin noted that the disorder had early onset and was characterized by a progressive and sustained deterioration of cognitive and behavioral functions. Eugen Bleuler introduced the term schizophrenia, "split mind", in 1911. Unlike Kraepelin, Bleuler stressed the symptomatology, including the "basic symptoms": disordered association, flat affect, ambivalence, and autism (Moskowitz and Heim 2011).

The Diagnostic and Statistical Manual, 3rd edition, DSM-III, was published in 1980, and had an impact worldwide. One of the main objectives for the creation of this version of DSM with its so called operational diagnostic criteria, with obvious symptom criteria for all psychiatric diagnoses, was that a certain minimal set of criteria, and subsequently diagnosis, should define a certain mental disorder in an objective and reliable manner (Williams and American Psychiatric Association 1980).

To diagnose a syndrome or a disease, ie a nosological entity, according to DSM-III or later revisions, the diagnosis should, in addition to being distinguished by a defined symptom constellation, show uniformity in typical syndrome or disease characteristics. These nosological characteristics concern typical and typically associated clinical features, family history (heredity), course, including age of onset, prevalence, and differential diagnosis (Williams and American

Psychiatric Association 1980). Through systematic clinical studies, the knowledge of psychiatric disease characteristics at least partially improved over the years, and led to revisions of the DSM (American Psychiatric Association 2000).

Typical of most psychiatric diagnoses in the DSM - also in the versions DSM-IV, DSM-IV-TR and DSM-5 - is a considerable overlap of symptom criteria between different diagnoses. The diagnoses schizophrenia and autism spectrum disorder, ASD (autism, Aspergers syndrome and pervasive developmental disorder not otherwise specified, PPD-NOS), also have overlapping criteria in the DSM (American Psychiatric Association 2000).

In a review published a year ago, some important, both overlapping and differing, symptoms and nosological features of ASD and schizophrenia were discussed (Fitzgerald 2012). The distinctive symptoms and features have traditionally been taken as indicative of ASD and schizophrenia falling into two separate nosological entities. Important distinctive symptoms and other nosological features of ASD and schizophrenia are the so-called Schneiderian first rank symptoms, age of onset, brain size, and heredity. These symptoms and features are central in the discussion under I) some general and II) some other aspects below.

Even very practised clinicians, in our experience, frequently miss mild or subclinical depressions, as well as manic episodes with mainly irritable, not euphoric, mood and psychotic symptoms. This might be the main reason why many “non-affective” psychiatric diagnoses and concepts have been maintained over a very long time. An important example of such a “non-affective” psychiatric diagnosis is schizophrenia (Angst et al. 1983).

In our clinical work we have found that the identification of affective episodes generally requires careful assessment, including formal rating of the affective symptoms. In research, as well as in our own clinical experience in adult psychiatry, proper rating is required for diagnosis both in depression, mixed episodes (with concomitant depressive and manic symptoms, see below) and hypomania or mania (Brownhill et al. 2005, Lotfi et al. 2010, Phelps and Ghaemi 2006). In our experience, without such a rating, mild depression, and hypomania or mania with predominantly irritable mood, as well as states with rapidly changing mood or with a mix of depressive and manic symptoms, are extremely easily overlooked in clinical settings. Typically, psychotic symptoms are carefully noted by the clinician, while affective symptoms are overlooked.

Last decades, research has revealed that neurodevelopmental disorders, NDD:s – ie in this article ASD, ADHD, and conditions that appear to be mixtures thereof, of which certain forms sometimes are called Multiple Complex Developmental Disorder, McDD (Lahuis et al. 2009) – are prevalent in the population, across all ages (Brugha et al. 2011, Faraone and Antshel 2008). NDD:s are strongly associated with affective disorders (De-Long 2004, McGough et al. 2005, Munesue et al. 2008, Lugnegård et al. 2011). Further, psychotic symptoms, particularly auditory hallucinations, have proved to be common in at least the young normal population, without always indicating disease, although the presence of hallucinations in children and early teens means increased risk for later psychiatric illness (Kelleher et al. 2012). These findings all immensely affect psychiatric work.

The following section briefly describes some important aspects of our everyday clinical practice concerning patients who received a diagnosis of schizophrenia. Relevant literature and our experience in line with this literature are discussed in the further

sections of this article. The discussion illustrates the development of knowledge in terms of psychiatric diagnoses.

Our clinical experience in adult psychiatry concerning patients diagnosed with schizophrenia

Four of us (PS, RT, SÅ, MF) each have well more than 20 years of clinical experience as senior psychiatrists, and two of us (ACI and BP) as clinical psychologists. Our clinical experience, as described in this section, comes equally from both in- and out-patient care in psychiatric clinics with catchment areas of about 200 000 inhabitants. The patient records, in the clinic where four of us have worked for many years, are electronic since 15 years. Older paper records (sometimes older than 50 years) were scanned and hence are easily and instantly accessible through the electronic patient records. In cases where both the patient had a diagnosis of schizophrenia and older close relatives were psychiatrically ill, and at the same time both were patients of ours, we had the opportunity of reading patient records even older than 60 years, both in- and out-patient records.

Patients with a diagnosis of schizophrenia, in the clinics where we worked, fulfilled criteria according to DSM-III or later revisions of DSM, in the last three decades. Interestingly, almost none of our patients received this diagnosis in the last decade. Instead, patients who earlier would receive a diagnosis of schizophrenia, in the last decade received a diagnosis of a NDD, generally ASD, and concomitantly a diagnosis of a bipolar disorder.

An important marker of the diagnostic change concerning the diagnosis of schizophrenia was the revision of DSM-IV to DSM-IV-TR. One of our patients had some 10-15 years ago, in his early twenties, been hospitalized in the psychiatric ward due to a serious suicide attempt. He also had persecutory ideas and heard voices. In the next few years he had several short episodes with irritability, hostility and violent outbursts, where he was hospitalized. After a thorough psychiatric investigation he was given a diagnosis of schizophrenia. Some time thereafter, the patient was referred to a specialized psychiatric facility abroad, because of suspicion of concomitant autistic disorder. Based on this consultation an investigation was made by an outside specialist, who diagnosed paranoid schizophrenia and Asperger's syndrome – this was to this time, just a little more than a decade ago, considered almost sensational, as it was thought that the conditions defined by these two related diagnoses were mutually exclusive. In fact, DSM-IV, in 1994, stated that schizophrenia had to be ruled out if a diagnosis of Asperger's syndrome could be considered, a criterion that was dropped in the millennium revision, DSM-IV-TR (American Psychiatric Association 2000, Frances and American Psychiatric Association 1994).

Another patient exemplifying the diagnostic change was a young man who in his childhood after years of contact with a child and adolescent psychiatric facility was given a diagnosis of Asperger's syndrome. In his mid twenties he had several episodes where he was hospitalized in our psychiatric ward due to being agitated, irritable, violent and having psychotic symptoms (hearing voices and having paranoid delusions). Subsequently he received a diagnosis of schizophrenia.

Typically our patients with this diagnosis get increasingly isolated in their teens. These patients in this time generally have various depressive symptoms

with eg anhedonia, avolition and suicidal ideation or even suicidal attempts, apart from psychotic symptoms, that lead to psychiatric attendance. Some have episodes with irritability, hostility and violent outbursts. Such episodes, especially when frank psychotic symptoms are also present, often lead to psychiatric hospitalization. The mood is in these instances typically not euphoric. If, however, the patient is then interviewed and rated with a mania rating scale, other typical manic symptoms can often easily be detected, like eg pressured speech, motor agitation, grandiose ideas, disshelved clothing and poor sleep (not reported if the patient perceives little need for sleep). The severity of mania typically can fluctuate extremely within hours among such patients. The manic episode is hence easily overlooked, whereas psychotic symptoms often persist and are carefully noted in the patient record.

Reports from parents or other informants of our patients diagnosed with schizophrenia generally reveal different typical autistic traits in childhood. The patients may in their childhood eg have been socially awkward and had no or few friends, may have been bullied in school, may completely have devoted their time to special interests leaving no time for other activities and have been bound by routines or rules.

Generally in our clinical work with patients diagnosed with schizophrenia, there is no regular assessment over time of the patients' neurocognitive levels. Typically however, the social skills and the ability to work deteriorate progressively, so that patients with this diagnosis come to rely more and more on support for their social integration.

I) Some general aspects

There are no pathognomonic symptoms for the diagnosis of schizophrenia. The symptomatology is not more specific than that a combination of NDD (in particular ASD) and affective disorder can credibly explain the psychiatric conditions referred to by the diagnosis of schizophrenia. Psychotic symptoms of exactly the same kind as described in schizophrenia, eg auditory hallucinations and bizarre delusions, frequently occur in affective disorder (Baethge et al. 2005, Bräunig et al. 1998, Dunayevich and Keck 2000, Ohayon and Schatzberg 2002, Starkstein et al. 1996), and also in ASD (Hofvander et al. 2009). The so-called Schneiderian first-rank symptoms – delusions of being controlled by an external force; the belief that thoughts are being inserted into or withdrawn from one's conscious mind; the belief that one's thoughts are being broadcast to other people; and hearing hallucinatory voices that comment on one's thoughts or actions or that have a conversation with other hallucinated voices – are indeed more frequent in patients diagnosed with schizophrenia than affective disorders but also occur often in the latter (Rosen et al. 2011).

As a clinician, one is struck by the fact that most human traits and diseases are dimensional, ie "more or less", rather than categorical, "either-or". People are not either short or long, mentally retarded, or highly intelligent, have or do not have high blood pressure, susceptibility to myocardial infarction or stroke, etc. Diagnosis is due to practical reasons by contrast categorical. Significant for diagnoses as labels for illness is that they typically contain states of very different degrees of severity, from not significantly different from normality to severely disabling, ie they imply dimensionality. The diagnosis of schizophrenia holds in itself states of various degrees of severity, but

nevertheless signifies a serious state that is far from normality. The diagnosis of schizophrenia therefore implies a condition very different from normality – hence the categorical implication and stigmatizing effect of this diagnosis. Other important psychiatric diagnoses, such as ASD, ADHD and affective disorders or mood disorders in DSM, ie unipolar depression and bipolar syndrome, are, like schizophrenia and all other DSM-diagnoses, categorical, descriptive and "non-etiological" syndrome diagnoses. The DSM-diagnoses of ASD, ADHD and affective disorder however refer to conditions that, unlike conditions diagnosed as schizophrenia, in their mild forms may be difficult to discern from normality and hence imply dimensionality.

ASD and concomitant affective disorder do not give rise to conditions traditionally labelled schizophrenia, unless psychotic symptoms and progressive cognitive impairment also are present. In instances concerning our patients, where psychotic symptoms and progressive cognitive decline occur, previously a diagnosis of schizophrenia was given. We believe that ASD plus concurrent affective disorder, often with comorbid ADHD, better captures the condition in such cases. Psychotic symptoms occur in the context of both ASD and affective disorder, and progressive cognitive impairment in the context of affective disorder, at least in severe classic manic-depressive illness (Gildengers et al. 2009, Moorhead et al. 2007, Osuji and Cullum 2005).

Psychotic symptoms may thus be partly associated with the NDD, and partly with the concomitant affective disorder. These associations may explain the findings by Winokur (Winokur 1984) that psychotic symptoms appeared to be inherited similarly regardless of the severity of affective disorder, and regardless of whether it was unipolar or bipolar in close relatives. NDD:s often occur together with affective disorders, without necessarily giving rise to the clinical picture of schizophrenia. This possibly implies that both the NDD and the concomitant affective disorder have special features, when the clinical picture of schizophrenia or schizoaffective disorder occurs.

Of importance here is also that in certain cases, a patients symptoms of ASD are obvious only in episodes of affective disorders. This observation is supported by studies indicating that:

1. NDD:s appear to be strongly associated with personality disorders according to the DSM. ASD is often primarily associated with DSM's personality disorders in Cluster A: "odd" and "egocentric", and cluster C: "silent" and "anxious", and ADHD with personality disorders in cluster B: "dramatic" (Anckarsäter et al. 2006). ASD may also be associated with borderline personality disorder (Fitzgerald 2005), and
2. many patients meet the criteria – except for the criterion of life-long duration - for personality disorder according to the DSM, particularly for those in cluster A and C, during a depressive episode but not thereafter (Peselow et al. 1994).

II) Some other aspects

1. Affective disorder: subclinical-clinical and acute-chronic episodes as part of unipolar affective disorder or bipolar disorder, often as mixed episodes.

Episodes of unipolar affective disorder are characterized by depressed mood, "down". If the

disease includes episodes of both “down” and “up” or “spin-up”, it is called bipolar disorder. The latter condition is in the “up” episode, ie, hypomania or mania, characterized by elevated, expansive or irritable mood. Classic bipolar disorder, with episodes of full mania, is now called bipolar type I. Bipolar type II disorder and bipolar spectrum disorder, with hypomania instead of mania, are frequent in the population (Angst and Marneros 2001, Marneros 2001a, Angst et al. 2003). In the last decade it was realized that at least half of outpatients with depression in a general psychiatric population meet modified DSM-criteria by Jules Angst for a bipolar condition (Akiskal. 2007, Angst 2007, Skeppar and Adolfsson 2006).

The discovery of bipolar type II, in turn, led to the (re-) discovery of the common mixed episodes, especially in acute psychiatry (Marneros 2001b). Depressive mixed episodes in the clinical context refer to episodes of DSM major depression occurring simultaneously with three or more hypomanic symptoms (Benazzi 2008). Hypomanic and manic mixed episodes refer to hypomania and mania according to DSM concomitant with three or more depressive symptoms (Vieta and Morralla 2010). Identification of clinically defined mixed episodes leads in our experience to improved diagnosis of affective disorder.

In our experience, subclinical or undetected NDD:s are very often present in typical early teen onset of unipolar affective disorder or bipolar type II, or early adulthood onset in bipolar type I. Psychiatric comorbidity, especially depression and anxiety disorders, is extremely high in NDD:s (Ghaziuddin 2005, Hesslinger et al. 2003, Mazefsky et al. 2012). We suspect that NDD:s are a common prerequisite for the onset of affective disorder at the typical age of onset. NDD:s are in our experience much less pronounced in affective disorders than in conditions diagnosed as schizophrenia or schizoaffective disorder. An important parallel here is the presence of minor physical anomalies (MPA): the more MPA, the more pronounced the neurodevelopmental disorder seems to be (behold Section 7 below).

So-called schizotypal symptoms (reclusiveness, paranoid and idiosyncratic thinking, etc.) are strongly associated with ASD (Barneveld et al. 2011). Our clinical suspicion that NDD:s, often subclinical NDD:s, are a common prerequisite of affective disorders is supported by a large longitudinal study of the interaction between schizotypal symptoms and depression in Angst’s Zuerich-cohort. In that epidemiological study depression generally seems to be driven by schizotypal symptoms (Roessler et al. 2011).

In a study utilizing a symptoms inventory of 140 patients diagnosed with schizophrenia, of 40 with schizoaffective disorder and of 89 with affective disorder (Angst et al. 1983), it was concluded that:

“The hypothesis of a basic affective disorder common to all endogenous psychoses seems to be justified empirically” (p. 259).

These findings are consistent with our clinical experience: Patients whose psychiatric condition traditionally is diagnosed as schizophrenia, during their lengthy “relapse-free” periods exhibit chronic, usually subclinical or mild, depression, sometimes with chronic psychotic symptoms. “Relapses of schizophrenia” in our experience very often mean manic episodes with irritable mood and psychotic symptoms. We are convinced that, to detect this, a clinical assessment of affective symptom severity, should be made by the clinician at appointments with the patients in question. In this assessment, the use of an expert rating instrument,

such as the MADRS (Montgomery and Asberg 1979), and, if possible in the same consultation a self-rating instrument, such as the BDI (Beck and Beck 1972), for rating depression severity should be included. At an acute episode of schizophrenia, mania should always be suspected and consequently always, if possible, be assessed with a mania rating scale, such as the YMRS (Young et al. 1978).

2. About the illness course

The age of onset, AOO, of episodes of affective disorders, is typically in the early teens or early adulthood (Angst et al. 2003). AOO in patients diagnosed with schizophrenia is typically the teenage years or early adolescence, whereas a NDD should be diagnosable in childhood. In our experience less severe NDD:s, typically remain undetected or subclinical most of the time, only to become clinically obvious during affective illness episodes.

The course of typical bipolar type I, classic manic-depressive illness, often includes progressive impairment of cognitive and social functions, associated with increasing disease duration and increasing number of affective episodes (Malhi et al. 2007, Osuji and Cullum 2005, Post et al. 2012, Torrent et al. 2012). This progressive impairment in bipolar type I is, at least in some cases, probably not different from the course in the diagnosis of schizophrenia. Patients with bipolar type I in old age generally experience a much faster and more comprehensive progression of cognitive impairment than controls (Gildengers et al. 2009).

3. ASD, heritability and gender. Autism and schizophrenia.

Common to all autistic disorders are deficiencies in social and emotional reciprocity, in nonverbal and verbal communication, and limited imagination. Most scientists agree that Kanner autism (Blacher and Christensen 2011), Asperger’s syndrome (Sanders 2009) and unspecified autism, PDD-NOS (Huerta et al. 2012), are phenotypes or syndromes, caused by genetic anomalies. They are equal enough to be included in a single autism spectrum. In DSM-5, published in May 2013, all these states are included in the diagnosis of autism spectrum disorder (American Psychiatric Association 2013, Via et al. 2011, Wing and Potter 2002). ASD is, as mentioned, not uncommon in the general population: in a study on adults published 2011 the prevalence was almost 1% (Brugha et al. 2011).

ASD is highly heritable. Hence the pairwise concordance rate among monozygotic twins is much higher than among dizygotic twins, in one registry study 88% and 31%, respectively (Rosenberg et al. 2009).

Most patients with ASD have normal IQ (Autism and Developmental Disabilities Monitoring Network Surveillance Year 2000 Principal Investigators and Centers for Disease Control and Prevention 2007). The gender distribution shows a strong male dominance for Asperger’s syndrome, but in recent years a more even gender balance for the entire autism spectrum has been shown (Latif and Williams 2007). Explanations for the fact that Asperger’s syndrome is detected and diagnosed more often in men might be that women generally function better socially, at least on a superficial level, and clinicians are more familiar with the syndrome as it expresses itself in males (Yamasue et al. 2009). Deficits

in the ability to function socially are often the most obvious characteristic of ASD.

About 75 % of young adults with an NDD suffer from psychiatric comorbidity, including other NDD:s – in this context: ASD often occurs together with ADHD (Biederman et al. 1993, Ghaziuddin 2005, Giedd 2000, Hesslinger et al. 2003, Joshi et al. 2010, Mazefsky et al. 2012, Tantam 2000).

In recent years, due to the strong overlap, clinically, genetically and to a significant degree also neuro-anatomically, between ASD and schizophrenia, many psychiatric researchers have come to question the earlier view that these two diagnoses describe two inherently different conditions (King and Lord 2011, Kolvin 1971). In a newly published Swedish study, more than half of patients with DSM-IV schizophrenia diagnosis met strict criteria for ASD (Unenge Hallerback et al. 2012).

4. Family history and twin studies in ASD, schizophrenia, schizoaffective and affective disorder, and genetics in ASD, affective disorder and schizophrenia.

The family history of patients with a diagnosis of schizophrenia frequently reveals ASD, often in combination with ADHD and affective disorders among close relatives (Ghaziuddin 2005, Mortensen et al. 2010, Subotnik et al. 1997, Varghese et al. 2011). In a recently published article about a family study of ASD, schizophrenia and bipolar disorder with data derived from three very large registers, a strong association between these three nosological entities was found, suggesting that they share common etiological factors (Sullivan et al. 2012). This association was especially strong between ASD and schizophrenia (Sullivan et al. 2012). In both schizophrenia and unipolar schizoaffective disorder, a positive family history of unipolar depression is typical (Subotnik et al. 1997). In bipolar schizoaffective disorder a positive family history for bipolar disorder is typical (Kendler et al. 1995, Winokur et al. 1995).

Many twin studies comparing concordance among monozygotic and dizygotic twins in bipolar type I and schizophrenia were conducted in the last 80 years. They have shown much higher concordance for monozygotic than for dizygotic twins, ie the heritability is high and about equal for both these two diagnoses (Bertelsen et al. 1977, Cardno and Gottesman 2000, Onstad et al. 1991). Earlier family studies have shown that if some members of a particular family are diagnosed with schizophrenia, then close relatives will rarely have bipolar type I, but quite often diagnoses of unipolar depression, or unipolar, or sometimes bipolar, schizoaffective syndrome. These findings have traditionally been perceived as important indicators that would speak for schizophrenia and bipolar disorder as separate, independent disorders (Zerbin-Rudin. 1979). Manic episodes characterized by irritable, not elevated, mood, are in our experience, as mentioned earlier, very often or even usually missed in clinical assessment. If psychotic symptoms, eg hallucinations, delusions, irritability and disorganized behaviour, are present the manic episode with irritable mood is often perceived as a relapse of schizophrenia. This might be the explanation for the negative correlation between the diagnoses of bipolar type I and schizophrenia in the earlier twin and family studies.

Interestingly, if in the twin study about bipolar type I of Bertelsen et al. (Bertelsen et al. 1977) a broad

definition of affective illness is applied, then the pairwise concordance rate of monozygotic twins rises from 58% in bipolar type I to 84% (Kelsoe 2003), which is almost as high as for ASD in many twin studies (Rosenberg et al. 2009).

Simply put, we mean that those with bipolar type I in the family and the twin studies above during manic episodes had elevated (= euphoric) mood, whereas those with a diagnosis of schizophrenia during their manic episodes had irritable mood. In line with this notion of ours, based on our clinical experience, seem the findings in one study of bipolar disorder, published 2012, to be, where psychotic symptoms were associated with affective episodes characterized by anger, aggressiveness and hostility (Ballester et al. 2012). The clinical area involving differences between manias with elevated versus with irritable mood needs more research (Hanwella and de Silva 2011).

Genetic research comparing schizophrenia and ASD in the past decade has indicated that these conditions, as well as schizophrenia and affective disorder (specifically bipolar disorder), in fact share many aberrations (Gauthier et al. 2011, Ingason et al. 2011, Malhotra et al. 2011, Moreno-De-Luca et al. 2010, Voineskos et al. 2011, Wang et al. 2010). This research has strongly contributed to leading several psychiatrists to question Kraepelin's dichotomy of dementia praecox versus manic-depressive illness, and thus the concept of schizophrenia in its current meaning (Craddock and Owen 2010, Owen et al. 2011).

5. Idiosyncratic thinking in ASD can sometimes not be distinguished from delusions.

Often-described characteristics in individuals with ASD are idiosyncratic thinking and language (Loveland et al. 2001). The thought content and the language of these individuals have such a specific significance and meaning that it is difficult or impossible to understand for others. Idiosyncratic thinking is seen over a continuum: from "odd thoughts" to delusions, ie with thoughts of "psychotic character", which are not all modifiable or can not even be questioned by others. Common in idiosyncratic thinking is so-called magical thinking. In DSM:s schizotypal personality disorder (SZP) magical thinking is typical. Symptoms of SZP are common in ASD (Barneveld et al. 2011).

6. Neuropsychology in ASD and schizophrenia

Disabilities that currently are described in schizophrenia and NDD:s have much in common from the neuropsychological perspective (Nyden et al. 2010, Patniyot 2011). In this context, the cerebral functions defined as frontal lobe or executive functions are central.

The ability to self-direct is crucial to how well we succeed in society. Disorders of self-control or executive functioning are, at least partly, located in the frontal lobes. Executive functions are a collection of neurocognitive impairments that refers to the ability to interpret and process information, and control the individuals's behaviour and affects (Stuss 2011). Deficits in executive function concern: attention, problem solving, planning skill, ability to understand the context, self-directing, processing capacity and processing speed. These are the shortcomings that tend to cripple patients with ASD and those diagnosed with schizophrenia most.

The similarities between these two diagnoses

concerning cognitive deficits are striking (Boucher and Mayes 2011, Cheung et al. 2010, Eigsti 2011, Krabbendam and Jolles 2002, Travers et al, 2011). The differences in these diagnoses can be understood as differences between ASD with and without concomitant affective disorder. The neurocognitive deficits seen in ADHD also overlap considerably with schizophrenia (Oie and Rund 1999).

Increasing cognitive impairment over the years in patients diagnosed with schizophrenia may, as mentioned earlier, be due to the course of affective disorder in these patients (Gildengers et al. 2009, Moorhead et al. 2007, Osuji and Cullum 2005). The similarity of deficits in social cognition in ASD and schizophrenia are also striking (Derntl and Habel 2011).

7. Anatomy, neurology and neuroanatomy

Many studies report findings of, on a group level, a generally smaller brain size in schizophrenia, ADHD, bipolar type I and McDD (in the former three conditions smaller than controls) than in ASD (Hajjma et al. 2012, Hoogman et al. 2012, Lahuis et al. 2008, Reite et al. 2010, Selvaraj et al. 2012). Brain size in classic autism is on average larger in children aged 2-5 years, but not in neonates, adolescents or adults, compared to controls (Freitag et al. 2009, Redcay and Courchesne 2005). In adults neither autism nor Aspergers syndrome nor PDD-NOS is associated with increased cerebral size but with decreased cerebellar size (Hallahan et al. 2009).

In patients meeting criteria for ASD and with concomitant bipolar type I it is possible that the brain size is generally smaller than in controls, but this question was to our knowledge hitherto not studied. Since there seem to be many complications regarding general brain size in all the above-mentioned conditions (de Zeeuw et al. 2012, Rimol et al. 2012, Yamasaki et al. 2010), the question of general brain size is not further discussed here.

Neuroanatomical studies have revealed both common and distinctive findings in the brain in ASD and schizophrenia (Cheung et al. 2010, Sasamoto et al. 2011, Sugranyes et al. 2011). Divergent findings may be a result of the following: conditions hitherto termed schizophrenia are in fact conditions that occur when ASD is complicated by concurrent affective disorder. Neuroanatomical findings that distinguished healthy controls from patients with affective disorder in a study published last year, at least in part, support this assumption (Delvecchio et al. 2012).

One of the common specific brain regions involved in both affective disorders, in NDD (ASD and ADHD), and in conditions diagnosed as schizophrenia, is the prefrontal cortex, pfc (Dichter 2012, Kahnt et al. 2012, Morris et al. 2012, Townsend et al. 2013), crucial in its position and functions between the frontal lobes with their executive function and the limbic system/other deeper brain structures. The same neurotransmitter systems, ie the dopaminergic, the glutamatergic, the serotonergic and the GABAergic system, are of great importance in all these conditions (Cho et al. 2007, Chou et al. 2013, Cortese 2012, Dell'Osso et al. 2013, Edden et al. 2012, Fatemi et al. 2011, Hashimoto et al. 2013, Heinz and Schlagenhaut 2010, Lerond et al. 2013, Park and Kang 2013, Silvetti et al. 2013, Takahashi et al. 2013, Zmigrod et al. 2013) and they all have powerful influences on many of the common specific brain regions, including the pfc (Almada et al. 2009, Driesen et al. 2013, Floresco 2013, Thomases et al. 2013). The affinity of specific pharmaceuticals to

various specific neurotransmitter systems may hence explain the beneficial therapeutic effects of a given pharmaceutical compound on disparate conditions, diagnosed as NDD (ASD or ADHD), affective disorder or schizophrenia.

The presence of minor physical anomalies, MPA, and neurological soft signs, NSS are equally elevated in autism and schizophrenia (Gualtieri et al. 1982, Neelam et al. 2011, Ozgen et al. 2010, Tani et al. 2006). Examples of MPA are high brow, greater than normal distance between the eyes, low-set ears and "four-finger hand-line". There are no for schizophrenia pathognomonic MPA or NSS. Among patients with bipolar type I, MPA also occurs more frequently than in controls, but occurs even more frequently in patients with ASD or a schizophrenia diagnosis (Akabaliev et al. 2011). Studies indicate that the more MPA a patient has, the more severe is the ASD (Cheung et al. 2011, Geurts et al. 2012).

8. Pharmaceuticals

Antipsychotics, or neuroleptics, as they were called earlier, are in fact drugs with mainly anti-manic and mood stabilizing effect (Cookson 2001). In practice, these drugs have been used in treating acute mania since they became available, often as an adjunct to treatment with typical anti-manic/mood stabilizing medications, such as lithium or valproate. Several of these drugs are used in intramuscular depot form as mood stabilizing drugs (White et al. 1993).

Positive tests in terms of job performance were made with stimulants as adjunctive treatment of patients with schizophrenia diagnosis in the early 1980s (Cesarec and Nyman 1985). Also with antidepressants as adjunctive therapy, there have been positive trials in schizophrenia (Cornblatt et al. 2007).

The schizophrenia drug aripirazol, which is a partial dopamine agonist, has been shown to have positive effects in ADHD and positive effects in double-blind studies of irritability in ASD (Ercan et al. 2012, Marcus et al. 2009). The agent is in Sweden also approved for the acute treatment of mania and for long-term prophylactic treatment of bipolar type I. However aripirazol often gives increased anxiety, perhaps because of its dopamine agonist effect (El-Mallakh et al. 2012).

Conclusions

Affective disorders, including bipolar type I, show increased prevalence in patients with NDD:s, including ASD, compared to controls. If the manic episodes of the affective disorder in patients with NDD:s are characterized by euphoric (ie, elevated) mood, the diagnosis of bipolar type I is obvious and easy to make, especially if the patient previously had distinct depressive episodes and a positive family history of bipolar type I. The patient will then receive both the NDD diagnosis, such as Asperger's syndrome, and the diagnosis of bipolar type I.

If, however, the manic episodes of the affective disorder in patients with NDD:s are characterized by irritable mood, and if psychotic symptoms such as paranoia and auditory hallucinations are also present, the manic episodes often remain undetected and the episodes are interpreted instead as acute episodes of schizophrenia. Identifying mania in such cases is facilitated by formal interview including the use

of an instrument rating mania. Aside from irritable mood, other typical manic symptoms are then easily identified, such as pressured speech, wound up thinking, restlessness, grandiose ideas, decreased need for sleep, sloppy dress, and so on. Patients with ASD and bipolar type I with manic episodes characterized by irritable mood, who are diagnosed with schizophrenia, in our experience usually have long-lasting mild or subclinical depression, in addition to the psychotic symptoms. The depression is not detected unless the clinician conducts a formal interview including the use of a rating instrument for depression.

Our clinical findings here need to lead to research which further systematically studies irritable and euphoric mood in mania, prolonged mild or subclinical depression in bipolar type I, cognitive impairment in the long-term course of bipolar I, psychotic symptoms in affective disorders, and how all these factors are related to NDD and especially to ASD.

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