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Autism: a transdiagnostic, dimensional, construct of reasoning?

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Abstract

The concept of autism has changed across time, from the Bleulerian concept, which defined it as one of several symptoms of dementia praecox, to the present-day concept representing a pervasive development disorder. The present theoretical contribution to this special issue of EJN on autism introduces new theoretical ideas and discusses them in light of selected prior theories, clinical examples, and recent empirical evidence. The overall aim is to identify some present challenges of diagnostic practice and autism research and to suggest new pathways that may help direct future research. Future research must agree on the definitions of core concepts such as autism and psychosis. A possible redefinition of the concept of autism may be a condition in which the rationale of an individual's behaviour differs qualitatively from that of the social environment due to characteristic cognitive impairments affecting reasoning. A broad concept of psychosis could focus on deviances in the experience of reality resulting from impairments of reasoning. In this light and consistent with recent empirical evidence, it may be appropriate to redefine dementia praecox as a developmental disorder of reasoning. A future challenge of autism research may be to develop theoretical models that can account for the impact of complex processes acting at the social level in addition to complex neurobiological and psychological processes. Such models could profit from a distinction among processes related to (i) basic susceptibility, (ii) adaptive processes and (iii) decompensating factors involved in the development of manifest illness.

Introduction

Recently, at the FENS conference New Insights into Psychiatric Disorders through Computational, Biological and Developmental Approaches in Copenhagen, September 2016, several scientists called for new ideas and approaches to inform and guide future development of psychiatric research. The present contribution to this special issue of EJN on autism is an offer in response to this request. The theoretical considerations presented here are an attempt to identify the present challenges of autism research and to try to bridge the apparent gap that exists between the clinical world and theoretical models of mental illness. In light of clinical examples drawn from the field of child and adolescent psychiatry and relating to the original concept of autism, the present article focuses on how clinical experience may enlighten the development of overall theoretical models. The hope is that such models may help guide future research to move a step further in the direction of a more coherent understanding of the concept of autism and related concepts as well as of the mechanisms involved in the development of mental disorder in general.

The ideas presented here represent a further development of previously suggested theoretical ideas linking autism, schizophrenia and psychosis (Aggernæs, 2016). In developing these previous ideas, the present author owes much inspiration to Craddock & Owen (2010), Kapur *et al.* (2005), Aggernæs *et al.* (Aggernæs, 1975; Aggernæs *et al.*, 1981) and Piaget (1967). Another early source of inspiration has been the Italian sociologist Alberoni (1984) and his concept of the nascent state, a psychotic-like state thought to be involved in the dynamics of the development of society.

The overall aim is to identify core challenges in previous clinical and scientific practices and possible new pathways that may be fruitful to follow in the future in order to suggest new potential directions for autism research.

As recently suggested, it is possible to argue for the following three hypotheses (Aggernæs, 2016):

A phenomenological transdiagnostic hypothesis

Differences in age-related symptom expression, severity of illness, comorbidity of conditions, and a focus on psychosis may

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be what separate autism from schizophrenia at the clinical and phenomenological level. The same kind of cognitive impairments may operate in autism and schizophrenia and may manifest themselves at different timepoints and levels of cognitive complexity; see Figs 1 and 2.

A neurodevelopmental cognitive hypothesis

Cognitive challenges increase across the course of development, and at different levels of cognitive complexity, some individuals may reach the limits of their cognitive abilities. Due to cognitive impairments and merely as the result of events relating to typical development, some cognitively vulnerable individuals may experience enduring stress. This may increase their risk of developing clinically manifest disease; see Figs 1 and 2.

A conceptual hypothesis of psychosis

Cognitive impairments with no measurable abnormal changes within the neurotransmitter systems may be sufficient for psychosis to develop. Cognitive impairments may distort the experience of sensory input and result in cognitive discrepancies in which sensing or understanding the salient features of a cognitive experience may reflect a distorted picture of reality. The individual may not be aware that his or her thinking deviates from normal.

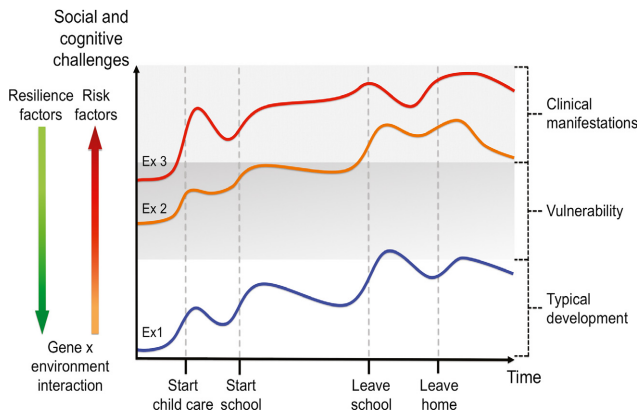

FIG. 1. Psychopathological courses. Ex 1 – Example 1: Neurotypical course; Ex 2 – Example 2: Schizophrenia; Ex 3 – Example 3: Autism.

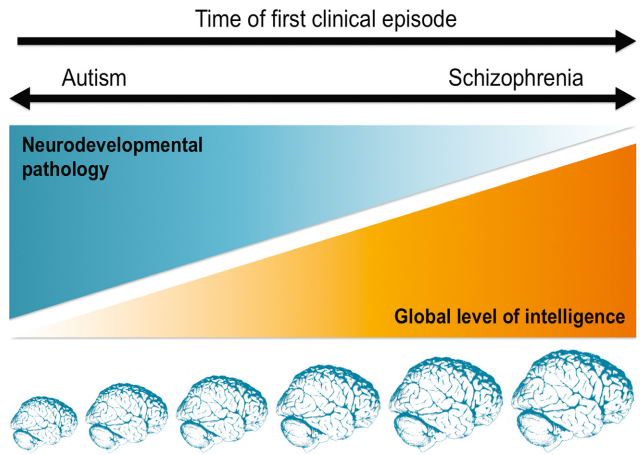

FIG. 2. Neurodevelopmental model.

These ideas may represent a dimensional transdiagnostic view and may be consistent with a model of the complex relationship between biological variation and some major forms of psychopathology including autism and schizophrenia suggested by Craddock & Owen (2010).

The overall assumption is that what may connect autism with schizophrenia is a characteristic rigidity of thought reflecting cognitive impairments comparable in nature but only becoming visible when susceptible individuals reach the limits of their cognitive abilities at different levels of cognitive complexity across the normal course of development (Aggernæs, 2016). In schizophrenia the rigidity of thought is clinically observed as a proneness to experience the imaginary world as being real (Aggernæs *et al.*, 1981), whereas in autism it is manifested by a concrete, inflexible type of thinking that may reflect difficulties with the handling of concepts or abstract language (Aggernæs, 2016). If this assumption is true, then from a neurocognitive perspective, clinical symptoms of schizophrenia may result from cognitive impairments comparable in nature but less severe than those of autism. The neurocognitive impairments may result from a genetic susceptibility whereby both autism and schizophrenia may represent neurodevelopmental disorders, even though the time of onset for the two disorders may differ (see Figs 1 and 2).

How, then, is autism to be distinguished conceptually from schizophrenia? Is it merely a matter of severity of illness, comorbidity, or the time of onset that separates the two conditions? Does it make sense to distinguish between these two phenomena at all if their aetiologies are alike and common pathogenic processes are involved in their development?

To answer such questions, it may be informative to relate to the original concept of autism developed by Bleuler and first published in 1911 (Bleuler, 1978). Since Bleuler did not distinguish between autism spectrum disorders and schizophrenia, his clinical description of the phenomena related to these disorders is unbiased by the current distinctions between autism spectrum disorders and schizophrenia in the international diagnostic guidelines and therefore may be a good starting point for a discussion.

Materials and Methods

The present theoretical contribution critically evaluates the concept of autism. The article contains an analysis and discussion of the original concept of autism and its relation to recently suggested hypotheses, the international diagnostic guidelines, clinical diagnostic practice, clinical challenges, prior and present theory and present empirical evidence. In addition to the concept of autism, the present article includes an analysis and discussion of the concept of psychosis. Finally, a discussion of both concepts in relation to the challenges of autism research and suggestions for new pathways to follow is included.

The Bleulerian concept of autism

According to Bleuler (2011), autism is a symptom related to the psychopathology of dementia praecox or the group of schizophrenias, a cerebral disease with primary symptoms in the form of disturbances of associations (Bleuler, 1978). Bleuler suggests that pathways established by experience appear to lose meaning and significance in dementia praecox. Secondary to the disease process and as a direct consequence of the loosening of associations, symptoms

including the phenomenon of autism may appear, with secondary symptoms being disturbances of affect; distortions of reality, including hallucinations and delusions; thought disorders; and ambivalence, among others. Bleuler (2011) suggests that the symptom of autism evolves as a direct consequence of a schizophrenic splitting of the psyche and that the inner life assumes pathological predominance (Bleuler, 1978). Characteristic of autistic thought content is a tendency for the patient to adhere to his or her ideas. The thoughts remain incorrigible and assume complete reality value for the patients while the subjective reality value of real life disappears. If the ideas of reality as presented by the psychiatrist are not in logical contact with the ideas of the patient, the patient may substitute his own meaning for that of the psychiatrist. The patients may no longer differentiate between reality and fantasy, or the real and autistic worlds may become entangled with one another or exist side by side. As an example of autistic thought content, Bleuler (2011) describes an episode in which a patient with dementia praecox asks when he can leave the mental hospital (Bleuler, 1978, p. 373). The answer given to the patient is that he may leave 'when he is well'. In response, the patient answers that he 'can go on foot'. Bleuler interprets this episode as an example of how the patient, in contrast to the established conditions of his discharge, assumes another set of conditions that he thinks can be met, namely, the expenses of his journey home.

As evident from the above description, Bleuler considers dementia praecox a degenerative cerebral disease and autism a symptom resulting from a loss of function, the loss of meaning and loss of associations, indicating an inherent assumption that these functions have already been acquired. Furthermore, the interpretation of the abovementioned example not only implies that the patient has an intention to follow his own wishes and adhere to his ideas – in this case, the release from hospital – but also may imply that the patient is aware of his choice of another set of conditions and may understand the difference between the two sets of conditions.

The very precise descriptions made by Bleuler allow the reader the option to reinterpret the content of his theory in light of present evidence and the recent theories now guiding our understandings. With autism now considered a developmental disorder, some questions may be relevant to raise regarding the content of the assumptions that previously guided Bleuler while developing his theory: Is there in fact an actual *loss* of intellectual function including a loss of associations and loss of meaning involved in the development of autism and/or schizophrenia? If not, how may the apparent loss of cognitive function be explained? Furthermore, what may the rationale of the patient be? Does the inner life of the patient assume a pathological predominance as suggested by Bleuler?

According to the previously suggested hypotheses, there may be no actual loss of intellectual functions. Rather, the associations and the ability to understand the meaning were never established. Instead, unrecognized cognitive impairments relative to the general level of cognitive development may be at play in the previous example, with neither the patient nor the psychiatrist being aware that the patient is unable to understand concepts like 'being well', let alone the difference between the two different sets of conditions. Furthermore, the rationale of the patient may be a very simple one, with the intention of the patient guided solely by his perspective resulting from an impaired ability to take or integrate another perspective. As such, the rationale of the patient may not result from a predominant inner life or from conscious or unconscious complexes. He may simply not realize that he is ill, and therefore, from his perspective, there is no hindrance to his leaving the hospital since he can easily walk home.

Autism and schizophrenia – a historical perspective

From a historical perspective, the concepts of autism and schizophrenia have changed markedly across times. While Bleuler (2011) defined the concept of autism as a characteristic symptom of dementia praecox, the group of schizophrenias, which was considered a degenerative disease (Bleuler, 1978), the current concepts of autism and schizophrenia represent separate disorders, reflected in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) by the distinction between autism spectrum disorders and schizophrenia spectrum disorders (American Psychiatric Association, 2013). According to the DSM-5 criteria, psychosis and psychosis-related symptoms appear to be the central features of schizophrenia spectrum disorders, whereas the core features of autism spectrum disorders are impairments in social interaction and communication as well as restricted, repetitive patterns of behaviours, interests or activities.

The present-day view is in sharp contrast to that of Bleuler, who considered both autism and distortions of reality (positive psychotic phenomena) to be various expressions or symptoms of the same basic disease group, dementia praecox, covering the group of schizophrenias (Bleuler, 1978). In common, both of these symptoms have definitions related to the concept of reality, though in different ways.

Bleuler (2011) assumes that the sense of reality in autism may not be totally lacking, but fails in relation to matters threatening to contradict complexes thought to trigger and maintain the condition (Bleuler, 1978). He reserves the term autism for conditions with an observed partial or total detachment from reality. Characteristic of autism are the inability to cope with reality and inappropriate reactions to outside influences that may include a lack of consistence between expressed wishes and actions and a marked indifference. Bleuler thus appears to distinguish between the experiences of 'distortions of reality', for example, hallucinations and delusions, and a 'partly and totally lacking sense of reality', the latter related to the phenomenon of autism (Bleuler, 1978). Such a distinction may be in line with the distinctions reflected by the two main hypotheses formulated by Maher (2006) concerning the relationship between delusions and hallucinations: the anomalous experience hypothesis and the basic reasoning hypothesis. Whereas the anomalous experience hypothesis suggests that a delusion may arise in response to an attempt to explain anomalous conscious experiences, the basic reasoning hypothesis dating back to Kraepelin (1889) suggests that a basic defect exists in the reasoning of deluded individuals (Maher, 2006). At first glance, these two hypotheses may appear to be mutually exclusive. However, when one focuses more closely on the content, what appears to separate these two hypotheses from one another may be merely the focus on an attempt to explain an experience at a conscious level. The anomalous experience hypothesis does not exclude the possibility of a concurrent defect of reasoning. Therefore, both of these hypotheses may turn out to be consistent with the *conceptual hypothesis of psychosis*.

A basic assumption of the redefined concept of psychosis reflected by the *conceptual hypothesis of psychosis* is that characteristic cognitive impairments related to reasoning with no measurable abnormal changes within the neurotransmitter systems may be sufficient for psychosis to develop and that no awareness of the deviation of thinking may be necessary. As previously discussed (Aggernæs, 2016), this assumption may be in line with observations by Aggernæs *et al.* (1981). These authors suggest that patients with schizophrenia are prone to a characteristic inflexible way of thinking also transiently observed across the typical cognitive development of

children and reflected in a tendency to experience nonexistent items as being real rather than existing items as being unreal. Interestingly, these observations may be consistent with the assumption by Bleuler that the sense of reality may not be totally lacking in autism as well as his observations that individuals with autistic symptoms may show good contact with their social environment with regard to everyday life (Bleuler, 1978). In line with Aggernæs *et al.* (1981), but years ahead, Bleuler recognized that autistic thought also occurs as a normal phenomenon (Bleuler, 1978). An example of this is a child who tells a lie without knowing that he is lying. The observations that deviances of thinking observed in schizophrenia and autistic symptoms may also be present across the typical cognitive development of children may be consistent with a dimensional approach to mental illness and the *neurodevelopmental cognitive hypothesis.* Furthermore, the observations may be in accordance with the suggested *phenomenological transdiagnostic hypothesis* and the suggestion that the rigidity of thought observed in patients with schizophrenia may reflect common cognitive impairments observed at a more severe level in patients with autism spectrum disorders (Aggernæs, 2016).

From the discussion above, it appears to be relevant to examine how an attempt to explain an experience at a conscious level or the lack of such an attempt may affect the resulting clinical expression of psychosis. Central to the discussion appears to be the question of what is the central feature of the phenomenon of psychosis. Does psychosis include a deviance of experience from reality that includes both distortions of reality and a partly or totally lacking sense of reality, or is the core feature restricted merely to distortions of reality that may result from an attempt to explain an experience at a conscious level? The present-day concept of psychosis appears to be narrowly focused on distortions of reality as a core feature. This may, in turn, be what separates the present-day diagnostic categories of autism spectrum disorders and schizophrenia.

Autism – the clinical use of the concept

Today, the concept of autism appears to have various meanings in the fields of child and adolescent psychiatry and adult psychiatry. In adult psychiatry, autism may reflect a disorder of the self, a core condition related to schizophrenia (Parnas, 2011), rather than a symptom of a developmental disorder. Such a view may be in line with the Bleulerian concept of autism. Furthermore, it is possible to encounter the use of the term autism simply to designate a symptom of social withdrawal. To my knowledge, there is no practice of systematic assessment in adult psychiatry focusing on the developmental history. This is surprising in light of the increasing evidence of premorbid symptoms, for example, cognitive symptoms prior to the development of schizophrenia (Nuechterlein *et al.*, 1994; Bredgaard & Glenthoj, 2000), and the suggestion that schizophrenia may be a neurodevelopmental disorder rather than a neurodegenerative disease (Tsuang, 2002). Furthermore, it appears to run contrary to the increasing evidence from birth cohort and high-risk studies in support of a neurodevelopmental approach to schizophrenia (Brüne, 2005; Clemmensen *et al.*, 2016; Laurens & Cullen, 2016).

In child and adolescent psychiatry, in accordance with the DSM-5 and the Tenth Revision of the International Classification of Diseases and Related Health Problems (ICD-10) diagnostic guidelines of mental disorders (World Health Organization, 1992; American Psychiatric Association, 2013), the term autism refers to autism spectrum disorders, which are considered neurodevelopmental disorders. A previous statement by Frith (2003) may illustrate how a change from the Bleulerian view of autism as a symptom of a degenerative disorder to the more recent view of autism as a developmental disorder has had an important impact related to the inherent assumptions of the disease. In her classic book 'Autism: Explaining the enigma' in which she describes the historical change in comprehension of the concept of autism, she states that the time of onset of a disorder is of crucial importance because a disorder that affects the normal course of development differs from a disorder that occurs later in life (Frith, 2003 p. 69). According to Frith (2003), both the condition described by Kanner (1943), with early onset and common comorbidity with intellectual disability, and that described by Asperger (1944), with later onset and normal language and cognitive development, may be various expressions of the developmental disorder of autism. The historical importance of the paradigm shift introduced by Kanner and Asperger and the impact of the change of view to consider autism a developmental disorder rather than a symptom of a degenerative condition cannot be underestimated.

Only a few years ago, the reported prevalence of autism spectrum disorders was approximately 1.5 : 1000 (Lord & Bailey, 2002). Today, reports of the prevalence of autism spectrum disorder reach the level of the hitherto reported prevalence of schizophrenia. For example, studies have reported an estimated prevalence of autism spectrum disorders of approximately 1 : 100 among children and adolescents in Denmark (Parner *et al.*, 2008; Elberling *et al.*, 2016). A suggestion in line with Waterhouse (2008) may be that the change in incidence results from increased awareness, increasing services for autism, changes in diagnostic criteria, and refined diagnostic procedures, now allowing for the identification of less severe cases of pervasive developmental disorders. Possibly these cases were previously recognized and classified using other diagnoses representing other conditions including schizophrenia. Alternatively, perhaps they were not recognized at all unless the individuals were observed later on in adult psychiatry, in this case possibly admitted because of secondary acquired conditions, for example, in the form of depression or psychosis. The idea of a lost generation of people who were previously excluded from a diagnosis of an autism spectrum condition and the possible implications has previously been discussed by Lai & Baron-Cohen (2015). These authors point to the importance of delineating differential diagnoses, comorbidities, and overlapping behaviour with other psychiatric diagnoses, including anxiety, depression, obsessive-compulsive disorder, psychosis, personality disorders, and other neurodevelopmental disorders. Such a view may be in line with the *phenomenological transdiagnostic hypothesis* and with previous observations by Bleuler. Regarding the onset of disease, Bleuler (2011), by careful examination of case histories, could identify autistic character anomalies consisting of a tendency to seclusion, withdrawal and irritability as being present in more than half of individuals suffering from dementia praecox (Bleuler, 1978). Bleuler suggested these anomalies to be the first symptoms of the disease, rather than merely a disposition to the disease. He described these children as unable to play with others and tending to follow their own ways, much in line with the characteristic symptoms of children with autism spectrum disorders as depicted in the DSM-5 and ICD-10 criteria (World Health Organization Geneva, 1992; American Psychiatric Association, 2013).

In a previous review, Myhr (1998) examined the distinction between different categories of pervasive developmental disorders and to what extent they reflected observed clinical data. The author focused on continuities and distinguishing features between disorders and related to the diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). Using this approach, Myhr (1998), in line with some previous studies, could identify two

overlapping subgroups of pervasive developmental disorders, a lower-functioning group and a higher-functioning group. While the first group was characterized by greater developmental compromise, social aloofness and a greater number of autistic symptoms, the second group showed higher IQ, fewer autistic symptoms, and more prosocial behaviour. Myhr, while suggesting a dimensional approach, concluded that subtypes of pervasive developmental disorders resemble each other and can be seen as existing on a continuum (Myhr, 1998). The differences between different subcategories appear to reflect IQ, adaptive behaviour and number of autistic symptoms rather than any distinctive symptomatology.

Surprisingly, and despite the increasing evidence in support of a dimensional approach that overall has guided the recent revision of the DSM-criteria, a categorical approach to autism spectrum disorders has guided the recent revision of the DSM-5 criteria regarding autism (American Psychiatric Association, 2013). Now, a distinction exists between autism spectrum disorders and social (pragmatic) communication disorders with the feature of restrictive, repetitive patterns of behaviour, interests or activities being what separate the one from the other. Such a distinction may be relevant insofar as it represents the view that these two conditions reflect phenomena of different origin. If not, the separation of the two conditions into distinct categories may distract researchers from considering a common cause and exploring their dimensional aspects. Some evidence that may be in support of the relevance of a distinction is found in the results of a study by Ronald *et al.* (2006), which examined the aetiological overlap between the three symptom domains of social impairments, communication impairments and restricted repetitive behaviours in a sample of 8-year-old twin pairs recruited from the general population. The three symptom domains were identified by the three subscales of the Childhood Asperger Syndrome Test. The researchers found low phenotypic correlations between the three subscales and high heritability for extreme autistic-like traits and autistic-like traits as measured on a continuum with no significant shared environmental influences. By genetic model fitting, distinct genetic influences were identified for the three components reflected by the subscales. According to the researchers, these results suggest that the triad of impairments defining autism spectrum disorders is heterogeneous genetically and indicate that homogeneity may exist across symptoms within autism spectrum disorder, whereas genetic heterogeneity may explain autistic-like traits. In contrast to this conclusion, Valla & Belmonte (2013) suggest an alternative triad of primary autistic traits that include the three trait categories of social interaction deficits, cognitive inflexibility, and sensory abnormalities. Based on a review of relevant factor analytic and correlational behavioural studies, they conclude that this triad may reflect more accurately the factor structure of autistic traits (Valla & Belmonte, 2013). These authors suggest that ritualistic behaviours are the result of developmentally emergent, compensatory mechanisms for interactions between cognitive inflexibility and sensory abnormalities. They offer a developmental dynamic interactionist model to explain the behavioural co-variance of initially independent social and nonsocial autistic traits resulting from dynamic trait interactions over the course of development.

Repetitive phenomena may be associated with stress (Gabriels *et al.*, 2013; Tordjman *et al.*, 2014; Yang *et al.*, 2015). What if restrictive, repetitive patterns of behaviour result from adaptive processes related to stress, rather than from other, more basic causes characterizing the distinction between autism spectrum disorders and social (pragmatic) communication disorders? Then, in line with the *phenomenological transdiagnostic hypothesis*, the two categories may actually represent various expressions of the same basic condition, for example, different expressions related to the level of severity of illness, comorbidity, age-related challenges or environmental risk factors affecting the expression of illness. This suggestion may be in line with the developmental dynamic interactionist model suggested by Valla & Belmonte (2013) and the ideas suggested by Belmonte *et al.* that some of the cognitive symptoms observed in autism spectrum disorders may develop as compensatory changes resulting from the interaction of normal cognitive development with abnormal neural information processing (Belmonte & Yurgelun-Todd, 2003; Belmonte *et al.*, 2004b). If this is true, then the present distinction between the two conditions may be at risk of repeating history in parallel to the previous change from the concept of dementia praecox to the distinction between autism spectrum disorders and schizophrenia.

The transdiagnostic challenge

More than hundred years ago, Bleuler (1911) was already aware of the inherent challenges involved in the process of delimiting conditions clinically and phenomenologically only on the basis of symptoms (Bleuler, 1978). During the process of classifying mental illness, the clinical psychiatrist may tend to focus on some symptoms while at the same time ignoring others (Gillberg, 2010). Gillberg (2010) use the term ESSENCE (Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations) to cover a group of often-overlapping neurodevelopmental syndromes including autism spectrum disorders and attention deficit disorders observed in preschool children. By the term, he emphasizes that the clinician may be at risk of overlooking the complexity of the neurodevelopmental conditions covered by the acronym as well as the comorbidity occurring between the symptoms.

Although it may appear easy to classify autism and other disorders given the vast abundance of diagnostic instruments and rating scales, in real life a few points on a Likert scale may be what separate autism spectrum disorders from social anxiety, obsessive-compulsive disorder, or schizophrenia. Furthermore, the clinical picture of schizotypal personality disorder may be difficult to distinguish from autism spectrum disorder or schizophrenia. Symptoms may overlap (Solomon *et al.*, 2011; Cochran *et al.*, 2013; Kästner *et al.*, 2015). The distinction among these conditions may, at times, be only a matter of focus or degree of severity of illness. Comments on the distinction between schizotypal personality disorder and Asperger syndrome from the Diagnostic and Statistical Manual of Mental Disorders DSM-IV-TR (American Psychiatric Association, Washington, 2000) may illustrate such a challenge. Regarding the distinction between the two disorders, the manual states that it may be very difficult to differentiate between schizotypal personality disorder and milder forms of autistic disorders including Asperger syndrome except by 'the even greater lack of social awareness and emotional reciprocity and stereotyped behaviours and interests' (American Psychiatric Association, 2000 p. 700). The manual does not contain any guidance regarding how to carry out such a differentiation. Another example of this challenge is one described by Kumra *et al.* (1998). These authors examine a condition named multidimensionally impaired disorder, characterized by the presence of both autistic traits and attention deficit hyperactivity disorder (ADHD) symptoms, and choose to consider it as belonging to the schizophrenia spectrum similar to very early-onset schizophrenia. They are aware, however, that the condition is highly similar to another condition described by the Yale Child Study Center, multiplex developmental disorder, considered by this group to be a disorder belonging to the autism spectrum. These complex disorders may exemplify the difficult and

somewhat arbitrary choices involved in the clinical and phenomenological distinction between autism and schizophrenia. The comorbidity between conditions, a focus on psychosis as suggested by the *phenomenological transdiagnostic hypothesis*, and the final choice of perspective may be the factors that separate autism spectrum disorders from schizophrenia in the present example.

From different perspectives, descriptions of almost identical behaviour may appear very dissimilar, and commonalities vanish simply because of a difference in focus. A comparison between the ICD-10 criteria for Asperger syndrome and *schizotypal disorder* with the latter written in italics may illustrate this point (World Health Organization Geneva, 1992). The descriptions differ with regard to the criteria of onset and the duration of symptoms. The symptoms are classified using different concepts, perspectives and details. Despite these differences, it seems possible to identify characteristic features of most symptoms in the classification of both disorders. While the focus of the description of Asperger syndrome is on the restrictions symptoms may impose on the behaviour of an individual, the description of schizotypal disorder, in contrast, appears to reflect the perspective of a 'wondering' social environment observing behaviour deviating from the norm. The following comparison of symptom criteria may illustrate how the symptoms may be 'translated' to each other. A 'failure adequately to use eye-to eye-gaze, facial expression, body posture, and gesture ….' may be consistent with *'behavior or appearance that is odd, eccentric or peculiar…'*. Furthermore, a 'lack of socio-emotional reciprocity as shown by an impaired or deviant response to other people's emotions; or lack of modulation of behavior according to social context; or a weak integration of social, emotional and communicative behaviors' may be in line with a *'poor rapport with others and a tendency to social withdrawal'*. In addition, 'a restricted, repetitive repertoire of interests, activities or special interests' may be described as *'vague, circumstantial, metaphorical, overelaborate, or stereotyped thinking, manifested by odd speech or in other ways without gross incoherence'*.

From an anthropological perspective, different clinical subcultures may exist in clinical settings as illustrated by the apparent differences in clinical practice and use of concepts in the fields of adult psychiatry and child and adolescent psychiatry. Pattern recognition may help guide the clinical psychiatrist during the diagnostic process; however, this may be at the risk of distracting the psychiatrist from paying attention to relevant differential diagnosis. Since the course of illness may depend on the perception of the clinical symptoms, it is likely that the diagnostic process by itself may influence the course of illness. For these reasons, there is a need to go beyond the symptom level and try to identify the common mechanisms that may underlie and give rise to the many different clinical expressions of autism, schizophrenia and related conditions.

Increasing evidence suggests an association between autism and schizophrenia spectrum disorders (Burbach & van der Zwaag, 2009; Guilmatre *et al.*, 2009; Rapoport *et al.*, 2009; Craddock & Owen, 2010; Moreno-De-Luca *et al.*, 2010; Solomon *et al.*, 2011; Sugranyes *et al.*, 2011; Eack *et al.*, 2013; Chung *et al.*, 2014; Chisholm *et al.*, 2015; Kirov, 2015). With the awareness of a possible overlap, several models have developed to explain the multiple shared phenotypic traits and common risk factors and to account for the increasing evidence suggesting a genetic overlap (Chisholm *et al.*, 2015). Future research may not only need to account for the heterogeneity of both conditions but also need to take the dimensional nature of these disorders into consideration and to examine evidence on multiple levels to be able to identify possible common biological markers. From a different perspective, based on the clinical appearance of conditions, the clinician must work with the same knowledge while delimiting mental illness.

Autism – the clinical challenge and cognitive markers

The severity of autistic core symptoms may vary significantly among children and adolescents with autism spectrum disorders and across age (Wiggins *et al.*, 2006; Daniels & Mandell, 2014). While it may not be possible to quantify the autistic core symptoms, it is possible to measure individual variations in autism-related cognitive markers across age and various psychiatric conditions. For decades, cognitive theories of autism have guided autism research as well as clinical practice (Rajendran & Mitchell, 2007). Previous research has demonstrated that the core symptoms of autism are associated with a wide range of underlying autism-related cognitive markers. These include deficits of mentalization or *theory of mind* (Frith & Happe, 1994), impaired ability to integrate inputs coherently as stated by *theory of weak central coherence* (Happe & Frith, 2006), executive dysfunctions (Hill, 2004), and dysfunctions in conceptual cognitive reasoning observed as impairments of imagination and abstract thinking (Ropar & Peebles, 2007; Alderson-Day, 2011; Alderson-Day & McGonigle-Chalmers, 2011). Several studies have examined the use of autism-related cognitive markers for clinical assessment (e.g. Hill, 2004; Happe & Frith, 2006; Schuwerk *et al.*, 2015). Despite promising results, unfortunately, the data lack sufficient consistency and power to provide a foundation for the development of cognitive normative tools for psychiatric screening of autism. The results are in line with those of a recent study that examined the relationship among selected cognitive abnormalities, impairments of theory of mind, executive dysfunctions and a local processing bias as well as their relation to various behavioural measures in two groups of children (Cantio *et al.*, 2016). The authors compare the results between a group with autism spectrum disorders and a group with neurotypical development. They find that although impairments of theory of mind and executive functions do not relate to the behavioural measures, these cognitive measures are able to differentiate between the two groups, with some of the cognitive tasks relating to each other. In light of their results, they do not exclude that it may be possible for a single universal cognitive cause to underlie the wide range of diagnostic symptoms in autism.

Williams *et al.* (2014, 2015), while testing the complex information processing model of autism previously suggested by Minshew *et al.*, have recently examined problem solving and adaptive functioning in individuals with autism spectrum disorder compared to individuals with typical development. The researchers used measures of conceptual reasoning reflecting problem solving and a report measure of adaptive functioning. Their findings indicate that individuals with high-functioning autism may have weaker conceptual reasoning ability compared to individuals with typical development of similar age and cognitive ability. Furthermore, their results suggest that flexibility of thought may potentially be more important for adaptive functioning in a natural environment than conceptual reasoning or problem solving (Williams *et al.*, 2014). Their results also indicate that although language may serve as a compensatory mechanism for learning, even relatively able adolescents and adults with autism may struggle with an inherent weakness in concept formation that challenges information processing as the demands of tasks increase (Williams *et al.*, 2015).

Recent studies provide new evidence showing that individuals with autism spectrum disorders have a reduced ability to integrate contextual task signals in the presence of noise stimuli (Sinha *et al.*, 2014; Van de Cruys *et al.*, 2014). Other studies demonstrate

impaired executive and social cognitive skills during test conditions that demand implicit monitoring of contextual signals (Froehlich *et al.*, 2012; Lawson *et al.*, 2014; Schuwerk *et al.*, 2015; Zaidel *et al.*, 2015). These results may be in agreement with recent hypotheses suggesting that the ability to integrate sensory input with previous experience and predict events may depend on cognitive load and the level of noise and that the autistic core symptoms and autism-related markers may result from deficits in predictive coding (White *et al.*, 2009; Van Eylen *et al.*, 2015).

A decrease in signal-to-noise ratio may result from abnormal brain connectivity, with either overconnected or underconnected networks affecting the information capacity of the networks (Belmonte & Yurgelun-Todd, 2003; Belmonte *et al.*, 2004a,b). The concept of connectivity, however, is complex. It may be possible to differentiate between local connectivity within neural assemblies and long-range connectivity between functional brain regions and to distinguish between the physical connectivity associated with synapses and tracts and the computational connectivity associated with information transfer (Belmonte *et al.*, 2004a). In autism spectrum disorders, high local connectivity may be observed together with low long-range connectivity. Increasing evidence suggests that the cerebellum and development of abnormal connectivity may be involved in autism, consistent with a preparatory theory suggesting that the fundamental purpose of the cerebellum is to predict internal conditions needed for a particular mental or motor operation and to set those conditions in preparation for the operation at hand (Courchesne & Allen, 1997).

From a clinical point of view, to go beyond the symptom level and identify possible cognitive markers may not be an easy task. The identification of deviances in play depends on knowledge-based expectations of what is relevant for the child's age and level of development. The quality of the developmental history information gathered from parents, teachers and other informants and the observations carried out by the clinical staff all have an impact on the result of the overall assessment. The observed deviances must be compared to what may be expected for an individual's age and in light of the global level of intelligence of the individual.

How do the disturbances of associations observed by Bleuler (2011) appear at the symptom level? Is it possible to identify a rigidity of thought reflecting characteristic cognitive impairments that may connect autism and schizophrenia, as suggested by *the phenomenological transdiagnostic hypothesis* and *the neurodevelopmental cognitive hypothesis*? Furthermore, is it possible to identify neurocognitive impairments, for example, executive dysfunctions or impairments of mentalization, of the ability to integrate inputs coherently, or of imagination and abstract thinking that may only become visible when susceptible individuals reach the limits of their cognitive abilities at different levels of cognitive complexity across the course of normal development, as suggested by *the neurodevelopmental cognitive hypothesis*?

Observed disturbances of associations

As suggested by the examples to follow, rigidity of thought may appear in different ways depending not only on the level of cognitive complexity related to a context but also on the ability of an individual to integrate previous experience with present experiences and to adapt depending on the global level of intelligence. Depending on the character of the observed challenges related to the integration of information and difficulties with generalization, it may be possible to divide the clinical appearance of symptoms into several categories:

Lack of integration between earlier experience and experiences in the present moment, including challenges in connecting events in time and space – literal type of thinking

Examples of literal thinking may be the following: A parent tells her toddler about a plan for the afternoon: 'We are going to the beach!', or 'We are going to have an ice cream!', or 'We are going to visit Aunt Rosy!'. The child becomes frustrated when he/she realizes that something else is going to occur first, for example, getting dressed, travelling by car, etc. In this case, the child perceives the invitation as if the event were going to occur immediately after the message, as the immediate next step in an order of events. The child is not aware of all the implicit actions needed ahead of the event.

Partial integration – challenges in generalizing from experience and connecting events in time

As illustrated above, in the context of a present situation, it may be a challenge for an individual with autism to predict future events and to adapt his/her behaviour accordingly. A cognitively vulnerable individual may have to consciously rather than automatically determine what is going on and what will happen. Depending on the complexity of the context, cognitively susceptible individuals may therefore constantly be at work trying to grasp what is happening and how to adapt accordingly. Depending on their global cognitive level, they may be more or less successful. The challenge in a present context may therefore differ markedly from the challenge related to grasping events in a context from a retrospective perspective. Some individuals may be able to grasp events from a retrospective perspective, for example, when a day has become a concrete event rather than an unknown, yet are unable to cope in the present moment and to generalize experiences and predict future events related to similar known contexts. Such challenges may be very difficult to identify in a clinical setting since the gathering of history information generally focuses on events that have already occurred in the past. An example of such a challenge may be the following: The parents of a 7-year-old boy with high-functioning autism wonder why he always rejects going to school in the morning. Each day they have conflicts and do not know how to motivate him; however, whenever they pick him up in the afternoon he has always had a good day and looks happy. This boy is unable to generalize and plan his day in light of previous experiences. Each morning he has no idea about what the day will bring, and he must constantly observe what is going on in order to determine what to do, for example, he must imitate the behaviour of the others in order to adapt. In contrast, at the end of the day, the boy knows what the day was like.

Partial integration – challenges in generalizing from experience and connecting contexts in space

Another challenge for an individual may be to generalize from previous experience in order to predict future events and to adapt behaviour accordingly when relevant in a new yet similar context. Here, the time aspect may not be important. What may be important is to be able to recognize in this new context what it has in common to a similar previous context. An example of such a challenge may be the following: A teenage girl is out shopping in a supermarket together with her mother. When the mother tells her that they are going to pay, the young girl moves directly to the desk and ignores the queue of people waiting to pay. While correcting the teenager, the mother tells her that they will have to queue up in order to pay.

The following week, when in the same supermarket, the girl queues up as told by her mother. However, while visiting another supermarket chain two weeks later, the teenager once again walks directly to the desk to pay while ignoring the queue. The mother then asks why she did not queue up. From the response of the teenager, the mother realizes that the girl was only able to generalize the experience to the particular supermarket where the mother corrected her the first time. She was unable to transfer the experience to other supermarkets or supermarket chains unless explicitly told.

Integration of own experience with future behaviour without concurrent integration of the expectations from the social environment

At an even more complex level, the behaviour of an individual may occur without concurrent integration of the expectations from the social environment, which may result from an impaired ability to take or integrate another perspective, with neither the individual nor the social environment being aware of it. The following example and the interpretation may be in line with the previous referred clinical example reported by Bleuler (2011) and may illustrate how lack of awareness or misinterpretation of the intentions of a cognitively vulnerable individual may give rise to misunderstandings, or even suggestions of manipulation. In this case, an adolescent with Asperger syndrome or schizophrenia admitted to a psychiatric ward had instructions to ask for advice when in need of help and to seek his appointed contacts among the staff when feeling bad. However, observations showed that the young man, contrary to the instructions, always went to seek advice from another person among the staff, a behaviour interpreted as obstructive. After careful examination of the situation, the staff realized that the reason why the young man always went to this particular staff member was simply that he knew this person from a previous admittance and felt safe. The patient had previously experienced that this particular staff member was able to help. The young man seeks solutions that he knows may work, but he is unable to predict how his actions may be perceived by the social environment, in this case the staff, and therefore does not adjust his behaviour accordingly. In line with the interpretation of the example by Bleuler, the rationale of the young man may also here be a very simple one rather than a more complex one, with the intention of the patient guided solely by his perspective resulting from an unrecognized impaired ability to integrate another perspective in his actions. If this is the case, then the present example may represent an example of deficits of mentalization.

As illustrated by the previous clinical examples, the difficulty in integrating previous experience with the present and in predicting the future may relate to the context and the ability to adapt. The challenges related to the task of integrating all impressions in a complex context, for example, in a social context, may depend on whether the information is explicitly stated or implied, consistent with the recent findings by Callenmark *et al.* from their study of explicit vs. implicit social cognition in autism spectrum disorder (Callenmark *et al.*, 2014). They examined the difference in response to explicit (prompted) and implicit (spontaneous) social cognition performance in a group of adolescents with autism spectrum disorder and a group of adolescents with neurotypical development. The authors found impairments in implicit (unprompted) but not explicit social cognition performance in the autism spectrum disorders group, suggesting that explicit, prompted answer formats may decrease the complexity of social cognition demands in a test situation whereas implicit, open formats may be closer to a complex real life situation. These results may illustrate the characteristic and frequently observed challenge in autism of understanding an implied message. Likewise, the results are in line with the frequent clinical observations showing that individuals with autism spectrum disorders may have comprehension difficulties unless the meaning of a context is explicitly stated.

Theory of mind, hypo-theory-of mind and hyper-theory-of-mind

As illustrated in the last example above, the behaviour of an individual may occur without concurrent integration of the expectations from the social environment resulting from an impaired ability to take or integrate another perspective, suggesting deficits of mentalization (Frith & Happe, 1994). The example illustrates what may occur in a social context when neither the individual nor the social environment is aware of the cognitive impairments. As illustrated above, the lack of social reciprocity may go both ways, with neither the patient nor the social environment understanding the intention of the other. A suggestion is that this may cause stress for the patient and may contribute further to his symptoms, increasing the risk of social withdrawal, anxiety, depression or psychosis, a suggestion that may be in line with the results of the studies on stress in autism conducted by Corbett *et al.* (2008, 2009, 2012, 2016) and Bishop-Fitzpatrick *et al.* (2015, 2017).

Impairments of theory of mind are observed not only in autism (Frith & Happe, 1994) but also in schizophrenia (Brüne, 2005). A recent meta-analysis based on 37 studies assessing mentalizing abilities either verbally or visually in adults with autism spectrum disorder or schizophrenia concluded that the two groups may share some cognitive processing deficits associated with mentalizing impairments (Chung *et al.*, 2014). The estimated effect sizes of impairments in verbal and visual mentalizing tasks for both clinical groups were statistically large and at a similar level. To identify and understand disorder-specific features of mentalizing in the future, the authors suggest the use of longitudinal designs that can compare the evolution of mentalizing abilities across the two disorders and the development of novel tasks that tap into specific psychological constructs or neural circuitry.

A recent study focuses on alterations in mentalization and their association with psychotic experiences, defined as psychotic symptoms present in the absence of psychotic illness (Clemmensen *et al.*, 2014). The authors distinguish between an exaggerated type of theory of mind, hyper-theory-of-mind, associated with psychotic disorder, and a hypo-theory-of-mind, the latter associated with a diagnosis of autism and negative symptoms. In a population-based sample of children, the researchers identify patterns of association between hyper-theory-of-mind and psychotic symptoms, with hyper-theory-of-mind strongly associated with delusional ideas having paranoid content. The authors are able to replicate these findings in a smaller high-prevalence study. They also find an increased risk of psychotic experiences in children with hypo-theory-of-mind; however, they do not replicate this finding in their second sample. The authors suggest that their results may be in line with a theory (Shamay-Tsoory *et al.*, 2007; Montag *et al.*, 2011) suggesting that general impairments of mentalization may be a vulnerability marker for psychosis, with other, more specific alterations of mentalization having a mediating role. Finally, they conclude that it may be relevant to apply more differentiated measures of theory of mind not only in research but also as part of clinical assessment.

Another study, conducted by Ciaramidaro *et al.* (2015), showed results that may be consistent with those of Clemmensen *et al.* (2014). In a study using functional magnetic resonance imaging (fMRI), these authors tested a hypo-hyper-intentionality hypothesis

suggesting that mentalizing problems in autism spectrum disorders differ from those in schizophrenia. This hypothesis was developed by Bara *et al.* (2011) and is part of a theoretical model of intention developed to examine the neurobiological bases of intention processing in both healthy people and people with impairments of the neurocognitive system underlying intention recognition. The hypothesis suggests that deficits in mental state attribution in autism are characterized by a tendency to treat people as devoid of intentions, in contrast to schizophrenia, wherein a tendency to over-attribute intentions to agents and physical events is observed. Ciaramidaro *et al.* (2015) examined neural responses and functional connectivity during the reading of others' intentions while comparing individuals with autism spectrum disorder, a group of individuals with paranoid schizophrenia and a group of gender- and IQ-matched control subjects. At the behavioural level, the group with autism spectrum disorder showed reduced accuracy, whereas the schizophrenia group showed increased reaction times. At the neural level, both clinical groups showed aberrant activation in core regions of the mentalizing network, the group with autism spectrum disorder showing less activation during the experimental condition while the schizophrenia group showed increased activation in the control condition. The results of the connectivity analyses were consistent with the idea that mind-reading problems in schizophrenia are due to an overactive intention-detection module, whereas mind-reading problems in autism spectrum disorders are due to an underactive intention-detection module.

Interestingly, the results both of the study by Clemmensen *et al.* (2014) and that of Ciaramidaro *et al.* (2015) may be in line with the previous suggestion that the difference between the anomalous experience and the basic reasoning hypotheses (Maher, 2006) may be merely a focus on the attempt to explain an experience at a conscious level and the resulting clinical expression of psychosis. If this is true, hyper-theory-of-mind may occur when cognitively vulnerable individuals attempt to explain experiences at a conscious level resulting in distortions of reality. On the other hand, hypo-theory-of-mind may be observed in individuals with known or unknown impairments of reasoning that may result in either a totally or a partly lacking sense of reality, with the latter not excluding the possibility of concurrent hyper-theory-of-mind.

To define the central features of psychosis, two options now emerge. A narrow definition of psychosis may focus on symptom appearance, in clinical constructs with a focus on positive symptoms in line with the present-day definition of schizophrenia (World Health Organization, 1992; American Psychiatric Association 2013). Another definition of psychosis may focus on the impairments of reasoning and on the resulting deviances in the experience of reality observed in both autism spectrum disorders and schizophrenia. This latter definition of psychosis represents a broader concept that may reflect a dimensional view. Such a view may be consistent with the ideas by Belmonte *et al.* that some of the cognitive symptoms observed in autism spectrum disorders may develop as compensatory changes resulting from the interaction of normal cognitive development with abnormal neural information processing (Belmonte & Yurgelun-Todd, 2003; Belmonte *et al.*, 2004b). The latter definition of psychosis appears to contrast with the suggestion by Crespi & Badcock (2008) that psychosis and autism may represent diametrical disorders of the social brain. From a theoretical, evolutionary genetic point of view, these authors have developed a theory, the imprinted brain theory, suggesting that psychosis and autism represent two extremes on a cognitive spectrum with normality at its centre (Badcock & Crespi, 2006; Crespi & Badcock, 2008). They consider social cognition underdeveloped in autism and overdeveloped to the level of dysfunction in psychosis. Crespi & Badcock (2008) suggest that the deviations from normal social brain development are mediated in part by alterations in developmental and metabolic systems affected by genomic imprinting.

Various patterns of executive dysfunctions

Executive dysfunctions are characteristic findings in autism as well as schizophrenia (Hill, 2004; Greene *et al.*, 2008). From a clinical point of view, in preschool children, symptoms of autism spectrum disorders may be difficult to distinguish from ADHD, and the conditions may overlap (Gillberg, 2010; Rommelse *et al.*, 2010). Although autism spectrum disorders are relatively stable, conditions first identified as autism may later be recognized as ADHD, or vice versa (Gillberg, 2010).

In toddlers and preschool children with ADHD, the executive dysfunctions may appear as impairments in selective attention, impulse control, and hyperactivity. In autism spectrum disorders, the clinical appearance of impairments in the ability to imagine may appear quite similar, including transient attention, sudden and unexpected reactions, and random and purposeless activity. Despite these similarities, observable differences in the patterns of symptoms between children with ADHD and autism spectrum disorders may sometimes help guide the clinician to distinguish between the two conditions. In autism, the executive dysfunctions may depend on type of activity and motivation. What may initially appear to be the result of deficits of selective attention may turn out to be the result of either a lack of motivation to engage in an observed activity or a lack of ability. It is striking to observe how an apparently hyperactive and impulsive child who is unable to focus his/her attention on simple pretend play may be deeply engaged for hours in construction play.

In autism, impairments related to the ability to imagine can be observed during playing sessions. The difference in behaviour related to construction and pretend play illustrated in the example above may reflect differences in the challenges related to these two kinds of activity. These challenges may not be apparent to parents or other adults around the child, for example, in kindergarten or school. Frequently, clinicians receive reports suggesting that a child is very creative and has a vivid imagination while collecting history information. This, however, does not exclude the need for a careful examination of the child's ability to play in a clinical setting. Even advanced constructions may in essence represent the result of a very concrete activity. The child may follow some very basic rules, which may appear strange and hence creative to outside viewers. Furthermore, what initially appears to be advanced roleplay may turn out to be copy play, with the child repeating dialogues observed on television or in movies. The mental processes involved in construction play may be of another character compared to those necessary to conduct pretend play, which may involve more complex mental processes relating former knowledge to present information and future prediction.

From a theoretical point of view, cognitive impairments may relate to different thought processes that could involve different brain processes and different levels of associations and control. As suggested by Eslinger & Grattan (1993), frontal lobe and frontal-striatal substrates may be involved in different forms of human cognitive flexibility, and two separate cognitive components of executive functions can be identified: *reactive flexibility* and *spontaneous flexibility*. Whereas the first concept, reactive flexibility, refers to the ability to change attentional focus and strategies according to outside requirements, the second concept, spontaneous flexibility, refers

to the ability to initiate a strategy and continuously evaluate whether the strategy is working (Eslinger & Grattan, 1993).

Inspired by Eslinger & Grattan (1993) and consistent with their suggested concepts, at the phenomenological level, it may be possible to distinguish between two different kinds of imagination, a *deductive imagination* and an *inductive imagination*. In deductive imagination, an abstract way of thinking, new information may evolve in a process where new ideas and former knowledge relate to each other in a reflective mind process. This kind of imagination may involve top-down control and depend on an associative brain function. In inductive imagination, on the other hand – in essence a concrete way of thinking – a pattern is recognized and followed in a systematic way. Whereas top-down control could also be involved in this kind of thinking, reflection may not necessarily be part of or integrated in this thought process. A suggestion is that the phenomenological and cognitive levels relate to each other as follows: a deductive imagination may reflect reactive flexibility, while an inductive imagination could reflect spontaneous flexibility.

The *phenomenological transdiagnostic hypothesis* and the *neurodevelopmental cognitive hypothesis* suggest that a link between autism and schizophrenia consists of common cognitive impairments operating at different levels of cognitive complexity, clinically appearing as a characteristic rigidity of thought observed whenever cognitively susceptible individuals reach the limits of their cognitive abilities (Aggernæs, 2016). Is it possible that this rigidity of thought is associated with impairments of cognitive flexibility and may relate to one or both separate cognitive components of executive functions suggested by Eslinger and Grattan? If so, how are they related, and is it possible to differentiate between more basic and secondary processes and to identify how they relate to different brain substrates?

A suggestion could be that the basic cognitive alterations involved in autism and schizophrenia relate to *reactive flexibility*, underlying the observed impairments of *deductive imagination* and reflected at the symptom level in the rigidity of thought. This may explain why individuals with autism spectrum disorders and schizophrenia often appear socially and emotionally immature relative to their overall cognitive level. The suggestion may be consistent with evidence indicating low-level perceptual abnormalities in autism spectrum disorders and their possible explanations as hypothesized in the theory of autism and abnormal development of brain connectivity by Belmonte *et al.* (2004a) and the preparatory theory of the involvement of the cerebellum in autism by Courchesne & Allen (1997).

The cognitive component *spontaneous flexibility* could be involved in inductive imagination and compensatory strategies. This may explain why some individuals with autism, as suggested by the *theory of weak central coherence* (Happe & Frith, 2006) have remarkable islands of abilities unrelated to and striking in light of their overall cognitive abilities. The idea that some of the cognitive symptoms observed in autism spectrum disorders may develop as compensatory changes has already been noticed by others (Belmonte & Yurgelun-Todd, 2003; Belmonte *et al.*, 2004b). These researchers suggest that weak central coherence may emerge as a secondary property resulting from the interaction of normal cognitive development with abnormal neural information processing. They suggest that the abnormal higher-level cognitive abnormalities observed in autism may be the result of compensatory developmental changes resulting from low-level perceptual abnormalities rather than specific impairments in global processing. The authors report that a failure to delimit activation within an abnormally connected network may be observed as hyperarousal in response to sensory input and decreased ability to select among competing sensory inputs. They also refer to evidence of observed cardiovascular, neuroendocrine and neurochemical indices of arousal in novel and stressful situations in support of their prediction and to physiological and behavioural observations of the extent and intensity of perceptual processing. Belmonte *et al.* (2004b) suggest that autism, in light of the present neurobiological evidence, may be viewed as the result of the interaction of normal development with abnormal constraints not only at the cognitive level but also at the cellular and molecular level.

A suggestion is that stress involved in the development of manifest clinical disease may result in impairments of spontaneous flexibility that possibly render basic impairments of reactive flexibility more visible and may reveal the need for time-demanding adaptive mechanisms to cope. This may be consistent with the suggestions of Belmonte *et al.* (Belmonte & Yurgelun-Todd, 2003; Belmonte *et al.*, 2004b) and may explain the observed differences in explicit vs. implicit social cognition performance demonstrated by Callenmark *et al.* (2014).

Individual records and clinical observations suggest that some individuals with autism, particularly females, may use learned strategies to conceal social difficulties and thereby camouflage their social communication difficulties, which may require considerable cognitive effort and lead to increased stress, anxiety and depression (Lai & Baron-Cohen, 2015; Lai *et al.*, 2016). To explore the phenomenon, Lai *et al.* (2016) operationalized camouflaging in adults with autism and without intellectual disability as the quantitative discrepancy between the person's 'external' behavioural presentation in social–interpersonal contexts and the person's 'internal' status. The results showed that women with autism had higher camouflaging scores than men with autism, with substantial variability in both groups. The operationalized camouflaging measure was not significantly correlated with age or IQ. A predicted relationship between executive functions and camouflaging in women with autism was observed; however, since all analyses of the relationships between camouflaging and clinical symptoms and cognitive abilities were correlational in nature, no causal relationships could be inferred. The authors suggest future studies to apply designs that are able to test hypotheses concerning the cognitive bases of camouflaging and the examination of sex/gender-differential relationships. Instead of operationalizing camouflaging as external–internal discrepancy, another option, according to the authors, may be to operationalize it by social imitation capacities based on the hypothesis that camouflaging heavily involves social imitation and adaptation.

To identify the cognitive processes involved in the pathogenesis of autism and schizophrenia, it could be relevant to focus on those cognitive deficits that may contribute to impaired *reactive flexibility* and a reduced capacity for deductive imagination. A suggestion is that this phenomenon is at the core of the central pathogenic processes involved in the development of both autism and schizophrenia and at the core of treatment-resistant schizophrenia. Likewise, in line with the suggestion by Lai *et al.* (2016) and consistent with Belmonte *et al.* (2004b), it may be relevant to identify and distinguish from the more basic processes those time-demanding cognitive processes that may be involved in adaptive coping and may be affected by the secondary stress-related processes that, according to the *neurodevelopmental cognitive hypothesis*, are suggested to be involved in the development of manifest clinical illness.

Rethinking the concept of autism

What is the core of autism? A disorder of contact, social withdrawal, reciprocity, empathy or impaired imagination? Apparently, the less visible the handicap, the greater the challenge may be for

the individual as well as for the social environment to become aware, understand and realize that something is abnormal.

To direct research, it is important to agree upon a definition of the phenomenon of autism. In light of the previous discussion, the following definition of the concept of autism is proposed:

> A condition in which the rationale of the behaviour of an individual resulting from recognized or unrecognized cognitive impairments differs qualitatively from the rationale of the social environment.

Defined as such, autism may represent a social phenomenon, the result of a mismatch between expectations and the ability to fulfil them. As such, autism may act as a signal transmitted to the social level, similar to the suggestion that psychosis may act as a signal transmitted to the social level making the social environment aware of processes taking place within an individual and in the social interaction (Aggernæs, 2016). Regarded as such, the signal transmits information about challenges resulting from a discrepancy between incoming and outgoing information that occurs somewhere in the biopsychosocial system in which the individual plays an active part and at whose centre the individual is located. The neurobiological processes contributing to the phenomenon must be somewhat global in character and of sufficient impact to allow signal transmission all the way to the social level.

Whereas the concept of psychosis focuses on how an experience may be related to reality, autism as a concept may be related to the social aspects of an experience and its relationship to the social environment. What both of these phenomena have in common may be a basic impairment of reasoning. This suggestion may be in line with the *phenomenological transdiagnostic hypothesis* suggesting common cognitive impairments in schizophrenia and autism, consistent with Bleuler (1911) and his suggestion that disturbances of associations are among the fundamental symptoms of dementia praecox (Bleuler, 1978). From a historical point of view, the term dementia praecox may cover not only the present clinical condition of schizophrenia but also the clinical condition of autism spectrum disorders. From a clinical point of view, the described concepts of autism and psychosis may therefore reflect different expressions of the same basic phenomenon. Whereas psychosis may reflect behaviour related to deviances in the experience of reality, autism may reflect behaviour related to a rationale that differs from that of the social environment resulting from deviances in cognition.

How do impairments of reasoning and the attempt to explain an experience at a conscious level affect the clinical expressions of the phenomena of psychosis and autism? In light of the previous discussion, such questions appear to be important to answer for future research.

It may be possible to distinguish among different clinical expressions of autism depending on whether the social environment is aware of the condition or not. As illustrated in the example above, the failure of perspective taking and empathy may lie not only with the affected individual but also with the social environment. How does that affect the clinical expression? The clinical appearance may also depend on the awareness of the individual. Some individuals with autism spectrum disorders may be aware of their difficulties, but they may be unable to explain or understand the reason why and therefore be unable to compensate.

Evidence challenging diagnostic borders

Symptom appearance may depend on the character of the basic experience of an individual, neurobiological in nature (Belmonte *et al.*, 2004a,b). From a neurobiological point of view, the same genes may be involved in the development of a variety of mental disorders including autism and schizophrenia (Burbach & van der Zwaag, 2009; Craddock & Owen, 2010; Robinson *et al.*, 2016). The evidence indicating that genes and neurobiological mechanisms are involved in the development of autism spectrum disorders and schizophrenia opens up the potential for neurobiological treatment targets (Belmonte *et al.*, 2004b; Cuthbert & Insel, 2013; Waterhouse & Gillberg, 2014).

Increasing empirical evidence suggests that autism spectrum disorders and schizophrenia may share genes (Burbach & van der Zwaag, 2009; Cox & Butler, 2015; Elia *et al.*, 2010; Guilmatre *et al.*, 2009; Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013a,b; McCarthy *et al.*, 2014; Moreno-De-Luca *et al.*, 2010; Rapoport *et al.*, 2009; Kirov, 2015). Evidence from genome-wide association studies has shown that many frequent inherited alleles may be involved in the development of mental illness including autism spectrum disorders and schizophrenia, each contributing with only small effects (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013a,b; Plomin *et al.*, 2009; Robinson *et al.*, 2016). *De novo* variant analyses of new mutations using family-based whole-genome or whole-exome sequencing approaches shows evidence that such mutations may be involved in the development of neuropsychiatric disorders including autism spectrum disorders and schizophrenia (McCarthy *et al.,* 2014; Robinson *et al.*, 2016), and increasing evidence now indicates that a few rare genetic variants, copy number variants (CNVs), may contribute with larger effects in these disorders (Burbach & van der Zwaag, 2009; Craddock & Owen, 2010; Kirov, 2015).

Interestingly, these convergent genetic findings challenge the categorical approach currently guiding the understanding of mental disorders. The genetic overlap between disorders may indicate that autism spectrum disorders and schizophrenia can arise from a shared neurodevelopmental vulnerability or may involve similar pathogenic mechanisms (Burbach & van der Zwaag, 2009). Genetic risk factors for autism spectrum disorders can also be found in the general population, and since the effects of that risk are unclear, a recent study chose to examine the genome-wide links between autism spectrum disorders and typical variation in social behaviour and adaptive functioning using several large autism spectrum disorder consortia and population-based resources (Robinson *et al.*, 2016). These researchers found genome-wide genetic links between autism spectrum disorders and typical variation in social behaviour and adaptive functioning evidenced through both LD score genetic correlation and *de novo* variant analysis. Their results indicate that multiple types of genetic risk for autism spectrum disorders influence a continuum of behavioural and developmental traits.

In addition to the increasing evidence in support of shared genetic risk factors involved in the development of autism and schizophrenia spectrum disorders, increasing evidence indicates that common information-processing deficits including psychophysiological deficits (Aggernaes *et al.*, 2010; Oranje *et al.*, 2013; Madsen *et al.*, 2014, 2015; Sinclair *et al.*, 2016) and neurocognitive impairments (Simon *et al.*, 2005; Greene *et al.*, 2008; Sugranyes *et al.*, 2011; Eack *et al.*, 2013; Chung *et al.*, 2014) may be involved in the development of autism spectrum disorders and schizophrenia.

A study directly comparing global and regional brain volume structural alterations in individuals with autism spectrum disorder, schizophrenia and typical development found no overall global grey matter or white matter differences between groups (Radeloff *et al.*, 2014). The results from the analysis of regional data, however,

although considered preliminary, indicated alterations of social brain areas in both disorders (Radeloff *et al.*, 2014). Compared to individuals with schizophrenia, subjects with autism spectrum disorder displayed smaller grey matter volume in the left insula.

Epidemiologic evidence indicates that perinatal factors, birth in an urban area and a family history of mental illness are associated with the risk of autism (Larsson *et al.*, 2005; Lauritsen *et al.*, 2005). The highest risks of autism associated with a family history of mental illness were reported for siblings of children within the spectrum of pervasive developmental disorders (Lauritsen *et al.*, 2005). A parental history of schizophrenia was associated with a higher risk of autism than a parental history of depression (Larsson *et al.*, 2005). Such evidence may be in line with the model of the complex relationship between biological variation and some major forms of psychopathology suggested by Craddock & Owen (2010) and supports the strong line of evidence for genetic factors involved in the development of autism but also indicates that environmental factors may be involved. The results raise important questions as to their interpretation. How is the risk of mental illness of a parent transmitted to the child? In addition to the option of transmission directly via a genetic pathway, environmental factors may be involved. Despite evidence that parental psychopathology is linked to an increased risk of adult psychopathology, some children do not develop psychopathology (Davidsen *et al.*, 2015). There is limited evidence on the relationship among maternal mental illness including schizophrenia, the mother–infant relationship and infant development. The scarce evidence points to a need for research to further explore the biopsychosocial mechanisms of risk and to investigate sources of resilience in the development of offspring of parents with mental illness. An example of such an effort is an ongoing study exploring the mechanisms of transmission of health and risk in parents with complex mental health problems and their offspring, the WARM study (Harder *et al.*, 2015). This study plans to identify very early risk markers for non-optimal development in infants of mothers with severe mental illness and to explore transmission mechanisms of risk from parent to infant while focusing on three possible mechanisms: stress, maternal caregiving representation and mother-infant interaction.

The increased risk of autism associated with urbanization (Lauritsen *et al.*, 2005) parallels similar findings observed in epidemiological research on schizophrenia (Marcelis *et al.*, 1998, 1999). The schizophrenia researchers suggested that the high rates of psychosis observed in urban areas were the result of environmental factors associated with urbanization. By detailed analysis, Marcelis *et al.* (1999) were able to distinguish between the risk related to urban residence around the time of illness onset and the risk related to urban place of birth. These results suggested that environmental factors associated with urbanization increase the risk for schizophrenia before rather than around the time of illness onset.

Several studies have demonstrated an association between stress and autism (Corbett *et al.*, 2008, 2009, 2012, 2016; Bishop-Fitzpatrick *et al.*, 2015). Studies of stress in autism have compared the responses in individuals with and without autism spectrum disorders at different ages and in various situations. The results of these studies are consistent, all indicating that children, adolescents and adults with autism spectrum disorders experience more stress than control groups without autism spectrum disorders (Corbett *et al.*, 2008, 2009, 2012, 2016).

Children with autism show more within- and between-subject variability in circadian rhythms compared to neurotypical control subjects, with both groups demonstrating increased salivary cortisol in anticipation of re-exposure to a perceived stressor (Corbett *et al.*, 2008). The greater within-child variation suggests clear disturbances in the limbic HPA axis that point to fundamental dysregulation and increased susceptibility to external factors.

Exploring plausible relationships between cortisol and psychological measures of stress and sensory functioning, Corbett *et al.* (2009) found that higher observed symptoms of stress are related to lower cortisol in autism, indicating chronic stress, since lower cortisol is observed in conditions of chronic stress and in social situations characterized by unstable social relationships. Their results support a complex interplay between physiological and behavioural stress and sensory sensitivity in autism and plausible developmental factors influencing stress reactivity across the groups. It is unclear if the alterations contribute to the neuropathology of autism or if the manifestation of the disorder results in alteration of neuroendocrine functioning, or both.

Evidence from a longitudinal study indicates that children with autism spectrum disorders show enhanced and sustained social stress that increases with age (Corbett *et al.*, 2012).

Results from studies in adults indicate that stress is associated with social functioning but not global functioning in adults with autism spectrum disorders and that perceived stress and stressful life events are significantly associated with social disability in individuals with autism spectrum disorders (Bishop-Fitzpatrick *et al.*, 2015, 2017). The social and communication deficits inherent in autism spectrum disorders may cause adults to experience more stress; however, it is also possible that this relationship works in the other direction, such that individuals with better social functioning experience less stress.

The reported evidence indicating that individuals with autism spectrum disorders show enhanced and sustained social stress increasing with age may be consistent with the previous suggestion that a discrepancy between the cognitive ability of an individual and the social and cognitive challenges may give rise to stress that may worsen cognitive impairments, further contributing to symptom appearance and increasing the risk of developing manifest clinical disease; see Fig. 1 (Aggernæs, 2016). This suggestion may also be in line with recent evidence from a high-risk study of schizophrenia showing that abnormalities in HPA axis function were associated with poorer cognitive performance (Cullen *et al.*, 2014).

A possible relationship among stress, anxiety, depression and camouflaging as suggested by Lai *et al.* (2016) warrants further investigation of the causal relationships between stress and adaptive mechanisms. The idea of a lost generation (Lai & Baron-Cohen, 2015) raises important questions: where are these people now, and how are they coping? What is the relationship between stress and undiscovered impairments of reasoning? This question may be important to answer for future research.

In summary, the increasing neurobiological evidence indicating an overlap between autism and schizophrenia is in contrast to the present view reflected in the international diagnostic guidelines suggesting that these disorders represent different disease entities. The evidence may be in support of a transdiagnostic, dimensional approach to mental illness and in line with the multilevel model of the complex relationship between biological variation and psychopathology suggested by Craddock & Owen (2010).

Although increasing neurobiological evidence may indicate that neuropsychiatric disorders such as autism spectrum disorders and schizophrenia share pathogenic mechanisms, the differences in phenotypic expression and time of onset call for an explanation. While some mechanisms may be shared, others may vary both within and between the two conditions. The significance of environmental factors, the influence of adaptive mechanisms and the influence of

factors affecting stress responsivity and neuroendocrine reactivity on the development of clinically manifest disease need further exploration.

How to interpret results

As noted by Kim & State (2014), the increasing empirical evidence suggesting that common genetic variants are involved and contribute to different neuropsychiatric disorders including autism spectrum disorders and schizophrenia may challenge psychiatric diagnostic nosology. The underlying validity of the current disease categories, which rely on biologically heterogeneous categories, as the gold standard for diagnosis has been questioned (Cuthbert & Insel, 2013). The DSM and ICD categories do not map well onto the increasing evidence from genetics, systems neuroscience and behavioural science. Therefore, in 2009, the National Institute of Mental Health (NIMH) initiated the Research Domain Criteria (RDoC) project with the intention to build a framework of research that can inform future versions of psychiatric nosology. Their ambition is to develop new ways of classifying mental disorders based on dimensions of observable behaviour and neurobiological measures while applying a translational approach. Such an approach may be consistent with Robinson *et al.* (2016). These authors suggest that their findings may support the application of a continuum model rather than a categorical approach in future studies of the biology involved in neuropsychiatric disease. Commenting on a categorical approach, they state that the traditional categorical psychiatric diagnoses ignore the possible association of neuropsychiatric-associated genes with intermediate outcomes such as intelligence, adaptive functioning and social and communicative abilities (Robinson *et al.*, 2016). This view is in line with a similar suggestion by Plomin *et al.* (2009), stating that qualitative disorders can be interpreted simply as being the extremes of quantitative dimensions.

From a clinical rather than a neurobiological starting point, several researchers have reached the same conclusion, and in line with Plomin *et al.* (2009), Cuthbert & Insel (2013) and Robinson *et al.* (2016), they also question the validity of the current disease categories (e.g. Myhr, 1998; Szatmari, 2000; Gillberg, 2010). Gillberg (2010) has stressed the point that syndromes, to some extent, are arbitrary endpoints or cutoff points on normal distribution curves and that most syndromes may comprise a mixture of symptoms collected from different normal distribution curves, a view in line with the *phenomenological transdiagnostic hypothesis*. He concludes that rather than being discrete categorical disorders, these syndromes represent brain dysfunctions and neurodevelopmental problems.

Myhr (1998) has emphasized the need to apply a dimensional view and argued for the need, when designing studies, to avoid the circularity involved in defining a sample and then looking for differences in the sample that may be related to the definition of it. A dimensional view of pervasive developmental disorders opens the way for an understanding that the three core impairments currently used to define autism spectrum disorders may be manifested in different ways and to different degrees. Rather than symptoms, other measures related to aetiology, outcome, and treatment response must be studied, for example, IQ or adaptive function, to identify and separate from one another different subtypes of disorders along the autistic spectrum (Myhr, 1998). Myhr (1998) refers to results by Waterhouse *et al.* (1996), who have found that the most powerful discriminating factors between two examined groups of high-functioning and low-functioning autism were IQ and level of adaptive function as measured by the Vineland Adaptive Behaviour Scale.

In a longitudinal design following and comparing the outcome of preschool children with autism or Asperger syndrome on variables independent of the defining criteria, Szatmari *et al.* (2000) have found that children with autism who had developed verbal fluency at follow-up were very similar to the children with Asperger syndrome at study enrolment. Based on their results, the authors proposed to think of the pervasive developmental disorder subtypes in terms of different developmental trajectories rather than to argue that they represent different disorders or are on a continuum of severity. Regarding the classification of the international diagnostic guidelines, in particular referring to the DSM-IV and ICD-10 criteria, Szatmari (2000) discusses the diagnostic validity of the different categories of the pervasive developmental disorders and considers different approaches to the conceptualization of these categories. The author refers to several lines of evidence, including evidence from family studies and the results of the just-mentioned longitudinal study, suggesting that the neurobiological mechanism underlying variation in symptoms is different from that for level of functioning. Based on this evidence, Szatmari (2000) concludes that a dimensional approach as articulated in the notion of autistic spectrum disorders is problematic. Since more than one underlying dimension exists, an alternative approach is needed that can incorporate both dimensions in a developmental context. The pervasive developmental disorders, therefore, may be better conceptualized as different developmental pathways that are a function of both symptom severity and level of functioning. In line with the RDoC project, although from a different starting point, Szatmari (2000) emphasizes that the underlying model of the diagnostic criteria must be reconceptualized according to available empirical data.

In a recent letter, Waterhouse & Gillberg (2014) advised against unitary models of autistic brain dysfunction and, in line with the suggestion by Gillberg (2010), recommended that the focus be changed to the exploration of individual variation in brain measures within autism. They refer to evidence demonstrating that many varied brain dysfunctions may be associated with autism spectrum disorders (Waterhouse & Gillberg, 2014). Furthermore, they argue that brain dysfunctions observed in autism spectrum disorders may not be unique to these disorders. As an example, they mention underconnectivity, which, in addition to autism, has also been reported in other neuropsychiatric disorders including schizophrenia. Waterhouse & Gillberg (2014) advise researchers to take autism spectrum disorders apart to identify the many varied single and aggregate brain dysfunctions in order that effective translational research can be conducted.

Belmonte *et al.* (2004b) appear to be in line with Waterhouse & Gillberg (2014) when they state that a broadening of studies beyond the strict diagnosis of autism holds a great deal of promise for identifying which components of the autistic syndrome are genetically transmitted and how these components interact. According to Belmonte *et al.* (2004b), many subtle genetic, biochemical and immunological factors at the neural level may affect normal brain development and lead to fundamentally altered neurocomputational properties. These neural alterations may affect activity-dependent processes and learned cognitive strategies and result in behavioural effects, producing a syndrome whose surface behavioural properties may have only indirect aetiological significance. In this light, neurocognitive impairments may result from neurobiological vulnerability, and the cognitive experience may relate to the neurobiological experience and develop modified by the character of cognitive impairments. The contents of both the *phenomenological transdiagnostic hypothesis* and the *neurodevelopmental cognitive hypothesis* appear to be in line with these suggestions by Belmonte *et al.*

(2004b) and with their hypothesis suggesting that age of onset, rate, and duration of aberrant brain growth are related to the severity and age of onset of autistic behaviours.

Despite differences in starting points, research foci and theoretical frameworks, all the cited researchers appear to agree on the need for new theoretical approaches to direct future research on autism spectrum disorders, schizophrenia and other neuropsychiatric disorders. Most of these researchers argue for a change from the traditional categorical approach to a dimensional approach, with some in addition emphasizing the need to apply a translational approach and to include a developmental context in future models.

A dimensional, transdiagnostic approach

How are clinical manifestations to be delimited in the future? Is it possible to identify more basic phenomena that may relate to brain structure and function, for example, anxiety, emotions, compulsion, attention, and cognitive phenomena? If so, how do such basic phenomena relate to each other and affect the overall clinical manifestations?

To predict the likelihood and course of mental illness, theoretical models are needed (Cuthbert & Insel, 2013). As apparent from the previous discussion, however, challenges exist regarding how to interpret the increasing and already vast amount of clinical and neurobiological evidence.

How can theoretical models explain the observed biological and clinical heterogeneity? Is it possible to induce explanations from the increasing biological evidence, although questioned by Waterhouse & Gillberg (2014)? On the other hand, is it possible to induce explanations from the increasing clinical evidence? As questioned by some and demonstrated by others (Myhr, 1998; Szatmari, 2000; Szatmari *et al.*, 2000; Gillberg, 2010; Waterhouse & Gillberg, 2014), inherent methodological problems are related to research approaches that refer to categorical, clinical diagnoses based on symptoms.

Several authors call for a change to a translational approach and to the development of theoretical models that are informed by the increasing biological and clinical evidence (e.g. Belmonte *et al.*, 2004a,b; Craddock & Owen, 2010; Waterhouse & Gillberg, 2014). Rather than inducing models directly from observed evidence, a deductive approach may turn out to be more constructive.

As apparent from the previous discussion, and possibly in line with the suggestions by Belmonte *et al.* (2004b) and the strong evidence indicating that social stress is involved in the dynamics of autism spectrum disorders and schizophrenia, future theoretical models may need to distinguish among at least three different kinds of mechanisms involved in the development of clinically manifest disease: (i) basic susceptibility related to a neurobiological vulnerability (e.g. genetic variants affecting neurodevelopment and resulting in neurocognitive impairments), (ii) compensating mechanisms (e.g. cognitive ability (IQ), level of adaptive functioning), and (iii) releasing mechanisms (e.g. prolonged stress that may be caused by various factors). These mechanisms and the processes involved may both interact and operate at different levels and, in the end, contribute to the clinical, behavioural manifestations of mental illness.

As recognized by Belmonte *et al.* (2004b), secondary dysfunctions may mask primary abnormalities, with important implications for studies that may be at risk of overlooking cognitive and perceptual features at low levels of processing that may be closer to the core dysfunction than the diagnostic features on which most studies tend to focus.

In line with a dimensional and transdiagnostic view, more basic phenomena that may relate to brain structure and function and their deviations in relation to expected normal variation across development may contribute to the development of mental illness and to the heterogeneous psychopathological expressions of illness. As stated by Szatmari (2000), and consistent with Belmonte *et al.* (2004a,b), research could more profitably focus on the genetic, epigenetic, and environmental variables that determine the pathway a child will follow. An important point stressed by Szatmari (2000), Valla & Belmonte (2013) and Belmonte *et al.* (2004b) and needed to be accounted for in future theoretical models appears to be to acknowledge that the autism spectrum disorders may be better conceptualized as different developmental pathways. As stated by Szatmari (2000) this calls for an alternative approach to research that need to incorporate more than one dimension in a developmental context. Another important consideration stressed by Gillberg (2010) and covered by his term ESSENCE is that most clinical syndromes comprise a mixture of symptom collections from different normal distribution curves. This point raised by Gillberg cannot be underestimated and may be consistent with the suggestions of the *phenomenological transdiagnostic hypothesis*. A major challenge for future research will be to identify which relevant dimensions to include in future models and to develop theory that can explain the dynamic relationship across and along these dimensions and predict how these interactions finally may result in the many varied, heterogeneous clinical manifestations of mental illness.

In line with the suggestions by Belmonte *et al.* (2004b), it may be important to distinguish between the significance of primary processes affecting brain development and secondary compensatory processes that both may affect basic cognitive processes and to examine how the resulting cognitive impairments may affect the development of manifest disease.

To help explain how diversity may result from more universal phenomena the previously introduced *phenomenological transdiagnostic hypothesis* may be included in future theoretical models to help explain how common causes may contribute to the various clinical expressions of mental illness. To explain the heterogeneity of autism spectrum disorders and schizophrenia, future theoretical models may also have to include the complex processes related to neurodevelopment as suggested by the *neurodevelopmental cognitive hypothesis* and to distinguish between symptoms resulting from the age related primary and secondary processes involved in the development of manifest disease. It may be difficult to readjust to the new expectations and requirements related to development. Subtler cognitive deficits may not be recognized. Therefore, awareness of an underlying vulnerability may not occur until after manifest disease appears in the form of secondary conditions such as compulsions, anxiety, depression or psychosis resulting from enduring stress.

In contrast to symptoms more directly related to basic brain phenomena, for example, anxiety, emotions, and cognition, the relationship of the phenomena of psychosis and autism with the brain may be more indirect. The suggested redefinition of the two concepts reflects that these phenomena may represent experiences related to deviances of reasoning. Such deviances may result from characteristic cognitive impairments and from the experiences of reality and social expectations related to the environment. The suggested redefinition of the concepts of autism and psychosis may affect future diagnostic delimitation of the clinical conditions of autism spectrum disorders, schizophrenia and related disorders and call for the inclusion of social mechanisms in future theoretical models of the development of mental disorder.

The challenges of future research

How may prior theory, previous empirical evidence, the included clinical examples and the suggested new theoretical ideas shape future research? To develop coherent, overall theoretical models that may be able to explain and predict the development of autism spectrum disorders, schizophrenia and related disorders, one may need to incorporate mechanisms operating within and between many levels, for example, genetic, physiological, cognitive, psychological and social, and from an individual point of view one must include both internal and external processes. What occurs in the transmission of signals from one level to another, for example, from the genetic to the neurostructural level, the neurophysiological to the neurocognitive level, or from the psychological to the social level? During this process, a simplification of the signal may occur while transmission of the overall information occurs between different levels. As part of the process of developing such complex multilevel models, an important task appears to be to agree on the definition of relevant theoretical concepts including the concepts of psychosis and autism. There is a need for awareness of the inherent assumptions that have hitherto guided clinical practice and research on mental illness in order to choose the direction of future research. These tasks may also help to identify inconsistencies in the relationship between theoretical constructs and clinical constructs.

It appears that there is a need to distinguish between different kinds of mechanisms involved in the development of clinically manifest disease:

1 A basic vulnerability, genetic in origin and dependent on gene-environment interactions. In autism and schizophrenia research, the identification of primary cognitive dysfunctions is important, for example, to examine the possible importance of impairments related to reactive flexibility.
2 Adaptive mechanisms involved in adaptation to a primary susceptibility and to the changing requirements according to development. Adaptive mechanisms may include individual cognitive strategies that depend on the global level of intelligence or a supportive social environment.
3 Decompensating mechanisms that may include the results of enduring stress resulting from social and cognitive challenges related to normal development, stress resulting from major life events or trauma, or misuse of drugs or alcohol. It may be important to identify how stress-related events affect cognition, for example, to examine the possible influence on spontaneous flexibility and related effects.

If it is possible to identify the basic biological susceptibility behind the development of autism spectrum disorders, schizophrenia and related disorders and to distinguish adaptive processes from the decompensating or releasing factors involved in the development of manifest disease, then hopefully, the task to identify resilience and risk factors will become easier.

In addition to neurobiological research approaches, other research strategies may be required to help guide research in new directions. Among such additional strategies, the application of methods from other scientific fields, for example, social science, may prove to be valuable. A possible strategy may be to apply social anthropological research strategies that, via their qualitative explorative scientific methods, may be able to raise new questions and thereby add new information that may help further develop the overall theoretical models needed to guide research. Furthermore, it may prove valuable to integrate and refine previous theories in the process of developing new overall theoretical models and, in light of these, to reinterpret the results of previous studies with due consideration for their methodological limitations.

To understand the risk and development of autism spectrum disorders and schizophrenia, it may be essential to understand the processes that occur at the social level and, as part of the theory, to include hypotheses about the pathogenic processes related to social mechanisms: how autism may represent a construct reflecting a social phenomenon, defined in a social context and resulting from social interactions that by themselves may form the appearance of the phenomenon. Therefore, in future theoretical models of the development of autism spectrum disorders and schizophrenia, it may be relevant to involve the significance of social interaction. It may be relevant to explore the relationship between social expectations and the ability of an individual to fulfil such expectations. Another matter of importance may be to examine how unrecognized cognitive impairments may affect the rationale of an individual's behaviour and make the rationale differ qualitatively from that of the social environment.

Conclusions

Autism research could learn from history and from the experiences of clinical psychiatry in addition to a reliance on the increasing empirical evidence. The concepts guiding clinical practice and research have changed across time depending on theory and empirical evidence. The challenge of the clinical psychiatrist is to disentangle these contributions at the symptom level in each individual case and from a retrospective point of view. During the diagnostic process, the psychiatrist himself becomes part of and may influence the process. In contrast, the task of the neuroscientist is to predict the likelihood of mental illness in general and to do so from a universal point of view.

To be able to test hypotheses and predict outcomes, we need to agree on concepts and develop multilevel theoretical models to inform the overall approach of research. The clinical expressions of mental illness may evolve and be modified by processes that depend on how they are conceived and defined, by themselves influencing symptom appearance and the course of illness. In addition to hypotheses induced from the vast and increasing amount of neurobiological empirical data, it is reasonable to suggest that research can also profit from hypotheses that focus on the significance of processes taking place at the social level. A future challenge of autism research may be to develop theoretical multilevel models that can also account for the impact of complex mechanisms acting at the social level and how these processes interact with the processes taking place at and between other levels involved, including the genetic, biological (structural and physiological), neurocognitive and psychological levels. To acknowledge the importance of what is occurring at the social level, the model must account for not only the contribution of impairments of social cognition but also how mental illness develops in a social context and may depend on what occurs in social interaction.

Future autism research should contribute knowledge that may increase the overall understanding of the mechanisms behind all processes involved in the development of clinical symptoms. Central tasks of future investigation may be to identify which processes are involved at each level and how they interact, including how information is transmitted between levels. An important future task will be to disentangle the contribution of (i) basic vulnerability, (ii) adaptive mechanisms, and (iii) decompensating mechanisms that may be involved in the development of clinically manifest disease. The hope is that such an approach may help to identify all the processes involved in the development of autism spectrum disorders, schizophrenia and related disorders and how

each of these processes contributes to the final manifestation of the various clinical conditions.

In line with Bleuler (2011), though revised in light of empirical evidence, it may be appropriate to redefine dementia praecox as a developmental disorder of reasoning. As such, the term may not only cover the DSM-5 diagnosis of autism spectrum disorders and schizophrenia but also include social (pragmatic) communication disorders (American Psychiatric Association 2013). To relate clinical and conceptual constructs, a possible redefinition of autism at a conceptual level may be a condition in which the rationale of an individual's behaviour differs qualitatively from that of the social environment as a result of cognitive impairments that may involve impairments in the cognitive constructs reactive and spontaneous flexibility (Eslinger & Grattan, 1993). Furthermore, a broad concept of psychosis may focus on the impairments of reasoning and on the resulting deviances in the experience of reality observed in both autism spectrum disorders and schizophrenia. These concepts may be consistent not only with the Bleulerian concept of autism (Bleuler, 1978) but also with the neurodevelopmental model suggested by Craddock & Owen (2010), the previously suggested link between schizophrenia, autism and psychosis (Aggernæs, 2016), and, finally, a dimensional transdiagnostic approach. As apparent from the previous discussion, the suggested concepts and hypotheses also may be in line with the ideas suggested by Belmonte *et al.* (2004b) and Gillberg (2010) as well as other researchers calling for a change to a translational dimensional approach embedded in a developmental context.

Future perspectives

The suggested redefinition of the concept of autism and a dimensional transdiagnostic approach may potentially have far-reaching consequences. It may not only affect the future diagnostic delimitation of autism spectrum disorders and related disorders but also question the overall concept of 'normality' and, as a consequence, influence the overall concept of 'mental disorders', thereby possibly affecting the generally accepted principles for delimiting psychiatric disorders while going beyond the symptom level. If such an approach proves successful, it may create the basis for an integration of previously different preunderstandings that have long guided clinical diagnostic classification. Finally, this may result in the application of new research strategies contributing new evidence that may ultimately change the ways mental illness is handled. The NIMH's RDoC Initiative is an example of such an endeavour intended to move beyond heterogeneous diagnosis and establish dimensional constructs including concepts based on biology in addition to behaviour (Cuthbert & Insel, 2013) (www.nimh.nih.gov/research-priorities/rdoc/index.shtml). Hopefully, the present contribution will add another milestone along the same highway.

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Conflict of interest

The author declares no competing interests with regard to the present manuscript.

Author contributions

Bodil Aggernæs is the only author of the present review and is fully responsible for the content.

Abbreviations

ADHD, Attention Deficit Hyperactivity Disorders; CNV, Copy Number Variants; DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; EJN, the European Journal of Neuroscience; ESSENCE, Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations; FENS, Federation of European Neuroscience Societies; ICD-10, the Tenth Revision of the International Classification of Diseases and Related Health Problems; NIMH, the National Institute of Mental Health; RDoC, Research Domain Criteria.

References

Aggernæs, A. (1975) The concepts: disturbed state of consciousness and psychosis. *Acta Psychiat. Scand.*, **51**, 119–133.

Aggernæs, B. (2016) Rethinking the concept of psychosis and the link between autism and Schizophrenia. *Scand. J. Child Adol. Psychiat. Psychol.*, **4**, 4–11.

Aggernæs, A., Paikin, H. & Vitger, J. (1981) Experienced reality in schizophrenia: how diffuse is the defect in reality testing? *Indian. J. Psychol. Med.*, **4**, 1–13.

Aggernaes, B., Glenthoj, B.Y., Ebdrup, B.H., Rasmussen, H., Lublin, H. & Oranje, B. (2010) Sensorimotor gating and habituation in antipsychotic-naive, first-episode schizophrenia patients before and after 6 months' treatment with quetiapine. *Int. J. Neuropsychoph.*, **10**, 1383–1395.

Alberoni, F. (1984). *Movement and Institution*. Columbia University Press, New York.

Alderson-Day, B. (2011) Verbal problem-solving in autism spectrum disorders: a problem of plan construction? *Autism Res.*, **4**, 401–411.

Alderson-Day, B. & McGonigle-Chalmers, M. (2011) Is it a bird? Is it a plane? category use in problem-solving in children with autism spectrum disorders. *J. Autism Dev. Disord.*, **41**, 555–565.

American Psychiatric Association (2000). *Diagnostic and Statistical Manual of Mental Disorders DSM-IV-TR*, 4th edn., Text Revision. American Psychiatric Association, Washington DC.

American Psychiatric Association (2013) *Diagnostic and Statistical Manual of Mental Disorders: DSM-5*, 5th edn. American Psychiatric Association, Washington DC.

Asperger, H. (1944) Die 'autistischen psychopathen' im kindesalter. *Archiv für Psychiatrie und Nervenkrankheiten*, **177**, 76–136.

Badcock, C. & Crespi, B. (2006) Imbalanced genomic imprinting in brain development: an evolutionary basis for the aetiology of autism. *J. Evol. Biol.*, **19**, 1007–1032.

Bara, B.G., Ciaramidaro, A., Walter, H. & Adenzato, M. (2011) Intentional minds: a philosophical analysis of intention tested through fMRI experiments involving people with schizophrenia, people with autism, and healthy individuals. *Front. Hum. Neurosci.*, **5**, 1–11.

Belmonte, M.K. & Yurgelun-Todd, D.A. (2003) Functional anatomy of impaired selective attention and compensatory processing in autism. *Brain Res. Cogn. Res.*, **17**, 651–664.

Belmonte, M.K., Allen, G., Beckel-Mitchener, A., Boulanger, L.M., Carper, R.A. & Webb, S.J. (2004a) Autism and abnormal development of brain connectivity. *J. Neurosci.*, **24**, 9228–9231.

Belmonte, M.K., Cook, E.H. Jr, Anderson, G.M., Rubenstein, J.L.R., Greenough, W.T., Beckel-Mitchener, A., Courchesne, E., Boulanger, L.M. *et al.* (2004b) Autism as a disorder of neural information processing: directions for research and targets for therapy. *Mol. Psychiatry*, **9**, 646–663.

Bishop-Fitzpatrick, L., Mazefsky, C.A., Minshew, N.J. & Eack, S.M. (2015) The relationship between stress and social functioning in adults with autism spectrum disorder and without intellectual disability. *Autism Res.*, **8**, 164–173.

Bishop-Fitzpatrick, L., Minshew, N.J., Mazefsky, C.A. & Eack, S.M. (2017) Perception of life as stressful, not biological response to stress, is associated with greater social disability in adults with autism spectrum disorder. *Autism Dev. Disord.*, **47**, 1–16.

Bleuler, E. (1978) *Dementia Praecox or the Group of Schizophrenias. Monograph Series on Schizophrenia No. 1*. International Universities Press, Ninth Printing, New York.
Bleuler, E. (1911) *Dementia Praecox oder Gruppe der Schizophrenien*. Deuticke, Leipzig.
Bredgaard, R. & Glenthoj, B.Y. (2000) Information processing and attentional dysfunctions as vulnerability indicators in schizophrenia spectrum disorders. *World J. Biol. Psychiatry*, **1**, 5–15.
Brüne, M. (2005) "Theory of Mind" in Schizophrenia: a review of the literature. *Schizophrenia Bull.*, **31**, 21–42.
Burbach, J.P. & van der Zwaag, B. (2009) Contact in the genetics of autism and schizophrenia. *Trends Neurosci.*, **32**, 69–72.
Callenmark, B., Kjellin, L., Rönnquist, L. & Bölte, S. (2014) Explicit versus implicit social cognition testing in autism spectrum disorder. *Autism*, **18**, 684–693.
Cantio, C., Jepsen, J.R.M., Madsen, G.F., Bilenberg, N. & White, S.J. (2016) Exploring 'The Autisms' at a cognitive level. *Autism. Res.*, **9**, 1328–1339.
Chisholm, K., Lin, A., Abu-Akel, A. & Wood, J.S. (2015) The association between autism and schizophrenia spectrum disorders: a review of eight alternate models of co-occurrence. *J. Neurosci. Biobehav. Rev.*, **55**, 173–183.
Chung, Y.S., Barch, D. & Strube, M. (2014) A meta-analysis of mentalizing impairments in adults with schizophrenia and autism spectrum disorder. *Schizophrenia Bull.*, **40**, 602–616.
Ciaramidaro, A., Bölte, S., Schlitt, S., Hainz, D., Poustka, F., Weber, B., Bara, B.G., Freitag, C. *et al.* (2015) Schizophrenia and autism as contrasting minds: neural evidence for the hypo-hyper-intentionality hypothesis. *Schizophrenia Bull.*, **41**, 171–179.
Clemmensen, L., van Os, J., Skovgaard, A.M., Væver, M., Blijd-Hoogewys, E.M., Bartels-Velthuis, A.A. & Jeppesen, P. (2014) Hyper-Theory-of-Mind in children with psychotic experiences. *PLoS ONE*, **9**, e113082.
Clemmensen, L., van Os, J., Drukker, M., Munkholm, A., Rimvall, M.K., Væver, M., Rask, C.U., Bartels-Velthuis, A.A. *et al.* (2016) Psychotic experiences and hyper-theory-of-mind in preadolescence–a birth cohort study. *Psychol. Med.*, **46**, 87–101.
Cochran, D.M., Dvir, Y. & Frazier, J.A. (2013) "Autism-plus" spectrum disorders. *Child Adolesc. Psychiatr. Clin. N. Am.*, **22**, 609–627.
Corbett, B.A., Mendoza, S., Wegelin, J.A., Carmean, V. & Levine, S. (2008) Variable cortisol circadian rhythms in children with autism and anticipatory stress. *J. Psychiatry Neurosci.*, **33**, 227–234.
Corbett, B.A., Schupp, C.W., Levine, S. & Mendoza, S. (2009) Comparing cortisol, stress, and sensory sensitivity in children with autism. *Autism Res.*, **2**, 39–49.
Corbett, B.A., Schupp, C.W. & Lanni, K.E. (2012) Comparing biobehavioral profiles across two social stress paradigms in children with and without autism spectrum disorders. *Mol. Autism.*, **3**, 13.
Corbett, B.A., Muscatello, R.A. & Blain, S. D. (2016) Impact of sensory sensitivity on physiological stress response and novel peer interaction in children with and without autism spectrum disorder. *Front. Neurosci.*, **10**, 278.
Courchesne, E. & Allen, G. (1997) Prediction and preparation, fundamental functions of the cerebellum. *Learn Memory*, **4**, 1–35.
Cox, D. & Butler, M. (2015) The 15q11.2 BP1–BP2 microdeletion syndrome: a review. *Int. J. Mol. Sci.*, **16**, 4068–4082.
Craddock, N. & Owen, M. (2010) The Kraepelinian dichotomy – going, going but still not gone. *Brit. J. Psychiat.*, **196**, 92–95.
Crespi, B. & Badcock, C. (2008) Psychosis and autism as diametrical disorders of the social brain. *Behav. Brain. Sci.*, **31**, 241–261.
Cross-Disorder Group of the Psychiatric Genomics Consortium (2013a) Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs. *Nat. Genet.*, **45**, 984–994.
Cross-Disorder Group of the Psychiatric Genomics Consortium (2013b) Identification of risk loci with shared effects on five major psychiatric disorders: a genome-wide analysis. *Lancet*, **381**, 1371–1379.
Cullen, A.E., Zunszain, P.A., Dickson, H., Roberts, R.E., Fisher, H.L., Pariante, C.M. & Laurens, K.R. (2014) Cortisol awakening response and diurnal cortisol among children at elevated risk for schizophrenia: relationship to psychosocial stress and cognition. *Psychoneuroendocrinology*, **46**, 1–13.
Cuthbert, N. & Insel, R. (2013) Toward the future of psychiatric diagnosis: the seven pillars of RDoC. *BMC Med.*, **11**, 126.
Daniels, A.M. & Mandell, D.S. (2014) Explaining differences in age at autism spectrum disorder diagnosis: a critical review. *Autism*, **18**, 583–597.
Davidsen, K.A., Harder, S., MacBeth, A., Lundy, J.M. & Gumley, A. (2015) Mother–infant interaction in schizophrenia: transmitting risk or resilience? A systematic review of the literature. *Soc. Psych. Psych. Epid.*, **50**, 1785–1798.
Eack, S.M., Bahorik, A.L., McKnight, S.A., Hogarty, S.S., Greenwald, D.P., Newhill, C.E., Phillips, M.L., Keshavan, M.S. *et al.* (2013) Commonalities in social and non-social cognitive impairments in adults with autism spectrum disorder and schizophrenia. *Schizophr. Res.*, **148**, 24–28.
Elberling, H., Linneberg, A., Rask, C.U., Houman, T., Goodman, R. & Skovgaard, A.M. (2016) Psychiatric disorders in Danish children aged 5-7 years: a general population study of prevalence and risk factors from the Copenhagen Child Cohort (CCC 2000). *Nord. J. Psychiatry*, **70**, 146–155.
Elia, J., Gai, X., Xie, H. M., Perin, J.C., Geiger, E., Glessner, J. T., D'arcy, M., deBerardinis, R. *et al.* (2010) Rare structural variants found in attention-deficit hyperactivity disorder are preferentially associated with neurodevelopmental genes. *Mol. Psychiatry*, **15**, 637–646.
Eslinger, P. & Grattan, L. (1993) Frontal lobe and frontal-striatal substrates for different forms of human cognitive flexibility. *Neuropsychologia*, **31**, 17–28.
Frith, U. (2003). *Autism: Explaining the Enigma*, 2nd Edn. Blacwell, Oxford.
Frith, U. & Happe, F. (1994) Autism: beyond "theory of mind". *Cognition*, **50**, 115–132.
Froehlich, A.L., Anderson, J.S., Bigler, E.D., Miller, J.S., Lange, N.T., Dubray, M.B., Cooperrider, J.R., Cariello, A. *et al.* (2012) Intact prototype formation but impaired generalization in autism. *Res. Autism Spectr. Disord.*, **6**, 921–930.
Gabriels, R.L., Agnewa, J.A., Pana, Z., Holta, K.D., Reynolds, A. & Laudenslager, M.L. (2013) Elevated repetitive behaviors are associated with lower diurnal salivary cortisol levels in autism spectrum disorder. *Biol. Psychol.*, **93**, 262–268.
Gillberg, C. (2010) The ESSENCE in child psychiatry: early symptomatic syndromes eliciting neurodevelopmental clinical examinations. *Res. Dev. Disabil.*, **31**, 1543–1551.
Greene, C.M., Braet, W., Johnson, K.A. & Bellgrove, M.A. (2008) Imaging the genetics of executive function. *Biol. Psychol.*, **79**, 30–42.
Guilmatre, A., Dubourg, C., Mosca, A.L., Legallic, S., Goldenberg, A., Drouin-Garraud, V., Layet, V., Rosier, A. *et al.* (2009) Recurrent rearrangements in synaptic and neurodevelopmental genes and shared biologic pathways in schizophrenia, autism, and mental retardation. *Arch. Gen. Psychiat.*, **66**, 947–956.
Happe, F. & Frith, U. (2006) The weak coherence account: detail-focused cognitive style in autism spectrum disorders. *J. Autism Dev. Disord.*, **36**, 5–25.
Harder, S., Davidsen, K., MacBeth, A., Lange, T., Minnis, H., Andersen, M.S., Simonsen, E., Lundy, J.M. *et al.* (2015) Wellbeing and resilience: mechanisms of transmission of health and risk in parents with complex mental health problems and their offspring – The WARM Study. *BMC Psychiatry*, **15**, 310.
Hill, E.L. (2004) Executive dysfunction in autism. *Trends. Cogn. Sci.*, **8**, 26–32.
Kanner, L. (1943) Autistic disturbances of affective contact. *Nervous Child*, **2**, 217–250.
Kapur, S., Mizrahi, R. & Li, M. (2005) From dopamine to salience to psychosis–linking biology, pharmacology and phenomenology of psychosis. *Schizophr. Res.*, **79**, 59–68.
Kästner, A., Begemann, M., Michel, T.M., Everts, S., Stepniak, B., Bach, C., Poustka, L., Becker, J. *et al.* (2015) Autism beyond diagnostic categories: characterization of autistic phenotypes in schizophrenia. *BMC Psychiatry*, **15**, 115.
Kim, Y.S. & State, M.W. (2014) Recent challenges to the psychiatric diagnostic nosology: a focus on the genetics and genomics of neurodevelopmental disorders. *Int. J. Epidemiol.*, **43**, 465–475.
Kirov, G. (2015) CNVs in neuropsychiatric disorders. *Hum. Mol. Genet.*, **24**, R45–R49.
Kraepelin, E. (1889). *Psychiatrie*. Abel, Leipzig.
Kumra, S., Jacobsen, L. K., Lenane, M., Zahn, T. P., Wiggs, E., Alaghband-Rad, J., Castellanos, F. X., Frazier, J. A. *et al.* (1998) "Multidimensionally impaired disorder": is it a variant of very early-onset schizophrenia? *J. Am. Acad. Child Psy.*, **37**, 91–99.
Lai, M.C. & Baron-Cohen, S. (2015) Identifying the lost generation of adults with autism spectrum conditions. *Lancet Psychiatry*, **2**, 1013–1027.
Lai, M. C., Lombardo, M. V., Ruigrok, A. N., Chakrabarti, B., Auyeung, B., Szatmari, P., Happé, F. & Baron-Cohen, S. (2016) Quantifying and exploring camouflaging in men and women with autism. *Autism*, **29**, pii: 1362361316671012 [Epub ahead of print].
Larsson, H.J., Eaton, W.W., Madsen, K.M., Vestergaard, M., Olesen, A.V., Agerbo, E., Schendel, D., Thorsen, P. *et al.* (2005) Risk factors for

autism: perinatal factors, parental psychiatric history, and socioeconomic status. *Am. J. Epidemiol.*, **161**, 916–925.
Laurens, K.R. & Cullen, A.E. (2016) Toward earlier identification and preventative intervention in schizophrenia: evidence from the London Child Health and Development Study. *Soc. Psych. Psych. Epid.*, **51**, 475–491.
Lauritsen, M.B., Pedersen, C.B. & Mortensen, P.B. (2005) Effects of familial risk factors and place of birth on the risk of autism: a nationwide register-based study. *J. Child Psychol. Psyc.*, **46**, 963–971.
Lawson, R.P., Rees, G. & Friston, K.J. (2014) An aberrant precision account of autism. *Front. Hum. Neurosci.*, **8**, 302.
Lord, C. & Bailey, A. (2002) Autism spectrum disorders. In Rutter, M. & Taylor, E. (Eds), *Child and Adolescent Psychiatry*, 4th Edn. Blackwell Science Ltd., Oxford, pp. 636–663.
Madsen, G.F., Bilenberg, N., Cantio, C. & Oranje, B. (2014) Increased prepulse inhibition and sensitization of the startle reflex in autistic children. *Autism Res.*, **7**, 94–103.
Madsen, G.F., Bilenberg, N., Jepsen, J.R., Glenthøj, B., Cantio, C. & Oranje, B. (2015) Normal P50 gating in children with autism, yet attenuated P50 amplitude in the Asperger subcategory. *Autism Res.*, **8**, 371–378.
Maher, B.A. (2006) The relationship between delusions and hallucinations. *Curr. Psychiat. Rep.*, **8**, 179–183.
Marcelis, M., Navarro-Mateu, F., Murray, R., Selten, J.P. & Van Os, J. (1998) Urbanization and psychosis: a study of 1942-1978 birth cohorts in The Netherlands. *Psychol. Med.*, **28**, 871–879.
Marcelis, M., Takei, N. & van Os, J. (1999) Urbanization and risk for schizophrenia: does the effect operate before or around the time of illness onset? *Psychol. Med.*, **29**, 1197–1203.
McCarthy, S.E., Gillis, J., Kramer, M., Lihm, J., Yoon, S., Berstein, Y., Mistry, M., Pavlidis, P. *et al.* (2014) De novo mutations in schizophrenia implicate chromatin remodeling and support a genetic overlap with autism and intellectual disability. *Mol. Psychiatry*, **19**, 652–658.
Montag, C., Dziobek, I., Richter, I.S., Neuhaus, K., Lehmann, A., Sylla, R., Heekeren, H.R., Heinz, A. *et al.* (2011) Different aspects of theory of mind in paranoid schizophrenia: evidence from a video-based assessment. *Psychiat. Res.*, **186**, 203–209.
Moreno-De-Luca, D.; SGENE Consortium, Mulle, J.G.; Simons Simplex Collection Genetics Consortium, Kaminsky, E.B., Sanders, S.J.; GeneSTAR, Myers, S.M., et al. (2010) Deletion 17q12 is a recurrent copy number variant that confers high risk of autism and schizophrenia. *Am. J. Hum. Genet.*, **87**, 618–30.
Myhr, G. (1998) Autism and other pervasive developmental disorders: exploring the dimensional view. *Can. J. Psychiat.*, **43**, 589–595.
Nuechterlein, K.H., Dawson, M.E. & Green, M.F. (1994) Information-processing abnormalities as neuropsychological vulnerability indicators for schizoprenia. *Acta Psychiat. Scand. Suppl.*, **384**, 71–79.
Oranje, B., Aggernaes, B., Rasmussen, H., Ebdrup, B.H. & Glenthøj, B.Y. (2013) P50 suppression and its neural generators in antipsychotic-naive first-episode schizophrenia before and after 6 months of quetiapine treatment. *Schizophrenia Bull.*, **39**, 472–480.
Parnas, J. (2011) A disappearing heritage: the clinical core of schizophrenia. *Schizophrenia Bull.*, **37**, 1121–1130.
Parner, E.T., Schendel, D.E. & Thorsen, P. (2008) Autism prevalence trends over time in Denmark: changes in prevalence and age at diagnosis. *Arch. Pediat. Adol. Med.*, **162**, 1150–1156.
Piaget, J. (1967). *La psychologie de l'intelligence*. A.Colin, Paris.
Plomin, R., Haworth, C.M. & Davis, O.S. (2009) Common disorders are quantitative traits. *Nat. Rev. Genet.*, **10**, 872–878.
Radeloff, D., Ciaramidaro, A., Siniatchkin, M., Hainz, D., Schlitt, S., Weber, B., Poustka, F., Bölte, S. *et al.* (2014) Structural alterations of the social brain: a comparison between schizophrenia and autism. *PLoS ONE*, **9**, e106539.
Rajendran, G. & Mitchell, P. (2007) Cognitive theories of autism. *Dev. Rev.*, **27**, 224–260.
Rapoport, J., Chavez, A., Greenstein, D., Addington, A. & Gogtay, N. (2009) Autism spectrum disorders and childhood-onset schizophrenia: clinical and biological contributions to a relation revisited. *J. Am. Acad. Child Psy.*, **48**, 10–18.
Robinson, E.B., St Pourcain, B., Anttila, V., Kosmicki, J.A., Bulik-Sullivan, B., Grove, J., Maller, J., Samocha, K.E. *et al.* (2016) Genetic risk for autism spectrum disorders and neuropsychiatric variation in the general population. *Nat. Genet.*, **48**, 552–55.
Rommelse, N.N.J., Franke, B., Geurts, H.M., Hartman, C.A. & Buitelaar, J.K. (2010) Shared heritability of attention-deficit/hyperactivity disorder and autism spectrum disorder. *Eur. Child Adolesc. Psychiatry*, **19**, 281–295.
Ronald, A., Happé, F., Bolton, P., Butcher, L.M., Price, T.S., Wheelwright, S., Baron-Cohen, S. & Plomin, R. (2006) Genetic heterogeneity between the three components of the autism apectrum: A twin study. *J. Am. Acad. Child Psy.*, **45**, 691–699.
Ropar, D. & Peebles, D. (2007) Sorting preference in children with autism: the dominance of concrete features. *J. Autism Dev. Disord.*, **37**, 270–280.
Schuwerk, T., Vuori, M. & Sodian, B. (2015) Implicit and explicit Theory of Mind reasoning in autism spectrum disorders: the impact of experience. *Autism*, **19**, 459–468.
Shamay-Tsoory, S.G., Shur, S., Barcai-Goodman, L., Medlovich, S., Harari, H. & Levkovitz, Y. (2007) Dissociation of cognitive from affective components of theory of mind in schizophrenia. *Psychiat. Res.*, **149**, 11–23.
Simon, T.J., Bisch, J.P., Bearden, C.E., Ding, L., Ferrante, S., Nguyen, V., Gee, J.C., McDonald-McGinn, D.M. *et al.* (2005) A multilevel analysis of cognitive dysfunction and psychopathology associated with chromosome 22q11.2 deletion syndrome in children. *Dev. Psychopathol.*, **17**, 753–784.
Sinclair, D., Oranje, B., Razak, K. A., Siegel, S.J. & Schmid, S. (2016) Sensory processing in autism spectrum disorders and Fragile X syndrome —From the clinic to animal models. *Neurosci. Biobehav. Rev.*, **76**, 235–253.
Sinha, P., Kjelgaard, M.M., Gandhi, T.K., Tsourides, K., Cardinaux, A.L., Pantazis, D., Diamond, S.P. & Held, R.M. (2014) Autism as a disorder of prediction. *Proc. Natl Acad. Sci. USA*, **111**, 15220–15225.
Solomon, M., Olsen, E., Niendam, T., Ragland, J.D., Yoon, J., Minzenberg, M. & Carter, C.S. (2011) From lumping to splitting and back again: atypical social and language development in individuals with clinical-high-risk for psychosis, first episode schizophrenia, and autism spectrum disorders. *Schizophr. Res.*, **131**, 146–151.
Sugranyes, G., Kyriakopoulos, M., Corrigall, R., Taylor, E. & Frangou, S. (2011) Autism spectrum disorders and schizophrenia: meta-analysis of the neural correlates of social cognition. *PLoS ONE*, **6**, e25322.
Szatmari, P. (2000) The classification of autism, Asperger's syndrome, and pervasive developmental disorder. *Can. J. Psychiat.*, **45**, 731–738.
Szatmari, P., Bryson, S.E., Streiner, D.L., Wilson, F., Archer, L. & Ryerse, C. (2000) Two-year outcome of preschool children with autism or Asperger's syndrome. *Am. J. Psychiatry*, **157**, 1980–1987.
Tordjman, S., Anderson, G.M., Kermarrec, S., Bonnot, O., Geoffray, M.M., Brailly-Tabard, S., Chaouch, A., Colliot, I. *et al.* (2014) Altered circadian patterns of salivary cortisol in low-functioning children and adolescents with autism. *Psychoneuroendocrinology*, **50**, 227–245.
Tsuang, M. (2002) Schizophrenia: genes and environment. *Biol. Psychiat.*, **47**, 210–220.
Valla, J.M. & Belmonte, M.K. (2013) Detail-oriented cognitive style and social communicative deficits, within and beyond the autism spectrum: independent traits that grow into developmental interdependence. *Dev. Rev.*, **33**, 371–398.
Van de Cruys, S., Evers, K., Van der Hallen, R., Van Eylen, L., Boets, B., de-Wit, L. & Wagemans, J. (2014) Precise minds in uncertain worlds: predictive coding in autism. *Psychol. Rev.*, **121**, 649–675.
Van Eylen, L., Boets, B., Steyaert, J., Wagemans, J. & Noens, I. (2015) Executive functioning in autism spectrum disorders: influence of task and sample characteristics and relation to symptom severity. *Eur. Child Adoles. Psy.*, **24**, 1399–1417.
Waterhouse, L. (2008) Autism overflows: increasing prevalence and proliferating theories. *Neuropsychol. Rev.*, **18**, 273–286.
Waterhouse, L. & Gillberg, C. (2014) Why autism must be taken apart. *J. Autism Dev. Disord.*, **44**, 1788–1792.
Waterhouse, L., Morris, R., Allen, D., Dunn, M., Fein, D., Feinstein, C., Rapin, I. & Wing, L. (1996) Diagnosis and classification in autism. *J. Autism Dev. Disord.*, **26**, 59–86.
White, S.J., Burgess, P.W. & Hill, E.L. (2009) Impairments on "open-ended" executive function tests in autism. *Autism Res.*, **2**, 138–147.
Wiggins, L.D., Baio, J. & Rice, C. (2006) Examination of the time between first evaluation and first autism spectrum diagnosis in a population-based sample. *J. Dev. Behav. Pediatr.*, **27**(2 Suppl), S79–S87.
Williams, D.L., Mazefsky, C.A., Walker, J.D., Minshew, N.J. & Goldstein, G. (2014) Associations between conceptual reasoning, problem solving, and adaptive ability in high-functioning autism. *J. Autism Dev. Disord.*, **44**, 2908–2920.
Williams, D.L., Minshew, N.J. & Goldstein, G. (2015) Further understanding of complex information processing in verbal adolescents and adults with autism spectrum disorders. *Autism*, **19**, 859–867.
World Health Organization (1992). *ICD-10: the ICD-10 Classification of Mental and Behavioral Disorders: clinical Descriptions and Diagnostic Guidelines*. World Health Organization, Geneva.

Yang, C.-J., Tan, H.-P., Yang, F.-Y., Wang, H.-P., Liu, C.-L., He, H.-Z., Sang, B., Zhu, X.-M. *et al.* (2015) The cortisol, serotonin and oxytocin are associated with repetitive behavior in autism spectrum disorder. *Res. Autism Spect. Dis.*, **18**, 12–20.

Zaidel, A., Goin-Kochel, R.P. & Angelaki, D.E. (2015) Self-motion perception in autism is compromised by visual noise but integrated optimally across multiple senses. *Proc. Natl Acad. Sci. USA*, **112**, 6461–6466.