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REVIEW

Raising attention to attention deficit hyperactivity disorder in schizophrenia

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Abstract

Schizophrenia and attention deficit hyperactivity disorder (ADHD) are two psychiatric disorders with a negative impact on quality of life of individuals affected. Although they are classified into distinct disorders categories, attentional dysfunction is considered as a core feature in both conditions, either at the clinical then pathophysiological level. Beyond the obvious clinical overlap between these disorders, the Research Domain Criteria approach might offer an interesting perspective for disentangling common circuits underpinning both disorders. Hence, we review evidences regarding the overlap between schizophrenia and ADHD, at the clinical level, and at the level of underlying brain mechanisms. The evidence regarding the influence of environmental risk factors in the emergence of both disorders, and their developmental trajectories is also reviewed. Among these, we will try to elucidate the complex relationship between stimulants use and psychotic symptoms, discussing the potential role of ADHD medication in inducing psychosis or in exacerbating it. We aim that, taken together, these findings may promote further investigation with important implications both for clinicians and research. In fact, considering the amounting evidence on the overlap between schizophrenia and ADHD, the delineation of their boundaries might help in the decision for diagnosis and treatment. Moreover, it may help to promote interventions focused on the prevention of both schizophrenia and ADHD, by the reduction of recognized environmental risk factors.

Key words: Attention deficit disorder with hyperactivity; Central nervous system stimulants; Psychotic disorders; Schizophrenia; Toxic psychoses

Core tip: In line with the translational approach of viewing disorders in terms of dysregulation of brain basic mechanisms, there is increasing evidence of overlap between different mental disorders. Here, we explore relationships between attention deficit hyperactivity disorder and schizophrenia, in light of recent insights into potential common etiological mechanisms explaining some of the observed overlap in both disorders. Using evidence from clinical epidemiology and neuropsychology, we propose a biologically-based reconsideration of these brain diseases. We have also summarized environmental risk factors for both disorders, aiming to promote awareness

regarding the need of appropriate interventions to prevent the onset and development of these diseases.

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INTRODUCTION

There is a mounting interest in discovering the links between neurodevelopmental disorders and psychiatric disorders in adulthood. Although the relationship between schizophrenia and attention deficit hyperactivity disorder (ADHD) has been poorly studied, it has been reported that the majority of individuals with schizophrenia, and their offspring, show early symptoms including attentional difficulties.

The concept of attention dysfunction in schizophrenia has changed over time, since the first descriptions of the disorder. Kraepelin made a distinction between active attention (*i.e.,* aufmerksamkeit) and passive attention (*i.e.,* auffassung) in schizophrenia, indicating with the former the ability to voluntary keep attention fixed for a period of time, whereas the latter concerned the attraction towards external stimuli[1]. Years later, these concepts have been called vigilance and distractibility respectively[2]. Also Jung explored cognitive features of schizophrenia. Using his word association task, he elaborated that attention of patients with schizophrenia appeared to be caught up in a series of feeling-organized ideas[3] , resulting from an internal distraction[4]. Jung's theory strongly influenced Bleuler.

In Bleuler's conceptualization, schizophrenia was characterized by two types of symptoms (*i.e.*, fundamental and accessory), and psychotic symptoms were considered as secondary to fundamental symptoms[5]. In fact, whereas accessory symptoms had a waxing and waning course, fundamental symptoms were more stable over time[5,2]. Regarding attention, Bleuler[5] reported that the tendency to fatigue sometimes was the cause of the reduction of attention.

Since impaired attention is a core characteristic of ADHD, and since the individuals who developed schizophrenia-spectrum disorders in adulthood have more often a history of childhood ADHD[6], it would be of interest exploring the relationship between ADHD and schizophrenia. In line with the focus of Research Domain Criteria project[7,8], we aim to use clinical epidemiological and neuropsychological findings as a point of departure for discussing the need of future investigation on potential common aberrations in fundamental neural system and neuropsychological functioning of these illnesses, that may impact on their treatment responsiveness, level of impairment and recovery processes.

CLINICAL EPIDEMIOLOGY

A history of ADHD symptoms has been commonly found in a sub-set of individuals who develop schizophrenia in adulthood[9-13], and ADHD is diagnosed in a high proportion of children at genetic risk for schizophrenia[14]. In the prospective longitudinal study of Kim-Cohen *et al*[15], more than 50% of adults with schizophrenia met the criteria for another psychiatric disorder in early adolescence, and ADHD, conduct disorder and oppositional defiant disorder were, among them, the most frequently reported. Moreover, a retrospective study performed by Rubino *et al*[16] found that a diagnosis of ADHD in childhood was most predictive of schizophrenia in adulthood compared to unipolar depression. Follow-up studies focusing on adult outcome of childhood ADHD[17,18] confirmed that youth with ADHD constitute a high risk group for developing a wide range of psychiatric diseases[17], and that children and adolescents with ADHD were 4.3 times more likely to develop schizophrenia later in adulthood compared to controls[18]. Moreover, females with ADHD presented a greater risk ratio for schizophrenia (RR = 20.1, 95%CI: 4.1-58.6), compared to males with ADHD (RR = 2.9, 95%CI: 1.1-6.8). Interestingly, duration of treatment with stimulants was not associated significantly with the development of schizophrenia[18]. Taken together, these findings indicate that children and adolescents with ADHD are at higher risk of developing schizophrenia than those who do not have ADHD.

NEUROPSYCHOLOGICAL FUNCTIONING

There are only a few studies comparing attentional dysfunction in schizophrenia and ADHD, and in some cases research findings are difficult to compare because of the definition of attention used, and also because of the varying methodology. As Luck *et al*[19] (2008) reported, the term "attention" has been defined so broadly in literature that it is difficult to compare the extent of attentional deficits among the disorders. Moreover, the interrelation between attention and other cognitive functions, such as working memory and executive functioning, it make difficult to isolate the attention deficit from disturbances in other cognitive functions. Another methodological concern is that studies performed in these groups typically use different versions of continuous performance tests (CPTs): whereas the CPT versions used in schizophrenia typically require the subjects to uphold vigilance to a multitude of stimuli, and to respond only to few of them, in ADHD the CPT protocol requires subjects to respond almost continuously[20,21]. This is because the goal is to investigate diminution in attention in schizophrenia, and to study the inhibition of impulsive responses in ADHD. Results show that adults with ADHD are more impaired to auditory

CPT compared to controls[22], presenting a slower reaction time, more errors of omission and late responses. Conversely, patients with schizophrenia present a reduced sensitivity without the increase of omission errors, considered measures of sustained attention[23,24]. Such differences have been suggested as reflecting distinct neurobiological underpinnings: a compromised ability to discriminate target from non-target noise stimuli in schizophrenia, and a difficulty in deciding if a stimulus is or not the target in ADHD[25].

Event-related potentials have been extensively used as measures of attention, and abnormalities have been found both in schizophrenia and ADHD. Specifically, patients with schizophrenia appear to be characterized by the inability to suppress the auditory event-evoked potential P50[25], by an amplitude reduction and a prolonged latency of auditory P3[26]. Since P50 alterations in P50 auditory evoked response-a measure of sensory gating-have also been found in first-degree relatives of patients with schizophrenia[27,28], in subjects with schizotypical personality[29], and in patients in remission who are not pharmacologically treated[30], dysfunction in sensory gating has been proposed as a potential biological marker for schizophrenia. However, a defective gating P50 is present also in other neuropsychiatric disorders, such as bipolar disorder[31,32], panic disorder[33], or post-traumatic stress disorder[34]. It seems that sensory gating dysfunction in schizophrenia has a genetic basis[35,36], and is associated with the chromosome 15q14locus of the gene encoding the α7 nicotinic receptor agonists[37,38]. Also the prepulse startle inhibition (PPI)-a measure of sensory motor gating-has been found impaired in schizophrenia, confirming the dysfunction in automatic or pre-attentional gating.

Moreover, altered visual N2 and P3[39,40] have been found in schizophrenia, although not in all studies[41,42]. N2 and P3 abnormalities are not specific to schizophrenia, having been also found in some studies with childhood ADHD[43-47]. A recent study performed on adolescents with early onset schizophrenia and subjects with ADHD on auditory oddball task and a visual go/no-go task found that the early schizophrenia group showed reductions in auditory oddball P3 and N2 amplitude, as well in the go/no-go visual P3[48]. Conversely, ADHD group showed a different ERP pattern, characterized by reduced visual N2 in the go/no-go task and a normal P3 amplitude in the go/no-go and auditory oddball tasks. However, previous results in ADHD[49-51] suggest that such P3 differences could be the results of developmental trajectories, tending to normalize with age[48].

PPI has been consistently reported as normal in ADHD[52-54], but a recent study found an abnormal P50 suppression also in ADHD[52]. This finding seems in line with the hypothesis that the attention deficit associated with ADHD may reflect a different neural substrate compared to schizophrenia.

Some studies have used measures of visual scanning in order to investigate the relationship between ADHD and schizophrenia. Indeed, even eye movements involve attentional processes, and increased anticipatory saccades are thought to represent an inability to select task appropriate behavior, which leads to increased task-inappropriate attentional shifts[55]. Deficits in early visual processing have been largely reported in schizophrenia[56-58]; studies of smooth pursuit eye movement have consistently shown greater anticipatory saccades in children of schizophrenic parents[55], adult schizophrenia[59,60] and children and adolescents affected by the disease[61] . However, increased premature saccades have been found also in ADHD during an oculomotor delayed response task[59,60]. Even though impairment in inhibiting responses to task irrelevant information seems to be present in both groups, patients with schizophrenia appeared to be more compromised, since it has been found they also have impaired selection of appropriate targets[59,60] .

Studies investigating affect recognition reported some differences in visual scanning style[62-64], and brain imaging studies seem to support the notion that impairment noticed in schizophrenia and ADHD involve different circuits. For example, perception of negative emotions in schizophrenia has been associated with decreased responses in both amygdala and medial prefrontal cortex[65,66], whereas a fMRI study performed by Hare *et al*[67] showed an amygdlar activation in subjects with ADHD during evaluation of negative emotions. Impairments in emotion perception in ADHD and schizophrenia may result from different abnormalities in prefrontal and subcortical circuits, key regions for emotional processing and also for motivational behavior. It would worthwhile to explore this further.

EPIGENETICS

A heritability estimate of 80% has been reported for schizophrenia[68], whereas it ranges from 60% to 80% in ADHD[69]. Although increasing evidence points towards the role of genetic factors in etiology of both schizophrenia and ADHD, environmental risk factors have been also explored and implicated[70,71]. Epigenetics concerns the functional modification of a genome expressions that is not associated with an alteration in sequence of the nucleotide[72]. Interactions between genes and environment are the basis of epigenetics, and are responsible for modifications in the expression of the genetic background of the individual, contributing to psychopathology[73]. In fact, potential epigenetic factors may confer risk for both disorders at various developmental phases, and environmental factors seem to have important roles in the etiology of psychotic illnesses both in pre- and post-natal periods[74]. Therefore, the early perinatal period is fundamental for proper brain development, and potential stress-inducing factors have been associated with schizophrenia, but also with ADHD[75,76].

Environmental risk factors

Studies on incidence and prevalence of both disorders show variations in rates according to place and time. Although this variance could be explained by the use of different methodologies and diagnostic classifications, analysis of these aspects may help to recognize potential environmental risk factors for the development of both these disorders.

A recent study performed on the health database of the Kaiser Permanente Southern California showed an ADHD prevalence rate of 0.36% in 2006 and of 0.65% in 2009[77], that is clearly in contrast with the overall prevalence of 2.9%-5.2% of the disorder as reported in adults[78]. In a meta-regression analyses to 135 studies, Polanczyk *et al*[79] found that differences in ADHD prevalence estimates could be mostly explained by methodological issues characterizing these studies. Therefore, the higher incidence of ADHD could be attributed to the lack of standardized assessment in most studies.

However, in literature some modifiable risk factors have been implicated in the pathophysiology of ADHD, which should be also taken into account. Among these, the most frequently mentioned are prenatal substances exposure, nutritional deficits and psychosocial factors[76]. Recently, low birth weight has been found significantly associated with ADHD even after controlling for environmental and genetic variables shared within twin pairs[80]. Prenatal maternal stress has been linked to increased risk of ADHD[81,82], and maternal smoking during pregnancy is the most cited among prenatal risks for the disorder[83,84], such as alcohol and illicit substances use during pregnancy[85]. Concerning nutritional factors, there are some controversial findings on the associations between low iron and ferritin and ADHD emergency, with some studies reporting such associations[86,87], and others do not[88,89]. However, deficiencies of folate, zinc, magnesium and polyunsaturated fatty acids have been shown to increase risk for ADHD[76,84].

Regarding schizophrenia, a review by McGrath *et al*[90] reporting incidence data for schizophrenia from 1965 to 2001, showed an incidence rate of 15.2 per 100000 and a range of 7.7-43 per 100000, suggesting an influence of environmental factors on these different rates, since genetic differences seem unlikely to explain such variations. Moreover, risk for schizophrenia seems to increase for individuals raised in urban areas, compared to those living in rural areas[91-93], providing support to the environmental hypothesis. Among peri-natal risk factors for schizophrenia, infections, nutritional deficits, toxins, and other sociocultural factors have been reported[71,94]. Infections during pregnancy with viruses such as rubella, varicella-zoster, polio, herpes as well parasites as toxoplasma, have been demonstrated to increase risk for the disease[71,95]. Maternal infections and inflammatory processes have been involved in preterm labor[96,97]. Obstetric complications are reported as factors contributing susceptibility for schizophrenia[71] and, as in ADHD, also in schizophrenia low birth weight was found associated with an increased risk to develop the disorder[98]. Although it is not possible to establish a causal effect, literature on nutritional deficiencies and schizophrenia susceptibility show some evidence of iron and vitamin D deficiencies as maternal risk factor for schizophrenia[71], such as a decreased choline[99]. Interestingly, considering that amniotic choline activates fetal α7-nicotinic acetylcholine receptors and promotes cerebral inhibition, it seems plausible that the increase of such activation through choline supplementation may protect infants from future mental diseases[100].

Stimulants and psychosis

In examining relationship between schizophrenia and ADHD, it is necessary to consider the fear regarding the potential of psychostimulants in producing psychosis or in increasing risk to develop schizophrenia. On this issue, literature reports controversial findings. A study reported that 77% of youth with psychosis had been exposed to psychostimulants[101]. The age of onset of psychosis was lower in subjects exposed to psychostimulants compared to non-exposed individuals[102], and there are some reports describing the emergence of hallucinations and delusions in ADHD induced by stimulant medication[103].

Both methylphenidate and *d*-amphetamine are considered effective and well tolerated pharmacological agents, and are still considered first-line choice for the treatment of ADHD[104]. Even though there is reluctance to treat patients with ADHD and psychosis with such medications, several studies show that stimulant treatment is safe. In fact, there are case studies demonstrating that stimulants have been well tolerated in subjects with psychosis, with or without concomitant antipsychotic treatment[105-109], with positive effects on cognition[110,111]. It has been suggested that the positive effect of methylphenidate, described in some studies, may be due to a regulation of frontal hypodopaminergic state[110,112]. In fact, methylphenidate affects dopamine D1 receptors in frontal regions improving cognition, whereas antipsychotics block D2 receptors in mesolimbic systems, without influencing D1 receptors[110]. On the other hand, it has been suggested that small but repeated doses of stimulants produce some alterations in the brain resulting in psychotic symptoms resembling schizophrenia[113]. This theory of sensitization has received support from some animal experiments[114], but has been also debated[115]. Curran *et al*[116] performed a systematic review investigating relationship between stimulant use and psychosis in humans. They examined 32 experimental studies, of which 28 involved the administration of a single dose of oral or intravenous dexamphetamine or methylphenidate to patients with schizophrenia. Their review reported evidence that a large administration of stimulant medication can produce a psychosis, usually lasting only some hours, and that positive symptoms

make individuals more likely to experience a worsening of psychotic symptoms. However, they did not found sufficient support for the sensitization theory, except in two studies[117,118].

Unfortunately, literature on adult ADHD as comorbid condition in psychotic symptoms is still scarce, and there is a lack of recommended pharmacological interventions for the treatment of patients affected by both conditions. Trying to differentiate some peculiarities of psychosis in presence of ADHD, Bellak *et al*[119] proposed a separate diagnostic category called ADD Psychosis. According to Bellak and colleagues, attention deficit disorder (ADD) could impact on the development of personality predisposing the individual, in some cases, to psychosis during the years of late adolescence or early adulthood, with distinctive features. In fact, ADD Psychosis was different from Schizophrenia because of rare or no hallucinations (that were brief and simple if present), concrete thinking (no thought disorder), poor impulse control, little or no social withdrawal, soft neurological signs, presence of dyslexia or dysgraphia, lack of response by neuroleptics, and favourable response to psychostimulants.

On the basis of case reports by Huey *et al*[120], Bellak *et al*[119], Pine *et al*[121], Opler *et al*[112] suggested a trial of psychostimulants in patients presenting both ADD and psychosis, with a poor response to neuroleptics. The cited studies show no worsening of psychotic symptoms but an amelioration of both attentional deficits and psychotic symptoms, probably by increasing perfusion to the frontal lobes[112].

In evaluating controversial results in literature regarding psychosis-induced by stimulant medication, Kraemer *et al*[122] suggested that psychosis in ADHD may be due to the combination of methylphenidate with other substance such as cannabis, alcohol, or illegal drugs. It is also possible that psychosis co-existed with ADHD, or even that psychosis was be the result of a undetected bipolar disorder, rather than to the stimulant treatment effect. Therefore, further research is needed in order to elucidate the potential of psychostimulant in producing psychotic symptoms. This is especially important considering that ADHD is currently recognized as a disorder affecting the entire course of life, consequently the use of psychostimulant medication could be continued over the lifespan[123].

Genetics and Neurobiology

The hypothesis regarding shared underpinnings between ADHD and schizophrenia has been supported by recent studies by Hamshere *et al*[124] and Larsson *et al*[125]. Such observation is consistent with an observation of an overlap in genetic susceptibility between ADHD and schizophrenia for rare copy number variants reported elsewhere[126]. Moreover, recent evidence from Hart *et al*[127] showed that SNPs associated with response to a dopaminergic drug challenge were enriched for those SCNPs associated with disorders usually treated with dopaminergic agonists (*i.e.,* ADHD) and antagonists (*i.e.,* schizophrenia), consequently SNPs nominally associated with schizophrenia and ADHD resulted associated with d-amphetamine response. They also found that the increased euphoric effects of d-amphetamine resulted associated with a decreased risk for both schizophrenia and ADHD. As has been suggested, these results provide support for the dopamine involvement in the pathogenesis of these disorders, and the acute amphetamine response may be further explored as an endophenotype for both schizophrenia and ADHD. However, it has been found a higher risk of a comorbid bipolar disorder rather than schizophrenia in people with ADHD[125]. This may be due to the fact that ADHD and bipolar disorder share more symptoms than ADHD and schizophrenia[128]. Irritability, distractibility, overactivity and impulsivity are very common among individuals with ADHD and/or bipolar disorder, and may therefore be of limited utility in differentiating the two groups, and their impact on the emergence of psychosis. Comparative studies examining common substrates across these disorders are warranted.

CONCLUSION

Until now only a few studies have made efforts to unravel the genetic and neurophysiological aetiology of ADHD symptoms in schizophrenia. It is still uncertain whether ADHD comorbid with psychosis constitutes a more severe subgroup of psychosis[129], or is an index of the severity of psychosis[102]. ADHD and schizophrenia share some features that require further investigation because it is possible that attentional disturbance characterizing both disorders may be fundamentally different.

The first difference of course is that attentional dysfunction emerges before 12 years of age in ADHD (DSM 5, APA 2013)[130], whereas this is not reported for Schizophrenia. Therefore, this difference has to be considered in the assessment.

Direct comparisons between these disorders will add to our knowledge of potential common aberrations in fundamental neural systems, and allow the identification of neural systems that are critical for the characterization of brain abnormalities and structural endophenotypes detectable by neuroimaging. Research is also needed in order to clarify the controversies regarding the differential diagnosis between BD and ADHD, and the relationship of these disorders with the emergence of psychosis in people using stimulant drugs.

Taken together, the findings reviewed above suggest the importance of screening for an ADHD diagnosis in neuroleptic refractory adult patients with psychosis. Although follow-up studies are warranted in order to have a better understanding of the risks and benefits of combining antipsychotics and psychostimulants in such clinical settings, the few studies, in which ADHD symptoms have been assessed in the second place,

did not report additional risk to the augmentation with drugs for ADHD treatment to antipsychotics in the stabilization phase. Deepening our understanding of the circuits underpinning these disorders may offer insights into phenotypes and more targeted interventions, which may also lead to plan early intervention and prevention.

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