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Original article

Can neuropsychological testing facilitate differential diagnosis between at-risk mental state (ARMS) for psychosis and adult attention-deficit/hyperactivity disorder (ADHD)?

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ABSTRACT

Background: Patients with an at-risk mental state (ARMS) for psychosis and patients with attention-deficit/hyperactivity disorder (ADHD) have many overlapping signs and symptoms and hence can be difficult to differentiate clinically. The aim of this study was to investigate whether the differential diagnosis between ARMS and adult ADHD could be improved by neuropsychological testing.
Methods: 168 ARMS patients, 123 adult ADHD patients and 109 healthy controls (HC) were recruited via specialized clinics of the University of Basel Psychiatric Hospital. Sustained attention and impulsivity were tested with the Continuous Performance Test, verbal learning and memory with the California Verbal Learning Test, and problem solving abilities with the Tower of Hanoi Task. Group differences in neuropsychological performance were analyzed using generalized linear models. Furthermore, to investigate whether adult ADHD and ARMS can be correctly classified based on the pattern of cognitive deficits, machine learning (i.e. random forests) was applied.
Results: Compared to HC, both patient groups showed deficits in attention and impulsivity and verbal learning and memory. However, in adult ADHD patients the deficits were comparatively larger. Accordingly, a machine learning model predicted group membership based on the individual neurocognitive performance profile with good accuracy (AUC = 0.82).
Conclusions: Our results are in line with current meta-analyses reporting that impairments in the domains of attention and verbal learning are of medium effect size in adult ADHD and of small effect size in ARMS patients and suggest that measures of these domains can be exploited to improve the differential diagnosis between adult ADHD and ARMS patients.
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1. Introduction

Young adults seeking help at psychiatric services frequently suffer from adult attention-deficit/hyperactivity disorder (ADHD) or an at-risk mental state (ARMS) for psychosis. Although the latter is not yet accepted as an official diagnosis, it is increasingly identified and treated in clinical practice for the following reasons. First, it is now well established that patients who meet ARMS criteria not only have a largely increased risk of developing psychosis, but also suffer from psychopathological symptoms and impaired psychosocial functioning requiring clinical attention [1]. Second, although comorbidity with other psychiatric disorders, particularly with affective and anxiety disorders, is high [2], the specific psychopathology of ARMS patients is not adequately addressed by existing diagnostic categories [3,4]. Consequently, the European Psychiatric Association (EPA) has recently issued evidence based recommendations for the early detection [5] and treatment [6] of these patients. Furthermore, attenuated psychosis syndrome, which was defined according to the most frequent ARMS criterion, has been placed in Section 3 of the Diagnostic and

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Statistical Manual of Mental Disorders, 5th Edition (DSM-5) [7] as a new disorder for further study.

The distinction between adult ADHD and ARMS for psychosis can be a challenging task for clinicians because these disorders have many overlapping signs and symptoms, such as difficulties concentrating, lack of attention and other cognitive deficits [8,9], disorganized behavior, performance problems in school or at work, and problems with relationships [10,11]. Additionally, both disorders can present with restlessness, nervousness, irritability, hypersensitivity, sudden lack of interest, initiative, energy and drive, low frustration tolerance, as well as poor resilience to stress [12,13]. Furthermore, both disorders frequently occur in early adulthood and both are considered neurodevelopmental in origin [14,15]. Moreover, ADHD in childhood has been found to be associated with an increased risk of schizophrenia in adulthood both in prospective follow-up [16,17] and retrospective studies [18,19]. Likewise, individuals genetically at-risk for schizophrenia [20,21] and patients with psychosis [22] have been found to more frequently demonstrate ADHD-like features than healthy controls. It has been suggested that the overlap between ADHD and psychotic disorders is due to shared genetic [23] and environmental risk factors, particularly obstetric complications [24]. Another potential explanation is that – due to their similar clinical manifestation – ADHD is a frequent misdiagnosis of early signs of psychotic disorders [17].

Missclassifying patients with an ARMS for psychosis as ADHD patients can lead to inappropriate and even potentially harmful treatment of these patients. Specifically, since ADHD is most commonly treated with stimulant drugs which exert their pharmacological effects via increasing the levels of dopamine [25], and since increased levels of synaptic dopamine are implicated in the generation of psychotic symptoms [26], treating ARMS patients as ADHD patients could potentially exacerbate (pre-)psychotic symptoms in these patients [for review, see Ref. 27].

A possible way to improve differential diagnosis between these two disorders is to take the neuropsychological performance profile into account. Although current meta-analyses indicate that – compared to healthy controls (HC) – both adult ADHD and ARMS for psychosis patients show impairments across a wide range of cognitive domains, the degree and pattern of impairments seem to differ. While adult ADHD patients were found to be most strongly impaired in sustained and selective attention, inhibition, and verbal learning and memory with effect sizes in the small to medium range [9,28,29]. ARMS patients showed the largest impairments in speed of processing, social cognition and verbal learning with, however, mostly small effect sizes [8].

However, to our knowledge, no study has directly tested cognitive performance differences between adult ADHD and ARMS patients. Furthermore, it is currently unknown whether potential differences on the group level could be exploited to facilitate diagnostic classification on the individual level by means of automated pattern recognition or machine learning methods. This is unfortunate because neuropsychological testing is already routinely conducted in early detection services for both disorders and has shown promise in the classification between ADHD and various other psychiatric disorders, including mood and anxiety disorders [30–33], autism spectrum disorders [34], and borderline personality disorders [35], and between ARMS for psychosis and depressive disorders [36].

Thus, the aim of this study was 1) to directly test neuropsychological performance differences between adult ADHD, ARMS for psychosis patients, and HC in the domains of sustained attention and impulsivity, verbal learning and memory, and problem solving abilities and 2) to estimate the classification accuracy of machine learning model predicting group membership from all neurocognitive performance measures combined.

Based on the above mentioned meta-analyses [8,9,28,29], we hypothesized that both patient groups would show worse cognitive performance in all tested domains relative to healthy controls and that adult ADHD patients would show larger deficits than ARMS patients in the domains of attention and impulsivity and verbal learning and memory, but not problem solving abilities. Furthermore, we expected that classification between adult ADHD and ARMS patients based on all neuropsychological performance measures combined can be achieved with moderate to high accuracy.

2. Methods

2.1. Study design

In this cross-sectional study, the cognitive performance of three groups was compared: 1) patients with adult ADHD, 2) patients with an ARMS, and 3) healthy controls (HC). All participants provided their written informed consent. The study was approved by the by the local ethics committee (Ethikkommission der Nordwest- und Zentralschweiz) and conformed to the Declaration of Helsinki.

2.2. Recruitment of patients with adult ADHD

Patients with adult ADHD were recruited via the ADHD Special Consultations Unit of the Outpatient Department of the University of Basel Psychiatric Hospital between 2010 and 2014. All referrals to this Unit underwent an extensive ADHD screening procedure conducted by two independent experts and including a clinical interview, a self-rating and an observer-rating scale. School certificates and/or reports from teachers on behavioral problems were also considered. The procedure conformed to general standards for clinical diagnostics and followed the recommendations for the diagnostics and management of ADHD [37]. The diagnosis was not made solely on the basis of rating scales, but it also took into account a full developmental and psychiatric history. Instruments applied in the diagnostic process were the Wender-Reimherr Adult Attention Deficit Disorder Rating Scale (WRAADDS) [38] (German version: [39,40]) and the Conners' Adult ADHD Rating Scales (CAARS) [41]. Former symptoms in childhood were assessed systematically with the short version of the Wender Utah Rating Scale (WURS-k) [42] (German version: [43]). To check for current symptoms, a combination of the results from the clinical interview and the rating scales was used. An ADHD diagnosis was given when an individual met at least six criteria of the dimension of inattention and/or six criteria of the dimension of hyperactivity/impulsivity according to DSM-IV. Only patients who met the diagnostic criteria for ADHD and who were at least 18 years old were included into this study. Exclusion criteria were an intelligence quotient (IQ) $<$85, schizophrenia or other psychotic disorders, a current or most recent episode of a manic disorder or current severe major depressive disorder, acute stress disorder, or substance intoxication or withdrawal.

2.3. Recruitment of patients with an ARMS for psychosis

ARMS patients were recruited and assessed between March 1, 2000 and December 31, 2016 as part of the Basel Früherkennung von Psychosen (*FePsy*) study, a prospective multilevel study, which aims to improve the early detection of psychosis. A detailed description of the study design can be found elsewhere [44,45]. In brief, individuals suspected to be in their early (prodromal) phase of psychosis were referred to our specialized early detection clinic at the Outpatient Department of the Psychiatric University Hospital Basel, Switzerland. All referrals to the clinic during the

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