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Review

Long-term trajectories of cognitive deficits in schizophrenia: A critical overview

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ABSTRACT

Background: Cognitive disturbances are widely pronounced in schizophrenia and schizophrenia spectrum disorders. Whilst cognitive deficits are well established in the prodromal phase and are known to deteriorate at the onset of schizophrenia, there is a certain discrepancy of findings regarding the cognitive alterations over the course of the illness.
Methods: We bring together the results of the longitudinal studies identified through PubMed which have covered more than 3 years follow-up and to reflect on the potential factors, such as sample characteristics and stage of the illness which may contribute to the various trajectories of cognitive changes.
Results: A summary of recent findings comprising the changes of the cognitive functioning in schizophrenia patients along the longitudinal course of the illness is provided. The potential approaches for addressing cognition in the course of schizophrenia are discussed.
Conclusions: Given the existing controversies on the course of cognitive changes in schizophrenia, differentiated approaches specifically focusing on the peculiarities of the clinical features and changes in specific cognitive domains could shed light on the trajectories of cognitive deficits in schizophrenia and spectrum disorders.

1. Introduction

Currently cognitive deficit is considered a core feature in schizophrenia [27,31,34,59]. Cognitive impairment in schizophrenia is widespread, almost universal; occurring in more than 70% of patients [79], and having high reliability in patients, as compared to the healthy individuals – effect size is approximately 1.0, which is almost two times bigger than in current indicators for structural brain disorders obtained by magnetic resonance imaging (MRI) [24,47,61,84]. It is argued that the cognitive deficit in schizophrenia is generalized [25,69], although being more pronounced in a number of cognitive functions such as episodic memory [1,3,83], processing speed [24], verbal fluency [48], attention [28,78], executive function and working memory [7,66,67,84]. Cognitive deficits are already detected in the premorbid phase of schizophrenia with a moderate effect size ($r \approx 0.5$) [47,48,109] and they are thought to be a strong predictor of adverse social and occupational outcomes of the disease [15,102]: the most predictive in this respect are the disturbances of social cognition [93,81,101,103].

Cognitive impairment is revealed in unaffected first-degree relatives of patients with psychosis but to a lesser extent [52,55,91,95,99,107,108], probably due to their genetic vulnerability [32,92,98].

Although cognitive deficits persist through the long-term course of schizophrenia [53,88], the changes in cognitive functioning through the illness have not been definitively outlined. It has been repeatedly shown that cognitive deficits are present in the premorbid phase and are likely to deteriorate prior to and around the first psychotic episode (especially during the first five years of the disease) with a modest partial treatment improvement, and relative stability thereafter with heterogeneity across

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patients [11,64]. There are studies indicating that antipsychotic therapy leads to a moderate improvement in the effect size 0.5 [63,96]. However, in the vast majority of cases, cognitive impairment remains unchanged throughout the disease [16,34,46,53,96,112].

Curiously enough, studies focused on the cognitive course at the different stages of schizophrenia identify ambiguous results. The main constraint of these studies is that the majority of them are based on a fairly short length of follow-up. Thus, in a meta-analysis of 53 longitudinal studies of cognition in schizophrenia [96] the test-retest period was only 12 months, with a median of 4 months. It should be also noted that a large proportion of the studies are focused on the course of cognitive deficits followed by therapeutic intervention, mainly using second-generation antipsychotics. In fact, long-term longitudinal studies of the course of cognitive deficits in schizophrenia are rare, even though "cognition" constitutes one of the eight dimensions of schizophrenia in DSM-5.

The main aim of the present review is to focus on the literature that covers the course of the cognitive deficits estimated over a period of not less than 3 years.

2. Methods

Target articles were identified through a PubMed search using combined search terms ("schizophrenia" OR "psychosis") AND ("cognit*" OR "neuropsycholog*") AND ("longitudinal" OR "follow-up" OR "course" OR "trajectory"). The search was limited to studies published before June 2014 (last search: 16 June 2014). Additional studies were also identified by reviewing the reference lists of all retrieved studies.

Inclusion criteria for the article selection are that they: are written in English; provided data on the trajectories of cognitive functions for individuals with schizophrenia; the follow-up period was at least three years. The first two authors (A.S. and I.G.) independently reviewed all the papers collected regarding the suitability for inclusion. Any disagreements were resolved by discussion.

3. Results

The studies that were identified as relevant from this literature search are described in the Table 1.

3.1. Cognitive disturbances in the prodromal phase

It is well established that cognitive impairment is present in patients even before the onset of the first psychotic episode, in its prodromal phase. In this regard, one may wonder when it first occurs.

In a large study, Jones et al. [58] evaluated the educational tests in a cohort of individuals born in 1946 and detected poor cognitive performance of children at the age of 8, 11 and 15 years who subsequently developed schizophrenia as compared to their peers, the deficit increasing gradually, showing the worst scores in 15-year-old.

In another study, Fuller et al. [31] reported the results of a survey using the Iowa Tests of Basic Skills and the Iowa Tests of Educational Development in children and adolescents across the State of Iowa in grades 4, 8 and 11 (9, 13 and 16 years of age, respectively), who later developed schizophrenia (70 people). The scores of patients in grades 4 and 8 did not significantly differ from those of the unaffected individuals, but the 11th grade composite scores were significantly worse. Moreover, the scores for grade 11 were significantly lower than those for grade 8 and sometimes for grade 4. Therefore, it was concluded that the critical period in which cognitive impairment could emerge in individuals who later developed psychosis was between the ages 13–16 years.

Alternatively, Reichenberg et al. [86] explored the data from the survey of a birth cohort from Dunedin (New Zealand) which included 1037 children; 35 persons out of the cohort subsequently developed schizophrenia. Cognitive functions were evaluated by the Wechsler Intelligence Scale for Children-Revised at age 7, 9, 11 and 13 years. The authors indicate that the performance of cognitive tests in these 35 children improved with maturation. However, in several tests (information, similarities, vocabulary, and picture completion), the authors detected a significant developmental lag in contrast to the cohort of control subjects at all measured points and this developmental lag even increased in a number of tests (block design, arithmetic, and digit symbol). The latter finding is stressed as a very important issue, as the processing speed, estimated specifically by the Digit Symbol Subtest, is known to be the most prominently affected neurocognitive function in schizophrenia patients [24], and the progressive growth of the developmental lag in the processing speed in children and adolescents may possibly explain the depth of its disturbance in adult patients [86].

To date, three hypotheses of the premorbid cognitive impairment course in patients with schizophrenia have been proposed. Based on the assumption of a progressive decline in cognitive function (*deterioration hypothesis*) in the premorbid stage, those individuals who subsequently develop schizophrenia experience a progressive decline in cognitive capabilities, while their peers continue to improve the corresponding functions [31,85]. In accordance with the *developmental deficit hypothesis*, there is a consistent delay (quantitatively measured) in cognitive function development: the emerging linear improvement of cognitive performance that occur in ontogenesis in both healthy children and children who are developing schizophrenia subsequently differs at the same point value [85,106]. Finally, according to the *developmental lag hypothesis*, the patients exhibit a slow improvement in cognitive functioning prior to the onset of psychosis, although lagging behind healthy peers, which by itself progressively increases the cognitive deficits [8,26,29,86]. These concepts can be considered not as independent entities but in combination, referring to the dynamics of individual cognitive performance (e.g. developmental deficit in knowledge acquisition, concept formation, verbal reasoning processes and developmental lag in the ability to focus attention, process information quickly, and maintain and manipulate this information) [86].

Thus, cognitive deficits, which are detectable in the premorbid stage of subjects who subsequently develop schizophrenia, can already be diagnosed in childhood, and are most prominently present in adolescence. What then is the trajectory of their further development?

3.2. Course of cognitive functioning after the onset of psychosis

The severity of cognitive impairment in the prodromal phase falls within the range 0.4–0.5 SDs [62,109], which is substantially less than in patients after the onset of psychosis (reaching 0.9–1.40 SDs in patients with first episode patients and chronic patients) [47,74,84]. One can expect that the decline in cognitive functioning may continue even after the onset of psychosis [59].

However, despite the obvious robustness of the data, this issue has not yet been clarified. A number of meta-analyses and systematic reviews underscore the stability of cognitive deficits after a first psychotic episode, although the authors indicate a number of significant analysis limitations in the present research field [16,57,96].