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## Age or age at onset? Which of them really matters for neuro and social cognition in schizophrenia?



Magdalena Linke<sup>a,\*</sup>, Konrad S. Jankowski<sup>b</sup>, Agnieszka Ciołkiewicz<sup>a</sup>,  
Małgorzata Jędrasik-Styla<sup>a</sup>, Dorota Parnowska<sup>a</sup>, Anna Gruszka<sup>a</sup>, Mirella Denisiuk<sup>a</sup>,  
Marek Jarema<sup>a</sup>, Adam Wichniak<sup>a</sup>

<sup>a</sup> Third Department of Psychiatry, Institute of Psychiatry and Neurology, Sobieskiego 9, 02-957 Warsaw, Poland

<sup>b</sup> Faculty of Psychology, University of Warsaw, Stawki 5/7, 00-183 Warsaw, Poland

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### ABSTRACT

In schizophrenia patients, both an older age and earlier age at onset of the disease are related to worse cognitive functioning. As patients with later schizophrenia onset are also older, analysing the two effects separately can be misleading, as they can either be spurious or cancel one another out. The purpose of the present study was to elucidate the effects of age and onset-age on cognition in schizophrenia patients. Individuals with schizophrenia ( $N=151$ ), aged 18–59 years, were examined with a MATRICS Consensus Cognitive Battery (MCCB) to get a full picture of their cognitive performance. Results showed age and age at onset indeed interrelated. Regression analyses revealed later onset of schizophrenia related to better social cognition. Patients' older age was related to a slower performance in symbol coding task, less effective executive functions, worse visual learning, lower attention, and lower total score in the MCCB. In the above regression analyses we controlled doses of antipsychotic medications. The results suggest that a previously found relationship between older age and social cognition might be spurious, and strengthen observations that it is specifically later onset-age which fosters better social cognition in schizophrenia patients.

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### 1. Introduction

Cognitive deficits are salient clinical features of schizophrenia that impact functioning and are crucial to effective treatment. There is a broad range of cognitive functions that are defective in schizophrenia patients, particularly attention, speed of processing, working memory, learning, motor, executive, and social cognitive functions (Kern et al., 2011; Schaefer et al., 2013).

#### 1.1. Age and cognitive functioning in schizophrenia

Schizophrenia is considered a neurodevelopmental disorder, but it is still under debate whether it is rather a degenerative process or a static encephalopathy. Some researchers argue that schizophrenia is characterised by relatively stable neuropsychological deficits (Rund, 1998; Ekerholm et al., 2012), particularly during an early phase, with degenerative-like process in older age (Kurtz, 2005). Others, however, claim the existence of neuropsychological decline progressing from the premorbid stage to

the chronic form of disease (Azadmehr et al., 2013; Meier et al., 2014), varying across cognitive functions, with processing speed, learning, executive, and motor functions being the most susceptible to deterioration with older age, and deficits in verbal abilities, delayed memory, and social cognition that remain stable during the lifespan (Green et al., 2012; Meier et al., 2014). This suggests different pathophysiological mechanisms underlying deficits in specific mental functions and could be a reflection of different age-related brain alterations in different brain structures. Studies have reported that some brain areas and structures (e.g. those related to memory and emotional reactions) are affected in the early stage of schizophrenia, but age in a physiological way (Chiapponi et al., 2013). Other brain areas (e.g. responsible for social cognition) are impaired before onset of psychosis and worsen only during the acute phase, and some (e.g. linked to certain types of learning and memory) are affected around the onset of psychosis and continuously worsen over time (Chiapponi et al., 2013). Overall, ageing is accompanied by cognitive decline in the general population (Dodge et al., 2014), but schizophrenia patients show age-related brain tissue loss suggesting abnormal brain maturation in the third and fourth decade of life (Van Haren et al., 2008). Such changes suggest that brain ageing progresses differently in schizophrenia patients than in healthy individuals

\* Corresponding author. Tel.: +48 22 2182338; fax: +48 224582 510.

E-mail address: [m.linke@ipin.edu.pl](mailto:m.linke@ipin.edu.pl) (M. Linke).

(Koutsouleris et al., 2014). An aging-related decline in white matter integrity is accelerated in schizophrenia individuals (Kochunov et al., 2013), as is an aging-related decline in cognition (Granholt et al., 2000). This results in worse performance in several cognitive domains in schizophrenia patients, compared to healthy elderly individuals (Silver and Bilker, 2013).

### 1.2. Age of onset and cognitive functioning in schizophrenia

Age of onset is also considered an important determinant of cognitive deficits in schizophrenia. Patients of an early age at schizophrenia onset perform more poorly in many cognitive domains, than do those with late onset, and show a different course of cognitive deterioration and clinical picture (Luoma et al., 2008; Zaytseva et al., 2010). Early onset schizophrenia is commonly diagnosed when occurred before 18–19 years old (Burke et al., 2008; Zaytseva et al., 2010). Brain maturation in adolescence might be interrupted by disease and results in worse cognitive functioning. There is evidence showing significant parietal grey matter loss in adolescents with early onset schizophrenia (Burke et al., 2008).

### 1.3. Research question

In summary, in schizophrenia patients, older age and earlier age at onset of the disease are known to be related to worse cognitive functioning. However, if patients with late onset schizophrenia and early onset schizophrenia are randomised, then the former group is also older compared to the latter one. Thus, taking into account that patients with later schizophrenia onset are presumably also older, analysing the effects of age and onset-age separately can be misleading, as the effects can either be spurious or cancel one another out. The purpose of the present study was to elucidate the effects of age and onset-age on cognition in schizophrenia patients using the most comprehensive cognitive battery to get a full picture of patient performance in all crucial areas for schizophrenia cognitive domains. This is the first study using the MATRICS Consensus Cognitive Battery (MCCB), especially developed to examine cognition in schizophrenia patients, in the context of age and onset-age. We also aimed to control for doses of antipsychotic medications in our analyses.

## 2. Methods

### 2.1. Subjects

#### 2.1.1. Recruitment, inclusion and exclusion criteria

Clinically stable individuals ( $N=151$ ) carefully recruited between 2010 and 2013 from inpatients of two psychiatric wards F9 and DZ, and outpatients from mental health clinic of the Institute of Psychiatry and Neurology in Warsaw were included in the sample (Table 1). F9 ward is an open unit for young people (up to 35 years old) with schizophrenia, while DZ is a day care ward for schizophrenia

patients with no age limits, but mostly serves to older, chronically ill patients. All patients met ICD-10 diagnostic criteria for schizophrenia and did not meet the following exclusion criteria: other psychiatric ICD-10 diagnoses, somatic and neurological disorders that could affect cognitive functions, history of head injuries, substance dependence in the past 6 months, substance abuse in the past month or excessive lifetime alcohol or substance use other than nicotine. Patients data were collected in the following manner. First, a psychiatrist taking a patient to a ward interviewed a patient and his/her family member. The gathered information on the course of disease (age at onset, number of hospitalisations, and number of episodes), other psychiatric diagnoses, history of head injuries, and alcohol or psychoactive substances use was compared with information from the past clinical histories. Patients for whom doubts regarding the use of psychoactive substances appeared were laboratory tested for the presence of these substances. They were also warned that tests will be repeated at some time during the stay. Patients who consented to participate in the study were again interviewed by a researcher (psychologist or psychiatrist) prior to cognitive assessment. Namely, semi-structured interview was conducted concerning course of disease, alcohol or other psychoactive substances use, smoking, personal data, current medications. Information about outpatients were collected using the same semi-structured interview, and from the patient's psychiatrist who knew the history of disease for several years. The Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987) was also completed for patients. For seven subjects the PANSS data were missing.

#### 2.1.2. Sex distribution

In the final sample there were 49 women and 102 men. Greater number of males than females in the sample can reflect sex differences in the risk of schizophrenia (Aleman et al., 2003) and the sex ratio of patients in F9 ward (where the majority of patients were recruited). Increased prevalence of males in F9 ward can be also ascribed to the specificity of this ward. Namely, F9 is designed for patients in good condition to activate them and bring back to professional/social activity. As in Poland there is a higher social pressure on men to undertake professional activity, families more frequently press on men than on women to go to the activation-like wards.

#### 2.1.3. Age at onset of illness

Mean age at onset of illness was 23.1 (S.D.=6.2) and varied from 12.5 to 50.4 years. The numbers of participants at a given age at onset of schizophrenia were as follows: < 15 years seven participants, 15–19 years 49 participants, 20–24 years 49 participants, 25–29 years 26 participants, 30–34 years 12 participants,  $\geq 35$ –39 years eight participants.

#### 2.1.4. Antipsychotic treatment

At the baseline, participants were on stable doses of second-generation antipsychotics for a minimum of 4 weeks: olanzapine ( $N=41$ ; Chlorpromazine (CPZ) equivalent (Woods, 2003; American Psychiatric Association, 1997)  $M=310$ ; S.D.=109), aripiprazole ( $N=32$ ; CPZ equivalent  $M=264$ ; S.D.=108), clozapine ( $N=18$ ; CPZ equivalent  $M=686$ ; S.D.=317), quetiapine ( $N=15$ ; CPZ equivalent  $M=626$ ; S.D.=283), risperidone ( $N=15$ ; CPZ equivalent  $M=332$ ; S.D.=128), amisulpride ( $N=11$ ; CPZ equivalent  $M=163$ ; S.D.=55), sertindole ( $N=7$ ; CPZ equivalent  $M=89$ ; S.D.=24), and ziprasidone ( $N=5$ ; CPZ equivalent  $M=266$ ; S.D.=0), seven participants were on first-generation medications (CPZ equivalent  $M=117$ ; S.D.=109). Some patients ( $N=48$ ) received more than one antipsychotic drug.

### 2.2. Procedure and materials

After providing written informed consent patients' cognitive functions and psychiatric symptoms were assessed. A Polish academic translation of the MCCB (Jędrasik-Styla et al., 2012) was used to assess cognition. The battery consists of (abbreviation of the test, mean  $\pm$  S.D. of raw scores for this sample): the Trail Making Test – Part A (TMT,  $43.1 \pm 24.6$ ), Brief Assessment of Cognition in

**Table 1**  
Sample means and S.D. of demographic and clinical variables.

Sample	F9 (n=96)	DZ (n=30)	Outpatients (n=25)	Total (N=151)
Age	27.3 (4.9); 18–39	45.1 (9.5); 29–59	30.8 (8.5); 19–54	31.4 (9.6); 18–59
Onset age	21.2 (4.2); 12–34	29.5 (7.9); 18–50	22.5 (5.6); 13–38	23.1 (6.3); 12–50
Duration of illness (years)	6.1 (5.1)	15.5 (9.9)	8.3 (7.0)	8.4 (7.6)
Number of hospitalisations	4.5 (6.4)	7.7 (12.6)	4.2 (4.6)	5.1 (7.9)
Number of episodes	3.1 (3.1)	7.4 (10.9)	4.5 (4.2)	4.2 (5.9)
Education (years)	13.7 (2.6)	14.3 (2.6)	14.1 (3.3)	13.9 (2.7)
Positive symptoms	10.0 (3.5)	12.1 (5.0)	9.9 (3.9)	10.4 (3.9)
Negative symptoms	14.2 (6.2)	15.5 (6.9)	11.7 (5.6)	14.0 (6.3)
General psychopathology	25.6 (8.3)	28.4 (8.8)	23.4 (5.9)	25.8 (8.2)
PANSS total score	50.1 (15.2)	56.0 (18.7)	45.0 (13.1)	50.4 (15.9)

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