Evaluation of higher order cognitive dysfunction in patients with early or adult onset schizophrenia

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Introduction

Cognitive impairments in schizophrenia are a constant and well replicated feature of the disease [1]. Early onset schizophrenia (EOS, onset ≤18y) is known to have lower premorbid functioning and worse outcome than patients with adult onset schizophrenia (AOS, onset >18y) [2,3] . EOS patients are thought to suffer more pre/perinatal complications causing lesions that interact with brain development occurring later on. There is evidence that early onset is associated with neuropsychological impairments [4], suggesting brain damage as a possible etiologic factor occurring on a continuum with regard to age of onset.

The aim of this study was to test neurocognitive performance and its electrophysiological correlates of patients with either EOS or AOS compared to healthy controls in response inhibition and visual working memory (WM) tasks.

Subjects and Methods

Table 1: General characteristics of the sample

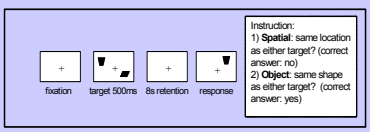
	EOS	EOC	AOS	AOC	p value
n	19	19	21	21	
Age	23,06 (5,41)	22,89 (5,07)	37,75 (4,29)	38,13 (4,74)	
Gender					
Female	6 (31,57%)	6 (31,57%)	10 (47,61%)	10 (47,61%)	ns
IQ (MWT-B)	106,8 (11,40)	107,6 (16,75)	104,7 (16,94)	107,1(12,79)	ns
Psychopathology					
F20	8		11		ns
F25	11		10		ns
PANNS positive	8,84 (3,77)		9,9 (3,81)		ns
PANNS negative	9,84 (3,93)		13,95 (3,87)		<0.05
PANNS general	29,73 (6,05)		32,19 (6,4)		ns
PANNS total	59,42 (14,01)		66,04 (14,6)		ns
Age at onset	15,84 (1,28)		31,47 (4,11)		<0.001
Years of disease	6,68 (3,31)		5,65 (1,87)		ns
CPZ equivalent (mg)	487,72 (402,38)		909,21 (523,40)		ns
Number of Obstetric/Perinatal Complications*	1,26	0,89	0,57	0,86	ns

Fully remitted outpatients with EOS (n=19), AOS (n=21) as well as controls matched for age and education (early onset controls, EOC n=19; adult onset controls, AOC n=21) were included.

*Obstetric complications interview according work of McNeil, T. F., E. Cantor-Graae, et al. (1994). "Obstetric complications in histories of monozygotic twins discordant and concordant for schizophrenia." Acta Psychiatr Scand **89**(3): 196-204.

Spatial and object WM were assessed by an integrated *Delayed Response Task.*

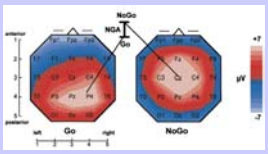
Fig. 1: Schematic representation of the integrated spatial and object working memory task



Correct responses were recorded for three time delays (0-8-16 sec), and the percentage of decrement in the performance was calculated.

Response Inhibition was assessed by a cued *Continuous Performance Test (CPT-OX)* with simultaneous 64-channel EEG recording of the event-related potentials (ERP) elicited during the Go and NoGo condition. Subjects were instructed to press a button every time a letter "O" followed directly by letter "X" appeared on screen, an to supress the response when it was directly followed by any other letter. A topographical assessment of the p300 fields was performed, with calculations of Go and NoGo centroid locations as well as the NoGo anteriorization (NGA) value, according to the work of Fallgatter and col. [5] .

Fig. 2: Display of grand average maps of brain electrical field during Go and NoGo conditions, with the location of 21 electrodes selected for analysis (cruces).



The integer numbers from 1-5 in the vertical and horizontal lines permit the quantification of electrode and centroid locations. The subtraction of the anterior-posterior values for the NoGo-centroid location from the respective Go centroid location results in the NoGo-anteriorisation (modified according to [5]).

Literature:

[1] Gur, R., M. Calkins, et al., *The Consortium on the Genetics of Schizophrenia: Neurocognitive Endophenotypes.* Schizophr Bull, 2007. 33(1): 49–68.

[2] Remschmidt, H., *Early-onset schizophrenia as a progressive-deteriorating developmental disorder: evidence from child psychiatry.* J Neural Transm, 2002. 109(1): 101-17.

[3] Lay, B., et al., *The psychosocial outcome of adolescent-onset schizophrenia: a 12-year followup.* Schizophr Bull, 2000. 26(4): p. 801-16.

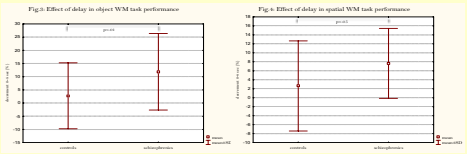
[4] White T., H.B., Ward J., O'Leary D., Andreasen N., *Neuropsychological Performance in First-Episode Adolescents with Schizophrenia: A Comparison with First-Episode Adults and Adolescent Control Subjects.* Biol Psychiatry, 2006. 60: p. 463-471.

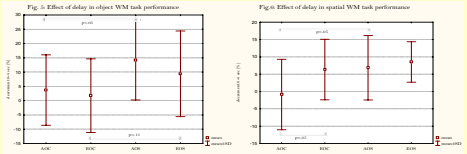
[5] Fallgatter, A. J., D. Brandeis, et al. (1997). "A robust assessment of the NoGo-anteriorisation of P300 microstates in a cued Continuous Performance Test." Brain Topogr **9**(4): 295-302.

[6] Lee, J. and S. Park, *Working Memory Impairments in Schizophrenia: A Meta-Analysis.* Journal of Abnormal Psychology, 2005. 114(4): p. 599-611.

Results

Delayed Response Task
Schizophrenic patients showed a greater decrement in performance during the 0-8 sec time delay in both object and spatial WM tasks (Fig. 3, 4). No further decay during the 8-16 sec delay was observed for any of the tasks. Comparing the performance related to factor "age of onset", we found that AOS had a significant decline in performance in the 0-8 sec interval in comparison to AOC in both object and spatial WM tasks. Between EOS and EOC there was a trend of worse performance of patients from the 0-8 sec delay in the object WM task and no difference in the spatial WM task. No statistically significant differences comparing EOS vs. AOS for any delay in any WM task were found (Fig. 5, 6).

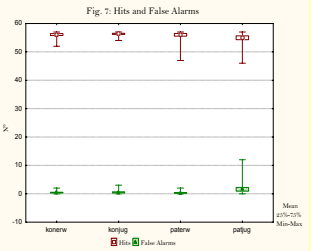


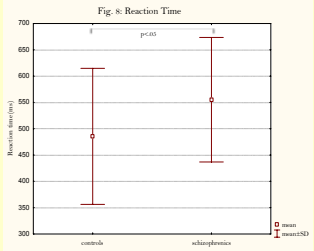


AOC: Adul Onset Controls; EOC:Early Onset Controls; AOS:Adult Onset Schizophrenics; EOS: Early Onset Schizophrenics.

CPT-OX Task

Behavioral Results: No significant differences between groups in the behavioural scores of the CPT were found, though EOS presented a greater variance in the number of False Alarms (Fig. 7). Schizophrenic patients showed a higher reaction time for the correct responses (hits) comparing to controls, with no differences in the amount of hits, false alarms or misses found in the behavioural part of the CPT (Fig. 8).





ERP Results:

The main electrophysiological values analysed are outlined in Table 2. The latency (ms) for the Go peak in the Pz reference channel was significantly higher for the AOC vs. EOC. This difference was not observed comparing EOS vs. AOS. The NGA value was similar between patients and controls. No significant differences in this value between EOS and AOS were found.

Table 2: Electrophysiological parameters and S.D.

	EOS	AOS	EOC	AOC
Go latency RMS (ms)	349.3±41.4	368.5±64.8	338.7 ±46.5	359.6 ±61.31
Go amplitude RMS (μv)	3.69±0.55	3.5±0.77	3.82±0.40	3.47±0.87
NoGo latency RMS (ms)	404.7±88.1	415.3±69.5	385.0±55.81	413.0±68.4
NoGo amplitude RMS (μv)	3.37±.79	3.11±.74	3.29±.6	2.88±.6
Go latency Pz (ms)	338.5±32.8	355.8±43.4	323.3±24.8	363.9±55.8**
Go amplitude Pz (μv)	3.75±.3	3.59±.55	3.81±.35	3.66±.5
NoGo latency Cz (ms)	365.0±39.1	390.5±41.3§	362.2±32.3	371.3±22.5
NoGo amplitude Cz (μv)	3.17±.39	2.93±.44	3.11±.38	2.87±.49
NGA RMS	0.32±.96	0.38±1.0	0.52±.65	0.58±.87
NGA Pz-Cz	0.56±.38	0.67±.56	0.70±.37	0.79±.45

ANOVAs were conducted with groups (EOS, AOS, EOC, AOC) as factors and each electrophysiological value as dependent variable.

* *p<0.01 comparing AOC with EOC.

§Trend of statistical significance (p<.1) comparing AOS with AOC and EOS.

Discussion

Former observations presented in the literature regarding object/visual WM impairments in schizophrenia [6] were replicated, although no differences between EOS and AOS were found. The lack of differences found may be due to the nature of the paradigm applied. The DRT assesses WM maintenance functions, what is different to the paradigms used in other studies that involve manipulation of the information stored [4] .

The CPT-OX paradigma used is adapted for psychiatric populations, and a low error rate was expected. The present sample, independently of age of onset, presented high IQ scores and educational level, as well as low level of positive psychopathological scores and were treated mainly with atypical antipsychotics. AOS also showed more negative symptoms than EOS. Half of the sample was composed of schizoaffective disorder. These findings could have contributed to the absence of classic electrophysiological signs of response inhibition impairment, like NoGo-anteriorisation, and similar performance in WM tasks of EOS in comparison to AOS. Differences in higher order neuropsychological performance related to age of onset of schizophrenia remains a controversial issue.

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