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Original article

Cognition and autonomic function in schizophrenia: Inferior cognitive test performance in electrodermal and niacin skin flush non-responders

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ABSTRACT

Background: Patients with schizophrenia suffer from a broad range of cognitive disturbances. The impact in terms of functional outcome is significant. There are also several reports of disturbed autonomic regulation in the disease. The present study examined cognitive function as well as psychophysiological parameters in patients with schizophrenia and healthy controls.
Methods: Twenty-five patients and 14 controls were investigated with electrodermal activity (EDA), an oral niacin skin flush test and a comprehensive neurocognitive test program including the Wechsler battery (WAIS-R), Fingertapping Test, Trail Making Test, Verbal Fluency, Benton Visual Retention Test, Wisconsin Card Sorting Test and Rey Auditory Verbal Learning Test.
Results: The patients generally had inferior test results compared to controls. Further analysis revealed that the EDA non-responding patient group explained this variation with significant lower test results than controls. On executive tests, EDA non-responders also performed significantly worse than EDA responding patients. The small group of niacin non-responding patients exhibited an even lower overall test performance. Delayed niacin flush also correlated inversely with psychomotor function and IQ in the patients.
Conclusion: The findings support the hypothesis of a neurodevelopment disturbance affecting both autonomic function and higher cortical function in schizophrenia.

1. Introduction

Cognitive dysfunction is a core feature in schizophrenia and one of the major causes of poor functional outcome in the disease. Neuropsychological testing will reveal a stable array of cognitive dysfunction in schizophrenia, such as disturbances in attention, episodic and working memory, psychomotor speed, information processing and cognitive flexibility [44]. Executive function in particular, has been associated with coping abilities in everyday life and also with insight, a strong prognostic factor for good outcome [29]. Recently, executive function tested with the Wisconsin Card Sorting Test has been related to autonomic regulation in schizophrenia [30]. Studies on autonomic functioning in schizophrenia have mainly focused on two different research areas; one dealing with cardio-respiratory control [1,2] and the other with the electrodermal system.

Electrodermal activity (EDA) refers to alterations in skin conductance caused by rapid changes in sweat duct activity triggered by fluctuations in autonomic nervous system (ANS) activity. The skin is a better conductor for electricity in the presence of external stimuli and EDA is accordingly related to attention, arousal and emotion [8]. A vast number of publications report both tonic and phasic EDA disturbances in schizophrenia [8,39,45,46]. Tonic EDA refers to the skin conductance level (SCL) and the occurrence of spontaneous fluctuations in conductance attributed to alertness and arousal. Phasic EDA variations like skin conductance responses (SCR) are useful for the study of attention, information processing and stimulus significance–parameters of importance in overall cognitive function. In schizophrenia two main findings are reported; the failure to elicit SCR to innocuous stimuli (EDA non-responding) and a higher autonomic activity including elevated SCL and impaired habituation to repeated stimuli. A bimodal distribution has thus been suggested in

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schizophrenia with both non-responders and hyper-responders [15]. EDA aberrations have been linked to poor symptomatic [10] and functional outcome [27,40,46]. EDA has also been associated with cognitive dysfunction in schizophrenia [5,23] although most studies used a limited selection of tests and not an extensive test battery.

Niacin (nicotinic acid) is a water-soluble substance belonging to the vitamin B group. In humans, niacin may be further converted to the ubiquitous oxidation-reduction enzyme nicotinate adenine dinucleotide (NAD) with essential roles in metabolism. Niacin is an important cholesterol and triglyceride lowering agent but the side effects, especially the capacity to induce a prolonged vasodilatory skin flush, has restricted its medical use. The skin flush typically affects the face and upper part of the body, and in this way the reaction resembles emotional blushing. In fact, niacin-stimulated facial flushing is reported to be more pronounced in persons with social anxiety [12]. Peripherally, the local flush reaction starts with niacin acting on the nicotinic acid receptors in epidermal Langerhans cells resulting in increased prostaglandin (PG) formation from arachidonic acid substrate. The vasoactive prostaglandins PGD2 and PGE2 then act on specific PG-receptors in capillary endothelian cells to cause vasodilatation and flushing [21]. Whereas EDA studies skin conductance, the niacin test therefore studies changes in blood flow and skin temperature.

In schizophrenia, a lower sensitivity to niacin is reported with both oral [14,17,38] and topical tests [3,6,28,32,33,36,42,43,48,49,52]. Further, blunted flush is demonstrated in antipsychotic-free patients [47,51] and in relatives to schizophrenia probands [6,26]. The disturbance may have the character of lower flush magnitude, slower flush development or both. While a recent study reported an association between reduced niacin sensitivity and functional impairment [31], there are no previous studies on niacin sensitivity and cognition in schizophrenia. Differences in niacin-induced skin flushing and EDA in the same patients with schizophrenia compared to controls have previously been shown [38]. An association in response patterns between the two response systems in patients was also reported [38] and confirmed at retesting [37].

The aim of the present study was to study cognition, EDA and niacin test reactivity in patients with schizophrenia and healthy controls. Our first hypothesis was that autonomic disturbances in the form of phasic EDA-abnormalities relate to cognitive dysfunction in schizophrenia. Our second hypothesis was that a blunted niacin response relates to cognitive dysfunction in schizophrenia.

2. Methods

2.1. Participants

The study was approved by the Regional ethical review board in Uppsala. All subjects received oral and written study information before giving written consent to participate. The cognitive assessments were part of a larger project with several physiological measurements in patients with schizophrenia and controls. Both newly diagnosed and chronic patients, aged 18–50 years, with a DSM-IV diagnosis of schizophrenia or schizophreniform disorder were recruited consecutively.

Twenty-five patients and 14 controls were administered a neurocognitive test battery. Ten patients were antipsychotic naïve at the time of physiological measurements, one was on first generation antipsychotics and 14 on second-generation antipsychotics. All participants were assessed with the Positive and Negative Syndrome Scale (PANSS) [22], the Extrapyramidal Symptom Rating Scale (ESRS) [7] and the Strauss-Carpenter scale for social outcome [50]. Physiological measurements were undertaken before treatment with antipsychotics started in first episode patients. Neurocognitive testing was carried out in a stabilized phase of illness and typically occurred two months after the physiological assessments. The test battery was administered during 2–3 sessions depending on the participants' motivation. In the patient group there were some dropouts on specific tests. All participants fulfilled the psychomotor tests, Trail making tests and Benton Visual Retention Test. Twenty-three patients completed the Controlled Word Association Test, 22 patients the Wechsler Adult Intelligent Scales and Wisconsin Card Sorting Test, and 20 patients the Rey Auditory Verbal Learning Test. All controls completed all tests. The healthy controls were recruited through newspaper advertisement and matched for age and gender.

Characteristics of patients and controls are exhibited in Table 1, where also niacin and EDA parameters are presented for the sake of understanding. The differences between patients and controls in these parameters are previously reported [38].

2.2. Procedures

2.2.1. EDA testing procedure

A non-task, long stimulus interval EDA-paradigm was used and the test was administered about 3.5 h after food intake. The participants were seated in a comfortable armchair. The ambient laboratory temperature during the test sessions was 22 °C (21.9 ± 0.8). The participants were given a standardized verbal information and Standard Beckman 8 mm silver/silver chloride electrodes, were then attached with adhesive collars to the distal phalanxes of the left hand index and middle fingers. A sodium chloride paste (0.58 g sodium chloride, 6 g hydroxyethyl cellulose, and water to 100 g) was applied between the skin and the electrode surface. The auditory stimuli were delivered with the Simple Stimulus Habituation Test (SSHT) software. After a non-stimulation phase of 120 s, 21 orienting tones (1000 Hz, 85 dB) with a varied interval between 20 and 40 s were presented binaurally over stereo headphones. After 750 s the test was completed. Recordings of skin conductance during the first 15 auditory stimuli were used for data analysis.

2.2.2. EDA data scoring

The programme Acq*Knowledge III* for the MP100WS (Biopac Systems, Inc., Santa Barbara, CA, USA) was used for scoring of physiological data. SCL was defined as the conductance value at onset of each tone and a mean was computed for 15 stimuli. A skin conductance response (SCR) was defined as an increase of 0.05 μS or more and this definition was applied for both orienting responses following stimuli (SCRs) and non-specific conductance responses (NS.SCRs) [9]. SCRs were preliminarily assessed within a response window of 1 to 5 s after every stimulus onset. Then a narrower window for SCR was constructed from the median latency ± 1 s for each participant [24]. NS.SCRs were spontaneous fluctuations in conductance exceeding 0.05 μS and not related to any stimuli. NS.SCRs were scored in a time-window from 10 s after the previous tone to the time for the next stimulus. The number of NS.SCR was transformed to a rate per minute format (NS.SCR/min). A dichotomous response/non-response criterion was obtained and a failure to elicit a SCR to any of the two first tone stimuli was thus defined as EDA non-responding [24]. A habituation index was created from the number of trials (stimuli) before the occurrence of two consecutive tones without a SCR present.

2.2.3. Niacin skin-flush response

The niacin skin-flush test immediately followed the EDA investigation. The participants had then been fasting for approximately 4 h. Oral body temperature was measured and thermistors for skin surface temperature were affixed to the left and right earlobes and connected to a Dual Channel Temperature Monitor 400 (Vital Signs, Totowa, NJ, USA). Standardized information about