Behavioural Brain Research 193 (2008) 101–107

Contents lists available at ScienceDirect

Behavioural Brain Research

journal homepage: www.elsevier.com/locate/bbr

Research report

Deficient associative learning in drug-naive first-episode schizophrenia: Results obtained using a new visual within-subjects learned irrelevance paradigm

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ARTICLE INFO

Article history:
Received 10 April 2008
Accepted 28 April 2008
Available online 4 May 2008

Keywords:
Learned irrelevance
Latent inhibition
Information processing
First-episode schizophrenia
Drug-free
Repeated measurements
Translational paradigm
Within-subject design

ABSTRACT

One of the key features of schizophrenia is the inability to filter out irrelevant stimuli which consequently leads to stimulus overload. There are different methods which aim at investigating these deficient filter mechanisms; one of these is the learned irrelevance (LIrr) paradigm. LIrr refers to the retardation of associative learning that occurs if the conditioned stimulus (CS) and the unconditioned stimulus (US) are preexposed in an explicitly unpaired manner prior to the establishment of the association between the stimuli. In the present study we used a recently developed computerized within-subject visual LIrr test. We measured 11 drug-naive first-episode schizophrenia patients and compared their performance to that of 17 healthy control subjects. LIrr was observed to be intact in normal individuals but disrupted in drug-naive first-episode schizophrenia patients. After one month elapsed, 5 of the 11 patients and 16 of the 17 control subjects were retested in a follow-up study. By this time, patients had been medicated with antipsychotic drugs for at least 3 weeks. While healthy controls exhibited a robust LIrr effect, patients still failed to show LIrr. Correlations were found between the performance of unmedicated patients and the depression component of the PANSS psychopathology scale.

1. Introduction

Disturbances in attention and preattentive information processing are considered to be key features of schizophrenia [24]. One consequence of deficient information processing is the inability to filter out irrelevant stimuli [2,3,19,32] which leads to stimulus overload. Various techniques are available to assess information processing deficits at different levels [3] for example, prepulse inhibition of the acoustic startle reflex (PPI) and auditory P50 evoked potential [3] delineate the dysfunctions at a preattentive level. In contrast, latent inhibition (LI) and LI-related paradigms measure processes not on a reflex but rather on an attentive and cognitive level. The phenomenon of LI is considered to reflect the ability of normal individuals to ignore irrelevant, inconsequential stimuli. Therefore, LI becomes manifested as a retardation of associative learning, e.g. classical conditioning, due to the subject's prior familiarity with the conditioned stimulus (CS) [21,23]. If the CS is repeatedly preexposed without reinforcement, the formation of the association between the CS and an unconditioned stimulus (US) is delayed. Disrupted or reduced LI refers to unaffected associative learning although the CS had been preexposed and is considered to reflect dysfunctions in information processing. This implies that individuals with reduced LI learn the CS-US association faster than normal controls after CS preexposure [1,14]. LI was found to be disrupted in drug-free acute schizophrenia patients [10,32], in patients who were treated with antipsychotic drugs [1,28] as well as in chronic schizophrenics under constant medication [1].

Acute schizophrenia, which is manifested in psychosis, is thought to be primarily due to a surplus of the neurotransmitter dopamine [16] in the mesocorticolimbic dopamine system. Indeed, psychosis-like symptoms [20] and LI disruption [12,30] can be induced in normal subjects by administering the indirect dopamine agonist amphetamine.

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doi:10.1016/j.bbr.2008.04.025

Based on these findings it is suggested that excessive dopamine might play a crucial role in reducing LI in schizophrenia patients. Therefore, antipsychotic drugs which antagonize dopamine receptors are suggested to reinstate disrupted LI [9]. But the findings are inconsistent and somewhat controversial regarding the impact of antipsychotic medication on LI in schizophrenia. In studies involving medicated acute schizophrenia patients some groups reported intact LI [32], while others found LI disruption [28,34]. On the other hand, in drug-free acute schizophrenia patients some studies showed normal LI [29] while others showed reduced LI [13,32]. This discrepancy may be due to the use of different test methods for LI measurement in the various studies. In the present study, we employed an advanced LI-related paradigm [6,25,36]. The new paradigm measures a phenomenon closely related to LI, learned irrelevance (LIrr). The difference between LI and LIrr is that in an LIrr paradigm both the CS and the US are preexposed. It is of critical importance that the CS and the US are presented in an explicitly unpaired manner in order to prevent associative learning in the preexposure phase. The present LIrr paradigm offers a number of advantages over traditional LI procedures. First of all, it employs a within-subject design. Second, in contrast to former LI paradigms, the CS-US contingency is impossible to learn. Former LI paradigms were often based on the paradigm of Ginton et al. [7] in which a white noise stimulus (=CS) predicted the increment of a number on a counter (=US). This CS-US contingency can be easily learned by the subjects which makes the LI measurement relatively insensitive, prone to ceiling effects and precludes repeated measurements.

To date, there are three published studies applying the LIrr test in healthy control subjects [6,25,36] and schizophrenia patients [6,36]. All groups reported robust LIrr in healthy subjects. Moreover, Gal [6] as well as Young [36] and coworkers consistently found disrupted LIrr in schizophrenia patients, regardless of the status of the disorder (first-episode or acute) or medication. As the LIrr results were in line with previous studies employing an LI procedure [1,11,13,22,28], it was assumed that similar and possibly identical processes may underlie the phenomena of LI and LIrr [36].

What is unique about the present study is that we tested completely drug-naive first-episode schizophrenia patients and healthy control subjects on two occasions with the LIrr paradigm. At baseline the patients suffering from the first episode of schizophrenia were completely drug-naive. At the follow-up, the patients had been treated with antipsychotic drugs for at least three weeks which enabled an examination of the impact of antipsychotic drugs on LIrr. Baruch et al. [1] applied a similar study design, but they did not differentiate between acute and first-episode schizophrenia patients. Moreover, in Baruch's study all patients were under antipsychotic medication on both testing occasions. Measuring drug-naive first-episode schizophrenics is the main feature of the present study as it allows the investigation of LIrr at the breakout of schizophrenia without any pharmacological interventions. By assessing the patients with a standardized psychopathology scale on both occasions, we also investigated the change in psychopathology over sessions. Based on the findings of previous LI as well as LIrr studies and assuming that LIrr is very closely related to LI, we expected drug-naive first-episode schizophrenia patients to show LIrr disruption at baseline. Upon follow-up we expected LIrr reinstatement as a result of antipsychotic medication because antipsychotic drugs are suggested to antagonize excessive dopamine which is thought to be responsible for the disruption LI and LIrr. Normal control subjects were expected to show a robust LIrr effect in both test sessions as the LIrr paradigm enables repeated measurements of LIrr [25].

2. Materials and methods

2.1. Subjects

The study was carried out at the Psychiatric Services of Canton Aargau, Switzerland.

Eleven drug-naive first-episode schizophrenia patients (9 inpatients, 2 outpatients) underwent the test procedures. Their data were compared to those of 17 healthy subjects matched by gender and age category. Subjects were presented with a complete description of the study and test procedures. Thereafter a written informed consent was obtained from each subject. Demographic and clinical data were collected (Table 1). The study protocol and consent forms were reviewed and approved by the Ethical Committee of the Psychiatric Services of Canton Aargau, Switzerland.

2.2. First-episode schizophrenia patients

In the first test session we tested 11 first-episode schizophrenia patients who were either recruited from the acute wards of the Psychiatric Hospital Königsfelden, Canton Aargau, Switzerland or were referred by external psychiatrists. None of the patients had ever been treated with antipsychotic drugs before. The patients were not admitted to the study if they had a history of neurological disease, head injury or substance dependence (except for nicotine and cannabis consumption).

Prior to testing, the patients were interviewed and screened according to DIA-X criteria [35] by an experienced psychiatrist (KCL). In addition, the patients were assessed with the Positive and Negative Syndrome Scale (PANSS) [18]. The follow-up test was performed approximately 1 month after baseline testing, at a time when the patients had been medicated for at least 21 days. Only 6 of the initial 11 patients were willing to participate in the second test session. Before testing they were subjected to a screening procedure similar to the one used at baseline which also included the PANSS. Three of the 6 patients were treated with atypical, one with typical antipsychotic drugs. One patient received a combination of typical and atypical neuroleptics, while another one was not medicated at all. The data of this unmedicated patient were excluded from analysis of the follow-up test. Thus, in the second session the data of 5 patients were analyzed.

2.3. Healthy control subjects

Seventeen healthy control subjects were tested at baseline and 16 in the follow-up test. They were recruited by means of an electronic advertisement on the job service web page of the Swiss Federal Institute of Technology and the University of Zurich.

The main inclusion criteria for control subjects were that they were between 18 and 35 years old and consumed at least 10 cigarettes a day. Smokers were required as control subjects because the majority of schizophrenia patients are heavy smokers

Table 1
Demographic and clinical data; only those PANSS scores are indicated which are relevant and/or mentioned in the text

	Baseline (0 month)		Follow-up (following 1 month)	
	FE patients	Controls	FE patients	Controls
N (f/m)	11 (3/8)	17 (3/14)	6 (1/5)	16 (3/13)
Mean age (S.D., range)	20.7 (2.97, 18–27)	23.7 (2.23, 20–29)	21 (3.4, 18–27)	23.4 (1.99, 20–29)
Positive symptoms (S.D., range)	16.5 (5.28, 7–26)		11.3 (3.2, 8–16)	
Negative symptoms (S.D., range)	16.9 (4.35,12–24)		18.2 (7.8, 7–29)	
General psychopathology (S.D., range)	35.4 (6.36, 25–43)		33.5 (12.18, 20–55)	
Depression (S.D., range)	9.5 (2.38, 6–14)		8.7 (2.42, 6–13)	
Thought disorder (S.D., range)	10.4 (3.67, 4–18)		7.5 (2.07, 5–10)	
PANSS total score (S.D., range)	68.8 (12.4, 49–83)		63.0 (21.13, 38–98)	
Antipsychotic medication (*N*)			Typ. (1) Atyp. (3) Comb.: (1) None: (1)	

FE = first-episode schizophrenia patients. PANSS = positive and negative symptom scale. S.D. = standard deviation of the mean. Typ. = typical antipsychotic medication. Atyp. = atypical antipsychotic medication. Comb. = combination of typical and atypical antipsychotic medication.