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Perceptual and cognitive effects of antipsychotics in first-episode schizophrenia: The potential impact of GABA concentration in the visual cortex

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ABSTRACT

Schizophrenia is characterized by anomalous perceptual experiences (e.g., sensory irritation, inundation, and flooding) and specific alterations in visual perception. We aimed to investigate the effects of short-term antipsychotic medication on these perceptual alterations. We assessed 28 drug-naïve first episode patients with schizophrenia and 20 matched healthy controls at baseline and follow-up 8 weeks later. Contrast sensitivity was measured with steady- and pulsed-pedestal tests. Participants also received a motion coherence task, the Structured Interview for Assessing Perceptual Anomalies (SIAPA), and the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). Proton magnetic resonance spectroscopy was used to measure gamma-aminobutyric acid (GABA) levels in the occipital cortex (GABA/total creatine [Cr] ratio). Results revealed that, comparing baseline and follow-up values, patients with schizophrenia exhibited a marked sensitivity reduction on the steady-pedestal test at low spatial frequency. Anomalous perceptual experiences were also significantly ameliorated. Antipsychotic medications had no effect on motion perception. RBANS scores showed mild improvements. At baseline, but not at follow-up, patients with schizophrenia outperformed controls on the steady-pedestal test at low spatial frequency. The dysfunction of motion perception (higher coherence threshold in patients relative to controls) was similar at both assessments. There were reduced GABA levels in schizophrenia at both assessments, which were not related to perceptual functions. These results suggest that antipsychotics dominantly affect visual contrast sensitivity and anomalous perceptual experiences. The prominent dampening effect on low spatial frequency in the steady-pedestal test might indicate the normalization of putatively overactive magnocellular retino-geniculo-cortical pathways.

1. Introduction

Patients with schizophrenia often report anomalous perceptual experiences that are subjectively and phenomenologically different from hallucinations and other positive psychotic symptoms. These experiences include disturbingly high intensity of environmental stimuli, feelings of being flooded and inundated, and inability to focus attention to relevant details (Bunney et al., 1999; Klosterkötter et al., 2001; Phillipson and Harris, 1985), which is most prevalent and severe in the auditory and visual sensory modalities (Bunney et al., 1999; Martín-Reyes et al., 2010; Mendoza Quiñones et al., 2007).

In a series of studies, we explored the possible psychophysical correlates of anomalous perceptual experiences, with a special reference to the visual modality (Kéri et al., 2005; Kiss et al., 2010). Initially, we used the framework of the retino-geniculo-cortical magnocellular (M) and parvocellular (P) visual pathways, which originate in the retina and are theoretically responsible for the processing of different kinds of stimulus features (M pathways: low spatial frequencies [rough resolution of objects], luminance contrast, motion; P pathways: high spatial frequencies [fine resolution of objects], color contrast, form) (Nassi and Callaway, 2009). However, despite the fact that this perceptual hypothesis received an extensive attention in the literature of schizophrenia (e.g., reviewed by Butler et al., 2008; Javitt, 2009), the exact psychophysical distinction of M and P pathways has been debated (Goodbourn et al., 2012; Merigan and Maunsell, 1993; Skottun and Skoyles, 2007).

During past decades of research, Pokorny and colleagues developed a new method for the separation of putative M and P pathways, which

Abbreviations: ANOVA, analysis of variance; c/d, cycles/degree; Cr, creatine; GABA, gamma-aminobutyric acid; HSD, honestly significant difference; M, magnocellular; P, parvocellular; PANSS, Positive and Negative Syndrome Scale; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; SIAPA, Structured Interview for Assessing Perceptual Anomalies.

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became popular in clinical research (reviewed by Pokorny, 2011). In the pulsed-pedestal paradigm, the target detection period, during which participants are requested to detect a briefly flashed low-contrast grating, is preceded by an adaptation period containing a homogeneous high luminance field. During the target detection period, the luminance of the background field is abruptly reduced, which saturates M pathways, but not P pathways. Therefore, the pulsed-pedestal paradigm shifts information processing toward the P pathways. In the steady-pedestal condition, M pathways are not saturated and therefore briefly presented stimuli with low contrast and low spatial frequency are thought to be dominantly processed by these pathways (Fig. 1; for a critical review and comparison with other methods, see Skottun and Skoyles, 2011).

Using the steady-/pulsed-pedestal tasks in drug-naïve first-episode schizophrenia patients, Kiss et al. (2010) found abnormally heightened sensitivity for putatively M-biased stimuli, indicating an overactive visual response. A similar finding was reported by Antal et al. (1998) and Chen et al. (2003) using conventional contrast sensitivity measurements. Critically, higher M-biased contrast sensitivity values were associated with increased scores on a standardized scale for anomalous perceptual experiences (Kiss et al., 2010).

The primary purpose of the present study was to investigate the effect of short-term antipsychotic medication on visual contrast sensitivity and anomalous perceptual experiences in first-episode schizophrenia. Given that, by the inhibition of dopamine D_2 receptors in the retina, antipsychotics have a profound effect on contrast processing (Bulens et al., 1989; Harris et al., 1990; Kéri et al., 2002), we hypothesized rapidly dampened contrast sensitivity and, if it is indeed related to anomalous perceptual experiences, a parallel amelioration of subjective sensory symptoms. Second, we assessed higher levels of visual processing, that is, the perception of coherent motion. Extensive evidence suggests that motion perception is impaired in schizophrenia and that it is related to higher levels of cortical information processing (area MT/V5) (Chen, 2011). However, the effect of antipsychotic medications on motion processing has not been clarified. Third, we administered a battery of neuropsychological tests to tackle changes in neurocognition (attention, memory, visual-spatial processing, and language) during therapy. Past studies revealed a mild beneficial effect of antipsychotics on neurocognition (for meta-analyses, see Woodward et al., 2005, 2007). Finally, we measured gamma-aminobutyric acid (GABA) concentration in the occipital cortex before and after antipsychotic therapy and compared that with perceptual changes. This final aim of the study was based on the findings of Yoon et al. (2010) who identified a strong positive correlation between occipital GABA concentration and visual inhibition (orientation-specific surround suppression). These authors hypothesized that decreased GABA concentration in the visual cortex of patients with schizophrenia caused weakened visual inhibition (Yoon et al., 2010).

2. Material and methods

2.1. Participants

Twenty-eight patients with first-episode schizophrenia and twenty healthy control volunteers participated in the study. Some of the participants have been included in previous studies where details of recruitment have been described (Kéri et al., 2010; Kiss et al., 2010; Szamosi et al., 2012). There were two recruitment centers in Southern Hungary and Budapest. Patients were referred from the whole country. None of the patients received previous treatment with psychotropic medications, and they were therefore drug-naïve at the time of baseline assessment. The mean duration of untreated psychosis was 9.7 months (SD = 6.1). All participants received the Structured Clinical Interview for DSM-IV Axis I Disorders, Clinician Version (SCID-CV) (First et al., 1996). We used the Positive and Negative Syndrome Scale (PANSS) for the evaluation of clinical symptoms (Kay et al., 1987). Exclusion criteria included neurological disorders, head injury, and history of psychoactive substance misuse. All participants had normal or corrected-to-normal visual acuity. The clinical and demographic characteristics are depicted in Table 1. The study was carried out in accordance with the Declaration of Helsinki and was approved by the local ethics board. After a full description of the study, participants gave written informed consent.

2.2. Medications

We first assessed the patients in a drug-naïve state (baseline). This baseline assessment was followed by 8 weeks of treatment. The dose and type of antipsychotic medications administered to patients were at the discretion of the treating physician who was blind to the aims of the study. All clinical scales and tests were administered by trained and supervised clinical psychologists and psychiatrist who were blind to the medication status of the patients. Patients received the following medications: haloperidol (n = 1, 4 mg/day); olanzapine (n = 10,

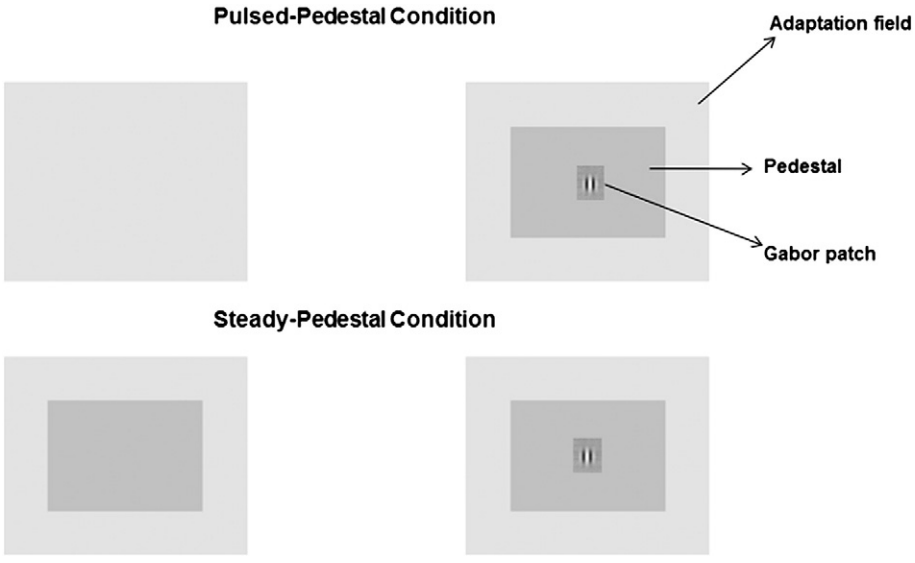

Fig. 1. Contrast sensitivity measurements. In the pulsed-pedestal test, the luminance of the background field is abruptly reduced to saturate magnocellular (M) pathways and to bias information processing toward the parvocellular (P) pathways. In the steady-pedestal paradigm, the luminance of the background field is constant.