Schizophrenia Research 134 (2012) 232–238

Contents lists available at SciVerse ScienceDirect

Schizophrenia Research

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

Sensorimotor gating and clinical outcome following cognitive behaviour therapy for psychosis

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ARTICLE INFO

Article history:
Received 20 July 2011
Received in revised form 31 October 2011
Accepted 14 November 2011
Available online 3 December 2011

Keywords:
Prepulse inhibition
Startle
Schizophrenia
Symptoms
Antipsychotics
Medication resistance

ABSTRACT

Background: Prepulse inhibition (PPI) of the startle response refers to the ability of a weak prestimulus to transiently inhibit the response to a closely following strong sensory stimulus. PPI provides an operational index of sensorimotor gating and is reduced, on average, in people with schizophrenia, relative to healthy people. Given the variable response to Cognitive Behaviour Therapy for psychosis (CBTp) and positive associations between pre-therapy brain and cognitive functions and CBT outcome across disorders, we examined whether pre-therapy level of PPI is associated with clinical outcome following CBTp.

Method: Fifty-six outpatients stable on medication with at least one distressing symptom of schizophrenia and willing to receive CBTp in addition to their usual treatment were assessed on acoustic PPI. Subsequently, 28 patients received CBTp (CBTp + treatment-as-usual, 23 completers) for 6–8 months and 28 continued with their treatment-as-usual (TAU-alone, 17 completers). Symptoms were assessed (blindly) at entry and follow-up.

Results: The CBTp + TAU and TAU-alone groups did not differ demographically, clinically or in PPI at baseline. The CBTp + TAU group showed improved symptoms relative to the TAU-alone group, which showed no change, at follow-up. Pre-therapy PPI level correlated positively with post-CBTp symptom improvement.

Conclusions: Relatively intact sensorimotor gating is associated with a good clinical response following a 6–8 months course of NICE compliant CBTp in schizophrenia. Pharmacological or psychological interventions capable of improving PPI may enhance the effectiveness of CBTp in people with schizophrenia, particularly in those who fail to show clinical improvement with currently available antipsychotic drugs and adjunctive CBTp.

1. Introduction

Despite marked symptom improvement with the use of antipsychotics in acutely ill patients with schizophrenia (Kasper, 2006), the long-term outcome for up to 40% of patients remains unsatisfactory as they continue to suffer from one or more distressing symptoms despite remaining medication compliant (Conley and Kelly, 2001; Potkin et al., 2009). Additional benefits of cognitive behaviour therapy for psychosis (CBTp) have been reported for such patients (reviews, Pilling et al., 2002; Zimmermann et al., 2005; Pfammatter et al., 2006; Wykes et al., 2008), and symptom improvement may continue even after therapy is terminated (Sensky et al., 2000; Sarin et al., 2011). CBTp is now recommended for the treatment of psychosis in both the National Institute for Health and Clinical Excellence (NICE) updated guidelines in the UK (NICE, 2009) and the Schizophrenia Patient Outcomes Research Team (PORT) Treatment Recommendations in the US (Dixon et al., 2010). The beneficial effects of CBTp, however, are seen with modest effect sizes and to a meaningful degree in only about 50% of patients who undergo this therapy (Pilling et al., 2002; Pfammatter et al., 2006; Wykes et al., 2008). Uncovering the determinants of effective CBTp may a) help to maximise its benefits by targeting the most relevant population, and b) to identify methods to help those who do not show a sufficient response with current antipsychotic medications and CBTp.

A number of studies have focussed on specific predictors of clinical response to CBTp (Garety et al., 1997; Kumari et al., 2009, 2010; Penades et al., 2010; Premkumar et al., 2010, 2011). Cognitive flexibility about delusions (Garety et al., 1997), better cognitive insight (Perivoliotis et al., 2010), and lower conviction scores (Brabban et al., 2009) have all been found to be predictors of a good outcome on

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0920-9964
doi:10.1016/j.schres.2011.11.020

delusional thinking. More recently, Penades et al. (2010) reported a positive association between verbal memory and clinical outcome following CBTp. Although we did not find a direct association between symptom improvement following CBTp and pre-therapy cognitive performance, assessed with a number of tests commonly employed in schizophrenia research (Premkumar et al., 2011), we did observe greater hippocampal grey matter volume in CBTp responders, compared to CBTp non-responders in the same sample (Premkumar et al., 2009). This latter finding can be regarded consistent with that of Penades et al. (2010), given the positive association between hippocampal volume and memory in schizophrenia observed across a number of previous studies (review, Antonova et al., 2004). Furthermore, our functional magnetic resonance imaging (MRI) studies have demonstrated that pre-therapy brain activity and functional connectivity between brain regions involved in cognitive flexibility and self-other distinction predict clinical outcome following CBTp (Kumari et al., 2009, 2010). Specifically, we found a positive association between CBTp responsiveness and dorsolateral prefrontal cortex (DLPFC) activity and its connectivity with the cerebellum (Kumari et al., 2009), most likely mediated by PFC–cerebellum contributions to executive processing (Bellebaum and Daum, 2007).

The present study aims to further advance this field by investigating the relationship between pre-CBTp level of sensorimotor gating function, as assessed by prepulse inhibition (PPI) of the acoustic startle response, and the clinical outcome following CBTp. PPI refers to a response reduction in reaction to a strong startling stimulus, 'pulse', if this is preceded shortly by a prestimulus, 'prepulse', too weak to evoke a measurable startle response itself (Graham, 1975). PPI provides an operational index of sensorimotor gating: while information processing resources are targeted at the prepulse, any incoming information (i.e. the pulse) is attended to at reduced level, thereby protecting the processing of the initial stimulus (i.e. the prepulse) (Geyer et al., 1990). Since the first demonstration by Braff et al. (1978), a large number of studies have shown reduced PPI, on average, in people with schizophrenia (e.g. those reviewed in Braff et al., 2001; Meincke et al., 2004; Swerdlow et al., 2006; Kumari et al., 2007), especially in those who have thought disorder (Perry and Braff, 1994; Perry et al., 1999), hear uncontrollable voices (Kumari et al., 2008a) or have poor global functioning (Swerdlow et al., 2006). Some studies also report small-to-moderate positive associations between reduced PPI and poor performance on measures of attention (Karper et al., 1996; Kumari et al., 2007) and executive function, in particular cognitive flexibility (Butler et al., 1991; Kumari et al., 2007), in schizophrenia, suggesting that deficient gating may interfere with higher order cognitive function. Given these observations, and previous findings indicating that relatively intact (pre-therapy) executive processing is associated with good clinical responsiveness to CBT across many disorders, including depression (Moorey et al., 2001; Julian and Mohr, 2006) and generalized anxiety disorder (Mohlman and Gorman, 2005), we hypothesised that there would be a positive association between pre-therapy PPI level and clinical response to CBTp in patients with schizophrenia. In addition, we explored the relationship between pre-therapy level of startle habituation and CBTp response. Reduced habituation has been found in people with schizophrenia (e.g. Geyer and Braff, 1982; Braff et al., 1992; Takahashi et al., 2008); it is thought to reflect their inability to ignore the repetitive functionally insignificant stimuli and to result in sensory overload (Geyer and Braff, 1987; Geyer et al., 1990).

2. Methods

2.1. Participants and design

The study included 56 outpatients, 54 with paranoid schizophrenia and 2 with schizoaffective disorder, who were willing to receive 6–8 months of CBTp in addition to the treatment and care they were already receiving from mental health professionals. The clinical diagnosis was made by a trained psychiatrist using the Structured Clinical Interview for DSM-IV (SCID; First et al., 2002). Of 56 patients, 28 received CBTp for 6–8 months in addition to their usual treatment (CBTp + TAU group) and 28 continued to receive treatment as usual (TAU-alone group) during the course of this investigation. This investigation has been carried out as part of a larger project examining MRI, neuropsychological and clinical predictors and correlates of responsiveness to CBTp. The sample of patients included in this report thus overlaps with the samples examined in our recent reports (Kumari et al., 2009, 2010, 2011; Premkumar et al., 2009, 2010, 2011). However, none of these published reports examined or reported any psychophysiological (startle) data.

The patients in the CBTp + TAU and TAU-alone groups were recruited from the same geographical area (South London, UK) and were identified by their local treating psychiatric consultants as suitable for CBTp. All included patients were required to be on stable doses of antipsychotics for ≥2 years and on the present antipsychotic for >3 months, to receive a rating of ≥60 on the Positive and Negative Syndrome scale (PANSS) (Kay et al., 1987), and to have at least one persistent positive symptom (a score of 3 or above on at least one of the positive symptoms items of the PANSS, which they experienced as distressing).

As described in Kumari et al. (2011), the recruitment of patients and the creation of study groups followed a cohort case-controlled design. It involved the following steps: (i) a patient referred by his/her local consultant and accepted for CBTp by the Psychological Interventions Clinic for Outpatients with Psychosis (PICuP), South London and Maudsley NHS Foundation Trust, (ii) study introduced to the patient by PICuP staff, (iii) patient contacted by a member of the research team if interested in taking part, (iv) if found suitable, patient recruited as part of the CBTp + TAU group, and (v) another patient with similar demographic and clinical characteristics (to that of the patient included in the CBTp + TAU group) recruited for the TAU-alone group via local consultants and studied over the same interval as the CBTp + TAU group. With the resources then available to the South London and Maudsley NHS Foundation Trust, out of all patients potentially eligible for CBTp, only around 10% patients were referred for CBTp. There were no explicit biases in which patients received CBTp. Allocation of CBTp was driven by clinical resource limitations of the NHS Trust and not by patient characteristics. The researchers were independent of clinical decisions about which patients were referred for CBTp. All patients underwent clinical assessment at entry and follow-up (6–8 months later).

Of 56 patients, 3 (1 CBTp + TAU, 2 TAU-alone) did not provide usable startle data. Of remaining 53 patients, 23 patients of the CBTp + TAU group and 17 patients of the TAU-alone group completed follow-up clinical assessment, and had remained on the same type and dosage of antipsychotic medication during the follow-up period. Table 1 presents clinical and demographic characteristics of the final sample.

The study was approved by the research ethics committee of the Institute of Psychiatry and the South London and Maudsley NHS Foundation Trust. All participants provided written informed consent after the study procedures had been explained to them.

2.2. Cognitive behaviour therapy for psychosis (CBTp) and treatment-as-usual (TAU) procedures

After baseline clinical and PPI assessments, the CBTp + TAU group received 6–8 months of CBTp following the procedures described in a published manual (Fowler et al., 1995). Therapy sessions were conducted weekly or fortnightly, as preferred by the patient, for up to one hour. Patients received an average of 16 sessions, as recommended by NICE guidelines in the UK (NICE, 2009), at the PICuP clinic. The therapists were supervised by one of the two investigators (EK,