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Serum brain-derived neurotrophic factor levels associate with cognitive improvement in patients with schizophrenia treated with electroacupuncture

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ABSTRACT

Accumulating evidence supports that acupuncture has been successfully used for the treatment of neurological disorders to improve cognitive function. This study was set to evaluate the efficacy of electroacupuncture (EA, using two acupoints: *Baihui* and *Shenting*) on clinical symptoms, cognitive function and brain-derived neurotrophic factor (BDNF) levels in patients with schizophrenia. Sixty-one inpatients diagnosed schizophrenia with DSM-IV criteria were recruited. The participants were randomly divided into an experimental group (n=30) and a control group (n=31). The patients were evaluated using the Positive and Negative Symptom Scale (PANSS), the Wisconsin Card Sorting Test (WCST) and Wechsler Memory Scale (WMS) at baseline and after EA treatment. There were no significant differences in the PANSS scores and serum BDNF levels between the experimental group and the control group, either at baseline or at the end of the 4-week study period. However, the EA treatment appeared to have significant benefits on memory and moderate benefits on executive functions and problem solving. Significant positive correlation was observed between the increase of BDNF levels and memory improvement after EA treatment. Our results indicated that EA treatment could improve cognitive function, and the cognitive benefits positively associate with serum BDNF levels in patients with schizophrenia.

1. Introduction

Patients with schizophrenia display a variety of cognitive deficits, which are often one of the core characteristics of schizophrenia and have been associated with functional impairment in domains like work, interpersonal relationships and daily living (Fervaha et al., 2014; Kontaxaki et al., 2014; Nuechterlein et al., 2014). Cognitive deficits in schizophrenia (CDS) can exhibit in attention, executive functions, processing speed, learning and memory (Keefe and Harvey, 2012).

Although CDS is a recognized clinical phenomenon, the underlying neurobiological mechanisms remain mostly unknown. The role of brain-derived neurotrophic factor (BDNF) in cognition has been studied. Increasing evidence shows that BDNF plays an important role in dendritic arborization, synaptic plasticity, cell resilience and apoptosis control (Nieto et al., 2013; Yeh et al., 2012). In animal models, it has been shown that inhibition of BDNF signaling by gene knock-out impairs spatial learning and memory (Minichiello et al., 1999). Recent studies have reported that serum BDNF levels decreased in patients with mild cognitive impairment (Yu et al., 2008) and Alzheimer's disease (Leyhe et al., 2008). In schizophrenia, Zhang et al. (2014) showed that BDNF levels were significantly lower in patients than healthy controls. Furthermore, BDNF was found to be positively correlated with immediate memory and the total score of the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), a commonly used tool to assess cognitive function (Zhang et al., 2014). Another study also suggested that the role of BDNF in patients with chronic schizophrenia, was associated with cognitive impairment, especially immediate memory (Zhang et al., 2012).

CDS adds significantly to illness burden, and currently there are no FDA approved medications to treat CDS (Opler et al., 2014). Though some second-generation antipsychotics had some benefits on CDS, a uniform positive cognitive improvement was not observed (Nielsen et al., 2015). Treatment of CDS remains a considerable clinical challenge.

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Acupuncture, a key component of Traditional Chinese Medicine (TCM), is also a complementary and alternative medicine (CAM) practice. Clinical and animal studies indicated that acupuncture could improve the cognitive function in Alzheimer's disease (Guo et al., 2002; Lin et al., 2016; Zhou et al., 2015). Our previous animal studies also supported the neuro-protective function of acupuncture in Parkinson's disease (Jia et al., 2009; Liang et al., 2003). In addition, it has also been used to treat psychiatric disorders (Bosch et al., 2013b; Chan et al., 2015). A systematic review and meta-analysis suggested that acupuncture combined with antidepressants was effective in depression, and this treatment combination appeared to result in greater therapeutic efficacy than selective serotonin reuptake inhibitor (SSRI) therapy alone (Chan et al., 2015). The utility of acupuncture on schizophrenia was studied and its beneficial effects on positive, negative, and general symptoms in patients with schizophrenia have been reported (Bosch et al., 2015b, 2013a; Reshef et al., 2013).

Acupuncture, including traditional acupuncture, electroacupuncture, laser acupuncture, and acupoint injection, has been shown to be relatively safe with few adverse effects (Wang et al., 2013). Acupuncture involves the stimulation of specific points (acupoints) by inserting needles into the skin. Electroacupuncture (EA) is based on the traditional acupuncture, with the additional application of an electric pulse to some meridians and acupoints to enhance the effects. The common acupoints in previous reports for psychiatric and cognitive disorders were in the governor vessel, such as *Baihui* (DU20) and *Shenting* (DU24) acupoints (Allam et al., 2008; Zhang et al., 2013). However, the effects of acupuncture on cognitive impairment in schizophrenia have not been studied.

In view of the beneficial effects of acupuncture for cognitive impairment, and the important implication of BDNF in cognition and schizophrenia, it is of interest to explore the effects of acupuncture on schizophrenia and the association between cognitive impairment and BDNF levels in patients with schizophrenia. In the present study, we compared the cognitive function and serum BDNF levels in schizophrenia patients with or without EA treatment in a clinical sample of Chinese patients. We also examined the relationship between serum BDNF levels and cognitive function.

2. Methods

2.1. Study design

This was an assessor-blinded randomized controlled trial. The participants were randomly divided into a treatment group and a control group. EA treatment was performed and the main outcome measures were determined by different persons.

The study proposal was reviewed and approved by the Ethics Committee (IRB) of Beijing Anding Hospital. All subjects provided written informed consent for participation, after the procedure had been fully explained and questions answered.

2.2. Subjects

Sixty-three inpatients with schizophrenia were recruited into the study from Beijing Anding Hospital. All patients met the following inclusion criteria: (1) age 18–59 years, Han Chinese ethnicity; (2) Met the diagnosis of schizophrenia based on the Diagnostic and Statistical Manual of Mental Disorders, fourth Edition (DSM-IV); and (3) had been receiving stable doses of clozapine or risperidone for at least 10 weeks before entry into the study. The exclusion criteria were as following: current substance abuse; type 1 or 2 diabetes; thyroid disease; pregnancy; significant medical conditions including severe cardiovascular, hepatic or renal diseases, and unstable psychiatric conditions.

2.3. Clinical assessments

The diagnosis of schizophrenia was established according to DSM-IV, using the Structured Clinical Interview for DSM-IV (SCID). All patients were also assessed using the Positive and Negative Syndrome Scale (PANSS). The cognitive assessments included the Wechsler Memory Scale (WMS) and Wisconsin Card Sorting Test (WCST).

Subjects were divided into two groups. 32 patients continued their usual antipsychotic medications (control group), and 31 patients received both antipsychotic medications and EA treatment (EA group). The duration of EA treatment lasted for 4 weeks. The cognitive assessment and serum BDNF assay were performed at baseline and after treatment.

2.4. EA treatment

The details of the intervention followed the Standards for Reporting Intervention in Clinical Trials of Acupuncture (STRICTA 2010) (MacPherson et al., 2010). Acupuncture was administered by a trained acupuncturist who had practiced acupuncture for 15 years. Each patient was scheduled for a total of 12 sessions, 3 times a week over a period of 4 weeks. The selected acupoints included those were proved effective for cognitive function in the previous study, as well as points, namely *Baihui* (DU20) and *Shenting* (DU24) (Allam et al., 2008; Zhang et al., 2013). In addition, other acupoints, like *Neiguan* (PC6) and *Zusanli* (ST36) *Sanyinjiao* (SP6) and *Hegu* (LI4) were also used based on the TCM evaluation of the individual presentations. The acupuncture needles (sterile, single-use, size 0.25 mm × 25 mm, manufactured in Suzhou Medical Appliance Factory, China) were inserted to a depth of 15–25 mm in *Baihui* acupoint and 10–15 mm in *Shenting* acupoint. All patients in EA group reported the '*De-Qi*' sensation, a local sensation of heaviness, numbness or tingling, that accompanies the insertion and manipulation of needles during acupuncture. Once the sensation was elicited, the handles of the needles inserted into acupoints were connected to an electrical input (sparse dense wave, frequency 20–80 Hz, pulse width 0.5 ms, intensity 2–3 mA) via an EA device (KWD-808, Changzhou Yingdi Electronic Medical Device Company, China) for 30 min. In the control group, neither needling nor electrical stimulation was given. No other TCM treatments, such as herbs, moxibustion, cupping, massage, exercise, dietary advice, or lifestyle modification were given to either group during the study period.

2.5. Neuropsychological tests

One experienced evaluator who was blind to the group assignments conducted the neuropsychological tests. The WMS test was used to evaluate memory deficit in patients with schizophrenia. This test includes ten subtest, such as knowledge, orientation, mental control, logical memory, digital span, visual memory and associative learning. These subtests are synthesized by the memory quotient (MQ) to evaluate memory ability. The WCST was used to assess executive function and problem solving. In this computerized test, subjects match cards on a monitor to one of four key cards. They are not told how to match the cards, but instead are told whether their matches are correct or not. If the subject matches correctly 10 consecutive times, the matching rule changes, but the subject is not told of the rule change. The scores, including categories completed (CC), percentage correct responses (PCR), percentage perseverative errors (PPE), percentage conceptual level responses (PCLR) and failure to maintain a set (FM) were analyzed.