Schizophrenia Research 153 (2014) 87–95

Contents lists available at ScienceDirect

Schizophrenia Research

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

A pilot study on the effects of cognitive remediation on hemodynamic responses in the prefrontal cortices of patients with schizophrenia: A multi-channel near-infrared spectroscopy study

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ARTICLE INFO

Article history:
Received 21 September 2013
Received in revised form 17 January 2014
Accepted 19 January 2014
Available online 18 February 2014

Keywords:
Schizophrenia
Near-infrared spectroscopy (NIRS)
Working memory (WM) task
Neuropsychological Educational Approach to Cognitive Remediation (NEAR)
Cognitive rehabilitation
Neurocognitive deficits

ABSTRACT

The regional neuronal changes taking place between before and after cognitive rehabilitation are still not characterized in schizophrenia patients. In addition, it is not known whether these regional changes are predictive or correlated with treatment response. We conducted a preliminary quasi-experimental study to investigate the effects of a Neuropsychological Educational Approach to Cognitive Remediation (NEAR), one of the cognitive remediation therapies, on neurocognitive functioning assessed by the Japanese version of the Brief Assessment of Cognition in Schizophrenia (BACS-J), and on prefrontal and temporal hemodynamic responses during working memory (WM) task (2-back, letter version) using 52-channel near-infrared spectroscopy (NIRS). We assessed 19 patients with schizophrenia or schizoaffective disorder twice with an interval of 6 months. Moreover, taking into consideration the possible practice effect, we assessed 12 control patients twice with an interval of 6 months. The NEAR group, in comparison with the control group, showed significant improvement in two subcomponents of BACS-J, that is, motor speed and executive function along with the composite scores. The NEAR group also showed a significant increase in brain activation in the bilateral cortical regions associated with WM, and in comparison with the control group the between-group differences were restricted to the right frontopolar area. In addition, the amount of enhancement in some cognitive subcomponents was positively correlated with the magnitude of an increase in hemodynamic response during WM task predominantly in the right hemispheres. These findings suggest that neurocognitive deficits in schizophrenia and their neural dysfunction may be improved by NEAR, and NIRS may be a useful tool to assess the changes of the neural activity underlying the improvement of neurocognitive functioning elicited by neurocognitive rehabilitation.

1. Introduction

Cognitive impairment in schizophrenia is now considered to be a core symptom along with the positive, negative and mood symptoms. Of these 4 core symptom categories, cognitive impairment has been demonstrated to result in the greatest difficulties in daily functioning, such as those related to working capacity and daily living. Cognitive regions that show marked impairment in schizophrenia include attention (vigilance), executive function, long-term and learning memory, working memory, and verbal fluency (Green, 1996; Rund and Borg, 1999; Green et al., 2000; Pantelis and Maruff, 2002; Sharma and Antonova, 2003). In a meta-analytic review by Green et al. (2000), the authors subdivided the functional outcome into three general categories; a) psychosocial skill acquisition, b) social problem solving/instrumental skills, and c) community/daily activities. They found that secondary verbal memory was reliably related to every outcome domain, and immediate memory was related to psychosocial skill acquisition. Card sorting and verbal fluency were both associated with community outcomes, and vigilance was linked to skill performance. Moreover, they suggested that the total amount of variance in functional outcome that can be explained by neurocognition in general was approximately 20–60% (Green et al., 2000), however, in a more recent study the amount was downsized to 20–40% (Couture et al., 2006). Green et al. (2004) also suggested that longitudinal studies revealed considerable support for longitudinal associations between cognition and community outcome in schizophrenia.

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http://dx.doi.org/10.1016/j.schres.2014.01.031

Cognitive impairment is already present in the prodromal phase of schizophrenia and is exacerbated when the first episode occurs; moreover, there is often little subsequent change. Meier et al. (2013) demonstrated that there is substantial neuropsychological decline in schizophrenia from the premorbid to the post-onset period, particularly in the field of processing speed, learning, executive function, and motor function, but the extent and developmental progression of decline varied across mental functions. For instance, processing speed deficits increased gradually from childhood to beyond the early teen years, whereas verbal deficits emerged early but remained static thereafter. Cognitive impairment did not change even when positive symptoms or other psychiatric symptoms are improved after drug therapy (Bratti and Bilder, 2006); in fact, a longer duration of untreated psychosis (DUP) typically results in more marked cognitive impairment (Perkins et al., 2005). However, the degree of cognitive impairment greatly varies among different individuals. Whereas approximately 15% of patients remain within the normal range on almost all aspects of cognitive function, most patients score 1–1.5 standard deviations (SD) lower on cognitive function assessments than healthy individuals (Bilder et al., 2000; Heinrichs, 2004). Although a wide range of cognitive properties are impaired, and much research has been conducted to understand how the cognitive impairments in schizophrenia impact daily functioning, an overall picture has not yet emerged. It is more or less an established fact that cognitive impairment has a crucial effect on social turning points; for example, levels of impairment in verbal memory, attention, and executive functioning are predictors of goal achievement in society (Green et al., 2004). Furthermore, attentional impairments continue to hinder the acquisition of life skills even after the effects of social skills training or other forms of rehabilitation have been manifested (Medalia and Choi, 2009); therefore, therapies targeting cognitive impairment are crucial. Currently, the typical effect size of atypical antipsychotic agents for cognitive impairment is small (0.2–0.5) (Woodward et al., 2005; Keefe et al., 2007), and their effects are limited when used alone. On the other hand, there are great expectations for the non-pharmacological treatment of cognitive rehabilitation. Cognitive remediation has been indicated to improve neuropsychological functioning (Krabbendam and Aleman, 2003; Twamley et al., 2003; McGurk et al., 2007; Wykes et al., 2011; Ikezawa et al., 2012), although not all (Ueland and Rund, 2004; Dickinson et al., 2010). However, little research has been conducted on the effects of cognitive rehabilitation on brain function (Wykes et al., 2002; Haut et al., 2010; Bor et al., 2011; Subramaniam et al., 2012).

We have become interested in one of the cognitive remediation therapies "Neuropsychological Educational Approach to Cognitive Remediation (NEAR)" (Medalia and Freilich, 2008; Medalia and Choi, 2009), which was theoretically based on neuropsychology, educational psychology, learning theory and cognitive psychology. NEAR is an evidence-based approach to cognitive remediation specifically developed for use with psychiatric patients. NEAR is a group-based treatment that provides a positive learning experience to each and every client, to promote independent learning, and to promote optimal cognitive function in everyday life.

Near-infrared spectroscopy (NIRS) is a neuroimaging tool that offers several advantages: it is noninvasive, easy to set up, requires minimal constraints, does not occupy a large space, and works silently. NIRS is therefore suitable for assessing prefrontal activation in patients with severe mental illnesses, including schizophrenia. Indeed, NIRS has been used to assess brain functions in many psychiatric disorders (Kameyama et al., 2006; Pu et al., 2012, 2013; Takizawa et al., 2013).

In the present pilot study, we investigated the feasibility of NIRS during performance of a working memory (WM) task as an assessment tool for detecting changes in brain function associated with the pre–post intervention effects of 6 months of NEAR on neuropsychological improvement. We also explored the feasibility of NIRS data as a predictor of the effects of NEAR when neurocognitive functioning and psychiatric symptoms were treated as outcome measures.

2. Methods

2.1. Patients (Table 1)

After a complete explanation of the study, informed consent was obtained from the participants. The protocol of this study was approved by the Ethics Committee of Tottori University. Inclusion criteria were outpatients or inpatients (a) with a diagnosis of schizophrenia or schizoaffective disorder according to DSM-IV-TR criteria, (b) between 13 and 65 years old, (c) able to sit for a one-hour session, (d) willing to participate in the study, and (e) the treatment being recommended by their doctors. Exclusion criteria were patients (a) with active substance or alcohol abuse or post detox within 1 month, or (b) with traumatic head injury within the past 3 years. The diagnoses were made by two expert psychiatrists.

Nineteen patients with schizophrenia or schizoaffective disorder participated in the study. Twelve were paranoid schizophrenia, 2 disorganized schizophrenia, 1 undifferentiated schizophrenia, 1 residual schizophrenia, and 3 were schizoaffective disorder. As can be seen by the mean PANSS scores at baseline (Table 2), the symptom severity of the patients was mild to moderate level (Leucht et al., 2005; Levine et al., 2008).

Although the medications were changed throughout the whole period as little as possible, there were 7 patients whose medications needed to be changed because of clinical decisions. The change in the medication status of these 7 patients was only related to daily dosage levels.

Moreover, we assessed 12 control patients, meeting the inclusion criteria (a), (b) and exclusion criteria (a), (b), twice with an interval of 6 months, taking into consideration a possible practice effect, which may have affected the scores of neuropsychological tests. They did not receive any cognitive training program including NEAR. Although the age was not significantly different from the NEAR group, the onset age was significantly younger and the duration of illness was longer than those of the NEAR group suggesting more chronicity in the control group. Moreover, the daily dosage level of antipsychotic drugs was significantly lower than the NEAR group. Besides these between-group differences, the level of cognitive function assessed using BACS-J was not significantly different between the two groups.

The NEAR group and the control group were nonrandomized, and thus, the study design was quasi-experimental.

2.2. NEAR program

The NEAR program consisted of two one-hour computer sessions per week and an additional group meeting session lasting 30 to 60 min once a week. The subjects completed approximately six months of NEAR sessions before being assessed for the efficacy.

In each computer session, patients engaged in some educational computer software that involved various domains of cognitive function including attention, memory, and executive function (see Supplementary Table 1), taking into account the profiles of the patients' cognitive impairments. The computer software also involves various levels of complexities and is adapted to personal level of cognitive abilities and the subject's interest.

The main aim of the group meeting sessions is to contextualize the computer training into their everyday activities. More specifically, the patients would talk about the difficulties they meet in their everyday activities and try to relate them to certain cognitive regions and finally to the computer software they are engaged in. The process should lead to enhancing motivation and generalization of cognitive skills to daily life. The fidelity of both computer sessions and group meeting sessions were checked by a supervisor, who had already undergone training to become a trainer.