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Brain effects of computer-assisted cognitive remediation therapy in anorexia nervosa: A pilot fMRI study

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ABSTRACT

Poor cognitive-behavioral flexibility is considered a trait marker in anorexia nervosa (AN) that can be improved by cognitive remediation therapy (CRT). The present pilot study aimed at identifying changes in brain function potentially associated with CRT in AN. Data was obtained from a randomized, controlled trial. Twenty-four patients were assessed before and after 30 sessions of either CRT or a non-specific neurocognitive therapy. Voxel-wise analysis of whole brain functional magnetic resonance imaging was applied. Brain activation was measured during response inhibition and task switching. Although results did not reach significance, we found tentative support for CRT-related increases in brain activation in the dorsal putamen during task switching and in the dorsolateral prefrontal, sensorimotor and temporal cortex during response inhibition. These pilot findings provide viable pathways for future research on brain changes underlying CRT in AN.

1. Introduction

Cognitive-behavioral flexibility refers to the ability to switch between tasks and motor plans. This involves the inhibition of a predominant, automatic response, and the selection and execution of an alternate response (Monsell, 2003). Patients with anorexia nervosa (AN) feature difficulties in this domain which may contribute to the lack of treatment response in this population (NICE, 2004; Halmi et al., 2005; Wu et al., 2014). Evidence is growing, however, that cognitive remediation therapy (CRT) could improve this cognitive function in AN as well as AN psychopathology and quality of life (Brockmeyer et al., 2014; Dingemans et al., 2014; Tchanturia et al., 2014). This treatment approach consists of a range of simple exercises that were designed to foster more flexible and holistic thinking styles. Yet, it is unclear which neural mechanisms underlie CRT for AN.

Fronto-striatal loops, including the prefrontal and sensorimotor cortex and the striatum subserve cognitive control functions including task switching and response inhibition (Koechlin et al., 2003; Redgrave et al., 2010). Particularly, the dorsolateral prefrontal cortex (DLPFC) is a key region in this regard (Crowe et al., 2013; Hussein et al., 2014). In conjunction with the prefrontal cortex, also temporal and parietal regions are involved in response inhibition (Simmonds et al., 2008; Obeso et al., 2014). Furthermore, the dorsal striatal system is involved in controlled and automatic behaviors, thus being relevant for response inhibition and task switching (Yin and Knowlton, 2006; Hikosaka and Isoda, 2010).

In AN, there is converging evidence of DLPFC hypo-activity during response inhibition (Lock et al., 2011; Oberndorfer et al., 2011; Wierenga et al., 2014) and task switching (Sato et al., 2013) and altered striatal activation during the execution of cognitive control tasks (Wagner et al., 2007). Corresponding to CRT studies in schizophrenia and mood disorders (Haut et al., 2010; Meusel et al., 2013; Vianin et al., 2014), we hypothesized that brain changes in response to CRT involve increased activity in the cortical control network and striatum during task switching and response inhibition.

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2. Methods

Participants took part in a randomized-controlled trial with two parallel groups that is described in detail elsewhere (Brockmeyer et al., 2014). Patients were randomly assigned to receive either CRT ($n=20$) or non-specific neurocognitive training (NNT; $n=20$) as an add-on to treatment as usual (TAU). Of the 40 patients who were randomized, 31 completed the intervention and took part in the follow-up assessment (for a detailed description of the trial and the main results regarding changes in cognitive set-shifting see Brockmeyer et al. (2014)). Of these, 24 were also eligible and agreed to participate in functional magnetic resonance imaging (fMRI) before and after treatment. Participants provided written informed consent and received financial compensation for their participation in the study. The procedure was approved by the institutional ethics committee.

2.1. Participants

Participants were recruited from two inpatient units for eating disorders and from an outpatient center of a university hospital. Diagnostic assessment was based on the Structured Clinical Interview for DSM-IV Axis I disorders (Wittchen et al., 1997). All participants met the criteria for a principal DSM-IV diagnosis of AN. Exclusion criteria were: (a) suicidal intentions or an acutely life-threatening condition, (b) current substance abuse or dependence, and (c) current or past schizophrenia, bipolar disorder, or organic mental disorder. For demographic and clinical characteristics of the sample see Table 1.

2.2. Treatments

As described in detail elsewhere (Brockmeyer et al., 2014), a modified CRT approach was used that focused exclusively on flexibility and used more training sessions including also computer-assisted tasks to intensify training. NNT resembled CRT in all aspects but focused solely on attention, memory, and logical deduction instead of flexibility. Both treatment conditions comprised 9 face-to-face sessions and 21 computer-assisted homework sessions (45 minutes each), all delivered over a 3-weeks period. TAU consisted of either weekly outpatient psychotherapy (CRT: 42%, NNT: 42%) or multimodal inpatient treatment (i.e., weekly individual and group psychodynamic psychotherapy, body therapy, art therapy, nutrition management, symptom-oriented behavioral interventions such as food diaries, treatment contracts, meal plans, and family interventions). It should be noted, however, that during the 3 weeks of training, a maximum of 3 individual and group therapy sessions were offered.

2.3. fMRI paradigm

We used a visual target-detection task in an event-related design (Zastrow et al., 2009). The task reflects two major components of cognitive-behavioral flexibility: the inhibition of a prepotent response (response inhibition) and the selection and execution of an alternate response (task switching) (Monsell, 2003). The stimuli were images of vehicles of different colors and sizes (see Supplementary material A). Participants were required to classify each stimulus on the basis of its shape as target, non-target, or standard stimulus. They were required to respond to standard stimuli by pressing a standard button and to target stimuli by pressing an alternate button. Participants were also asked to inhibit their behavioral response towards non-target stimuli. All stimuli were centered on a white background for 500 ms, with an inter-stimulus interval of 1000 ms, where a € sign was presented ("EURO"). In each of the 10 runs, infrequently occurring target (5 per run) and non-target (5 per run) stimuli were embedded in frequently occurring standard stimuli (154 per run). The infrequent target and non-target stimuli were separated by a minimum of nine standard stimuli to allow adequate spacing between events to prevent an overlap of event-related hemodynamic responses. The standard stimuli were always images of cars. A new target stimulus (vehicle other than car) was introduced before each run and presented visually for 5000 ms. In the next run the target stimulus of the former run became the non-target stimulus of the current run. To become familiar with the task and the handling of the response buttons within the scanner, a short experience course of 33 trials was completed before the regular scanning session. The task included a total of 10 runs. For each correct response to a target stimulus a reward of 50 EURO CENTS was paid. After each run, the actual reward and the total reward were presented for 3000 ms ("REWARD"). Poor task switching ability was operationalized as frequent perseverative errors (i.e. less accuracy in the responses to target stimuli). Correspondingly, perseverative errors to the infrequently occurring non-target stimuli (i.e. failed inhibition) were considered indicative of poor response inhibition. As we were particularly interested in task switching immediately after rule change, we focused the analyses on target and non-target stimuli presented initially after a rule change. Therefore we analyzed the responses to the first two targets and non-targets per run. For each event (target, non-target) a specific baseline, which consisted of the three preceding and six subsequent standard stimuli, was created (target-standard, non-target-standard). This baseline was chosen to control for simple brain activations associated with automated button-presses to standard stimuli (Zastrow et al., 2009).

Table 1
Demographic and clinical characteristics.

	CRT ($n=12$)		NNT ($n=12$)		*t* test/chi-square test
	Mean/%	SD	Mean/%	SD	
Age (years)	22.82	5.72	28.27	10.25	NS
Ethnicity (% Caucasian)	100	–	100	–	NS
Body mass index (kg/m^2)	15.13	1.63	14.72	1.78	NS
Duration of illness (years)	8.05	6.63	6.32	6.10	NS
AN subtype (% restricting subtype)	75	–	92	–	NS
Comorbid diagnoses (%)					NS
Any	83	–	67	–	NS
Major depressive disorder	75	–	67	–	NS
Obsessive-compulsive disorder	25	–	17	–	NS
Anxiety disorder	17	–	25	–	NS
Posttraumatic disorder	9	–	9	–	NS
Psychotropic medication (%)	9	–	9	–	NS

CRT, cognitive remediation therapy; NNT, non-specific neurocognitive therapy.