Research Highlights

Imaging in Medicine

Application of functional neuroimaging to evaluating the efficacy of cognitive rehabilitation in neurological populations

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With the increasing availability of various neuroimaging techniques, as well as the continuous advancements in technology, neuroimaging applications in rehabilitation have expanded greatly in recent years. Alterations on neurofunctional imaging have been shown to be related to disease pathology, as well as impairments in specific cognitive domains across multiple neurological populations [1–3]. Such neuroimaging technologies have thus been recently applied to the study of cognitive rehabilitation efficacy in neurological populations.

Researchers have theorized that improvements in cognition, independent of the disease process, such as in response to cognitive rehabilitation, would result in measureable changes on functional scans. Functional techniques recently applied to evaluate cognitive rehabilitation effectiveness have included both functional MRI (fMRI) and functional and resting state connectivity [4–6]. Early thought leaders in the application of functional neuroimaging to evaluate changes in cognition have theorized that functional imaging techniques might be applied to test the belief that the effectiveness of cognitive rehabilitation is the result of plasticity in the processing of the brain [7]. One might thus hypothesize that improvement in cognitive deficits following cognitive rehabilitation would also lead to changes in patterns of brain activation.

Initial research examining the brain's response to cognitive training demonstrates both increases and decreases in cerebral activity following treatment [8]. In healthy individuals, Olesen *et al.* [8] noted increased activation on fMRI in parietal and frontal cortices and decreased activation in the anterior cingulate after 5 weeks of working memory training. Work from our group [4] showed greater activation on fMRI following a ten-session memory intervention in persons with multiple sclerosis (MS) in the frontal, parietal, precuneus and parahippocampal regions. Similar results were noted by Fillipi and colleagues [6] in the dorsolateral prefrontal cortex and precuneus, also in persons with MS. Changes in cerebral activity were correlated with cognitive improvement in both Chiaravalloti *et al.* [4] and Filippi *et al.* [6]. Similar findings have been noted in cognitive rehabilitation studies in both schizophrenia [9] and mild cognitive impairment [10] patients.

In addition to an evaluation of changes in brain function with cognitive rehabilitation, it is hoped that, in the future, functional neuroimaging will provide clinicians with information regarding who will and will not benefit from specific forms of cognitive rehabilitation. That is, neurofunctional markers prior to treatment may predict who may or may not show a benefit from treatment. Functional neuroimaging may further be used to maximize the efficacy of specific cognitive rehabilitation tools through the identification of changes in brain functioning associated with improvements in the treated domain (e.g., working memory). The identification of a targeted brain region associated with a particular outcome may lead to the identification of other means by which one can maximize such changes in those brain regions through cognitive rehabilitation or other types of intervention (e.g., transcranial direct current stimulation or medication) and examine the resultant cognitive performance.

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Given the extensive rationale for applying functional neuroimaging to the field of cognitive rehabilitation, it is encouraging to note that a few recent studies have reported changes in functional neuroimaging following cognitive rehabilitation interventions. Two of the most recent articles are summarized below. For details, the reader is encouraged to read the full publications.

Evaluation of: van Paasschen J, Clare L, Yuen KS *et al.* Review of cognitive rehabilitation changes memory-related brain activity in people with Alzheimer disease. *Neurorehabil. Neural Repair* 27(5), 448–459 (2013).

The current study examines the neurofunctional changes on fMRI from pre- to post-treatment with an 8-week behavioral intervention for cognitive deficits in persons with early stage Alzheimer's disease (AD). A total of 19 participants were assigned to a treatment group (n = 7) or a control group (n = 12). Participants underwent scanning procedures during a nonfamiliar face-name encoding and recognition task both prior to and following treatment. There were no differences noted between the groups in behavioral performance. However, a differential response to treatment was noted on the recognition task, with the treatment group showing significant increases in activation in bilateral prefrontal areas and the bilateral insula, while the control group showed decreases in the same regions. No changes were noted from before to after treatment on the encoding task.

The authors discuss the findings in light of the limited work on neurofunctional changes from before to after cognitive rehabilitation in AD. They hypothesize that the increased activation during recognition performance was due to a partial restoration of recognition functioning from treatment in brain areas within the frontal lobes that are less impacted in early-stage AD. Thus, the application of neuroimaging in the current study afforded investigators with additional sensitivity in their ability to measure the brain's response to treatment and draw some conclusions regarding response to treatment in distinct brain regions. This suggests that, in this case, neuroimaging could potentially be used as a biomarker of brain plasticity. Future work with larger sample sizes could potentially seek to identify persons that benefit from treatment from those that do not at a neuroanatomical and neurofunctional level. Such data could be used to inform clinical care and maximize the efficacy of the treatment paradigm for the targeted population.

Evaluation of: Parisi L, Rocca MA, Mattioli F *et al.* Review of changes of brain resting state functional connectivity predict the persistence of cognitive rehabilitation effects in patients with multiple sclerosis. *Mult. Scler.* doi:10.1177/1352458513505692 (2013) (Epub ahead of print).

The currently reviewed study examined the long-term efficacy of a 12-week cognitive rehabilitation paradigm in persons with MS via an evaluation 6 months after treatment completion. Outcome measures included both neuropsychological performance data and functional neuroimaging data, namely resting state (RS) functional connectivity (FC). A total of 18 individuals with MS with cognitive deficits were randomly assigned to a treatment group (n = 9) or a control group (n = 9). All participants completed a neuropsychological evaluation pretreatment, after 12 weeks of treatment and at the 6-month follow-up evaluation. RS fMRI was obtained at baseline and follow-up, but not at 6 months post-treatment. The treatment paradigm consistent of 12 weeks of cross-domain interventions, addressing attention, information processing and executive functioning.

Results indicated an improvement in attention, executive functioning, depression and quality of life from before to after treatment in the treatment group, but not the control group. Performance on tests in each of these domains was correlated with changes in RS FC in networks underlying cognitive functioning, as well as the anterior cingulum. While neuroimaging was not repeated at the long-term follow-up, neuropsychological assessment was repeated and changes in RS FC from baseline-to-immediate follow-up were utilized to predict the long-term maintenance of the treatment effect over this 6-month period. RS FC changes in the default mode network from before to after treatment predicted cognitive performance and less severe depression at the 6-month follow-up. By contrast, RS FC changes from baseline to immediately post-treatment in the executive network predicted better quality of life 6 months post-treatment. Findings from this study are interesting in that neuroimaging parameters, such as RS FC can clearly be engaged to help predict the long-term maintenance of cognitive changes over time. Depression and quality of life can also be potentially predicted by such imaging parameters. Future research should seek to replicate these results and examine the clinical utility of such data.

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