CORE HEALTH foundation

resilient mind
rethinking brain injury recovery

Research Program

Future best practice in neurorehabilitation will likely consist of two primary components: neuroplastic recovery techniques and stem cell regeneration. These two treatment methods may be applied independently but will likely be used in tandem in order to achieve maximal gains.

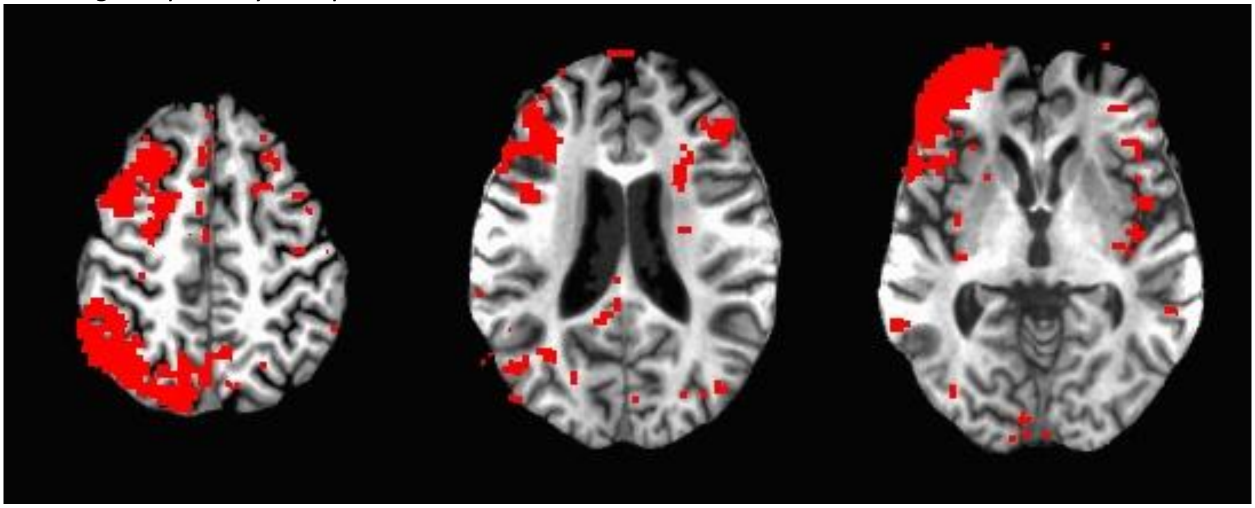
Stem cell implantation offers the hope that autologous cells can be utilized to regenerate traumatically damaged cortical and subcortical areas. Although studies in other countries have demonstrated success in the harvesting, implantation, and integration of pluripotent cells for the treatment of neurological illness/injury, inadequate research controls leave these findings in question. However, it is anticipated that FDA-approved Phase 1 and Phase 2 trials in the United States will commence in the next few years. CORE Foundation researchers have already been in discussion with leading US-based stem cell researchers to facilitate Phase 2 trials in the post-acute population. Establishing this technology as an effective treatment component in the chronic phase of the rehabilitation continuum is a critical step towards a permanent cure for traumatic brain injury.

Neuroplastic improvement, which consists of the re-establishment of pre-injury synaptic connections, re-consolidation of white matter pathways, and functional reorganization of non-injured cortex, holds the most immediate promise for meaningful recovery. Existing therapeutic protocols modified to focus on recovery of function (such as constraint-induced therapy) have already proven efficacious. Other attempts to maximize the brain's healing and development capacity (through the use of medication, nutraceuticals, cardiovascular conditioning, virtual-reality software, etc.) have also demonstrated positive outcomes. However, many questions remain which, without clear answers, limit the development and application of neuroplastically-based treatment efforts. Of particular concern is the relationship between fMRI/fDTI findings and clinical treatment. Establishing standard neuroimaging protocols for the evaluation of therapeutic efforts will allow rehabilitation professionals to methodically advance clinic-based practice.

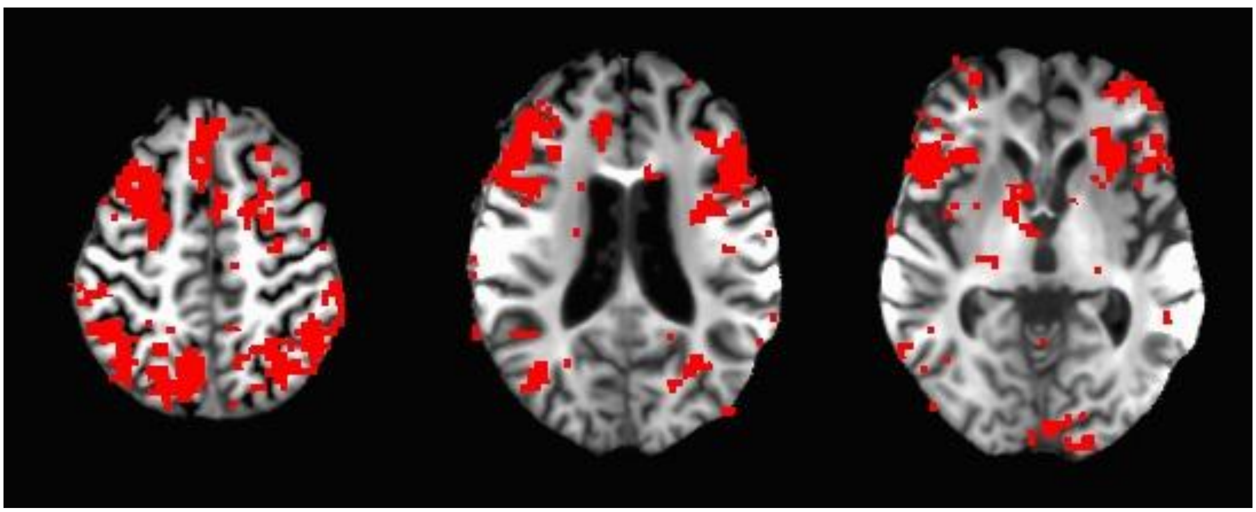
Currently, the CORE Foundation has begun preliminary clinical trials to establish practical, high-intensity, functional neuroimaging procedures, as well as normative and injured-population datasets, in order to assist CORE Health Care therapists in the design of evidence-based interventions. While this will be a multi-year effort, initial findings are already suggesting fresh ways to understand and potentially address deficits seen in the majority of brain-injury patients.

Figure 1 illustrates results from a pilot study where the patient (receiving inpatient post-acute rehabilitation including intense cognitive rehabilitation and enhanced cardiovascular exercise) performed a 1-back task in the MRI scanner and independent component analysis was used to evaluate "active" networks. During the initial scanning session, the primary network associated with the 1-back task was lateralized to the right hemisphere, while a second component was also lateralized to the right (not shown). Six months later, only one, more robust, network component was found and that component was bilateral, similar to the bilateral component found for a healthy control subject.

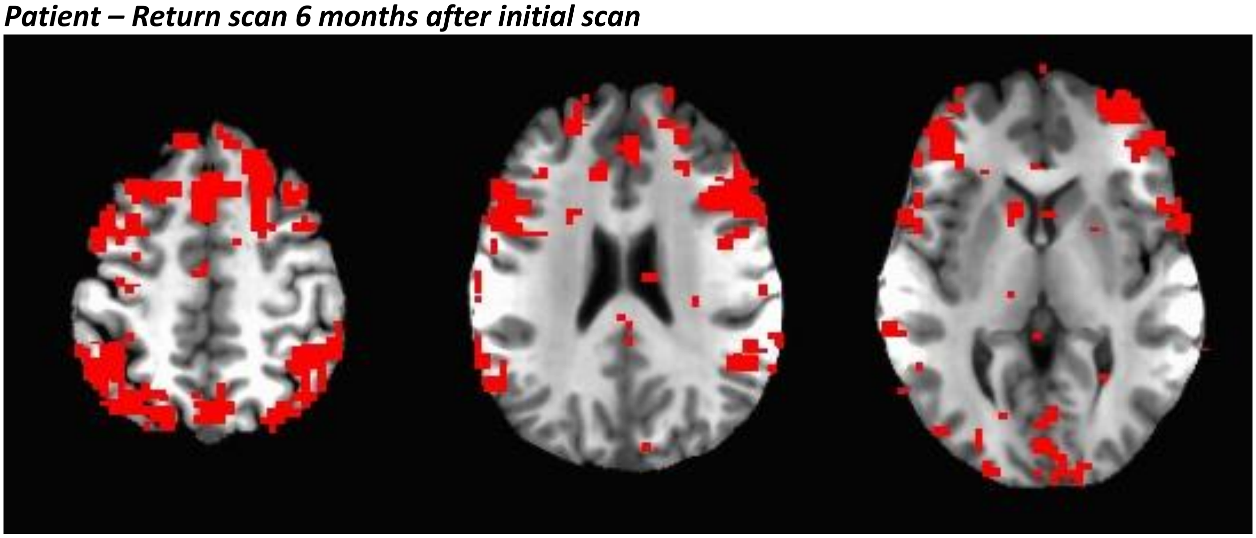
Figure 1 (on next page) : *Select axial slices (radiological view, i.e. left is on the right, MNI coordinate system) showing the primary component related to a one-back task.*



Patient- Initial Scan



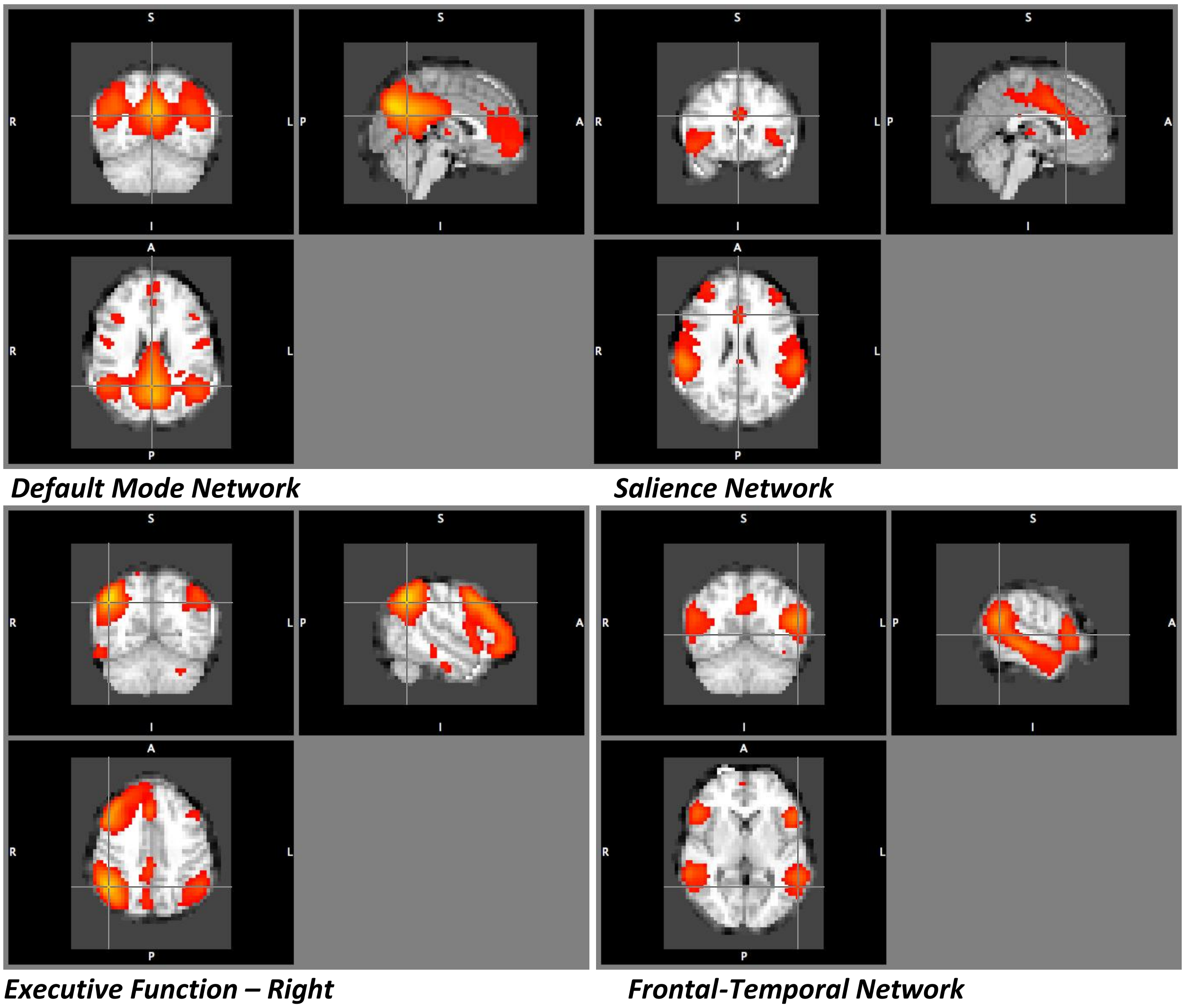
Patient – Return scan 6 months after initial scan



Healthy Control Subject

Another promising avenue of neuroimaging research is the evaluation of resting state networks. There are networks within the brain that show low frequency synchronization during resting state fMRI scans. There are several networks that are consistently detected during these scans (Figure 2) and the quality of the detected networks in brain injured subjects can be compared to that of healthy controls to identify abnormalities within the networks.

Figure 2: *Examples of networks detected using independent component analysis at the group level for healthy control subjects.*



These networks can be analyzed at rest or during a cognitive task to determine if the networks are abnormally altered when stressed. CORE has performed pilot studies looking at these low frequency synchronous networks and the initial results are promising. When a cognitively demanding task is performed by TBI patients, the temporal connectivity of some of these networks often contains more high frequency components than normal, suggesting a “noisier” and potentially less efficient connection.

While certainly preliminary in nature, these findings, if supported by additional subject numbers, raise many questions which may have important clinical implications:

1. What lateralization and activation changes are to be expected throughout the chronic phase of TBI?
2. Which of these changes are functionally beneficial or harmful?
3. In what way does treatment impact cortical activation and/or network responsivity?
4. What types of treatment are most efficacious in achieving targeted changes?
5. And specific to our preliminary finding as regards to potential post-TBI alterations of the non-primary networks, do these alterations have a functional consequence? Might these alterations contribute to the difficulties, commonly seen among TBI patients, of impaired task readiness and inefficient switching among tasks? If secondary networks related to a specific task are in a state of 'decreased readiness', might this be amenable to pharmacological or functional treatments?

Guided by a greater understanding of activation and network changes post-TBI and driven by real-time, patient-specific neuroimaging data, clinical treatment may evolve to have very different techniques and goals than therapy as traditionally practiced. Rather than focusing on face-valid efforts to improve functional abilities (i.e., practicing memory tasks in order to improve memory), clinical techniques may be developed that would allow for a more efficient path to cortical processing improvements for patients based on their damage profiles. For instance, helping patients to maintain multi-network readiness may have a much greater functional return than that achieved by current cognitive therapy tasks.

The CORE Foundation remains committed to:

1. Advancing the role of neuroimaging in clinical practice beyond that of diagnostics,
2. Developing neuroplastically-based therapies, and,
3. Using these techniques to guide and solidify gains made possible by stem cell implantation.

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