Session Title: Serial Neuroimaging Over Time
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Proposed Discussion Questions:
1) For motor activation paradigms, what are the better techniques to employ: e.g., how should we interpret a change in TMS excitability, BOLD magnitude or volume, and ROI and remote distribution of activity over time after stroke?

2) Can we establish standards for reproducibility in longitudinal studies? How should we account for changes in performance, effort, and experience on an acutely evoked signal at the moment of testing given the ongoing neurobiological changes of the brain over weeks and months? What are the best movement (kinematics, force, directionality, speed, normalcy of the action, etc.) and statistical methods to guide the interpretation of these changes over time within and across subjects and between a single subject and a large control group?

Summary of the presentations:
To start the session off, John Detre presented some of the issues relating to the use of fMRI serially over time. Citing studies including Thulborn, 1999 [1], Karbe 1998 [2], Saur et al 2006 [3] it was pointed out inconsistencies found with fMRI studies. In some studies activation shifted from contralesional to ipsilesional and correlated with functional outcome. Other showed contralesional activation did not predict a good functional outcome. Activation is not clearly understood as to what is really going on neurally in the brain. We can not be sure the location of activation necessarily represents areas of neural activity that relates to function. There are limitations in using inferences about neural function using BOLD in serial studies. It is dangerous to infer physiology from a p-value.

Richard Wise (facilitator) then offered a brief presentation of alternative uses for serial imaging providing examples from research of Speech and Rotated speech. One suggestion was the use of serial imaging not for prediction but to suggest treatment. It was recommended to take an established stroke syndrome - even if the patient problem is rare. Understand clearly the lesion and see what images are derived prior to and after intervention. Clever experimental design can help deal with minimizing the performance confound (particularly in language studies).

Summary of the Discussion:
Serial imaging could be useful in predicting outcome of the patient and possibly in elucidating neural mechanisms of recovery. Much of the discussion focused on what result in an fMRI study actually provides insight into mechanism. Proposed suggestions included: 1) Deviations from a previously defined "normal" network or pattern of activation, 2) A pattern seen at time point one that predicts subsequent recovery or lack thereof at time point two, 3) Identification of critical periods/ windows for therapeutic interventions based on the evolution of activation patterns. However there remains a concern that fMRI primarily reflects task execution, and the neural substrate for execution of the task and for recovery may be two different things.

Serial imaging could also be useful in characterizing the time course of response to an intervention. The experimental paradigm should be as constrained as possible to limit the performance confound. It may be possible to control for performance effects by comparing delta versus absolute measures, thereby controlling for baseline performance. An alternative strategy is to examine resting (low frequency) BOLD connectivity since this may be independent of a performance confound. However some discussants felt that resting BOLD only relates to resting function and if you want to see what the brain is doing during activation, you need to measure during activation.

When using fMRI in a test/ retest manner in order to look at the impact of an intervention one should keep mind of the following: 1) Pick an intervention that has positive functional or impairment outcomes, 2) have a hypothesis/ theory as to what you think the intervention is doing to guide where you will look with fMRI. This will help in being able to related the changes seen in fMRI to the intervention versus to just a change in behavior.

Interventions were discussed at length without a clear consensus on what interventions are best to use. Some argued for interventions that make changes on an impairment level (not generalizable necessarily to function performance), other felt that interventions needed to show meaningful change in function. One point of consensus was that interventions should be:

> a) theory driven (one should have a clear idea of what one thinks the intervention is doing and to use that information to guide applications of serial imaging
>
> b) shown to be effective in bringing about a change in behavior (proof of principle)
>
> c) studied with respect to the activation patterns associated with being a treatment responder/ non-responder

When should you do serial imaging / how do you decide which time points you will use?
 One typically chooses to use pre/ post intervention or scanning after you see some sort of behavioral change/ improvement. Multiple scan may be useful in tracking time-course of recovery as well as using them as serial predictors.

What are the reliable biomarkers?
Spatial pattern effects may be better markers for change than just use of magnitude changes with serial imaging.

A interesting result would be one in which a behavior is regained after injury AND the activation is different from "normal". This is an interesting finding that might suggest a recovery mechanism that can be studied in more detail.

What are the best approaches (both for fMRI and performance outcome measures)?
A) One suggestion is the use of ASL (perfusion fMRI). This technique can allow one to evaluate adequacy of baseline perfusion to determine if one can even get a BOLD signal. It can be helpful in reducing the noise (low frequency drift) in fMRI. ASL may be

particularly useful when testing using low task frequency (e.g. long task blocks, repeated scanning over days/weeks). Other benefits of ASL include that it measures a biological parameter exclusive of the subject and is stable to hardware changes which makes it's use conducive for multisite trials.

B) The use of DTI was also proposed. It may be better to use structural measures (that are independent of variation seen with functional activation measures). Is it possible that DTI would provide a more stable measure to relate to functional change?

C) Possibly combinations of methods will provide the greatest insight (PET and fMRI, EEG and fMRI, TMS and fMRI for examples)

D) Consistent use of performance outcome measures across studies would be helpful. Measures vary or are not fully explained. Some measures are purely impairment based measures while others are functional performance measures.

E) What are the best analysis methods? Are there new ways of evaluating data that improve interpretability of fMRI findings? New analyses beyond just pre/ post analyses were suggested and discussed in more detail in the previous session.

F) Single case designs is another approach – comparing the various patterns of activation seen with single cases. This could be done statistically if patterns are determined to be different.

Synthesis/ Recommendations:
Serial imaging has its limitatiosn but is still valuable if care is taken in experimental design, data collection and data analyses. Recommendations relating to type of imaging to use include Perfusion fMRI and use of DTI. These are newer approaches that address some of the limitations of using BOLD fMRI. These have their limitations as well and should be considered to avoid over-interpretation of data. Combinations of methods such as PET and fMRI, EEG and fMRI, TMS and fMRI may provide the best insight. When using serial imaging it is important to try to control for the performance confound. One suggestion was to make sure task completion in scanner was something the patient could do at all time points and that it was tightly controlled. It is important to consider the functional outcomes that are used in imaging studies as well as the interventions that may be used to understand mechanisms associated with recovery. Outcomes should be standardized and ideally include not only impairment but functional performance measures as well. Interventions used in serial imaging studies should be know to bring about functional performance gains, should be theory driven and with a hypothesis as to how the intervention is thought to provoke the system. Targeted analyses designed a priori can then be carried out, to shed light on mechanisms of recovery. Different experimental designs are suggested in the use of serial imaging going beyond pre/ post design studies. Examples include single case designs to characterize recovery patterns in detail, or studies of patients with well established pathology, comparisons of patterns of activation in responders and nonresponders with a particular interest in studying those with positive behavioral outcomes and new patterns of activation.

1.	Thulborn, K.R., P.A. Carpenter and M.A. Just, *Plasticity of language-related brain function during recovery from stroke.* Stroke, 1999. **30**(4): p. 749-54.
2.	Karbe, H., A. Thiel, G. Weber-Luxenburger, K. Herholz, J. Kessler and W.D. Heiss, *Brain plasticity in poststroke aphasia: what is the contribution of the right hemisphere?* Brain Lang, 1998. **64**(2): p. 215-30.
3.	Saur, D., R. Lange, A. Baumgaertner, V. Schraknepper, K. Willmes, M. Rijntjes and C. Weiller, *Dynamics of language reorganization after stroke.* Brain, 2006. **129**(Pt 6): p. 1371-84.