Reducing Inter-session Variablity for Longitudinal fMRI of Individual Subjects

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Introduction

To improve efficacy of fMRI for longitudinal studies of neurological diseases, such as stroke and multiple sclerosis, in individuals, inter-session variability must be low. FMRI has shown modest inter-session reproducibility of map pixels when using two or fewer runs; however, no studies have attempted to assess or reduce variability using multiple-run averaging. The laterality index (LI) (contralateral minus ipsilateral divided by contralateral plus ipsilateral activation) has been shown to change significantly during stroke recovery (1,2), and shows greater reproducibility in healthy volunteers compared to absolute measures such as counting fMRI map pixels (3). For studies over the course of recovery, it is desirable to have a measurement sensitive to changes in LI on the order of 0.1. Our hypothesis was that inter-session variability of LI of fMRI activity in primary motor and prefrontal cortices would decrease as the number of intra-session runs increased for a finger flexion task and working memory task, respectively, and will help determine the number of intra-session runs required to assess longitudinal changes in LI during neurological disease progression or recovery.

Methods

Four healthy volunteers underwent 3 separate fMRI sessions. Each session consisted of 4 runs of (i) a motor task: visually paced finger flexion at 3 rates (0.75 Hz, 1.5 Hz, self paced) randomized into 9 blocks (12 sec task, 24 sec rest) and (ii) a 2-back task: a series of numbers presented serially (3 seconds per digit) and the volunteer was required to respond on a keypad to digits presented 2 digits previously (8 alternating blocks of 30 sec task, 30 sec rest; a visual cue during rest also required a keypad press). Images were collected using a 3 Tesla MR scanner (GE Healthcare, Waukesha, WI) and gradient-echo EPI (TR/TE = 1500/30 ms, slice thickness = 5mm, 96x96 matrix, field of view = 24 cm). Analysis was performed using FSL (www.fmrib.ox.ac.uk/fsl) with the following pre-statistics processing: motion correction; non-brain removal; spatial smoothing using a Gaussian kernel of FWHM 6mm; and high pass temporal filtering. Time-series statistical analyses were carried out using FILM (FMRIB's Improved Linear Model). Z-statistic images were thresholded using clusters determined by $Z>2.3$ and a (corrected) cluster significance threshold of $p=0.01$. Registration to high resolution images was carried out using FLIRT. Primary motor cortex (M1) and pre-frontal cortex (PFC) regions of interest (ROIs) were determined using anatomical MRI. LI was calculated for the ROI appropriate for each task for all runs separately. For each session, LI was calculated by successively averaging LI over runs (run 1, run 1+2, run 1+2+3, run 1+2+3+4). Inter-session variability per number of runs was calculated as the standard deviation (SD) in LI calculated from the appropriate number of runs.

Results

Inter-session variability decreased as runs per session increased (see Fig. 1). For the motor task, an analysis of variance revealed a significant effect of number of averaged runs on SD of LI across sessions [$F(18)=3.55$, $p=0.02$], where inter-session variability for all 4 runs combined was significantly lower ($p< 0.05$) than that measured for only 1 or 2 runs combined. For working memory, analysis of variance did not reveal any significant effects, possibly as a result of the large variance in LI across subjects. In addition, inter-session variability increased for the 2-back task when including 4 runs compared to 3.

Conclusions

These preliminary data suggest that 3-4 intra-session runs are required to precisely determine LI in a single session and to detect changes in LI over subsequent sessions in individual subjects on the order of 0.1. We speculate that the increase in variability after 3 runs for the 2-back task may be due to reduced attention. By assessing inter-session variability in this manner, we can determine how to use our fMRI session time most efficiently, as this is extremely important for studying patients. This technique can be used, as our initial experiences have demonstrated, for stroke patients <72 hours post-stroke, as it is short (< 1 hour), simple, and reproducible.

References

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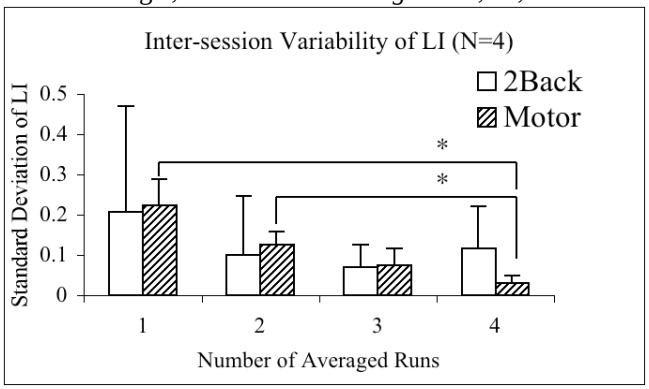

Figure 1. The average inter-session variability of LI over 3 imaging sessions (measured as the SD of LI) for 4 subjects during the finger flexion task (for primary motor cortex) and the 2-back task (for prefrontal cortex). A significant decrease in LI variability when combining 3 or 4 intra-session runs was found compared to just using 1 run (*$p < 0.05$).