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Brain signal variability relates to stability of behavior after recovery from diffuse brain injury

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Abstract

Variability or noise is an unmistakable feature of neural signals; however such fluctuations have been regarded as not carrying meaningful information or as detrimental for neural processes. Recent empirical and computational work has shown that neural systems with a greater capacity for information processing are able to explore a more varied dynamic repertoire, and the hallmark of this is increased irregularity or variability in the neural signal. How this variability in neural dynamics affects behavior remains unclear. Here, we investigated the role of variability of magnetoencephalography signals in supporting healthy cognitive functioning, measured by performance on an attention task, in healthy adults and in patients with traumatic brain injury. As an index of variability, we calculated multiscale entropy, which quantifies the temporal predictability of a time series across progressively more coarse time scales. We found lower variability in traumatic brain injury patients compared to controls, arguing against the idea that greater variability reflects dysfunctional neural processing. Furthermore, higher brain signal variability indicated improved behavioral performance for all participants. This relationship was statistically stronger for people with brain injury, demonstrating that those with higher brain signal variability were also those who had recovered the most cognitive ability. Rather than impede neural processing, cortical signal variability within an optimal range enables the exploration of diverse functional configurations, and may therefore play a vital role in healthy brain function.

Keywords

Variability; Noise; Multiscale Entropy; Magnetoencephalography; Traumatic brain injury; Attention

Introduction

The brain exhibits a substantial degree of noise and signal variability. This has been shown at all measurable levels of neural activity, from the synapse level (Katz and Miledi, 1970; Kleppe and Robinson, 2006) and ion channels (Steinmetz et al., 2000; White et al., 2000),

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and hemodynamic responses (Neumann et al., 2003). Such fluctuations in neural signal have sometimes been regarded as detrimental for neural processes and "noise" is often treated as a nuisance variable in analyses (Faisal et al., 2008). However, we are beginning to understand that irregularities in brain signal may provide fundamental information about the coordination dynamics among neural networks that cannot be gleaned from mean brain activity alone (Garrett et al., 2011; McIntosh et al., 2008; Vakorin et al., 2011). Noise in brain signal may be indicative of a more complex neural system that has enhanced information processing capacity and is capable of alternating between multiple functional states. Synthetic data have shown that uncorrelated Gaussian noise works to destabilize a neural network from equilibrium, thus facilitating explorations of other functional configurations (see Deco et al., 2011 for review), and as functional networks emerge and disintegrate they cause perturbations in the signal over time (Honey et al., 2007). In addition, empirical studies have quantified the information content of neural activity by using entropy-based metrics that capture the variability or irregularity of the brain signal. These studies have shown brain signal variability increases during development (McIntosh et al., 2008; Mišić et al., 2010), while increasing variability is indicative of maturation throughout infancy (Lippé et al., 2009). This work suggests that variability or reduced regularity in brain signal may play a role in healthy brain functioning, however variability has not been extensively examined in cases of neuropathology.

Here we extend these theoretical principles to cases of traumatic brain injury (TBI) that provide a lesion model to probe the relationship of variability in brain signal to healthy brain function. Neurologically, TBI is characterized by diffuse axonal injury (DAI) (Gentleman et al., 1995) and widely distributed volume loss (Levine et al., 2008). Therefore, distributed neural networks are most likely to be impacted by the injury, resulting in network disintegration. In addition, DAI can be particularly concentrated in posterior medial regions (Gentry et al., 1988), which overlap with regions identified as core hubs of anatomical connectivity (Hagmann et al., 2008) and could affect widespread integration of function. Clinically, TBI is associated with behavioral inconsistency, an observation that has been supported experimentally by enhanced response variability in attention-demanding tasks (Stuss et al., 1994; Stuss et al., 1989). The functional substrate underlying this behavioral variability has not been clearly shown.

To characterize brain signal variability, we calculated multiscale entropy (MSE; Costa et al., 2002), a measure that examines the temporal predictability of a time series across several temporal scales. In a healthy functioning brain, it is thought that neural activity consists of an optimal balance between functional specialization and functional integration of neural regions (Tononi et al., 1994). This interplay gives rise to more complex or variable signals which reflect an increased number of underlying metastable activity states and an overall greater information processing capacity of the system. MSE is a metric that can quantify this information processing capacity, with higher values of MSE indicating less temporal predictability or regularity and therefore greater information content. Because MSE assigns lower entropy values to both highly deterministic and completely random signals, which can both be described more simply mathematically, it is an explicit measure of the complexity or "structural richness" of a signal. Indeed, MSE assigns consistent values across different sampling periods to simulated 1/f noise, which contains long-range correlations, yet shows decreased values for uncorrelated white noise, thereby reflecting that 1/f noise is inherently more complex that white noise, which is completely random. In the current study, we also use the term variability to refer to the signal complexity measured by MSE. In addition, the multiscaled facet of the index is relevant to neurophysiological time series, where information has been shown to change dynamically over multiple temporal scales (Honey et al., 2007). As neural integration is mediated through reentrant signaling along anatomical connections (Sporns et al., 1991; Tononi et al., 1992), structural damage resulting from TBI

may affect integration of firing patterns, and therefore lead to reduced variability of brain activity states. In addition, because higher brain MSE is a marker for greater information processing, it is assumed to be related to improved behavioral performance.

We calculated variability in brain signals measured using magnetoencephalography (MEG) using MSE in ten healthy participants and ten participants with diffuse damage caused by TBI during a visual feature-integration task which has demonstrated sensitivity to behavioral variability in TBI patients (Stuss et al., 1989). If brain signal variability is related to optimal neural functioning by facilitating transitions between states (Deco et al., 2009; Ghosh et al., 2008), it is likely the spatial extent of the distributed damage caused by TBI would decrease brain signal variability, and this decrease in potential configurations would consequently result in increased behavioral variability.

Materials and Methods

Participants

Ten patients (6 males) with moderate to severe TBI at least on year prior to participating in this study were recruited along with ten healthy comparison subjects (3 males). All subjects were right-handed, native English speakers and were screened for previous neurological injury, major medical conditions, and history of psychiatric illness. Patients were screened for contusions, infarcts, subarachnoidal hemorrhages, and intracranial hemorrhages by examination of an acute clinical computed tomography (CT) scan. Two other sets of comparison subjects were used for the purposes of characterizing the TBI patients' neuropsychological status and structural neuroimaging data (Table 1).

Neuropsychological Status, Injury Severity, and Neuropathology of TBI sample

TBI patients were recruited from consecutive admissions as part of the Toronto TBI study (Fujiwara et al., 2008; Levine et al., 2008; Turner and Levine, 2008). All patients had sustained a TBI as a result of a motor vehicle accident and were in the chronic stage of recovery (i.e. at least one year post-injury) at the time of study participation (see Table 1). Despite their significant injuries, all patients demonstrated good functional recovery as evidenced by a return to pre-injury employment or academic status. Injury severity was determined by Glasgow Coma Scale (GCS), corresponding to the recommended 6-hour GCS score (Teasdale and Jennett, 1974). Severity in one case (1054) was upgraded from that indicated by the GCS due to extended post-traumatic amnesia. Seven of the ten patients underwent a separate high-resolution structural magnetic resonance imaging (MRI) protocol (Levine et al., 2008). Interpretation by a board-certified radiologist specializing in TBI indicated evidence of neuropathology related to DAI (i.e. hemosiderin deposits) localized to the frontal lobes (6 patients), parietal lobes (4 patients), the temporal lobe (2 patient), the corpus callosum (2 patients), the basal ganglia (1 patient), and the thalamus (1 patient). With one exception, there were no focal cortical contusions greater than 3 mm in diameter. Patient 1047 had a lesion in the right temporal pole that was .713 $\mu L \times 10^4$ in volume. Because of the small size of this lesion the patient was retained. Whole-brain volumetric measures of grey matter, white matter, and cerebral spinal fluid (CSF) following our published image analysis methods (Levine et al., 2008) showed evidence of global atrophy relative to age- and education-matched comparison subjects (see Table 1). Taken together, the radiological interpretation and significant volume loss in the TBI patients are consistent with DAI.

Eight out of the ten patients underwent neuropsychological testing. Neuropsychological test data were compared with a local sample of age, education, and socioeconomically-matched control subjects. TBI patients demonstrated average to high average performance on the verbal subtask of the Shipley Institute of Living Scale (Zachary, 1986). TBI patients also

performed normally on other neuropsychological tests of attention and executive functioning, including (with one exception) a task explicitly measuring executive control within working memory.

Seven out of the ten patients underwent functional magnetic resonance imaging (fMRI) scanning using the same attentional task paradigm as was used in this study. The results from this experiment are reported in Raja Beharelle et al. (2011).

Visual Feature-Matching Task

Experimental design was based on a previous behavioral study that examined the relationship between reaction time and varying degrees of complexity on a feature integration task in TBI patients (Stuss et al., 1989).

During MEG scanning, subjects were shown geometric shapes under three conditions. In each condition, the stimuli were presented at random and considered either “Target” or “Nontarget”. The stimuli had three different components (shape, color, and line orientation within the shape), and each of these could appear in one of four possible states. The shapes were a circle, square, triangle, or cross. The colors were red, blue, green, or yellow. The line orientation was vertical, horizontal, backward slanting, or forward slanting. The three conditions were as follows (See Figure 1 for examples):

1. Single-Feature Condition: One of four geometric shapes selected as the Target was presented randomly. The remaining three shapes were Nontargets. Both Target and Nontarget shapes shared two of three dimensions (i.e. color and line orientation). Subjects made their choice based solely on shape.
2. Multi-Feature Condition: The Target had one randomly selected combination of components. Nontargets were all other stimuli.
3. Redundant Condition: The stimuli were characterized by the same components as in the multi-feature and single-feature conditions, but no state specific to the Target could ever appear in the Nontarget. For example if the Target was a red circle with vertical lines, no Nontarget appeared as red, a circle, or with vertical lines. Hence the stimuli were as complex as in the multi-feature condition, but most of the information was redundant.

Participants rested their index and middle fingers on a two-button pad. At the beginning of each block, a target stimulus was presented for 6 seconds. Four seconds after the target stimulus disappeared, a series of 48 test stimuli were presented at inter-stimulus intervals varying between 2.5 second and 7.5 seconds. Participants were orally instructed to press the response button indicating whether the test stimulus matched the target stimulus. Each test stimulus remained on screen for 2 seconds or until a response was made. Twenty-five percent of the test stimuli matched the target in each block. Stimuli were intermixed with visual fixation on a cross, which was taken as the baseline condition for brain activity.

Reaction time measurements were taken for each trial. In order to assess variability in performance, the coefficient of variation (standard deviation/mean) on the reaction time (cvRT) measures was calculated for each subject and condition. It is considered an index of intra-individual variability. All reaction times less than 300 ms or greater than 2000 ms were excluded.

Data Acquisition and Analysis

MEG—All MEG recordings were performed in a magnetically shielded room using a 151-channel whole-head first order gradiometer system (VSM-Med Tech Inc.) with detection

coils uniformly spaced 31 mm apart on a helmet-shaped array. Head position within the MEG was determined by monitoring the position of indicator coils on the nasion and bilateral periauricular points, at the start and end of each recording session. Participants sat in a comfortable chair with a screen 28 inches away, with 8 degrees of visual angle for stimuli. A photodiode was implemented to record precise arrival time of the visual stimuli on the screen.

Structural MRI—Structural MRI scans were obtained to help localize the sources of the MEG signals. Subjects were scanned on a 1.5T scanner, (GE Medical Systems, Milwaukee, WI). T1-weighted axial anatomical images with in-plane resolution of 256×256 and 128 slices (1.4mm thickness) were recorded using T1-weighted fast spoiled gradient echo (FSPGR) imaging.

MEG data analysis—The magnetic field data were digitized at 625 Hz and filtered with 60-Hz notch and 100-Hz low pass filters. Epochs with MEG signal variations larger than 3 pT were treated as artifacts and excluded from further analysis. Data were epoched into [−500 2000] ms epochs with a [−500 0] ms pre-stimulus baseline. Synthetic Aperture Magnetometry (SAM; Robinson and Vrba, 1999), a non-linear spatial filtering technique was applied to the data within four frequency bands: Alpha (8–16 Hz), Beta (16–28 Hz), Gamma (30–60 Hz) and High Gamma (60–90 Hz). Power changes at each frequency relative to the 200 ms pre-stimulus time period were computed for seven 200-ms windows centered at time points 100, 200, 300, 400, 500, 600 and 700 ms after stimulus onset. Each participant's data were represented as a pseudo-t SAM volumetric map. Individual SAM volumes were then transformed to common stereotactic space (MNI space) based on their anatomical MRI. Significant task-related changes in brain activity were identified using group permutation tests on the mean SAM volume (Robinson and Vrba, 1999). Regions with significant brain activity ($p < .05$) on permutation results for one or more frequency and time interval combination were considered active. This was done to capture all the task related activity for any time interval and frequency band. Based on the control group data, 20 regions were identified as active. Source waveform of each region was constructed for each individual subject based on the weights estimated by SAM, and this was considered a 'virtual' channel that was used for spectral power and MSE computations (see below). The regions underlying the virtual channels were identified using the coordinates of Talairach and Tournoux (Talairach and Tournoux, 1988).

Baseline Spectral Power—Spectral power distribution of the baseline signal across single trials was calculated using Fast Fourier Transform. The signal was first normalized (mean = 0, standard deviation = 1) to calculate relative contributions of different frequency bands to the total spectral power. With a 625 Hz sampling rate and 500 ms baseline signal, this gave us 312 time points at 5 Hz frequency resolution.

MSE Computation—To characterize brain signal variability, we calculated multiscale entropy (MSE; Costa et al., 2002) a measure that examines the temporal predictability of a time series across several temporal scales. Crucially, we focused on the single-trial variability/predictability within an individual (intra-individual) (MacDonald et al., 2006), rather than predictability of the signal across individuals in a group (inter-individual).

Specifically, the MSE algorithm measures sample entropy (Pincus, 1991; Richman and Moorman, 2000) of the signal at successively downsampled time series, where scale 1 indicates the original time series and scale t indicates a more coarse-grained time series generated by averaging t adjacent points together. MSE computation was selectively computed for Nontarget trials which required response inhibition and were therefore likely to engage the most attention. We introduced an additional trial selection procedure based on

total global field power (gfp). Gfp was calculated as a sum of squared amplitudes across all sensors and all time points for the trial duration. The 100 trials with the lowest gpf for each subject were selected for MSE analysis (McIntosh et al., 2008). This minimized the potential presence of trials contaminated with residual high amplitude artifacts and assured that all subjects had the same number of trials from which MSE was computed.

MSE analysis (Costa et al., 2002, 2005; Goldberger et al., 2000) was performed on the signal from the selected trials from each channel using two steps: 1) The downsampled or "coarse-grained" time series were constructed by averaging data points from the original time series within non-overlapping windows of increasing length. Time series were generated for 30 temporal scales with different sampling periods. [sampling rate (625hz) * epoch (2.5ms)/50 time points in an epoch = coarsest temporal scale allowable (30)] 2). Sample entropy was calculated for each time series and plotted as a function of the sampling period for each participant. Sample Entropy calculates the conditional probability that two sequences of (m+1) data points will match each other, given that they match for the first m data points. Since the Sample Entropy metric is the negative of the natural logarithm of this ratio, higher values of sample entropy are associated with less predictable and more variable time series.

Statistical Analyses

Behavior—A repeated-measures analysis of variance (ANOVA) was used to look at differences between TBIs patient and controls in mean reaction time, variability in task performance (measured by cvRT), and accuracy in each condition. Because the standard deviation tends to scale with the mean, we used cvRT to avoid this confound.

Evoked responses, baseline spectral power, and MSE—A partial least squares (PLS) approach (McIntosh et al., 1996; McIntosh and Lobaugh, 2004) was used to look for overall differences in evoked responses within each data epoch, baseline spectral power, and MSE across task conditions between controls and TBI patients. PLS is a multivariate analysis technique that can be used to identify dimensions, called latent variables (LVs), that relate any set of independent measures, such as the experimental design, to a set of dependent measures, in this case, evoked responses and spectral power across channels and MSE across channels and sampling periods within each subject group (McIntosh et al., 1996). Similar to canonical correlation, PLS carries out the computation of the optimal least squares fit to the correlation between two blocks of measures. PLS can be thought of as a modification of conventional principal components analysis, where singular value decomposition (SVD) is carried out on the mean-centered covariance matrices of task design and neural activity of interest.

We first analyzed generalized group variability effects between TBI patients and controls across task conditions. In order to do this, we used mean-centered task PLS to identify both the virtual channels and the MSE sampling periods that covaried by group and task condition. MSE values derived for the first 30 time scales from the MEG signal across all three task conditions were used in this analysis. The data matrix containing subjects in each group by MSE values across channels and sampling periods was mean-centered with respect to the column grand average. Singular value decomposition (SVD) was then applied to the matrix to generate mutually orthogonal LVs, with decreasing order of magnitude of covariance accounted for. Each LV consisted of: (i) a pattern of design scores identifying the contrasts between tasks and groups, (ii) a singular image showing the distribution across channels and sampling periods, and (iii) a singular value representing the covariance between the design scores and the singular image. The design scores can be thought of as a set of contrasts that code the effects resulting from the SVD. The significance for each LV

as a whole was determined using permutation tests (Edgington, 1980). At each permutation, the data matrix rows were randomly reordered and a new set of LVs was calculated. The singular value of each new LV was compared to the singular value of the original LV. A probability was assigned based on the number of times a statistic from the permuted data exceeds this original value (McIntosh et al., 1996). We used 500 permutations. An LV was considered significant if the *permuted* $p < .05$. The reliability of each MSE value for each channel was assessed using bootstrap testing (Efron and Tibshirani, 1986; Sampson et al., 1989). The MSE values were considered stable if they had a bootstrap ratio greater than ±3, corresponding to an estimated 99% confidence interval (Sampson et al., 1989). In addition, 95% confidence intervals were estimated for the effect in each group and task condition. If the confidence interval crossed zero, the effect was not considered reliable. For each subject, an MSE score was calculated. The MSE score is similar to a factor score and indicates how strongly an individual subject expresses the patterns on the latent variable. The score is the dot product of the subject's raw MSE data and the singular image from the latent variable, and emphasizes the pattern of MSE across channels and sampling periods that are most related to the group and task differences (McIntosh et al., 2004).

Similar analyses were carried out using PLS to investigate group effects on evoked responses during the task and pre-stimulus, baseline spectral power.

Brain-behavior PLS was also used to examine group effects on the relationship between MSE and task accuracy, cvRT, and speed of performance (measured by mean RT). For this analysis, the time series and the average of behavioral performance across all three conditions was used. A second analysis was carried out looking at the relationship between MSE and behavior within each task condition separately. Similar to mean-centered task PLS, in brain-behavior PLS, SVD was run to identify robust LVs. These LVs represent either similarities or differences between groups and tasks in the correlations of behavior between MSE and behavior (McIntosh and Gonzalez-Lima, 1998). Statistical significance and reliability were assessed using the same resampling procedures for mean-centered task PLS.

Results

TBI patients did not show differences in behavioral performance compared to controls on mean reaction time (meanRT), within-subject cvRT, and accuracy. A two-way factorial ANOVA revealed no main effect of group $F(1,51) < 1$, p = n.s. or task condition $F(2,51) < 1$, p = n.s. and there was no interaction between the two $F(2,51) < 1$ for meanRT (Figure 2a). A second two-way factorial ANOVA showed no main effect of group $F(1,51) < 1$, p = n.s or task condition $F(2,51) = 1.2$, p = n.s, and there was no interaction $F(2,51) < 1$, p = n.s for within-subject cvRT (Figure 2b). A final two-way factorial ANOVA revealed no main effect of group $F(1,51) < 1$, p = n.s. or task condition $F(2,51) < 1$, p = n.s. and there was no interaction between the two $F(2,51) < 1$ for accuracy (Figure 2c). Although both groups showed similar trends on the standard deviation of RT, the standard deviation tends to scale with the mean, and therefore we used cvRT to avoid this confound.

Evoked responses comparisons for TBI patients and controls

PLS revealed no significant group differences between TBI patients and controls when evoked responses were compared within the data epoch.

Spectral power comparisons between TBI patients and controls

TBI patients showed less low frequency spectral power compared to controls, however this difference was not significant (*permuted* $p > .05$). At higher frequencies, patients and

controls did not show differences in spectral power distribution (See Figure 3 for a representative channel).

MSE differences between TBI patients and controls

Sample entropy measures were lower for TBI patients across all channels. This difference was strongest at coarse (i.e. increasing values above a 24 ms sampling period on the x-axis) sampling periods (See Figure 4B for a representative MSE curve). The sample entropy values of one TBI patient were several standard deviations below the range of the other subjects' entropy values. This subject was removed as an outlier from all analyses. Statistical analysis using PLS showed MSE for TBI patients was significantly lower than that of controls (*permuted p* = .0439). This difference was robustly expressed (i.e. with a bootstrap ratio greater than ± 3 corresponding to an estimated 99% confidence interval) in the right and left cuneus (Talairach coordinates: 16 −78 16; −23 −75 12), and right precentral gyrus (37 −2 28; 23 −19 50).

MSE-behavior relationships in TBI patients and controls

We first analyzed the relationship between brain signal variability and behavioral performance across all conditions. There was a significant relationship (*permuted p* =.012) between brain signal variability (MSE) and cognitive function. Greater brain signal variability was robustly (i.e. within an estimated 99% confidence interval) related to better accuracy and increased stability in reaction times in healthy participants and increasingly stable responses only in patients with traumatic brain injury (Figure 4D). Figure 4A depicts the regions which expressed these relationships between brain signal variability and better accuracy and more stable response times. These regions included left and right pre- (−35 −16 55; −50 −4 35; 31 −16 50; 23 −19 50; 37 −2 28) and postcentral gyri (−43 −21 55; 23 −26 50), left and right precunei (−14 −79 40; 17 −48 50), left caudate (−2 19 8), left anterior cingulate (−2 22 −8; −1 34 24), left cingulate gyrus (−7 −8 35), and right paracentral lobule (2 −37 55). The sampling periods for which the MSE-behavior relationships are reliable are indicated in Figure 4C. The group variability-behavior correlations and the bootstrap estimated confidence intervals for accuracy, and variability in reaction time are indicated in Figure 4D and 4E. The effects are reliable for groups and behavioral measures where the confidence intervals do not cross zero. Therefore, there was no reliable relationship between brain signal variability (MSE) and accuracy in TBI patients or MSE and average reaction time in either group.

We also examined the relationship between MSE and the neuropsychological measures that the TBI patients showed the most deviation from the control sample (the Trail Making Test and the Wisconsin Card Test). MSE did not significantly relate to the performance of the TBI patients on these measures (*permuted p* > .05 for both tests).

Critically, we were interested in further studying effects specifically on variability in behavior within the context of distributed brain damage due to TBI, and thus examined how MSE related only to behavioral variability (cvRT) within each task condition separately. For the single-feature condition, the PLS analysis revealed no significant LV. Greater brain signal variability was significantly (*permuted p* = .012) related to more stable reaction times for the multi-feature condition (Figure 5). Correlations between MSE and cvRT for each group are shown in Figure 5C and 5D. The regions where MSE was reliably associated with lower cvRT on the multi-feature condition primarily expressed the association at coarser sampling periods and included left middle occipital gyrus (−29 −76 12), left and right pre- (−35 −16 55; −50 −4 35; 37 −2 28; 31 −16 50; 23 −19 50) and postcentral gyri (−43 −21 55; 23 −26 50), left and right precunei (−14 −79 40; −28 −51 45; 17 −48 50), left caudate (−2 19 8), left anterior cingulate (−2 22 −8; −1 34 24), and right paracentral lobule (2 −37

55). The regions where MSE was reliably associated with greater behavioral variability primarily expressed the associations at finer sampling periods (i.e. values below 24 ms sampling period on the x-axis) and included right precentral gyrus, left caudate, left anterior cingulate, and left cingulate gyrus. The regions and sampling periods at which MSE-behavior relationships are reliable are depicted in Figure 5A and 5B, respectively.

TBI patients express this pattern of negative association between cvRT and brain signal variability more strongly than controls. Examining bootstrap estimated confidence intervals around the correlations of MSE to behavioral variability in TBI patients and controls do not overlap. In addition, we compared the correlations between the two groups directly using the procedure described in Zu (Zu, 2007), which uses the bootstrap estimated confidence intervals to compare two correlations to make use of non-symmetrical intervals around a correlation coefficient. The difference between the two correlations 0.47, with 95% confidence intervals upper and lower bounds for this difference at 0.71 and 0.34 respectively. Importantly, this indicates that the correlations for each group are distinct, with TBI patients showing a significantly stronger correlation.

The LV generated for the redundant condition also reached significance (*permuted p* = . 0399). The regions that showed a reliable inverse association between MSE and variability (See Table S1a for coordinates) all expressed this association at finer time scales (less than 10), except the left postcentral gyrus which also showed a reliable negative association between MSE and variability at scale 26. The regions where MSE was reliably associated with more variability (see Table S1b for coordinates) expressed these associations primarily at mid-range scales (between 5 and 20).

Discussion

Our findings demonstrate that more variability or irregularity in neural signal is related to less variability in behavioral responses in healthy and TBI subjects and greater accuracy in healthy subjects. We demonstrate a direct correspondence across subjects between brain signal and behavioral variability by showing that variability in brain signal increases proportionately across subjects as reaction times become more stable. Finally, we show that the relationship between brain signal variability and more stable (i.e. less variable) reaction times is statistically stronger in TBI patients than controls, indicating that those patients with more variable or complex brain signals are also those patients who have recovered better behaviorally after the injury. Our results argue against the notion that variability in brain signals impairs neural processes, and instead suggest an important role of brain signal variability, which has been shown to indicate increased information processing capacity, in a healthy functioning brain.

Notably, we identified the inverse relationship between brain signal variability and behavioral variability in midline regions including precuneus, paracentral lobule, and anterior cingulate. Our findings complement recent data showing brain signal variability in posterior midline regions increases with development, where reaction times also tend to become more stable (Mišić et al., 2010). These midline regions have been shown to occupy a central anatomical position based on their high number of connections with the rest of the brain (Hagmann et al., 2008). Recent studies have shown that the precuneus and paracentral lobule constitute part of an anatomical structural core due to their dense connections to other regions of the brain and their efficient linkages to these areas. This topographical centrality of these regions suggests their prominent role in the functional integration of information from spatially segregated neural regions, which may in turn account for the relationship between greater variability in these regions and more consistent task performance.

Perhaps as a consequence of their functional connectivity (Bullmore and Sporns, 2009), these regions have also been shown to partially compose part of an intrinsically organized network reflecting resting state processing that is characterized by task-independent deactivations (Gusnard and Raichle, 2001; Raichle and Mintun, 2006; Shulman et al., 1997). Recent simulations have suggested that noise within areas including those identified in this study, plays a role in the emergence of the intrinsic patterns of functional connections and allows the brain to maintain an adaptive, metastable network configuration (Deco et al., 2009). Our findings complement these simulations by showing that, as in previous developmental research (McIntosh et al., 2008), subjects who demonstrate lower variability in these regions also have reduced consistency in behavior. In addition, reduced consistency in behavioral responses may be due to poorer inhibitory function (Bellgrove et al., 2004). This reduction in brain signal variability may reflect an overall decrease in flexibility in exploring the repertoire of possible functional neural states.

We additionally identified that greater brain signal variability related to better accuracy and more stable response times in left and right pre- and postcentral gyri. Likely these regions were related to the sensory and motor components of the task. The identification of precentral regions in both the average and within-condition analyses may reflect the fact that all three task conditions require the subject to generate a motor response. In addition, the involvement of postcentral regions in both analyses may reflect the sensory-motor integration required for generating responses to all three task conditions.

Furthermore, we set out to examine whether TBI patients, who in previous work have been shown to have distributed damage due to DAI (Levine et al., 2008; Povlishock and Katz, 2005), have lower neural variability compared to controls. We found lower neural variability in TBI patients with DAI (see Table 1), which was robustly expressed in the posterior midline regions (right and left cuneus). Lower variability may be most noticeable in these regions due to greater structural damage. Posterior midline regions are particularly susceptible to axonal damage in TBI (Gentry et al., 1988), and volume loss (Levine et al., 2008; Yount et al., 2002). Volumetric MRI analyses showed that our TBI sample did have greater tissue loss in the posterior midline compared to controls.

Although the lower variability suggests that there is less differentiation in neural activity patterns in TBI patients, this was not reflected in the behavioral performance outcomes of TBI patients and controls, where measures may not be sensitive enough to capture this deficit. Despite the significant TBI, at the time of participation all patients had made a good recovery by gross clinical standards and did not show deficits on neuropsychological testing. However as a result of the diffuse damage, patients may still experience cognitive effects, including behavioral inconsistency and difficulty accomplishing complex tasks. The lower brain signal variability may support the observation that TBI patients report cognitive changes even in cases where task performance is normal.

While the variability in reaction time measures could have been related to spectral power distribution alone instead of resorting to the MSE analysis, it has been shown that spectral power and MSE are not redundant measures (McIntosh et al., 2008). For example, jittering the phase of the Fourier coefficients of a signal in frequency space has no effect on the spectral power distribution, but does change MSE results. This indicates MSE is sensitive to dependencies within the neural time series that do not affect the spectral power distribution. This sensitivity is emphasized by the fact that we find stronger differences for TBI patients relative to controls only with the MSE measure, but not with evoked responses or spectral power.

Importantly, TBI patients showed a significantly stronger inverse link between brain signal variability and variability in reaction time than controls in the multi-feature condition, which involved the most task complexity. In other words, recovered TBI patients with higher brain signal variability show better behavioral functioning. The enhanced relationship in TBI patients in this condition may be a reflection of the fact that TBI patients have compensated for brain damage and achieved the ability to sustain performance throughout the task. Indeed recent research has shown that variability in phase synchronization among EEG channels predicts recovery from coma induced by TBI (Nenadovic et al., 2008). Diffuse damage, which is fundamental to TBI neuropathology (Farkas and Povlishock, 2007; Povlishock and Katz, 2005), affects processes that depend on large-scale neural interactions. Interestingly, the seven TBI patients from this sample who also underwent the same task paradigm with fMRI scanning showed increased activation during the multi-feature condition in regions identified as having the inverse relationship between brain signal and behavioral variability such as precuneus, anterior cingulate, paracentral lobule as well as recruitment of a larger set of regions (Raja Beharelle et al., 2011). It may be the case that involvement of a larger set of regions during this condition in TBI patients may contribute to the information processing reflected by the increased brain variability identified in this study. Of the three task conditions, the multi-feature condition requires that subjects integrate all three dimensions of the stimulus in order to perform the task adequately. Those TBI patients with higher variability at coarser temporal sampling periods in this condition may be the most successful at integrating neural information at a global level.

The association between higher brain signal variability and more stable reaction times was most strongly expressed at coarser sampling periods. These temporal scales have been related to more distributed brain activity rather than local dynamics. In a high-resolution EEG study, Nunez et al. (2001) examined the relationship of increasingly larger epoch lengths in resting state alpha rhythms to global phase coherence at the peak alpha frequency. The correlation coefficients monotonically increased with epoch length, suggesting more stability in the global phase structure at coarser temporal scales. This same principle can apply to the temporal scales in MSE, where coarser temporal scales may capture stability in global communication. Conversely, it may be the case that relationships between MSE and variability in behavior at the finer temporal scales reflect local processing (Vakorin et al., 2011). We find that in the multi-feature condition, increased brain signal variability in the finer scales predicts more variable reaction times in several of the same midline regions that were identified as having an inverse relationship between brain and behavioral variability in the coarser scales. This suggests that for the multi-feature condition, which requires complex visual-feature integration, there is a tradeoff between global and local processing, where the occurrence of more local processing is disadvantageous, leading to more unstable responses in the task. Similarly, we identified an inverse relationship between brain and behavioral variability at the finer scales for the redundant condition. The redundant condition includes stimuli that are as complex as the multi-feature condition, but can be performed by only focusing on one feature of the target without having to integrate all three features. The relationship between brain and behavioral variability was expressed primarily in visual areas, reflecting the fact that the condition was visually, but not conceptually complex. For the redundant condition, the occurrence of more local processing in visual areas is advantageous and relates to more stable reaction times, suggesting this condition does not require more long-range processing during feature-integration.

Finally, we examined whether brain signal variability was related to mean reaction time to clarify whether the measure indicated cognitive processes occurring during the task or was related to more general aspects of performance. While brain signal variability and accuracy were correlated in comparison subjects, there was no reliable relationship to mean reaction time. This indicates that brain signal variability may be more related to cognitive processes

required to solve the task than the physiological factors underlying increased speed of response.

One limitation of our study is that we cannot identify additional characteristics of the TBI patients who show higher brain signal variability and corresponding increased stability of reaction times. We were unable to detect any significant relationships between brain signal variability and any severity measures such as PTA or GCS or any of the measures of volume loss. As volume loss is only an indirect marker of DAI, additional information using diffusion tensor imaging (DTI) would have more directly been able to measure DAI in our TBI sample and may have been able to provide further information regarding the structural integrity of neural networks in the TBI patients showing higher versus lower brain signal variability.

Conclusion

In patients with TBI, diffuse axonal injury is associated with reduced variability in neural activity, particularly in posterior midline regions. In both patients and healthy controls, brain signal variability increased proportionately across subjects as reaction times became more stable. This relationship was statistically more robust for patients with brain injury than for healthy participants, indicating that those patients with greater brain signal variability are also those who have better behavioral recovery after the injury. The degree of neural variability may therefore be considered an index of functioning in recovered patients following significant brain injury.

Our findings argue against the strict idea that variability in cortical dynamics may impede neural processing. Instead, we demonstrate that these fluctuations play a meaningful role in healthy brain functioning in controls and patients undergoing neurocognitive recovery from diffuse brain injury. Taken together with the extant modeling work (Deco et al., 2009), increased brain signal variability represents an ability to explore a greater repertoire of functional states and an increased capacity in information processing, which may be what is reflected by the improved behavioral responses in the participants with better recovery. Consistent with the behavior of a nonlinear system, cortical signal variability, or noise, at an optimal level enables the exploration of diverse potential functional configurations (Deco et al., 2009), but when variability is outside of this optimal range, the brain’s function is compromised (Winterer et al., 2006).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Patients with traumatic brain injury show less brain signal complexity compared to controls
- Greater brain complexity relates to improved behavioral performance
- Patients show this relationship statistically more strongly than controls

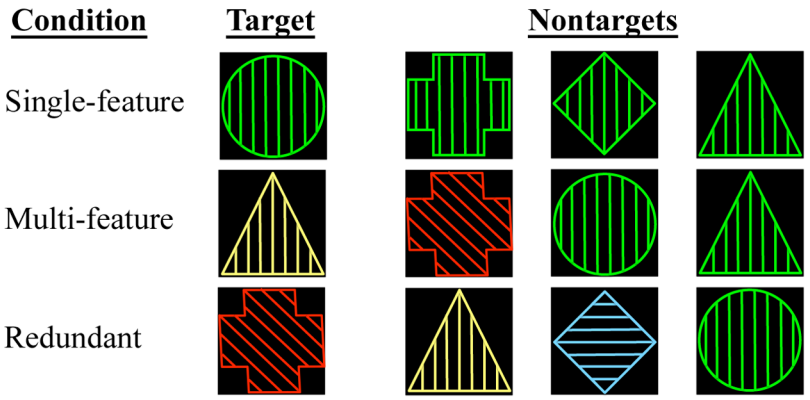

Figure 1. Depiction of the single-feature, multi-feature, and redundant task conditions

For each condition, examples of a target and of nontargets are shown. For the single-feature condition, subjects had to make the decision based on shape only. For the multi-feature condition, the target and the non-targets may share one or more features (shape, color, and orientation), requiring subjects to integrate all three visual features. For the redundant condition, the target and the non-targets do not share any features, allowing the subject to make the decision based on one feature only.

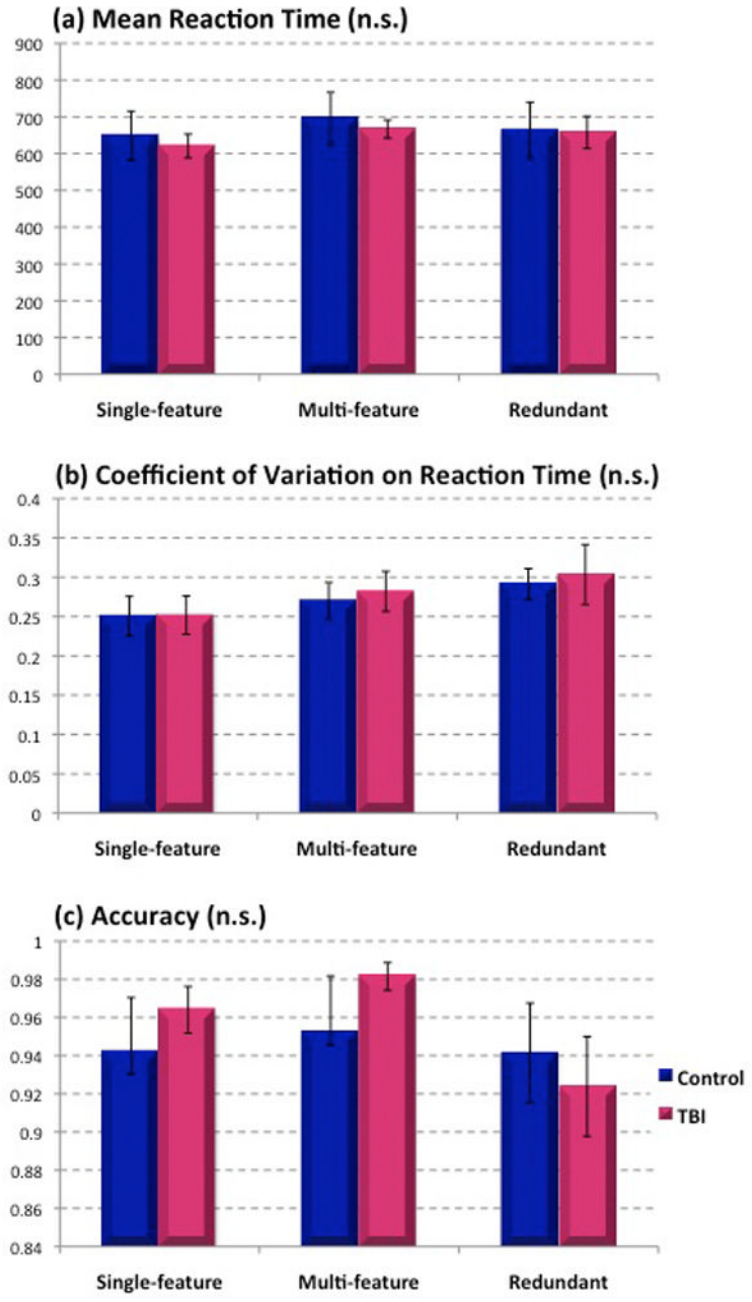

Figure 2. Group behavioral results for mean reaction time, coefficient of variation, and accuracy

No significant differences were found between TBI patients and controls on all three behavioral measures for all three task conditions, indicating that the recovered post-TBI patients showed relatively normal behavioral function. Error bars indicate group standard errors.

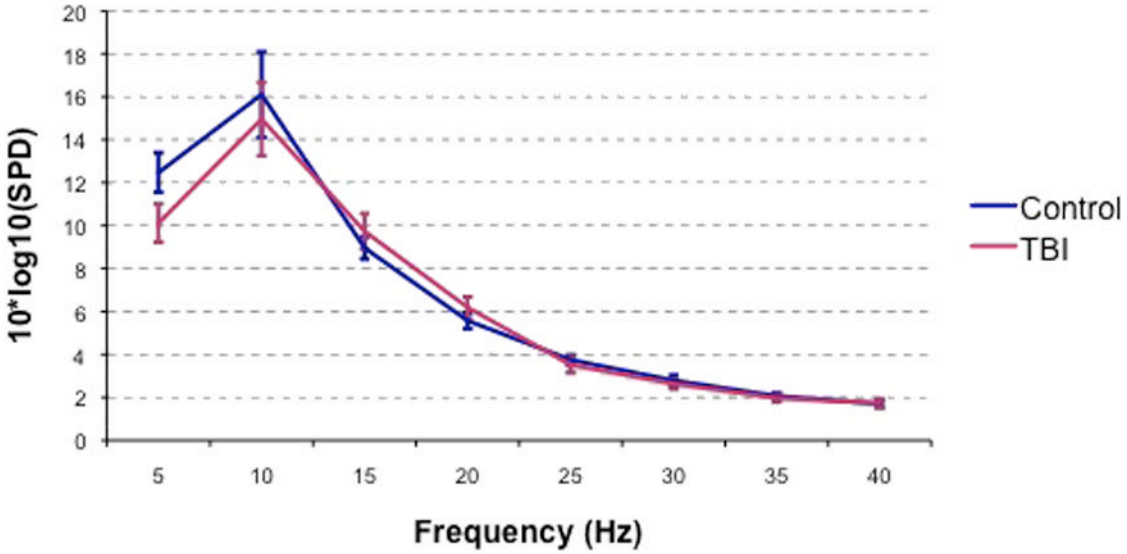

Figure 3.
Group average results for spectral power distribution (SPD) during the baseline period at the left middle occipital gyrus channel. Error bars indicate group standard errors

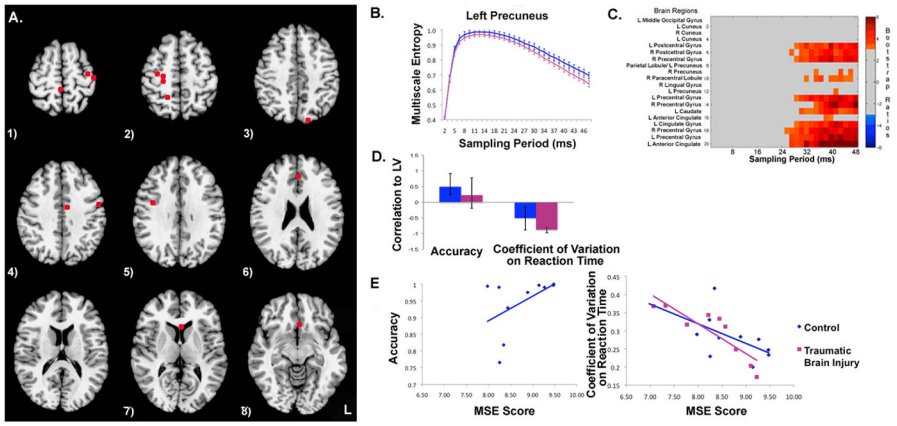

Figure 4. The relationship between brain signal variability and behavioral performance

A. Brain regions robustly expressing the relationship between brain signal variability and the behavioral measures are indicated with red circles. The anatomical labels for these regions are as follows: 1) R Paracentral Lobule (2 −37 55); L Precentral Gyrus (−35 −16 55); L Postcentral Gyrus (−43 −21 55) 2) R Precentral Gyrus (31 −16 50; 23 −19 50); R Postcentral Gyrus (23 −26 50); R Precuneus (17 −48 50) 3) L Precuneus (−14 −79 40) 4) L Cingulate Gyrus (−7 −8 35); L Precentral Gyrus (−50 −4 35) 5) R Precentral Gyrus (37 −2 28) 6) L Anterior Cingulate (−1 34 24) 7) L Caudate/L Anterior Cingulate (−2 19 8) 8) L Anterior Cingulate (−2 22 −8). All coordinates are given according to Talairach and Tournoux (Talairach and Tournoux, 1988). *B.* Group averages for MSE estimates in a representative brain region (left precuneus) plotted against the sampling period of each time scale. Similar MSE curves were obtained for all regions and showed lower variability for traumatic brain injury patients compared to controls, particularly in the coarser sampling periods, corresponding to larger sampling period windows. Error bars indicate group standard errors for each sampling period. *C.* Regions and sampling periods coded in warm colors showed a reliable relationship between brain signal variability and the behavioral measures. In these regions, higher brain signal variability robustly related to better accuracy in comparison subjects and stability in performance in both groups. *D.* The relationship between brain signal variability and each group behavioral measure. Correlations were reliable if confidence intervals did not cross zero (i.e. for accuracy in controls and variability in reaction time (cvRT) in both groups). The relationships between greater variability and more stable and accurate performance for both groups are shown in *E*. The MSE score indicates how strongly the subject expresses the pattern identified in the latent variable. There was no reliable relation to performance speed.

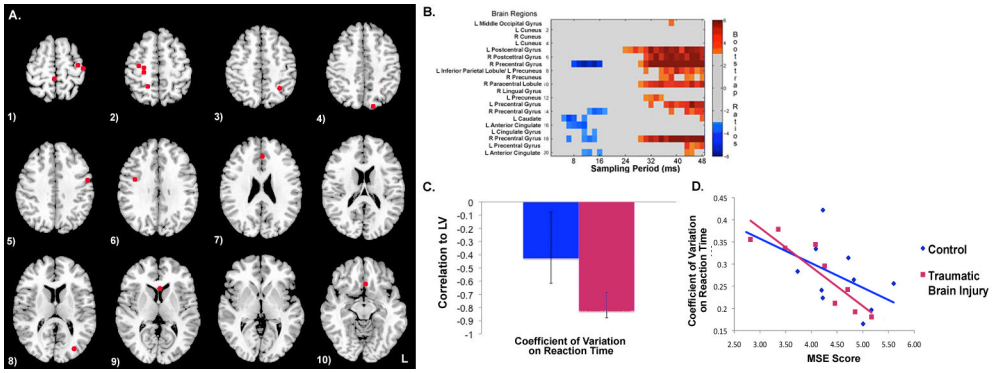

Figure 5. The relationship between MSE and variability in reaction time for the multi-feature condition

A. Brain regions robustly expressing an inverse relationship between MSE and variability in reaction time (cvRT) in the multi-feature condition are indicated with red circles. The anatomical labels for these regions are as follows: 1) R Paracentral Lobule (2 −37 55); L Precentral Gyrus (−35 −16 55); L Postcentral Gyrus (−43 −21 55) 2) R Precentral Gyrus (31 −16 50; 23 −19 50); R Postcentral Gyrus (23 −26 50); R Precuneus (17 −48 50) 3) L Inferior Parietal Lobule/L Precuneus (−28 −51 45) 4) L Precuneus (−14 −79 40) 5) L Precentral Gyrus (−50 −4 35) 6) R Precentral Gyrus (37 −2 28) 7) L Anterior Cingulate (−1 34 24) 8) L Middle Occipital Gyrus (−29 −76 12) 9) L Caudate/L Anterior Cingulate (−2 19 8) 10) L Anterior Cingulate (−2 22 −8). All coordinates are given according to Talairach and Tournoux (Talairach and Tournoux, 1988). *B.* Regions and sampling periods coded in warm colors expressed a reliable relationship between variability and variability in reaction times in controls and TBI patients. Regions and sampling periods coded in cool colors expressed the inverse relationship. In these regions, higher brain signal variability robustly related to stability in performance for the multi-feature condition, and this relationship was expressed significantly more strongly in traumatic brain injury patients compared to controls. The group correlations are shown in *C. D.* The relationships between greater variability and more stable performance during the multi-feature condition for both groups. The MSE score indicates how strongly the subject expresses the pattern identified in the latent variable.

Table 1

TBI patient demographics, acute injury characteristics, structural neuroimaging data, and neuropsychological test data

Three separate control groups were used. Demographics are compared to the MEG control subjects (N=10). Structural neuroimaging data are compared to age-matched healthy adults (N=12) (Levine et al., 2008). Neuropsychological data are compared to age-, education-, and socioeconomic-matched healthy adults (N=27) (Levine et al., 2006).

	1047	3646	3651	1054	3652	3639	3649	3656	2750	3658	Patient means (sd)	Control means (sd)
Demographics												
Age (yrs)	47	28	26	26	24	31	30	28	35	40	31.5 (7.2)	27 (5)
Education (yrs)	16	16	18	17	17	15	16	17	19	n/a	16.8 (1.2)	n/a
Injury Characteristics												
Glasgow Coma Score	14	6	3	9	7.5	9	10.5	9	12	4	8.4 (3.4)	
Loss of Consciousness (hrs)	.017	96	120	26	n/a	5	168	168	504	192	142.1 (154.1)	
Post Traumatic Amnesia (hrs)	168	1080	1176	240	504	504	n/a	1176	n/a	504	669 (414.0)	
Time since Injury (yrs)	3.7	2.7	1.9	3.7	2.1	2.0	2.7	2.1	2.9	1.3	2.51 (.8)	
Severity Classification	Mod	Sev.	Sev.	Sev.	Sev.	Mod.	Mod.	Mod.	Mod.	Sev.		
Neuroradiological Data												
Grey Matter Volume**	53.4	60	60.8	61.4	62.6	61.83	62	n/a	57.3	n/a	59.9 (3.1)	63.1 (1.6)
White Matter Volume***	42.8	42.4	43.2	43.3	42.7	41.5	41.5	n/a	44.6	n/a	42.75 (1.0)	46.8 (1.8)
Total Cerebral Spinal Fluid***	26.9	21.2	20.1	19.2	18.6	20.7	20.6	n/a	22.1	n/a	21.2 (2.6)	16.3 (1.9)
Select Neuropsychological Tests												
Shipley Institute of Living Scale (verbal)	34	36	34	28	29	34	29	n/a	35	n/a	32.4 (3.2)	30 (4)
Verbal Fluency (# of words generated	47	33	53	49	51	35	45	n/a	40	n/a	44.1 (7.4)	40 (10)
Symbol-Digit, written (# correct)	58	45	61	69	56	51	69	n/a	65	n/a	59.3 (8.5)	59 (10)
Symbol-Digit, oral (# correct)	66	49	83	88	67	64	88	n/a	65	n/a	71.3 (13.8)	72 (12)
Trail-making test (B-A)	41	25	10	25	21	12	25	n/a	29	n/a	23.5 (9.7)	31 (15)
Wisconsin Card Test (perseverations)*	16	14	10	11	10	13	11	n/a	10	n/a	11.9 (2.2)	20 (9)
Self-Ordered Pointing (total)	7	8	4	4	3	6	4	n/a	1	n/a	4.6 (2.3)	6 (4)

Significant group differences are indicated with an asterisk to the right of each measure

* = $p < .05$,

** = $p < .01$,

*** = $p < .001$.