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Appendix-I-MRI-2020

Basic Concepts in Brain Organization, Magnetic Resonance Imaging, and Quantitative Assessment of Regional Brain Volumes and Diffusion Tensor Imaging Data.

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BASIC CONCEPTS IN BRAIN ORGANIZATION, MAGNETIC RESONANCE IMAGING AND TRAUMATIC BRAIN INJURY

Brain Organization:

The human brain is composed of more than 100 billion cells, including neurons and supporting glial cells. Electrochemical signals are used to encode and transmit information within brain cells, with neurotransmitters used to transfer information from one neuron to another across synapses. Neurons have three key parts: (1) the dendrites, which bring information into the cell, (2) the cell body, which integrates the information, and (3) the axon, which takes information to the next cell. Within the brain, cell bodies often cluster together in what is known as gray matter. The outermost gray matter region of the brain is known as the cerebral cortex. Axons often travel together in tracts, in what is known as the white matter, where they connect different parts of the brain. Cells may be arranged differently in different parts of the cortex. This, along with the specific local and distant interconnections between cells gives rise to cortical specialization and networks – that is, the brain is partly organized into functional modules that are interconnected to support different calculations and behavioral abilities.

Magnetic Resonance Imaging

Magnetic Resonance Imaging (MRI) is a non-invasive technique for evaluating structure and function. By examining how the hydrogen protons of water molecules behave when placed within a steady magnetic field and bombarded by pulses of radio-wave energy, the MRI system can reconstruct a picture of the brain's anatomy. By altering the parameters and sequence of radio-wave pulses, it is also possible to explore the white matter interconnections between brain regions, brain biochemistry, metabolism, and hemodynamics.

Imaging evaluations in patients with brain injury often include T1-weighted, T2-weighted, FLAIR, SWI and DTI sequences. T1-weighted imaging provides exceptional gray-white matter differentiation and a detailed picture of brain anatomy. T2 and FLAIR imaging are especially useful for identifying edema and lesions in the white matter. SWI – susceptibility weighted imaging – is very sensitive to iron deposition associated with bleeding caused by stroke or small hemorrhages that may be caused by traumatic brain injury and other conditions. DTI – Diffusion Tensor Imaging -- examines the diffusion properties of water within the brain. DTI provides insight into the integrity of axonal tracts (which normally restrict the direction of water diffusion to be along [rather than across] the direction of the tracts).

Clinical, visual inspection of MR data can often reveal major pathologies like tumors, multiple sclerosis, and severe head trauma. Milder injuries, however, such as those associated with a concussion, rarely produce MR changes that can be seen on routine visual inspection. Quantitative analyses of regional brain volume (that is, the measurement of the size of various brain regions as visualized on T1-weighted images), and a quantitative assessment of the integrity of white matter pathways (as indexed by Fractional Anisotropy (FA) on DTI), offer more sensitive, objective evaluation of brain compromise.

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<u>Volumetric Analyses</u>

The brain is a 3-Dimensional structure that can be divided into small cubes, known as voxels. For MRI images, an automated computer algorithm can, in each voxel, measure the amounts of gray matter, white matter, and cerebrospinal fluid (CSF). The computer can also divide the brain into regions-of- interest, based on known structural-functional relationships. For example, the computer can determine which voxels comprise brain regions like the hippocampus or primary motor cortex and thereby calculate the total amount of brain tissue in these regions for each individual client. These methods provide quantitative measures of the actual volume of brain structures for each client, and they allow for a statistical comparison of the client's data with respect to data from a large group of neuro-typical subjects.

For volumetric analyses, Quantify uses SPM12 to correct for bias-field inhomogeneities, transform the data into MNI space, segment the data, and extract volume-related metrics. For region of interest volumetric analyses, MATLAB scripts are then used to divide the brain into 107 cortical and subcortical areas derived from TD-Brodmann (Lancaster, 2000) and AAL atlases (Tzourio-Mazoyer, et al., 2002). Figure 6 shows cortical regions from the TD-Brodmann atlas. Additional AAL atlas areas of interest include the basal ganglia and other subcortical motor nuclei, the thalamus, hippocampus, amygdala, and corpus callosum. To correct for variability in overall head/brain size, values are scaled for each individual prior to statistical evaluation.

The Quantify normative database is made up of volumetric and DTI data from more than 1,000 neurotypical subjects collected as control subjects across 36 research studies at the Mind Research Network (MRN) in Albuquerque, NM, on a Siemens 3.0 Tesla TIM-TRIO system using a 12-channel head coil.

Different physical scanners introduce some variability into volumetric measures, even when they are nominally of the same configuration. Therefore, to compare client data obtained on one scanner with normative control data obtained on a different scanner, there is a need to harmonize data metrics across sites, prior to statistical analyses. Several procedures are implemented to accomplish this. First, data acquisition parameters at the client scanner are set to be comparable to those used in the collection of the Quantify control datasets. Second, data analysis software algorithms, procedures, and processing pipeline used to assess client data and the Quantify control data are the same. Third, prior to statistical analyses, data metrics from the client scanner are harmonized to those of the MRN scanner using a human physical phantom scaling procedure (see Palicios et al., 2017; Venkatraman et al., 2015). Briefly, the same human subject was scanned on both the client and MRN machines. For volumetric scaling, a single multiplicative factor is derived for each ROI. These procedures allow client data to be validly evaluated with respect to the Quantify normative database.

MATLAB scripts are then used to perform statistical analyses Statistical evaluation of client data is based upon comparison of client metrics with sex and age-range matched control subjects drawn from the Quantify database, typically with an age range of +/- 10 years. Standard univariate procedures are used to generate Z-scores for each individual metric.

To account for multiple comparisons, a Benjamini-Hochberg procedure with a false discovery rate of 25% is additionally applied. All procedures are performed in a completely automated and objective manner free of any bias or client information other than gender and age. Table 1, below, provides specific data processing steps:

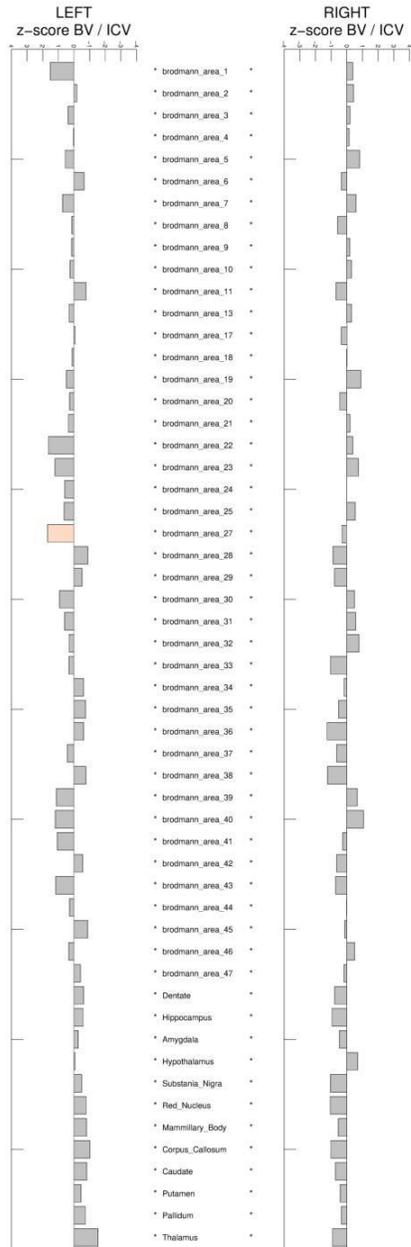$$\left(\, \Omega \, \mu^A \, \text{N} \, \tau \, \textit{í} \, f \, \gamma \, \right)$$

Table 1:

VOLUMETRIC STEPS	SOFTWARE	COMMAND/ACTIVITY
1. Convert Dicom data to NIFTI	MRICRON	DicomConvert
2. Reorient to AC-PC	SPM12	Reorient-to
3. Grey/White/CSF Segmentation	SPM12	Segmentation-NativeSpace
4. Grey/White/CSF Segmentation	SPM12	Segmentation-StandardSpace
5. Extraction of ROI volumes	MATLAB	AAL and TD-Brodmann Templates
6. Application of scaling factors	MATLAB	Site and region specific factors
7. Database Comparison Statistics	MATLAB	Gender/age-range match, BH correction
8. Plot Generation	MATLAB	Bar plots and scatter plots.
9. Table Generation	MATLAB/Excel	Data tables
10. Quality Control Check	Senior Neuroscientist	Review of data and QC metrics
11. Generation of spatial maps	Senior Neuroscientist	Presently done by hand in GIMP

Figure 1 provides an example of the bar plot outputs which show statistical results (steps 7 and 8).
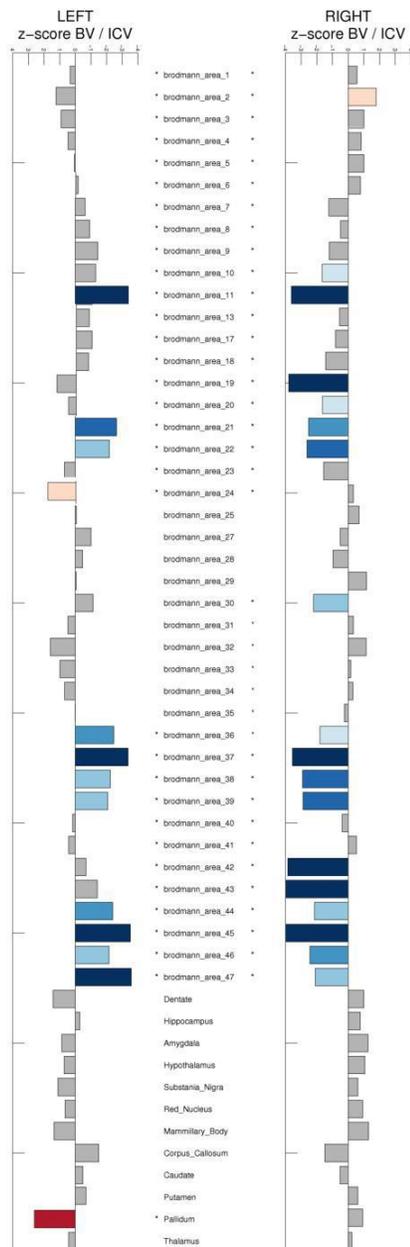
Figure 1: Main Bar Plot Outputs. Bar plots show z-score deviations from the normative database, in the indicated region. Examples are shown for a neurotypical control subject and an example client dataset. Gray indicates regions that are not statistically significant (-1.645 < z < 1.645; p>0.05). Red indicates that a region has an atypically large volume (z > 1.645; p<0.05). Blue indicates that a region has an atypically low volume (z < -1.645, p<0.05). To correct for multiple comparisons, a Benjamini- Hochberg procedure is used with a False Discovery Rate of 25%. A region is ultimately considered to show a statistically significant deviation from normal if, and only if, it is abnormal on individual, isolated evaluation(p<0.05) and it survives correction for multiple comparisons. Such regions are designated by an *. For the example control subject, left Brodmann area 27 has a z-score of ~ 1.71, which is above of p<0.05 threshold of z = 1.645, so the bar is colored red. However, this observation does not survive correction for multiple comparisons, so it is not ultimately considered to be significant (so no * is indicated). In contrast, the example client has 27 regions of significantly low volumes (blue bars with z-scores < -1.64) and three regions with abnormally high regional volumes. All of the client regions that are significant on individual isolated evaluation survive correction for multiple comparisons. That is, each of these 30 regions (27 low; 3 high) is ultimately considered to show statistically significant deviation from normal (as indicated by the *).

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Diffusion Tensor Imaging (DTI)

Diffusion tensor imaging provides insight into the integrity of white matter tracts by measuring the diffusion properties of water within the brain. For example, if you put a drop of ink in the middle of the ocean, the ink would spread (diffuse) in all directions equally. This is called isotropic diffusion. Now imagine that the ocean was filled with a bunch of pipes running in a common direction. In this case, the ink would spread in a preferred direction along the pipes, since it cannot easily penetrate into/across the pipes. When the ink diffuses in a preferential direction, this is called anisotropic diffusion. The brain is like the ocean filled with pipes – axons running within oriented fiber tracts. So, within the brain, water diffuses in preferred directions based on the local white matter anatomy. Using Diffusion Tensor Imaging the preferred direction of water movement within each voxel can be characterized by Fractional Anisotropy (FA), a value from 0 to 1, where 0 indicates isotropic diffusion and 1 indicates fully restricted diffusion in a single direction.

Typical diffusion tensor images color code the preferred directions of tracts, with color intensity indicating FA values. A process known as tractography can be used to reconstruct tract trajectories based upon FA values.

Just as was described for region-of-interest analyses in volumetric assessments, a computer algorithm can identify white matter tracts within the brain of each client and determine the average FA value for each tract. This client-specific value can then be statistically assessed with respect to a normative dataset.

For DTI, the FNIRT algorithm in combination with the DTIFIT tool in FSL is used to compute FA maps with SPM alignment to the MNI FA template and subsequent extraction of tract-based FA values within the 48 fiber tracts defined by the Johns Hopkins University MRI Atlas of Human White Matter (Mori et al., 2009). Table 2, below, provides the processing steps. For FA harmonization across scanners, a two-step procedure is used. As was the case for volumetric data, human phantoms are evaluated at both client and MRN sites. A global linear scaling factor is then derived by calculating the average FA value across all brain regions-of-interest. Then, a set of additional region-specific multiplicative factors is derived, with both the linear and multiplicative factors applied to the client data to achieve harmonization with the Quantify database. The Quantify analysis outputs include bar graphs and scatter plots similar to those provided for volumetric analyses, plus a demonstrative figure showing which tracts are abnormal.

Table 2:

DTI STEPS	SOFTWARE	COMMAND/ACTIVITY
1. Convert Dicom data to NIFTI	MRICRON	DicomConvert
2. Eddy Current and Motion Correction	FSL	eddy.qc
3. Calculation of Fractional Anisotropy	FSL	dtifit
4. TBSS normalization to standard space	FSL	FSL_reg/FNIRT
5. Extraction of ROI FA average FA	MATLAB	JHU template
6. Application of scaling factors	MATLAB	Site and region specific factors
7. Database Comparison Statistics	MATLAB	Gender/age-range match, BH correction
8. Plot Generation	MATLAB	Bar plots and scatter plots.
9. Table Generation	MATLAB/Excel	Data tables
10. Coloring of abnormal tract ROIs	Custom Code	
11. Quality Control Check	Senior Neuroscientist	Review of data and QC metrics

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