Building Brain Volume e-bank and a Platform as Surrogate Biomarkers

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Background:

In basic and clinical neuroscience, the in vivo MRI-derived quantitative characterization of the human brain, such as subcortical brain volumes are beginning to demonstrate important potential applications. Alterations in subcortical brain volumes are manifested in normal aging [1-3], Alzheimer's disease [4,5], Huntington's disease [6-12], and schizophrenia [13-16]. Longitudinal and cross-sectional imaging-based biomarkers of disease will likely be of great utility in better understanding brain disorders and in evaluating therapeutic efficacy [17,18]. The previous report in structural imaging studies have revealed that experience plays a role in sculpting the structure of the brain. Relative enlargement of functionally relevant brain regions has been shown to correlate with improved or better performance in domains as diverse as second language acquisition [19,20], musical ability [21], spatial navigational ability [22], and specific motor skills [23]. Moreover, in the case of spatial navigation and juggling, regional brain volume appears to be modulated by experience in a behaviorally meaningful manner, as individuals with the greater volume show better performance [24]. Overall, the data suggest that experience can modify brain structure and that morphometry is a valuable tool for studying human brain plasticity in vivo [25]. It would follow that sustained biases in behavior such as those mediated by culture could influence brain structure or function.

Age

The effects of age on different brain volumes have been well documented. Among them total gray or cortical gray matter [26-37], white matter[27, 28, 32, 34,37,38], hippocampus [30,31,36,39], amygdale [30,39], thalamus[37], pons [37,40,41,42], caudate nucleus[30, 43, 44], putamen [44], globus pallidus [44], cerebellum [30, 40, 41, 45,46], and ventricular spaces [37,39,44] were all well studied. While semi-automated techniques for the quantification of global gray and white matter are often used (e.g. [27,28]), exact measurements of specific subcortical structures are typically obtained by manually tracing their boundaries in MR images. This

requires high technical and neuroanatomical skills, and is quite time consuming. Thus, morphometric reports are usually limited to one or a few such structures. Knowledge of the relative age decline of different brain volumes is, therefore, limited by the use of different samples, scanning protocols and volumetric techniques.
With the advancement of computed technology, automated brain volume calculation is available.

Gender

The existence of sexual dimorphism in cerebral morphology has been reported. Many previous quantitative magnetic resonance imaging (MRI) studies of brain volume have shown that, while gray matter (GM), white matter (WM) and brain size are smaller in women than in men–even after statistical control for sexual dimorphism in body size[45-47], but the relative proportions of GM tissue volume were higher in women[48,49]. Such regional sexual dimorphism and higher GM/WM ratio in women in anatomical subregions have also been described with region of interest (ROI)-based methods [48,50,51]. Regions of significant sexual dimorphism in ROI studies have not been consistent because of intra- and interrater reliability issues and different ROI definitions. This may be due to time-consuming and also manual error. We can apply the computer aided automation measurement to verify the sexual dimorphism in Taiwanese people and compare to the western data.

Machine

Manual measurements are difficult, time consuming, and susceptible to rater bias in measurement of cerebral volume. The accurate and reliable measurement of subcortical brain volumes from MRI data is important factor and possible. It can take a trained anatomist several days to manually label a single high-resolution set of structural MR brain images. To facilitate efficient, operator-independent subcortical region-of-interest (ROI) quantification, several automated and semiautomated algorithms have been proposed, including atlas-based methods[52-57], tensor-based morphometry [58-59] and boundary shift integral methods [60-64]. Although the accuracy validation of automated segmentation methods has been performed against regional manual measurements derived from both in vivo and post-mortem brain scans[65,66], the influence of image acquisition and data analyses parameters on the reliability of the derived measures has received relatively little systematic investigation [60,61,66,67]. Furthermore, the measurement of reliability also provides a means for assessing the impact of measurement error on sample size requirements. Defining the reliability of subcortical morphometric methods is therefore important.

Reliability in MRI-derived automated morphometric measures can be influenced by several sources of variance, including subject-related factors, such as hydration status [68], instrumentrelated factors, such as field strength, scanner manufacturer, imaging magnetic gradients [69], pulse sequence, and data processing-related factors, including not only software package and version but also the parameters chosen for analysis [70,71]. All of these factors may affect the ability to detect morphometric differences between groups in typical cross-sectional studies (e.g., morphometric differences between two subject groups, where each subject is scanned once and all subjects are scanned on the same scanner). Longitudinal studies of normal development, aging, or disease progression face additional challenges associated with both subject-related factors as well as instrument related factors (e.g., major scanner upgrades, across-session system instabilities). For studies that combine data acquired from multiple sites it is critical to understand and adjust for instrument-related differences between sites, such as scanner manufacturer, field strength, and other hardware components. Thus, detailed quantitative data regarding the degree to which each of the factors outlined above contributes to variability in morphometric measures would be helpful for both study design and interpretation. Recent publications discuss such studies with regard to the reproducibility of cortical thickness measures [71] and tensor based-morphometry [66]. We shall compare the available data from different machine, different tesla, different acquisition pulse sequences, and also different timing, in order to understand the effect of such factors on the measurement of brain volume.

Leukoaraiosis

Cerebral small vessel disease (SVD) includes white matter lesions (WML) and lacunar infarcts and is a frequent finding on computer tomography (CT) and magnetic resonance imaging (MRI) scans of elderly people [72]. It is associated with vascular risk factors, such as hypertension, atherosclerosis, diabetes mellitus and atrial fibrillation[73-75]. In cerebral SVD symptoms are due to either complete (lacunar syndromes) or incomplete infarction (WML) of subcortical structures leading to accompanying complaints including the lacunar syndromes, cognitive, motor (gait) and/or mood disturbances [76]. The prevalence of WML and lacunar infarcts varies considerably across studies from 5-95% and 8-28% respectively, depending on the population studied and the imaging technique used [72,77]. There is evidence of an increased risk of cognitive decline, dementia, gait and balance disturbances and parkinsonism among individuals with SVD, although prospective studies are scarce [78-81].

However, individuals with a virtually identical WML burden on conventional Fluid

Attenuated Inversion Recovery (FLAIR) imaging present with a wide variance in cognitive and motor performance ranging from no complaints at all to subjective cognitive complaints and mild parkinsonian signs to dementia and parkinsonism. Apparently there are other factors that determine whether identical appearing WML on FLAIR lead to for example cognitive or motor decline in one person, while leaving others unaffected. One of the other factors could be the presence the coexisting manifestations of cerebral SVD on conventional MRI such as lacunar infarcts and cerebral microbleeds which might influence the cognitive and motor performance [82]. As identical appearing WML on conventional MRI are actually histopathologically heterogeneous [83], it could be that only the WML with a high loss of microstructural integrity are related to cognitive and motor impairment. It is also important to realize that only a small proportion of the white matter (usually less than a few percent) is affected by SVD, even among individuals with severe SVD [84]. As conventional MRI is not sensitive to early loss of microstructural integrity in the normal appearing white matter (NAWM), possible changes in this largest part of the white matter cannot be assessed [85,86].

We propose that we shall collection data of brain images from our routine examinations to:

1. Set up the effect of age on the brain in different cortical and subcortical regions with automated measurement of their thickness and volume. As well as the possibility set up the development of the different brain regions in time period.
2. Set up the effect of gender on the brain in different cortical and subcortical regions with automated measurement of their thickness and volume.
3. Set up the effect of different machine, imaging pulse sequences, aging of the machine, and different magnetic field in the measurement of the cortical and subcortical regions of brain.
4. Set up the effect of leukoaraiosis in different grades in the measurement of the cortical and subcortical regions of brain and their correlation with clinical manifestation.
5. Set up the effect of different neurodegenerative disease in the measurement of the cortical and subcortical regions of brain.
6. Set up the effect of destructive brain disease such as infarction, traumatic and post-operative encephalomalacia in the measurement of the cortical and subcortical regions of brain.

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Methods:

Cortical reconstruction and volumetric segmentation was performed with the Freesurfer image analysis suite, which is documented and freely available for download online (http://surfer.nmr.mgh.harvard.edu/). This software package used for a number of procedures.

Briefly, this processing includes motion correction and averaging[1] of multiple volumetric T1 weighted images (when more than one is available), removal of non-brain tissue using a hybrid watershed/surface deformation procedure [2], automated Talairach transformation, segmentation of the subcortical white matter and deep gray matter volumetric structures (including hippocampus, amygdala, caudate, putamen, ventricles)[3,4] intensity normalization, tessellation of the gray matter white matter boundary, automated topology correction [5,6], and surface deformation following intensity gradients to optimally place the gray/white and gray/cerebrospinal fluid borders at the location where the greatest shift in intensity defines the transition to the other tissue class [7,8].

Once the cortical models are complete, a number of deformable procedures can be performed for in further data processing and analysis including surface inflation [9], registration to a spherical atlas which utilized individual cortical folding patterns to match cortical geometry across subjects [10], parcellation of the cerebral cortex into units based on gyral and sulcal structure [11,12], and creation of a variety of surface based data including maps of curvature and sulcal depth.

This method uses both intensity and continuity information from the entire three dimensional MR volume in segmentation and deformation procedures to produce representations of cortical thickness, calculated as the closest distance from the gray/white boundary to the gray/CSF boundary at each vertex on the tessellated surface [8] The maps are created using spatial intensity gradients across tissue classes and are therefore not simply reliant on absolute signal intensity. The maps

produced are not restricted to the voxel resolution of the original data thus are capable of detecting submillimeter differences between groups.
Procedures for the measurement of cortical thickness have been validated against histological analysis [13] and manual measurements [14,15]. Freesurfer morphometric procedures have been demonstrated to show good test-retest reliability across scanner manufacturers and across field strengths [16,17].

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Materials:

Since the FreeSurfer software accept T1weighted images for processing, so the data available for our study will be done as retrospective process. Those qualified subjects received MR examinations in National Taiwan University Hospital since 2010 will be recruited. The exclusion criteria included; poor quality imagines such as motion or metallic artifacts, significant imaging distortion due to in-homogeneity of the magnetic field, significant structural anatomic distortion due to remarkable diseases or operative change, no T1-weighted images available for processing, and the data that is not accepted by the software. All these will be double checked by experienced neuroradiologists. For every study mentioned above, minimum of 500 subjects should be recruited for each group after evaluation and chart reviewed.

For the PC we used (16G ram, CPU Intel CoreDuo 2.8GhZ), it takes 8 to 24 hours for finishing the processing for 8 cases.

Statistical analysis

The relationships among cortical and subcortical measures (volume and thickness) and different parameters were examined with a vertex by vertex general linear model (GLM). A separate GLM was evaluated for each vertex to assess regional variation in each measure. The significance of contrasts of the regression parameters were computed using t-tests. In addition to p value maps, we created binarized maps demonstrating the unique and overlapping regional patterns of each effect measured.