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Examining brain volumetry and morphometry in relation to body mass index and coffee consumption: magnetic resonance imaging approaches

Ph.D. thesis

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Abbreviations

BMI – Body Mass Index

FA – Flip-angle

FOV – Field of view

FSL – FMRIB Software Library

GM – Gray matter

MR – Magnetic Resonance

MRI – Magnetic Resonance Imaging

ROI – Region of interest

TE – Echo time

TI – Inversion time

TR – Repetition time

VBM – Voxel-based Morphometry

Introduction

Several invasive or non-invasive methods are available to assess the possible functions of different brain areas in human. Before the era of modern imaging and electrophysiology, the possible ways to study the functions of different brain areas were mostly lesional models or direct electric stimulation of the cortex during neurosurgery. The number of available methods and methodologies has grown rapidly and by now, the non-invasive and minimal-invasive methods have more-or-less replaced the invasive ones. In this thesis, I will review two non-invasive magnetic resonance imaging (MRI) based methods - and present our novel findings based on these methods – which are suitable to track or compare brain volumetric or morphometric alterations. These methods are automated MRI volumetry (henceforth volumetry) and voxel based morphometry (VBM).

Technical background

Volumetry

There are a few software tools available (both commercial and freeware) to automatically process and evaluate MRI volumetry. Today, FreeSurfer (http://surfer.nmr.mgh.harvard.edu/) is one of the most often used software packages (set of software tools) to study the cortical and subcortical anatomy. It consists of a surface based and a volume based stream. In the first one, the applied automatic tools construct models of the boundaries between cortical white and gray matter and pial surface as well. Once we assessed the 3 main surfaces in every slice creating 3 separate surfaces in the three dimensional space, an array of anatomical measurements becomes possible, including cortical thickness, surface area, curvature, and surface normal at each point on the cortex. The second

(volume-based stream) has two main purposes, (i) to preprocess MRI volumes and (ii) to label subcortical tissue classes. The software offers the possibility to inflate and/or flatten the surfaces for improved visualization. The main advantage of FreeSurfer is that while this package runs reliably on good quality datasets, most parts of its pipeline are automated, which makes it ideal for use on large data sets.

Voxel-based morphometry

There are several VBM implementations, which may differ in some steps, while identical in others. I would like to present a general view on how the "optimized" VBM protocol is used in practice. The steps I will present are the ones used by the FSL-VBM script a member of FSL tools, freely available in the FSL software library. In the first step, the input images are sorted in a new subdirectory, the next step is to run the brain extraction on the images to remove non-brain tissues. This part of the pipeline can be customized to achieve the best possible results. The second step of the FSL-VBM protocol is to create the study-specific gray-matter template. For this, the brain-extracted images of every subject are segmented into gray-matter (GM), white-matter and cerebrospinal fluid. As the result of this registration a 4D image is generated containing the registered GM images. This is averaged to create the study-specific GM template at the isotropic resolution of $2x2x2mm^3$ in standard space. In the next step, the script will non-linearly register all the GM images to the study-specific template; the new 4D merged image will be smoothed and a non-parametric permutation based test will be applied to look for differences between the groups of the population or correlation between the population itself and the distribution of a measured parameter (e.g. daily caffeine intake or BMI).

Background literature review

Caffeine's main action – unlike other psychoactive compounds – is evoked via the adenosine receptors. Drury and Albert Szent-Györgyi were the first ones who demonstrated the cardiac effects of caffeine in 1929. Since then, it is well-known that adenosine receptors play a crucial role in cardiac and brain functions. Caffeine's main mechanism of action is blocking A_1 and A_{2A} adenosine receptors. Adenosine receptors are prevalent throughout the whole body and are important in many biological processes like neuronal functioning, inflammation signaling, cell proliferation, etc. Highly selective ligands and validated antibodies are available to precisely localize the A_1 and A_{2A} receptors in the brain. A_{2A} receptors are mainly located in the basal ganglia, caudate putamen, tuberculum olfactorium, olfactory bulb, nucleus accumbens and hippocampus, but at lower levels they are also expressed in the rest of the brain, while A_1 receptors are present in almost all parts of the brain, but can be primarily found in the hippocampus, cerebellum and cerebral cortex. Recent studies found that there is a modest inverse association between coffee and all-cause mortality and this association can be mainly explained by a reduction in deaths due to cardiovascular disorders. The association between lower mortality and higher coffee consumption is stronger in women than men. There is an association between higher coffee consumption and lower risk for stroke, Parkinson disorder, Alzheimer's disease, and dementia. Also, dysfunction of memory performance is normalized by chronic caffeine consumption, which is documented in both epidemiological as well as in animal studies. Thus, coffee seems to have beneficial effects on cardiovascular health, and it may have a role in treating or preventing some brain disorders and memory impairment. The above discussed properties of caffeine and its

beneficial effects carry the question of weather caffeine itself is associated with any kind of visible and measurable difference in brain morphology or not. Although the required methodologies are available to “extract” this information from structural MRI images, there were no previous studies trying to establish such association.

38 years ago, an editorial was published in the Lancet that named obesity as “the most important nutritional disease in the affluent countries of the world”, yet its prevalence has sharply increased during the last four decades.

Obesity is simply defined as a condition of abnormal or excessive fat accumulation in adipose tissue, to the extent that health may be impaired. Obesity has numerous health consequences ranging from the increased risk of premature death to many non-fatal but serious debilitating issues that have adverse effect on the quality of life. Obesity is the major risk factor for several non-communicable diseases such as non-insulin dependant diabetes mellitus, cardiovascular diseases, cancer, etc. and associated with various psychosocial problems in industrialized countries. The body mass index (BMI), or Quetelet index, is a heuristic approximation for human body fat based on an individual's weight and height, BMI=weight (in kg) / height^2 (in meters). During the century-long usage of the index, studies based on large populations and long follow-up durations have demonstrated a relationship between elevated BMI and mortality from all causes, especially from vascular disorders. Obesity is a risk factor for many brain disorders including cerebrovascular, Parkinson’s and Alzheimer’s diseases. These brain disorders as well as hypertension alone are associated with structural brain abnormalities even in the pre-clinical phases. Nearly half a dozen studies were carried out with different MRI methods (volumetry, VBM, MR spectroscopy) to find an association between BMI and different properties

of the brain, including metabolite concentrations, gray matter density, volumes, etc. However, contradictory results were found, mainly because these studies examined relatively old subjects, thus were inappropriate to be controlled for all possible confounding factors.

Aims

This thesis, besides giving a detailed overview of the two methods, has two main goals:

1, To investigate the relationship between coffee consumption habits and brain morphology characterized by the volume of total brain, neocortex, and subcortical brain structures (basal ganglia, hippocampus, accumbens region) where caffeine is supposed to act.

2, Examine the relationship between BMI (body mass index) and the volumes of the structures within the reward system (hippocampus, amygdala, accumbens, caudatum, putamen, and orbitofrontal cortex) showing a prominent role in the food/energy intake regulation.

Subjects and methods

The subjects were recruited via an advertisement placed on notice boards across the University of Pécs. 45 (aged 23.2±2.7 years) healthy right-handed, Caucasian, female, graduate or postgraduate university students were recruited for the Caffeine-study, while 103 (44 male and 59 female, aged 23.34±2.67 years) healthy, right-handed, Caucasian university students were included in the BMI-study. Mutual exclusion criterion were left-handedness, drug- and/or alcohol abuse, neurological disorders, etc. Each of them completed the same questionnaire regarding caffeine consumption (coffee, cola, tea, caffeine tablets, chocolate, and energy

drinks) or feeding habits, smoking, alcohol consumption, medications and health issues. The questionnaires were evaluated and the results were summed in SPSS 17.0 (SPSS Inc., Chicago, IL) for further processing. All measurements were performed in The Diagnostic Centre of Pécs, on a 3 T Siemens Magnetom TRIO human whole-body MRI scanner (Siemens AG, Erlangen, Germany) with a 12-channel head coil. For volumetric analysis, a T1-weighted axial MPRAGE sequence was used to measure with the following parameters: TR/TE/TI:1900/3.41/900 ms, FOV: 240 mm, 256×256 matrix, slice thickness: 0.94 mm, (0.94×0.94 mm in plane resolution), slice number: 160, FA: 9°, bandwidth: 180 Hz/pixel, FOV Phase: 87.5%. Freesurfer was used for volumetric analysis, while FSL-VBM was used for whole brain and ROI-based VBM analysis.

Results

The results showed that both caffeine intake and coffee consumption have a u-shape association with the hippocampal volume. Based on caffeine intake and coffee consumption, the subjects were sorted into three groups (low, moderate, high caffeine intake or coffee consumption). Both the daily coffee consumption and the daily caffeine intake (that contains caffeine intake from coffee and all other sources) showed a significant correlation with the hippocampus, in such way that subjects with low coffee consumption or caffeine intake have larger hippocampus compared to the “moderate” group ($p=0.002$ and $p=0.003$ for coffee consumption and caffeine intake respectively). The “high” groups also showed significantly larger hippocampus, compared to the “moderate” groups ($p=0.013$ and $p=0.023$, for coffee consumption and caffeine intake respectively). The origin of this volume difference was localized by ROI-based VBM analysis. The source of the volumetric difference was the head

region of the hippocampus. Because of many reasons, the two sexes were analyzed separately, during the examination of the BMI and brain morphology. As a result of our examinations, we concluded that the relative volume of the right amygdala significantly correlates with the BMI in men ($R=0.52$, $p=0.001$). This relationship was much more pronounced in the overweight population (BMI > 25 Kg/m^2) $R=0.96$ $p<0.001$).

Discussion

To our knowledge this is one of the very first studies, exploring the association between brain morphology and coffee consumption or caffeine intake in humans using MR imaging. The most robust caffeine-induced changes in animals affect the hippocampus: the very same structure which was found to be altered in our study. Our study suggests that coffee consumption might cause morphological alterations in the human hippocampus (although causality can not be established). We suppose that our study might potentially help in understanding function-related morphological changes in the human brain.

The main finding of our study is that the volume of the right amygdala showed a correlation with the BMI although it may be true only for the overweight male population. We investigated a young and healthy population; therefore, it is very unlikely that our findings are the consequences of obesity-associated brain disorders. Our findings may suggest that an association between body weight and the morphological changes in the reward system can be demonstrated by MRI. Thus, our study suggests further evidence to the fact that food intake, body weight regulation and the pathophysiology of obesity are different in the two sexes. Although the demonstrated methods can be effectively used in basic research, they also have emerging clinical importance.

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Publications

Number of publications in peer-reviewed journals: 13
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