The Minnesota Women Healthy Aging Project

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The Minnesota Women Healthy Aging Project is an effort to understand how the brain changes with age and why some brains are more resilient than others. Using a unique methodology, researchers are evaluating the brain status of a number of women by taking multiple, multimodal measurements and relating those measures to cognitive abilities, language skills, and genetic information. The goal is to create a comprehensive databank that will provide information by which to characterize brain status, assess changes over time, and associate them with genomic makeup, cognitive function, and language ability. The project was initiated in 2010 and is being conducted through the University of Minnesota and the Minneapolis Veterans Affairs Health Care System. This article describes the project, which is the first of its kind, and its progress thus far.

The brain is the most complex organ in the body. It consists of more than 100 billion cells. (Compare that with the human population, which is only 7 billion.) Unlike the cells of any other organ, brain cells interact extensively with each other every millisecond. The brain's nature as a dynamic, massively interconnected network is the basis for its ability to process information. It is also the basis for learning, memory, and plasticity. These latter properties are formalized as changes in brain function, and they take place throughout our lives. These changes are cumulative, as illustrated by how our education, memories, habits, and injuries build on each other, whether we like it or not. Our understanding of the brain's cumulative nature forms the basis for all sorts of interventions, giving us hope that they will have a lasting effect.

The changes that take place in our brains are highly individualized and are influenced by our genetic/genomic makeup, environmental influences, and disease processes. We know that the manifestation and impact of brain disease vary from one individual to another. For example, acute brain infection or the formation of Alzheimer's plaques can affect different people quite differently. However, we do not understand the underlying mechanisms behind these changes.

One thing we do know, however, is that the effect of environmental insults can vary according to the age of the individual. Aged brains are more vulnerable to these insults, as are the developing brains of infants and adolescents. In fact, the concept of brain vulnerability now has a prominent place in our thinking about susceptibility to disease and disease prevention.

The $64,000 question is how to assess brain vulnerability for specific insults and diseases at given points in the lifespan. Such knowledge would allow for potential intervention—either preventing the occurrence of insults, protecting brain function (eg, by pharmacotherapy), or changing lifestyle and the social milieu.

Understanding how the brain changes with age and why some brains are much more resilient than others is one of the primary goals of the Minnesota Women Healthy Aging Project (www.brain.umn.edu/mnwomen.html). The project is the first attempt to comprehensively evaluate the status of the brains of a number of individuals over time using multiple, multimodal measurements and relate those measures to cognitive, language, and genetic information. The goal is to create a comprehensive databank containing information that can be used to characterize brain status over time.

About the Project

The project was initiated in 2010 with the support of a group of women from Minnesota and various foundations as well as the University of Minnesota and the Minneapolis Veterans Affairs Health Care System. It has a cross-sectional and a longitudinal component. One hundred new women ages 30 to 100-plus years of age will be studied each year; those women

will be re-evaluated annually. More than 100 women have been studied to date.

Participants are recruited from the Women Veterans Comprehensive Health Center of the Minneapolis VAHCS. Upon arrival at the Brain Sciences Center at the Minneapolis VAHCS, all are asked to provide informed consent. The women then go through a number of tests including a cognitive assessment, a speech evaluation, resting-state magnetoencephalography (MEG), and MR imaging. In addition, blood is drawn for DNA analysis. The cognition and language assessments and the MEG test are repeated every year; the MR tests are taken from subjects younger than 70 years old and are repeated every five years; blood is drawn only once. The protocol has been approved by the appropriate institutional review boards.

Cognitive function is assessed using the Montreal Cognitive Assessment (MoCA). It consists of 30 questions that test visuospatial/executive functioning, ability to name objects, memory, attention, general language skills (fluency), abstraction, delayed recall, and orientation.

Speech and language are assessed using a new technique.[1] Spontaneous ("tell us a story") and evoked ("describe this picture") speech are recorded at 44.1 kHz for one minute using state-of-the-art CD-quality audio recording equipment. Sound spectrograms are then analyzed for speech structure and language use, and various quantitative measures are derived for further analysis and association with other data.

Magnetoencephalography data are acquired at 1,017 kHz for one minute while the subject rests using a high-spatial-density system with 248 axial gradiometer sensors. From these data, 30,628 synchronous neural interactions (SNIs) between all possible pairs of sensors are computed. The SNI data reflect communication among neuronal populations; these interactions are the essence of brain function. Information about SNIs forms the basis for evaluating functional brain health and has been shown to identify certain brain diseases (eg, functional abnormalities in persons with post-traumatic stress disorder).[2-4]

Structural magnetic resonance imaging (sMRI) is done to assess gray-matter volume. The data are acquired using a Philips 3T Achieva XL magnet with a SENSE 8 channel head coil. Approximately 500,000 voxels per brain are analyzed. In the first analysis, the volume of about 100 separate brain regions is calculated using FreeSurfer software (www.surfer.nmr.mgh.harvard.edu). This provides a coarse-grain, volumetric analysis of areas of the brain. In the second analysis, called voxel-based morphometry, the density of each voxel is assessed for a fine-grain analysis of each area.[5] Typically, gray-matter volume decreases with age but at rates that are different for different people, for different areas of the brain, and for men and women. In that sense, one can talk about "gray-matter age" versus chronological age. A person may be 68 years old but have the gray-matter volume of a 50-year-old. Defining brain age based on measurements (as contrasted with chronological age) is a pervasive theme in this project.

Diffusion tensor imaging (DTI) is used to assess the integrity of the white matter and to visualize major tracts for rough anatomical connectivity. Each voxel is assigned a fractional anisotropy value. Typically, low fractional anisotropy values indicate damage to the white matter.

Functional MRI (fMRI) is used to assess blood-oxygenation level dependent activation. This measure indirectly reflects local brain activity. Data are acquired every two seconds for five minutes while the subject is at rest. From these data, a rough measure of functional resting-state connectivity is computed.[6] This measure informs us about the nature of interactions between various areas of the brain. The MEG measurements are the gold standard, as they directly reflect neural activity. The resting fMRI measurements are second-best, as they only indirectly relate to neural activity; but they are easily accessible because MRI machines are readily available.

Magnetic resonance spectroscopy (MRS) is used to roughly assess neuron health. Typically, we consider the ratios of N-acetyl aspartate, glutamine+glutamate, and choline over creatine.

Participants also are asked to provide demographic and lifestyle information. It is well-known that educational level, exercise, smoking, medical conditions such as hypertension, diabetes, and high cholesterol can affect cognitive function and increase the risk for development of dementia.[7] Therefore, taking these factors into consideration is an important aspect of the project.

Finally, DNA is assessed for specific brain-related polymorphisms that are related to cognitive function[8,9] such as the alleles for apolipoprotein-E, brain-derived neurotrophic factor, and catechol-O-methyl transferase.

Data Management

All data will be entered in a relational database. Although the database will contain approximately 30 GB of data per subject, it will be set up in a way that will facilitate data extraction and calculation of targeted relations among variables of interest. Large-scale data analysis will be supported by the high-performance computing cluster at the Brain Sciences Center. The complexity of this project requires the use of informatics approaches.

One focus is the derivation of scores that will express the status of an individual subject with respect to several domains. Scores for three domains will be derived initially, and more will be added as needed. The first is relative score (R-score). Essentially, it reflects how healthy a brain is compared with others in the same sex and age group. The second is normative score (N-score). The N-score reflects how healthy a brain is as compared with a younger one. The third is the global Euclidean distance score (G-score), which is an indication of how similar two brains are over all the measurements.

A major challenge will be finding effective and efficient ways to combine measures of brain structure and function with information about cognition, language, and genetics to characterize brain status over time. Although the Minnesota Women Healthy Aging Project's focus is women, it is anticipated that it will one day be extended to men and that the data could also provide insight

into whether there are differences between various ethnic and racial groups.

Conclusion

Brain science is on the cusp of a new era. For the first time ever, the structure and function of the brain can be assessed comprehensively; brain health can be promoted; and susceptibility to brain disease at various stages of life can be assessed, modified, and even forecasted. All of this has become possible because of advances in brain imaging, biomedical engineering, molecular neurobiology, and genomics. In addition, we are gaining greater understanding of how environmental insults can affect the brain and which brains are more vulnerable to those influences, as well as the importance of early intervention for disorders of the brain, the feasibility of prevention of such disorders, and the possibility of altering brain function to ameliorate disease symptoms and promote brain health. The challenge now is to combine the information we have in ways that will help us make sense of it. When we do, we will have an unprecedented understanding of how the brain changes during the lifespan. **MM**

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