Published in final edited form as:

Neuroimage. 2009 February 1; 44(3): 914–922. doi:10.1016/j.neuroimage.2008.07.062.

The Myth of the Normal, Average Human Brain—The ICBM Experience: (1) Subject Screening and Eligibility

John C. Mazziotta^{1,3,4,5}, Roger Woods^{1,2,5,6}, Marco Iacoboni^{2,5,6}, Nancy Sicotte^{1,5}, Kami Yaden^{1,6}, Mary Tran⁶, Courtney Bean⁶, Jonas Kaplan^{2,6}, Arthur W. Toga^{1,3,5}, and Members of the International Consortium for Brain Mapping (ICBM)

¹ Department of Neurology, David Geffen School of Medicine at UCLA, Los Angeles, CA

² Department of Psychiatry, David Geffen School of Medicine at UCLA, Los Angeles, CA

³ Laboratory of Neuroimaging, David Geffen School of Medicine at UCLA, Los Angeles, CA

⁴ Department of Radiological Sciences and Pharmacology, David Geffen School of Medicine at UCLA, Los Angeles, CA

⁵ Brain Research Institute, David Geffen School of Medicine at UCLA, Los Angeles, CA

⁶ Semel Institute, David Geffen School of Medicine at UCLA, Los Angeles, CA

Abstract

In the course of developing an atlas and reference system for the normal human brain throughout the human age span from structural and functional brain imaging data, the International Consortium for Brain Mapping (ICBM) developed a set of “normal” criteria for subject inclusion and the associated exclusion criteria. The approach was to minimize inclusion of subjects with any medical disorders that could affect brain structure or function. In the past two years, a group of 1,685 potential subjects responded to solicitation advertisements at one of the consortium sites (UCLA). Subjects were screened by a detailed telephone interview and then had an in-person history and physical examination. Of those who responded to the advertisement and considered themselves to be normal, only 31.6% (532 subjects) passed the telephone screening process. Of the 348 individuals who submitted to in-person history and physical examinations, only 51.7% passed these screening procedures. Thus, only 10.7% of those individuals who responded to the original advertisement qualified for imaging. The most frequent cause for exclusion in the second phase of subject screening was high blood pressure followed by abnormal signs on neurological examination. It is concluded that the majority of individuals who consider themselves normal by self-report are found not to be so by detailed historical interviews about underlying medical conditions and by thorough medical and neurological examinations. Recommendations are made with regard to the inclusion of subjects in brain imaging studies and the criteria used to select them.

Over the course of the last 100 years, there have been a number of attempts to develop atlases that describe human brain anatomy, both as an end in itself and also as a tool for organizing and referencing new neuroscience information [Talairach and Tournoux, 1988; Bailey and von

Submitted by: John C. Mazziotta, M.D., Ph.D., Director, Brain Mapping Center, Chair, Department of Neurology, UCLA Brain Mapping Center, 660 Charles E. Young Drive South, Los Angeles, CA 90095, Email: mazz@loni.ucla.edu, Phone: (310) 825-2699, Fax: (310) 794-7406.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Bonin, 1951; von Economo and Koskinas, 1925; Friston et al., 1994, 1995]. These efforts have provided new and useful information for neuroscience research as well as for clinical applications. Nevertheless, the large and previously undefined variance of brain structure and function, across individuals in the population, limits the range of applications for past atlases. This is because the early atlases [Talairach and Tournoux, 1988; Bailey and von Bonin, 1951; von Economo and Koskinas, 1925; Brodmann, 1909] were based on the analysis of a single brain or, at best, a few. Thus, there was only limited data available to capture and quantify this variance for the brain as a whole or for its subparts.

In 1993, the International Consortium for Brain Mapping (ICBM) was formed to develop a probabilistic atlas and reference system for the normal brain in adult individuals between the ages of 18 and 90 [Mazziotta et al., 1995; Mazziotta et al., 2001a, b]. This effort has involved participation of laboratories on four continents and the collection of data from thousands of normal human subjects to be assembled and distributed as a probabilistic reference tool and atlas with many potential applications. The concept that a normal, average human brain could be identified was a basic premise of the group. Time and experience have taught us otherwise. We have learned that it is unrealistic to think that a specific brain can be identified as the mean point in any distribution of the variance for the whole brain or its subparts in a population. Two critical factors are important in considering this issue: subject selection/exclusion and the manner by which the variance of brain structures is distributed anatomically in the human population.

This is an important realization. The carefully defined phenotype of the human brain can be used for clinical diagnostic purposes, as a template to which research studies can be applied, as a source of reference on brain structure and function and its probabilistic variance as well as a means for defining the brain's phenotype in order to discover genotypic and behavioral relationships with it [Gurnett and Trevathan, 2006].

This report focuses on defining the criteria and finding the subjects to be included in such a database that represents the normal, average human population across the adult lifespan. Identifying “normal” subjects for human imaging research occurs on a daily basis, worldwide. How good are we at identifying normal subjects? The answer to this question must begin by defining the illusive term “normal.” The definition of normal is basically an opinion that is arbitrarily defined by consensus, often for convenience and frequently debated [Cutler et al., 1984; Sokoloff, 1975]. In the ICBM Consortium we faced the same situation. Unlike many imaging studies reported in the literature, we chose not to rely solely on self-reporting of a subject's background medical information and demographics but rather, to rigorously interview and examine subjects to verify, as best as possible, those features in their backgrounds which might place them outside of the stringent definition of “normal” that we adopted. In defining the set of exclusion criteria, we drew upon previous experience, reports and guidelines [Cutler et al., 1984; Shtasel et al., 1991], we focused on rejecting subjects with historical or physical findings that had the potential to affect brain structure, in particular, and brain function, as well. Subjects were excluded not only for neurological, neurosurgical and psychiatric disorders but also for systemic problems that could affect the nervous system.

Defining a subject group for a brain imaging study, for inclusion in a normative database or for any research purpose, requires careful definition of the subject inclusion and exclusion criteria as well as meticulous procedures for measuring the validity of historical information obtained from such subjects. To not do so contaminates the resultant data that is collected, increases its variance and, potentially, results in erroneous conclusions. With our goal of developing a probabilistic atlas and database of the normal brain across the adult life span, inclusion of individuals with medical, neurological or psychiatric abnormalities, had the

potential to skew the resultant database and alter the probabilities for brain structure and function outside of those defined by criteria set forth for our definition of “normal.”

In this report, we focus on the most recent screening of subjects for the program at one site (UCLA) as representative of our experience throughout the consortium.

Methods

All subjects who participated in this project as well as all of the screening materials, exclusion criteria and procedures for applying them were approved by the UCLA Institutional Review Board. All subjects signed an informed consent describing the process, risks and benefits. They were also given a Subject's Bill of Rights.

The process of selecting subjects for inclusion in the study had three phases. In the first step, subjects who responded to advertisements that publicized the project were screened by telephone. In the second step, those who passed the telephone screen received a series of physical examinations and in-person interviews. The third and final step was the imaging of those subjects who passed phase 2 and is the subject of a separate publication.

A. Definition of “Normal” and Exclusion Criteria

The overall philosophy of defining the exclusion criteria for the cohort to be entered into the ICBM database and reference system was that included subjects should be unrelated and devoid of underlying medical, neurological, neurosurgical or psychiatric disorders that would skew the probabilistic distributions for structural or functional brain anatomy. This required the elimination of subjects with any known underlying medical, neurological, neurosurgical or psychiatric illnesses. We also excluded subjects who had a defined headache syndrome, implanted or embedded metal or electronic devices, trauma to the nervous system or excess alcohol use (Table 1). We required that subjects not have been exposed to anesthesia in the previous year, with some minor exceptions, and that they had not had any neurosurgical, cerebrovascular, oncological or cardiac surgery at any time in their life, even if it was performed with local anesthesia. The use of prescription, over-the-counter or illicit drugs was a basis for exclusion with the exception of the occasional use of drugs for disease prevention and as specified in Table 1. In the physical examination, subjects had to have a systolic blood pressure ≤ 140 mm Hg and a diastolic blood pressure ≤ 90 mm Hg [Pickering et al., 2005]. There were also criteria for pulse, oximetry, and visual and auditory acuity (Table 2). On physical examination, subjects were excluded if they had stigmata of alcohol or IV drug use, evidence of chronic or acute systemic disorders, surgical scars indicative of an exclusionary procedure not revealed in the history, a mini-mental scale [Folstein et al., 1975] score of less than 28 or any abnormal neurological signs.

We debated whether to extend these exclusion criteria further, considering the elimination of subjects with hypercholesterolemia, diabetes mellitus, very high or low body weights as well as those who have first degree relatives with psychiatric disorders thought to have genetic contributions (e.g., major depression, autism, schizophrenia). Because of practical and financial considerations, these factors were not used for exclusion but some were recorded and entered into the database for possible future analyses.

B. Telephone Screening

The purpose of the telephone screening was to eliminate as many subjects as possible who would not qualify, thereby saving the time and subject burden of interviewing and examining individuals who could be eliminated by an efficient, telephone-based process. The general structure of the telephone interview and the specific background and medical screening

questions associated with it are provided in Table 3. In addition to providing the general background about the purpose of the study, the time commitments, procedures, payments and confidentiality issues, the subjects were asked their age, primary language and their visual acuity for near objects, as part of the scanning process involves reading small print during fMRI studies. The medical screening questions focused on the use of medications, medical, neurological or psychiatric disorders, inherited nervous system diseases and practical matters that would obviate or complicate scanning such as dental braces or claustrophobia.

In most cases, subjects were either eliminated by this screening process or advanced to the next phase of screening, the in-person interview and physical examination (Tables 1 and 2). In some cases, however, subjects were uncertain about how they should respond to a question. These individuals were given the option of having a second telephone conversation with a participating physician investigator of the study. If they declined, they were excluded. If they accepted, the investigator would further explore and verify whether their answers to questions that they deemed ambiguous qualified them for further evaluation or excluded them.

C. In-Person Interviews and Examinations

Potential subjects were scheduled for this phase of the study and, at this point, signed informed consent materials. They then were evaluated in-person with a structured medical history interview. The details of the exclusion criteria associated with medical history are listed in Table 1.

Subjects who were not eliminated by the interview and history then had a physical examination including the measurement of blood pressure, pulse and oximetry. A general medical examination was conducted as well as a neurological examination including mental status testing. Lastly, subjects were tested for auditory and visual acuity. The exclusion criteria based on physical examination findings are provided in Table 2.

Table 4 lists historical and physical data that was collected but not used as exclusion criteria. These data were collected because there was the possibility that relationships between these variables and brain structure or function might be identified in the future and, as such, it would be useful to have such information in the database to perform correlational studies. These data included the history of a first degree relative with presumed inherited psychiatric disorders, the calculation of body mass index [Gazdzinski et al., 2008; National Heart, Lung and Blood Institute, 1998], abdominal girth, a blood sample from which DNA was extracted and stored for future phenotype-genotype studies, and a battery of neuropsychological and handedness tests (Demographic And Neurocognitive Inventory—DANI—http://ric.uthscsa.edu/icbm_dani/).

Individuals who passed the in-person interview and physical examination were then approved for inclusion in the imaging component of the program. Subjects with abnormal structural brain imaging by MRI were excluded by separate criteria and will be described in a separate publication.

D. Data Analysis

Statistical analysis of the results of subject screening employ the use of a 2×2 table with Fisher's Exact Test performed on a statistical website (<http://home.clara.net/sisa/index.htm>).

Results

In response to newspaper and other advertisements promoting participation in this study, 1,685 individuals responded and participated in the telephone interview. Of those callers, 532 individuals passed the phone-screening phase of the study. Thus, only 31.6% of those

interviewed qualified based on the brief and efficient telephone screening. Of the 532 individuals who qualified for the in-person history and physical examinations, 184 failed to schedule or keep appointments for in person screening. Of the remaining 348 potential subjects, 180 passed the second phase of the screening process involving in person histories and physical examinations and were eligible for scanning (Figure 1). Thus, only 51.7% of those individuals who passed a relatively extensive telephone screening process and participated in the in-person testing, actually qualified for scanning. This represents 10.7% of all individuals who answered the original solicitation advertisement which clearly stated that the subjects had to be healthy.

The reasons for excluding subjects based on in-person histories and physical examinations are provided in Figure 2. The percentage of subjects excluded generally increased with subject age (Figure 2C). The most common exclusion factor was high blood pressure. The next most common factors were abnormalities on neurological or medical examinations. A minority of individuals were excluded because of illicit drug use, mini-mental scale scores of less than 28, poor auditory acuity, medication use, embedded metal or their refusal to sign the informed consent. The distribution of exclusion causes was roughly similar between men and women with the exception of blood pressure where a significantly greater number of men were excluded (47 out of 184 men versus 20 out of 164 women, $p < 0.001$) (Figure 2B). The distribution of subjects excluded for high blood pressure by age is shown in Figure 3. Most subjects excluded because of high blood pressure were between the ages of 40 and 80 with the greatest number occurring in the sixth decade of life. The average values for systolic and diastolic blood pressure by age groups in subjects included in the study or excluded because of high blood pressure or other causes are listed in Table 5. Some subjects were excluded for reasons other than high blood pressure but are not included in this table because they were eliminated from the study before their vital signs were taken (based on historical features during the in-person interview). Four subjects in the high blood pressure group were also eliminated prior to measuring their blood pressure because they revealed during the interview that they were on anti-hypertensive medications (despite being asked about medication use during the telephone screening) and, thus, were excluded because of high blood pressure by virtue of the interview rather than the physical finding. These differences are noted in Table 5.

Discussion

Many human brain imaging studies, particularly those involving normal subjects, rely on self-reporting as a means of identifying “normal” individuals. To determine how much attention to detail is provided in the evaluation of normal subjects or controls, a literature review was undertaken. Two years of published manuscripts (2005 and 2006) from *NeuroImage* were reviewed to identify those that included normal subjects either as the primary participants or as controls for a reference group. A total of 474 manuscripts were reviewed. While many manuscripts were vague about these procedures, it was clear that the vast majority (~75%) either relied on self-reporting or did not mention the methods for screening these subjects at all (Figure 4). 24.1% performed in-person histories and approximately 7.4% included neurological and general medical examinations of their subjects. Thus, detailed screening of subjects for experiments requiring normal controls was limited to self-reporting or not considered worthy of attention to describe methodologically. This underscores the theme of this paper, namely, that the proper selection of normal subjects and control groups is a vital part of the experimental design in neuroimaging studies and that attention to detail and validity of results must be ensured by in-person evaluation in terms of history and physical examination.

In the ICBM project, we used an extensive set of exclusion criteria and a much more carefully defined definition of the “normal” state. Such definitions are always arbitrary and typically devised through practicality and convenience, usually by consensus of the participating investigators. That was the case for this project as well. Nevertheless, an extensive list of

exclusion criteria were agreed upon to better ensure that the resulting data set would include individuals who did not have previous or current medical factors that might affect brain structure or function.

Even in this more tightly defined situation, subjects who had disorders that we wanted to omit could still have been included. One example is occult hyperlipidemia. We eliminated individuals who were on cholesterol lowering agents but did not perform serum lipid profiles to identify undiagnosed subjects. The same is true for diabetes mellitus. In addition, we relied on self-reporting with regard to alcohol consumption and illicit drug use. While some of these individuals could be identified by the physical stigmata associated with long-term use of these agents (e.g., needle track marks, ascites, etc.), such physical findings would only be evident in advanced cases. It was also unlikely that we could detect undiagnosed psychiatric disease unless the patient was manifesting overt signs of the disorder during our contact with the subject. Despite these shortcomings, the battery of screening procedures employed ensures a much higher degree of valid criteria for including “normal” subjects than self-reporting would enable.

The screening process was designed to eliminate individuals with known medical, neurological, neurosurgical or psychiatric disease. It also eliminates individuals who chronically utilize prescription, over-the-counter or illicit drugs with the exception of drugs used as prophylaxis for infectious disease in travelers, altitude or motion sickness, medications for needle stick injuries or vaccinations. We also accepted subjects who were on antibiotics more than a month prior to evaluation and, under certain circumstances, non-steroidal anti-inflammatory drugs, pain medications or sedatives (Table 1). We did accept the use of contraceptive agents and hormone replacement therapy as well as multi-vitamins, aspirin and acetaminophen were acceptable if used occasionally.

Subjects were eliminated for any procedure requiring general anesthesia in the previous year, with certain limited exceptions, and any neurosurgical, cerebrovascular, oncological or cardiac surgery irregardless of the anesthesia used. These criteria plus thorough general medical and neurological examinations would eliminate almost all subjects with underlying medical, neurological or neurosurgical disorders. Potential subjects with defined headache syndromes were also eliminated because of their association with structural or functional brain abnormalities [Kruit et al., 2004, 2005, 2006] despite the fact that the clinical significance of such changes on MRI is a matter of ongoing debate. By historical criteria we eliminated subjects with head trauma or injuries to the spinal cord and peripheral nerves as well as those with implanted metal or electronic devices that would obviate scanning. The careful measurement of blood pressure, pulse, oximetry as well as visual and auditory acuity eliminated other risk factors. This is particularly true for high blood pressure and the resultant potential for cerebral ischemic changes [Vermeer et al., 2003a, 2003b; Jeerakathil et al., 2004].

Findings on neurological exam that typically excluded subjects age 60 or greater included mild parkinsonian features, tremor, peripheral neuropathy or evidence of old central nervous system injury possibly related to previous but undiagnosed cerebral infarction. Even minimal signs on neurological exam are associated with structural brain changes [Dazzan et al., 2006]. Physical examination also provided the opportunity to eliminate subjects that had stigmata of alcohol or illicit drug use, cardiac murmurs, carotid bruits or scars from previous surgery not reported during the in-person interview.

While subjects may pass through historical and physical evaluations without detecting evidence of medical or neurological disorders, it is well accepted that this does not ensure that abnormalities will not be seen on structural brain imaging [Grossman and Bernat, 2004; Illes et al., 2006; Vernooij et al., 2007; Weber and Knopf, 2006]. In previous reports, it has been

demonstrated that subjects with otherwise normal screening studies can still have arachnoid cysts, vascular abnormalities, intracranial tumors and cerebral aneurysms identified on structural MRI studies. When any of our subjects were excluded because of undiagnosed disorders, they were told about the historical or physical findings associated with this conclusion and recommendations were made to them so that they could seek appropriate clinical follow-up.

As is clear from the data presented here, the most unrecognized abnormality that resulted in subject exclusion in this study was high blood pressure. This was true for both men and women, although it was more common in men. While the peak rejection rate occurred for individuals in their 60's, high blood pressure was found in subjects across the entire age span and most prominently between ages 40 and 80. Since high blood pressure usually is associated with an insidious onset and a sub-clinical course until it results in significant cardiac, cerebrovascular or other events, this result is not surprising. High blood pressure is a well-known cause of cerebrovascular disease and is associated with white matter abnormalities and "silent" infarcts on MR imaging, particularly with T2 weighted or FLAIR pulse sequences [Jeerakathil et al., 2004; Vermeer et al., 2003a, 2003b]. Eliminating subjects with high blood pressure was, thus, an important goal of our screening procedures and proved to be effective in identifying those subjects who were unaware of their problem. This served a secondary value in that these individuals were identified and made aware of the situation so that they could seek appropriate clinical evaluation and treatment.

It was surprising to us that only slightly over 31% of individuals successfully passed a detailed telephone screen, considering the original solicitation for their participation clearly stated that subjects were required to be healthy. Even more striking was the fact that nearly half of the subjects who passed a detailed telephone interview failed the in-person history and physical examinations. The reasons for this situation are noteworthy (Table 6). In some instances, subjects were unaware of their medical problems. This is clearly true for subjects we evaluated who had undiagnosed high blood pressure or mild cognitive impairment, since such subjects will only be identified if they are formally evaluated for these problems. Subjects can be confused by terminology or jargon used in solicitation advertisements or even in initial screening questions. We found this to be the case with the term "inherited disorder." Subjects often required considerable explanation of these terms in order to clearly understand their meaning in the context of the study. As such, it is important to use the most basic lay terminology in describing criteria reflecting a subject's personal medical history, family history or past diagnoses.

Some subjects appeared to intentionally attempt to deceive the investigators. We encountered two general categories in this group. The first is the "professional subject" who obtains a significant income by participating in medical research. Motivated by financial reasons, these individuals will provide whatever answers to questions they feel will allow them to be participants in the study [Elliot and Abadie, 2008]. An alternate reason for direct deception by subjects is to avoid embarrassment. Often subjects are recruited for imaging studies by colleagues (e.g., fellow graduate students or faculty members) and do not want to admit to their friends or co-workers that they have an underlying neurological or psychiatric disorder, take particular medications or are in need of financial remuneration. Most institutional review boards try to avoid utilization of subjects in studies who have contact with investigators in other settings so as to avoid coercion of the subject into participation. In the situation revealed in this project, an additional factor for excluding potential subjects who are known to members of the investigational team, is to avoid putting the potential subject in the awkward circumstance of revealing to someone, whom they know in another context, that they have an underlying medical problem or financial hardships.

A number of subjects reported that they had a past medical problem but did not consider it relevant or important. This was most often true if the symptoms were mild, such as individuals with infrequent migraine headaches. Subjects also vary in their personal criteria for the definition of excessive alcohol use which tended to exceed the limits employed in medical research studies.

Subjects may be unaware or minimize the significance of mild prior cardiac disease, particularly heart murmurs. They may dismiss important disorders if they are far distant in time, for example, past head trauma with loss of consciousness, cardiac disorders, or cancer that was diagnosed, treated and “cured.” However, even congenital and corrected cardiac disorders can alter brain structure and function [Miller et al., 2007]. Spinal cord or cardiac surgery, particularly if performed during childhood were viewed by potential subjects as closed issues, no longer relevant to their current health status. All of these factors combine to lead subjects to self-report their normality when they are, in fact, not normal.

We encountered a number of individuals in the current study who had previously qualified for studies as normal subjects based on their self-report but who, upon thorough in-person history and examinations were rejected from this study because of underlying medical disorders or medication use.

Normal subjects must be chosen to fit the experimental situation. In our case, the exclusion of as many potential confounding factors as possible was the goal. In other situations, e.g., comparison with a disease group, representative normals may be more valid controls. No single definition fits all experimental requirements. Regardless of the selection criteria, the responsibility exists to verify the medical status of such subjects with objective testing. Without such an approach, the result will be an invalid description of the brain imaging phenotype. Erroneous phenotypes would then propagate incorrect conclusions about relationships between phenotype and behavior or phenotype and genotype.

As a result of this experience, not only at the UCLA site, but throughout the ICBM consortium, we have concluded that it is vital, in any brain imaging study, to have well thought out and carefully defined criteria for subject inclusion and exclusion, a face to face medical interview by a physician and careful measurements of vital signs as well as the medical and neurological examinations of the subjects. The elimination of almost nine out of ten subjects who considered themselves normal in this cohort provides some measure of the magnitude of the problem associated with self-reported normality. Individuals in society have a very vague definition of what is normal and what is not, from a medical research perspective. To accept their vague definition will contaminate scientific data collections, analysis and the conclusions derived from such data sets.

Acknowledgements

Support for this work was provided by a grant from the Human Brain Project (Grant Numbers P20-MHDA52176 and 5P01-EB001955), the National Institute of Biomedical Imaging and Bioengineering, National Institute of Mental Health, National Institute for Drug Abuse, National Cancer Institute and the National Institute for Neurologic Disease and Stroke. For generous support the authors also wish to thank the Brain Mapping Medical Research Organization, Brain Mapping Support Foundation, Pierson-Lovelace Foundation, The Ahmanson Foundation, Tamkin Foundation, William M. and Linda R. Dietel Philanthropic Fund at the Northern Piedmont Community Foundation, Jennifer Jones-Simon Foundation, Capital Group Companies Charitable Foundation, Robson Family and Northstar Fund. The project described was supported by Grant Numbers RR12169, RR13642 and RR00865 from the National Center for Research Resources (NCRR), a component of the National Institutes of Health (NIH); its contents are solely the responsibility of the authors and do not necessarily represent the official views of NCRR or NIH.

References

Bailey, P.; von Bonin, G. The isocortex of man. Urbana University Press; 1951.

Neuroimage. Author manuscript; available in PMC 2010 February 1.

- Brodmann, K. Vergleichende Lokalisationslehre der Großhirnrinde in ihren Prinzipien dargestellt auf Grund des Zellenbaues. Barth, Leipzig: 1909.
- Cutler NR, Duara R, Creasey H, Grady CL, Haxby JV, Schapiro MB, Rapoport SI. Brain imaging: Aging and dementia. *Annals of Internal Medicine* 1984;101:355–369. [PubMed: 6235763]
- Dazzan P, Morgan KD, Chitnis X, Suckling J, Morgan C, Fearon P, McGuire PK, Jones PB, Leff J, Murray RM. The structural brain correlates of neurological soft signs in healthy individuals. *Cerebral Cortex* 2006;16:1225–1231. [PubMed: 16251504]
- Elliot C, Abadie R. Exploiting a research underclass in phase 1 clinical trials. *New England Journal of Medicine* 2008;358:2316–2317. [PubMed: 18509119]
- Folstein MF, Folstein SE, McHugh PR. Mini-Mental State: A practical method for grading the state of patients for the clinician. *Journal of Psychiatric Research* 1975;12:189–198. [PubMed: 1202204]
- Friston KJ, Holmes AP, Worsley KJ, Poline JB, Frith CD, Frackowiak RSJ. Statistical parametric maps in functional imaging: A general linear approach. *Human Brain Mapping* 1995;2:189–210.
- Friston KJ, Worsley KJ, Frackowiak RSJ, Mazziotta JC, Evans AC. Assessing the significance of focal activations using their spatial extent. *Human Brain Mapping* 1994;1:214–220.
- Gazdzinski S, Kornak J, Weiner MW, Meyerhoff DJ, Nat R. Body mass index and magnetic resonance markers of brain integrity in adults. *Annals of Neurology* 2008;63:652–657. [PubMed: 18409192]
- Grossman RI, Bernat JL. Incidental research imaging findings: Pandora's costly box. *Neurology* 2004;62(6):849–850. [PubMed: 15037680]
- Gurnett CA, Trevathan E. Defining the phenotype to discover the genotype. *Neurology* 2006;66(11):1622–1623. [PubMed: 16769931]
- Illes J, Kirschen MP, Edwards E, Stanford LR, Bandettini P, Cho MK, Ford PJ, Glover GH, Kulynych J, Macklin R, Michael DB, Wolf SM. Working Group on Incidental Findings in Brain Imaging Research. Ethics. Incidental findings in brain imaging research. *Science* 2006;311(5762):783–784. [PubMed: 16469905]
- Jeerakathil T, Wolf PA, Beiser A, Massaro J, Seshadri S, D'Agostino RB, DeCarli C. Stroke risk profile predicts white matter hyperintensity volume: The Framingham study. *Stroke* 2004;35:1857–1861. [PubMed: 15218158]
- Kruit MC, Launer LJ, Ferrari MD, van Buchem MA. Infarcts in the posterior circulation territory in migraine. The population-based MRI CAMERA study. *Brain* 2005;128:2068–2077. [PubMed: 16006538]
- Kruit MC, Launer LJ, Ferrari MD, van Buchem MA. Brain stem and cerebellar hyperintense lesions in migraine. *Stroke* 2006;37:1109–1112. [PubMed: 16497982]
- Kruit MC, van Buchem MA, Hofman PAM, Bakkers JTN, Terwindt GM, Ferrari MD, Launer LJ. Migraine as a risk factor for subclinical brain lesions. *JAMA* 2004;291(4):427–434. [PubMed: 14747499]
- Mazziotta JC, Toga AW, Evans AC, Fox P, Lancaster J. A probabilistic atlas of the human brain: Theory and rationale for its development. *NeuroImage* 1995;2:89–101. [PubMed: 9343592]
- Mazziotta J, Toga A, Evans A, Fox P, Lancaster J, Zilles K, Simpson G, Woods R, Paus T, Pike B, Holmes C, Collins L, Thompson P, MacDonald D, Schormann T, Amunts K, Palomero-Gallagher N, Parsons L, Narr K, Kabani N, LeGoualher G, Boomsma D, Cannon T, Kawashima R, Mazoyer B. A four-dimensional atlas of the human brain. *J Am Medical Informatics Assoc* 2001;8:401–430.
- Mazziotta J, Toga A, Evans A, Fox P, Lancaster J, Zilles K, Simpson G, Woods R, Paus T, Pike B, Holmes C, Collins L, Thompson P, MacDonald D, Schormann T, Amunts K, Palomero-Gallagher N, Parsons L, Narr K, Kabani N, LeGoualher G, Boomsma D, Cannon T, Kawashima R, Mazoyer B. A probabilistic atlas and reference system for the human brain. *Philosophical Trans: Biological Sciences* 2001;356(1412):1293–1322.
- Miller SP, McQuillen PS, Hamrick S, Xu D, Glidden DV, Charlton N, Karl T, Azakie A, Ferriero DM, Barkovich AJ, Vigneron DB. Abnormal brain development in newborns with congenital heart disease. *New England Journal of Medicine* 2007;357:1928–1938. [PubMed: 17989385]
- Mulder LJMM, Spierings ELH. Non-lateralized pain in a case of chronic paroxysmal hemicrania? *Cephalalgia* 2004;24(1):52–53. [PubMed: 14687013]

- National Heart, Lung and Blood Institute. NIH Publication 98-4083. Washington, DC: US Government Printing Office; 1998. Clinical guidelines of the identification, evaluation, and treatment of overweight and obesity in adults.
- Pickering TG, Hall JE, Appel LJ, Falkner BE, Graves JW, Hill MN, Jones DH, Kurtz T, Sheps SG, Roccella EJ. Council on High Blood Pressure Research Professional and Public Education Subcommittee, American Heart Association. Recommendations for blood pressure measurement in humans: An AHA scientific statement from the Council on High Blood Pressure Research Professional and Public Education Subcommittee. *J Clin Hypertens (Greenwich)* 2005;7(2):102–109. [PubMed: 15722655]
- Shtasel DL, Gur RE, Mozley D, Richards J, Taleff MM, Heimberg C, Gallacher F, Ruben G. Volunteers for biomedical research. Recruitment and screening of normal controls. *Arch Gen Psychiatry* 1991;48:1022–1025. [PubMed: 1747017]
- Sokolof, L. Cerebral circulation and metabolism in the aged. In: Gershon, S.; Raskin, A., editors. *Aging*. Vol. 2. New York: Raven Press; 1975. p. 45-54.
- Talairach, J.; Tournoux, P. Co-planar stereotactic atlas of the human brain: 3-dimensional proportional system: An approach to cerebral imaging. Stuttgart, Germany: Thieme; 1988.
- Vermeer SE, den Heijer T, Koudstaal PJ, Oudkerk M, Hofman A, Breteler MMB. Incidence and risk factors of silent brain infarcts in the population-based Rotterdam scan study. *Stroke* 2003a;34:392–396. [PubMed: 12574548]
- Vermeer SE, Hollander M, van Dijk EJ, Hofman A, Koudstaal PJ, Breteler MMB. Silent brain infarcts and white matter lesions increase stroke risk in the general population: The Rotterdam scan study. *Stroke* 2003b;34:1126–1129. [PubMed: 12690219]
- Vernooij MW, Ikram MA, Tanghe HL, Vincent AJ, Hofman A, Krestin GP, Niessen WJ, Breteler MM, van der Lugt A. Incidental findings on brain MRI in the general population. *New England Journal of Medicine* 2007;357:1821–1828. [PubMed: 17978290]
- von Economo, K.; Koskinas, GN. *Die Cytoarchitektonik der Hirnrinde des erwachsenen Menschen*. Berlin: Springer Verlag; 1925. von Economo, K. & Koskinas, G.N. *Die Cytoarchitektonik der Hirnrinde des erwachsenen Menschen*. Berlin: Springer Verlag
- Weber F, Knopf H. Incidental findings in magnetic resonance imaging of the brains of healthy young men. *J Neurol Sci* 2006;240(12):81–84. [PubMed: 16256141]
- Wöber-Bingöl Ç, Wöber C, Karwautz A, Auterith A, Serim M, Zebenholzer K, Aydinkoc K, Kienbacher C, Wanner C, Wessely P. Clinical Features of migraine: A cross-sectional study in patients aged three to sixty-nine. *Cephalalgia* 2004;24(1):12–17. [PubMed: 14687007]

Figure 1.

Potential study participants as a function of the phases of the screening process. Of the 1,685 potential subjects who responded to the telephone advertisement, 31.6% passed the telephone screen. Of these, 348 were seen for in person history and physical exam and 180 were eligible after testing. Thus, only 51.7% of those tested in person passed this phase of screening. Only 31.6% of subjects who responded to the advertisement passed the telephone screening and only 10.7% of all subjects who responded to the advertisement were ultimately eligible for the study and scheduled for scanning.

Figure 2. Number of subjects excluded after passing telephone screening. **A.** The reasons for their exclusion, **B.** Exclusion causes by gender, **C.** Exclusion by age group.

Figure 3.

Number of subjects excluded because of elevated blood pressure as a function of age. In parentheses for each age range are the percent of all subjects screened in the age range who were excluded on blood pressure criteria, followed by the percentage of those subjects who were excluded because of blood pressure criteria out of all excluded subjects in the age range.

Figure 4.

Results of a literature review of manuscripts from 2005 and 2006 in *NeuroImage* to determine what methods of screening each published study utilized to select normal subjects. As shown, 74.4% of studies relied on self-reporting or did not mention how the subjects were screened. Approximately 24.1% obtained a specific medical history (12.7% only performed histories, 6.8% conducted a history and neurological examination and 4.6% utilized a questionnaire and history) and 7.4% performed physical examinations (6.8% conducted a history and neurological examination and 0.6% performed neurological exams and questionnaires). 0.8% of studies used questionnaires only and no studies reported only performing a neurological exam nor did any studies utilize our method of a questionnaire, history and neurological exam. Abbreviations: H = History, NE = Neurological Exam and Q = Questionnaire.

Table 1
Exclusion criteria applied to subject histories.

Subject Exclusion Criteria	
A. Medications - Current and Past	
1. Prescription Drugs	
a. Any medication except those listed below in A4	
2. Over-the-Counter Medications	
a. Any if used on a daily basis for more than 3 weeks except as exempted below in A4	
3. Illicit Drugs	
a. Any	
4. Exemptions	
a. Prescription Drugs	
1. Antibiotics (no more recently than one month ago)	
2. Non-steroidal anti-inflammatory drugs (No more recently than one month ago and for no longer than 3 weeks consecutively)	
3. Pain medications or sedatives administered for surgical or diagnostic procedures (see B1)	
4. Contraceptives-oral, subcutaneous or regional	
5. Hormone replacement therapy	
b. Over-the-Counter Drugs	
1. Multi-vitamins	
2. Aspirin	
3. Acetaminophen	
c. Drugs for Disease Prevention	
1. Prophylaxis for infectious disease in travelers	
2. Prophylaxis for altitude sickness	
3. Prophylaxis for motion sickness	
4. Medications for needle stick injuries	
5. Innoculations/Vaccinations	
B. Surgery	
1. Any procedure requiring general anesthesia in the previous year except:	
a. Tonsillectomy and/or adenoidectomy before age 25	
b. Wisdom tooth extraction before age 25	
c. Caesarian section	
d. Tubal ligation	
e. Vasectomy	
2. Any major neurosurgical, cerebrovascular, oncological or cardiac surgery, even if done under local anesthesia.	
C. Medical, Neurological or Psychiatric Illnesses	
1. Any	
D. Headaches	
1. Diagnosis of migraines, cluster headaches or other defined headache disorder. [Wober-Bingol et al., 2004; Mulder and Spierings, 2004]	
E. Implanted or Embedded Metal	
1. Any that would preclude MR imaging (e.g., dental braces, shrapnel) or is indicative of an underlying medical condition (e.g., coronary artery stent)	
F. Trauma	

Subject Exclusion Criteria
1. Any trauma leading to loss of consciousness, concussion, spinal cord or peripheral nerve injury.
G. Alcohol Usage
1. Men: ≤ 2 drinks/day
2. Women: ≤ 1 drink/day

Table 2
Exclusion criteria on physical examination.

Physical Examination Exclusion Criteria	
A. Blood Pressure: Systolic >140, Diastolic >90 [Pickering et al., 2005]	
B. Pulse: >100 or <50, irregularity	
C. Oximetry: Oxygen saturations <95%	
D. Visual Acuity: Near: >20/30 in both eyes	
E. Auditory Acuity: ≥40dB Threshold Shift (moderate loss and greater)	
F. General Exam:	
1. Stigmata of alcohol abuse or IV drug use	
2. Evidence of chronic or acute systemic disorder (e.g., heart murmur, bruits)	
3. Surgical scars indicative of exclusionary procedure not revealed in history (see Table 2), e.g., cardiac, cranial or spinal surgery.	
G. Neurological Examination:	
1. Mini Mental Score <28 [Folstein et al., 1975]	
2. Any abnormal neurological signs	

Table 3
Telephone screening of subjects.

Telephone Screening	
1. Purpose of Study	
2. Outline of Time Commitments, Procedures and Payments	
3. Statement about Confidentiality	
4. Background Information	
a. Are you between the ages of 18-90?	
b. Is English your first language?	
c. Are you willing to participate in two or three 1.5-hour sessions that would include behavioral and cognitive tests, brain imaging, and drawing a blood sample?	
d. Are you able to read fine print with glasses?	
5. Medical Screening	
a. Do you have known medical or neurological diagnosis?	
b. Have you ever received medication or other treatment for a psychiatric disorder?	
c. Have you ever had migraine headaches, meningitis, head concussion or trauma, encephalitis or been in a coma?	
d. Do you currently take any medications?	
e. Have you ever taken any medications on a chronic basis other than vitamins, aspirin, or diet supplements?	
f. Are there any inherited neurological or psychiatric diseases in your family?	
g. Do you wear metal braces on your teeth?	
h. Have you had surgery requiring general anesthesia within the last year?	
i. Do you have asthma, high blood pressure, diabetes, heart disease or high cholesterol levels?	
j. Are you uncomfortable in small, closed spaces?	
6. If yes to questions in #5 are you willing to speak to one of the investigators in more detail to see if you qualify for the study?	

Table 4

Historical and physical examination data that were collected but not used as exclusion criteria.

Non-Exclusionary Data Collected	
A. History of first degree relatives with psychiatric disorders thought to have genetic contributions (e.g., major depression, autism, schizophrenia)	
B. Body Mass Index (BMI) [NIH Pub #90-4083]	
BMI = Weight (kg)/[height (m)] ²	
Underweight ≤ 18.5 kg/m ²	
Overweight 25-29.9 kg/m ²	
Obese ≥ 30 kg/m ²	
C. Abdominal Girth	
Men > 102 cm	
Women > 88 cm	
D. DANI (Demographic and Neurocognitive Inventory) a battery of neuropsychological tests (http://ric.uthscsa.edu/icbm_dani/).	

Table 5

Average blood pressure ($\pm$ SD) by decade for subjects included and excluded from the study. For subjects whose initial blood pressure (BP) exceeded the study limits (systolic >140 , diastolic >90), the measurement was repeated up to three more times. If the average of the subject's blood pressures fell below the study cutoff values, the subject was included. For excluded subjects their average blood pressure value was used to compute the group averages in this table. Parentheses indicate total subjects in a given group (only some of whom had BP measurements) while the number preceding the parentheses is the number of subjects in that group whose blood pressure was averaged to compute the group value. The difference between the values are the subjects excluded in the group without having their BP measured. See text for details.

Age Range	Included Subjects		Excluded for Other Causes		Excluded for Hypertension	
	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic
18-29	121.65	70.31	119.44	70.06	154.61	86.06
SD	11.89	7.96	8.34	4.79	9.6	6.48
N	64	64	9 (21)	9 (21)	3	3
% of 18-29	72.7%	72.7%	10.2% (24.9%)	10.2% (24.9%)	3.4%	3.4%
30-39	121.2	74.83	121.5	70.33	149.12	87.24
SD	12.44	9.15	14.03	15.17	3.97	11.93
N	31	31	6 (15)	6 (15)	7	7
% of 30-39	58.5%	58.5%	11.3% (28.3%)	11.3% (28.3%)	13.2%	13.2%
40-49	123.63	74.82	122.39	77.17	165.27	91.28
SD	14.38	7.87	7.64	8.08	23.41	11.33
N	30	30	9 (17)	9 (17)	13	13
% of 40-49	50.0%	50.0%	15.0% (28.3%)	15.0% (28.3%)	21.7%	21.7%
50-59	127.68	78.86	123.5	63.75	165.99	86.65
SD	11.84	9.22	8.81	6.6	22.46	17.06
N	32	32	4 (9)	4 (9)	12 (14)	12 (14)
% of 50-59	45.1%	45.1%	7.27% (16.4%)	7.27% (16.4%)	21.8% (25.5%)	21.8% (25.5%)
60-69	129.25	76.92	127	76.5	156.25	91.22
SD	12.03	7.27	8.49	4.95	11.19	15.63
N	16	16	2 (10)	2 (10)	17 (18)	17 (18)

Age Range	Included Subjects		Excluded for Other Causes		Excluded for Hypertension	
	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic
% of 60-69	36.4%	36.4%	4.55% (22.7%)	4.55% (22.7%)	38.6% (40.9%)	38.6% (40.9%)
70-79	131	71.4	130.05	70	158	88.76
SD	5.79	8.62	12.02	7.07	14.67	15.05
N	5	5	2 (5)	2 (5)	7 (8)	7 (8)
% of 70-79	27.8%	27.8%	11.1% (27.8%)	11.1% (27.8%)	38.9% (44.4%)	38.9% (44.4%)
80-90	124.5	71	138	78	169.25	84.38
SD	20.51	5.66	0	0	20.86	1.94
N	2	2	1 (1)	1 (1)	2	2
% of 80-89	40.0%	40.0%	20.0% (20.0%)	20.0% (20.0%)	40.0%	40.0%
Unknown	0	0	140	74	170.75	99.25
SD	0	0	0	0	5.75	3.25
N	0	0	1 (16)	1 (16)	2	2
% of Unknown	0%	0%	5.56% (88.9%)	5.56% (88.9%)	11.1%	11.1%
All Ages	123.94	73.99	123.31	71.97	157.66	90.56
SD	12.58	8.82	9.91	9.06	14.92	11.87
N	180	180	34 (66)	34 (66)	63 (102)	63 (102)
% of All Ages	51.7%	51.7%	9.77% (19.0%)	9.77% (19.0%)	18.1% (29.3%)	18.1% (29.3%)

Table 6

Possible reasons subjects report that they are normal but are subsequently excluded by history and physical examination criteria.

Common Unknown Medical Problems
1. Unaware of the problem (e.g., hypertension, mild dementia)
2. Confused by the questions or terms (e.g., “inherited disorders”)
3. Deception-“professional subjects” or embarrassed
4. Do not consider the issue relevant (mild symptoms, occurred long ago)