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Population Neuroscience: Why and How

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Abstract: Population neuroscience endeavours to identify environmental and genetic factors that shape the function and structure of the human brain; it uses tools and knowledge of genetics, epidemiology, and cognitive neuroscience. Here, I focus on the application of population neuroscience in studies of brain development. By describing in some detail four existing large-scale magnetic resonance (MR) imaging studies of typically developing children and adolescents, I provide an overview of their design, including population sampling and recruitment, assessments of environmental and genetic "exposures," and measurements of brain and behavior "outcomes." I then discuss challenges faced by investigators carrying out such MR-based studies, including quality assurance, quality control and intersite coordination, and provide a brief overview of the achievements made so far. I conclude by outlining future directions vis-à-vis population neuroscience, such as design strategies that can be used to evaluate the presence of absence of causality in associations discovered by observational studies. *Hum Brain Mapp 31:891–903, 2010.* © 2010 Wiley-Liss, Inc.

Key words: epidemiology; genetics; neuroimaging; adolescence; GWAS

BACKGROUND

There is growing interest in explaining the role of environment, genes and their interplay in shaping the structure and function of the human brain. Given the variety of environmental factors and the challenges of genetics of complex traits, these questions are best addressed at a population level, hence the emergence of population neuroscience as a field situated at the intersection of cognitive neuroscience, genetics and epidemiology (Fig. 1).

Point of Departure: Brain and Behavior

In the last century, great strides have been made towards understanding the structural and functional organization of the human brain. Studies of patients with discrete brain-lesions have discovered a number of specific brain–behavior relationships, such as that between the hippocampal system and memory [Scoville and Milner, 1957]. Electrical stimulation of the cerebral cortex revealed functional organization of motor and sensory areas [Penfield and Rasmussen, 1950]. And functional neuroimaging studies of the last two decades underscored the importance of a network nature of the brain functional organization: particular circuits are recruited to support specific behaviors in a given context [Jirsa and McIntosh, 2007]. Not surprisingly, we have also learned that the various structural and functional features of the human brain show a tremendous range of values across individuals, even in the absence of a frank psychiatric or neurological disorder. The key

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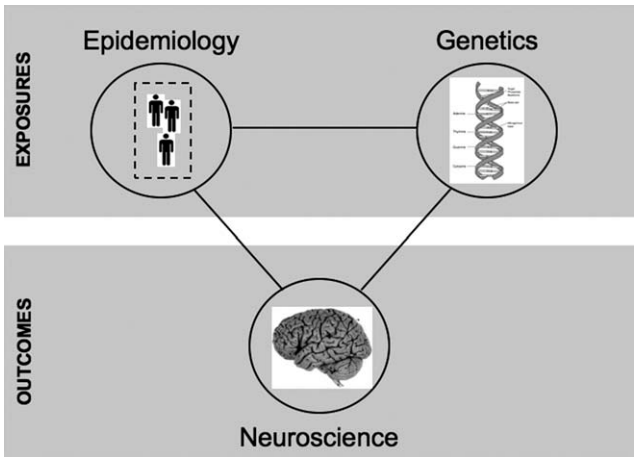

Figure 1.
Population neuroscience. Traditionally, epidemiology and genetics attempt to identify "exposures" in the individual's environment and genes, respectively, as factors affecting the health of populations. Cognitive neuroscience provides the knowledge of brain and behavior "outcomes" that, ultimately, inform about possible pathways leading to good or ill mental health.

question thus arises. What shapes our brains? What are the genetic and environmental factors that generate this impressive interindividual variability in the structural and functional organization of the human brain?

Genomics

Twins studies of the human brain [Peper et al., 2007] and behavior [McGue and Bouchard, 1998] suggest that, depending on the trait under study, between 50% (e.g. ceberellar volume, personality) and 80–90% (e.g. brain volume, general cognitive ability) of variance is explained by genetic factors. The human genome contains over 3 billion chemical building blocks (i.e. base pairs made of adenine, thymine, cytosine, and guanine), and about 26,000 genes containing 233,785 exons and 207,344 introns [Sakharkar et al., 2004]. On the basis of a genome-wide analysis of gene expression throughout the mouse brain, we know that at least 80% of all genes in the genome are expressed in the brain [Lein et al., 2007]. Given the polygenic nature of complex brain/behavior traits, a single gene is likely to explain only a small portion of variance in a given trait (less than 5%). Furthermore, a given phenotypic trait may emerge through a gene interacting with other genes [e.g. Nicodemus et al., in press] and/or with the environment [e.g. Lotfipour et al., 2010]; the environment may also modify gene expression in long-term fashion [epigenetics; e.g. McGowan et al., 2009]. Not surprisingly, small single-gene effects riding on a complex genetic and environmental background could be revealed only in large samples of individuals [power calculations: e.g. Klein, 2007; Schaid, 2006; Spencer et al., 2009; Fig. 2] using various strategies for mapping quantitative trait loci associated with complex traits [McCarthy et al., 2008; Lander and Schork, 1994].

Enviromics

Twin studies also suggest that a substantial portion of the interindividual variance in brain structure is accounted for by environmental factors [Peper et al., 2007]. These range from robust developmental influences, such as malnutrition during pregnancy [e.g. Odabas et al., 2005], to infinitely more subtle variations in the individual's experience, such as playing a musical instrument [e.g. Schlaug, 2001]. Given the wide variety of environments and experiences, it is not surprising that we have no catalogue of the "envirome," hence the need for "enviromics" [Anthony, 2001]. But the undeniable importance of environmental influences on the human brain throughout the lifespan, and their interplay with variations in genome to influence the human transcriptome and epigenome, makes it imperative for us to develop new strategies to capture and quantify the details of the individual's environment, from conception onwards. Epidemiology and anthropology are but two classical disciplines that are likely to provide guidance in such efforts.

Phenomics

Human genome and envirome shape the phenome. As suggested by others [e.g. Bilder et al., 2009; Freimer and

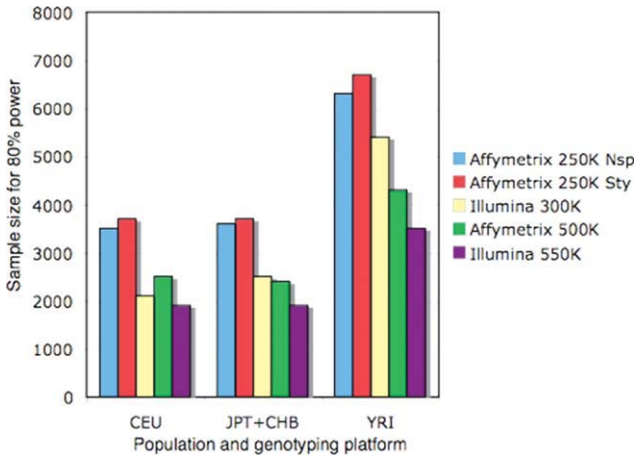

Figure 2.
Sample size in genome-wide association studies. Total individuals required for 80% power. The computations assume the number of cases equals the number of controls and a genotype relative-risk of 1.75. CEU, JPT+CHB, and YRI are the HapMap populations. Affy 250 K Nsp and Affy 250 K Sty represent the two chips that make up the Affymetrix 500 K genotyping system. CEU, Utah residents with ancestry from northern and western Europe; JPT, Japanese in Tokyo, Japan; CHB, Han Chinese in Beijing, China; YRI, Yoruba in Ibadan, Nigeria. (Reproduced with permission from Klein, BMC Genet, 2007, 8, 58, ©).

Sabatti, 2003], coordinated efforts vis-à-vis quantitative characterization of the human phenome (phenomics) are essential. In this context, magnetic resonance (MR) imaging represents a unique tool for the acquisition of multiple brain phenotypes in a highly effective and reliable manner and, as such, a tool suitable for population studies. At the same time, MR-based phenotypes alone are not sufficient, hence the need for careful quantitative assessment of behavior and cognition, and other relevant (e.g. physiological and biochemical) measures.

POPULATION NEUROSCIENCE

With the hundreds of genes and environments, and their combinations, the complexity of the task at hand seems overwhelming. How do we identify which of the many possible genetic and environmental factors shape a particular structural and functional property of the human brain? Putting aside the candidate-gene approach, with its advantages and disadvantages [Zhu and Zhao, 2007], can we attack this complexity by considering a large number of genetic and environmental variations at once? The main practical challenge of this approach lies in the need for high-throughput high-fidelity assessment of "exposures" (genome and envirome) and "outcomes" (phenome) in hundreds or thousands individuals.

Thanks to the technological and conceptual achievements of the Human Genome Project (1990–2003) and subsequent efforts (e.g. HapMap; http://hapmap.ncbi.nlm.nih.gov/), *genetic exposures* (i.e. DNA variations) can be readily assessed across the entire genome with one of the most commonly used tools for identifying associations between genotypic and phenotypic variations, namely single-nucleotide polymorphisms (SNPs); it is estimated that about 10 million SNPs occur commonly in the human genome. Current genotyping platforms capture variations in the individual's genome with 600,000 to 1.2 million SNPs. Given the fast growing efficiency and declining cost of high-throughout platforms, such as Illumina or Affymetrix, obtaining genome-wide coverage in a large number (>1,000) of individuals is feasible and affordable. Fidelity of genotyping platforms is high, with the error rate in allele identification being lower than 1% [Fridley et al., 2008; Nishida et al., 2008].

Environmental exposures are assessed in a variety of ways designed to sample the individual's history in a general fashion (e.g. food availability during early childhood) or with a focus on specific exposures (e.g. amount of white fish in the child's diet). As I will review below, most of the information about an individual's past and current environment and experiences is derived from reports provided by the individual or his/her parents. Other sources of information may include medical records, survey-based information about a particular neighborhood or workplace, or various proxy measures such as the socioeconomic position of a family. Actual measurements of exposures are feasible in some cases (e.g. plasma levels of ω-3 fatty acids). Fidelity of environmental assessment is, unfortunately, rather low; for example, test–retest reliability of the recall of many nutritional components in a dietary recall study was found to be around 0.5 [Burton et al., 2009].

Brain and behavior outcomes (phenome) represent the quantitative traits of interest and, in the context of population neuroscience, occupy the primary position vis-à-vis data collection. Magnetic resonance imaging (MRI), structural and functional, is the most common tool used to derive a large variety of quantitative brain phenotypes. Assessment of behavior/cognition varies from the very basic to the rather extensive. Both sets of phenotypes will be described in some detail in the following section. Fidelity of these assessments is likely to vary widely across the phenotypes, being higher for structural MRI and lower for functional MRI and behavior (Fig. 3).

Overall, the primary goal of the majority of population-based neuroimaging studies is to identify genetic and environmental factors (exposures) that shape the various structural and functional brain phenotypes (outcomes). To illustrate several key aspects involved in designing such studies, the next section describes in some details four ongoing large-scale studies of brain development carried out in typically developing children and adolescents.

DESIGNING LARGE-SCALE NEUROIMAGING STUDIES

How do we design population-based neuroimaging studies of the "healthy" brain? I will now review the design of four ongoing paediatric MR-based studies: (1) a cohort established in the Child Psychiatry Branch of the National Institutes of Mental Health [NIMH-CHPB; Lenroot et al., 2007]; (2) NIH Pediatric MRI Database [NIH-PD; Evans et al., 2006]; (3) the Saguenay Youth Study [SYS; Pausova et al., 2007]; and (4) the Imagen Study [Schumann et al., in press]. As these studies were conceived at different times and with different primary goals, the four designs illustrate the advantages and disadvantages of including, or not, particular exposures and outcomes. After providing a brief description of each study, I will review their differences and commonalities, and then conclude this section by highlighting some of the challenges associated with this type of work.

NIMH-CHPB

This cohort was conceived in 1989 as a normative study of brain structure during childhood and adolescence; it is carried out at one acquisition site (Bethesda, MD). One of the primary goals of the study has been the comparison of normative data with MR images acquired in parallel studies of psychiatric disorders of childhood including both common (e.g. attention deficit hyperactivity disorder, ADHD) and rare (e.g. childhood-onset schizophrenia)

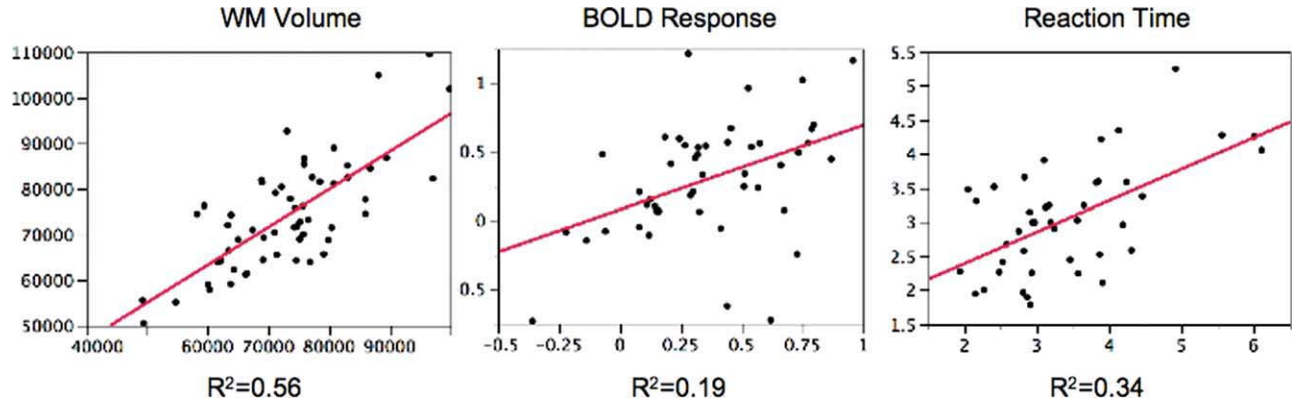

Figure 3.

Within-subject Time 1 to Time 2 correlations in brain and behavior. These plots illustrate the degree of similarity in structural and functional MRI measures and a behavioral measure across two time-points. The data were collected in the same set of children at Time 1 (10 years of age) and Time 2 (11.5 years of age) in a longitudinal study carried out in the author's laboratory at the Montreal Neurological Institute. WM volume: white-matter volume [in mm^3] in the right frontal lobe; BOLD Response: mean BOLD response [in %change] to angry faces in the left amygdala; reaction time: reaction time [in s] in a task requiring discrimination of affect in faces. Note that the variance between the Time 1 and Time 2 measurements is due to both measurement errors and developmental changes. Direct comparisons of Time 1 and Time 2 data suggest, however, that only the behavioral data show statistically significant (developmental) effect of visit in these three examples.

conditions [e.g. Giedd et al., 1996; Lenroot et al., 2007]. It is a longitudinal study with the participants' age at the time of initial recruitment ranging from 3 to 25 years, and the visits repeated in 2–4 year intervals. The sample comes primarily from the local community and, in terms of the recruitment strategy, this study has relied to a great extent on the interest of NIH employees working on the Bethesda campus. As a consequence, this is a multiethnic sample with an average estimated IQ of 113. Given that this was the very first large-scale MR study of brain structure in typically developing children and adolescents, it was designed primarily as an observational MR study with little data collected on genetic and environmental exposures, other than the socioeconomic status (SES) of the families; DNA collection was added at a later point. Behavioral and cognitive assessments are not extensive (Table I). The neuroimaging protocol includes T1-weighted (T1W) images; diffusion tensor imaging (DTI) and functional MRI were added at later stages in a subset of participants.

NIH-PD

This project was initiated in the mid 2000s as a multicenter study where MR acquisition took place at six sites in the United States of America. It is also a normative study of brain development that complements the NIH-CHPB cohort in two important ways, namely by including a large group of infants and young children (age 7 days to 4 years) and by adding other MR sequences [Evans et al., 2006]. It is a longitudinal study, with the older children (5–18 years) scanned three times in 2-year intervals and the younger children (7 days to 4 years) scanned up to five times, with intervals as short as 3 months. The sample has been ascertained through population-based sampling: each of the six acquisition sites recruited participants using site-specific demographic targets calculated according to the Census 2000 data. The resulting sample is multiethnic and includes a wide range of SES characteristics; the average IQ is 110. No genetic data are collected. Assessment of environmental exposures is limited to variables related to SES and prenatal exposures (e.g. cigarettes, alcohol, drugs). Behavioral and cognitive assessments are more extensive than those in the NIH-CHPB cohort [Table 1; Waber et al., 2007]. The NIH-PD project includes several MR sequences: T1-, T2- and PD-weighted images, as well as T1 and T2 (single slice) relaxometry are acquired in all participants. Diffusion tensor images and MR Spectroscopy are acquired at a subset of the acquisition sites.

SYS

The Saguenay Youth Study was initiated in the mid 2000s as an investigation of genetic and environmental factors shaping the adolescent brain and body; MR acquisition takes place at a single site in Canada (www.saguenay-youth-study.org). Adolescents (12–18 years) and their biological parents are recruited from a population with a known genetic founder effect, namely the population of the Saguenay Lac-Saint-Jean (SLSJ) region of Quebec, Canada. At this point, it is a cross-sectional study where multiple quantitative phenotypes relevant to mental, cardiovascular and metabolic health is acquired using an

TABLE I. An overview of four population-based MR studies of brain development

	NIMH-CHPB	NIH-PD	SYS	IMAGEN
Sample (*n*)	400	500	700 (1,000)	1,000 (2,000)
Age range	3–25 years	7 days to 18 years	12–18 years	14 years
Design	Longitudinal, multi-ethnic population	Longitudinal, multi-ethnic population	Cross-sectional, founder population (white Caucasian)	Cross-sectional, multi-ethnic population
Recruitment	Local community	Population sampling (census-based targets)	High schools	High schools
Genetics	Candidate genes	None	DNA (adolescents, both biological parents)	DNA (adolescents)
Environment	Socioeconomic status	Socioeconomic status Pregnancy (smoking, alcohol, drugs)	Socioeconomic status Pregnancy (smoking, alcohol, drugs) Infancy (e.g. breast feeding) Childhood (e.g. maternal care, stressful life events, food availability/variety) Adolescents (e.g. diet, sleep)	Socioeconomic status Pregnancy (smoking, alcohol, drugs) Stressful life events
Neuroimaging	T1W images, 1.5-mm thick axial slices, 1.5T GE scanner	T1W, T2W, PDW images, T1 and T2 relaxometry, 1.5T GE, and Siemens scanners	Brain: T1W, T2W, PDW images, MTR; Abdomen: fat, kidney volume; 1.0T Philips scanner	Structural: T1W images, DTI; Functional: Face Task, MID Task, Stop-signal Task, Global-cognition Task; 3 T scanners (GE, Philips, Siemens, Bruker)
Behaviour/ Cognition	Child and Parent Diagnostic (Psychiatric) Interview for Children	Diagnostic Interview Schedule for Children	DISC Predictive Scale (psychiatric symptoms)	DAWBA and SDQ (psychiatric symptoms)
	Child behavior checklist	Child Behavior Checklist	Positive youth development, personality (NEO PI), antisocial behavior	Personality (NEO FFI, TCI-R)
	Intelligence (WISC-III/ WISC-IV subtests)	Personality (TCI)	Drug experimentation, sleep, sexuality	Substance use (SUPRS, ESPAD, DAST, AUDIT, MAST, FTND, TLFB)
	Spatial working memory, Go/ No-Go task	Intelligence (WASI, WISC-III subtests)	Intelligence (WISC-III)	Intelligence (WISC subscales)
	Academic skills (reading, spelling)	Memory (CVLT)	Memory (CMS)	Executive functions (CANTAB)
	Grooved Pegboard and Handedness	Executive functions (Cantab, NEPSY)	Executive functions (e.g. stroop, fluency, working memory, attention)	Face perception
		Academic skills (calculation, passage comprehension, letter word)	Face perception, Body-image perception	Handedness and fine motor skills
		Handedness and fine motor skills	Reward/Impulsivity	
			Phonological processing Academic skills (math, math fluency, reading, spelling) and Number sense Handedness and Fine motor skills	

NIH-CHPB, National Institutes of Health- Child Psychiatry Branch; NIH-PD, National Institutes of Health – Pediatric MRI Database; SYS, Saguenay Youth Study.
DAWBA, Development and Well Being Assessment Interview; SDQ, Strengths and Difficulties Questionaire; SUPRS, Substance Use Risk Profile Scale; ESPAD, European School Survey Project on Alcohol and Drugs; DAST, Drug Abuse Screening Scale; AUDIT, Alcohol Use Disorders Identification Tests; MAST, Michigan Alcohol Screening Test; FTND, Fagerstrom Test for Nicotine Dependence; TLFB, Time Followback Interview.

extensive 15-h protocol spread over several days [Pausova et al., 2007]. By design, half of the participants were exposed to maternal cigarette smoking while the other nonexposed half has been matched to them by maternal education. A family-based design was used, with adolescent siblings and their biological parents being fully (all assessments) and partially (a subset of assessments) phenotyped, respectively. Recruitment takes place in high schools across the SLSJ region. The sample is of a single ethnicity (white Caucasians) and, given the 50% inclusion rate of adolescents born to mothers who smoked during pregnancy and the matching procedure, it is of lower SES than the general population of the region; the average IQ is 105. Samples of DNA are collected in all adolescents and their biological parents. Assessment of environmental exposures covers prenatal period (e.g. smoking, alcohol), infancy (e.g. breastfeeding), childhood (e.g. food availability, maternal care, stressful life events), and adolescence (e.g. diet, sleep). Behavioral and cognitive assessments are extensive and include both self-reports of psychiatric symptoms, components of positive youth development and personality, as well as a thorough assessment of cognitive abilities [Table I and Kafouri et al., 2008; Pausova et al., 2007]. In addition, all adolescents are assessed with a detailed cardiovascular and metabolic protocol. MR sequences include T1W, T2W, and PDW images, magnetization transfer (MT) images (as an index of myelination) and abdominal images (extra- and intra-abdominal fat, kidney volume).

IMAGEN

This project started in 2007 as a multicenter cross-sectional study of the genetic and neurobiological bases of individual variability in impulsivity, reinforcer sensitivity and emotional reactivity; MR acquisition takes place at eight acquisition sites located in the United Kingdom, Ireland, France and Germany [Schumann et al., in press]. This is the only large paediatric cohort that includes both structural and functional MRI in all participants. Adolescents (14-year old) are recruited primarily through local high schools. The sample is multiethnic, with a wide range of the parental education level. Samples of DNA are collected in all participating adolescents. Assessment of environmental exposures is limited to the main SES characteristics, stressful life events and prenatal exposures (e.g. smoking, alcohol). Behavioral and cognitive assessments include a basic assessment of cognition and a detailed assessment of the main outcomes of interest, namely impulsivity, reward processing and substance use (Table I). MR sequences include structural (T1W, DTI) and functional imaging, with the latter consisting of four paradigms: a Face Task, a Monetary-Incentive Delay Task, a Stop-Signal Task, and a Global-Cognition Task.

Differences and Commonalities

Given the variety of primary goals and the time of inception, the four large-scale studies of brain development range significantly in their approaches to the selection and recruitment of typically developing children and/or adolescents from the local population, the collection of genetic and environmental variables and the inclusion of specific MR sequences.

In the case of *selection and recruitment*, the NIH-CHPB and NIH-PD studies represent two extremes, with the former being a convenience sample and the latter a stratified random sample. It should be pointed out, however, that using a random-sampling strategy does not necessarily yield a random sample in the final dataset. This is chiefly due to two reasons. First, given the volunteer nature of neuroimaging studies, there is a self-selection bias in the initial stage of recruitment. Second, depending on the stringency of the exclusion criteria, a varied number of potential participants are excluded from the final sample. In this respect, the NIH-CHPB and NIH-PD studies are more exclusionary than the SYS and IMAGEN studies. Overall, true randomness and representativeness of population-based samples is difficult if not impossible to achieve in studies of this nature.

The *availability of DNA* and, therefore, the potential for genetic analyses varies across the four studies from no DNA having been collected in the NIH-PD study to DNA being collected in adolescent participants and their biological parents in the SYS cohort. Furthermore, it is possible that the multiethnic population of the NIH-CHPB and the IMAGEN studies would require a larger sample size in order to reveal particular genotype–phenotype relationships, as compared with the single ethnicity of the SYS cohort recruited from a population with a known genetic founder effect [Kristiansson et al., 2008].

As seen in Table I, assessment of the *environment* varied widely across the studies. All four studies collected basic SES characteristics, which may serve as a proxy of the "social context of early life" [Taylor et al., 2002] and a possible marker of the "stressfulness" of the family environment [Adler et al., 2000]. All but one of the studies documented a possible exposure of the fetus to maternal cigarette smoking and alcohol/drug use. Two studies collected information about stressful life events and one of the studies extended environmental assessment to other variables, such as breastfeeding, food availability, and type of care during childhood. Overall, assessment of environmental exposures relies mostly on parental recall; it is rarely verified using independent sources (e.g. medical records) and often attempts to capture events that occurred in the relatively distant past, such as during pregnancy.

When it comes to behavioral and cognitive "outcomes," all four studies assessed current psychiatric symptoms, using self-reports or structured interviews, and general intelligence, the latter estimated from a limited number of subscales in the NIH-CHPB and the Imagen studies. Three studies (NIH-PD, Imagen, SYS) use either the NEO-PI and/or TCI to assess personality. Two of the studies (NIH-PD and IMAGEN) used various subtests of CANTAB to assess executive functions. Being focused

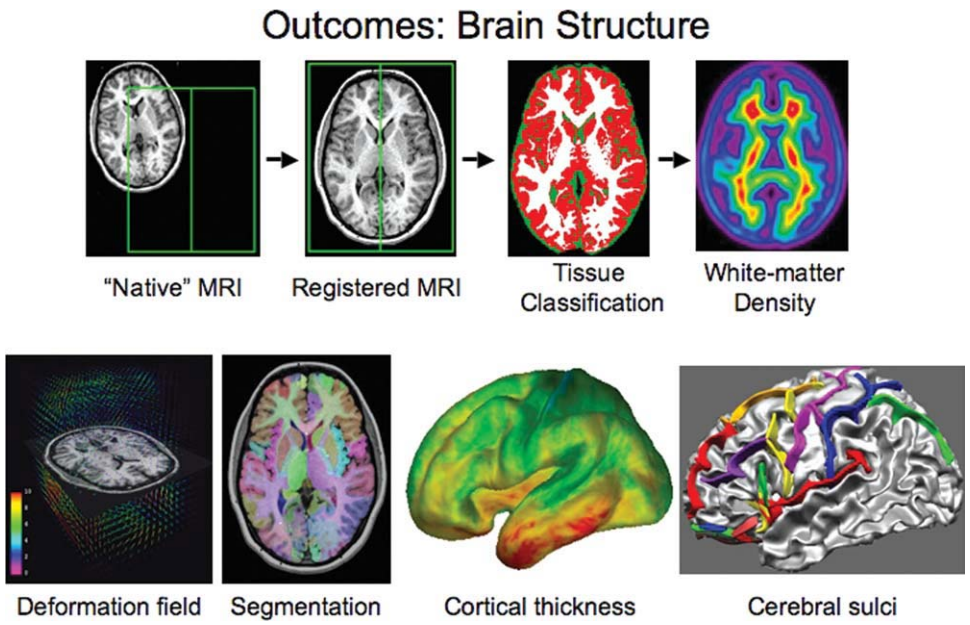

Figure 4.

Outcomes: brain structure. Various quantitative measures of brain structure can be derived from T1-weighted images using automatic image-processing pipelines. These include 3D maps of white- and gray-matter "densities," deformation fields capturing differences in local shapes, segmented volumes of different brain structures (e.g. hippocampus), cortical thickness and folding. Reprinted from Paus 2005.

on adolescence, the SYS study and specially the IMAGEN study include an extensive assessment of substance use.

Finally, *the brain* "outcomes." All fours studies include T1-weighted images of the brain, which provide a wealth of quantitative phenotypes including brain size, global and regional (e.g. hippocampus, corpus callosum) volumes of gray and white matter, cortical thickness and folding, as well as gray-matter and white-matter "densities" (Fig. 4). The IMAGEN Study and, in part, the NIH-PD dataset also acquired DTI images, which allow for the characterization of white-matter microstructure, in global, voxel-wise and tract-based manners. The SYS includes acquisition of MT images used to calculate an MT ratio (MTR), an indirect index of myelination [Paus, 2010]. Finally, the IMAGEN Study is the only of the four studies collecting functional MR datasets quantifying, respectively, the brain response to social stimuli (the Face task), processing of rewards (the Monetary-Incentive Delay Task), response inhibition (the Stop Signal Task) and to motor responses to a series of visual and auditory stimuli presented simultaneously (the Global Cognition Task). This fMRI dataset will provide a number of functional measures derived from voxel-wise and regional analyses of the fMRI time-series, both in terms of the brain response to a particular probe in a given set of regions (Fig. 5A) and, most importantly, various measures of coordinated activity across regions, namely functional connectivity (Fig. 5B).

Challenges

Conducting large-scale studies of brain and behavior faces several challenges, including sampling and recruitment of participants, data collection, quality assurance and quality control, intersite coordination, databasing, and protection of confidentiality.

As pointed out in the section above, various sampling and recruitment strategies can be employed to reach the high numbers of volunteers in population-based neuroimaging studies. Putting aside representativeness of the resulting (phenotyped) samples discussed above, what are the yields of the different strategies? In the NIH-PD study, for example, 8% of the contacted families consented to the initial screening interview and 1.1% entered the actual study [Waber et al., 2007]. In the SYS cohort, the initial response rate was about 19%, with about 9% entering the study. In the Imagen Study (Nottingham site), 25% of the approached adolescents proceeded to the screening phase, with about 17% being scanned/tested. Clearly, substantial efforts are necessary to achieve the desired sample size. Furthermore, selection biases specific to MR imaging include, for example, exclusion of adolescents with braces or loss of data in individuals more likely to move during scanning (e.g. children with attention-deficit hyperactivity disorder).

Quality assurance is paramount for ensuring that procedures used to collect behavioral and imaging data, often over many years, are maintained at the highest possible

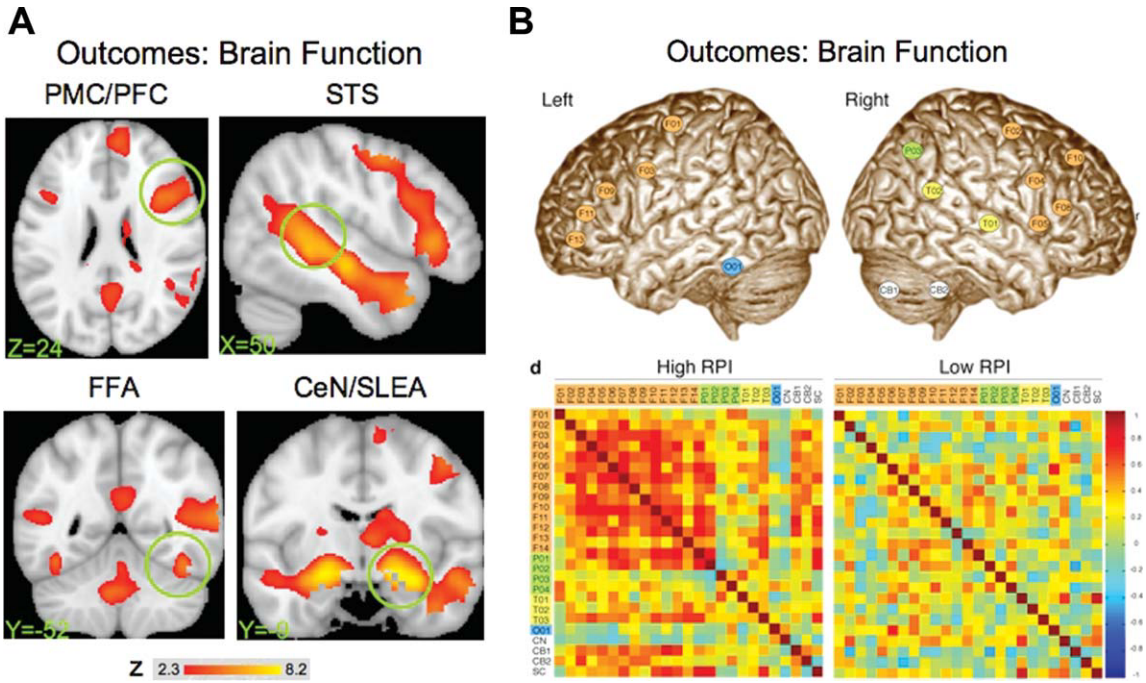

Figure 5.

Outcomes: brain function. Functional MR images provide a variety of measures, such as the mean BOLD response in various brain regions (**A**) or estimates of functional connectivity (**B**). Examples shown here are based on fMRI data acquired in the author's laboratory in 10-year-old children watching video-clips of faces (A) and hands (B). Regions included in the correlation matrix were identified with partial least squares. PMC, premotor cortex; PFC, prefrontal cortex, STS, superior temporal sulcus; FFA, face fusiform area; CeA, central amygdala; SLEA, sublenticular extended amygdala. Circles indicate brain regions identified by labels above each brain image. Plots shown in (B) are reprinted from Grosbras et al. [2007].

standard. For the behavioral/cognitive data, this can be achieved by certifying the testers at the beginning of their engagement and at regular intervals (e.g. every 12 months) thereafter. For multicenter studies, regular conference calls and meetings of the relevant staff are useful in addressing various issues in a manner consistent across the sites. On the MR side, inclusion of phantom scans acquired at regular intervals, as well as before and after any software or hardware upgrades, is of high importance; for example, it allows one to assess between-site variations in signal-to-noise ratio or in phantom geometry [Fu et al., 2006].

Quality control of the acquired data reduces noise in subsequent analyses both by discovering and correcting errors and by excluding uncorrectable data points from the analyses. Manually entered data (e.g. scores based on the neuropsychological assessment) require particular care that may be achieved, for example, by a random check of data in the database against the hard copy. Most automatically uploaded data, from computer-based assessments or scanned questionnaires, can be checked using procedures such as range checks or cross-validations. The imaging data can be quality controlled at two stages, namely shortly after the transfer of data from the MR console to the database and after each image-processing step using a web-based interface.

Given the interdisciplinary nature of population-based neuroimaging studies, intersite coordination is essential for achieving smooth and efficient communications between the groups contributing their unique expertise, often located at physically distant sites even when data acquisition takes place at only one site. Obviously, it is essential for the success of studies acquiring data across multiple sites. The tools used in this context include, for example, web-based deposition of the study protocol, regular conference calls (biweekly) and meetings of the team members (annual).

Analysis of the complex datasets collected in such studies require robust *databases* capable of handling large number of variables (>10,000) in a rigorous manner. As described in detail elsewhere [Evans et al., 2006; Pausova et al., 2007], such relational databases are typically built with MySQL/PHP programming tools. All datasets/variables are related via the participant's unique identifier. In the SYS project, for example, a six-digit identification code is assigned automatically to each family member; this code is combined with the family identification number. These codes are assigned at the recruitment stage and are used on all documents, from paper-based questionnaires and testing forms, through electronic files saved during various computer-based acquisitions (e.g. CANTAB) to MR images

TABLE II. Publications based on the NIH-CHPB study

First/last author	Title	Journal	Publication year
Giedd/Rapoport	Quantitative magnetic resonance imaging of human brain development: ages 4-18	Cerebral Cortex	1996
Giedd/Rapoport	Quantitative MRI of the temporal lobe, amygdala, and hippocampus in normal human development: ages 4-18 years	J Comparative Neurology	1996
Giedd/Rapoport	A quantitative MRI study of the corpus callosum in children and adolescents	Brain Res Dev Brain Res	1996
Giedd/Rapoport	Sexual dimorphism of the developing human brain	Prog Neuropsychopharmacol Biol Psychiatry	1997
Lange/Rapoport	Variability of human brain structure size: ages 4-20 years	Psychiatry Res	1997
Giedd/Rapoport	Brain development during childhood and adolescence: a longitudinal MRI study	Nat Neurosci	1999
Giedd/Castellanos	Development of the human corpus callosum during childhood and adolescence: a longitudinal MRI study	Prog Neuropsychopharmacol Biol Psychiatry	1999
Paus/Evans	Structural maturation of neural pathways in children and adolescents: in vivo study	Science	1999
Thompson/Toga	Growth patterns in the developing brain detected by using continuum mechanical tensor maps	Nature	2000
Eckert/Giedd	The epigenesis of planum temporale asymmetry in twins	Cerebral Cortex	2002
Gogtay/Thompson	Dynamic mapping of human cortical development during childhood through early adulthood	Proc Natl Acad Sci U S A	2004
Wallace/Giedd	A pediatric twin study of brain morphometry	J Child Psychol Psychiatry	2006
Gogtay/Thompson	Dynamic mapping of normal human hippocampal development	Hippocampus	2006
Lenroot/Giedd	Sexual dimorphism of brain developmental trajectories during childhood and adolescence	NeuroImage	2007
Shaw/Giedd	Cortical morphology in children and adolescents with different apolipoprotein E gene polymorphisms: an observational study	Lancet Neurology	2007
Giedd/Neale	Structural brain magnetic resonance imaging of pediatric twins	Human Brain Mapping	2007
Schmitt/Giedd	A multivariate analysis of neuroanatomic relationships in a genetically informative pediatric sample	NeuroImage	2007
Shaw/Wise	Neurodevelopmental trajectories of the human cerebral cortex	J Neuroscience	2008
Schmitt/Giedd	Identification of genetically mediated cortical networks: a multivariate study of pediatric twins and siblings	Cerebral Cortex	2008
Ordaz/Giedd	Are there differences in brain morphometry between twins and unrelated singletons? A pediatric MRI study	Genes Brain Behav	2009
Shaw/Giedd	Effects of the Val158Met catechol-*O*-methyltransferase polymorphism on cortical structure in children and adolescents	Molecular Psychiatry	2009
Lenroot/Giedd	Differences in genetic and environmental influences on the human cerebral cortex associated with development during childhood and adolescence	Hum Brain Mapping	2009
Wallace/Giedd	A bivariate twin study of regional brain volumes and verbal and nonverbal intellectual skills during childhood and adolescence	Behavior Genetics	2010
Schmitt/Giedd	A twin study of intracerebral volumetric relationships	Behavior Genetics	2010
Tiemeier/Giedd	Cerebellum development during childhood and adolescence: a longitudinal morphometric MRI study	NeuroImage	2010

The list includes publications describing findings obtained in typically developing children and adolescents (singletons and twins).

(raw and derived). Such procedures also ensure confidentiality of the participants; no identifying information is entered on any forms or computers/MR console at any point. Besides the actual development and maintenance of the database, the most time consuming step is the consistent naming of the hundreds and thousands of variables. A simple and yet intuitive system is required to ensure that future users of the database, often not associated with the conception of the project and data acquisition (e.g. graduate students, postdoctoral fellows and collaborators), can navigate through the entire dataset with relative ease.

ACHIEVEMENTS TO DATE

To date, more than 3,000 brain and behavior datasets have been acquired in typically developing children and adolescents across the four pediatric studies reviewed here. What have we learned? The rich set of publications

TABLE III. Publications based on the SYS study

First/last author	Title	Journal	Publication year
Pausova, Paus/ Watkins	Maternal smoking and the offspring brain and body during adolescence: design of The Saguenay Youth Study.	Human Brain Mapping	2007
Paus/Pausova	Morphological properties of the action-observation cortical network in adolescents with low and high resistance to peer influence	Social Neuroscience	2008
Toro/Paus	Prenatal exposure to maternal cigarette smoking and the adolescent cerebral cortex	Neuropsychopharmacology	2008
Paus/Pausova	Corpus callosum in adolescent offspring exposed prenatally to maternal cigarette smoking	NeuroImage	2008
Syme/Pausova	Intra-abdominal adiposity and the metabolic syndrome in adolescence: gender differences and underlying mechanisms	Archives of Pediatrics & Adolescent Medicine	2008
Toro/Paus	Brain size and folding of the human cerebral cortex	Cerebral Cortex	2008
Perrin/Paus	Growth of white matter in the adolescent brain: role of testosterone and androgen receptor	Journal of Neuroscience	2008
Kafouri/Paus	Maternal cigarette smoking during pregnancy and cognitive performance in adolescence	International Journal of Epidemiology	2009
Herve/Paus	Handedness, motor skills and maturation of the corticospinal tract in the adolescent brain	Human Brain Mapping	2009
Perrin/Paus	Sex differences in the growth of white matter during adolescence	NeuroImage	2009
Toro/Paus	Brain volumes and Val66Met polymorphism of the BDNF gene: Local or global effects?	Brain Structure and Function	2009
Syme/Pausova	Sex differences in blood pressure and its relationships to body composition and metabolic health in adolescence	Archives of Pediatrics & Adolescent Medicine	2009
Pausova/Paus	A common variant of the FTO gene is associated not only with increased adiposity but also with elevated blood pressure in French-Canadians	Circulation: Cardiovascular Genetics	2009
Syme/Pausova	Prenatal exposure to maternal cigarette smoking and accumulation of intra-abdominal fat during adolescence	Obesity	2009
Lotfipour/Paus	Orbitofrontal cortex and drug use during adolescence: role of prenatal exposure to maternal smoking and BDNF genotype	Archives of General Psychiatry	2009
Lotfipour/Paus	Prenatal exposure to maternal cigarette smoking interacts with a polymorphism in the alpha6 nicotinic acetylcholine receptor gene to influence drug use and striatum volume in adolescence	Molecular Psychiatry	2010
Pausova/Paus	Functional variation in the androgen-receptor gene is associated with visceral adiposity and blood pressure in male adolescents	Hypertension	2010
Paus/Pausova	Sexual dimorphism in the adolescent brain: Role of testosterone and androgen receptor in global and local volumes of gray and white matter	Hormones and Behavior	2010

based on the NIH-CHPB cohort clearly demonstrated that, for example, the human brain continues to mature structurally beyond early childhood and that this maturation proceeds along different trajectories in the different brain regions, in girls and boys, in participants with low and high IQ and under the varied influence of genes and environment (Table II). The SYS project has told us that sex-specific maturation of white matter is influenced by testosterone in a manner suggesting growth of the axon rather than myelin, that maternal smoking during pregnancy is associated with a number of differences in the brain structure of the adolescent offspring, and that the effects of environment (e.g. PEMCS) or experience (e.g. drug experimentation) influence the brain by interacting with specific genes (Table III). And the NIH-PD cohort is beginning to contribute novel knowledge regarding the nature of brain development during infancy and early childhood [Leppert et al., 2009]. The SYS and IMAGEN studies are currently conducting the first genome-wide analyses of the structural and functional brain phenotypes. Arguably, these and future findings from these four studies would have been difficult to achieve without the coordinated effort and resources invested by the three funding agencies (National Institutes of Health, Canadian Institutes of Health Research, The Sixth Framework Program of the European Union), tens of investigators, students and fellows, and hundreds of participants. Where do we go from here?

FUTURE DIRECTIONS

The natural evolution of large-scale MR-based studies of brain structure and function over the past 15 years clearly

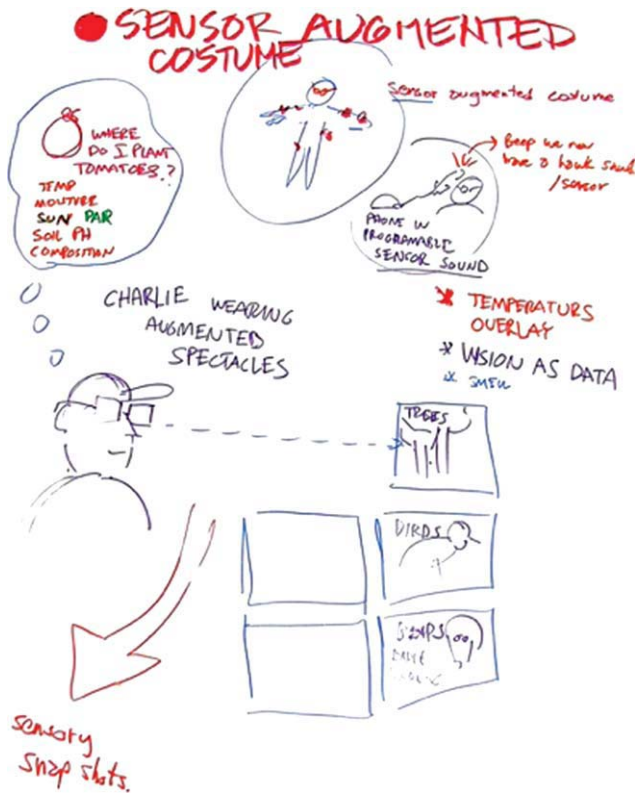

Figure 6.

Sensor augmented costume. A drawing illustrating ideas for the use of sensors for data gathering generated by a participant of a workshop organized by the Stanford Center for Innovations in Learning. Reprinted from Pea et al., 2004.

indicates the move from designs that include only brain "outcomes" to those also rich in measures of genetic and environmental "exposures". As the field develops, it is likely that we will see increasing sophistication in gathering high-fidelity information about the individual's environment, both personal (e.g. life habits, diet) and surrounding (e.g. family, neighbourhood). New technological developments may be brought to bear on efficient and objective data gathering in this domain. For example, at a workshop organized by the Stanford Centre for Innovations in Learning [Pea et al., 2004], workshop participants suggested various ideas for the use of sensors in data gathering (e.g. "sensor augmented costume", Fig. 6). A combination of sensor-based technology and/or mobile phones [Kim et al., 2008] with computer-based analysis of collected signals/images would provide a powerful tool for obtaining a series of snapshots of the individual's daily activities and environment. In terms of longitudinal data, it might be possible to make use of information gathered during the purchase of various goods, including food, so that one can build a long-term profile akin to customer profiling used by marketing companies (e.g. http://www.manifolddatamining.com/index.htm). Appropriate modifications of such technologies and data handling would be mandatory to ensure full protection of confidentiality and ethically acceptable use of the information gathered in this manner. Until such ethical issues are resolved, such approaches could be used at a neighborhood rather than an individual level.

In the same way as the level of sophistication is likely to increase on the "exposure" side, so it will on the "outcome" side. Clearly, new MR sequences are being developed that will provide new ways of extracting quantitative information about the structural and functional brain phenotypes. In the last 10 years, for example, addition of DTI and MTR have enriched considerably our ability to investigate the genetic and environmental factors influencing structural properties of white matter and, in turn, functional connectivity. Further developments will likely increase specificity of the MR-based measurements so that one can distinguish changes in the various cellular compartments in both grey and white matter. This work will also require parallel studies in experimental animals where the combination of in vivo (MRI) and ex vivo (histology, gene expression) approaches in the same individual allows one to discover the neurobiological underpinnings of a given MR signal.

Most of the current population-based MR studies are observational and, as such, they can only discover associations between exposures and outcomes [but see, for example, Pearl, 2009 and Spirtes, 2005 for the modeling of causal influences from observational data]. Causality can be injected into these studies in several ways, including longitudinal design, Mendelian randomization and intervention. *Longitudinal studies* can disentangle the cause-and-effect relationship in cases where the two events of interest are separated in time and the exposures and outcomes have been collected at all time points. In the case of a brain–behavior relationship, for example, a longitudinal design would enable the researcher to determine whether episodes of depression precede structural changes in the anterior cingulate cortex or *vice versa*. But in many cases of environmental exposures, such a time line cannot be established unless a birth-cohort design is used. *Mendelian randomization* provides an excellent alternative for establishing causality vis-à-vis environmental exposures. While being "randomized" vis-à-vis inheritance of other traits, a functional genetic variant may act as a proxy for an environmental exposure [Ebrahim and Davey Smith, 2008; Sheehan et al., 2008]. For example, the known association between breastfeeding and IQ may be due to a number of factors, from mother–infant attachment to various macro and micronutrients contained in breast milk. A recent study of a gene variant (FADS2) known to influence plasma levels of polyunsaturated fatty acids suggests that, at least in part, this particular exposure "leads" to the higher IQ [Caspi et al., 2007]. But the ultimate test of causality involves experimental manipulation (intervention) and hence the need for randomized control trials (RCTs) to test the effects of various exposures (e.g. diet) on brain

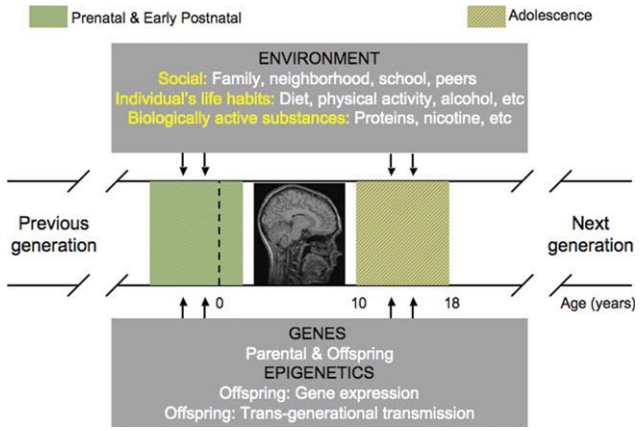

Figure 7.

Population neuroscience and the developing brain. Population neuroscience integrates research on pathways underlying effects of environmental and genetic "exposures" on brain and behavior "outcomes" throughout the individual's life and across generations.

and behavior outcomes. As suggested by Wareham [2008], "Mixed approaches combining data from large-scale observational studies with smaller intervention trials may be ideal."

In conclusion, population neuroscience has been making great strides in gathering new knowledge about genetic and environmental factors that shape our brains (Fig. 7). Although the studies considered here focus on brain development, from birth, through childhood to adolescence, other initiatives use similar approaches to study population samples at later stages of human development [e.g. DeStefano et al., 2009]. And yet another set of studies target patients with brain disorders such as attention-deficit hyperactivity disorder, schizophrenia or dementia [e.g. Kelly et al., 2007; Lawrie et al., 2008; Shen et al., in press]. Put together, the next decade is likely to bring a great deal of new knowledge about genetic and environmental risk factors, as well as biomarkers and predictors, underlying both vulnerability and resilience to mental disorders that emerge at different points in life.

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