Neuroimaging in health psychology: Methods, concepts, and applications

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How might the brain link environmental, social, behavioral, psychological, and biological factors to risk for and resistance against acute and chronic physical illnesses? Can understanding the roles of brain structure and function in physical health and disease across the lifespan guide new efforts to improve public health and individual wellbeing? Noninvasive neuroimaging methods to measure human brain structure and function afford ever-expanding opportunities to address these and other open questions in health psychology and related disciplines such as health neuroscience (Erickson et al., 2014; Inagaki, 2020). This chapter describes common neuroimaging methods to address basic and translational questions about the brain in the context of health psychology. It then presents interpretive heuristics derived from health neuroscience, offering empirical illustrations of studies that conceptualize the brain as a *predictor*, *mediator*, and *outcome* of health and illness processes across the lifespan. The chapter concludes with a perspective on new avenues for health neuroscience.

Common Human Neuroscience Methods and Measures

Structural and functional neuroimaging methods are among the most common neuroscience methods employed in psychology, but they have a shorter history of use in health psychology. Structural neuroimaging methods quantify the amount or volume of *in vivo* brain tissue, as well as other morphological features. The latter include measuring regional variation across the brain in the cortical surface area and thickness or tracing white matter tracts that comprise neural circuits and networks. These and other morphological features can exhibit plasticity throughout development and later life, especially in association with factors of interest to health psychologists (e.g., psychological stress, health behaviors, etc.). By contrast, functional neuroimaging methods assess changes in local hemodynamic and metabolic activity in the brain across behavioral and psychological states. Functional methods can also assess statistical

associations of hemodynamic and metabolic activity patterns across brain regions over time, thought to reflect inter-regional communication patterns of "functional connectivity." The most common of these structural and functional neuroimaging methods are reviewed next.

Structural Brain Imaging Methods and Measures

Frequently used structural neuroimaging methods include structural magnetic resonance imaging (sMRI), diffusion-weighted imaging (DWI), and susceptibility-weighted imaging (SWI). Both sMRI and DWI are popular in health psychology, so we focus on those below, but SWI is of growing interest in studies of cerebrovascular health and psychosocial determinants of brain aging and dementia risk (Shaaban et al., 2019).

Structural Magnetic Resonance Imaging. sMRI helps visualize and quantify *in vivo* brain anatomy and morphology, especially grey and white matter tissue. Grey matter is comprised of neuronal cell bodies, dendrites, axon terminals, and other non-myelinated parts of neurons. White matter is comprised of glial cells (e.g., oligodendrocytes) and their associated processes (e.g., myelin sheathing). In some cases, however, the appearance of certain types of white matter are signs of degenerative and inflammatory pathology (i.e., white matter hyper-intensities). Using conventional sMRI, researchers can quantify global (whole-brain) and regional indices of the amount or density of tissue present, the surface area and thickness of the cortex, and the presence of tumors and abnormalities. Although structural measures can be derived manually, automated approaches are also widely used, e.g., automated segmentation methods for identifying different subfields in a given brain structure such as the hippocampus. In essence, MRI works by applying a combination of strong magnetic fields (measured in Tesla units such as 3T or 7T), magnetic field gradients, and radio waves to induce polarization in (most commonly) the brain's hydrogen atoms (found in abundance in water and fat), in turn localizing

this polarization in 3D space. This method works because different types of tissues, fluids, and cells are differentially impacted by these gradients and radiofrequency pulses, allowing the imaging of particular tissue types (e.g., grey vs. white matter) or even neurophysiological parameters (e.g., blood flow). For more on MRI physics, see Martinez (2018), Plewes & Kucharczyk (2012). Ultimately, sMRI is a valuable technique for health psychology. For example, health psychologists might wish to examine how health behaviors (e.g., physical exercise, sleep) or health status (e.g., cardiovascular disease risks, systemic inflammation) may predict the magnitude of change in total brain volume. Other health psychologists might examine how chronic life stressors or early life adversity are associated with volumetric differences in brain structures or accelerated cortical thinning in later life.

Diffusion-Weighted Imaging. DWI is an MRI acquisition technique that measures the diffusion of water molecules in the brain. To do so, it applies magnetic field gradients that are sensitized to a particular diffusion direction and repeats this process multiple times in multiple directions. In turn, diffusion tensor imaging (DTI) uses mathematical models to estimate the direction and magnitude of the water diffusion measured in DWI. DTI can thus be used to map the direction and structural properties of cellular components (e.g., myelin) in white matter tracts that connect brain areas. One application of DTI is *tractography*, "tracing" white matter fiber tract connections. Rather than relying on post-mortem examinations or tract-tracing injections, DTI tractography allows researchers to noninvasively map white matter connections within and between brain structures. Within DTI, *streamline tractography* is a typical method wherein the projection of a given tract or fiber pathway can be traced along the direction of fastest diffusion or *throughput,* often assessed with computational methods (e.g., algorithms) and expert user evaluation. This approach forms the basis of many tract-tracing studies, revealing the physical,

"wired" connections between white matter structures. See O'Donnell & Westin (2011) and Tian et al. (2020). While sMRI provides insight into the volume and thickness of brain structures, DWI methods offer a rich picture of the brain's structural interconnections (i.e., white matter *structural connectivity*). Structural connectivity is important because it reveals the neuronal architecture likely underpinning the brain's *functional connectivity*, or how different brain regions work together in functional networks. Structural connectivity is sensitive to development and experience, creating meaningful between-person variation in how different brain structures are wired together (e.g., Hagmann et al., 2010; Teicher et al., 2016). Similar to sMRI, DWI can be used in health psychology to understand the importance of health behaviors, health status, developmental environment (e.g., pollution, early life adversity), and life experiences (e.g., trauma, chronic stressors) for brain health outcomes such as the density of connections across the whole brain or between regions, as well as axonal degradation due to aging or pathology.

Functional Brain Imaging Methods and Measures

Common functional methods include functional magnetic resonance imaging (fMRI), positron emission tomography (PET), perfusion imaging using arterial spin labeling (ASL), functional near infrared spectroscopy (fNIRS), and magnetoencephalography (MEG). At present, fMRI and PET are popular functional neuroimaging methods, so we focus on these methods.

Functional Magnetic Resonance Imaging. fMRI provides an indirect, *in vivo* measure of local neuronal activity. Increased neuronal activity produces a local hemodynamic response that captures shifts in the ratio of oxygenated to deoxygenated hemoglobin, known as the blood oxygen level-dependent (BOLD) signal. MRI can capture the magnitude of the BOLD signal because oxygenated and deoxygenated hemoglobin have different magnetic properties. Importantly, changes in the BOLD signal *indirectly* correspond to neuronal activity (Logothetis,

2002). Furthermore, this signal is slightly lagged, beginning 1-3 seconds after neuronal activity, peaking 6 seconds after, and decaying after 20-25 seconds. As such, fMRI affords good spatial resolution of anatomy (e.g., on the order of millimeters or sub-millimeter), but has relatively poor temporal resolution relative to electrophysiological methods that can detect neural changes on the order of milliseconds (but see Jung et al., 2021). For fuller introductions, see Huettel et al. (2014) and Wager & Lindquist (2015). By far, fMRI is the most popular functional neuroimaging technique used in health psychology. For instance, it has been used to identify the functional brain regions and networks involved in health status, motivations, and behaviors (e.g., the neural correlates of cardiovascular risk, systemic inflammation, and appetite, e.g., Althubeati et al., 2022; Ginty et al., 2017; Kraynak et al., 2018). Similarly, other fMRI studies examine longitudinal and cross-sectional relations between physical or psychosocial environments (e.g., food insecurity, childhood maltreatment) with brain function, with the hypothesis that brain function mediates environmental effects on physical and mental health, cognitive development and aging, and psychosocial adjustment (e.g., Čermaková et al., 2022; Chu et al., 2019).

Positron Emission Tomography. PET can assess regional brain metabolic processes in healthy and diseased states. Cerebral blood flow (CBF) and glucose metabolism are among the most common phenomena studied with PET (Paulson et al., 2010). Radiolabeled tracers are injected, and these tracers elicit gamma rays that the PET scanner detects and localizes to quantify regional changes in blood flow, metabolic activity, and the composition and absorption of biochemicals such as neurotransmitters. Common positron emitting radioisotopes used include ^{18}F (fluoride), ^{11}C (carbon), and ^{15}O (oxygen). For example, PET with fluorodeoxyglucose (FDG-PET) tracks regional glucose metabolism, which is closely linked to neuronal activity (Barros et al., 2005). Thus, FDG-PET can indirectly measure neuronal activity at rest and during

different behavioral states. Similarly, ^{15}O-PET can measure blood flow, enabling researchers to identify areas of ischemia, tumor presence, and neurodegeneration. Development of radiotracers or *ligands* for biochemicals and their receptors continues to accelerate PET work on physical and mental health, such as tracing dopamine metabolism in studies of reward and addiction or amyloid plaque accumulation in studies of dementia and aging (Hatano et al., 2006; Klunk et al., 2004). PET can also be used to examine amino acid transport, protein synthesis, and regional pH levels using ligands such as DL-tryptophan, L-glutamate, L-leucine, and ^{11}C-DMO. For more, see Heurling et al. (2017) and Hooker & Carlson (2019). While PET may be less frequently used in health psychology relative to fMRI, it is still an invaluable tool for questions that cannot be as easily examined with fMRI. For example, health neuroscientists may wish to trace specific neurotransmitter functions or aspects of brain metabolism, as relevant for studies of cardiovascular health, appetite, addiction, pain, psychological stress, depression, and dementia.

Methodological Considerations for Design and Analysis

Although the above neuroimaging methods offer health neuroscientists a diverse toolkit, each method brings its own set of limitations and considerations for study design, analysis, and conceptual inference. Special consideration should always be given to matching the questions at hand to the method and metrics used, as well as to method-specific inferential limitations. We next discuss these method-specific considerations for design, analysis, and interpretation.

Structural Imaging Design. In addition to sMRI's excellent spatial resolution, this method affords two other benefits: (1) MRI scanners are available at many research universities and medical campuses, and (2) sMRI is amenable to repeated administration in the context of longitudinal and intervention studies. However, there are several caveats that MRI researchers should consider; furthermore, because DWI is based upon MRI, it shares many of these issues.

First, although there are no known health risks of MRI, the strong magnetic field can induce ectopic heartbeats and other abnormal heart rhythms, and higher magnetic fields of 7T or 10T can induce vertigo and nausea in some individuals. Due to the strong magnetic field, all participants, researchers, and technologists must follow intensive safety protocols to ensure that ferromagnetic metals are kept away from the MRI scanner. Separately, because participants are placed in the narrow bore of the MRI scanner, individuals who are prone to claustrophobia may not be able to participate. Indeed, some individuals find the MRI experience to be stressful, potentially confounding research (Muehlhan et al., 2011). All known sMRI and DWI signals are sensitive to noise induced by subtle head movements (i.e., *motion artifacts*) and to systematic variation induced by breathing, the pulse, etc. These artifacts may be further exacerbated in specific research populations. For instance, it can be difficult for young children or adults with Parkinson's to remain still, leading to special considerations when including these populations. Finally, between-person variations in brain anatomy—whether due to naturally occurring individual differences, developmental stages, aging, or even the presence of lesions or pathology—make between-person structural comparisons challenging. See Eliot et al. (2021), Gray et al. (2009), and Mulcahy et al. (2019).

Functional Imaging Design. As reviewed above, structural neuroimaging generates measures of brain structure that can be examined as correlates, predictors, or outcomes of health-related processes. However, health neuroscientists are often interested in psychological processes and their underlying neurobiological substrates that contribute to health and disease states; as such, they tend to rely more upon methods like fMRI and PET. Given that fMRI builds upon MRI, fMRI is similarly susceptible to motion artifacts, but this is more problematic for fMRI because scans tend to be longer. Motion can also become confounded with task features or task

types (e.g., if a task induces startle). To minimize motion artifacts, fMRI tasks are designed to limit movement, with responses given on a hand-held button box. Another challenge is how best to adapt common behavioral paradigms used in health psychology, such as a psychosocial stress tasks, for in-scanner use in a way that minimizes motion artifacts while maintaining ecological validity. Similarly, fMRI users must consider how best to titrate task duration and stimulus onset to the temporal dynamics of the BOLD signal (which, as noted earlier, begins 1-3 seconds after neuronal activity and decays after 20-25 seconds). Nonetheless, even in the best-case scenarios, artifacts and outliers are bound to occur in the BOLD signal timeseries, but their influence can be reduced using signal preprocessing tools, censoring, and covariates (Huettel et al., 2014).

Relative to fMRI, PET offers diverse measures of neuronal and metabolic activity, but it is more expensive, invasive, and less widely available than fMRI. Similarly, while the temporal resolution of fMRI is on the scale of seconds, the temporal resolution of PET is longer (>1-2 minutes). Other disadvantages are that PET requires a cyclotron and physicists who maintain and oversee advanced instrumentation. Furthermore, the radioactive materials and ligands used in PET can only be given safely a few times to the same individual before it becomes unsafe, unlike fMRI wherein there are no known risks to repeated assessments. Yet PET is less susceptible to motion artifacts and can be more readily combined with psychophysiology, phlebotomy, and neuroendocrine assays, enabling health research that might be impractical with fMRI.

Experimental Design. Although functional neuroimaging is promising for psychological and behavioral questions, several issues should be considered when designing experimental tasks and conducting statistical analyses. *Task-based approaches* typically compare relative levels of brain activity between two or more experimental conditions (e.g., receiving social support from a friend vs. a stranger). Within fMRI, there are two broad task-based approaches, which can

sometimes be combined: blocked and event-related designs. A *blocked design* administers task conditions (e.g., images of high calorie vs. low calorie food) as separate blocks to maximize the time for a robust BOLD response to develop in each condition. Here, for example, an experimenter might administer a block of 10 trials in row in which participants see high calorie foods (e.g., for 30 seconds), alternating with a separate block of 10 trials with low-calorie foods (e.g., for 30 seconds). *Event-related designs* instead interleave stimuli in a stochastic trial-by-trial manner, supporting tasks wherein it is important to analyze neuronal responses during individual trials. Thus, the experimenter can vary (i.e., randomize) the stimulus type on a trial-by-trial basis. While fMRI supports both blocked and event-related designs, PET works best with a blocked design given its slower temporal resolution. There is also growing interest in *resting state paradigms* to explicate the ongoing magnitude and organization of functional brain activity in the absence of an ongoing behavioral task (Damoiseaux et al., 2006). These paradigms are thought to tap into trait-like phenotypes of brain function (Vaidya & Gordon, 2013), which may then be related to individual differences relevant for physical health and health psychology.

Neuroimaging Analysis. There are two general classes of analytical approaches to quantify functional and structural measures: mass-univariate vs. multivariate models. By far the most frequent, mass-univariate approaches often use the general linear model (GLM) framework (Monti, 2011). With GLM, researchers can model within-participant (and for functional imaging, within-task) effects by specifying different levels of analysis that reflect scans within individuals (if there are multiple scans), individual-level effects, and group-level effects, accounting for data interdependencies. Here, the goal is to determine whether a given model predictor or condition is associated with observed variability across voxel timeseries. Yet functional methods capture several hundred or thousand variables that often exhibit moderate to high levels of

multicollinearity. Moreover, individual variables are likely noisy and unstable, potentially elevating false positive rates. To this end, dimensionality reduction approaches (e.g., PCA, ICA) derive latent factors of brain structure or function, while advanced classification and regression approaches use cross-validation to identify brain features that reliably classify or predict outcomes (Calhoun et al., 2017; Davatzikos, 2019; Woo et al., 2017).

Regional vs. Whole-Brain Analysis. In addition to the above design and analysis considerations, neuroimagers face two choices that impact their design and analysis approaches. First, neuroimagers must decide whether they will take a regional vs. whole-brain approach or some combination of both and, second, whether they will focus on functional activation vs. connectivity metrics or both. In working with structural measures, researchers often are interested in the volume or integrity of a specific structure (e.g., hippocampus) or the density and integrity of structural connections (e.g., white matter tracts) between regions. Similarly, functional measures can focus on regions-of-interest (ROIs) or examine voxel-wise signals across the whole brain. An ROI approach offers two advantages (Poldrack, 2007). First, when there are strong theoretical justifications to examine specific regions, ROIs serve as principled, *a priori* tests of region-specific hypotheses. ROI approaches also reduce the number of statistical tests, minimizing Type-I errors. Yet ROI approaches are less frequently used today due to the recognition that behavioral and psychological functions are not localized to specific regions but instead likely emerge from the context-dependent and distributed co-action of multiple regions or *functional networks* (Yeo et al., 2011). As such, focusing only on ROIs may lead literatures to develop fragmented, inaccurate summaries of how neural processes link to behaviors and states.

A whole-brain approach arguably provides a more comprehensive account of brain structure and function (Kragel et al., 2018; Petersen & Sporns, 2015). When combined with

replication and cross-validation methods, whole-brain approaches also provide stronger tests of the *specificity* of effects, examining the whole population of a given individual's voxels and showing which regions and systems consistently or reliably relate to the processes of interest. Measuring single voxels across any imaging method can be inherently unreliable, but aggregating signals across voxels within regions and across the brain improves reliability and the signal-to-noise ratio. As such, although both ROI and whole-brain approaches aggregate signals across voxels, a whole-brain approach provides greater reliability and signal-to-noise ratio than the ROI approach. The cost to whole-brain approaches is that because statistical tests are performed on every voxel, whole-brain analyses are susceptible to inflated Type-I error rates (i.e., false positives). This concern can be somewhat (although not totally) ameliorated by combining statistical thresholds at each voxel with spatial (e.g., cluster-extent) thresholds across voxels (e.g., using random field theory). For example, to minimize the risk of false positive errors, whole-brain analyses typically apply a statistical correction for multiple comparisons, such as the Benjamini-Hochberg correction for False Discovery Rate (FDR) or the Bonferroni correction for Family Wise Error (FWE). Because whole-brain functional neuroimaging tests effects on hundreds of thousands of voxels simultaneously, such corrections are critical relative to other methods and measurement modalities used in health psychology and neuroscience.

Activation vs. Connectivity. Functional neuroimaging can assess either activation or connectivity. Functional activation (or, conversely, deactivation) reflect changes in brain activity (e.g., percent change in BOLD signal or CBF) observed between given conditions (e.g., a stressor condition > control condition with a fixation cross), known as a *contrast*. Importantly, "activation" and "deactivation" are artificial terms that are relative to their comparisons (e.g., there was greater activation in the insula, amygdala, and anterior cingulate in the stress condition

relative to control); these terms do not necessarily mean that neurons are more vs. less neurophysiologically active or that neurons are turning "on" vs. "off" (Singh, 2012).

Given growing interests in distributed networks across the brain, neuroimagers are increasingly using metrics of functional connectivity between given ROIs or across multivariate whole-brain patterns. Functional connectivity tests associations between two or more co-occurring voxel time series either at rest, during a task, or during a manipulated behavioral state. Functional connectivity can be model-based or data-driven and undirected or directed. *Model-based approaches* test a hypothesized set of functional connections (e.g., dynamic causal modeling), whereas *data-driven approaches* identify patterns and regions that covary together over time (e.g., independent component analysis). *Undirected connectivity* estimates the covariation of timeseries between regions or voxels; the simplest approach to estimate undirected connectivity involves calculating the Pearson correlation coefficient between two timeseries for specific brain regions. For example, a health neuroscientist might examine how brain regions co-activate together in time in response to painful stimuli. On the other hand, *directed connectivity*, also termed effective connectivity, uses principles such as Granger causality to infer the temporal ordering of regional activations. Directed connectivity methods and related automated search algorithms rely on techniques such as auto-regressive models which have a long history of quantitative development for other types of intensive timeseries data (Henry & Gates, 2017). A health neuroscience application of directed connectivity might examine how neural activity in one brain region during painful stimulation might propagate to additional brain regions. Other undirected and directed methods test connectivity changes over time or between experimental conditions (e.g., dynamic functional connectivity, psychophysiological interaction analyses). See Bullmore & Sporns (2009) and Meier et al. (2016).

Broader Neuroimaging Caveats and Pitfalls

Health psychologists who wish to study the brain have many options in terms of modality (structural vs. functional), design (resting state vs. task-based), domains (ROI vs. whole-brain; regions vs. networks), and analytic strategies (mass-univariate vs. multivariate). Generally, the field of neuroimaging is moving away from ROI-based, mass-univariate approaches and toward whole-brain, multivariate, and network-based approaches. Innovations in statistical methods and computing platforms make these changes increasingly feasible. Ultimately, researchers' decisions depend upon the available equipment and research question at hand. However, there are broader caveats and pitfalls that health neuroscientists should consider, including confounders and biological constraints or issues with sample size, generalizability, reliability, and replicability, etc. We close this section by highlighting some of these caveats and pitfalls.

Confounders and Biological Constraints. As in health psychology and behavioral medicine, there are important biological confounds and constraints to consider, which are also relevant in neuroimaging. For example, the BOLD signal can vary according to metabolic state, recent sleep, and age (Fukunaga et al., 2008; Grady & Garrett, 2014; Iacovella & Hasson, 2011). These confounds add additional considerations in health neuroscience studies, to ensure that brain metrics are varying due to the task, question, or populations of interest, rather than due to extraneous state or trait factors. Biological confounders are also not just problematic in functional but also structural approaches like DTI wherein factors such as time of day or recent water intake can correlate with brain-derived metrics (e.g., Thomas et al., 2018).

Sample Size, Generalizability, Reliability, and Replicability. Given that neuroimaging studies are expensive, studies have historically used small convenience samples, e.g., undergraduate students (Marek et al., 2022). Studies are increasingly encouraged to recruit more

representative, diverse samples through methods such as stratified sampling, oversampling under-represented groups, and multi-site collaborations. Relatedly, recent reviews have raised important issues around the lack of robustness and reliability of neuroimaging findings, especially when linked to self-report, behavior, or individual differences as would be commonly examined in health neuroscience (Bossier et al., 2020; Elliott et al., 2020; Kragel et al., 2021).

As such, careful methodological and psychometric work is needed to determine whether functional neuroimaging tasks reliably elicit activity in hypothesized brain regions and across hypothesized brain networks. New tasks or adapted tasks should be piloted first in the scanner to examine how the scanner environment and constraints may alter the reliability and ecological validity of the task. Neural activity in response to the same task can also vary across multiple sessions, which may in part be driven by other biological or psychological confounds (e.g., physiological state, practice effects, etc.). This latter point can be especially problematic for longitudinal or repeated measure brain imaging studies.

Inferential Pitfalls. It is easy to incorporate neuroimaging methods into a study or grant, but much more difficult to analyze and interpret what results mean. Here, there are two well-known inferential pitfalls to avoid. First, in traditional GLM approaches to fMRI or PET, condition differences (contrasts) are examined by creating a group average of the brain map and neural activity therein. However, this can lead to Simpson's paradox, wherein the regions of functional activity or connectivity extracted may not reflect activity in any one individual brain (Roberts et al., 2016). Mixed effects and hierarchical approaches (e.g., nesting individual-level brain maps within a group-level brain map) can help minimize this.

Another inferential pitfall is describing neuroimaging results in unwarranted causal language. A large majority of structural and functional studies in health neuroscience are cross-

sectional, correlational studies interested in identifying how individual differences in brain structure or function relate to individual differences in physiological, mental, behavioral, or environmental factors. However, it is not uncommon to see researchers use causal language, discussing the "neural mechanisms" of a phenomenon or providing overly strong inferences about the direction of causality between variables that are only statistically correlated. Relatedly, *reverse inferences* are logical fallacies that have long been noted as problematic (Sarter et al., 1996), but continue to occur (Poldrack, 2011). For illustration, reverse inferences occur when researchers conclude that because they found amygdala activity in response to their study's task and given prior work implicating the amygdala in negative emotion, this must mean that participants were feeling negative emotion during the task. Reverse inference issues can also extend to functional networks, where nomenclature such as the "reward network," "salience network," or "executive control network" may lead researchers to reify and infer psychological processes only from the observed brain imaging data itself. Yet interpretive caution is critical, given that there are many reasons why activity in a brain region or network could be observed.

Ultimately, human neuroimaging brings unique challenges but when understood, applied, and interpreted carefully, it can add value to health psychology by revealing biological, psychological, and environmental pathways in health and disease. To do this, health neuroscientists may start with a health-related factor of interest (e.g., psychosocial support) and consider which pathways and measures might be most biologically plausible, as discussed next.

The Brain as Predictor, Outcome, and Mediator of Physical Health and Illness

Health neuroscience provides a conceptual framework for designing and interpreting research studies, as well as developing applications that rely on brain imaging measures as relevant for health-focused inquiries. Within this perspective, the brain is a central organ for

health and disease, wherein the determinants, concomitants, and consequences of health are tied to lifelong, bidirectional, dynamic interactions between brain and body, brain and environment, and brain and behavior (Erickson et al., 2014; McEwen & Gianaros, 2010). Given the complexity of pathways linking the brain to health, a programmatic approach to health neuroscience involves systematically examining the brain as a predictor, outcome, and mediator of physical health and illness. To help illustrate this, we next discuss how health neuroscience studies have examined the brain as a health predictor, outcome, or mediator (see **Figure**).

Brain as a Predictor of Health and Disease Outcomes

One central hypothesis in health neuroscience is that the brain is an important *predictor* of health and disease outcomes. Thus, much work in health neuroscience seeks to verify, describe, and explain the pathways by which brain structure and function promote downstream health-relevant biological, psychological, and behavioral factors. In these studies, the brain is often examined as a *conceptual predictor* (as in cross-sectional studies) or a *causal predictor* (as in longitudinal or experimental studies).

Brain as Conceptual Predictor. Before employing expensive longitudinal studies, experimental manipulations (e.g., temporarily blocking certain neural receptors), or rare patient samples (e.g., where there is brain abnormality or damage), one important starting point is to examine the brain as a correlate or cross-sectional conceptual "predictor" of the health-relevant factor of interest. Many such studies focus on identifying individual differences in brain structure or function and then using these as correlates of health status, health behaviors, or psychosocial functions. The underlying assumption here is that these individual differences may explain variability in a given health outcome. For example, individual differences in neural activity evoked by stressful or negative emotional tasks can predict aspects of cardiovascular risk

(Gianaros et al., 2014, 2017, 2020). Specifically, different patterns of neural responses to stressful cognitive tasks (e.g., time-pressured Stroop task) and negative emotional images were linked to cardiovascular risk factors such as larger stress-related blood pressure reactions, systemic inflammation, and worse preclinical atherosclerosis, as measured by carotid artery intima-media thickness. Ultimately, cross-sectional studies that consider the brain as a conceptual predictor provide a useful starting point for a programmatic health neuroscience. These studies provide first steps in establishing specific neural patterns and pathways of structure and function that would be important to target in experimental or longitudinal approaches. However, these studies do not test their underlying causal assumption of brain as predictor.

Brain as Causal Predictor. One way to assess the brain as a *causal* predictor is to use longitudinal and quasi-longitudinal studies wherein researchers track brain structure or function links with health or related psychosocial or behavioral factors over time. For example, studies have examined the extent to which neural responses to persuasive health messages associates with future smoking reduction and cessation (Falk et al., 2010, 2011), how neural reactivity to rewarding stimuli and markers of brain structure associates with future weight and health behaviors (Demos et al., 2012; Yokum et al., 2012), and how individual differences in neural reactivity to threat associates with later reactions to life stress up to four years later (Swartz et al., 2015). Within the context of early life health development, studies show associations between parental brain function and children's later health outcomes and stress-related reactivity (Abraham et al., 2018). Other work demonstrates that structural measures of brain aging predict mortality risk (Cole et al., 2018), that stress-related amygdala activity predicts future clinical cardiovascular events above-and-beyond conventional risk factors (Tawakol et al., 2017), and

that regional brain activity during a cognitive stressor can predict the 2-yr longitudinal change in clinic blood pressure and cardiometabolic risk (Allen et al., 2020; Jennings et al., 2017).

Other ways to examine the brain as a causal predictor are to use experimental manipulations that temporarily alter brain function or to examine special patient populations where brain structures are degenerating, diseased, or damaged. For example, transcranial magnetic stimulation (TMS) is a type of noninvasive brain stimulation that allows researchers to stimulate neurons within a local brain region with magnetic fields. In health neuroscience, TMS has been used to identify and intervene on the neural correlates of addiction, with some success at reducing the use of substances such as cigarettes and cocaine (Gorelick et al., 2014). TMS can also examine cerebral cortical circuits that regulate peripheral physiology relevant to health (Makovac et al., 2017). Another common manipulation approach is to use a pharmacological agent to blockade a specific kind of receptor in the brain, such as beta-adrenergic receptors. Depending on the receptors of interest, sometimes pharmacological blockades can capitalize on the fact that certain chemicals cannot cross the blood-brain barrier, providing greater specificity in which receptors are blockaded. For example, *nadolol* is a beta-adrenergic receptor blockade that targets receptors primarily in the peripheral nervous system whereas *propranolol* acts on both central and peripheral nervous system receptors. By combining different blockades with functional neuroimaging (e.g., fMRI), researchers can pinpoint how signaling via a given kind of receptor in the brain causally impacts health-related biological, psychosocial, and behavioral factors. For example, to disentangle peripheral vs. central nervous system noradrenergic pathways in cardiovascular responses to acute stress, researchers could administer nadolol vs. propranolol vs. placebo in a double-blinded randomized control trial and then measure how cardiovascular stress reactivity and related neural activity in visceromotor regions that regulate

cardiovascular function might differ by drug administration.

Finally, studies with special patient populations where specific brain structures are impacted provide another critical avenue for understanding how the brain may causally relate to psychosocial function, behavior, and physical health (Ahmed et al., 2018; Buchanan et al., 2010). These studies often examine individuals suffering from neurodegenerative diseases (e.g., Alzheimer's disease, frontotemporal dementia), traumatic brain injuries, or damage due to lesions and tumors relative to healthy controls. One caveat is that there are complex interplays between health status, health behaviors, and environmental factors *prior* to the disease, injury, or damage which may be confounded with post-disease, injury, or damage effects.

Brain as Outcome and Mediator Bridging Environment and Health, Mind and Body

Another central theme in health neuroscience is that environmental influences, health or disease processes, and their interactions across the lifespan can alter brain structure and function. This hypothesis is affirmed across many cross-sectional and longitudinal studies, such as those examining how individual and developmental differences in brain morphology can be explained by chronic systemic inflammation, adiposity, adverse or isolating social environments, lifestyle habits (e.g., diet, exercise), environmental pollution, etc. (de Prado Bert et al., 2018; Gianaros et al., 2007; Layden et al., 2017; Muscatell, 2018). The health of other bodily systems, such as cardiovascular function and fitness, can also impact brain function and fitness. As an example, atherosclerosis impairs brain perfusion, whereas a lifestyle that promotes cardiorespiratory fitness is neuroprotective, especially as evidenced in mid and late life (Hillman et al., 2008; Li et al., 2019). Looking at the brain as a health outcome can also occur in a mediational context, such as studies wherein neighborhood disadvantage and racial residential segregation predict brain

morphology via intermediate biological and behavioral pathways (Gianaros et al., 2015; Hunt et al., 2020; Pohl et al., 2021; Zeki Al Hazzouri et al., 2022).

Recognizing that the brain is a target of health and disease leads to the recognition that the brain can also serve as an important *mediator* or pathway by which health and physiology shape the mind and behavior, and vice versa, wherein the brain transduces environmental signals and subjective states into tangible health consequences and processes (Hall et al., 2018; Miller et al., 2009). For example, structural imaging has examined the brain morphology mediating the association between systemic inflammation and cognitive function (Marsland et al., 2015) or as linking health intervention effects to cognitive benefits (Bherer et al., 2013). Similarly, functional neuroimaging has revealed the brain as a mediator between health messaging to behavior change (Cooper et al., 2019) and between social threat and psychological or physiological processes such as working memory, anxiety, or cardiovascular reactivity (Eisenbarth et al., 2016; Slavich & Irwin, 2014; van Ast et al., 2014). Beyond these examples, there are three ways that prior work has examined the brain as a mediator in health neuroscience.

Objective and Subjective Environments Impact the Brain and Health. Some theories argue that the brain makes predictions about what environmental events mean for the organism, in turn orchestrating physiological, psychological, and behavioral responses that shape downstream health and disease (e.g., McEwen & Stellar, 1993). Thus, both objective and subjective facets of the environment can shape health and wellbeing, with the brain as a "biological embedder" of environmental effects. For example, the environments that individuals inhabit vary along several objective factors: air, water, soil, and noise pollution; local weather patterns; population density; access to occupational and educational opportunities, affordable housing, healthcare and healthcare messaging, healthy foods, and health-promoting recreational

activities; as well as ongoing life circumstances such as managing a disease or facing discrimination (e.g., Brosso et al., 2021). These objective factors often coalesce together based on individuals' levels of socioeconomic advantage vs. disadvantage and majority vs. minority status, thus perpetuating chronic stressors and health disparities that accumulate as individuals age within their communities and social strata (Adler & Newman, 2002; Steptoe & Zaninotto, 2020). Similarly, subjective facets of the environment matter, including perceptions of social support and belonging vs. perceptions of social isolation or exclusion, perceptions of relative inequality and scarcity vs. equality and abundance (i.e., subjective social status), as well as appraisals of life stressors (Cohen, Murphy, & Prather, 2019; McEwen & Gianaros, 2010). For example, much work shows that the brain mediates social status and support effects on immune responses to acute social stress (Gianaros & Wager, 2015; Inagaki, 2018; Muscatell, Dedovic, et al., 2016). Other examples include ongoing research targeting how environmental pollution (e.g., air quality) over time negatively impacts brain function, leading to downstream cognitive declines and accelerated aging (de Prado Bert et al., 2018; Zhang et al., 2018).

Physiology and Health Matter for Psychology and Behavior via the Brain. Another large literature examines how underlying health, disease, and physiological processes can, via the brain, shape important psychological or behavioral outcomes such as psychological stress, mental health, cognitive functioning, and health-related decisions. This work can be divided into (1) longitudinal studies examining chronic or trait-level health and disease indicators and (2) experimental studies that manipulate a physiological system or pathway. Both types of studies can provide powerful demonstrations of the brain's role as mediator between the healthy vs. diseased body and behavioral functioning. Some exemplar studies include work examining brain morphology (e.g., cortical gray matter volume) as a mediator linking the association between

systemic inflammation and blood pressure to cognitive functioning across mid and late life (Marsland et al., 2015; Swan et al., 1998), which suggests that systemic inflammation may over time lead to grey matter shrinkage, which is associated with worse cognitive aging. Other exemplar studies examine how neural activity in regions such as the insula link acute and chronic inflammation to sickness behaviors and social affective outcomes such as social withdrawal and depression (Lekander et al., 2016; Muscatell, Moieni, et al., 2016; Slavich et al., 2010).

Brain as Mediator of Health: Sickness Behaviors and Perceptions. A more direct way to understand the brain's role as a mediator is to examine how the brain gives rise to *interoception*, which broadly includes the generation and perception of bodily states and sensations (Craig, 2003; Quigley et al., 2021). As such, interoception is likely foundational for many aspects of health and wellbeing, such as mental health, stress management, risk-taking, health motivation, and behavior change (Khalsa et al., 2018; Tsakiris & De Preester, 2018). Similarly, interoception appears to shift with age and disease status such as hypertensive heart disease (e.g., Bonaz et al., 2021; Khalsa et al., 2009; MacCormack, Henry, et al., 2021), suggesting that biological aging and disease-related pathophysiology can influence physiological and neural pathways supporting interoception. Understanding the role of the interoceptive brain as an outcome and mediator in physical and mental health, stress, disease, and aging is an important new direction for health neuroscience.

Future Directions in Health Neuroscience

Structural and functional brain imaging methods have revolutionized the questions that health psychologists can ask while helping reveal how the body and mind, physical and mental health can impact each other via the brain. Health neuroscience informs health psychology and behavioral medicine research by testing the interplay between environmental, behavioral,

psychological, and neurobiological processes as they unfold across life. Guided by themes and questions in health psychology, health neuroscience draws upon diverse fields such as cognitive, social affective, developmental, and clinical psychology and neuroscience, psychophysiology, psychoneuroimmunology, psychoneuroendocrinology, epidemiology, public health, and population neuroscience. However, neuroimaging techniques—and especially the quantitative and computational approaches to analyze brain imaging data—continue to develop. Although there are several measurement, analysis, and inference challenges that health neuroscientists face, as described throughout this chapter, the rapid and active development of better methods, measures, and modeling techniques promise that some of these issues may become less problematic. We close by foreshadowing future directions for health neuroscience.

The Promise of Health Neuroscience

Although still in its infancy, health neuroscience holds much potential for not only building a better understanding of brain function and structure in physical health and disease but also for guiding efforts to improve public health and individual wellbeing. Neuroscience more generally is moving towards a systems-level approach that models the brain as a dynamic network and set of subnetworks from which the mind and behavior can emerge and be constructed (Lindquist & Barrett, 2012). This perspective offers the insight that health more deeply helps create the mind, and that the mind (and more broadly, the world around us) shapes health for better or worse (Koban et al., 2021).

On the horizon, new methods are being developed to expand the utility and inferential power of neuroimaging. Ongoing areas of active innovation include improvements and novel techniques for multivariate methods, the use of dynamic, non-static in-scanner tasks and stimuli, ways to better capture interpersonal dynamics from within the scanner, ways to better map brain

function onto brain structure through multi-modal multi-scale methods, as well as an array of other techniques for improving generalizability from the scanner to the lab and real life. Ongoing statistical and computational work also seeks to tackle the unique quantitative challenges that brain data present (e.g., big data, high interdependencies), especially when considering temporal dynamics, network structures, and longitudinal effects.

Given the scale of questions and challenges ahead, health neuroscience should increasingly capitalize on its interdisciplinary nature to foster collaborations, open science, and team science approaches as already exemplified by the Human Connectome Project (HCP) and the Adolescent Brain Cognitive Development (ABCD) Study. Health psychology and neuroscience most typically examine cross-sectional individual differences—but we need a deeper understanding of the intra-individual dynamic interplay between health, the brain, and psychology across states and development. Large multi-site studies for health neuroscience are critical for increasing the sample size and scope of questions, generalizability, and reliability of effect estimates. However, to build a programmatic understanding of the brain as a predictor, outcome, and mediator, it is important that health neuroscience not leave behind the much-needed precision of experimentation and randomized control trials that can further disentangle pathways by which the brain is central for health and disease.

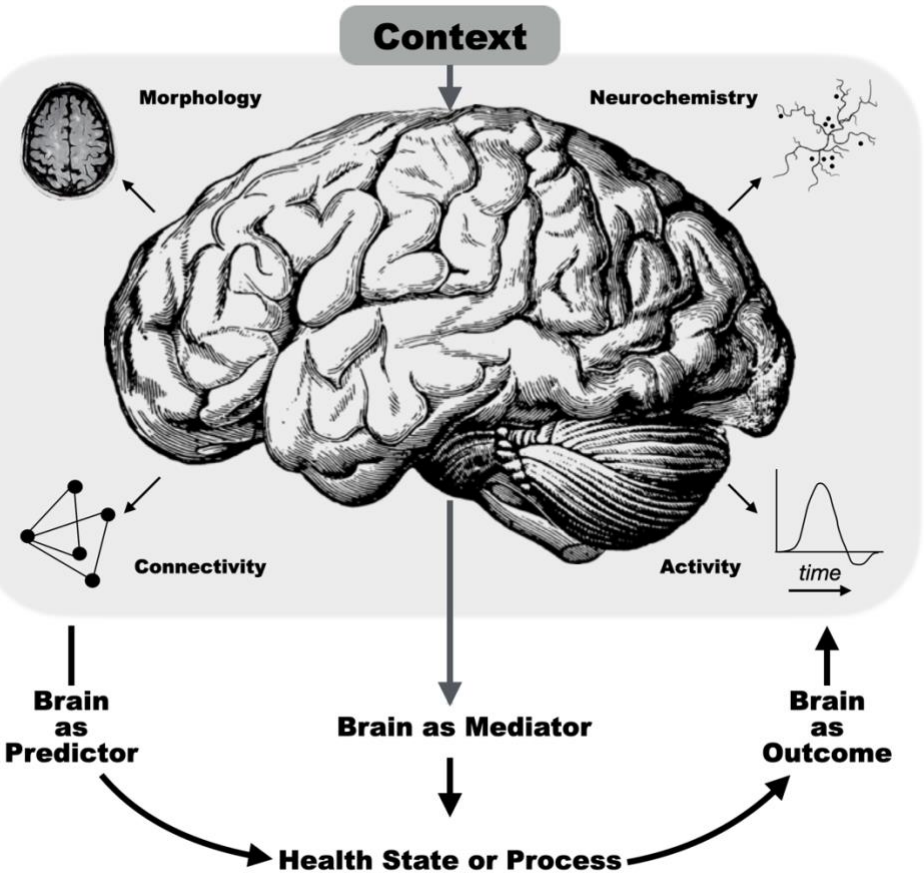

Figure. In a health neuroscience framework, the brain can be conceptualized as a predictor, mediator, or outcome of interest. Domains of variables derived from structural and functional neuroimaging methods include measures of brain morphology, connectivity, neurochemistry, and activity that can be used as predictor, mediator, or outcome metrics. Such metrics are interpreted within a given context, including historical, cultural, environmental, and social contexts that vary across the lifespan and across health and disease states. Factors of interest that can influence the brain (as an outcome) and can be influenced by the brain (as a predictor) include health behaviors, affective states, interoceptive processes, and aspects of systemic physiology, among other phenomena of interest in health psychology.

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