

Prediction as a Humanitarian and Pragmatic Contribution from Human Cognitive Neuroscience

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Neuroimaging has greatly enhanced the cognitive neuroscience understanding of the human brain and its variation across individuals (neurodiversity) in both health and disease. Such progress has not yet, however, propelled changes in educational or medical practices that improve people's lives. We review neuroimaging findings in which initial brain measures (neuromarkers) are correlated with or predict future education, learning, and performance in children and adults; criminality; health-related behaviors; and responses to pharmacological or behavioral treatments. Neuromarkers often provide better predictions (neuroprognosis), alone or in combination with other measures, than traditional behavioral measures. With further advances in study designs and analyses, neuromarkers may offer opportunities to personalize educational and clinical practices that lead to better outcomes for people.

Noninvasive neuroimaging has provided remarkable new insights into human brain structure and function in both health and disease. For over a century, understanding the human brain depended on naturally occurring brain injuries or unexpected consequences of neurosurgeries. From clinical cases such as Leborgne, Phineas Gage, H.M., and commissurotomy patients, we gleaned insights, respectively, into the roles of the left prefrontal cortex in language (Broca, 1861), the ventral prefrontal cortex in decision-making and social behavior (Harlow, 1868), the medial temporal lobe in memory (Scoville and Milner, 1957), and functional asymmetries between the cerebral hemispheres (Gazzaniga, 1970). Noninvasive neuroimaging has permitted a second wave of discoveries about the brain that has expanded the horizon of human neuroscience with examination of typical functions across many domains of the human mind, from perception and cognition to emotion, social and moral thought, and economic decision-making. Furthermore, such imaging has offered the first compelling evidence that neuropsychiatric and neurodevelopmental disorders reflect fundamental differences in brain structure and function. Uniquely, neuroimaging has revealed not only universal principles of functional brain organization but also neurodiversity: how such brain functions vary across people in relation to age, sex, personality, culture, and genetics. Here we review the progress in a novel application of neuroimaging: the use of such measureable neurodiversity to predict future human behavior. Such prediction may constitute a humanitarian and pragmatic contribution of human cognitive neuroscience to society, but this contribution will require rigorous science and also ethical considerations.

Neuroscientists, psychologists, and physicians are contemplating how human neuroimaging may best inform basic and clinical research. For basic research, there is discussion about

whether neuroimaging has informed cognitive theories beyond the mapping of psychological functions to neural networks (e.g., Mather et al., 2013). For clinical research, it is noteworthy that the 2013 revision of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), the defining document of diagnosis from the American Psychiatric Association, was little, if at all, influenced by the over 15,000 MRI studies of psychiatric disorders listed in PubMed (and this does not include studies using other methods, such as electroencephalography (EEG), magnetoencephalography (MEG), or positron emission tomography (PET)). Remarkable advances in genetics have also had little practical influence as yet on diagnosis or treatment of psychiatric disorders. Because psychiatric disorders are known to be heritable, and because these disorders must have a brain basis, it is likely that progress in genetics and neuroimaging will illuminate such disorders in the long run. Here we consider how neuroimaging may contribute to helping people in the nearer future.

This review focuses on structural and functional neuroimaging and considers findings in which an initial brain measure (a neuromarker) is associated with a future behavioral outcome. Some studies relate neuromarkers to individual differences in later perceptual or cognitive performance among typical or healthy people and have relevance for education and training. Other studies relate neuromarkers to individual differences among patients with a given diagnosis to future clinical status or response to treatment (neuroprognosis) and have relevance for neuropsychiatric disorders.

Such correlational or predictive studies differ from other kinds of studies in two main ways. First, in the case of group studies (e.g., comparison of patient and control groups), neuroimaging differences are most pronounced when there is greater homogeneity of a brain measure within each group so that groups are statistically separable. Conversely, greater heterogeneity of a

brain measure within a group is more likely to yield neuromarkers that correlate with variable outcomes. Second, for studies that examine response to treatment, individual differences may delineate **not the neural systems most affected by the disorder but, rather, heterogeneity among patients in the neural systems that are most important and variable for how a treatment yields benefits.** For example, if a behavioral therapy helps a patient with a disorder to learn how to regulate thoughts or emotions, then the neuromarkers associated with treatment response may be in neural networks that support such learning rather than in networks related to the etiology or progression of the disorder.

Neuroimaging Measures

Noninvasive neuroimaging measures provide indices of human brain structure and function that vary in their strengths and limitations. This review focuses on measures that maximize spatial information, specifically MRI-derived measures. Brain structure can be quantified by measuring volume, thickness, or density (voxel-based morphometry [VBM]). Microstructural properties of white matter pathways can be characterized by diffusion tensor imaging (DTI). Brain functions can be quantified via fMRI by activation studies that correlate experimental conditions or behavioral performance with neural activity, as indexed by changes in blood oxygenation level-dependent (BOLD) signals. During a resting state with no task or stimuli, there are spontaneous fluctuations in functionally related brain regions that correlate with one another, and the patterns of these correlations may reveal intrinsic functional relations of brain regions (Biswal et al., 1995). Resting-state fMRI, EEG, and MEG can elucidate these networks. Because it measures hemodynamic response, fMRI is inherently poor in temporal resolution, whereas EEG and MEG provide high temporal resolution (at the loss of spatial resolution).

For applications in education or medicine, there is a trade-off between measures that are task-dependent (activation fMRI, MEG, and EEG) versus measures that are task-independent (structural MRI and DTI, fMRI, MEG, and EEG resting state). On one hand, tasks can selectively invoke brain responses to salient stimuli (e.g., to print in children with reading difficulty or to sad facial expressions in depression). The advantage of this approach is that tasks and stimuli can be tailored to specifically assay salient mental operations. On the other hand, such tasks demand participant performance that can result in behavioral confounds, vary in design from study to study, and have not typically been developed to maximize reliability of measurement. In contrast, structural and resting state measures can be acquired in a consistent fashion, have promise for reliability (e.g., Shehzad et al., 2009; Wonderlick et al., 2009; Vollmar et al., 2010), can accommodate a broad range of participants (including infants), and are independent of task performance in the scanner.

Analytic Approaches: From Correlation to Individualized Prediction

An ultimate goal of the use of neuromarkers for neuroprognosis is to perform individualized predictions of educational or health outcomes. Most studies to date have related variation in baseline brain measures to variation in subsequent outcomes. Given that

such analyses hinge on knowledge of the outcomes, such analyses could be described more as postdiction than prediction (Whelan and Garavan, 2014). However, if neuromarkers are to become useful in practice, they must predict outcomes for new individuals based on models developed previously with other individuals. A cognitive neuroscience of prediction, therefore, needs to build on theory and methods that allow for effective creation, evaluation, and selection of prediction models (Pereira et al., 2009).

The term prediction is used in three different ways in relevant research. First, prediction can refer to a correlation between two contemporaneous values, such as height predicting weight. Second, prediction can refer to the correlation of one variable in a group at an initial time point to another variable in the same group at a future time point (an in-sample correlation). Third, prediction can refer to a generalizable model that applies to out-of-sample individuals. All studies reviewed here relate an initial brain measure to a future behavioral outcome, and the term correlation refers to in-sample findings, and the term prediction refers to out-of-sample generalizations.

Such research can be conceptualized as comprising three stages, beginning with within-sample correlations to discover relations of interest, progressing to predictive analyses in which predictions for individuals are derived from data from other in-sample individuals, and culminating in predictive analyses in which a model from one sample is used to predict outcomes in an independent sample (Figure 1). Each stage requires more participants, so that prior stages may justify larger-scale studies. The vast majority of findings to date are correlational (61 of the 72 reviewed here), but some studies reported predictive analyses (with only one study having fully independent samples) (Table 1).

The major limitation with correlational analyses reporting the significance of the overall fit of linear or multiple regression models to a data set is that findings are tied to the outcome for a particular group. From a predictive modeling standpoint, the error from this fit is typically termed the training error, whereas the error on an unseen data set would be called the test or generalization or prediction error. The training error is always an underestimate of the test error. The quality of a model can be evaluated by measuring its test error. Minimizing this error is the goal of building prediction models. One way to decompose the test error is to describe it as a sum of training error and optimism (Efron, 2004). Optimism is the difference between the test error, which is always higher, and the training error.

The most common approach for reducing optimism is to use a validation set in which some data are set aside to estimate the test error. In many studies of brain imaging, this limits the amount of data available for training because of small sample sizes. A common approach is to use cross-validation, in which one divides a data set into a number of folds. One fold is held aside as a test set, and data from the remaining folds (training data) are used to train the model. This model is then applied to the test set, and the model error is calculated. This procedure is repeated by considering each fold as a test set. The average error across the test folds is reported as the generalization error. If the number of folds equals the number of data points, then only one data point is held out for testing, and this is known as leave one out cross-validation. In general, this approach is unbiased

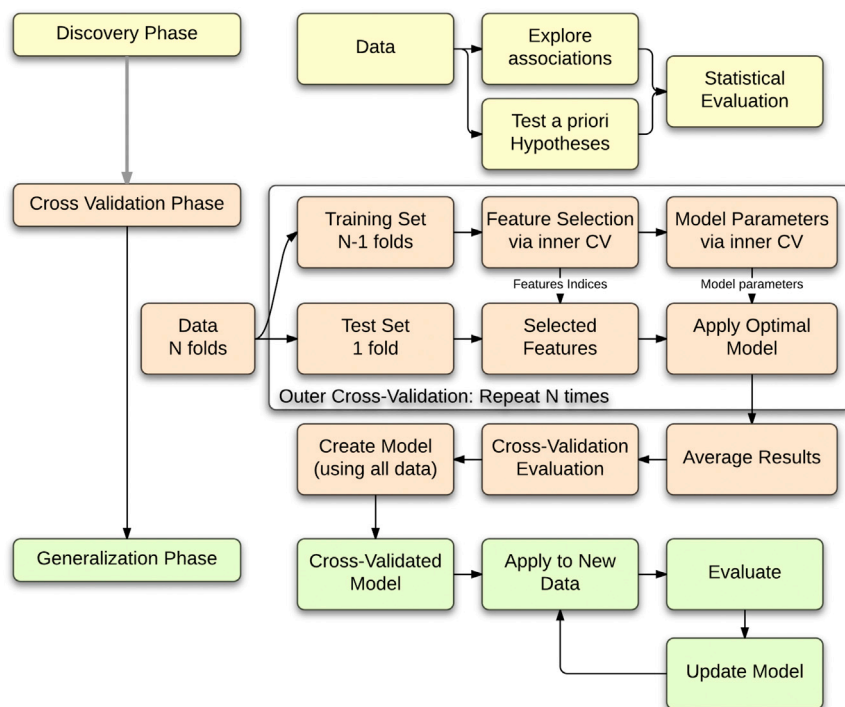


Figure 1. Three Stages of Predictive Model Identification

(1) Discovery phase. Explore and evaluate associations between baseline neuromarkers and behavioral outcomes.

(2) Cross-validation phase. A cross-validation routine is used to separate data into training and test sets. The model is built using training data and tested on out-of-sample test data. Upon successful evaluation of the performance of the model and features, all data are used to build a prediction model.

(3) Generalization phase. A prediction model built via cross-validation is applied to a new data set. The new data are then used to update the model.

results in a more conservative outcome than the correlational model, the difference varies across data sets. In all cases, however, predictive analyses will be necessary to translate correlational observations into educational or clinical practice.

Future Learning and Cognitive Performance in Adults

Variation in initial neuromarkers has been associated with subsequent learning or

but typically has a high variance in prediction error (Kohavi, 1995; Rao et al., 2008).

Another practical approach is to randomly split data into training and test sets (e.g., 10% of the data are in the test set). The splitting is repeated several times. On each iteration, a model is fit on the training data and tested on the test data. This results in a distribution of prediction errors that can provide a confidence interval for a given application. However, such procedures can still lead to increased optimism if models are chosen or their parameters are tuned after peeking at the test results (Koban et al., 2013). Selecting models and their parameters from cross-validation on the training data can reduce such optimism. The training data itself can be subjected to cross-validation and subdivided into training and test sets to determine which model is best suited for the training data. This procedure is called “nested cross-validation.” Because different models may be selected for each cross-validation split, the most selected model might be considered to be the “best” model. A variety of learning models coupled with cross-validation has been used in brain imaging. These range from linear, multiple, and logistic regression models to approaches such as support vector machines (SVM [Vapnik, 1999]) or least absolute shrinkage and selection operator (LASSO [Tibshirani, 1996]), relevance vector machines (Bishop and Tipping, 2000), and random forests (Breiman, 2001).

The difference between the amount of variability accounted for by within-sample correlations and out-of-sample predictions is rarely reported. Two within-sample correlational studies (Aharoni et al., 2013; Demos et al., 2012) were reanalyzed by a different investigator (R.A. Poldrack, personal communication), and the outcome variance accounted for by the generalizable model was far smaller than that for the within-sample correlation (see Aharoni et al., 2014). Although in most cases the predictive model

cognitive performance, and, in most cases, these variations occurred in the neural networks associated with the kind of learning. Larger volumes of the striatum correlated with superior video game skill learning (Erickson et al., 2010). This correlation was specific to the dorsal striatum volume, did not extend to the hippocampus or ventral striatum, and accounted for 23% of the variance in learning. The importance of the striatum for such skill learning is consistent with evidence that lesions of the striatum impair skill learning (e.g., Heindel et al., 1989). Superior word learning correlated with DTI measures of the left arcuate fasciculus, a white matter pathway connecting major left hemisphere language regions (López-Barroso et al., 2013).

Brain differences in language-related neural systems have also been related to variation in learning novel speech distinctions not present in a person’s native language. Superior learning was associated with anatomical differences, specifically greater asymmetry (left to right) in parietal lobe volumes and higher white matter density in left Heschl’s gyrus (Golestani et al., 2002, 2007). Larger anatomical structures in the language-dominant left hemisphere may support the rapid temporal processing needed to learn novel auditory distinctions that occur critically in the first 30–50 ms of nonnative language sounds. Resting-state functional connectivity has also been associated with variation in auditory language learning. Better learners of a nonnative speech contrast exhibited greater functional connectivity (correlation) than poor learners between inferior frontal and parietal regions thought to be major components of the left hemisphere language system (Ventura-Campos et al., 2013; other related studies are reviewed in Zatorre, 2013).

Neuromarkers have also correlated with musical and visual learning. For auditory learning of microtonal pitch discrimination (with intervals smaller than typically used in musical scales),

Table 1. Publications Cited in This Article that Used Cross-Validation Techniques to Measure Out-of-Sample Prediction Error

Publication	Sample Size	Application	Cross-Validation Method	Learning Model
Whelan et al., 2014	271	future adolescent alcohol misuse	10-fold	logistic regression with elastic net
Hoefl et al., 2007	64	future reading skills	LOO	linear regression
Ullman et al., 2014	62	future working memory capacity	LOO	nu-SVR
Ball et al., 2014	48	response to CBT in GAD and PD	out of bag	random forest
Doehrmann et al., 2013	39	SAD	stratified K-fold	linear regression
Hoefl et al., 2011	25	future reading gains in dyslexia	LOO	linear SVC
Supekar et al., 2013	24	response to math tutoring	4-fold	linear regression
Falk et al., 2010	20	persuasion-induced behavior change	2-fold	linear regression
Siegle et al., 2012	17 (cohort 1) 20 (cohort 2)	response to CBT for depression	out of bag	random forest
Bach et al., 2013	17	future reading skills	LOO	discriminant analysis
Costafreda et al., 2009	16	response to CBT for depression	LOO	PCA + linear SVM

LOO, Leave One Out; nu-SVR, nu-Support Vector Regression; CBT, cognitive behavioral therapy; GAD, generalized anxiety disorder; PD, panic disorder; SAD, social anxiety disorder; SVC, Support Vector Classification; PCA, Principal Component Analysis; SVM, Support Vector Machine.

individuals who, at baseline, exhibited higher slopes of fMRI activation in the bilateral auditory cortex to pitch-interval size exhibited greater learning over a 2-week training period (Zatorre et al., 2012). The higher slope of activation may reflect a finer-grained cortical encoding of pitch information that potentiates more rapid learning during training. People who were better at learning to make fine visual discriminations had, at baseline, stronger functional connectivity within portions of the visual cortex and between the visual cortex and prefrontal association areas (Baldassarre et al., 2012). These regions were also a subset of the regions that were activated by the discrimination task itself, suggesting that initial individual differences within the task-evoked neural networks encouraged or discouraged effective learning.

The studies mentioned above examined variation in learning across individuals, but individuals also vary across time in their performance and learning. Two fMRI studies exploited natural fluctuations in resting-state BOLD signals in an attempt to distinguish brain states within an individual that were associated with superior or inferior performance on vigilance and learning tasks. In both studies, stimulus presentation was triggered via real-time fMRI when BOLD signals in relevant brain regions were hypothesized to be in optimal or suboptimal states. In the vigilance task, an individual had better vigilance (faster reaction times) for the appearance of an unpredictable visual target when, before the appearance of the target, the BOLD signal was high in the supplementary motor area (a region associated with motor planning) and low in components of the default mode network (a network that is more active during rest than most tasks and that has been associated with internal self-reflection rather than external perceptual attention) (Hinds et al., 2013). In the memory task, an individual exhibited superior learning of scenes when BOLD signals were lower before the appearance of a scene in the posterior parahippocampal cortex, a region that is selectively responsive to scenes (Yoo et al., 2012). Therefore, brain states could be identified that predicted whether an individual was ready to be vigilant or ready to learn.

Future Learning and Education in Children

Reading and mathematics are the two foundations of education, and, accordingly, the focus of school curricula from elementary school through high school. The first major education experience for children is learning to read in early school years, after which they use those reading skills to learn all other subjects. Some children (5%–17%) have developmental dyslexia, which is a persistent difficulty in learning to read that is not explained by sensory, cognitive, or motivational factors or lack of adequate reading instruction (Shaywitz, 1998) and that is highly heritable (Pennington and Gilger, 1996). The best understood psychological cause of dyslexia is a weakness in phonological awareness, the understanding that spoken words are composed of discrete sounds (phonemes) that can be mapped onto letters or syllables (graphemes) (Bradley and Bryant, 1978), although several other putative causes have been identified (reviewed in Gabrieli, 2009).

Brain measures in infants have correlated with future success or failure in language and reading years before explicit reading instruction. Event-related potentials (ERPs), which are time-locked changes in electrical activity measured with EEG scalp electrodes, have revealed a risk for future language and reading difficulties in newborns within hours or days of birth. These studies typically involve infants from families with a history of language or reading difficulty to increase the proportion of infants who will progress to language and reading difficulty. ERP responses to speech sounds within 36 hr of birth discriminated with over 81% accuracy those infants who would go on to become dyslexic at age 8 (Molfese, 2000). Newborns, tested within a week of birth, had ERPs in response to speech sounds that correlated with language scores at 2.5, 3.5, and 5 years of age (Guttorf et al., 2005).

Some studies have reported that neuroimaging measures enhance or outperform traditional behavioral measures in forecasting children's reading abilities in future months and years. One study examined how children 8–12 years of age, identified by their teachers as struggling readers, fared from the beginning to the end of a school year in single-word decoding skills (the

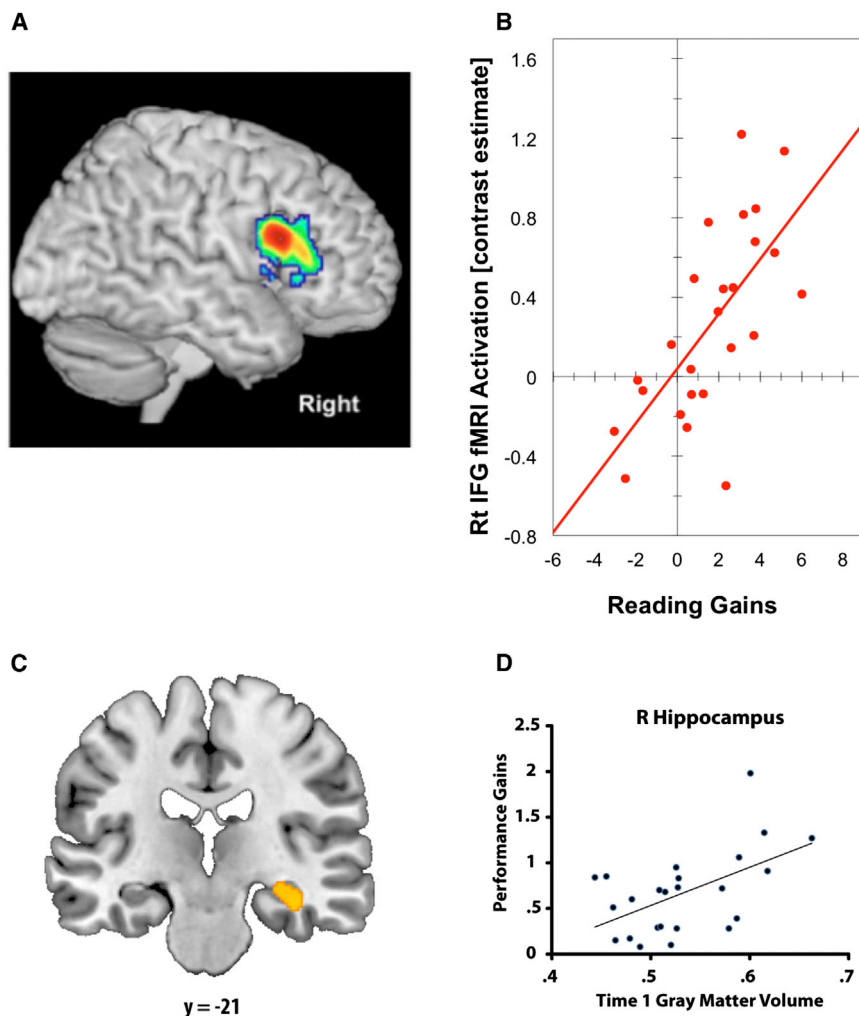


Figure 2. Functional and Structural Brain Measures Predicting Educational Outcomes

(A and B) fMRI predictor of reading gains in dyslexia. Greater activation for a phonological task in the right inferior frontal gyrus (Rt IFG) (A) predicted greater gains in reading 2.5 years later in dyslexic children (B). Each red circle is an individual (based on [Hoeft et al., 2011](#)).

(C and D) MRI predictor of math tutoring gains in students. Greater gray matter volume of the right (R) hippocampus (C) predicted greater performance gains in students after 8 weeks of tutoring (D). Each blue circle is an individual (from [Supekar et al., 2013](#)).

correlated with future reading gains, but the brain measures did yield such correlations (Figure 2). In combination, greater activation in the right prefrontal cortex (a region not typically engaged for reading single words at this age) and greater white matter organization of the right superior longitudinal fasciculus predicted, with 72% accuracy, whether a child would be in the compensated or persistent group. Multivoxel pattern analysis of whole-brain fMRI activation, a data-driven pattern classification analysis, yielded over 90% accuracy in classifying whether a dyslexic child, at baseline, would belong to the compensating or persistent group 2.5 years later.

Longitudinal studies have also found neuromarkers associated with future reading skills in children who were not selected on the basis of family history or

ability to read aloud pseudowords on the basis of phoneme-grapheme mapping rules ([Hoeft et al., 2007](#)). At the beginning of the school year, these children were evaluated with over a dozen behavioral measures of reading and reading-related skills, an fMRI task requiring rhyme judgments for pairs of printed words, and a VBM analysis of anatomic gray and white matter densities. The beginning-of-the-year behavioral measures accounted for 65% of the variance in end-of-year scores, and the brain measures accounted for 57% of that variance. The combination of behavioral and brain measures accounted for a significantly better 81% of the variance, demonstrating enhanced forecasting of student reading skills across a school year.

Among children with dyslexia, there is considerable variation in the degree to which individual children do or do not compensate for their reading difficulty by closing the gap between their actual and age-expected reading skills. A longitudinal study of older children (mean age of 14 years) examined how behavioral measures (17 tests of reading and reading-related skills), fMRI activation for a word-rhyming task, and DTI indices of white matter organization predicted which children, over the next 2.5 years, would compensate or persist in their reading difficulty ([Hoeft et al., 2011](#)). None of the standard behavioral measures

reading difficulty. In a 5-year longitudinal study, an auditory ERP measure (hemispheric lateralization of late mismatch negativity) in prereading kindergarteners significantly improved the forecasting of future reading performance in second, third, and fifth grades in combination with prereading skills ([Maurer et al., 2009](#)). Only the ERP measure (and not any behavioral measure) correlated with future reading performance in fifth grade. A visual ERP study with prereading kindergarteners also reported that the combination of behavioral measures and both ERP and fMRI responses to print explained up to 88% of the variance in second-grade reading ability ([Bach et al., 2013](#)). These studies suggest that neuromarkers in prereading kindergarteners may enhance the identification of children who will struggle to read even before reading instruction begins in school. This is important because current reading interventions are most effective in young, beginning readers, and effective intervention prior to reading failure may not only be more effective but also spare children the sense of failure that often accompanies early struggles in reading.

In older typical readers 9–15 years of age, fMRI activations in response to a word-rhyming task were associated with nonword reading skills up to 6 years in the future, with the specific

locations of activations depending upon the child's age (McNorgan et al., 2011). In younger children, greater activation in brain regions associated with phonological recoding (e.g., the inferior frontal gyrus) was associated with greater future reading skill, whereas, for older children, greater activation in brain regions associated with orthographic analysis of print (e.g., the fusiform gyrus) was associated with lesser future gains. These findings underscore how different developmental stages of learning to read, perhaps transitioning from a younger gaining of skill in single-word decoding (print-to-sound correspondence) to an older mastering of fluent visual analysis of connected print, may invoke relatively different components of the brain's reading circuitry.

There is also considerable variation in how well children can learn a second language. For native Chinese speakers around age 10, greater activation in response to English words and non-words in the left fusiform gyrus and left caudate correlated with superior English word-reading levels a year later (Tan et al., 2011). The putative visual word form area, which is highly responsive to learned print, is located in the left fusiform gyrus (Dehaene and Cohen, 2011). The leftward lateralization of neuro-markers may have been related to properties of alphabetic languages such as English because there is evidence that variation in microstructural properties of right hemisphere white matter pathways correlated with initial learning of Mandarin Chinese in young adults (Qi et al., 2014). The rightward lateralization of neuro-markers in native English speakers associated with future successful initial language learning may reflect the tonal and visuospatial properties, respectively, of spoken and written Mandarin Chinese. Therefore, neuromarkers correlated with second language learning may vary depending on the kinds of mental resources needed to learn different kinds of languages.

Mathematical problem-solving skills are the foundation of later performance in science and engineering. Academic skill in arithmetic relies on multiple cognitive processes, including working memory, the mental processes that support the maintenance and manipulation of goal-relevant information over brief time periods (reviewed in Raghubar et al., 2010). In a longitudinal study, children 6–16 years of age underwent behavioral testing (working memory, reasoning, and arithmetical abilities) and fMRI while performing a visuospatial working memory task (Dumontheil and Klingberg, 2012). Neuroimaging analyses focused on the intraparietal sulcus (IPS), a brain region associated with both visuospatial working memory and numerical representation. The working memory and reasoning measures were independent predictors of arithmetical performance 2 years later. The magnitude of visuospatial working memory activation in the left IPS also predicted future arithmetical performance. Combining the neuroimaging and behavioral data more than doubled the accuracy of predicting future mathematical ability compared with the use of only behavioral data.

The future growth of working memory ability in the same age range has also been better predicted by a combination of neuroimaging and behavioral measures than by behavioral measures alone (Ullman et al., 2014). Interestingly, although current working memory capacity correlated with activation in frontal and parietal regions, future capacity was best predicted by structural and functional measures of the basal ganglia and thalamus. Specifically, greater activation in the caudate and thalamus and

greater fractional anisotropy (FA) of surrounding white matter as measured by DTI predicted future growth in working memory over the next 2 years.

There is increasing interest in improving the effectiveness of learning through teaching that takes into account variation among students. One study examined whether neuromarkers could identify which children would benefit from a math tutoring program for third graders (ages 8 and 9) that encouraged students to shift from counting to fact retrieval as a basis for an arithmetic problem-solving strategy (Supekar et al., 2013). Individual differences in how much students benefitted from the tutoring program did not correlate with baseline behavioral scores on tests of intelligence (IQ), working memory, or mathematical abilities. Conversely, at baseline, greater right hippocampal volume and resting-state intrinsic functional connectivity between the right hippocampus and prefrontal and striatal regions correlated with future performance improvements (Figure 2).

Future Criminality

The criminal justice system is rife with demands for predictions of future behaviors as judgments are made about bail, sentencing, and parole. The demonstrated inaccuracy of expert clinical judgments (Monahan, 1981) has motivated the use of an actuarial approach that estimates risk for future antisocial behavior based on characteristics such as age, sex, criminal history, and drug use (e.g., Yang et al., 2010). Building on evidence that impulsivity (behavioral disinhibition) is a major risk factor for recidivism, brain activations to an impulse control task (go/no-go task) were examined in 96 male offenders who were then followed longitudinally (Aharoni et al., 2013). The likelihood that an offender would be rearrested over a 4-year period doubled when, at baseline, the offender had low activation in the anterior cingulate cortex, a region associated with cognitive control and especially the resolution of cognitive conflict. Although the correlation between baseline brain activation and future rearrest was significant, there was no or weaker correlation for other predictors (age, scores on a psychopathy checklist, lifetime substance abuse, or behavioral error rate on the scanner task).

Future Health

Studies have examined whether neuromarkers are related to future health-related behaviors such as alcohol abuse, drug abuse, or unhealthy eating. Alcohol use by underage drinkers is an important public health problem because such use in adolescents is risky and also associated with life-long alcoholism. Heavy or binge drinking is the primary source of preventable morbidity and mortality for the more than 6 million American college students (Wechsler et al., 2002). Early onset of alcohol use by age 12 is associated with numerous undesirable outcomes in adolescence (Gruber et al., 1996), and initiation of drinking before age 15, versus after age 20, quadruples the likelihood of alcoholism (Grant and Dawson, 1997).

In a longitudinal study, 12- to 14-year-olds with little or no history of substance abuse performed a go/no-go task of response inhibition while undergoing fMRI (Norman et al., 2011). About 4 years later, these adolescents were divided into two groups who did or did not transition to heavy use of alcohol. Widespread reductions in baseline activation, including in the prefrontal and

anterior cingulate cortices, were found in adolescents who later transitioned to heavy alcohol use relative to those who did not. Among adolescents 16–19 years of age with an ongoing history of substance use disorders, those who exhibited less prefrontal and greater parietal activation on the same task had higher levels of substance use over the following 18 months (Mahmood et al., 2013). Overall, the findings suggest that a relative weakness in the recruitment of anterior brain regions that are most associated with cognitive control of behavior may be a predisposition for early alcohol use or sustained substance abuse.

Adolescents who exhibited greater activation in response to monetary reward in the basal ganglia were more likely to engage in substance use (alcohol and drugs) a year later (Stice et al., 2013). In contrast, those who were already using substances at baseline exhibited lesser activation in the basal ganglia at baseline. These findings indicate that reward systems of the basal ganglia are also involved in substance abuse but that brain measures of future risk for substance use may be quite different than brain measures reflecting the consequence of current use of substances.

The largest study of future adolescent misuse of alcohol followed nearly 700 adolescents and collected detailed histories, personality measures, genetic information, structural and functional MRI data, and cognitive performance measures (Whelan et al., 2014). fMRI tasks examined inhibitory control, reward processing, and facial expressions of emotion. In 271 of these adolescents, a multidomain analysis was used to predict future binge drinking. The most robust brain predictors of future binge drinking came from the right precentral and bilateral superior frontal gyri, with contributions from several structural (gray matter volume) and functional (inhibitory control and reward outcome) features. In the predictive model, these brain measures were coupled with life events, personality measures, and an anxiety sensitivity subscale of the substance use risk profile scale. Any one feature in isolation had only a modest influence on prediction, and many of the features predicting future misuse were different from the features dissociating groups of binge drinkers and nonbinge drinkers. Such a study highlights the multiple causal factors for substance abuse and the scale of data needed to predict the future unfolding of such multifaceted processes.

Healthy eating to avoid or reduce obesity is also a major public health concern. Neuroimaging studies have reported that fMRI activations in response to food-related pictures forecast future changes in body mass index (BMI) over the next 6–12 months. Two studies examined the relation between baseline fMRI activations and weight gain over the following year in girls identified as having body image concerns. Activations in response to palatable food occurred in brain regions associated with reward anticipation (e.g., regions of basal ganglia) or reward valuation (e.g., the orbitofrontal cortex). In one case, dopamine-related genetic variation interacted with blunted brain activation to correlate with elevated risk for future weight gain (Stice et al., 2010). In another case, lateral orbitofrontal cortical activation during initial orientation to appetizing food cues correlated with future increases in BMI over a 1-year period (but behavioral patterns of response did not correlate with BMI increases) (Yokum et al., 2011).

Another study demonstrated the specificity of brain activations to food cues in relation to future weight gain (Demos et al., 2012). Women arriving at college saw pictures of food, sexual scenes, and control pictures during fMRI. At baseline and again toward the end of the school year, the women's weights and self-reports of sexual behavior were measured. A greater initial response in the reward-responsive nucleus accumbens for food pictures correlated with greater BMI gains 6 months later, whereas a greater initial response to sexual scenes correlated with greater sexual desire and more sexual experiences 6 months later.

In a related study, college-aged women participated in an fMRI study of brain responses to pictures of food and for response inhibition on a go/no-go task, followed by experience sampling via smartphone. Over the course of 1 week, they were periodically asked to report their desire to eat food, attempts to resist the temptation to eat, and whether or not and how much they actually ate (Lopez et al., 2014). Greater nucleus accumbens activation to food pictures correlated with greater desires for food, more likelihood to give in to the temptation to eat, and larger amounts eaten. Greater activation of the inferior frontal gyrus during response inhibition was associated with reduced surrender to temptation and less eating. Overall, these studies suggest that an interplay between the response to food cues that occurs in reward-sensitive striatal and orbitofrontal regions and the response in cognitive control regions of the lateral prefrontal cortex contributes to future healthy or unhealthy eating patterns.

Another health-related behavior is the use of sunscreens for protection against sunburn and some forms of skin cancer. In one study, participants saw slides communicating the importance and proper application of sunscreen (Falk et al., 2010). Participants also reported recent use of, intention to use, and attitudes toward sunscreen. Greater activation in the medial prefrontal cortex, a brain region associated with self-reference, correlated with changes in the use of sunscreen as measured by an unexpected self-report 1 week later. Brain measures accounted for about 25% of the change in use of sunscreen above and beyond self-reported changes in attitudes and intentions following presentation of the health information during scanning. Activation in the medial prefrontal cortex may broadly represent value because the magnitude of activation in that brain region (and the striatum) in response to individual consumer goods was associated with subsequent preferences for choosing those goods (Levy et al., 2011).

Some studies have examined how brain function at one point in time correlates with mental health outcomes at future time points independent of treatment. For example, greater amygdala activation to emotional facial expressions among patients with depression correlated with reduced symptoms of depression 6 months later, controlling for initial depression severity and medication status (Canli et al., 2005). In a memory paradigm with negative pictures, greater baseline activation for successfully recalled pictures in the posterior cingulate cortex and medial prefrontal cortex correlated with greater improvement in depressive symptoms 18 months later (Foland-Ross et al., 2014).

Future Response to Treatment

Biomarkers in general, and neuromarkers in particular, are not used currently to predict treatment response for neuropsychiatric disorders despite considerable evidence that any specific pharmacological or behavioral treatment is likely to be effective for some patients but ineffective for a considerable number of other patients. Measurement of treatment efficacy varies, but it typically involves a patient report or clinician observation, often via a structured interview or questionnaire. A highly effective treatment results in remission, the absence of symptoms, or in a substantial response, defined as an outcome in which the patient remains somewhat symptomatic but is much improved (Frank et al., 1991).

Across many neuropsychiatric diagnoses, remission or substantial response occurs in about 50% of patients for a given therapy. For depression, cognitive behavioral therapy (CBT) is effective in 40%–60% of patients (Hollon et al., 2002), and selective serotonin reuptake inhibitors are effective in 40%–60% of patients, although many patients who fail to respond to an initial treatment will respond to another treatment or combination of treatments (Souery et al., 2006). Similar 40%–60% success rates for a given pharmacological or behavioral treatment have been reported for generalized anxiety (Pollack et al., 2003), social anxiety disorder (Otto et al., 2000), and attention deficit hyperactivity disorder (Wender, 1998; Biederman et al., 2010). This variability in treatment response, which is not understood and not simply a consequence of disease severity, suggests that there are clinically important neurobiological differences among patients sharing a diagnostic label so that a specific treatment will be effective for some but not other patients.

To a remarkable degree, there is an absence of evidence about which treatment is likely to be effective for a particular patient. Although patients often do benefit from a second or third sort of attempted treatment, there is considerable human and economic cost for delaying effective treatment for patients and families who are often in crisis. The idea of personalized medicine, that people vary in their response to treatments and that more effective medicine can be practiced by knowing which treatment is most likely to benefit a particular patient, has been associated often with genetics. It seems plausible, however, that quantitative brain measures may also reveal variation among patients that provides an evidence-based rationale for what treatment is most likely to help a particular patient among currently available treatments.

Future Response to Pharmacological Treatment

Over 20 studies of depression have reported that pretreatment neuroimaging measures can correlate with or predict clinical improvement following pharmacological treatment (reviewed in Pizzagalli, 2011; Fu et al., 2013). In one study, prior to treatment, reduced subgenual anterior cingulate cortex (ACC) metabolism was measured by PET in patients who subsequently responded poorly to medicine relative to either healthy controls or patients who responded well to medication and who exhibited greater-than-normal metabolism (Mayberg et al., 1997). No clinical measure, such as depression severity, or behavioral measure, such as cognitive performance, distinguished the patients who would or would not respond to treatment. The subgenual ACC (Brodmann area 25) is especially salient for depression because it

has been shown to be functionally and structurally atypical in depression (Drevets et al., 1997) and has been a target for deep brain stimulation treatment of depression (Mayberg et al., 2005).

A meta-analysis of 20 studies on depression supported the conclusion that increased baseline activation of the ACC, extending into the orbitofrontal cortex, was associated with better treatment response but that decreased activation of the insula and striatum was also associated with better treatment response (Fu et al., 2013). In an fMRI activation study in which patients viewed faces with sad facial expressions of varying intensity, a machine learning approach (SVM and leave one out (LOO) cross-validation) identified patients who would have remission with 71% sensitivity/86% specificity (Costafreda et al., 2009). There is also evidence that structural brain measures at baseline were associated with treatment outcome. Across studies, a worse response to treatment has been associated with decreased gray matter volume in the left dorsolateral prefrontal cortex and also in the right hippocampus (Fu et al., 2013). Finally, repetitive transcranial magnetic stimulation (rTMS) is a less common treatment for depression, but resting-state functional connectivity measures have been associated with clinical response to such treatment (Salomons et al., 2014). Higher corticocortical connectivity and lower corticothalamic, corticostriatal, and corticolimbic connectivity at baseline were associated with better treatment response.

In an open-label study examining the efficacy of treating generalized anxiety disorder with venlafaxine, patients viewed faces with fearful or neutral expressions. Greater activations for fearful relative to neutral faces in the rostral ACC and lesser activations for fearful relative to neutral faces in the left amygdala both correlated with greater clinical improvement (Whalen et al., 2008). These correlations occurred despite no activation differences in the rostral ACC or amygdala either between patients and controls or between pretreatment and posttreatment in patients who did improve clinically in response to treatment. Such a finding underscores the idea that neuromarkers that are associated with treatment response need not reflect the same functions as those related to etiology.

Future Response to Behavioral Treatment

Perhaps the best validated kind of behavioral treatment for neuropsychiatric disorders is CBT, meta-analyses of which indicate it to be effective for many disorders, including depression, generalized anxiety disorder, panic disorder, and social anxiety disorder (e.g., Butler et al., 2006; Hofmann et al., 2012). Multiple studies have reported that CBT is similarly effective as pharmacological treatments for depression (DeRubeis et al., 2005), generalized anxiety disorder (Mitte, 2005), pediatric anxiety (Walkup et al., 2008), and social anxiety disorder (Heimberg et al., 1998). For disorders that are treated primarily with medications, CBT has been shown to enhance clinical outcome relative to other augmentations for obsessive-compulsive disorder (OCD) (Simpson et al., 2013) and schizophrenia (Grant et al., 2012).

Several neuroimaging studies have reported that pretreatment neuroimaging measures correlate with or predict the magnitude of clinical improvement following CBT in unipolar major depression, schizophrenia, and social anxiety disorder. The initial study

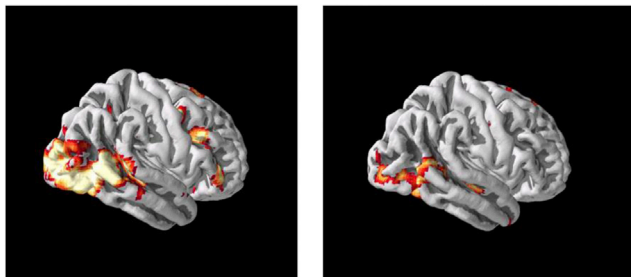


Figure 3. Functional Brain Measure Predicting a Clinical Outcome
Prior to treatment, patients with social anxiety disorder who exhibited greater posterior activation (left) for angry relative to neutral facial expressions had a better clinical response to CBT than patients who exhibited lesser activation (right) (based on [Doehrmann et al., 2013](#)).

relating pretreatment brain function to clinical efficacy of CBT occurred in 14 unmedicated patients with depression who viewed emotionally negative words prior to treatment. Both less sustained activation in the subgenual ACC and more sustained activation in the amygdala were associated with a greater improvement in response to CBT ([Siegle et al., 2006](#)). The finding that less sustained activation in the subgenual ACC was associated with a better future response to CBT was replicated and extended in a larger study of patients with depression ([Siegle et al., 2012](#)). This study is noteworthy in its use of a model generated from one cohort being used to predict the outcomes of an independent cohort.

For patients with schizophrenia being treated pharmacologically, about half respond beneficially to additional CBT treatment (e.g., [Wykes et al., 2008](#)). In one set of overlapping studies, patients receiving CBT exhibited clinical improvements relative to patients who did not receive CBT ([Kumari et al., 2009, 2011](#); [Premkumar et al., 2009](#)). The magnitude of clinical benefit among the patients receiving 6–8 months of CBT correlated with both baseline functional and structural measures. Patients who exhibited a stronger activation in the dorsolateral prefrontal cortex (DLPFC) during performance of a working memory task and who exhibited stronger DLPFC-cerebellar functional connectivity in the most demanding condition of the task derived a greater benefit from CBT ([Kumari et al., 2009](#)). In another fMRI study, patients read aloud single words, heard either their own or another person's voice that was or was not distorted, and then judged whether they had heard their own voice or that of another ([Kumari et al., 2010](#)). Across several contrasts, greater activation in the left inferior frontal gyrus and lesser inferior parietal and medial prefrontal deactivation were associated with a greater CBT benefit. A greater engagement of prefrontal regions in patients who benefitted more from CBT may be related to regulatory processes that can support effective CBT. There has also been some evidence for separable neuromarkers related to CBT response for positive symptoms (excess or distorted normal functions such as hallucinations or delusions) versus negative symptoms (diminished normal functions such as apathy or withdrawal) ([Premkumar et al., 2009](#)). Importantly, baseline symptom severity did not correlate with CBT response so that the neuromarkers provided measures associated with future CBT benefits that were not clinically evident at baseline.

Current behavioral measures poorly predict treatment outcome in social anxiety disorder, another disorder often treated with CBT. Prior to CBT, patients viewed angry versus neutral faces or negative versus neutral scenes during fMRI ([Doehrmann et al., 2013](#)). Consistent with the social nature of this anxiety disorder, activations in response to scenes were not associated with treatment outcome, but activations to angry relative to neutral faces were associated with CBT outcome. Greater activations in higher-order visual cortices were predictive of a superior treatment outcome ([Figure 3](#)). Initial greater clinical severity accounted for about 12% of the variance in treatment outcome, whereas the combination of baseline neuroimaging and clinical severity accounted for about 40% of the outcome variance. Similar findings were observed at a less conservative statistical threshold in prefrontal cortices, and it is possible that the relations between prefrontal and higher-order visuoperceptual cortices may support or constrain the self-regulatory processes that are taught in CBT (i.e., that these results revealed variation in the neural mechanisms that support CBT response rather than those of social anxiety disorder).

A study of patients with generalized anxiety disorder or panic disorder aimed to develop measures that might be sensitive to single-subject responses to treatment ([Ball et al., 2014](#)). Patients saw negative scenes and either maintained or reduced (via reappraisal) their emotional response to the scenes. A random forest classification was used to identify brain regions in which activations best predicted treatment outcome. There were greater activations for responders than nonresponders in the hippocampus during the maintenance of negative images and in the anterior insula and superior temporal, supramarginal, and superior frontal gyri during reappraisal of negative images. The neuroimaging measures yielded superior accuracy, sensitivity, and specificity in identifying individual patients as future responders or nonresponders to treatment than clinical or demographic variables. This study provides an example of data-driven analyses that are predictive even though the specific patterns of activation are not readily interpretable in a cognitive neuroscience framework.

For OCD, structural measures at baseline have been associated with variability in response to exposure therapy ([Fullana et al., 2014](#)). A thinner cortex in the left rostral ACC at baseline was associated with better responses to therapy. This same region was thinner overall in patients than in controls, so greater differences from controls were associated with better outcomes. The neuroanatomical locus is similar to that often observed in studies of depression outcomes, which raises the possibility that similar neural mechanisms may support behavioral therapies across diagnoses.

The studies mentioned above examined the relations between pretreatment neuromarkers and one kind of treatment, such as CBT, a medication, or rTMS. The relevant choice that must be made by a patient or physician, however, is not whether to pursue one kind of treatment but, rather, to select among alternative treatments. Therefore, an important and practical goal is to examine whether there are differential predictors of effectiveness for alternative treatments. One study employed PET imaging prior to patients being randomly assigned to a medication (escitalopram oxalate) or CBT to treat their depression ([McGrath](#)

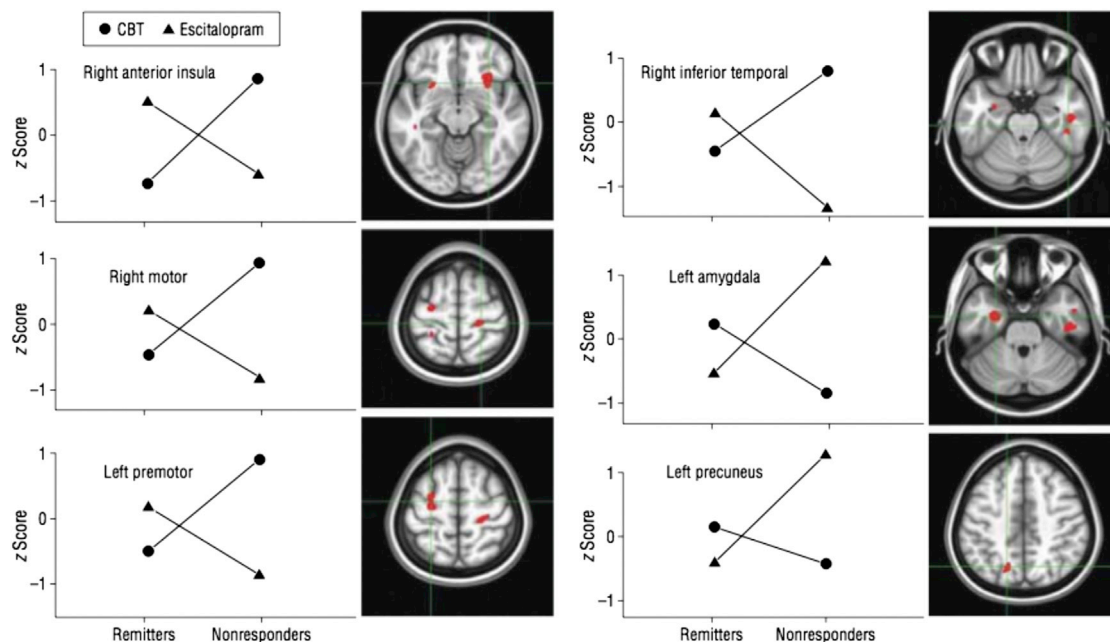


Figure 4. Treatment-Specific Biomarker Candidates for Treatment of Depression

Mean regional activity values for remitters and nonresponders segregated by treatment (either escitalopram given as escitalopram oxalate or CBT) are plotted for the six regions showing a significant treatment \times outcome analysis of variance interaction effect. Regional metabolic activity values are displayed as region/whole-brain metabolism converted to z scores (from McGrath et al., 2013b).

et al., 2013b). Six limbic and cortical regions showed a differential response to the two treatments, with right anterior insula hypometabolism correlating with future remission to CBT (and poor medication response) and right anterior insula hypermetabolism correlating with future remission to medication (but a poor response to CBT) (Figure 4). Subgenual ACC metabolism was higher in patients who failed to respond to either treatment than in patients who remitted from depression (McGrath et al., 2013a).

Another study with a small number of pediatric patients with generalized anxiety also found correlations between pretreatment brain functions and treatment outcomes but did not find differences between behavioral (CBT) and pharmacological (fluoxetine) treatments. Greater baseline activation of the amygdala to negative facial expressions was associated with better symptom improvement regardless of treatment type (McClure et al., 2007).

Future Relapse for Alcohol, Drug Addiction, Smoking, and Diet

Alcoholism, drug addiction, smoking, and obesity are major public health problems that share a similar treatment aim, namely abstinence from a substance that is harmful to the brain and body. Several studies have examined relations between neuro-markers and whether individuals abstain successfully or relapse into their health problems. Generally, these studies examined patients who recently became abstinent at the initiation or termination of a treatment program and then followed these patients over weeks or months to learn which patients continued to abstain versus those who relapsed. Improved identification of risk for relapse could support individualized treatment ap-

proaches that vary for those at minimal or maximal risk for relapse.

At least 60% of patients who seek treatment for an alcohol use disorder relapse within 6 months following treatment (Maisto and Connors, 2006; Udo et al., 2009), and there have been several studies in which baseline brain measures are associated with future abstinence versus relapse. In two studies of recently abstinent patients, greater activation of the putamen was associated with a greater likelihood of relapse 3 weeks or 3 months later (Braus et al., 2001; Grüsser et al., 2004). Other measures, such as self-reported intensity of craving, history of intake, or duration of abstinence before scanning, were not associated with likelihood of relapse. Both anatomic (Rando et al., 2011) and regional cerebral blood flow (Noël et al., 2002) studies reported that baseline measures of the medial prefrontal cortex were associated with likelihood of relapse. Similarly, patients who relapsed exhibited reduced volumes of the medial and/or lateral prefrontal cortex (Durazzo et al., 2011; Cardenas et al., 2011) and reduced white matter FA in frontal regions (Sorg et al., 2012) relative to patients who sustained abstinence. Broadly, a greater reward response to alcohol-related stimuli and lesser strength in cognitive control regions were related to relapse.

Relapse after treatment occurs at an estimated 50% rate within a year among individuals with stimulant dependence who seek treatment (Miller, 1996). Several neuroimaging studies have reported that neuromarkers can contribute to the identification of future abstinence or relapse. One group of patients with methamphetamine dependence underwent fMRI 3 or 4 weeks after cessation of drug use and near completion of a

28-day inpatient program and were followed for about a year, at which point about half of the patients had relapsed (Paulus et al., 2005). During fMRI, participants attempted to either predict where a stimulus would appear or to simply note that a stimulus had appeared. None of the multiple sociodemographic, baseline symptom, or use characteristics predicted relapse, but patients who would later relapse exhibited a greater activation in multiple brain regions than those who would not relapse, including the prefrontal, parietal, and insular cortices. A pattern of activation across right insular, posterior cingulate, and temporal regions correctly identified 20 of 22 patients who did not relapse and 17 of 18 patients who did relapse. Other studies have reported correlations between baseline fMRI activations and future relapse for cocaine use after 1 week (Prisciandaro et al., 2013), after a 10-week outpatient program (and a better predictor than subjective reports of craving) (Kosten et al., 2006), and after an 8-week outpatient program (Brewer et al., 2008; Jia et al., 2011). Specific locations of activations that correlated with future relapse varied across these studies, perhaps reflecting differences in experimental paradigms, analyses, or participants.

Tobacco smoking is the leading preventable cause of death in the developed world, with one billion tobacco-related deaths projected for the 21st century (World Health Organization, 2008). Identifying smokers at high risk for relapse could influence the design of cessation programs to fit with individual risk profiles. In one study, adult nicotine-dependent women underwent fMRI while viewing smoking-related and unrelated pictures before quitting smoking (Janes et al., 2010). The women then made an attempt to quit smoking, and prequit measures were related to subsequent success or failure in smoking cessation. A greater baseline activation to smoking-related pictures in the insula correlated with the likelihood of future relapse. The identification of insula reactivity as a correlate of future relapse is of interest because lesions to the insula in smokers were associated with reduced smoking that was immediate and without relapse (Naqvi et al., 2007). Smokers who did not quit successfully also exhibited reduced functional connectivity between an insula-containing network and dorsolateral prefrontal cortex and dorsal ACC, suggesting a weakness in interactions between brain regions associated with smoking desires with regions associated with cognitive control. A combination of brain functional data and a behavioral task resulted in 79% accuracy in identifying smokers who would or would not abstain from smoking. Future success in quitting smoking has also been associated with gray matter volumes in cortical and subcortical regions (Froeliger et al., 2010).

Brain measures may also help identify what sort of information presented to people aiming to quit smoking are likely to be effective. Ads aimed at encouraging people about to try to quit smoking were presented during fMRI, and relapse was followed for a month (Falk et al., 2011). A greater activation in the medial prefrontal cortex at baseline was associated with successful quitting. The addition of the brain measures to other measures (self-reported intentions, self-efficacy, and ability to relate to the ads) more than doubled the accuracy of a model accounting for changes in smoking behavior. In another study with a large number of smokers, increased activation in brain regions associ-

ated with self-reference, especially the medial prefrontal cortex, in response to individually tailored smoking cessation messages was associated with a better probability of quitting 4 months later (Chua et al., 2011).

Healthy eating is a goal for individuals with obesity, and there is evidence that brain measures at baseline are associated with short- and long-term outcomes in a weight loss program (Murdaugh et al., 2012). Obese individuals viewed high-calorie food versus control pictures before and after a 12-week weight loss program, with a 9-month follow-up. Greater baseline activation in the nucleus accumbens, insula, and ACC in response to high-calorie food pictures correlated with lesser weight loss after 12 weeks. Further, less successful weight maintenance at 9 months correlated with greater posttreatment activation in the insula, ventral tegmental area, and other regions. The relevant regions are associated with interoception (insula), reward (nucleus accumbens and ventral tegmental area), and cognitive control (anterior cingulate), which are all processes related to dietary decisions.

Future Response to Placebos

Positive medical responses to placebo treatments are often powerful and can rival the effectiveness of active treatments, such as medicines for depression (e.g., Walsh et al., 2002). Consequently, exploitation of placebo mechanisms may offer a safe therapeutic approach for some patients, but there is evidence for considerable variation in response to placebos (Walsh et al., 2002). Most studies of the brain basis of individual differences in placebo responses have focused on pain, in part because cortical and subcortical brain regions involved in pain have been relatively well characterized. Placebo analgesia (the positive influence of a placebo on experienced pain) was related to a pattern of increased activation in several cortical control regions and decreased activation in somatosensory activation during the anticipation of pain rather than activation during reported analgesia to pain itself (Wager et al., 2011). Patients with a better future response to placebo treatments exhibited lesser resting-state functional connectivity between the medial prefrontal cortex and insula during a pain-rating task (Hashmi et al., 2012). Furthermore, greater network efficiency during the resting state was associated with a better response to future psychologically mediated analgesia related to treatment for chronic knee pain (Hashmi et al., 2014). A range of other findings also indicates that functional and structural brain measures may help identify individual patients most likely to benefit from placebo treatments (reviewed by Koban et al., 2013).

Predicting Individual Futures with Neuromarkers: Hopes and Challenges

As reviewed above, neuromarkers obtained from noninvasive brain imaging have shown great promise for identifying children and adults more likely to learn well or poorly in particular domains; more likely to progress to unhealthy (or even criminal) behaviors; and more likely to respond to particular pharmacological, behavioral, or placebo treatments for many neurodevelopmental and neuropsychiatric disorders. Although the amount of scientific evidence is modest in many areas (with reading and depression having perhaps the greatest concentrations of studies to date), there are also numerous studies

reporting that predictive neuromarkers either outperform or significantly enhance traditional measures of individual variability, such as self-reports, clinical rating scales, or scores on educational or neuropsychological tests. It is these kinds of studies that express both a practical and humanitarian possibility of improving lives through recognizing individual differences in brain function and structure that greatly influence the diversity of educational and clinical outcomes and using that recognition to individually optimize educational and clinical practices.

Because of these hopes, the challenges of translating cognitive neuroscience measures into better futures for people need to be carefully identified and thoughtfully overcome. First, many of the reviewed studies were performed with relatively small samples, and, in particular, many of the older studies used statistical approaches that were overly liberal by current standards. Although such pioneering studies must often begin with modest resources because it is their outcomes that justify larger studies, the translation of such science to practical application now requires larger studies that can support more rigorous statistics. This is particularly true for studies of neurodiversity that focus on individual differences because there must be adequate sampling not only of a population as a whole but also of the diversity of individuals within that population. Second, studies must mature from correlations between baseline measures and clinical or educational outcomes to predictive models that apply the outcomes from one group (training set) to another group (test set) and, finally, to an individual. This is essential because use of such measures must operate with new individuals for whom a clinical or educational intervention is being planned. Third, few studies have integrated findings across multiple imaging modalities, even when the multiple brain measures could be made during a single MRI session. Combining multiple kinds of neuromarkers may enhance their predictive accuracy. Fourth, it will be important for future studies to involve plausible, alternative interventions (e.g., [McGrath et al., 2013b](#)) because the question is less often whether a person should receive help but, rather, which kind of help is most likely to rapidly improve the person's education, skills, or health.

Neuromarkers will be useful to the extent that they outperform, alone or in combination with traditional measures, measures that are otherwise available. Indeed, multiple studies have reported such value from neuromarkers, but other studies have not examined whether the neuromarkers significantly improve predictions above and beyond readily available measures. All forms of brain and behavioral assessment improve over time, and perhaps a new behavioral assessment will outperform neuromarkers in the near or distant future. At the same time, behavioral assessments in many educational and clinical areas have been developed and maintained over many years, so it is unknown when breakthroughs might occur. Perhaps neuroimaging measures will also be useful tools in developing a new generation of brain-validated behavioral assessments that can be readily used in schools, hospitals, and medical offices. At the conceptual limit, there ought to be a strong relation between measures of mind and brain so that a new generation of behavioral measures could capitalize on the novel insights of neuroimaging.

If neuroimaging remains necessary for optimal prediction, there could be concerns about the cost and availability of MRIs or other measures. In this regard, the cost of MRI imaging in particular has raised concerns about its potential wider use. One solution for availability could be to use more transportable technologies, such as wireless EEG devices, with assessment paradigms developed through coupled MRI and EEG studies. Any economic analysis, however, ought to include the costs of current practices in which patients are often inadvertently directed to treatments that turn out to be ineffective for that patient (often around half of patients for a given treatment in many cases) or in which children must demonstrate academic failure before receiving educational intervention. The cost of a neuropsychological assessment and report for an individual child or adult, for example, often exceeds that of an MRI.

If neuromarkers are proven to enhance prediction, there will be ethical and societal issues to consider. Because of their biological nature, brain measures can be overly valued and potentially divert public and scientific interest in behavioral and social factors ([Kagan, 2013](#)). If neuromarkers become more useful, they will provoke questions about how to most ethically use predictive information to help people rather than simply select people most likely to succeed. This important concern, however, must be weighed against the questionable validity of many current practices, such as the finding that parole decisions made by experienced judges appear to be greatly influenced by the time of day and proximity to a meal at which a case is reviewed ([Danziger et al., 2011](#)) or that medical schools continue to conduct interviews for admissions despite evidence that decisions based on such interviews have no correlation with objective measures of medical school performance ([DeVaul et al., 1987](#); [Milstein et al., 1981](#)). For in-patient treatments for substance abuse, there is little scientific justification for the prototypical 28-day treatment period. Even an imperfect predictive measure of relapse may lead to more rational treatment durations that are related to individual variation. Neuromarkers and neuroprognosis may offer practical and valuable contributions because so many current educational and medical decisions occur in the absence of scientific evidence that can guide those decisions.

This review considered mostly studies with relatively short-term longitudinal educational and clinical outcomes, but future research may also attempt to predict longer-term outcomes. Educational and medical practices often respond to crisis, such as failure in learning to read or coping with depression. Longer-term research may examine whether neuromarkers can help identify children at early risk with the hopes of diverting those children away from a trajectory toward failure and crisis, such as ongoing studies attempting to identify whether infants at familial risk for autism will or will not progress to autism over the next few years ([Bosl et al., 2011](#); [Wolff et al., 2012](#)). Such early predictions may require novel forms of intervention (e.g., language learning remediation in 2- or 3-year-olds that minimizes their difficulty in learning to read as 5- and 6-year-olds) with the hope that such children never experience the crises as children or adults that now initiate intervention.

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