On the Use and Misuse of Genomic and Neuroimaging Science in Forensic Psychiatry: Current Roles and Future Directions

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With rapid advances having been made across multiple levels of genetic, molecular, and cognitive neuroscience, new questions arise as to when, whether, and how this enhanced knowledge of the neurobiological basis of human behavior will affect social institutions such as the criminal justice system. While some of these questions have focused on the potential uses of neuroimaging for lie detection and other forms of mind reading, an additional point of intersection between law and neuroscience resides in forensic psychiatry. As in other areas of psychiatry, the enhanced understanding of brain function offered by novel in vivo imaging technologies holds great promise for improved reliability and validity in diagnosis and assessment. Although we are cautiously optimistic about the longer-term benefits that may accrue from the introduction of neuroscience into the courtroom, the current tools have significant limitations. These caveats must be weighed heavily given the potential of neuroscientific data to

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hold significant prejudicial, and at times, dubious probative, value for addressing questions relevant to criminal responsibility and sentencing mitigation.[1,2]

This article therefore summarizes, based on the current state of the science, the informational value provided to forensic psychiatry by two key neuroscientific domains with potential relevance to law: neuroimaging and genetics. This article is not intended to be comprehensive in terms of all possible uses of these technologies in any legal context, but rather limits its focus to forensic practice as it relates to the determination of insanity, diminished capacity, and mitigation. The first section reviews the current state of behavioral genetic research as it pertains to what is hereafter termed "legally relevant psychopathology" (LRP); that is, personality traits, behaviors, and diagnoses that may affect such forensic assessments (eg, impulsivity, substance abuse, antisocial personality disorder). The second section reviews basic principles of widely available neuroimaging tools and highlights some of the conceptual and analytical challenges of using these instruments to aid forensic assessment. Finally, in the third section, the authors look toward the future to identify certain trends that may overcome the limitations described in the preceding 2 sections.

FORENSIC GENETICS

On the occasion of the first draft release of the human genome, the full complement of inherited material possessed by the humans, Francis Collins (then the Head of the National Human Genome Research Institute) remarked, "What more powerful form of study of mankind could there be than to read our own instruction book." Although Collins likely intended this as a general comment on the utility of genetic information for understanding our evolutionary history and shared biology, this statement perhaps encapsulates a sentiment (or hope) that is increasingly held by many in the field of law: that analyzing an individual's DNA sequence can resolve the mystery of that individual's past and future behavior. However, whereas technological innovations of the last quarter century have rendered the human genome accessible to scientific inquiry in ways never before thought possible, the ethical, legal, and social implications of the resulting flood of genetic information are far from settled. With respect to the law, interest in the use of genetic information in the courtroom is often centered on two components of forensic psychiatry. First, criminal responsibility, that is, whether or not the genetic makeup of an individual influenced their behavior in such a way as to diminish their level of moral responsibility for a given criminal act, thereby mitigating their criminal liability; and sceond, criminal prediction, the extent to which information about the genetic makeup of an individual can be useful for determining that individual's future propensity toward criminality. Although a comprehensive and nuanced discussion of the implications of recent genetic discoveries for specific criminal contexts is beyond our expertise, we highlight several general issues pertaining to human behavioral genetics as a way of setting expectations for what is reasonable for legal thinkers to expect from genetics based on the state of the science.

In weighing the utility of genetic information for the determination of criminal responsibility and risk, it is instructive to contrast the goals of science with the goals of law. Scientific advances often proceed by use of inductive logic, whereby general conclusions are drawn from a collection of individual observations. For example, in genetic association studies, individuals with a certain genotype are grouped together and the frequency of a trait, behavior, or disorder is compared between the genotype groups. A statistically significant difference in the occurrence of that trait, behavior, or disorder between the two genotype groups is taken as an evidence of a positive genetic association. The strength of that association can be considered in terms of

(as one example) an odds ratio, in which a "risk" genotype is considered to confer a certain degree of increased susceptibility to that trait, behavior, or disorder, relative to the "nonrisk" genotype. This way, a general phenomenon is derived by averaging across multiple single data points—that is, we are "inferring up" from the specific to the general. However, there may be many individuals (depending on the strength of the association) who possess the "risk" genotype, yet are completely psychiatrically healthy. In contrast, the application of genetics in forensic and legal settings depends on a process of "inferring down" to a specific individual's mental status on the basis of group-level phenomena, such as prior statistically significant genetic associations. Several examples are included in the following sections to demonstrate the difficulties inherent to this approach.

First, let us consider the concept of heritability. It has been understood since ancient times that certain forensically relevant traits and behaviors (eg, antisocial behavior and aggression) seem to run in families. Indeed, the apparent inheritance of such traits and behaviors has piqued the interest of modern science, and the question of their heritability has been a major target of scientific investigation. Heritability refers to the proportion of population variance in a trait or behavior that is accounted for by genetic factors, and is commonly measured by comparing the degree to which a trait or behavior is shared between dizygotic and monozygotic twins. Importantly, heritability in this context has a very specific meaning: because heritability deals with how much of the variability across a large number of people can be attributed to genetic factors, the concept of heritability bears little relevance for the individual person. For example, multiple genetic studies of antisociality converge to suggest that genetic factors account for approximately half of the population variability in antisocial traits and behaviors.[3] This does not mean that, in a given antisocial individual, half of his or her behavior is due to his or her genes and the other half to his or her environment. Herein lies the problem in inferring down from heritability. Even given the knowledge that genetic factors play a large role in an LRP, and given the understanding that, for whatever legal reason, the presence or absence of genetic factors is relevant for a specific individual determination of criminal responsibility or risk, it is impossible to know whether, in a specific individual, genetic factors play any role whatsoever in the presenting clinical phenomenon.

Thus, the mere knowledge that a given (putatively) legally relevant psychiatric phenomenon is heritable is not useful from a legal standpoint because heritability does not provide information about genetic contributions to the behavior of any one individual. However, knowing that a trait or behavior is heritable is useful insofar as it represents an essential starting point for further genetic analysis. Given heritability, the next step is to identify specific inherited genetic variants and mutations that are responsible for the intergenerational transmission of a trait, behavior, or disease.

It should be recalled that genes provide instructions for making proteins. According to the traditional genetic dogma one gene directs the creation of one protein (although it is now known that a single gene can code for a multitude of distinct, but related, proteins), and this information is stored as a four-letter DNA code. These letters are the DNA base pairs (bp): A (adenine), T (thymine), G (guanine), and C (cytosine), and the specific sequence in which these letters are arrayed within a gene determines the composition and abundance of the resulting protein. In humans, approximately 99% of this sequence is shared across members of our species, and it is thought that the 1% that varies between individuals is incredibly important for determining individual differences in traits ranging from eye color and height to one's predisposition for developing a range of physical and mental illnesses.

Some traits and diseases are known to result, deterministically, from a single well-characterized mutation or set of mutations within a single gene. For example, sickle cell disease is caused by a single mutation, the substitution of an "A" with a "T" at a specific position in the DNA sequence of the hemolglobin-β (HBB) gene, which leads to a detrimental change in the function of the oxygen transport protein hemoglobin. Individuals who possess 2 copies of this mutation (ie, one from each parent) develop the disease with 100% certainty. Thus, the presence or absence of the mutated "T" allele determines the presence or absence of the disease, and knowing whether an "A" or a "T" is present at that specific place in the DNA sequence of the HBB gene conveys, with complete fidelity, information about the disease state of the individual. In such so-called monogenic or mendelian disorders, the heritability of disease (or, as is the case, trait, or behavior) can be traced clearly to the inheritance of the mutation within affected families.

It is taken for granted that genetic information pertaining to these types of monogenic disorders (eg, Down syndrome, fragile X, Huntington disease) can be of value in circumstances that require specific evidence to confirm the presence of an organic disorder leading to mental impairment. However, in the case of most of the traits, behaviors, and disorders that are relevant to law, mendelian inheritance is the exception, rather than the rule. Indeed, the genetic architecture of psychopathology that is potentially relevant to the law (eg, substance abuse, antisocial behavior, psychosis) is polygenic and multifactorial, with common polymorphic variants in multiple genes, each of small effect size, interacting with each other and with the individual environment to predispose the risk for psychopathology.[4] Therefore, given the genetic complexity of these disorders, it becomes meaningless to talk about, much less, test an individual for, a "gene for" violence or a "gene for" addiction (to give but two examples). Instead, we infer a causal (but, critically, nondeterministic) relationship between one or more variants and a disease, behavior, or trait, on the basis of a statistical analysis of the frequency of that variant in people who possess that disease, behavior, trait and in those who do not. Typically, this analysis is accomplished by comparing the distribution of alleles at one or more polymorphic sites within a given gene's DNA sequence between individuals with or without a disorder. If 1 allele is found to be "overrepresented" in ill individuals (ie, found more commonly in people with illness than would be expected by chance), it can be said that this allele is associated with the disease and an odds ratio can be computed to quantify the degree of increased risk for the disease conferred by possessing the overrepresented allele. Similar methods can be used to quantify the degree of variance in a continuous trait (eg, scores on personality tests measuring impulsivity and aggression) accounted for by a given genetic variant.

The genetic complexity of LRPs requires that genetic associations to an LRP be considered as evidence that risk-associated genetic variants increase susceptibility to an LRP in a nondeterministic manner. Testing an individual for an allele that has been previously statistically associated with an LRP provides low-fidelity information about the presence or absence of that LRP in the individual. Further, in a given individual with a clinically diagnosed LRP, it is impossible to determine, even if they do possess a risk-associated allele, whether possessing that allele is in any way relevant to their psychiatric status because such "risk" alleles are, considered in isolation, completely compatible with psychiatric health. Consistent with this notion, effect sizes for the genetic variants that have been most consistently associated with LRPs (eg, antisocial behavior) are typically small,[4] commonly with odds ratios of less than 2, and often less than 5% of the variability in risk for a given trait, behavior, or disorder accounted for by a single genetic marker.[5] Furthermore, nonreplications of single

genetic variants to clinical diagnostic phenotypes are common. To exemplify these issues, we consider the genetic factor that is most commonly considered with respect to LRPs, a polymorphic variant in the monoamine oxidase A (MAOA) gene.

MAOA encodes the mitochondrial catabolic enzyme monoamine oxidase A (MAO-A), which is important for degrading monoamine neurotransmitters such as serotonin.[6] Both human and animal studies point to a functional role for MAO-A in impulsive-aggressive behavior. For example, in a landmark article, Brunner and colleagues[7] examined a large Dutch kindred that was notorious for the high levels of impulsive and violent behavior demonstrated by some of its males. The characteristic behavioral phenotype, which stretched back for many generations, included mild mental retardation; extreme reactive aggression; and violent criminal behavior, including rape, assault and attempted murder, arson, and exhibitionism.[7] Affected males showed altered serotonin metabolism,[8,9] and females in this family were asymptomatic, which suggested that the heritable factor was located on the X chromosome.[7] Indeed, subsequent genetic analysis revealed the cause to be a point mutation (C936T) in the eighth exon of the X-linked *MAOA* gene. This mutation, which was present in all affected individuals, results in a premature stop codon. Thus, males who possess this mutation (and who have only one X chromosome) can be considered to have a functional knockout of their MAOA gene.[9]

We detail the Brunner finding of a highly functional but exceedingly rare mutation (it is not found outside of that one family) to contrast it with a polymorphic variant in the *MAOA* gene that has generated much interest for both psychiatry and law. In 1998, Sabol and colleagues[10] described a common, likely functional, so-called variable number of tandem repeats (VNTR) polymorphism in the upstream region of the *MAOA* gene. The *MAOA* u-VNTR (as it is sometimes called), is comprised of a repeated sequence of 30 bp; in vitro studies have shown that the presence of 3.5 or 4 repeats is associated with relatively higher *MAOA* expression (and are thus referred to as *MAOA*-H alleles), whereas the presence of 3 repeats results in relatively lower expression (*MAOA*-L allele).[10,11] Thus, by extension, individuals who possess 3.5 or 4 repeats of the 30-bp sequence have higher levels of *MAOA* (and therefore lower levels of serotonin) and individuals who possess 3 repeats of the 30-bp sequence have lower levels of *MAOA* (and therefore higher levels of serotonin). However, the functional significance of this variant in vivo has been called into question: one recent positron emission tomographic (PET) study showed no effect of this variant on MAOA protein levels in the living human brain.[12]

The discovery of the *MAOA* u-VNTR was greeted with great enthusiasm by psychiatric geneticists, who immediately began the search for associations of this variant to behavior and temperament. Given the linking of altered *MAOA* function to antisocial behavior by Brunner and colleagues,[7] special emphasis was placed on finding associations to manifest behavior and to traits that are empirically and conceptually related to aggression and impulsivity. Several behavioral instruments, diagnostic measures, and temperament indices have been used to test for an association between the MAOA-L allele and LRPs, including the *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition) diagnoses of antisocial personality disorder (in adults), conduct disorder (in children and adolescents), and impulsive-antisocial traits as measured by the Tridimensional Personality Questionnaire, Temperament and Character Inventory, and NEO-Personality Inventory-Revised (NEO-PI-R).[13] Although some significant effects have been found, the size of such effects are typically small (see earlier discussion); further, there are a number of nonreplications and prominent issues of allelic directionality (eg, associations of antisocial behavior to MAOA-H rather than to MAOA-L), which render interpretation difficult.[13,14] These

conflicting findings, to date, are consistent with the idea that LRPs are both genetically and phenotypically complex. There are likely to be multiple genes that interact, with each other and with environmental factors (see later discussion), to affect the development of LRPs and further there may be distinct patterns of genetic linkages to relatively heterogenous subphenotypes within a broad diagnostic category (eg, distinct genetic architectures for reactive vs instrumental aggression within the broad diagnosis of antisocial personality disorder). On the whole, genetic studies of the *MAOA* u-VNTR support the notion that single common genetic variants, considered in isolation, provide little legally useful or relevant information for any given individual.

In contrast to the small and inconsistent effect of the *MAOA* u-VNTR on LRPs when considered as a single factor, there is evidence for a robust and replicable effect of this variant when the role of early life environment is taken into account. In a landmark study, Caspi and colleagues[15] found no effect of the MAOA u-VNTR on antisocial behavior on its own; however, a significant effect emerged in individuals who had experienced childhood maltreatment. This finding of a gene-environment interaction has been replicated (including via meta-analysis) and extended since the initial report.[16] However, in reflecting on the relevance of this finding for law, it is instructive to consider the data more closely. Specifically, these studies often find a significant primary effect for childhood maltreatment (but not *MAOA* u-VNTR genotype) on risk for adult antisocial behavior and aggression; stratifying individuals who experienced maltreatment by *MAOA* genotype reveals that the size of the effect of maltreatment on adult psychopathology is relatively stronger in MAOA-L individuals than in MAOA-H individuals. Two points are salient here: first, the primary risk factor for LRP is not a genetic factor (*MAOA* u-VNTR allele status) but an environmental one (childhood maltreatment) and second, the effect of this environmental factor is significantly weaker in individuals carrying an MAOA-H allele. Thus, it is entirely valid to think of the *MAOA* genotype as exerting a protective effect by buffering (in MAOA-H individuals) the otherwise adverse impact of childhood maltreatment.[17] Considered in this light, that is, the *MAOA*-H as protective allele rather than the *MAOA*-L as a liability allele, what is the legal relevance of *MAOA* genotype in an individual with a history of childhood abuse? From the standpoint of determining criminal responsibility, is the absence of a protective factor completely equivalent to the presence of a liability factor?

The greatest challenge to the utility of genetic information in forensic settings is the fact that although a single genetic factor may confer a measurably increased risk for an LRP on average (ie, across a group of participants in one or more studies) it cannot be reasonably inferred that if present in any given individual on trial, this factor elevated, diminished, or in any way affected the risk for the particular individual. Consider one example: a defendant on trial for aggravated assault has a documented history of early life abuse, and genetic testing reveals that he possesses the 3-repeat allele of the 30-bp 5' upstream MAOA VNTR. Given that several prior studies have demonstrated that this combination results in a significantly increased odds ratio for aggressive or antisocial behavior,[15–17] it is understandably tempting for the defense to suggest that the defendant's genetic profile, together with his background, contributed to his behavior in ways that were beyond his control, thereby diminishing his responsibility. The problem with such an inference is that whereas this combination on average results in increased risk, this specific combination of factors in this specific individual may very well have no effect on his antisocial behavior. This kind of inference ignores a myriad other factors that may exert a tremendous influence on the relationship between the specific measured variable that is associated, at the population level, with an LRP, and with behavior in that individual. In particular, this inference ignores

the critical role of epistasis. Although only 1 genetic variant may be measured at a time, genetic variants do not exist in isolation to produce effects on brain and behavior. Rather, they exist as part of a complex and interacting network of genetic variation. It is increasingly understood in psychiatric genetics that epistatic interactions between variants can produce effects that would not necessarily be predicted on the basis of the main effects of the variants in isolation.[18–20] Thus, measuring 1 variant in isolation and making inferences about the causal role of that variant on an LRP can be misleading because, depending on an individual's larger genetic background, that variant, in that individual, may have either no effect or the opposite effect from what would be predicted on the basis of group-averaged population studies. Without being able to evaluate the full range of possible genetic and environmental factors that may increase, diminish, or nullify the effect of a particular genetic marker, it is challenging to infer accurately how much of an influence such a marker might have had for a particular individual on that particular individual's LRP.

On the whole, given the issues outlined earlier, it can be concluded that there are significant limitations with respect to the ability of genetic information to add value in addressing forensic questions pertaining to criminal responsibility, excepting of course cases in which the genetic diagnosis of simple, monogenic disorders is relevant to a particular case. However, we believe that these limitations are not necessarily insuperable. We do not wish to imply that the genetics of complex traits and disorders will never have a place in the courtroom, only that the present state of the science is such that the kind of genetic information currently available (or at least, most commonly offered in court) does not carry robust and reliable information about the cognitive capacities and mental state of an individual above and beyond what can be gleaned from clinical interviews and neuropsychological testing.

FORENSIC NEUROIMAGING

As with genetics, significant excitement has been generated by the possible application of neuroimaging in the courtroom, with proposed uses ranging from lie detection[21–24] and assessment of *mens rea*[25] to assessment of personality traits and diagnosis of LRP. The term neuroimaging encompasses a wide range of in vivo measurement techniques that may be used to capture different indices of brain structure and function. In humans, the most commonly used neuroimaging methods include electroencephalography (EEG), positron emission tomography (PET), single-photon emission computed tomography (SPECT), computed tomography (CT), and magnetic resonance imaging (MRI). As a class, these tools are thought to hold great promise in the advancement of medical diagnosis and the prediction of human behavior.[26]

Neuroimaging is advantageous because it is relatively accessible, noninvasive, and shows high reliability.[27] In a forensic context, use of neuroimaging may eventually be able to provide empirical evidence for the presence of an LRP, such as schizophrenia, which would be relevant in determining a defendant's capacity to have formulated criminal intent at the time of a crime. Similarly, neuroimaging evidence could theoretically provide compelling data to suggest impairment in neural processes required for cognitive control over impulsive behavior, which might aid a defendant seeking to plead down from a first- to a second-degree murder charge.

However, the current level of applicability of these techniques to the identification of LRP varies significantly. As stated earlier, the application of neuroimaging within the context of the courtroom hinges on the ability to infer down to the level of the individual. For reasons that are discussed later, many of the most widely publicized forms

of neuroimaging (eg, functional MRI [fMRI]) are poorly suited for drawing inferences about the brain status of a specific individual. This section provides a brief review of the methodologies involved in these techniques, with a particular focus of how the interpretation of their results may be influenced by field-specific jargon that could increase their prejudicial value in a courtroom context. Finally, the strengths and weaknesses of different imaging techniques within the context of forensic assessment for LRP are reviewed.

Neuroimaging for the Assessment of Brain Abnormalities

In considering the application of neuroimaging data to forensic assessment, a distinction must be drawn between whether the neuroimaging data are to be used for demonstrating the presence of brain abnormalities (in the form of congenital malformations, significant atrophy, or traumatic insults resulting from injury, stroke, etc) or for the direct assessment of an LRP. Arguably, the most straightforward and noncontroversial applications of neuroimaging data are in cases of the former, in which such data simply provide confirmation that a given individual has experienced some sort of brain damage. This function is primarily accomplished through the use of structural neuroimaging, including CT and structural MRI scans, both of which provide excellent means of assessing the presence or absence of gross morphologic abnormalities on an individual basis. However, simply determining that damage is present says little regarding the implications of such damage for criminal behavior. The use of neuroimaging for this purpose makes no attempt to form a direct link between the mere presence of brain damage and LRP. Rather, this gap is bridged by the standard forms of neuropsychological assessment that seek to reveal specific cognitive and behavioral impairments that have more direct relevance for a client's actions, for which neuroimaging data merely serve as context or precondition. For example, in the well-publicized case of Terry Schiavo, both EEG and CT images were presented to demonstrate the extent of brain atrophy that had occurred. However, the interpretation of this data regarding the diagnosis of a persistent vegetative state relied on the testimony of several expert witnesses in neurology and neuropsychology, not the neuroimaging data itself.[28] Similarly, in the case of an insanity defense, neuroimaging can be used to establish that an individual's brain has experienced some form of damage, but its utility for assessing whether an individual was able to know the difference between right and wrong at the time of the crime is not yet known.

Neuroimaging for the Assessment of an LRP

In contrast to addressing questions regarding the presence of brain abnormalities that may buttress the use of neuropsychological assessment, some scientists and legal experts have increasingly promulgated neuroimaging as an alternative, and more powerful, means of directly measuring LRP. In the eyes of its proponents, neuroimaging techniques hold the promise to catch the predispositions toward impulsivity, poor cognitive control, and the like that the current battery of assessment instruments fail to capture. Speculation on this second use of neuroimaging data in criminal law has generated equal enthusiasm and criticism among scholars and commentators, although at present, there are few examples from which to draw concrete information on how such data might be used in the courtroom.

To make claims that the presence of a brain abnormality may result in an LRP, it must be shown that either prior data has specifically linked the same abnormality to the same legally-relevant impairment, or there is sound reason to believe that the abnormality could produce such an impairment, given what is generally known about

its role or function. In both cases, information about typical brain function (as derived from group studies) must be inferred down to the individual level. However, as demonstrated in the discussion later, data reduction and analysis methods common to almost all neuroimaging techniques may significantly compromise the ability of these techniques to provide accurate or meaningful information about a specific person. The following sections, highlight specific steps in the analysis of imaging datasets that are most problematic for the purposes of individual prediction.

Normalization of Brain Images

Although the macro architecture of the human brain is shared across individuals, each person's brain shows variation in both subtle and gross morphologic aspects. Consequently, studies that seek to identify common loci of neurobiological processes using standard noninvasive brain imaging techniques are required to find ways to bring each individual brain into a "common space." Referred to as "normalization," this process uses a series of iterative algorithms to transform the data of each subject to match the spatial properties of a group average template. For the purposes of group analysis, it is reasonable to assume that errors in normalization will be randomly distributed, and will therefore cancel each other out when looking at group-averaged data. However, this assumption does not apply when trying to draw inferences from a particular individual. Consider an example in which a region of interest (ROI) for a specific neuroimaging task is the dorsal portion of the anterior cingulate cortex, which is known to exhibit several common sulcal variations.[29,30] What inferences could be drawn if no activation was shown in the area of anterior cingulate most commonly found in group studies but was present in a neighboring region? Such a pattern could suggest an impairment in the dorsal cingulate function that might be of relevance, or merely a normalization error reflecting a typical structural variation in the cingulate morphology for the individual in question.

Voxelwise Statistical Inference

All functional neuroimaging datasets divide the brain into 3-dimensional pixels, or voxels. Voxels are typically 3 to 4 mm^3, but may get smaller than 1 mm^3 when using particularly high-field strength magnets (eg, 7 Tesla strength or higher). Analysis of these voxels is typically performed on a per-voxel basis. That is, if the brain is divided into *n* voxels, the analysis will require *n* number of individual statistical tests. However, neither neuroimaging data nor the neural events are independent to the extent that would be necessary for voxelwise approaches to represent an ideal analytical technique. Increasing evidence suggests the presence of multiple state-dependent neural networks that are highly intercorrelated.[31] Moreover, sources of noise from MRI and PET imaging techniques are also correlated, despite sophisticated filtering techniques used to reduce their influence. The consequence is a reduced statistical power to detect real effects, leading to a high degree of type II error across many neuroimaging studies.[32] This elevated rate of false negatives, although still problematic in group studies, is a far more serious problem when attempting to assess data from a single individual when attempting to draw an inference about the presence or absence of an LRP.

Linking Neuroimaging Data to Brain States: Problems of Interpretation

Functional neuroimaging, be it through EEG, PET, SPECT or fMRI, provides an indirect measure of neuronal information processing. Of these measures, only EEG directly assesses the electric activity of neurons, although it is limited in its ability to accurately represent specific regions from which electric signals emanate. The other 3 techniques

provide measures of cellular metabolism. Because neuronal activity, including both the generation of an action potential ("firing") as well as the processing of received impulses from other neurons, is energetically demanding, isolating changes in metabolic activity may serve as a useful index for the engagement of neurons. Within the neuroimaging research literature, this type of engagement is often referred to as "activation." The term activation may be misleading, however, because it is really a nonspecific index of some form of neuronal process, which may range from a neuron firing to a neuron increasing the expression of a particular gene to a neuron entering a depolarized state (ie, becoming less likely to fire).[33] Consequently, although these measures may be used to identify general brain regions in which changes in metabolic activity are associated with completion of a specific behavioral task the functional significance of this change in metabolism is unknown.

In addition to the potentially misleading nature of terms such as "activation," another often-underappreciated aspect of fMRI is that it is highly state dependent. That is to say, there exists no baseline for brain activity; only relative changes in activity during an experimental condition as compared to a relevant control condition. Consider an example of an individual who is being charged for a crime involving an impulsive act of violence. His defense team has already shown that he performs poorly on cognitive tests that asses an individual's ability to inhibit a prepotent response, such as the go/no-go or stop-signal task, and they hope to sway the court further by showing that when performing these tasks in the scanner, his brain shows altered responses in brain regions that have been demonstrated to underlie the performance of these tasks in group studies. The first question is what neuroimaging result would provide evidence for a legally-relevant brain impairment? Perhaps the first guess might be that an individual with impairment would show less "activation" in this region, as is consistent with many group case-control studies.[34–37] Although this is certainly a reasonable hypothesis, failure to detect signal in expected regions might simply reflect poor statistical power (as discussed earlier). Alternatively, other case-control studies have suggested that impaired performance may manifest as greater "activation," indicating a neural network inefficiency.[38,39] For this latter interpretation, it is hypothesized that if the first group shows greater activation in a brain region to achieve the same level of performance as a second group, the activation of the first group is said to be less efficient than that of the second. Consequently, we are left with 2 plausible hypotheses for why more- or less-than-expected activity might reflect a functional impairment.

Taken together, technical limitations in neuroimaging analysis and interpretation significantly curtail the incremental value of these techniques in the assessment of LRP over the standard neuropsychological measures. These limitations include the problem of group versus individual brain morphology, the low statistical power of many neuroimaging studies, unanswered questions regarding the appropriate physiologic interpretation of functional neuroimaging data, and a lack of hypotheses that may definitively distinguish between the presence and absence of an LRP at the level of an individual.

FORENSIC NEUROSCIENCE IN THE NEXT DECADE

While this article has primarily focused on identifying limitations in the application of current genomic and neuroimaging technologies to forensic psychiatry, there have been recent developments in both areas that are likely to mitigate these limitations in the next 5 to 10 years. In this final section, we touch upon these promising advances.

Genetics

For genetics to be useful in forensic assessment, the field must move beyond a focus on single genetic variants in isolation to consider the impact of epistatic interactions between multiple genes on risk for LRPs, and between identified sets of multi-gene risk alleles and environmental influences. Multivariate datamining of large-scale prospective cohort designs will be important in determining the most robust, sensitive, and specific combination of genetic and environmental risk factors for use in legal settings. For example, a large sample longitudinal study that integrates detailed social, environmental, and mental health assessments with genome-wide sequencing, such as the recently launched National Child Study (www.nationalchildrensstudy.gov), can be interrogated with multivariate techniques to examine, in a data-driven manner, the precise combination of variables that is most predictive of LRPs. One question that will have to be decided by the courts, in consultation with neuroscience, is precisely how much of the variance in a specific LRP must be accounted for by such a combination of variables before it is considered relevant to the evaluation of criminal responsibility. We believe that a crucial next step for integrating genetic information into legal settings is the establishment of specific thresholds for the sensitivity, specificity, predictive utility of, and tolerance of subsequent nonreplication for, neurobiological measurements.

Neuroimaging

As stated earlier, although neuroimaging is clearly useful for the establishment of brain injury or trauma, its utility as a direct measure of LRP has yet to be established. However, recent breakthroughs in the analysis of neuroimaging datasets have emerged that may greatly enhance the ability to use these tools for individual diagnosis. A key advancement is the introduction of multivariate methods that use all the collected data points in a brain scan simultaneously, rather than treat them as individual voxels to be analyzed independently (as is typically done in current analytical methods). Consequently, concerns about warping, normalization, or differential recruitment of specific brain regions to perform a given task are ameliorated because interpretation of multivariate analysis is no longer constrained to a specific ROI.

Consistent with the idea that network-driven approaches show a greater power to provide neuroimaging-based assessments of LRP is their emerging success in diagnosing psychiatric and neurologic disorders. Within the last few years, both structural and functional neuroimaging data have been shown to accurately predict the onset of psychotic symptoms within a high-risk sample[40,41] and Alzheimer disease symptoms within a group of older individuals experiencing mild cognitive impairment.[42] In addition to prediction, these techniques have been increasingly shown to provide differential diagnosis, successfully discriminating between different mood disorders.[43] Finally, because multivariate techniques are able to integrate imaging and nonimaging data, a recent study found that the combination of neuroimaging and genetic data provided better accuracy for classification of individuals with schizophrenia than either technique alone.[44] Across these studies, the diagnostic accuracy rates have been as high as 85% to 90%, with sensitivity rates reaching more than 95%, indicating significant potential to improve on traditional clinician-based diagnostic methods.

Finally, public opinion is one other avenue through which neuroimaging and genetics may affect forensic psychiatry and the legal system generally. Current social institutions, including the law, explain human behavior through concepts of individual agency and free will, whereas these tools provide explanations that are purely mechanistic. As

the ability to understand and predict the causes of behavior continues to accrue, it is possible that the public perception of what criminal responsibility is and how it should be punished will shift. Indeed, some legal experts have argued that it is in the domain of the legislature and public opinion that neuroscience will ultimately exert its greatest influence over the law, as opposed to the courtroom itself.[45]

SUMMARY

In this review, we have detailed the current obstacles to the use of genomic and neuroimaging technologies to aid in forensic assessment, as well as discussed several recent developments that may help overcome these barriers. Although genomic and neuroimaging sciences are not yet making their impact felt on forensic practice, it seems likely that these technologies will increasingly play a role in the diagnosis of LRP.

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