Genome Medicine

COMMENTARY

From genotype to EEG endophenotype: a route for post-genomic understanding of complex psychiatric disease?

Eco JC de Geus[1,2,3]

Abstract

Twin and family studies have shown the importance of biological variation in psychiatric disorders. Heritability estimates vary from 50% to 80% for cognitive disorders, such as schizophrenia, attention deficit hyperactivity disorder and autism, and from 40% to 65% for affective disorders, such as major depression, anxiety disorders and substance abuse. Pinpointing the actual genetic variants responsible for this heritability has proven difficult, even in the recent wave of genome-wide association studies. Brain endophenotypes derived from electroencephalography (EEG) have been proposed as a way to support gene-finding efforts. A variety of EEG and event-related-potential endophenotypes are linked to psychiatric disorders, and twin studies have shown a striking genetic contribution to these endophenotypes. However, the clear need for very large sample sizes strongly limits the usefulness of EEG endophenotypes in gene-finding studies. They require extended laboratory recordings with sophisticated and expensive equipment that are not amenable to epidemiology-scaled samples. Instead, EEG endophenotypes are far more promising as tools to make sense of candidate genetic variants that derive from association studies; existing clinical data from patients or questionnaire-based assessment of psychiatric symptoms in the population at large are better suited for the association studies themselves. EEG endophenotypes can help us understand where in the brain, in which stage and during what type of information processing these genetic variants have a role. Such testing can be done in the more modest samples that are feasible for EEG research. With increased understanding of how genes affect the brain, combinations of genetic risk scores and brain endophenotypes may become part of the future classification of psychiatric disorders.

The importance of genetic factors in psychiatric disorders

Mental illness continues to incur negative attitudes, often characterized by fear, stigma and rejection, but the idea that it reflects a 'weakness of character' that can be overcome by sheer willpower is increasingly losing ground [1]. Most people now understand that psychiatric disorders are caused by a sick organ, just like heart disease, although in this case the organ happens to be the most complex organ we possess, the brain.

Appreciation of the importance of biological factors in psychiatric disorders has been strongly reinforced by evidence from twin and family studies that genetic variation between individuals has a key role in the risk for these disorders. Heritability estimates for cognitive disorders, such as schizophrenia, attention deficit hyperactivity disorder (ADHD) and autism, range from 50% to 80% [2-6]. For affective disorders, such as major depression, anxiety disorders and substance abuse, estimates range from 40% to 65% [3,7,8]. However, pinpointing the actual genetic variants responsible for this heritability has proven difficult. The most successful gene-finding approach, genome-wide association (GWA), has uncovered many genetic variants for conditions such as diabetes [9], Crohn's disease [10] and atherosclerotic risk [11,12], but this method has, as yet, not been as successful for psychiatric disorders [13]. For schizophrenia and autism only a handful of genetic variants have been identified [14-16], and there are currently no confirmed genetic variants associated with ADHD and depression.

*Correspondence: eco@psy.vu.nl
[1]Department of Biological Psychology, VU University, van der Boechorststraat 1, 1081 BT, Amsterdam, the Netherlands
Full list of author information is available at the end of the article

Can endophenotypes help us to find genetic variants that influence psychiatric disease?

The difficulty in identifying actual genetic variants probably relates to the complexity of psychiatric phenotypes, which in turn reflects the complexity of the brain processes that underlie them. To reduce this complexity it has been proposed to focus genetic studies on so-called brain endophenotypes [2,17-19]. The basic reasoning is that it may be easier to detect the effect of a genetic variant on a more elementary neurobiological trait because there may be fewer genetic variants with larger effect sizes involved in these traits. An important source of brain endophenotypes is electroencephalography (EEG). An EEG signal is recorded non-invasively from electrodes placed on the scalp and depicts the ongoing electrical activity of the brain. An event-related potential (ERP) is the brain's electrical response to the occurrence of a specific event. The event is usually a stimulus - a word or picture presented on a display - but it can also be generated internally, for instance by the intention to move a limb. An example of an ERP is the P3, a positive wave that occurs about 300 ms after a motivationally significant stimulus. The P3 reflects the activity of the locus-coeruleus-norepinephrine system [20], which facilitates the behavioral and cognitive responses to motivationally significant events, and it may be the central nervous system component of the fight-flight response [21].

Can EEG and ERP endophenotypes help identify and confirm novel genetic risk factors for psychiatric disease? To do so they must, first of all, be predictive of psychiatric disorders. There is a huge corpus of literature on the use of EEG or ERP endophenotypes as risk markers for psychiatric disorder. It is impossible to review this corpus in a few words here, but two examples may serve to illustrate it. First, frontal asymmetry of EEG α power (FA) has been studied extensively as a correlate of individual differences in emotional response. Greater left hemispheric activity has been associated with a tendency to approach things of interest, and greater right hemispheric activity with withdrawal-related tendencies [22,23]. Disturbances in the emotional dimension of approach versus withdrawal have a key role in the liability to develop psychopathology such as depression and anxiety disorders [24,25], with which the FA has indeed been found to be associated [2,26,27]. Second, reduced amplitude of the P3 is found in a variety of psychiatric and behavioral disorders, but most notably schizophrenia [28] and alcohol abuse [29]. The reduction in P3 amplitude reflects a genetic predisposition for these disorders rather than a mere functional consequence, because it does not normalize after successful treatment [28] and is also found in unaffected relatives [29]. The latter point is important. To tag a relevant part of the pathway from genetic variation to psychiatric disorder, the endophenotypes must be heritable traits and their heritability must arise partly from the genetic variants that also influence the psychiatric disorder [17].

Table 1. Heritability estimates for EEG/ERP traits*

EEG/ERP trait	Heritability estimates	References
Power α band	86-96%	[30-32]
Power θ band	80-90%	[30,32]
Power β band	70-82%	[30,32]
Peak frequency α band	71-83%	[33,34]
Path length α band	48-68%	[31]
Cluster coefficient β band	25-40%	[31]
Path length β band	29-42%	[31]
Cluster coefficient α band	37-45%	[31]
Long range temporal correlations α band	47%	[35]
Long range temporal correlations β band	42%	[35]
Frontal EEG asymmetry α band	1-37%	[36]
P50 amplitude attenuation	34%	[47]
N1 amplitude attenuation	45%	[47]
P2 amplitude attenuation	54%	[47]
Mismatch negativity	58%	[37]
Posterior N1 amplitude	50%	[38]
Posterior N1 latency	45%	[38]
Anterior N1 amplitude	22%	[38]
Anterior N1 latency	43%	[38]
Go/Nogo difference N2 amplitude	53%	[39]
Error positivity	52%	[40]
Error-related negativity	47%	[40]
P3 amplitude	50-80%	[37,41,42]
P3 latency	38-50%	[37,41,42]
Onset lateralized readiness potential	54-62%	[43]
Peak lateralized readiness potential latency	38-45%	[43]

*Data are from studies comparing the resemblance in monozygotic twins with that in dizygotic twins. If a measure was available at multiple electrodes, the electrodes with highest amplitude were selected. A range of heritabilities reflects either the variation in estimates across multiple studies or across multiple age groups within a single study.

In the Netherlands Twin Register, we have estimated the heritability of a variety of EEG and ERP endophenotypes, and similar work has been undertaken by colleagues from twin registries around the world [30-43]; Table 1 illustrates the findings from these studies. A striking genetic contribution is found to almost all EEG and ERP traits. Resting EEG power is even among the most heritable traits in humans. This high heritability does not simply reflect 'trivial' heritable similarities in the composition of the skull or other tissue layers between electrode and brain. Almost identical heritability

estimates are obtained when power is computed in signals from magnetoencephalography, which are almost undistorted by tissues covering the brain [44,45].

To return to the question of whether these heritable EEG and ERP endophenotypes can help to identify and confirm novel genetic risk factors for psychiatric disorders: GWA has been the most successful method for detecting novel potential genetic variants for complex traits. However, it has a limited ability to detect common variants with very small effect sizes and also rare variants with very low allele frequencies. Both limitations can be tackled by increasing the size of the (pooled) samples, although the second also needs increased depth of coverage of genomic variation, perhaps even by full sequencing. Unfortunately, the clear need for very large sample sizes in GWA studies strongly limits the usefulness of EEG/ERP measurements in the gene discovery phase. EEG/ERP measurements require controlled laboratory experiments with sophisticated and rather expensive equipment. They take up to at least 20 to 30 minutes and this may increase up to hours if error measurement is to be contained using the more complex derived measures [31]. Measuring EEG/ERP, in short, is too hard to do on the tens of thousands of subjects needed in a GWA, particularly when contrasted with the use of existing patient records or questionnaire-based assessment of psychiatric symptoms.

Endophenotypes can help us make sense of genetic variants influencing psychiatric disorders

The real value of brain endophenotypes may come after gene finding, when they help us confirm the biological meaning of the genetic variants that were detected using GWA on psychiatric symptoms and diagnoses. One of the lessons of successful GWA studies in other fields is that they point us to genetic pathways that were not previously known to be involved in the trait. Finding genetic variants for psychiatric symptoms and diagnoses needs, therefore, to be followed up by an understanding of what these 'psychiatric' genes do in the brain. Testing the association of the risk alleles with EEG and ERP endophenotypes can help us understand where in the brain, in which stage, and during what type of information processing the genetic variant has a role. Such testing can be done in more modest samples, which are more feasible for EEG research.

Could EEG and ERP endophenotypes be more widely applied, apart from helping us to understand how genetic variants cause psychiatric risk? The main system for classifying psychiatric disorders is the Diagnostic and Statistical Manual of Mental Disorders (DSM-V). This system is based on a tally of symptoms and their impact on daily functioning reported by patients or their caregivers. The DSM currently is undergoing substantial revision [46], and a question that repeatedly surfaces is whether we can use the combination of genetic risk scores and brain endophenotypes to better classify psychiatric disorders. Progress in research on the genetics of brain endophenotypes may be key to the successful development of such a classification system. This system would base our diagnostic procedures more solidly on biology and reinforce the notion that psychiatric disorders are disorders of the brain.

Abbreviations

ADHD, attention deficit hyperactivity disorder; DSM, Diagnostic and Statistical Manual; EEG, electroencephalography; ERP event related potential; GWA, genome-wide association.

Competing interests

The author declares that he has no competing interests.

Author details

[1]Department of Biological Psychology, VU University, van der Boechorststraat 1, 1081 BT, Amsterdam, the Netherlands. [2]Neuroscience Campus Amsterdam, VU University Medical Center, De Boelelaan 1085, 1081 HV, Amsterdam, the Netherlands. [3]EMGO+ Institute for Health and Care Research, VU University Medical Center, De Boelelaan 1117, 1081 HV, Amsterdam, the Netherlands.

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