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Transcend the *DSM* Using Phenotypes

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Identifying subtypes of specific disorders is an attractive exercise, as it expands our understanding of the individual's response to therapy, but it remains attached to the approach based on the Diagnostic and Statistical Manual of Mental Disorders (DSM), *which is rooted in behavior and frequently does not predict therapeutic response by any individual within the* DSM *grouping. Phenotypes are an intermediate step between genetics and behavior. These proposed electroencephalography (EEG) phenotypes are semistable states of neurophysiological function. The author proposes a framework allowing one to describe much of the observed EEG variance with a small number of phenotypical categories. These groupings cut across the* DSM *categories, and unlike the* DSM, *the phenotypes predict the individual's response to therapy, for neurofeedback as well as for medication.*

Introduction: The Concept of Phenotypes

Prior studies using statistical analysis of electroencephalography (EEG) have documented clusters of EEG/quantitative EEG (QEEG) features within psychiatric populations (John, Prichep, & Almas, 1992). Experience over the past 30-plus years with a large number of clinical EEGs and, more recently, decades worth of clinical and research experience with QEEG, as well as a review of the field's literature, have shown that a limited set of EEG patterns can characterize the majority of EEG variance.

In the perspective I'd like the reader to consider, these proposed EEG/EEG groupings might be considered as phenotypes, based on genetics. There is an indirect linkage between genetics and behavior, with an intermediate step. This intermediate step is one that is based on the expression of the genetics and other factors and constitutes the bridging between the person's genetics and behavior: the phenotype. These phenotypic EEG/QEEG divergence patterns constitute reliable indices of brain function and predict response to therapy.

It should be noted that these phenotypic patterns are not isomorphic with the established *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*) categories, although the phenotypes have powerful implications for therapeutic interventions, both with medication and with neurofeedback. One phenotype may be seen in a wide variety of *DSM* groupings, from posttraumatic encephalopathy, to affective and attentional related *DSM* groupings, to many more. These ideas have been published elsewhere (Johnstone, Gunkelman, & Lunt, 2005), although these concepts seem to have especially important perspective implications for this special issue of *Biofeedback* focusing on subtypes of specific *DSM* categories.[1]

The very concept of an EEG pattern's being a subtype of a specific disorder seems foundationally flawed to me because of the lack of specificity of the pattern for the *DSM* grouping. The theta-beta ratio being increased for age may be a metric that is sensitive to attention deficit hyperactivity disorder (ADHD), but the same increase in this ratio also may be seen in a wide variety of other clinical presentations as well as in the absence of ADHD, so the lack of specificity remains a problem. I'd like to invite the reader to transcend the *DSM*'s limited perspective through the use of phenotypes.

Enhancing Neurofeedback Through the Use of Phenotypes

Behaviorally based neurofeedback interventions have been used with great effectiveness in the hands of good clinicians and practitioners, as evidenced by our field's ever growing efficacy literature. This efficacy literature is based on actual clinical outcome data and provides support for the rapidly growing list of neurofeedback applications that can claim efficacy based on the jointly adopted Association for Applied Psychophysiology and Biofeedback (AAPB)/International Society for Neuronal Regulation (ISNR) efficacy template (La Vaque et al., 2002).

Recently, there have been several good publications detailing the state of the efficacy literature in biofeedback and neurofeedback, including the book by Yucha and Gilbert (2004), *Evidence-Based Practice in Biofeedback and Neurofeedback*, as well as several white papers on specific disorders, in a series sponsored by the AAPB and ISNR (Monastra et al., 2005; Moss, LaVaque, & Hammond, 2004).

The literature on medication response prediction suggests that a phenotypic perspective may help enhance our efficacy (Suffin & Emory, 1995). This was also suggested in the outcome improvement reported by Wright and Gunkelman (1998) when he added the QEEG approach to guide neurofeedback.

The presence of genetically linked EEG patterns provides a solidly data-based set of observations on which to propose an initial list of phenotypic patterns. One EEG pattern with genetic links is the low-voltage fast EEG (Gunkelman, 2001). This low-voltage fast pattern was characterized as a phenotype in a recently published study of phenotypic patterns in alcoholism (Enoch, White, Harris, Rohrbaugh, & Goldman, 2002) and by others who have identified the genetic link to Gene 4's regulation over gamma-aminobutyric acid receptors (Bierut et al., 2002).

Another EEG pattern with genetic links has been identified in some cases of idiopathic epilepsy (Haug et al., 2003). The paroxysmal epileptiform bursts seen in the EEG in these clinical cases may achieve many hundreds of microvolts, occasionally exceeding 400 to 600 ÌV, with spikes and slow components emerging from a relatively normal background EEG. In a survey of genetic factors in epilepsy, Kaneko, Iwasa, and Okada (2002) showed that the most common human genetic epilepsies display a complex pattern of inheritance and that the identities of the specific genes are largely unknown, despite recent advances in the science of genetics. They also show that the genetic markers of certain types of epilepsy have been identified, such as those with neurodegenerative characteristics and a small number of familial idiopathic epilepsies (Haug et al., 2003). A similar pattern of seizures and EEG phenotype is seen in a group of subjects with benign childhood epilepsy with centrotemporal spikes, found in three children with de novo terminal deletions of the long arm of Chromosome 1q. This suggests that this chromosomal location could be a potential site for a candidate gene (Vaughn, Greenwood, Aylsworth, & Tennison, 1996).

Characterizations linking genomic information, intermediate EEG phenotypes, and behavioral manifestation are likely to have important implications for therapeutics. The International Brain Database (Brain Resource Company) includes the EEG, event related potential, neuropsychological test measures, and genetic testing, thus making it unique in allowing an integrative approach that combines neurophysiology, neuroanatomy, cognition, and genetics. The M.I.N.D. Center at the University of California, Davis, uses the phenomic approach in working with pervasive developmental disorder/autism to avoid treating all clients alike in such a heterogeneous population and to help clarify research on clinical therapeutic effects.

Subtypes Versus Phenotypes

Although many studies have shown subtypes within a *DSM*-identified disorder, such as the work of Prichep et al. (1993) with obsessive-compulsive disorder and that of Chabot, Merkin, Wood, Davenport, and Serfontein (1996) identifying subgroups of ADHD, these subgroups do not have diagnostic specificity because they can be seen in other disorders. These EEG clusters did, however, predict treatment efficacy using medication in both the ADHD and obsessive-compulsive disorder studies. Suffin and Emory's (1995) article identified frontal theta in attentional problems, similar to the Chabot et al. findings in ADHD, but the same pattern was also identified in affective disorders. The behavioral grouping did not predict the EEG/QEEG pattern, nor did behavior groupings predict the proper pharmaceutical treatment, although the EEG patterns did predict the effective drug intervention in both studies.

The medication intervention, when clinically based on prospectively identifying the phenotype, was the basis for the highly effective intervention in treatment refractory depression in recent pilot work (S. Suffin, personal communication, 2003) at the Sepulveda Veterans Affairs in Los Angeles. The application of these principles was also at the heart of the doubling of the clinical efficacy in a recent study using QEEG to design the neurofeedback intervention for the attention deficit disorder/ADHD population tested, as compared to behaviorally based neurofeedback interventions (Wright & Gunkelman, 1998).

In an updated and abbreviated review of prior work (Johnstone et al., 2005), the Appendix offers proposed phenotypic patterns as well as a listing of the associated neurofeedback interventions. A reading of the original article is advised for more detail, especially with respect to medication response prediction.

Conclusion: An Introductory Framework for EEG/QEEG Phenotypes

It must be remembered that phenotypes may coexist, and the various combinations are too variable to be handled in this limited presentation. This appendix should not be construed as a replacement for professional assistance in designing a neurofeedback intervention, nor in

Appendix Electroencephalography (EEG)/Quantitative EEG Phenotypes		
Candidate Phenotype	EEG Findings	Associated Neurofeedback Approach
Low-voltage fast	Low-voltage EEG overall	Reward alpha activity posteriorly
Epileptiform	Transient spike/wave, sharp waves, paroxysmal EEG	Inhibit low and high frequencies; sensorimotor rhythm training; also consider slow cortical potential control
Diffuse slow activity (with or without slower alpha)	Increased delta and theta (1-7 Hz) with or without slower posterior alpha	Inhibit midline fronto-central activity slower than 10 Hz, add reward for anterior beta for increased stimulating effect
Focal abnormalities (not epileptiform)	Focal slow activity or focal lack of activity	Inhibit slower activity and reward higher frequencies (consider medical referral)
Mixed fast and slow	Increased slower activity, lack of organized alpha, increased beta	Inhibit slow frequencies, reward alpha and SMR, inhibit faster beta
Frontal lobe hypoperfusion disturbances	Frontally dominant excess theta or alpha frequency activity	Inhibit midline fronto-central activity below 10 Hz, reward anterior beta for increased effect
Frontal asymmetries	Frontal asymmetry primarily measured at F3, F4	Adjust frontal symmetry with alpha, theta, and beta
Excess temporal lobe alpha	Increased alpha activity generated in temporal lobe	Inhibit alpha over affected temporal region(s), and inhibit frontal slow activity
Faster alpha variants, not low voltage	Alpha peak frequency greater than 12 Hz over posterior and parietal cortex	Reward 8-10 Hz alpha at Pz, shift alpha frequency slower with alpha/theta protocol
Spindling excessive beta	Rhythmic beta with a spindle morphology, often with an anterior prominence	Inhibit beta's spindle frequencies, wide band inhibit; alpha-theta training may help
Persistent eyes-open alpha	Alpha doesn't attenuate by at least 50% with eyes open; it is generally slower alpha	Reward beta frequencies, inhibit alpha; reward higher frequency alpha

any way can this be used to fully characterize an individual's EEG/QEEG.

Note

1. The material is adapted from Johnstone, Gunkelman, and Lunt (2005), Clinical database development: Characterization of EEG phenotypes. *Clinical EEG and Neuroscience, 2,* 99-107, and is used with the permission of *Clinical EEG and Neuroscience*.

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