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Biomolecular Determinants of the Electrophysiological Output Regulating P3 Amplitude

From particles to waves: upstream processing providing for endophenotype production of variant EEG waveform recordings.

P300 (P3) amplitudes are significant range result values during electroencephalogram (EEG) recordings. Event-Related Potential (ERP) measurements specific for electrophysiologic and neurophysiological molecular chemistry processes become accessible through correlation of P3 waveforms and neuropathology (Begleiter et al). P3 is one target of transcranial Direct-Current Stimulation (tDCS) currently utilized to alleviate symptoms of major depressive disorder, schizophrenia, Parkinson's disease, and other neurologically based disturbances. Readings of P3 ERP patterns during clinical trials and medical testing are encouraged for investigating biochemical malfunctioning phenotypes which manifest in brain to behavior electrophysiological output. A repertoire of research exists confirming EEG accuracy and application as an integral feature for endophenotypic indicators of etiology and focalization demonstrating risk and disease progression for alcohol use disorder (AUD) along with common psychiatric comorbidities. P3 emission of latent amplitudes resulting from genetic molecular activities associated with the A1 allelic subsets and D2 Dopamine Receptor (DRD_2) polymorphisms. AUD exhibiting behaviors are indicated by decrease in inhibitory capacity. With P3 amplitude, inhibition is also occurring in the correlated P3 waveforms at genotypic contributing mechanisms and functionality process levels. Varied cognitive performance in comparison to control subject groups and differences in neuroelectrical activity exists. Low and delayed P3 amplitude and latency measurements during task administration trials are a useful diagnostic marker for risk assessment, relapse prevention planning, recovery progression and confirmation of hereditary predisposition for AUD (Jiminez et al).

AUD is a genetically inherited condition. Prior to ingestion of alcohol, symptom parallels are present and reported based on social-emotional cues and behaviors of the AUD positive subjects alongside histories of varying mental health conditions during adolescence categorized as disinhibitory disorders (DD aka Disinhibitory Disorder Spectrum) and Personality Disorders (PD) (Begleiter et al). These and other psychiatric early onset diagnoses are tangentially increased for risk potential with progression of AUD post initial alcohol ingestion. Research has been underway to authenticate whether DD and PD are diagnostically accurate considering AUD is genomically being expressed in early childhood through young adulthood.

However, a key AUD diagnostic criteria is an inability to control alcohol intake. Perhaps this epigenetic disease requires categorical reevaluation for diagnostic accuracy. In type 2 AUD, onset is simply activated by alcohol ingestion, but the psychological processes on a quantitative level are present and reported in clinical research such as seen during tests for ERP in EEG readings. Gene amplification parallels P3 waveform greater latency length when compared to genetically confirmed profiles of AUD negative subjects. The go/no-go task switching is performed through adolescence and adulthood when alcohol consumption is likely introduced to subjects. A notable endogenous determinant is a pronounced difference in allelic A1 length influencing neurological and hepatic biomolecular composition of Single Nucleotide Polymorphisms (SNPs) in metabolism of ethanol (ie acetylcholinerase functioning) compared to non-alcohol dependent subjects who do not develop physical alcohol dependence (Jimenez et al).

The objective in experimentation of P3 must be specified. P3 has a strong genetic load. There is a focal emphasis on specific SNPs and dopaminergic functionality. In numerous studies on AUD inheritance in progeny of paternal alcohol abuse positive and alcohol dependent first degree relatives, there are significant relationship associations. Presence of *TaqI*-A1 at 3' positive polymorphism allele group, which is incorporated with the ANKK1 kinase protein encoder, positively indicates confirmation will be found in subjects via P3 wavelength deficiencies in response timing during testing in the parietal and central neuroanatomy EEG recordings. These analyses were performed before the subjects initially ingest alcohol in life and are under the age of 17 years. Delayed response in task switching and stimulus response are the cognitive behavioral effects which are compared to control groups (Jimenez et al). The effects on a physio molecular level have shown they may be due to a reduced density during replication and transcription of A1.

The DRD_2 gene is a protein coding sequence located on human chromosome 11q22-23 and is integral to dopamine and $GABA_A$ receptor neurotransmissions. A region of DRD_2 includes the TaqI locus allele (rs1800497) and the adjacent Ankyrin Repeat and Kinase Domain Containing 1 (ANNK1) gene, which is located 10 kb downstream. These genes are co-regulated within the NTAD cluster, associated with neurogenesis and neurotransmission. This region encompasses 26 genotyped SNPs associated with alcohol dependence. The presence of the TaqI-A1 allele results in deleteriously lower DRD_2 density, decreasing dopaminergic activity and glucose metabolism in the midbrain. Furthermore, trans-ethnic Genome-Wide Association Studies (GWAS) have implicated the KLB and GCKR loci in alcohol consumption, with the strongest associations observed at SNPs rs7686419 and rs4665985. (Jimenez-Arriero et al., Hagerty et al., Blum et al.)

DRD_2 is a responsible contributor for dopamine synthesis regulation. Thus, the focus on the genetic markers of dopaminergic brain function causing alterations in attention and impulsivity processes emphasizes DRD_2's relevant linkage to AUD. During DRD_2 synthesis, there is linkage disequilibrium for *TaqI*-A1 making it an adequate genetic marker for AUD.

These genetic markers are substantially higher in lab test positivity rates of offspring and first degree relatives along with an association of P3 amplitude and wavelength latency and decreased activation abnormalities for AUD population under the age of 30 years (Hagerty et al). Due to naturally occurring decreases in P3 neuroelectrical output with aging, P3 becomes irrelevant as an indicator of AUD and alcohol dependence. This is interesting when compared to the diagnostic categories of the two types of AUD. Type one occurrences of AUD happen after the age of 30 years and type 2 AUD occurs before the age of 30 years. There is an inevitable correlation between genetic mutations associated with age progression and P3 output (Blum et al).

In conclusion, when assessing the risk factors of AUD several components are taken into consideration including social, economic, cultural, and inherited influences. The cumulative aspects are taken into consideration when evaluating diagnoses and treatment. One of the testing methods for heritable factors is performing an EEG and evaluating the results of the P3 activity recorded ERPs during stimulation in a controlled environment (Alexander et al). This method is cost-effective when compared to genetic profiling for A1 SNP abnormalities and proven to have psychiatric illness indications which can assist in finding heightened risks for AUD progression during a subject's lifespan. Latency and delay in P3 waveforms and stimulus neuroelectrical reactivity timing is an effective diagnostic marker, risk assessment and recovery plan indicator. Possibilities for disease progression measurement in AUD are evidenced in phenotypic genetic abnormalities linkage disequilibrium and allele density loss. These are due to neurological system genetic abnormalities with a sequential progression of deleterious cellular mass occurrences in the dopaminergic cascading system (Chen).

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