**Introduction**

Event related potentials are those potentials of electroencephalography which are evoked by preparation or perception for events. They can be endogenous or exogenous. Among endogenous, P3 has gained wide acceptance because it is associated by psychological processing, evoked by stimuli that are important to subject in some way. It is a broad component that peaks about 300-600 ms after stimulus onset with maximal amplitude at midline central or parietal recording sites at scalp. P3 latency from auditory stimulus is shorter than that evoked in response to visual stimulus. Some theories have proposed that P3 is evoked by unexpected stimuli, it reflects the updating of working memory, and its amplitude shows the amount of processing required. The evidence in complete favor of any one of these theories is however not convincing.

**ERP Habituation**

Habituation is a decrease in response magnitude caused by repeated stimulation. It is believed to be an important tool for studying the neural substrates of behavior, learning and information processing in the central nervous system. Habituation of event related potentials (P3) is usually studied by giving around 30-40 events in a block with 4-10 blocks being tested one after another. At the end of the session, these blocks are compared to each other for changes in P3 latency and amplitude. Habituation is reflected by a decrease in the amplitude with decrease or no change in latency.

Habituation can be of two types- Short term habituation and long term habituation. Short term habituation occurs due to refractory period of neurons or sensory gating. It is tested by the presenting paired stimulus, first stimulus stimulates the neuron as well as inhibitory pathways thus reducing the amplitude to second stimulus. It has most often been tested in P50, a wave that occurs after 40-90 msec. It has strong genetic component and is independent of stimulus intensity, attentional demands and psychological characteristics of stimulus. It is related to pre-attentive screening out the irrelevant stimuli.

Long term habituation occurs across blocks of stimuli lasting minutes and is explained on the basis of two theories-Dual Process Theory and comparator theory. Contrary to STH, it depends upon the stimulus intensity, psychological significance of stimulus and attentional resources. It has been most often investigated for P300 using odd-ball paradigm where one target stimulus is presented in between many non target stimuli. It is related to attentive process of orienting response.

**Habituation in Migraine**

Habituation in migraine is often seen as a basic pathophysiologica process and is impaired in patients, days before the headache thus representing the increased susceptibility of brain to provoking agents as well as a genetically determined abnormality that determines the risk of migraine attack.
Sinistchkin et al\textsuperscript{13} conducted an experiment using odd ball auditory paradigm with the hypothesis that migraineurs should show habituation to both target as well as non target stimuli since it is dependent upon the mitochondrial metabolism abnormality and noradrenergic or serotonergic abnormality.\textsuperscript{14} They found that migraine patients are characterized by reduced short term habituation of P50 on non-target tones only, or the sensory gating deficit. They proposed that it was not the result of abnormal refractory period, but was secondary to the inability to filter irrelevant stimuli resulting in the stimulus overload in the brain. It may lead to migraine attack under disturbed brain energy metabolism and abnormal cortical excitability.\textsuperscript{15,16} Attentional demands increase the amplitude of target P50 and lead to increased T/C ratio. However, this effect is not apparent in subjects with sensory gating deficit and hence was seen in healthy controls only.\textsuperscript{14}

In long term habituation, only the P300 for target stimulus was different between migraineurs and controls. P300 is related to evaluation of cognitive characteristic of the stimulus and fails to habituate if the subject has to provide attention to each stimulus. Stimulus discrimination required allocation of attentional resources while maintaining the signal value of the stimulus. Abnormal habituation on target conditions only, in migraineurs suggests that they fail to discriminate the stimuli.\textsuperscript{14}

MisMatch Negativity (MMN) is a particular type of event related potential that originates in the auditory and frontal cortex as an automatic response to change in auditory stimulation.\textsuperscript{17,18} It is a negative component that peaks at 100-200 ms during any deviant stimuli among the series of standard auditory stimuli and is independent of attentional processing. Its latency and amplitude were found to increase with the subsequent trial. Latency is related to the confidence in stimulus discrimination and because of this reason, it reduces with the number of testing in normal subjects.\textsuperscript{19} Increase in latency in migraineurs shows that they fail to anticipate the repetition of stimuli. Lack of reduction of amplitude of MMN shows that migraine subjects fail to habituate and it may increase the environmental load on the migraineur’s brain.

Studies using visual evoked potential show that amplitudes of N1-P1 and P1-N2 components remain unchanged or increase during repetitive stimulation between migraine attacks while they reduce in controls.\textsuperscript{20,22}

All of these studies show two basic problems in migraineurs- (i) increased amplitudes of averages of large number of trials and (ii) lack of habituation in successive trial blocks. However, this data should be interpreted with caution. Increased amplitude, however, indicates cortical hyperexcitability, but this happened only with large number of trials! In other words, it could be understood as reduced ability of cortex to habituate to a given stimuli, or that greater response was generated with successive suprathreshold stimuli.

**Habitation in TTH**

The studies of P300 in the TTH are scarce. Mazzotta et al (1995) and Chen et al (2007) reported that P3 latency or amplitude was not affected by the ictal or inter-ictal state in episodic TTH sufferers and it was not different from healthy controls or migraine without aura.\textsuperscript{23,24} Loss of habituation was not observed in episodic TTH patients.\textsuperscript{25,26}

**Neurobiology of habituation**

Habitation is a complex neurobiological phenomenon, and for cortical evoked activation it might crucially depend on the pre-activation excitability level. “Ceiling theory” is most often applied to explain the occurrence of an ‘augmenting’ or ‘reducing’ response to increasing stimulation intensities. According to this theory a low pre-activation level of sensory cortices allows a wider range of supra-threshold activation before reaching the ‘ceiling’ and initiating a ‘reducing’ response, i.e. habituation.\textsuperscript{27} There is evidence that the pre-activation level of cortical excitability depends on the so-called chemically addressed connections that help in ‘state-setting’ of cortical neurons, which originate in the brainstem and involve serotonin and noradrenaline as transmitters.\textsuperscript{28,29} Low inter-ictal activity of these systems, especially of the serotonergic pathway, could indeed be responsible for the observed electrophysiological abnormalities in migraineurs.\textsuperscript{30} It suggests that decreasing the cortical activation should produce lack of habituation in healthy subjects and increasing cortical activation should habituate EP in migraineurs. It
was confirmed by Ambrosini et al (2003) who had shown that low frequency rTMS (which causes cortical inhibition) lead to lack of habituation in healthy controls while the high frequency rTMS (causes cortical excitation) induced habituation in migraineurs. Hence, it can be taken as the protective mechanism, i.e., cortical habituation is dysfunctional in migraine and these patients are prone to bear all the stimuli reaching their cortex. It may by some unknown mechanism, activate the Trigemino-vascular system and induce the pain of the migraine. This theory points out why the migraineurs suffer subtle cognitive deficits which contribute to the burden of the disorder. These defects could be related to the deficits in the habituation, but further studies are required to assess the association.

This normalization of habituation in close temporal relation to the migraine attack shows that serotonergic activity increases causing higher 'pre-activation' level. This could be reason behind the increased brainstem activity observed during migraine.

Conclusion

Event related potentials can be used to visualize the brain “from within” to understand the process of information processing. In migraine and TTH patients it can be used to study the changes in cognitive functions and the effect of drugs in reversing the changes.

References