

The Application of EEG and Event Related Potentials in Psychiatry

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1. Short introduction into neurophysiological assessment

1.1. Introducing EEG recording, EEG spectrum analysis and Event Related Potential (ERP) analysis

By placing electrodes on the scalp it is possible to record the electrical activity of the brain; this is called an electro-encephalogram (in short an EEG). What is recorded by an EEG is the synchronous activity of large groups of brain cells in the cortex of the brain, measured as integrated electrical signals on the scalp (*Figure 1*). Interesting about electro-encephalography is that it provides insight into what the brain is doing with a very high time resolution, i.e. in the order of milliseconds.

Analyzing an EEG more closely (using mathematics) reveals that the oscillating waves that an EEG is made of have different characteristic frequencies (*compare Figure 2, 3 and 4*). Dividing an EEG in bands by frequency is interesting because different frequency bands are associated with different states of brain functioning. For example, being attentive is reflected in higher frequencies (fast waves) known as beta waves. On the other hand being distracted is reflected in lower frequencies (slow waves) known as theta waves (*Figure 4*). In parallel with this, a relationship has been found between abnormalities in specific frequency bands on the one hand and abnormal brain states on the other hand (e.g., Demos, 2005).

To illustrate: attention problems in individuals with attention deficit/hyperactivity disorder (ADHD) are often associated with increased activity in the theta band combined with decreased activity in the beta band (Lubar, 1995; Barry et al., 2003; Butnik, 2005). Fortunately, recent data show that stimulant medications can help in normalizing an abnormal balance between the theta and beta band in children with ADHD (e.g. Clarke et al., 2007).

Generally when EEG frequency characteristics are analyzed this entails:

1. Dividing an EEG into different frequency bands, such as delta (0.5-3.5 Hz), theta (3.5-7.5 Hz), alpha (7.5-12.5 Hz), beta (12.5-30 Hz) and gamma (30-100 Hz) (*Figure 3 and 4*)
2. Estimating the absolute or relative amount of activity (power) in a band
3. Calculating the balance (ratio) between two bands
4. Investigating left/right hemisphere symmetry with regard to frequency
5. Investigating the synchronization between different electrode positions on the scalp with regard to frequency (coherence analysis)

Usually EEG frequency or 'spectrum' information is not only expressed in numbers, but also in color-coded topographical maps. In such maps the value, for instance the power in the theta band, obtained at each electrode position is translated into a color, for instance red for high power and blue for low power. Interpolation is used to color the areas between the electrodes. In this way a topographical map can be created expressing where over the scalp theta shows the highest amount of power (*Figure 3*, second map from left). Some EEG systems, such as the Cognitrace system of ANT, enable the comparison of a frequency map of an individual patient to that of an age-matched reference group with a map expressing the statistical difference between the patient and the reference group (i.e. an SPM or z-score map) (*Figure 5*). By doing this it can be determined for instance, whether a certain amount of theta observed over the temporal cortex in a patient is too high compared to a group of healthy controls of the same age. This type of analysis is called quantitative EEG analysis, also known as qEEG. The use of such methods has been endorsed by American Psychiatric Association (APA) as useful in evaluation of psychiatric disorders, especially in identifying regional brain abnormalities.



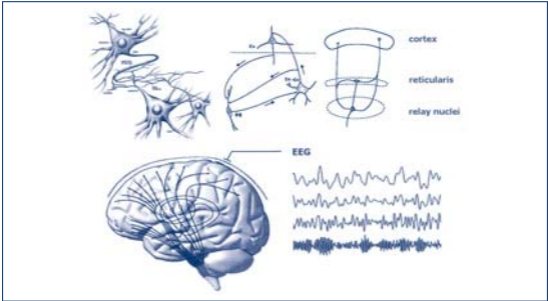


Figure 1. EEG consists of the synchronous activity of large (cortical) groups of neurons, measured as integrated electrical signals on the scalp (Figure copied from Evian Gordon, 2001; www.brain-dynamics.net).

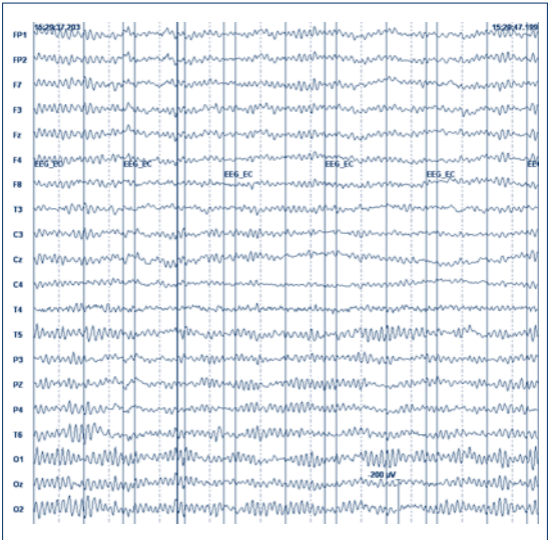


Figure 2. EEG in the time domain

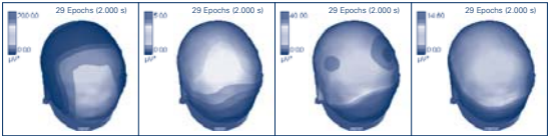


Figure 3. EEG in the frequency domain. Transforming EEG from the time domain (Figure 2) to the frequency domain is done mathematically by a Fast Fourier Transformation (FFT analysis). From left to right the amount of activity (power) in the delta (0.5-3.5 Hz), theta (3.5-7.5 Hz), alpha (7.5-12.5 Hz) and beta (12.5-30 Hz) band is shown in a topographical map.

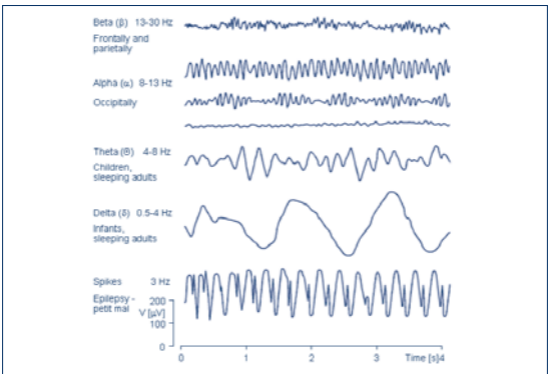


Figure 4. Different EEG frequency rhythms.



Figure 5. A patient with enhanced power in the theta band over the temporal cortex in comparison to an age-matched reference group. On the left the map of the patient is presented, in the middle the map of the reference group and on the right the statistical difference between the patient and the reference group in an SPM or z-score map.



The technique of Event Related Potential (ERP) averaging allows the investigation of a specific kind of information processing. Most ERP protocols involve an individual being provided an event or 'stimulus' to react to, for instance an infrequent high pitch tone for which a button press is requested. There are often at least two conditions that vary in some manner, for instance a frequent low pitch tone and an infrequent high pitch tone. As stimulus presentation and response giving is going on, an EEG is being recorded from the individual. The ERP is obtained by averaging the EEG signal from each of the presentations within a certain condition. Averages from one stimulus-response condition can then be compared with averages from the other stimulus-response condition(s) (*Figure 6*). ERPs allow the investigation of:

1. Basic functional pathways by recording of early ERPs or 'evoked potentials' (EPs) elicited by tones (Auditory EP, AEP), flashes or a pattern reversal (Visual EP, VEP) or electrical stimulation (Somatosensory EP, SEP)
2. Cognitive pathways by recording of ERPs related to the execution of attention, emotion or memory tasks

EPs/ERPs are wave patterns that are characterized by three features:

1. Polarity (positive or negative, which is often indicated by the letter 'P' or 'N' in the ERP name)
2. Latency (the time moment of peak occurrence after stimulus presentation, which is often indicated with the number in the ERP name)
3. The topographical distribution of the amplitude of the ERP peak over the scalp

The time resolution of ERP analysis is much higher than that of other neuro-imaging methods like functional MRI, SPECT and PET (i.e. in the order of milliseconds compared to seconds). On the other hand, compared to the other neuro-imaging techniques, ERP analysis has less location precision. This is due to the fact that the conducting properties of the brain attenuate and blur the scalp signal; further there are silent brain sources which can not be measured from the scalp surface and there is noise inherent to any real life measurement. However, during

the last years several promising advanced algorithms have been developed to overcome this problem. It is beyond the scope of this booklet to discuss these algorithms in detail, but an interested reader is referred to techniques such as MNE, sLORETA, swLORETA, LAURA and ECD. A main advantage of ERPs is their non-invasiveness, experimental flexibility and low costs. Moreover, they can easily be used for children and psychiatric individuals as well. As was mentioned above with respect to EEG frequency analysis, some EEG systems allow the comparison of individual EP results to the results of an age-matched reference group with a map showing the statistical difference (Figure 7). In this way abnormality in a specific form of information processing can be traced. The use of neurophysiology based testing involving frequency or EP analysis is quite common in the patient assessments of neurologists. However, as will be explained in following paragraphs the use of this type of testing is also of relevance to psychiatrists. In fact, a recent article in July 2005 for the APA makes the case for shifting responsibility for neurophysiology based testing from the Neurology Department to the Psychiatry Department (Pogarel et al., 2005). For further reading on neurophysiology please see Schaul (1998) or Luck (2005).

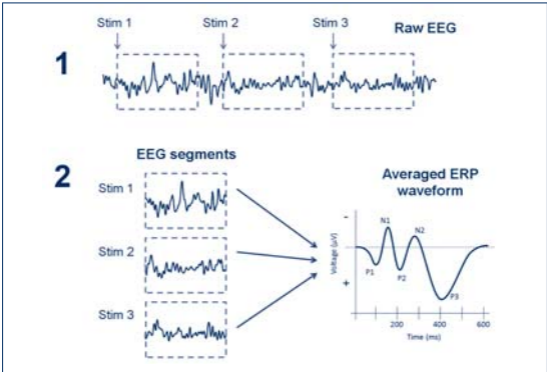


Figure 6. ERP averaging technique.

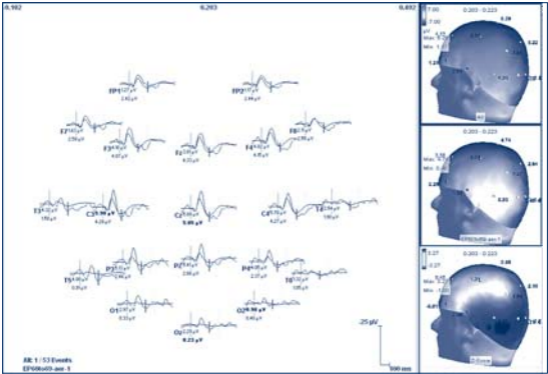


Figure 7. On the left the AEP of an individual patient is presented in comparison to the AEP of an age-matched reference group. On the right the amplitude map of the patient (upper picture) and the one of the reference group (middle picture) are given for the time-window of 203-223 ms. In the lower right picture the SPM map is shown.

1.2. Description of several EP and ERP protocols with relevance to psychiatry

LDAEP (Loudness dependent AEP)

The 'LDAEP' assesses the increase in amplitude of the N1, a negativity in the EP around 100 ms after stimulus presentation, and the subsequent positivity (P2) elicited by increasing tone loudness/sound level during auditory stimulation (e.g., Mulert et al., 2002; Linka et al., 2005) (Figure 8a-b). As will come back in paragraph 2.2., the clear association between the LDAEP and serotonergic neurotransmission makes this EP-complex very interesting for psychiatry.

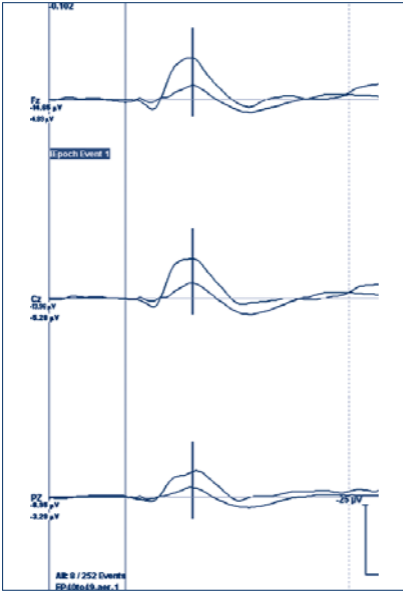


Figure 8a. An enlarged AEP in a patient (upper waveform) in comparison to the age-matched reference group (lower waveform).

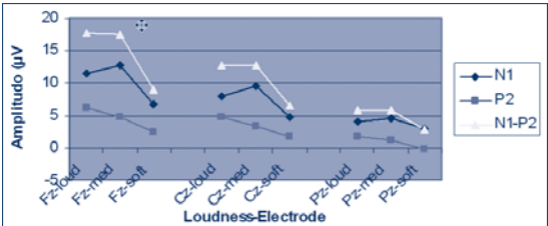


Figure 8b. The loudness dependency of the N1-P2 amplitude in graphic for the central-frontal, the central and the central-parietal electrodes (i.e. Fz, Cz and Pz).



P50

P50 assessment entails the recording of a very early positivity, occurring in the EP already 50 ms after stimulus presentation, in reaction to short clicks presented in pairs. Typically there is a lower P50 amplitude in response to the second click of the pair (*S2* in *Figure 9*) relative to that in response to the first one (*S1* in *Figure 9*). This suppression of the P50 amplitude in response to the second click, also called the 'P50 suppression ratio', is thought to be related to filtering of irrelevant auditory information in order to prevent sensory overload (e.g., Freedman et al, 1999). As will be touched upon in paragraph 2.1., patients with schizophrenia very often show a decreased P50 suppression ratio, which probably explains the sensory overload experienced by these patients.

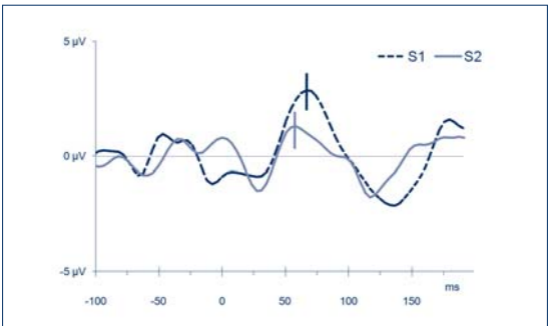


Figure 9. The P50 amplitude at a temporal electrode (*T3*) position in response to two clicks that were presented in pairs. The EP elicited by the first click of the pair (*S1*) is presented in a dashed line and the EP elicited by the second click (*S2*) is given in a solid line.

MMN

The Mismatch Negativity or MMN is a negative ERP component that is recorded between 100-200 ms in response to low-probability deviant sounds in a sequence of standard sound stimuli, when attention is directed elsewhere. The deviance between sounds can for

example be defined by a frequency (pitch) difference or a duration difference. Recently, it has been demonstrated that not only physical characteristics of the stimulus but also abstract properties can lead to the MMN. Especially the MMN evoked by a duration deviance has very high test-retest reliability. The MMN is best seen in the difference wave between the ERP in response to the standard and deviant sounds. The MMN is considered as the 1st step in the processes leading to conscious detection of differences in auditory context, i.e. the mnemonic comparison of a given stimulus with a previous one which has already build up a trace in memory. The violation of the previously formed memory trace produces the MMN. In hyper vigilant individuals an increased MMN can be observed. The fact that the MMN is not dependent on attention or cooperation of a patient makes this ERP especially interesting for psychiatry (for more details see Tervaniemi et al., 1999; Kujala et al., 2007) (Figure 10).

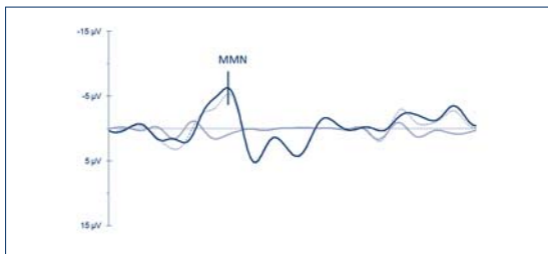


Figure 10. The MMN is best observable between 100-200 ms in the difference wave between the ERP in response to high probability standard sounds (light solid waveform) and low-probability deviant sounds (dashed waveform). Here a difference wave containing the MMN elicited by a deviance in duration of the sounds is presented (dark solid waveform).

P300

The P300, a positive ERP component around 300 ms after stimulus presentation, is typically generated in an auditory 'oddball' protocol in response to attended low-probability (deviant) target stimuli requiring an overt response (Figure 11). Typically the P300 amplitude in response to the low-probability target stimuli will be higher relative to that in response to the standard stimuli. The P300 is considered to be related to the maintenance of working memory when the mental model of the stimulus environment is updated (Donchin and Coles, 1988). In reality the P300 is an ERP-complex composed of two separate peaks, the P3a and the subsequent P3b. The P3a represents the conscious perception of deviance or novelty and is best seen at frontal and central electrodes (Fz and Cz). The P3b is maximal more posterior over the scalp (at Pz) and represents the conscious closing of an updating process regarding the stimulus environment in the context of memory. Further, the recording of the reaction times (RTs), hits and misses in response to the target (the deviant) stimulus can provide information about learning effects, alertness, attention and impulsivity in a patient. As will be described in paragraph 2. although the P300 complex is abnormal in various patient groups combining it with other EEG or ERP measures or monitoring it during the administration of a medication protocol does provide relevant information in psychiatric assessment.

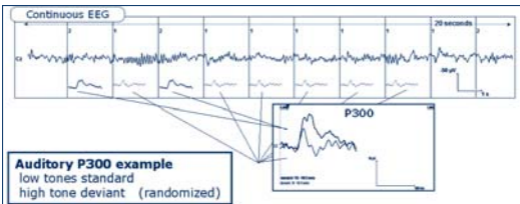


Figure 11. A graphic explanation of the protocol typically used to evoke a P300 component (i.e., an auditory 'oddball' protocol). The ERP in response to the standard stimuli is given with the lighter line and the ERP in response to the low-probability target stimuli is given with the darker line.

CNV

The Contingent Negative Variation (CNV) protocol entails the recording of the brain response to a warned reaction time task. Figure 12 shows a graphic explanation of the CNV protocol. Typically the ERP measured with a CNV protocol is divided into three different components or processes:

- 1) The one following the warning stimulus (*S1 in Figure 12*), which is related to the orientation response and to the S1 processing,
- 2) The CNV itself, which precedes the imperative stimulus (*S2 in Figure 12*) and which is related to motor preparation, time evaluation and S2 expectation and
- 3) The one following the motor act, the Post Imperative Variation, which is related to appraisal of the motor response and coping with the task.

This latter component can be negative or positive depending on task performance (PINV and PIPV, respectively in *Figure 12*) (Timsit Berthier and Geron, 1998; Rockstroh et al. 1982).

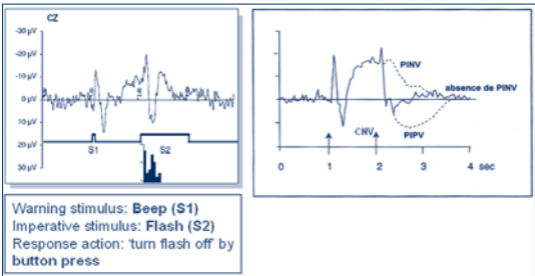


Figure 12. Graphic illustration of the protocol typically used to evoke a Contingent Negative Variation (CNV) (Left part of figure is copied from Timsit Berthier and Geron, 1998),



2. Rationale of the use of EEG/EP/ERP protocols in psychiatry

Current clinical practice often overlooks the use of neurophysiology based testing in the evaluation of psychiatric disorders. However, EEG/ERP protocols may prove to be important clinical tools in psychiatry, since research has shown that cortical neuronal dysfunction plays a major role in many psychiatric disorders (e.g. Pogarell et al., 2006; Halford, 2003). The correct application and interpretation of such protocols can offer several significant advantages, including:

- 1. Improved diagnostic precision**
- 2. Better prediction of treatment (drug) response**
- 3. Shortened time to final diagnosis and most effective (drug) treatment**
- 4. Ability to provide alternative treatment: Neuro-Feedback**

In the following paragraphs point by point a short clarification is given by presenting examples derived from clinical practice and the scientific literature.

2.1 Improved diagnostic precision

Unlike neurological assessment conventional psychiatric assessment does not entail exact quantitative measurements. Due to this psychiatric assessment can be rather subjective at times and may involve a trial-and-error approach. In attempt to solve this qualitative nature of conventional psychiatric assessment many studies have been conducted aimed at finding abnormalities in specific neurophysiological protocols among main psychiatric disorders. Indeed, this has resulted in evidence that main psychiatric disorders are related with abnormalities in specific EEG/EP/ERP protocols (e.g., Hansenne, in press). However, research has also shown that certain neurophysiological abnormalities can occur in multiple psychiatric disorders. This lack of specificity is probably related to the fact that EEG/EP/ERP abnormalities often represent discrete

symptoms or more precisely neurochemical abnormalities, which can occur in more than one psychiatric disorder. Nevertheless, using a combination of neurophysiological protocols could provide adequate diagnostic precision. Specifically, using 'disorder-specific protocols' consisting of a combination of several EEG, EP or ERP protocols that together represent the precise symptomatology and neurochemical imbalance of that respective psychiatric disorder. Below for several psychiatric pathologies a disorder-specific protocol is proposed (see also listed in Table 1).

A. Schizophrenia:

It has been shown that, relative to healthy individuals, schizophrenic individuals show a decreased P50 suppression ratio (e.g., Freedman et al., 1999). Moreover, this impaired P50 suppression ratio has been proposed as an endophenotype for schizophrenia, since it is present in patients with chronic schizophrenia, as well as in unaffected first-degree relatives and seems to be unaffected by typical antipsychotic medication (e.g., Price et al., 2006). Like a reduced P50 suppression ratio, a reduction in the MMN and P300 amplitude have also been proposed as endophenotypes for schizophrenia (e.g., Price et al., 2006; for clarification of these ERP protocols see again 1.2., see *Figure 13a and 13b* respectively for an example of a P50 and a P300 in a schizophrenic patient). Price et al. (2006) sought to compare and combine data from probands & family members of schizophrenic patients and healthy subjects who were all assessed on each feature with an electrophysiological battery consisting of four protocols among which the P50, MMN and the P300 auditory oddball protocol. The conclusion of this study was that a multivariate endophenotype, based on a weighted combination of electrophysiological features, provides greater diagnostic classification power than any single endophenotype. This is due to low correlations between measures. Importantly, a high classification power was found, in the order of 70-80 %. Concluding, the P50, MMN and the P300 in combination seem to be useful for the assessment of schizophrenia.



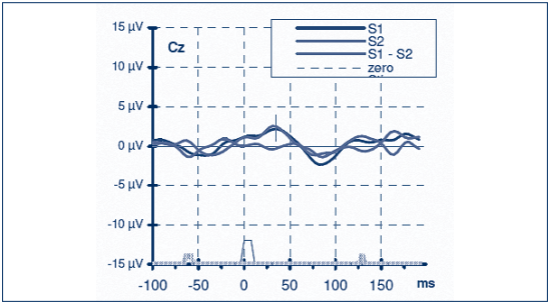


Figure 13a. The P50 component measured in a schizophrenic patient. There is no suppression of the P50 amplitude to the second tone (S2).

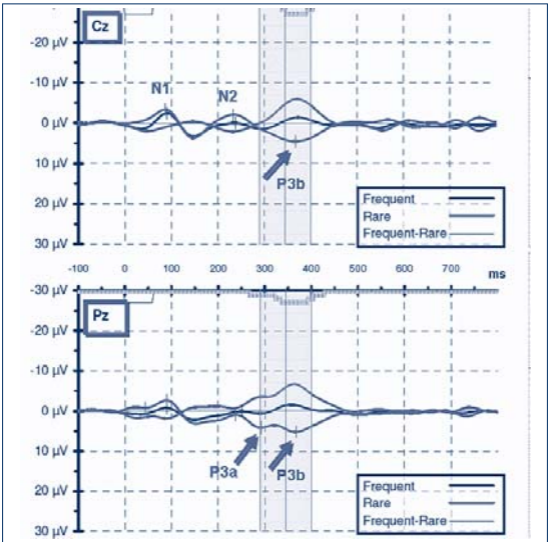


Figure 13b. A decreased P300-complex in a schizophrenic patient.

B. Attention Deficit/Hyperactivity Disorder (ADHD):

In a review by Barry et al. (2003) on electrophysiology in ADHD, it was concluded that in terms of resting EEG, the parameters most reliably associated with ADHD are elevated relative theta power, reduced relative alpha and beta power, and elevated theta/alpha and theta/beta ratios (Figure 14). In the same review, it was concluded that among the ERP deficits that have been associated with ADHD one of the most robust deficits is a decreased P300 auditory oddball amplitude (for explanation of this protocol see 1.2. or Figure 11) recorded posterior over the scalp. We propose that a combination of Quantitative EEG (QEEG) measures and the P300 auditory oddball protocol may provide a useful diagnostic tool in the assessment of ADHD.

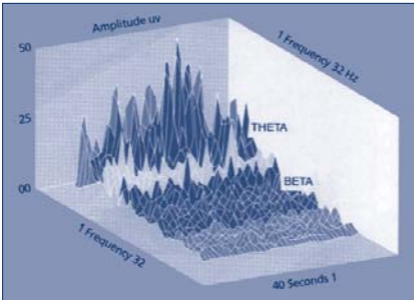


Figure 14. Distribution of the power in the different EEG frequency bands in a subjects with ADHD. It can be observed that there is great power in the theta band while there is little power in the beta band, which is assumed to be characteristic for subjects having attention problems (Figure copied from Demos, 2005).

C. Depression:

Evidence suggests that electrophysiology in depression is characterized by a decreased CNV (e.g., Timsit Berthier et al., 1987 and in preparation; for explanation of the CNV protocol see 1.2. or Figure 12). Additionally, often in depressive patients a Post Imperative Negative Variation,

a PINV, correlated with slow reaction time occurs (*Figure 12, on the left*). In controls instead there is a return to baseline after the imperative stimulus (e.g., Timsit-Bertier 1987 and in preparation). Also, a disturbed loudness dependence of the auditory N1/P2 response (LDAEP) has been described in relation to depression (e.g., Pogarell et al., 2006; Linka et al., 2005; for explanation of the LDAEP protocol see 1.2. but also 2.2.). When depression is assumed in a certain patient, the use of the CNV and the LDAEP protocols could provide more certainty.

D. Alzheimer's disease:

Individuals with Alzheimer's disease generally show reduced P300 amplitudes and elevated P300 latencies to task-relevant stimuli (e.g., Pogarell et al., 2006; for explanation of a typical P300 protocol see 1.2. and *Figure 11*). Further, in terms of resting EEG these patients usually show a decreased mean frequency of the EEG, an elevated delta and theta power and a decreased alpha and beta power. Moreover, a decreased EEG complexity, measured by EEG coherence analysis, has been related to Alzheimer's's disease (e.g., Jeong, 2004; Hegerl and Möller, 1997).

Table 1: Proposed Disorder-Specific Protocols

Disorder	Schizophrenia	ADHD	Depression	Alzheimer's Disease
	Decreased P50 suppression ratio	Elevated relative theta power in the resting EEG	Decreased Contingent Negative Variation (CNV) amplitude	Decreased mean frequency of the resting EEG
	Decreased Mismatch Negativity (MMN) amplitude	Decreased relative alpha/beta power in the resting EEG	Occurrence of a Post Imperative Negative Variation (PINV) correlated with slow reaction time (RT)	Elevated delta and theta power in the resting EEG
	Decreased P300 auditory oddball amplitude	Elevated theta/alpha and theta/beta ratios	Disturbed loudness dependence of the auditory N1/P2 response (LDAEP)	Decreased alpha and beta power in the resting EEG
		Decreased P300 auditory oddball amplitude		Decreased EEG complexity (measured by EEG coherence analysis)
				Decreased P300 amplitude (to task-relevant stimuli)
				Elevated P300 latency (to task-relevant stimuli)

Measures

Words of warning: It should be noted that the use of 'disorder-specific protocols' is a preliminary proposal. Further (validation) research is important. Additionally, the order of the individual protocols within the above suggested disorder-specific protocols may be of importance (in relation to fatigue, alertness, etc.). It may be sensible to start with active protocol (in which an overt response is requested) and end with passive one (e.g., start with the P300 and end with the P50 protocol).



2.2. Better predicted treatment response

Converging arguments from experimental studies support the hypothesis that the amplitude of the P300 and CNV as well as the loudness dependence of the auditory N1/P2 response (LDAEP) are regulated by central catecholaminergic and serotonergic neurotransmission (e.g., Linka et al., 2005; Pogarell et al., 2006; Timsit-Berthier, 2003; Mulert et al., 2007; for an explanation of these ERP protocols see 1.2.). *Figure 15* shows an illustration of the relation between serotonergic neurotransmission and the LDAEP. In a similar way, the suppression of the P50 amplitude in response to the second click of a “double click-paradigm” (i.e. sensory gating) is dependent on central acetylcholinergic neurotransmission, especially on the occupation of the α -7 nicotine receptor. Considering that the catecholaminergic, serotonergic and acetylcholinergic systems are the target of several psychotropes, neurophysiological assessment may offer reliable indicators to predict both favorable responses and drug intolerance in psychiatric patients. Importantly, neurophysiological assessment could provide a method to *objectively monitor drug effects*, which is presently lacking in psychiatric practice.

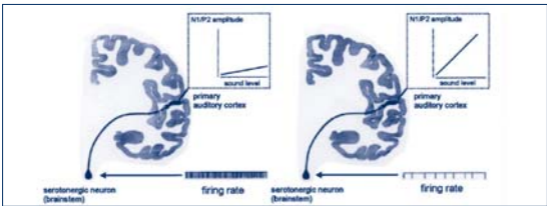


Figure 15. The association between serotonergic neurotransmission and the loudness dependence of the auditory evoked potentials (LDAEP, N1 and subsequent P2): a strong serotonergic neurotransmission (i.e., high firing rate of brainstem serotonergic neurons) is associated with a weak loudness dependence of N1/P2 amplitudes of the primary auditory cortex (left), and vice versa (right) (Figure copied from Pogarell et al., 2006).

Examples from the Literature:

- In depressed patients, a significant relationship between a strong LDAEP, indicating low serotonergic function, and a favorable response to selective serotonin reuptake inhibitors (SSRIs) has been demonstrated (e.g., Pogarell et al., 2006; Linka et al., 2005; Mulert et al., 2007).
- As is described in 2.1. Alzheimer's patients generally show reduced P300 amplitudes, which is thought to be related to a cholinergic dysfunction in these patients. Interestingly, it has been found that Alzheimer's patients with higher P300 amplitudes before treatment with cholinesterase inhibitors (CEIs) show a better response to treatment, as evidenced by their scores on dementia rating scales (e.g., Pogarell et al., 2006).

2.3. Shortened time to final diagnosis and most effective treatment

Apart from being more objective, neurophysiological assessment may also provide answers much faster concerning both the diagnosis itself as well as the most effective pharmacologic treatment.

Early diagnosis:

There is a need for reliable and efficient biological markers for early detection of people at risk for neuro-degeneration (e.g., Parkinson's disease, various types of dementias) for the administration of neuro-protective treatment. Evidence suggests that neurophysiological measures such as the P300 combined with QEEG parameters may be much more effective for early detection of neuro-degeneration than conventional techniques (Hegerl and Möller, 1997; Pogarell et al., 2006; Jeong, 2004).

Shortened search for effective drug treatment:

A child with ADHD undergoes, on average, about nine years' worth of treatment before the most effective treatment is found (personal communications with doctors). Patients with depression must often try several



different antidepressants before the correct medication is found. This time-consuming procedure may lead to increasing distress to the patients; the risk of self-harm, suicidality, and chronicity may increase as well (e.g., Pogarell et al., 2006). The use of a neurophysiological parameter for reliable prediction of individual responses to different drugs would allow immediate provision of adequate and effective drug treatment. This would help to shorten the disease process and thus to prevent the risk of chronicity or sustained therapy-resistance.

2.4. Ability to provide alternative treatment: Neuro-Feedback

Neuro-feedback utilizes the relationship between abnormal mental states and brain wave frequencies. The goal of neuro-feedback is to train clients to normalize abnormal EEG frequencies and to increase awareness of how a normalized EEG pattern “feels.” More specific, the aim is to teach clients how to produce a more optimal pattern of brain waves in order to attenuate or abolish an existing abnormal mental state.

Neuro-feedback uses basic principles of biofeedback to provide clients with immediate feedback of brain electrical activity, which should lead to their learning to regulate mental states. By using electrodes attached to the scalp, electrical activity of the brain is sent to and processed by an electroencephalograph and computer. Data are displayed to the client in a format resembling that of a video game. The game action is controlled by clients who meet preset training parameters. Each time the brain waves find their way to the preset state, the client is quickly rewarded with positive feedback. As clients learn to regulate their mental activity in this manner, pathological symptoms can diminish (e.g., Butnik, 2005 and Demos, 2005).

There is clinical evidence that neuro-feedback can be an effective treatment for several disorders: e.g., ADHD, Learning Disorder, Anxiety, Post traumatic Stress Disorder, addiction, epilepsy, victims of closed head injuries and headaches (e.g., Demos, 2005). However,

it should be noted that neuro-feedback treatment is still considered controversial. There are already some scientific studies showing promising results (e.g., Raymond et al., 2005; Levesque et al., 2006; Heywood and Beale, 2003), but there are inconsistencies and currently methodologically well-organized large-scale validation studies are lacking. Nevertheless, neuro-feedback could be a promising alternative treatment method (see also 3.1).

2.5. A final reason to use neuro-physiological assessment in psychiatry

Neurophysiological findings can provide insight into the natural history of the disorder. Accordingly, the discussion of neurophysiological findings with the patient (and relatives) might help to increase the understanding and acceptance of the disorder, modify the subjective experience of the disorder and increase the compliance to treatment.



3. The Cognitrace system

3.1. Introducing Cognitrace

Cognitrace is the clinical neuro-psychiatry system developed by the Dutch company, Advanced Neuro Technology (ANT). It provides the user with EEG, EP, and ERP protocols (see chapter 1 for an introduction into these techniques) that can be used with psychiatric disorders such as schizophrenia, ADHD, depression and Alzheimer's's disease (see Table 1 for protocols of value for these disorders). Cognitrace uses dedicated protocols for both recording and analysis. The streamlined workflow provides an easy-to-use and efficient environment for patient management, data acquisition, analysis, reporting and archiving. Importantly, Cognitrace is CE approved and has received FDA 510(k) approval.

Cognitrace consists of complete sets of measurements for neuro-psychiatry:

- EEG: Data is collected from multiple electrodes using a comfortable cap over a certain period of time (typically a few minutes). The data is automatically cleaned from artifacts that occurred during the recording (eye movements etc.), which can be reviewed by the technician or doctor. Next spectrum analysis is performed to map the electrical activity of the brain. Different frequency bands are displayed (alpha, beta, theta, delta) and can be automatically analyzed against age-matched reference data (find more details in 3.3.).
- VEP: Light stimulation of the patient is performed using a photic flash device. The recording is carried out at multiple electrodes; following this, artifact detection & rejection is done and the data is averaged. VEP averages are displayed and the results are compared with a VEP normative data set.
- AEP: This protocol is similar to the VEP only this time auditory stimuli (beeps) are presented to the patient. The AEP averages can also be compared with an AEP normative data set.
- P50: During this protocol the patient will listen to short clicks presented in pairs and the processing of the brain is again recorded at multiple electrodes. After

recording the automated reporting tool processes the data and presents a printable report to the technician or doctor. This report will consist of the averages elicited by the first and second tone, and the difference waves

calculated by subtracting the averages elicited by the first and second tone. These difference waves can be used to analyze auditory sensory gating in patients.

- P300 (Auditory oddball paradigm): A low and high pitch tones are presented to the patient. The order of presentation is pseudo-random with a likelihood of 20 against 80 for the high tones. The patient is asked to respond to the high pitch tones by clicking on a response pad. Reaction time and correctness are recorded with the continuous EEG. After the recording has been done, a report is generated which shows the brain responses at different electrodes together with reaction time data and spectra plot.
- Visual P300 (Visual oddball paradigm): This protocol is similar to the auditory P300 protocol only the audio presentation is replaced by visual presentations on a monitor.
- CNV: The patient receives a warned reaction-time task. Again, for this protocol, reaction time and correctness are recorded together with the EEG. After the recording the automated reporting tool processes the data and presents a printable report to the technician or doctor.
- VEP to pattern reversal: This protocol is similar to the VEP protocol with the photic device, only this time the patient is stimulated with a checkerboard pattern-reversal.

Recently the following protocols have also been added to the Cognitrace system:

- SEP: Electrical pulses are given to the patient and somatosensory processing of the brain is recorded at multiple electrodes.
- MMN: This component can be measured in Cognitrace in response to the processing of low-probability deviant sounds varying in *frequency* or in *duration*



from the standard sounds presented to the patients. After recording the automated reporting tool processes the data and presents a printable report to the technician or doctor.

- LDAEP: The loudness dependence of the N1 and subsequent P2 can be measured in Cognitrace in response to five different sound levels. Also, a device to calibrate sound level is available.
- Neuro-feedback: Both a visual and auditory EEG-feedback protocol has been implemented in Cognitrace. To obtain more information on these protocols, please ask ANT.

A recording session that includes for example the EEG, VEP, AEP, P300 (auditory and visual) and CNV protocols takes about 45 minutes (patient preparation, instructions and recording time). The offline analysis procedure adds another 15 to 30 minutes depending upon the type of patient and the number of stimulation protocols done for this patient. In clinical application the report is automatically created.

In addition to the above mentioned standardized recording protocols the system can be used for other protocols like:

- Regular clinical EEG recordings (eyes open, eyes closed, photic stimulation at different frequencies, optionally with digital video)
- Sleep recordings (requires bipolar and auxiliary inputs on the amplifier, optional)

Moreover, Cognitrace can be extended with the *Eevoke experiment generator* tool which allows the user to design and customize the stimulation protocols. These stimulations can be included in the standardized recording protocols.

The basis of the Cognitrace system is provided by the *Eemagine EEG software*. The workflow philosophy of Eemagine EEG contributes to the efficiency of the Cognitrace system. Well-defined templates outline the workflow of the recording, analysis and reporting. The highly interactive and intuitive display of patient

information, EEG traces, voltage and spectral analysis maps makes the review of results simple. Needless to say that all results are documented automatically. Cognitrace is the ideal neurophysiologic system for psychiatric research and patient evaluation.

3.2. Cognitrace system overview

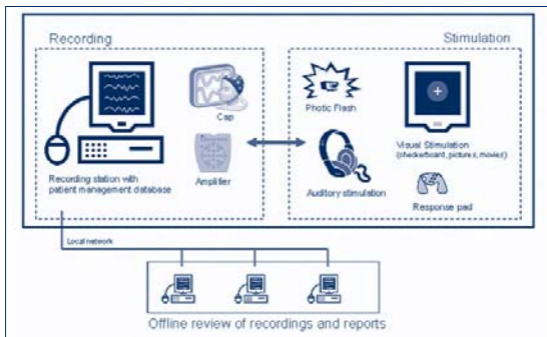


Table 2. Cognitrace System elements

Recording and Stimulation

- 24 channel amplifier
- Impedance LEDs on front amplifier
- PC for recording and stimulation
- Patient administration database
- Recording software
- Online averaging
- Stimulus presentation software
- Response keypad
- Audio card and headphones
- Device to calibrate sound level (optional)
- Photoc flash (optional)
- Electrical stimulator (optional)
- CRT for visual presentations of stimuli (optional)
- Color Printer (optional)
- Caps (optional)
- Starter kit for caps (optional)

Analysis and reporting

- 3d mapping of voltage (EEG) and FFT results
- Spectral analysis (online and offline)
- Statistical analysis
- Offline averaging and signal conditioning
- Automatic report generation for clinic application
- EEG, EP reference database (optional)
- Spike detection (optional)
- Review stations (optional)

Language supported

- English
- Dutch
- French
- German
- Spanish

3.3. Attractive features of Cognitrace for clinical practice

Reference data for EEG Eyes open/closed, AEP and VEP protocols

ANT has normative reference data available for statistical comparison between normal subjects and the patients. The reference data is divided into age groups: 5-7, 7-9, 9-13, 14-19, 20-29, 30-39, 40-49, 50-59, 60-69, and 70-79 years. Deviations are shown in z-score units. The reference database is an optional item that can be purchased with the Cognitrace system. When this database is purchased a comparison to normative reference data is automatically done during the analysis of the EEG, AEP and VEP protocols.

Patient Management & Administration

The patient management database in Cognitrace is for the administration of patients, data as well as for the analysis and report done for these patients. The database lists all patients and the recordings, analysis and reports corresponding to each patient. The database can be running on the Cognitrace system or installed on a centralized server. The patient information along with the recordings can be accessed from the recording system

as well as from any review station or other system running an up-to-date internet browser.

Network integration

Cognitrace can be set up to be running within the local area network of the department. With this EEG's and EP's can be reviewed over the network. All analysis, results and reports are automatically updated in the patient management database.

Cognitrace philosophy – open system

The Cognitrace system is a direct result of ANT's experience in the field of cognitive psychology. Since several years ANT is one of the leading manufacturers of cognitive EP/ERP research equipment. This includes systems for acquisition, cognitive stimulation and analysis. All of ANT products are designated for research applications, with the exception of Cognitrace system. The basis of the Cognitrace system is the research ERP system that ANT developed. For Cognitrace, the research system has been downscaled in terms of number of recording channels and functionality. Furthermore, it has been made more user-friendly and efficient for clinical application. Cognitrace is an open and modular system that can be easily adjusted and customized. Moreover, it can be extended with additional components such as the experiment generator for those users that wish to use the system for a wider range of patients/applications.

Training

With each Cognitrace system, a one-day training session is included. This training day can be either split in two half days of 4 hours or used in one whole day. This depends on the preference of the customer and is discussed at the time of purchase. Moreover, the type of training also depends on the equipment purchased.

Typically a training session includes:

- EEG recordings, impedance test, patient preparation and instruction, start recordings
- Patient Database management, create/edit patient
- Review of data, EEG/AEP/VEP analysis
- Reporting, edit reports



The contents of the training may be varied upon the experience of the customer. For instance, in case the customer has experience in EEG recording less time will be spent on this topic, and more time will be directed towards other subjects.

Internet Support

ANT offers to all of its customers Internet Support. This tool uses advanced communication

technology which facilitates an instantaneous connection between ANT and your PC, in order to provide remote technical assistance. Internet Support features include; remote application and screen sharing, file transfer, text chat and voice chat (VoIP). ANT virtually teleports your desktop to their Internet Support Team allowing them to take control of a remote PC, provide advice and communicate as if they were right there sitting beside you. This means instantaneous customer support for you and no more expensive travel or downtime waiting for assistance. With our internet support you resume working productively almost instantaneously.



Highest security has been one of primary concerns throughout the development of this Internet Support. Our 256bit AES encryption and strict security measures incorporated refuse unauthorized personnel access to your data, patient information, programs and systems: you do not have to open ports, change your network or firewall configuration or modify NAT tables. The Cognitrace system is always delivered with a free headset with microphone to make it possible to communicate with the Internet Support Team.

3.4. Selected user list of hospitals, institutes or practices

- Universitair Centrum St.-Jozef, Pr. Joseph Peuskens, Kortenberg, Belgium
- St. Elizabeth Ziekenhuis, Dr. Monte, Zottegem, Belgium
- Psychiatrie Guislain, Dr. Otte, Gent, Belgium

- ASZ Ziekenhuis, Dr. P. Mouton, Aalst, Belgium
- Psy. Zh "ZOETE NOOD GODS", Dr. G. De Bruecker, Lede, Belgium
- Clinique Notre-Dame, Dr. Michel Floris, Tournai, Belgium
- Hôpital Brugmann, Pr. P. Verbanck, Brussels, Belgium
- Cliniques Universitaires Saint-Luc, Dr Erik Constant, Brussels, Belgium
- Université de Liège, Dép. des Sciences Cognitives, Pr Michel Hansenne, Belgium
- Hôpital St. Luc, Pr. N. Zdanowicz, Bouge, Belgium
- Clinique Notre-Dame, Dr Joseph Francart, Chareloi, Belgium
- Private usage: Dr. E. Bouilon, Blaton, Belgium
- Private usage: Dr. G. de Bruecker, Lede, Belgium
- Private usage: Dr. G. Otte, Gent, Belgium
- C.H. Reine Fabiola, Dr. Pierre-Yves Libois, Montignies-Sur-Sambre, Belgium
- CHU Saint-Antoine, Paris, Dr. C. Peretti, France
- Dr. H. Matthis, Gossau, Switzerland
- Anti-aging Centre, Athens, Greece
- Path Medical Center, New York NY, USA (four systems)
- Spring Mountain Treatment Center, Dr. Matthews, Las Vegas NV, USA
- Curamed, Cherry Hill NJ, USA
- HBM Center, New York, NY, USA
- Chesapeake Neurology Insitute MD, USA
- Neurology Institute, Voorhees, NJ, USA
- Wayne State University, Dr. N. Boutros, Detroit MY, USA
- UHS Meridell Achievement Center Texas, Liberty Hill, TX, USA

and more ...



4. General conclusions

To summarize, the Cognitrace system of ANT can have an important role in psychiatry, because:

- It offers an objective measurement of abnormalities and is fully adapted to the needs of a clinical environment
- It provides disorder-specific neurophysiologic protocols which can contribute to the early detection and diagnosis of several psychiatric disorders and to a fast and objective selection of treatments.
- Discussion of neurophysiological findings with the patient (and relatives) might help to increase the understanding and acceptance of the disorder, modify the subjective experience of the disorder and increase the compliance to treatment.
- It gives the possibility of giving additional, alternative treatment protocols such as Neuro-Feedback



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