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Chapter 17

Electro-Physiological Approaches to Monitoring Neuro-Degenerative Diseases

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Additional information is available at the end of the chapter

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1. Introduction

Electrical brain activity is recorded by means of a variety of techniques, including different approaches, for instance surface field electrodes among others. Additionally, specific local neuronal responses are suitable for recording. As an example, those known as evoked response potentials allow to determine whether neural pathways and neuronal groups are performing properly.

Neuro-degenerative diseases involve lost of integrity of a number of neuronal nuclei; in turn, this represents significant changes in electrical brain activity that might be compared with unaltered individuals. Several experiments have shown the potential usefulness of evoked response potentials ERP brain correlates as bio-markers, diagnostic and prognostic tools of some neurodegenerative diseases. Also, neuropsychological tests have demonstrated correlations with electrophysiological findings, and are helpful to detect early cognitive decline or disease progression in neurodegenerative diseases.

Electrodiagnostic examination should make available useful information for researchers and physicians. Furthermore, it could help to the correct diagnosis of the illness, its differential diagnosis to the identification of the pathophysiological abnormalities probably responsible for the pathology

2. Electro-physiological techniques

- Surface electrode cortical EEG:

The electroencephalogram EEG is usually described in terms of its rhythmic activity, which is helpful in relating the EEG to the brain function [1]. Neuronal activity during information processing is represented by oscillations within local or widespread neuronal networks. These oscillations can be recorded by means of surface electrodes over the skull. The rhythmic activity in EEG is commonly divided in specific frequency bands: 0.5–4Hz (delta), 4–8Hz (theta), 8–10Hz (alpha 1), 10–12Hz (alpha 2), 12–30Hz (beta), and 30–100Hz (gamma) [2]. The FFT decomposes the EEG time series into a voltage by frequency spectral graph commonly called the "power spectrum", with power being the square of the EEG magnitude, and magnitude being the integral average of the amplitude of the EEG signal, measured from(+) peak-to-(-)peak), across the time sampled, or epoch [3]. As a result of this procedure the quantitative electroencephalogram QEEG is obtained [4], [5].

- Recording deep brain electrodes

Local field potential and action potentials can be captured by means of very fine conductive electrodes for research and surgical monitoring purposes [6], [7]. In addition, deep brain electrodes implanted into the brain are used to apply electrical stimulation in order to treat disorders that have electrical generators [6].

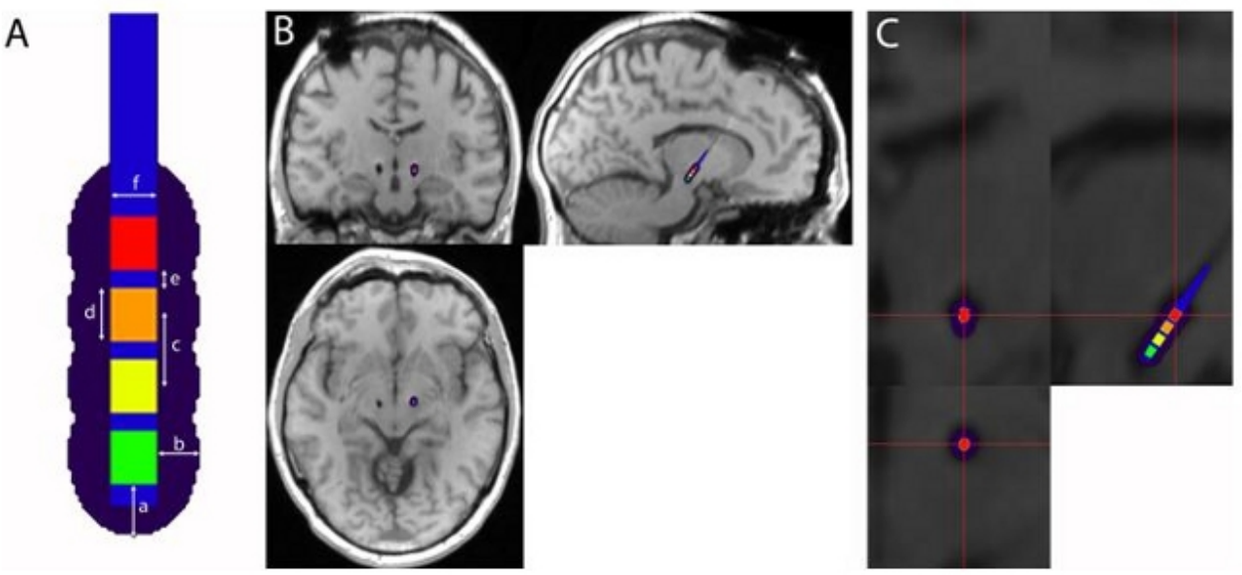

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Figure 1. Deep brain electrodes to treat Parkinson's disease: (A) Electrode with four active contacts (0, 1, 2 and 3 from ventral to dorsal and each 1.5 mm high at 0.5 mm intervals; total length 7.5 mm) was placed at the selected coordinates in the subthalamic nucleus with the most ventral contact (contact 0) placed in the ventral part of the nucleus *

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3. Alzheimer electroencephalographic patterns

The electroencephalogram EEG measures neuronal activity, and is an objective way to assess the degree of cognitive disturbance. Researchers have investigated how well cognitive function in dementia assessed by psychometric tests correlates with electrical brain activity (EEG). Results from such an experimental approach shows a slowing of the EEG, and an increase of dipole strength in the slow frequency bands, a more anterior equivalent dipole of alpha- and beta-activity, correlated with increasing cognitive deterioration in AD patients [8].

Relative power in different EEG frequency bands from EEG signals have been used in order to improve the diagnosis of AD. Frequency bands between 4 and 30 Hz have been systematically tested; the relative power of a certain frequency band is obtained by dividing the power of this frequency band by the power of the total frequency band. The frequency band 4-7 Hz is the optimal frequency range for detecting AD [9]. Progressive atrophy of hippocampus correlates with decreased cortical alpha power in AD patients. Moreover, the small hippocampal volume is measured in magnetic resonance imaging of the AD subjects [10], [11]. Additionally, the power of occipital, parietal, and temporal alpha sources is low in AD patients [10].

A promising study by Kann demonstrated the implication of the fast neuronal network oscillations in the gamma range (~30-90 Hz) in complex brain functions. Sensory processing, memory formation and, consciousness are brain functions highly vulnerable to neurodegenerative pathologies [12].

Cortical pathology in AD is related to decreasing fast frequency power; whereas increased slow frequency EEG power is observed in mixed dementia compared to AD. The quantitative EEG contributes to a better understanding of the electrical brain pattern in AD [13]. Slowing on qEEG is a marker for subsequent rate of cognitive and functional decline in mildly demented AD patients. Frequency bands analysis of EEG recordings from AD subjects shows lower parieto-occipital beta values, and higher frontocentral and parieto-occipital theta values. Additionally, lower parieto-occipital beta values are related to more decline in activities of daily living [14], [15]. Also, connectivity between frontal and parietal sites in AD patients is reduced, thus, resulting in significant decreased of coherence in the left fronto-parietal EEG [16].

In some cases there is no correlation between the increase of delta waves in the electroencephalogram, and the severity of mental deterioration of the AD patients, but this facts correlate by taking in account the intensity of delta waves rather than just their presence. The delta waves generated with participation of the cortex, thalamus, and brainstem seems to be more variable in different stages of AD. Measures of the theta activity discriminated between mild, marked, and severe cases of AD to some extent. The cognitive and EEG changes are probably related to atrophy of the cholinergic neurons in the hippocampal structures [17].

EEG recordings at rest and during visual stimulation processed by means of Fast Fourier Transform (FFT) are helpful to determine intra- and inter-hemispheric coherence in AD patients. Those studies have shown statistically significant phase dispersion especially at

occipital and parietal regions in AD [18]. Coherence analysis of the EEG during photic stimulation also is low in AD patients, irrespective of the stimulus frequency, due to a failure of normal stimulation-related brain activation. What is more, when coherence analysis is done from recordings of the brain´s left hemisphere and the right one, impairment of interhemispheric functional connectivity is found [15].

4. Alzheimer diagnosis

A combination of computed techniques to analyze EEG recordings, such as the Higuchi fractal dimension (HFD), spectral entropy (SE), spectral centroid (SC), spectral roll-off (SR), and zero-crossing rate (ZCR), results in a AD diagnostic accuracy of 78%. HFD is a quantitative measure of time series complexity derived from fractal theory. Among spectral measures, SE measures the level of disorder in the spectrum, SC is a measure of spectral shape, and SR is frequency sample below which a specified percent of the spectral magnitude distribution is contained. Lastly, ZCR is simply the rate at which the signal changes signs. Even though, the individual accuracies ranged from 60-66%, that itself is not enough to be clinically useful alone. Combining these features and training a support vector machine (SVM) represent a novel alternative computed technique to reach high diagnostic accuracy for AD [19].

An electrophysiological marker in the early detection of neurodegeneration is found in the EEG pattern during stimulation for visual evoked potentials (VEP) in mild AD patients. In mild AD the altered activity concentrates on deep structures of the left hemisphere, say hippocampus and midbrain [20]. Visual evoked potentials in diagnosed Alzheimer patients (ApoE epsilon4 carriers) have significantly longer peak latencies and a trend to higher interpeak latencies of late potential components. However, potential amplitudes are similar in carriers and no carriers. It appears that the ApoE epsilon4 allele mainly promotes neuronal dysfunction [21]. In an ERPs lexical-decision task AD patients do not display repetition priming for words repeated at long lags [22].

Neuropathological findings in AD correlate with sensory-affective dissociation. Pain anticipation and autonomic reactivity depend on both the cognitive status and the frequency bands of the electroencephalogram, especially delta and theta frequencies. The painful stimulation perception is well preserved in AD, however, the affective and cognitive functions, which are related to both anticipation and autonomic reactivity are very affected [23].

A helpful tool to confirm an AD diagnosis is the electrophysiological correlate of minipolymyoclonus and a bi-frontal negativity in the EEG that precedes the myoclonic jerk. This electrophysiological fact may reflect activity of a subcortical generator. [24].

Quantitative relative power analysis of magnetoencephalography recordings can find widespread abnormalities in oscillatory brain dynamics in AD patients. In the delta band the AD patients have a consistently higher relative power, especially in the right occipital area. Delta activity is increased in AD patients, whereas alpha, and beta activity was decreased. Particularly the beta band (13–30 Hz) shows a very significant decrease in relative power in

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AD. In the theta band the significant decrease in relative power of the left temporal region. In the beta band, all separate cortical regions demonstrated a significant decrease of relative power in AD [25]. Furthermore, the auto mutual information (AMI) provides a measure of future points predictability from past points in the magnetoencephalogram (MEG). Studies analyzing the (MEG) background activity in patients with AD, using the AMI reveals that the absolute values of the averaged decline rate of AMI is lower in AD patients than in control subjects. Thus, based on this kind of analysis is suggested that neuronal dysfunction in AD is associated with differences in the dynamical processes underlying the MEG recording [26].

REM sleep is a behavioral state characterized by atonia, and high frequency-low amplitude EEG among other features. Polysomnographic studies have found AD patients with REM sleep with-out atonia. The lack of atonia during REM sleep might involve alteration of the extrapyramidal motor control [27]. During quiet sleep in healthy human EEG there are components that consist of a brief negative high-voltage peak, usually greater than 100 μV, followed by a slower positive complex around 350 and 550 ms and at 900 ms a final negative peak, known as K-complex [28]; they are generated in response to external stimuli such as sounds, touches on the skin [29], and internal ones such as inspiratory interruptions [30]. They also occur in widespread cortical locations [28] though they tend to predominate over the frontal parts of the brain [31]. K-complexes synchronize the thalamocortical network during sleep, producing sleep oscillations such as spindles and delta waves [32]. Additionally, it has been suggested that K-complexes play an important role in memory consolidation [33]. In patients with Alzheimer disease, the electroencephalogram during wakefulness shows pathologic signs of abundant, delta activity. AD patients produced significantly fewer evoked K-complexes and had substantially smaller N550 amplitudes than controls. Even though observed increases in pathologic delta-frequency electroencephalographic activity, patients with Alzheimer disease have an impaired capacity to generate normal physiologic delta responses such as K-complexes during quiet sleep [34].

5. Alzheimer early detection

The progressive deterioration of AD patient progresses is caused by the loss of functional connectivity within neocortical association areas. Much more sensitive methods to identify early alterations of neuronal networks makes possible to predict the onset of AD. Diffuse slowing is correlated with the cognitive decline. This is a method to extract meaningful EEG parameters for the early diagnosis and staging of Alzheimer's disease [35]. Also, a clear difference between AD patients carrying the ApoE epsilon4 allele and no carriers is detected in the EEG; neurophysiological endophenotype of non-demented individuals at genetic risk for AD have increased excitability and dysfunction of deep brain and alpha rhythm-generating structures even decades before the first clinical symptoms of presumable dementia. Under hyperventilation the presence of the epsilon4 allele in AD relatives is associated with the manifestation of synchronous high-voltage delta-, theta-activity and sharp-waves, pronounced decrease in alpha and increase in delta and theta relative powers [36]. Mildly demented AD patients have an increase of relative delta power in the left side, and a decrease

for relative alpha power in the right side; this preserves a linear correlation, and allows to predicting activity daily living ADL loss timing, and general behavioral and cognitive deterioration in mild Alzheimer's disease [5]. The delta relative power in the left side predicts both the loss of ADL and death, whereas right theta predicted the onset of incontinence [37]. In addition, the qEEG measures is correlated with neuropsychological test scores related to abilities that are impaired in the early stages of disease, such as delayed recall and verbal fluency [11].

Prognosis of early AD onset can be done by means of calculating the REO/REC power ratio; this tool takes the spectral analysis of the EEG recorded under awake resting eyes closed (REC) and open (REO) conditions. Demented AD patients show an increased REO/REC power ratio in the 6.5-12 Hz band. Patients lacking a dominant peak in the 6.5-12 Hz band, but with high power in 1-6.5 Hz band have an earlier age of disease onset [38].

Increased risk of mortality in AD is associated with higher theta, lower alpha, and lower beta activity in the parieto-occipital EEG. Also, higher theta activity in the fronto-central EEG has a prognosis value. Decreases of beta and alpha activity on quantitative spectral EEG are independent predictors of mortality in patients with early Alzheimer disease [39].

IFAST (implicit function as squashing time) is an artificial neural networks (ANNs) assembly; it is capable of compressing the temporal sequence of EEG data into spatial invariants. This model represents spatial features of the EEG patterns at scalp surface by means of filtering EEG tracks according to four different frequency ranges (0.12 Hz, 12.2 - 29.8 Hz; 30.2 - 40 Hz, and Notch Filter 48 - 50 Hz). The spatial content of the EEG voltage is extracted by IFAST step-wise procedure using ANNs. The data input for the classification operated by ANNs are the connections weights of a nonlinear auto-associative ANN trained to reproduce the recorded EEG tracks. This method allows distinguish between mild cognitive impairment (MCI) stable and MCI subjects who will convert to Alzheimer's disease (MCI/AD), with a high degree of accuracy. Eyes-closed resting EEG data in individual MCI/AD subjects show significant differences in the 10-12 Hz band when compared to MCI subjects [40].

Event-modulated EEG dynamic analysis makes it possible to investigate the functional activation of neocortical circuits [41]. Evoked Response Potentials (ERP) brain correlates are useful preclinical markers to identify individuals at risk for AD. Additionally, the ERP measures can predict its presence. Asymptomatic PSEN1 mutation carriers have greater occipital positivity, but less positivity in frontal regions than control subjects. Those differences are more evident during the 200-300 msec period of the ERP. It seems like carriers rely more upon perceptual details of the items to distinguish between them, while control subjects may use frontally mediated processes to distinguish between studied and unstudied visual items [42].

An electrophysiological marker in the early detection of neurodegeneration is found in the EEG pattern during stimulation for visual evoked potentials VEP in mild AD patients compared to Elderly controls, and MCI. Elderly controls have a neural pattern with a right–left dominance; in MCI this pattern seems to be displaced from right hemisphere to the left one, while in mild AD the activity concentrates on deep structures of this hemisphere (hippo-

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campus and midbrain). Mild AD and MCI were more active for beta and gamma band, but at the same time beta and alpha band are more active than theta band. Elderly controls showed dominance of gamma and beta band in all significant areas. Mild AD and MCI have different neural patterns but show virtually similar frequency band activations, while elderly people differ from them in space and frequency bands [20].

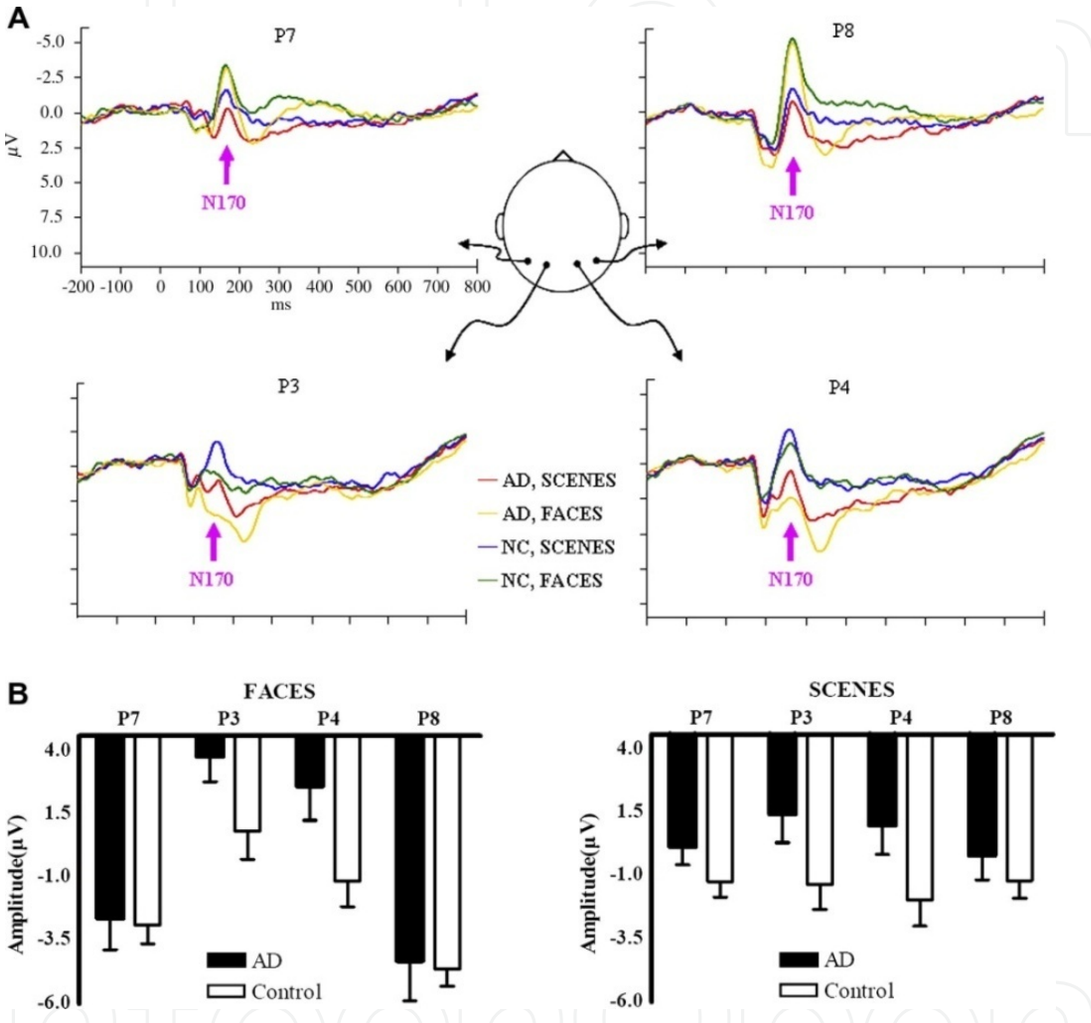

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Figure 2. Event-related potential study: Comparison between alzheimer diseases patients and normal control patients: (A) N170 at the four electrode sites; (B) the amplitudes of N170 between groups and types, AD: Alzheimer's disease. *

Visual ERP features have shown that different neural regions are responsible for the early visual processing in the structural encoding of scenes and faces. P100 is a part of the evoked response suitable to examine basic visual processing, N170 brings information about structural encoding, and N250 is related to familiarity. The pattern of P100 and that of N170 suggest that mild Alzheimer disease patients maintain basic visual processing and structural encoding abilities, and scene recognition is impaired earlier than face recognition in the course of

Alzheimer disease [43]. There is a diminished N400 component during a semantic categorization task in elderly subjects which suggest that due to the difficulty in accessing information there are deficient associative connections within the semantic network [44]. Auditory sensory and cognitive cortical potentials in persons with familial Alzheimer disease (FAD) mutations are abnormal approximately 10 years before dementia will be manifest. FAD mutation carriers had significantly longer latencies of the N100, P200, N200, and P300 components, and smaller slow wave amplitudes. Longer event-related potential latencies suggest slowing of cortical information processing in FAD mutation carriers [45]. The P300 latency is very useful in diagnosis, since it is found to be altered in cases with AD at an early stage, with very little cognitive degeneration [46].

6. Parkinson electroencephalographic patterns

Recordings in humans as a result of functional neurosurgery have revealed a tendency for basal ganglia neurons to oscillate and synchronize their activity, giving rise to a rhythmic population activity, manifest as oscillatory local field potentials. The most important activity is synchronized oscillation in the beta band (13-30 Hz), which has been picked up at various sites within the basal ganglia-cortical loop in PD. Dopaminergic medication and movement suppress this activity, with the timing and degree of suppression closely correlating with behavioral performance. for that reason synchronization in the beta band has been hypothesized to be essentially antikinetic in nature and pathophysiologically relevant to bradykinesia [47].

Post-movement beta synchronization is an increase in EEG beta power after movement termination. Parkinson patients have longer movement duration than controls, and also execute longer movement with their left hand, unrelated to the side of tremor. In Parkinson patients post-movement beta synchronization is significantly smaller contralateral to the tremulous hand movement. The post-movement beta synchronization has anterior shifting in Parkinson-patients; whilst in tremor dominant Parkinson's disease the asymmetric decrease of post-move beta synchronization is related to the laterality of tremor rather than bradykinesia [48].

Local Field Potentials LFP recording beta oscillatory activity is generated largely within the dorsal portion of the sub thalamic nucleus STN and can produce synchronous oscillatory activity of the local neuronal population. Recent studies suggest that beta (15-30 Hz) oscillatory activity in the subthalamic nucleus (STN) is severely increased in PD, and may interfere with movement execution [49].

Parkinson's disease is known to result from basal ganglia dysfunction. Electrophysiological recordings show abnormal synchronous oscillatory activity in the cortico-basal ganglia network in parkinsonian patients and animals. Also, it has been recorded an altered response pattern during movement execution in the pallidum of parkinsonian animals. In Parkinson animal models, spontaneous correlated activity increased later, after animals became severely bradykinetic, whereas synchronous oscillatory activity appeared only after major motor

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symptoms developed. Thus, causality between the emergence of synchronous oscillations in the pallidum and main parkinsonian motor symptoms seems unlikely. Consequently, the pathological disruption of movement-related activity in the basal ganglia appears to be a better correlate at least to bradykinesia and is probably the best responsible candidate for this motor symptom [50].

The observation of a voluntary movement executed by another person is associated with an alpha and beta EEG desynchronization over the motor cortex, thought to reflect activity from the human "mirror neuron" system. Movement observation is accompanied by bilateral beta reduction in subthalamic power and cortico-STN coherence in PD, which is smaller than the decrease observed during movement execution, but significant when compared with control conditions. Movement observation is accompanied by changes in the beta oscillatory activity of the STN, similar to those observed in the EEG. These changes suggest that the basal ganglia might be engaged by the activity of the human mirror system [51].

The difficulty that patients have in initiating voluntary movement in the absence of any external cues might be due to the fact that the amplitude of movement-related cortical potential is equal to those prior to random-choice movements. The implication is that processes involved in self-selection of movement are abnormal in Parkinson's disease [52].

Parkinson disease patients show deficits in simple visuo-perceptual functions. Moreover, PD patients had impairment in tasks requiring set shifting from one reaction to another that may suggest frontal lobe dysfunction. The memory deficit in PD may derive from lowered motivation or initiating behavior [53].

Looking for electrophysiological correlates of perceptual categorization in Parkinson's disease, visual event-related potentials (ERPs) in a natural scene categorization task become a suitable tool. In healthy control subjects, there is a significant early difference (150-250 ms poststimulus) between ERPs elicited by pictures containing animals and scenes without animals. In spite of relatively preserved basic-level visual functions, this is not the case in untreated PD patients. These results move up the possibility for striatal contributions to visual categorization and may present a novel protocol for further clinical studies [54].

It has been reported an oscillatory theta-alpha activity in the ventral subthalamic nucleus associated with impulse control disorders ICD in patients with Parkinson’s disease. This activity is distinct from that associated with L-dopa-induced dyskinesias LID and is also coherent with EEG activity recorded in frontal areas. The activity recorded in PD patients with impulse control disorders come out from the associative-limbic area (ventral subthalamic area), which is coherent with premotor frontal cortical activity. Patients with impulse control disorders display theta-alpha (4-10 Hz) activity (mean peak: 6.71 Hz) that is generated 2-8 mm below the intercommissural line. In PD the oscillatory activity of the subthalamic nucleus recorded through the electrodes implanted for deep brain stimulation displays dopamine-dependent changes whereby the OFF to ON motor state is signalled by a marked reduction in beta band activity [55]. Thus, dopaminergic side effects in Parkinson's disease are associated with oscillatory activity in the theta-alpha band, but at different frequencies and with different topography for the motor (dyskinesias) and behavioural (abnormal impulsivity) manifesta-

tions [6]. Diffuse lesions correlate with slowing of the EEG in patients with severe cognitive impairment [56], [57], [58]. All patients with dementia have an increase in slow waves in all the EEEG electrodes recording. In addition, all PD patients present diffuse slowing in the EEG with increased delta power [57].

Movement disorders in PD are due to the imbalance of inhibitory and excitatory processes involving motor cortical and subcortical neuronal circuits together with a nigrostriatal dopamine deficit [59]. A paired-pulse paradigm is usually used to study postexcitatory inhibition effect related to sensory gating mechanisms and synaptic processes in neurotransmitters release. There are two mechanisms that might explain paired-pulse inhibition phenomena. The first mechanism is the decrease in release probability of excitatory neurotransmitters from terminals of afferent axons. Another possible mechanism of the decrement of the second response on paired stimulation is connected with synaptically released GABA from terminals of inhibitory interneurons [60]. As the paired-pulse facilitation, paired-pulse inhibition is considered to be a form of a short-term synaptic plasticity. The investigation of cortical evoked potentials to paired-pulse sensory stimulation may provide additional information about mechanisms of neurological disturbances in PD [60].

7. Parkinson diagnosis

When individuals performed a reaching motor task (catching a ball in free fall), beta band asymmetry is observed. This result show a pattern of asymmetry in the somatosensory cortex, associated with a preparatory mechanism. With respect to task moment, after the ball's fall, the asymmetry is reduced. Moreover, the difference in asymmetry between the regions is related to a supposed specialization of areas (i.e., temporal and central). The temporal region is associated with cognitive processes involved in the motor action (i.e., explicit knowledge). On the other hand, the central sites are related to the motor control mechanisms per se (i.e., implicit knowledge). The premotor cortex shows a decrease on neural activity in the contralateral hemisphere (i.e., to the right hand). This finding is in agreement with others suggesting a participation of the frontal cortex in the planning of the apprehension task. This sensorimotor paradigm may be added to the inventory of tasks used to study clinical conditions such as depression, alzheimer and Parkinson diseases [61].

The corpus callosum (CC) is the morphological correlate of inter-hemispheric connectivity. Its integrity is of great importance for motor function and inter-hemispheric coordination of bimanual movements. Callosal fiber tracts are highly vulnerable as they are involved in number of neurodegenerative disease like parkinsonian syndromes and amyotrophic lateral sclerosis, even at early stages of the diseases. Transcraneal magnetic stimulation of the transcallosal inhibition may be performed by measurement of the ipsilateral silent period (iSP). The most common finding is a loss or a prolongation of the iSP latency [62].

As PD progresses, components of the autonomic, limbic, and somatomotor systems become damaged [63]. The substantia nigra and other regions of nuclear gray matter in the midbrain and forebrain become the focus of initially slight and then severe pathologic changes. At certain

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point, most individuals probably cross the threshold to the symptomatic phase of the illness, the pathologic process comes to involve the neocortex, and the disease is manifested in all its clinical magnitude. These diffuse lesions correlate with slowing of the EEG in patients with severe cognitive impairment [56], [57], [58].

The auditory evoked potentials of different latencies are useful in the evaluation of cognitive changes associated to PD. Middle latency auditory evoked potentials are abnormal in most PD patient. P300 is absent significantly more often in PD patients with cognitive impairment [64].

Parkinson Early Detection:

Spectral ratio is the sum of the power values in the alpha and beta waves divided by the sum of the values in the slow waves. Since, all patients with dementia have an increase in slow waves in all the EEEG electrodes recording, the spectral ratios decrease have significant predictive value in PD at all electrode locations except for the frontal pole. In addition, all PD patients present diffuse slowing in the EEG giving to delta power significance as predictive electrophysiological biomarker for dementia in PD [57]. ERP is also useful tool for the evaluation of neuropsychological impairments in PD. In the classic oddball task P300 is elicited by target. Even though, P300b findings in PD have shown inconsistent results, prolonged P300b latency in PD patients with dementia have been consistently observed [65].

The hazard of developing dementia is 13 times higher for those with low background rhythm frequency (lower than the grand median of 8.5 Hz) than for those with high background rhythm frequency. The QEEG measures of background rhythm frequency and relative power in the band are potential predictive biomarkers for dementia incidence in PD [57].

8. Huntington electroencephalographic patterns

Huntington's disease (HD) is an autosomal dominant inherited neurodegenerative disorder, with neurodegeneration mainly affecting the striatum. In Nogo as opposed to Go trials two fronto-central ERP components are elicited: the Nogo-N2 and Nogo-P3. These components are supposed to depend on (medial) prefrontal regions, especially the anterior cingulate cortex (ACC). In HD the Nogo-P3 demonstrates a strong attenuation, while the Nogo-N2 does not differ from controls. The decline in inhibition is likely mediated via a dysfunction in the ACC, which is known to be dysfunctional in HD. Moreover, the decline in response inhibition in HD is gene-associated. The differentially affected Nogo-components suggest that they rely on different neuronal circuits, even within the ACC. For HD this suggests that this structure is not entirely dysfunctional [66].

Cognition is affected early in Huntington disease, and in HD animal models there is evidence that this reflects abnormal synaptic plasticity. HD gene carriers and controls respond differently to theta burst stimulation, with controls having more inhibition than HD gene carriers. However, there is no difference between pre-manifest and early symptomatic HD gene carriers. Motor cortex plasticity is abnormal in HD gene carriers but is not closely linked to the development of motor signs of HD [67]. In vivo recording of field potentials in the dorsomedial

striatum evoked by stimulation of the prelimbic cortex in rats shows an altered plasticity, with higher paired-pulse facilitation, enhanced short-term depression, as well as stronger long-term potentiation after theta burst stimulation. This is a behavioral and electrophysiological evidence of a presymptomatic alteration of prefrontostriatal processing in an animal model for Huntington disease and suggests that supra-second timing may be the earliest cognitive dysfunction in HD [68].

The onset of Huntington disease (HD) might be atypical. Rarely, there is severe cognitive impairment and diffuse cortical atrophy before the onset of motor manifestations or symptoms of an extrapyramidal movement disorder. Thus, especial consideration must there be for patients with early dementia of unknown etiology [69].

The visually evoked potential is abnormal in patients with Huntington disease. Both early and late wave components are affected, and the averaged amplitude for the patients is reduced in comparison with normal control subjects. Despite striking attenuation and disorganization of the complex, latency of initial wave components is normal. The abnormality is not present in patients with a variety of other nonfocal cerebral disorders nor in children of patients with Huntington disease [70]. There are marked impairments of patients with HD in early visual sensory processing (early components). The early visual components show a significant latency shift (delay of about 50 milliseconds) in HD. In the search paradigms the P3 components differentiating target and standard stimuli is virtually absent in HD as is the ERP effect indexing word recognition. This is accompanied by a marked delay in search times and lower hit rates in the search tasks and grossly reduced recognition accuracy in the memory task. Deficits in visual search might be due to an impairment to deploy attentional resources across the visual field and/or an inability to control eye movements [71].

9. Huntington diagnosis

Huntington disease usually causes cognitive decline previously to motor symptoms. Studies performed in a HD animal model to assess this issue suggest that normal plasticity in prefrontostriatal circuits may be necessary for reliable and precise timing behavior. Furthermore, the behavioral analysis revealed poorer temporal sensitivity as early as 4 months of age, well before detection of overt motor deficits. At a later symptomatic age, animals were impaired in their temporal discriminative behavior [68].

10. Huntington early detection

It is well known that HD affects cognition earlier than motor system. The motor-evoked potential to burst stimulation is a suitable tool to evaluate motor synaptic plasticity. This might bring out clues about motor control decline related to HD before having symptoms of abnormal motor behavior [67].

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