Summary

In this short clinically oriented review, the value of electroencephalography (EEG) in the diagnostic evaluation of cognitive decline is discussed, based on the recommendations of the European and Dutch guidelines. In general, an EEG with diffuse slowing with or without focal abnormalities argues for the presence of an underlying neurodegenerative illness and against subjective memory complaints or a psychiatric illness such as a depression. The value of an EEG in the differential diagnosis between the most common causes of dementia is dependent on the specific clinical problem. One of the clinical problems in which EEG has the highest yield is the distinction between the two most common dementia types, i.e. Lewy Body Dementia (DLB) and Alzheimer’s Disease (AD): severe slowing of the background rhythm with a peak frequency in the theta frequency band (4 - 8 Hz) accompanied by frontal intermittent rhythmic delta activity (FIRDA) gives strong EEG support for DLB, whereas a diagnosis of AD is more likely when the EEG is normal or when only mild diffuse slowing is found. Furthermore, a normal EEG in an early onset dementia gives support for the diagnosis frontotemporal lobar degeneration. In addition, EEG is very useful when a metabolic, toxic or infectious encephalopathy is suspected. An EEG should be performed in subacute disease courses, with auto-immune encephalitis or Creutzfeldt-Jakob disease as possible causes, or when (temporal lobe) epilepsy is suspected. In conclusion, EEG is most valuable in a specific differential diagnosis together with the clinical context and other diagnostic tests. Distinct EEG patterns can then help to make one of the diagnoses a more or less likely cause of the patient’s symptoms.

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Key words: Electroencephalography, dementia, memory clinic, diagnostic tool

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Electroencephalography in the Differential Diagnosis of Dementia

Der Stellenwert der Elektroenzephalographie in der Differenzialdiagnose demenzieller Erkrankungen


This text is based upon a workshop during the 2016 annual meeting of the Dutch Clinical Neurophysiology Society.
L'électroencéphalographie dans le diagnostic différentiel des démences

Dans cette revue, nous discutons du rôle de l'électroencéphalographie (EEG) dans le diagnostic et l'évaluation clinique du déclin cognitif, en nous référant aux recommandations néerlandaises et européennes. D'une manière générale, un ralentissement diffus à l'EEG, avec ou sans anomalie locale, suggère la présence d'une maladie neurodégénérative sous-jacente, et parle contre un trouble subjectif de la mémoire, ou une maladie psychiatrique telle qu'une dépression. Le rôle de l'EEG dans le diagnostic différentiel des causes les plus courantes de démence dépend du contexte clinique. L'un des problèmes dans lesquels l'EEG est le plus à même de se révéler utile est la distinction parmi deux des causes les plus fréquentes de démence, c'est-à-dire la démence à corps de Lewy (DCL) et la maladie d'Alzheimer (MA): un ralentissement diffus marqué avec pic de fréquence dans la bande thêta (4-8 Hz), accompagné d'une activité delta rythmique intermittente au niveau frontal (FIRDA) suggère fortement une DCL, tandis que la présence d'une MA est plus probable en présence d'un EEG normal ou avec ralentissement diffus modéré. Par ailleurs, un EEG normal au cours d'une démence d'apparition précocé suggère une dégénérescence lobe fronto-temporale. L'EEG est également très utile si une encéphalopathie métabolique, toxique ou infectieuse est suspectée. Un EEG est recommandé en cas de progression lente si une encéphalite auto-immune, une maladie de Creutzfeldt-Jakob ou une épilepsie (du lobe temporal) sont une cause possible. En résumé, l'EEG peut s'avérer très utile dans certains diagnostics différentiels, en fonction du contexte clinique et en relation avec d'autres tests. Certains tracés EEG peuvent appuyer, ou contredire certains diagnostics suspectés.

Mots clés : Electroencéphalographie, démence, clinique de la mémoire, outils diagnostiques

Background

The diagnostic evaluation of patients with cognitive complaints, both in the Netherlands and in other (European) countries, is increasingly performed in specialized memory clinics and is often organized in the form of a one-day screening. The diagnostic decision making takes place at two different levels: the establishment of the presence or absence of the syndrome diagnosis “dementia” [1]; and the diagnosis of the underlying cause of the dementia, the “nosologic diagnosis”. The Dutch guideline “diagnosis and treatment of dementia” advises to perform additional assessments in the case of an established diagnosis of dementia, but with an uncertain nosologic diagnosis [2]. These may include MRI (or CT) imaging, but also electroencephalography (EEG), lumbar puncture or positron emission tomography (PET)/single-photon emission computed tomography (SPECT) scanning.

Several memory clinics offer EEG as an additional investigation, both as a standard examination during a day screening or as an additional test after the first assessment of the medical specialist [3]. The latest Dutch guideline on dementia which was published in 2014 gives recommendations when to perform an EEG during the diagnostic evaluation of cognitive complaints (Table 1). Important to note is that these recommendations are in line with the European guidelines on dementia and Alzheimer’s disease [4, 5]. Furthermore, it needs to be emphasized that these guidelines are aimed to give guidance to a broad range of professionals in dementia care, including primary care providers (e.g. general practitioner, specialized nurses), medical specialists (e.g. neurologists, nursing home physician specialists, geriatricians) and academic expertise centers. The first recommendation of the guideline, stating “not to perform an EEG on a routine basis during dementia diagnostic screening”, therefore needs to be interpreted in this context. A large proportion of the patients with dementia are elderly subjects with memory complaints, and there will be little doubt on the underlying disease, i.e. Alzheimer’s disease. This large patient group will be diagnosed and treated by the primary care physicians. The patient group that is referred to a memory clinic will therefore be a selected group, usually young, with more patients presenting with a nosologic dilemma. In these patients, the second and third recommendation of the guidelines will more often be applicable. These recommendations state to perform an EEG when there is a suspicion for Creutzfeldt-Jakob disease or temporal epilepsy. It can also be considered when in doubt of Lewy Body Dementia and when the differential diagnosis includes a metabolic, toxic or infectious encephalopathy. In addition, an EEG can provide support for or against a diagnosis when there is doubt on the existence of the underlying cause of dementia, depending on the differential diagnostic considerations. However, to be able to assess in which differential diagnostic considerations an EEG may be useful and to be able to actually differentiate between two diagnoses, knowledge on the different EEG patterns in the specific diagnoses is highly important.
This overview will therefore address the following question: “what are the EEG patterns observed in the most prevalent dementia diagnoses and what is the value of EEG in several of the most common diagnostic problems in a memory clinic?”. The recommendations of the guidelines will be further explained based on (recent) literature and complemented with expert opinion and illustrative cases. This text will mainly focus on straightforward visual assessment and spectral analyses of the EEG signals. Recently gained knowledge on more advanced techniques, such as functional connectivity analyses, machine learning algorithms or magneto-encephalography, will not be the focus of this review as they have no additional value in clinical practice at the moment. However, we will highlight some of these techniques as they are promising tools for clinical diagnostic use in the (near) future.

**EEG patterns in dementia**

**Alzheimer’s disease**

Alzheimer’s disease (AD) is the most prevalent dementia diagnosis. The a priori chance of this diagnosis in a specialized memory clinic is 30% [3]. In the typical form of AD there are disturbances in several cognitive domains, but the presence of slowly progressive episodic memory decline is most outspoken [1]. Atypical phenotypes of AD are posterior cortical atrophy, which is characterized by higher order visual disturbances, the variant of AD with logopenic aphasia as the main characteristic, and the frontal variant of AD, where the typical behavioural changes and executive dysfunction may resemble fronto-temporal lobe dementia [6, 7].

EEG findings in AD have often been described and consist of global slowing of the posterior dominant rhythm [8 - 11]. In early stages of the disease, relative theta power increases together with a decrease in relative beta power and slowing of the peak frequency (Figure 1). In later stages, further slowing occurs reflected by additional decreases in relative alpha power and increases in relative delta power [8]. However, in early stages of dementia the EEG can also be normal, especially in patients whose symptoms start at a later age (late onset dementia; defined as > 65 years) [12]. A normal EEG in an elderly patient with clinically evident dementia is in fact very likely due to AD. On the other hand, a normal EEG is less likely in patients with a symptom debut at a younger age (early onset; defined as < 65 years). Moreover, these younger patients have more severe diffuse and focal abnormalities than those with late onset AD. In this study, the positive predictive value of an abnormal EEG is 75 - 80% for the distinction between the total group of AD patients and cognitive normal individuals [12]. Furthermore, the severity of the EEG abnormalities is correlated with the severity of clinical symptoms and with the speed of future cognitive decline [8, 13].

In short, diffuse slowing of the EEG supports the diagnosis of AD, but a normal EEG does not exclude AD as a diagnosis. When the patient has an early onset of the cognitive symptoms, a normal EEG is less likely than when the onset is at an older age.

It is important to note however, that the value of EEG is higher in the clinical context and within a specific clinical differential diagnosis. For example, if a 70-year old man with evident cognitive disturbances including memory complaints has a normal EEG, it is more likely that the patient has AD as underlying diagnosis than dementia with Lewy Bodies, vascular dementia or Creutzfeldt-Jakob disease. Or: when a 60-year old patient with cognitive complaints and behavioural changes has a severely diffusely abnormal EEG, this argues for a diagnosis of AD with frontal characteristics and against the behavioural variant of fronto-temporal dementia. The EEG patterns in other causes of dementia are described below.

**Table 1:** Recommendations of Dutch guideline “diagnosis and management of dementia” (2014): electroencephalography (EEG) [2]

1. Do not perform an EEG on a routine basis during dementia diagnostic screening
2. Consider to perform an EEG when in doubt of the diagnosis Lewy Body Dementia and when a metabolic/toxic/infectious encephalopathy is suspected. When the diagnosis Alzheimer’s Disease is suspected, an EEG can be performed dependent on the differential diagnosis.
3. Perform an EEG when there is a suspicion for Creutzfeldt-Jakob disease of (temporal) epilepsy
Dementia with Lewy Bodies

Dementia with Lewy Bodies (DLB) is, behind AD, the most prevalent cause of dementia. The core symptoms of DLB are fluctuations in cognition, attention and alertness, repetitive visual hallucinations, and parkinsonism [14]. As especially in the early stages of the disease not all core symptoms may be evident, and its clinical picture often overlaps with that of AD, the distinction between the two diseases is sometimes difficult. As DLB lacks specific neuroimaging features that can support the diagnosis, EEG is the test of choice in this clinical dilemma. EEG abnormalities consisting of “prominent slow wave activity with temporal lobe transient sharp waves” are included in the diagnostic criteria of DLB as a suggestive feature [14].

Several studies have compared EEG patterns of patients with DLB and AD. In DLB, the slowing in the background rhythm is mostly more severe and more variable than in AD. Its peak frequency often falls in the theta range (13 of 18 pathology-confirmed DLB patients) and there is more admixture of delta activity in addition to theta activity than in AD [15, 16]. Besides the outspoken diffuse slowing of oscillatory activity, reactivity to eyes opening and closing is more severely affected and focal temporal abnormalities are more common. Finally, frontal intermittent rhythmic delta activity (FIRDA) has been described to be distinctive between the diagnoses as it is present in 17.2 - 33.3% of DLB patients compared to only 1.8 - 2.3% of AD patients [17, 18] (Figure 2). Two studies have described that the “Grand total EEG score” is a useful tool for the distinction between both diseases with a sensitivity of 72 - 79% and a specificity of 76 - 85% [17, 18]. This semi-quantitative visual scale (range 1 - 31) scores the background activity (peak frequency, diffuse slow wave activity, reactivity), focal abnormalities and paroxysmal and sharp wave activity, and is easy to apply in the clinical practice. In a large cohort of memory clinic patients, only 3% of the (not pathologically confirmed) DLB patients had a normal EEG [19].

A normal EEG or an EEG with only mild abnormalities therefore argues strongly against the diagnosis of DLB. Moderately severe diffuse slowing with focal abnormalities and the presence of FIRDA argues for the diagnosis of DLB and against AD.
Fronto-temporal lobar degeneration

The most common form of fronto-temporal lobar degeneration (FTLD), the behavioural variant fronto-temporal dementia, is characterized by dementia and in particular disturbances in behavior and executive functions [20]. It is associated with atrophy and/or hypometabolism (MRI and PET/SPECT, respectively) in the frontal/anterior temporal lobe. The other variants of FTLD, i.e. non-fluent progressive aphasia and semantic dementia, have language problems as debuting symptoms [21]. In the clinical setting, the distinction of FTLD with psychiatric illnesses or AD may be challenging.

Generally, normal or only mildly abnormal EEG patterns with preserved posterior dominant rhythm are found in patients with FTLD, even in the case of clinically evident dementia [22, 23]. In the last but one set of diagnostic criteria, a normal EEG was described as one of the supportive features of FTLD [24], but in the latest criteria EEG as a supportive test is not included anymore [20]. In a memory clinic population of a university hospital, a large majority (77%) of the FTLD patients had a normal EEG or an EEG with only mild focal abnormalities [19]. In a small group of pathology confirmed FTLD patients (n = 24), EEGs were described based on the appearance of the posterior dominant rhythm as normal, mildly abnormal (slowing of posterior dominant rhythm), or severely abnormal (sparse or absent posterior dominant rhythm, predominantly theta/delta activity). In 42% patients, a normal EEG was found, whereas only a minority (n = 2) had severe EEG abnormalities [23]. Both of the patients with severe EEG abnormalities had the temporal variant of FTLD. Furthermore, this study also found that the severity of the EEG abnormalities was associated with the severity of the dementia.

Vascular dementia

The clinical criteria for vascular dementia (VaD) comprise the diagnosis of dementia, the presence of large vessel or small vessel cerebrovascular disease demonstrated on brain imaging and a (time) relation between those features. The course of the disease may be associated with an abrupt start or with a stepwise deterioration [25].

In a study of 53 VaD patients, only a small proportion had a normal EEG (11%) and almost half of the patients with an abnormal EEG had both diffuse slowing and focal abnormalities [19]. Focal abnormalities are especially associated with large-vessel infarcts, while patients with subcortical ischaemic VaD, based on the presence of vascular white matter hyperintensities and lacunar infarcts, have an evidently diffusely slowed background pattern. In the distinction with cognitively

Figure 2.
A 68-year old male patient with fluctuating memory complaints and mild extrapyramidal signs that started a couple of years ago. Clinically, a DLB or AD was suspected as cause of his symptoms. His EEG (23 channels; source derivation) was moderately severely abnormal with an evident slowing of the background rhythm (peak frequency 6.3 Hz, only theta-delta activity at the posterior EEG channels) and FIRDA. This EEG pattern argues in favour of a diagnosis of DLB.
normal subjects, a sensitivity of 0.82 and a specificity of 1.0 was found for lower relative beta power (< 0.14) and a sensitivity of 0.94 and a specificity of 0.88 for higher relative theta power (> 0.20) [26]. However, in practice, the clinical problem is often the distinction with AD, instead of with cognitively normal subjects. As EEG patterns of VaD and AD may largely overlap and as neuro-imaging is key in the distinction between those two diagnoses, EEG does not have a central role in this specific differential diagnosis.

Creutzfeldt-Jakob disease

Sporadic Creutzfeldt-Jakob disease (CJD) is a fast progressive dementia with at least two of the following symptoms: myoclonus, visual or cerebellar symptoms, (extra-)pyramidal signs and/or akinetic mutism. For the diagnosis probable CJD at least one of the following typical abnormalities with regard to additional examination should be present: a typical EEG pattern, the presence of 14-3-3 protein in cerebrospinal fluid, or typical MRI abnormalities [27].

The typical EEG pattern in CJD consists of periodic sharp wave complexes (PSWC). These are strictly defined as generalized and/or lateralized periodic complexes with a duration of 100 - 600 ms and an inter-complex interval between 500 - 2000 ms. The inter-complex intervals of at least five consecutive complexes should differ less than 500 ms [28]. In two studies in which 214 respectively 150 pathologically confirmed CJD patients were compared to 77 respectively 56 controls (clinical suspicion of CJD but no evidence for CJD at autopsy), a relatively low sensitivity of 44 - 64% and a high specificity of 91 - 92% was found for EEG [28, 29]. The low sensitivity can be explained by the fact that in the early phases of the disease the EEG only shows non-specific diffuse slowing with occasional FIRDA. The typical PSWC is thus a relatively late sign in the disease course and becomes evident around twelve weeks after the onset of the first symptoms (see Figure 3). Moreover, the EEG has been shown to be positive in only a subset of CJD patients (usually molecular subtypes MM1 or MV1). In the last stages of the disease the EEG pattern changes into a low-voltage pattern and finally an iso-electric pattern. False positive findings sporadically occur in fast progressive AD, DLB, or limbic encephalitis [29, 30].

In short, an EEG with PSWC in a patient with fast progressive dementia points strongly towards CJD. When PSWC are not seen, one can consider to repeat the EEG after a couple of weeks.

Other neurological disorders

Temporal epilepsy

Temporal lobe epilepsy is an important diagnosis to consider in the differential diagnosis of dementia, as it theoretically is a treatable cause of the cognitive complaints. The Dutch and European guidelines for dementia advise to perform an EEG when (temporal lobe) epilepsy is suspected. As the clinical signs during temporal lobe seizures are often very subtle and could exist of only episodic amnesia without any other symptoms, this diagnosis can easily be missed [31, 32]. On the other hand, it is often not clear whether the epileptiform EEG discharges are the actual cause of the cognitive complaints and whether the use of anti-epileptic drugs will diminish the symptoms.

A case series described four patients with temporal lobe epilepsy as the cause of subacute cognitive complaints, mostly memory problems [31]. The EEG showed left temporal spikes in three patients and left central spikes in the fourth patient. None of them had clinically evident epileptic seizures, but in all of them the cognitive complaints disappeared or improved after treatment with carbamazepine. In a prevalence study of 1674 memory clinic patients who all underwent a 20-minute routine EEG during a diagnostic day screening, epileptiform EEG discharges were found in 42 patients (3%) [33]. These abnormalities were all focal and mainly localized in the temporal lobes. Some of these patients were already diagnosed with epilepsy, but 31 patients did not have a previous diagnosis of epilepsy. In six of these patients, a new diagnosis of epilepsy was made based on the combination of clinical symptomatology and the EEG abnormalities. Of the remaining 25 patients, a different correlate for the epileptiform discharges could be determined in 13 patients, such as the use of atypical antipsychotic drugs, migraine, a history of cerebrovascular accident, head trauma, or anoxic injury. Five patients were treated with an empirical treatment of anti-epileptic drugs based on clinical decision making, but in this retrospective study none had a more favourable course of the cognitive symptoms than untreated patients.

In addition to epilepsy as a rare cause of cognitive decline, patients with dementia have a 5 - 10 times increased risk of epilepsy compared to the general population in comparable age categories. In a large retrospective study with 1738 memory clinic patients, 63 patients (3.6%) were found to have epileptic seizures (mostly complex partial seizures) [34]. The underlying neurodegenerative diagnoses of these patients were mainly mild cognitive impairment, AD, VaD, DLB. When treated with anti-epileptic drugs, 79% of the patients had a good response on the seizures with seizure freeness or less than three seizures a year [34].
Figure 3.
A 62-year old female patient with left sided hemi-ataxia, gait problems and dysarthria that developed within 2 months. After a couple of weeks, progressive confusion and speech and swallowing problems started. The differential diagnosis consisted of auto-immune encephalitis or Creutzfeldt-Jakob disease. Her first EEG (23-channels; source derivation) shows remarkable but nonspecific diffuse slowing. A repeated EEG after one week, showed typical generalized periodic sharp wave complexes providing strong support for the diagnosis of CJD.
Taken together, temporal epilepsy is a very rare cause of cognitive disturbances, but the possible favorable reaction to anti-epileptic medication indicates that this diagnosis should be considered when there is an atypical course or when there are episodic cognitive complaints.

**Auto-immune encephalitis/encephalopathy**

When a patient has fast progressive cognitive disturbances that develop within days or weeks, limbic encephalitis should be included in the differential diagnosis. In a large proportion of these patients, the cognitive problems are associated with psychiatric symptoms, epileptic seizures or neurological impairment. In recent years, several antibodies have been discovered that can cause a fast progressive dementia: NMDAR, AMPAR, Caspr2, DPPX, GABABr, L1, Hu, GlyR [35, 36]. The findings in EEG have only been described in case reports. Although EEG findings are rather non-specific, they are mostly quite outspoken: prominent diffuse slowing (theta and delta waves) and temporal/frontal sharp waves or spikes or with lateralized periodic discharges (see Figure 4) [37]. In NMDA-encephalitis however, “extreme delta brushes” are a typical/pathognomonic EEG phenomenon [36, 38].

**Future techniques**

For clinical purposes, only visual analysis of the EEG has been used up to now, sometimes aided by quantitative spectral analyses techniques. For more than a decade however, it has been known that EEG contains more information than can be seen with “the naked eye” and new techniques have been developed to improve distinction between dementia types. A few of these new developments will be highlighted here, as they have potential to become a valuable clinical tool in memory clinic patients in the (near) future.

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*Figure 4.*

A 67-year old female patient with a history of recurrent major depressive episodes, presented with fast progressive memory complaints, depressed mood, weight loss, and episodes of malaise. There was doubt on whether her symptoms were of organic or psychiatric nature. Her EEG (23-channels, source derivation) showed both diffuse slowing of the background rhythm (peak frequency 7.3 Hz) and focal abnormalities consisting of delta waves in the left more than right temporal lobes. This EEG argues strongly for an organic substrate of her complaints and further evaluation for subacute cognitive decline was performed. A diagnosis of anti-AMPA encephalitis was eventually made and the patient was treated with corticosteroids and intravenous immunoglobulins.
First, the concept that the brain is a complex network, in which cognitive processes rely on the integrity and optimal organization of dynamic communication between brain areas, has been widely accepted in recent years. A large amount of literature involving functional connectivity and network analyses has provided evidence for disruption of the underlying functional network in many distinct brain disorders including dementia [39, 40]. Moreover, several studies have compared dementia types with respect to brain connectivity and network changes and described that network disruption in the specific dementia types, e.g. AD, DLB and FTLD, can manifest itself in distinct ways [41 - 43]. Second, these network features may also be combined with simple spectral or visual EEG analyses to increase classification accuracies between patient groups. When modern algorithms referred to as machine learning techniques are used, the features that perform best at distinguishing groups are extracted in an automatic way, and these methods have yielded accuracies around 80% - 90% for the distinction between AD and healthy controls [44]. It may also be worthwhile to combine EEG with features of other modalities such as MRI or cerebrospinal fluid, to reach optimal discriminatory values [45]. Finally, magneto-encephalography (MEG) is a technique that measures the magnetic fields of the electric neuronal activity and may provide more information than standard EEG, as it has a superior spatial resolution and is able to measure oscillatory activity of deeper (subcortical) regions that are inaccessible with EEG [46, 47]. For example, signature brain regions in specific dementia types, such as the deeper lying hippocampus in AD, which cannot be measured by EEG, can be targeted specifically in MEG. This study found that the peak frequency of the hippocampal activity correlated better with cognitive test scores in AD patients than cortical activity [48]. Although MEG is spatially better and provides more information about the underlying pathophysiological mechanisms of the disease and is therefore a promising future diagnostic tool.

Conclusion and discussion

The studies described in this review have investigated EEG mostly as an isolated diagnostic tool in the diagnosis of underlying causes of dementia. In clinical practice however, EEG has the highest value when it is used in clinical context and in combination with other diagnostic tests [49]. EEG can then be of help in a specific differential diagnosis to make one of the diagnoses a more or less likely cause of the patient’s symptoms.

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