How electroencephalography assisted in the diagnosis of mild cognitive impairment due to Alzheimer's disease.

Introduction

Alzheimer's disease (AD) presents an immense current and future healthcare burden. AD is the most common form of age-related dementia; in the global north, dementia prevalence is 24-33% of people aged 85 or older (Blennow et al., 2006). However AD is no longer a public health issue restricted to higher income countries Increasing life expectancy in the global south has led to over half (58%) of the present global dementia burden being carried by lower- and middle-income countries (Alzheimer's Disease International, 2015). Moreover, prevalence is increasing with population aging - in the UK, for example, dementia prevalence is set to increase by 40% over the next 12 years (Prince et al., 2014). As such, an affordable diagnostic tool for the improved management of patients and the development of disease modifying therapies is greatly needed (Hampel et al., 2010).

AD causes a slow, progressive decline in cognitive function. Along this continuum are three clinically separable phases: an asymptomatic phase, a symptomatic predementia phase, and, finally, dementia onset. Whereas clinical diagnosis of AD upon dementia onset is very accurate (between 91 and 98% (Blennow et al., 2006)), diagnosis of the symptomatic predementia phase lacks consistency; both clinically, and in AD research (Stephan et al., 2013). The symptomatic predementia phase is known, and referred to hereafter, as mild cognitive impairment (MCI). MCI is not only poorly diagnosed but, on diagnosis, is also poorly categorised according to its aetiology – be it normal ageing, AD, or other age-related dementias (Stephan et al., 2013). The ability to accurately diagnose MCI due to AD would present an important advancement in the clinical management of AD cases and research into disease modifying therapies.

In 2013, Vrije Universiteit, Amsterdam published research on the use of electroencephalography (EEG) in predicting MCI due to AD. This pioneering study by Poil et al., (2013), although not highly cited, is the latest and most convincing account supporting the case for widespread use of EEG for preclinical AD diagnosis. In this study, 86 patients diagnosed with MCI underwent resting state EEG recordings. Patients were followed up

clinically for a period of two years, after which, a diagnosis of AD or stable MCI was made. Data from 34 patients in the group was used to build a statistical classifier to differentiate stable MCI from MCI due to AD, using 6 EEG parameters. This classifier was then tested on the initial data of 30 separate participants. It identified 88% of those who progressed to develop AD (88% sensitivity) and 82% of those who would not progress to develop AD (82% specificity).

This essay will outline how it was that Poil et al. (2013) were able to use EEG to identify, with a sensitivity and specificity higher than some screening tools currently in use (such as the cervical smear test (Barut et al., 2015)), patients that went on to develop AD. The essay is divided into two sections. Firstly, it will discuss how EEG, as an imaging modality, is well suited to detecting pathological changes in AD. Secondly, it will discuss how the technical details of Poil et al's work allowed them, albeit retroactively, to make accurate diagnoses of MCI due to AD.

Alzheimer's disease as observed by EEG

EEG can be used to observe three levels of brain organisation that are disturbed in AD; namely: synaptic transmission, neural circuitry, and global network changes.

Synapses

EEG measures electrical activity caused by dipoles formed in the extracellular matrix around pyramidal neurons. Specifically, the dipoles observed are those originating from apical dendrites. They occur due to either the cellular influx of positive ions as a result of excitatory postsynaptic potentials or the cellular influx of negative ions and efflux of positive ions as a result of inhibitory postsynaptic potentials (Silva, 2009). These signals can be detected by individual contacts on the scalp for two reasons: firstly, pyramidal cell dendrites are organised, mostly, perpendicularly to the surface of the scalp; and secondly, the primate neocortex is organised into minicolumns of approximately 80-100 neurons that are grouped, via collateral connections, to form cortical columns (Mountcastle, 1997). This second point means that there is a synchrony in pyramidal activation and the dipoles generated resulting in an observable electrical field.

Neuropathology in AD is classically characterised by widespread neuronal cell loss, neurofibrillary tangles (formed by phosphorylated tau protein filaments) and senile plaques (formed by extracellular amyloid β deposits) (Citron, 2010). However, as shown by Terry et

al., (1991) synaptic density is also reduced in the brains of AD patients at post mortem. Moreover, a loss of synaptic density, and not increased neurofibrillary tangles or senile plaques, was shown to strongly correlate with performance in tests of cognitive function. As well as being clinically relevant to AD, synaptic change is also an early development in the neurodegenerative disease (Palop and Mucke, 2016).

Indeed, this can be observed in-vitro. Synaptic activity, particularly at low-pass-filter synapses produces amyloid plaques from the protein fragment amyloid β (Aβ) (Dolev et al., 2013). In turn, Aβ acts to regulate synaptic activity. By inhibiting Aβ degradation, Abramov et al., (2009) observed that raised synaptic cleft Aβ concentration increases vesicular neurotransmitter release and hence presynaptic strength increased 2.8-fold. Conversely, Kamenetz et al., (2003) found that, in hippocampal pyramidal neurons, overexpressing amyloid precursor protein in a minority of cells caused widespread synaptic depression over a longer timescale. This depression was dependant on gamma-secretase, an enzyme that processes amyloid precursor protein to form Aβ.

The above results show that departure from normal Aβ homeostasis can rapidly change synaptic functioning in cortical pyramidal neurons. As such, we can see how EEG would be appropriate for detecting early changes in AD.

Local Networks

A Fourier transformation converts the raw EEG signal into a power spectrum showing the contribution of five frequency bands to the amplitude of the overall signal. These frequency bands (or oscillations), in order of fastest to slowest, are named gamma, beta, alpha, theta and delta (Buzsaki, 2006). There is debate as to where in the cortex these oscillations come from, and which cortical networks give rise to them. An early interpretation of the slower frequencies was that they originated from further-away cortical structures whose signal was slowed by propagation through more brain medium (Voss and Clarke, 1976). Although brain medium does effect EEG signal, it cannot explain why slower frequencies are synchronous over a large neocortical area whereas faster frequencies are not. As such, it would seem logical that different cortical structures are responsible for producing the different rhythms. This has been observed in hippocampal slices of rats where three different oscillations are in operation that are generated independently (Penttonen and Buzsáki, 2003). Rather than simply being a by-product of cortical activity, the frequency of different neural oscillations are thought allow cell assemblies to communicate with, and influence other cell assemblies,

which in turn facilitates brain function (Buzsáki and Draguhn, 2004). Possible evidence for this lies in the linear natural logarithmic relationship between the different frequency bands. This relationship occupies a middle ground between complete phase synchrony of different oscillating networks and complete asynchrony – the natural logarithmic relationship allows networks to easily flux in and out of phase, enabling timely, sufficient and necessary communication (Penttonen and Buzsáki, 2003).

There is evidence in AD that this natural logarithmic relationship between oscillators is disturbed. Epidemiologically, it has been observed that AD confers a risk of epilepsy – a neurological condition caused by hypersynchrony of neural networks due to excitatory transmission. Hyperactive networks leading to seizure in AD largely originate in the hippocampus, an area with dense recurrent excitatory projections that experiences marked damage early on in the disease trajectory (Le Duigou et al., 2014; Noebels, 2011). Additionally, interactions between specific network oscillations are dysfunctional in transgenic mouse models of AD (Goutagny et al., 2013). Cross-frequency, phase-amplitude coupling between gamma and theta oscillations is recruited, in the hippocampus, during difficult working memory tasks (Axmacher et al., 2010). Goutagny et al., (2013), identified that this coupling was persistently altered in in-vitro hippocampal preparations of an AD transgenic mouse model. Importantly, these alterations occurred before significant amyloid load (but were nonetheless age-dependant). Lastly, interneuron dysfunction, though not, as yet, clearly implicated in AD, may play an important role. Interneurons have important clocking action that helps regulate oscillatory rhythms through GABAergic innervation of pyramidal neurons (Palop and Mucke, 2016). Interneuron dysfunction in AD is evidenced by depletion of Nav1.1 in an AD mouse model. Nav1.1 is a voltage gated sodium channel subunit that is predominantly expressed on interneurons. Importantly, these mice also show epileptiform activity (Verret et al., 2012).

Therefore, a bulk of evidence supports that network alterations likely play an early, and clinically relevant role in AD. As such, at another level of brain organisation, we see how EEG would be able to observe these changes.

Global network changes

As mentioned above, it is the communication between different brain areas that allows for cognition to occur. The evolutionary drive for this to be done at low metabolic cost has favoured small world network organisation in the adult brain – that is, highly interconnected

local circuitry with sparse long-range connections (Watts and Strogatz, 1998). This structural organisation is reflected in the distribution of oscillations in the cortex. Slower oscillations are better suited to long range communication, and so span a wider area, as information can travel further with each cycle. Short range communication however can occur at high frequencies as the temporal constraints are smaller (Buzsaki, 2006).

In AD the general pattern of EEG changes across the cortex is an increase in power of low frequency oscillations and a decrease in power of higher frequency oscillations (Nimmrich et al., 2015). This change is reflected again in coherence analysis of EEG signal which shows decreased coherence between high frequency oscillators but unchanged or even increased coherence of low frequency oscillators (Jeong, 2004). The integration of structural and functional changes in AD pathophysiology is an ongoing research challenge. While EEG changes in AD would logically cause an increase in synaptic path length, in actuality, the reverse is observed (Sanz-Arigita et al., 2010). However, network changes in AD *are* mainly driven by changes to highly interconnected areas which aligns with general pattern of EEG changes (Stam et al., 2009). It may be that differences in disease severity between patient populations in different studies has driven this confusion. Longitudinal functional and structural brain imaging would resolve this issue.

The evidence is thus less clear, than for network and synaptic alteration, on how appropriately EEG represents the global brain alterations in AD. However, given EEG measures the interconnectedness of brain areas, embedded within the signal collected at scalp electrodes *will be* information on the global, brain organisation changes in AD. The challenge, therefore, is not to improve the imaging technology, but rather with the interpretation of its results. The next section will examine how the EEG phenomenon can be used without requiring results to be interpreted.

The diagnosis of MCI due to AD by Poil et al., (2013)

This section looks at how Poil et al., (2013) were able to retroactively diagnose MCI due to AD from preclinical EEG recordings. Firstly, the importance of how EEG features were selected for diagnosis will be discussed. Secondly, this section will outline how an appropriate population fit was generated for the diagnostic tool. Lastly, this section will look critically at how Poil. et al., (2013) could have further improved their diagnoses.

Selection of EEG features to generate a diagnostic tool

Early work into the diagnosis of MCI due to AD, as done by Jelic et al., (2000), used only a few EEG measures to make prognoses (in this case changes to the relative power of theta and alpha frequency bands). Restrictions on the number of EEG biomarkers that could be included in the diagnostic possibly resulted from having a smaller literature base to draw from. Another factor restricting the use of multiple EEG features in diagnosis was a lack of more sophisticated statistics that could model large numbers of features in generating a biomarker. The benefit of using more features to generate a diagnostic tool, as done by Poil et al. (2013) (who used six), is that features that only explain a small amount of the variance between at-risk and non-at-risk groups can be included to generate an overall high specificity and sensitivity.

Other studies have focussed exclusively on the EEG markers of AD that are supported by a large literature base, for example the slowing of the alpha rhythm peak below 8 Hz (de Waal et al., 2011; Kramberger et al., 2013; Rodriguez et al., 2011). This focus on the content validity of EEG as a diagnostic tool does not acknowledge the inconsistencies that exist in the literature. For example, as discussed above, the characteristic network changes that occur in AD are not supported by graph analyses on the effects of AD on brain network characteristics (Nimmrich et al., 2015; Sanz-Arigita et al., 2010). Additionally, earlier it was discussed that slow oscillations are not *simply* a manifestation of the effect of electrical signals propagating through brain medium (Buzsaki, 2006). However, the brain medium, dura, bone, and skin that an electrical signal travels through to reach an electrode *may* affect the signal in unpredictable ways (Clarke et al., 2016; Voss and Clarke, 1976). As such, after understanding, as outlined above, that the EEG signal will *somehow* convey the pathological changes that occur in AD, a diagnostic tool can confidently be created using EEG; there need not be, however, a rigorous rational for each EEG feature it uses. Poil et al., (2013) achieve this using a machine-learning (genetic search) strategy to identify the best possible set of biomarkers out of a possible 177 extracted from each EEG trace. The set of EEG biomarkers was altered using 4 different rules a total of 5 times in each "generation". This created 20 new sets of biomarkers that were compared to the optimal biomarker in the previous set. The genetic algorithm carried out 100 generations. Testament to the importance of using this method was the presence of 4 of 6 diagnostic EEG changes being in the beta frequency band – which is a less discussed frequency in relation to AD (compared to gamma, alpha and theta frequencies) (Palop and Mucke, 2016; Walsh et al., 2017).

Fitting their diagnostic model to the wider population

Poil et al., (2013), importantly didn't overfit their classifier. If enough biomarkers are included it is possible to create a diagnostic tool that separates two groups perfectly, however this tool will not be generalisable to the general population. As such, researchers tested the classifiers generated by the genetic search strategy on a second set of EEG traces taken at a different time. This technique meant that the final, best, classifier had a predictive validity that enabled it to diagnose MCI due to AD in the separate, test population. Indeed, although other studies have employed similar machine-learning techniques to generate a diagnostic tool, and yielded higher sensitivity and specificity, they did not train and test their classifiers using separate data – so there is no indication of how their classifiers would perform on a different population (Moretti et al., 2011; Rossini et al., 2008). This is a similar problem to that of "double-dipping" present in the wider neuroimaging literature which has lead to suspiciously high correlations being generated in statistical analyses (Kriegeskorte et al., 2009).

Further improvements in diagnosing MCI due to AD using EEG

To accurately answer the question of how EEG assisted in the diagnosis of a patient it is important to look at how its use in diagnosis could be improved. Poil et al., (2013) were generating a classifier using a small sample size (n = 34), as such they were at risk of creating a model that overfit its training population. If the study was repeated using a larger sample size, researchers could include demographic variables within the model which would likely increase specificity and sensitivity. One obvious variable would be age. For example, de Waal et al., (2011) showed in a large sample (460 probable AD patients) that younger AD patients showed more prominent focal and diffuse EEG abnormalities. Another additional variable to include would be cognitive markers. For example, the mini mental state examination (MMSE) can diagnose mild dementia with a specificity and sensitivity of 100% and 55% respectively (Sabe et al., 1993). Although the sensitivity of the MMSE is low, this may not matter if used as one variable in a diagnostic tool.

Of course, any number of other variables could be included in a classifier such as genetic background, other neuroimaging results (such as structural magnetic resonance imaging). However, I think it important to stress that how, Poil et al., (2013) assisted in the diagnosis of AD in an affordable way (an EEG machine costs at least 10-fold less than an MRI scanner). This point is especially pertinent given that most of the AD burden currently lies in lower to middle income countries (Alzheimer's Disease International, 2015).

Conclusion

There is a current pressing need to be able to distinguish MCI due to AD from stable MCI. Considering this, the present essay addressed the question "how EEG assisted in the diagnosis of MCI due to AD" by focussing on one research group who, albeit retroactively, used machine-learning and EEG to effectively diagnose MCI due to AD. The question of *how* EEG assisted in this diagnosis was addressed from two directions. Firstly, the essay looked at how the EEG phenomenon is a manifestation of activity within the structures that are damaged in AD – and thus, as an imaging modality able to assist diagnosis. Secondly, this essay examined how EEG features, identified, and tested using machine-learning, can model the difference between two patient groups such that it can be used as diagnostic tool. This supports EEG being developed as diagnostic tool to be used in a clinical setting and to identify sample populations in AD research.

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