Final Report

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Title of Project: Electroencephalogram (EEG) in autoimmune encephalitis diagnosis and prognosis.

Summary
Autoimmune encephalitis (AE) is a rare brain disease that results when the body's immune system mistakenly attacks the brain leading to inflammation and injury. AE causes a range of disabling symptoms such as memory loss, personality and mood changes, involuntary movements, imbalance, and seizures. Some seizures can be so severe that the patient needs to be placed into an induced coma to stop them. Even once the inflammation has been treated and the patient recovers from the initial illness, many will have long-lasting symptoms. In fact, around one third will develop ongoing seizures (a condition known as epilepsy) and, in many cases, seizures recur despite treatment with anti-seizure medications (drug resistant epilepsy). This has a significant impact on patients' quality of life, engagement in social activities, education and employment. Of note, AE is not just one disease, but a group of different diseases caused by the abnormal immune attack on the brain. AE subtypes vary in terms of symptoms, severity and long-term consequences. Furthermore, individual patients within any one AE subtype will have different disease severities.

Electroencephalography (EEG) is a technique that measures brain electrical activity which can change in brain disease. It gives a real-time assessment of brain dysfunction and seizure risk. Given that EEG signals change depending on disease and severity of illness, they may be useful in subtyping disease, assessing seizure risk and potentially predict outcomes. For instance slower EEG rhythms ("delta" and "theta" frequencies) relate to brain disease.

AE is a rare disease and requires a multicenter approach to collect enough data for meaningful analysis. The Australian Autoimmune Encephalitis Consortium (AAEC) coordinated by Monash University is a collaboration involving 14 health systems across Australia that collects AE patient data.

This study aimed to collate and analyse EEG data gathered from AAEC patients to identify changes associated with disease subtype, clinical findings and prognosis. In particular, an automated EEG analysis program (Persyst®) was used to provide quantitative EEG analysis.

Hypothesis vs Findings
Firstly, we hypothesised that EEG signals would correlate to imaging findings. In anti-LGI1 autoimmune encephalitis, abnormal imaging findings (MRI scans) were often predominantly

seen on one side (i.e. “lateralised” to the right or left brain hemisphere). Relative EEG asymmetry index (REASI) which can help to lateralise EEG signals at specified frequencies can also be used to determine if specific frequencies are more prominent on one side of the brain compared to the other. Interestingly, REASI in the delta frequency band (chosen given it often reflects disease) did not correlate with MRI findings. Given MRI shows gross structural abnormalities and EEG reflects brain function, this suggests that abnormal brain functioning in autoimmune encephalitis may not always be entirely reflected by brain imaging.

Secondly, we hypothesised that EEG signals may have diagnostic utility. We measured several EEG parameters (“delta power”, “theta power”, “alpha power”, beta power”, “alpha delta ratio”) in electrodes over various brain regions (left and right hemisphere, left and right anterior quadrants, left and right anterior temporal). In our anti-LGI1 autoimmune encephalitis cohort, we did not find any lateralising differences in these parameters. That suggests that the disease is just as likely to affect either/both hemispheres.

Finally, we hypothesised that EEG parameters correlated with clinical severity and outcomes. We found an inverse association between left temporal ADR and the patient’s modified Rankin Scale (mRS) nadir in anti-LGI1 autoimmune encephalitis. This association was not seen for hemispheric ADR nor anterior quadrant ADR. Of note, lower ADR correlates with increased brain dysfunction and higher mRS indicates poorer patient functional status. Anti-LGI1 autoimmune encephalitis is known to affect the temporal lobes and this shows that EEG findings may not just identify regions of dysfunction but also the severity of that dysfunction. However, EEG parameters did not correlate with 12 month follow-up mRS.

Unanswered Questions

Given the rarity of this disease, accumulation of a larger data set is required to expand on and confirm the findings to date. This will be continued through the work of the AAEC. Ongoing studies to: compare EEG findings between different autoimmune encephalitis subtypes as well as with controls (e.g. temporal lobe epilepsy or non-epilepsy diagnoses); assess correlation of EEG signals with disease parameters and outcomes (e.g. development of epilepsy, cognitive outcomes) will help to further delineate the role of EEG in autoimmune encephalitis diagnosis and prognosis.

What these research outcomes mean

We show that EEG analysis provides unique information on brain dysfunction in addition to imaging techniques and this correlates with disease severity. It also aids in the identification of regional abnormalities which may help explain presenting symptoms. Further studies are required to compare EEG findings with control populations to delineate the diagnostic potential of these findings. This is important as biomarkers that help with the early diagnosis of autoimmune encephalitis allow for earlier initiation of immunotherapy and improved patient outcomes. Overall, this research has set the groundwork (EEG database set up, analytical skills) for ongoing studies into the utilization of EEG for diagnosis and prognosis in autoimmune encephalitis.