Reviewer's report

Title: Resting state in Alzheimer's Disease: a concurrent analysis of flash-visual evoked potentials and quantitative-eeg

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Reviewer: Vicente Iragui

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On the premise derived from the studies of resting functional connectivity suggesting that eye-open and eye-closed conditions involve separate brain networks, the authors attempt to analyze the impact of Alzheimer’s disease on brain networks involved in each of these conditions. To this end, they analyzed flash visual evoked potentials (F-VEPs) and quantitative-EEG (Q-EEG) in 11 controls and 19 patients with Alzheimer’s disease. Nine of the nineteen AD patients did not differ from controls, but 10 patients showed a P2 VEP latency difference between eye opening and eye closing conditions that was larger than that of controls.

The main EEG analysis measure used was the power of alpha compared with the sum of the delta and theta powers (alpha/slow wave ratio). There was no significant difference among groups in the eye-open condition. In the eye closed condition, the group with normal flash VEPs did not differ from controls, but the group with abnormal eye closure effect on VEPs did differ from controls, since the EEG power spectrum (alpha/slow wave ratio) in these patients was similar with eyes open and eyes closed, which the authors attributed to a reduction of alpha activity and an increase of delta power in the eye-close condition. The authors conclude that Alzheimer’s disease can impair control of neural systems involved in the eye closed condition and that the flash VEP is a reliable marker of such involvement.

Controls were not healthy subjects but were patients in the department of internal medicine, and therefore, they were not free of illness. Although it is stated that the patients reported no past or present history of neurological or psychiatric disease, details regarding the selection criteria and procedures to exclude visual, neurological and psychiatric illness would be desirable.

There are a number of methodological issues that should be addressed. Analysis of F-VEPs was done on only one channel (OZ-CZ derivation) and no less than 256 responses were averaged in each eye (4 blocks of 64 responses each). However, it is unclear whether each block constituted a separate average or all responses were averaged together. If the latter was the case, the lack of evidence from replication of averages to ensure consistency might have allowed artifact to be disguised as signal. This is particularly important in flash visual evoked potentials, given their variability from moment to moment.
Two independent observers evaluated the F-VEP data, and measures were accepted only if the P2 latency estimates differed by less than 5 milliseconds between observers. Otherwise, components were considered “missing” and discarded. One can envision instances in which the peak of a robust potential may not be well defined where two different observers would choose to different peak points, but where the potential is clearly present. According to the description in the paper, this patient would be discarded as not having a response, which would be inaccurate. This point should be clarified. It would be very helpful if recordings were presented in the paper illustrating the different findings.

The rational for averaging the latencies from each eye in each subject and its potential pitfalls should be stated. How many subjects included in the analysis had a missing P2 with stimulation of one eye and a good response from the other eye? Is this a normal response?

EEG was recorded from 16 scalp channels but analysis was limited to 6 channels “for sake of simplicity.” Since preliminary analysis found no EEG differences among groups within condition as a function of electrode site O1, O2, C3, C4, T3, T4) data from all channels for each frequency band were averaged in each subject and collapsed into one measure. The lack of topographical EEG differences reported by the authors is surprising and contrary to a large amount of evidence on the scalp distribution of EEG frequency bands (was the alpha power the in occipital and central electrodes?). It is unclear why the data from all 16 channels was not analyzed, since detection of brain networks involved in resting connectivity would have greatly benefited from such an approach. In addition, the pitfalls of averaging data across many channels to simplify analysis should be discussed.

The conclusions seem reasonable and the selection of references is quite appropriate, although the authors seem to place undue emphasis on a report by Coburn with the peculiar, unsupported contention that flash stimulation with eyes open elicits a pattern response. The tables and legends are clear an appropriate. As suggested above, illustrations of recorded data should be included.

In summary, major point to be addressed are as follows:

Selection of controls.
F-VEP methodology, analysis and rational for averaging responses from each eye.
EEG channel limitations and data collapse across channels.
Inclusion of data illustrations.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable
**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

None