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Writing Sample for WIN

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MEMO: I have a lot of points I would like to hit in the discussion of my paper, but I’m not sure the best way to start. The paper is about how we stimulated the brain in three patients with epilepsy and saw unusually long-lasting effects on breathing under certain conditions. We did more detailed work regarding the breathing, the nuances of the effect, and quantifying the brain—all of which I would like to discuss—but the most important point is that this can occur at all. *I would like feedback on how this start to my discussion section reads currently, and thoughts regarding order of content in a discussion section.*

*P.S. SUDEP = Sudden Unexpected Death in Epilepsy (already explained earlier in the manuscript)*

Discussion

Here we report that electrical stimulation and seizure within the amygdala is able to cause apnea and other abnormalities of breathing, and that this hypoventilation can persist for minutes even after stimulation or seizure in the amygdala has ceased. In previously reported patients, apnea was seen during amygdala stimulation, but breathing resumed within 15 seconds afterwards and no abnormal hypoventilation beyond that time was shown1-3. This novel finding of long-lasting breathing changes may have critical implications for understanding postictal mortality.

*Prevalence of the prolonged disrupted breathing phenotype*

It is unclear what proportion of epilepsy patients show prolonged postictal or post-stimulation hypoventilation, and how predictive this is of future SUDEP. It has recently been reported that periictal apnea is common, especially in temporal lobe seizures, but that prolonged postictal apnea is far less common4. Similarly, post-stimulation breathing changes are not always observed in our work, as we have studied numerous (18) other patients who did not show pronounced, long-lasting hypoventilation after the end of amygdala stimulation. However, we did note that the patients who did have prolonged breathing alterations (P352, P384, and P413) all had seizure foci involving the temporal lobe. Thus, it is possible that prolonged breathing disruption following stimulation or seizure could represent a biomarker specific to a subset of patients, and that abnormal connectivity of the mesial temporal lobe after years of uncontrolled seizures may be important for breathing to remain disrupted after the end of amygdala stimulation or seizure.

However, it is possible that the prevalence of prolonged breathing disruption is under-recognized. For seizures observed in epilepsy monitoring units, a typical clinical approach is to intervene by immediately asking the patient follow-up questions and performing a neurological exam. This would disrupt breathing signal immediately following the seizure and potentially mask changes by causing the patient to voluntarily breathe in order to talk. Thus, it is possible that postictal apnea or irregular breathing is more common than anticipated. We were able to gather valuable postictal data for P413 by adapting the intervention protocol for a partial seizure by limiting disruption of natural breathing patterns. Use of this approach when possible could reveal more instances of postictal breathing disruption than currently detected, and may be critical for understanding SUDEP events that occur when the patient is unlikely to be prompted to talk (alone, at night, in bed, etc.).

It is also possible that more patients may exhibit prolonged breathing disruption with amygdala stimulation, but were not detected due to variations in electrode placement. For the patients we describe in this report, site of amygdala stimulation was crucial in whether or not apnea occurred at all, and whether or not apnea persisted after stimulation ceased. Thus, it is possible that stimulation or seizure must occur in a specific location to cause acute and/or prolonged effects, even within the same patient. It is therefore possible that more patients with prolonged breathing changes could have been detected in our stimulation studies had their electrodes been placed in a slightly different location.

References

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2 Lacuey, N., Zonjy, B., Londono, L. & Lhatoo, S. D. Amygdala and hippocampus are symptomatogenic zones for central apneic seizures. *Neurology* **88**, 701-705, doi:10.1212/wnl.0000000000003613 (2017).

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