Review of: "Reinstating olfactory bulb derived limbic gamma oscillations alleviates depression"

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This paper tests the hypothesis that the olfactory bulbectomy (OBx) model of major depressive disorder (MDD) is caused by a lack of OB gamma band oscillatory input to the limbic system. OBx is a catastrophic surgery accompanied by significant blood loss and requires weeks of recovery. This leads to a confound with neurodegeneration. The current paper used DREADDs to silence the OBs bilaterally and chronically for several weeks. Additionally, they used short term silencing and cancellation / enhancement of gamma oscillations in an LPS model of MDD.

Several findings support the hypothesis that it's loss of OB input to the limbic system that causes the depressive phenotype. There are some differences dependent on the type of silencing. The open field test (OFT) is the gold standard for OBx depression, with hyperactivity and avoidance of the center the classic behaviors indicative of MDD. With chemogenetic silencing, animals avoid the center but are not hyperactive, and they do not exhibit anhedonia. Short term silencing does the opposite - anhedonia but not OFT hyperactivity/center avoidance. These opposite results are interesting and may help get at different mechanisms for anhedonia and anxiety in the OBx model.

The authors use closed-loop stimulation locked to the gamma bursts in the OB to determine whether gamma burst activity in the PC reduces depressive symptoms. In the LPS model of MDD, they stimulated to either enhance or cancel out gamma transmission to PC from OB. Enhancing gamma reduced depressive symptoms in LPS, and blocking gamma by stimulating in antiphase with the OB gamma did not reduce symptoms. The authors conclude that loss of gamma is the cause of OBx depression.

I am not sure I agree 100% with their conclusions, even though I have no substantive criticisms with the methods and results. Amplifying gamma is sufficient to reduce symptoms, but does canceling it out tell us that it is gamma per se that causes the antidepressant effect? Canceling out gamma does stimulate the fibers going in to the PC but what does the antiphase stimulation do exactly to the PC? Are the same number of action potentials produced, or is the antiphase stimulation doing something fundamentally different to the PC inputs?

For the rest of my comments, I need to tell a story, one which I shared with Gyuri the other day. I reminded him of our conversation years ago, when I discussed the idea that OBx depression is due to loss of OB input to the PC and the rest of the limbic system. I envisioned a similar experiment to this one. A few years later we met again at Walter Freeman's

Festschrift in Tucson, the day after Walter had passed away. We discussed the idea again and I told him we were working on it. We never got anywhere with what we tried and Gyuri rightly went ahead. No hard feelings at all, and I am really glad that you all did such a great job on this.

I think there is a crucial piece missing though, on the provenance of this idea, and it comes from Walter. I shared with Gyuri way back when we first spoke about this idea one of Walter's little-known papers, a 1968 J Neurophys article "Effects of surgical isolation and tetanization on prepyriform cortex in cats." This paper was published the same year as the Becker and Freeman paper cited in this report. While the Becker and Freeman paper shows that PC activity changes when the olfactory bulb is removed, the single authored 1968 paper gets at its cause.

The origin of the idea comes from Walter Freeman, as most good ideas in olfaction do. In the 1968 paper, he bulbectomized cats and showed that a normal shock stimulus to the remaining LOT no longer induced the normal oscillatory evoked potential in the PC – there was a single peak in voltage dying off after one cycle. Two hypotheses were considered, 1) the OB drives the oscillation in the PC, when the LOT is stimulated it produces an oscillatory evoked response in the OB, which drives the same response in the PC, and 2) the OB input is necessary for the PC to produce an oscillation.

The second hypothesis was the one favored by his results. He replaced the missing OB with tetanic 200Hz low level stimulation of the stump of the LOT and then stimulated with the normal larger shock stimulus during a pause in the tetanic stimulation. Et voila, the oscillatory evoked potential was reinstated in the PC. This relatively obscure paper showed an important role for the OB – it provides abundant excitatory drive to the rest of the system, keeping everything in the right dynamic range. These results were replicated for the entorhinal cortex by Kurt Ahrens (Ahrens and Freeman, Brain Research 2001).

The rescue of depressive behavior with gamma enhancement in the LPS model in the current study is intriguing, and the cancellation effect of the antiphase stimulation is compelling. Would the same type of stimulation rescue a silenced olfactory bulb? If it does not, does this mean that different mechanisms are at play for different models of depression? The methods used here may be able to make sense of the mechanisms and usefulness of different models of depression for different types of treatment studies. Already the difference in behavioral effects among the several methods post some very interesting questions.

I appreciate the space to tell Walter's story and the format of biorXiv that allows public discourse about research reports.