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Dear Jean

Enclosed please find our manuscript entitled *“Awakening: promoting transitions between different brain states in a probabilistic state space framework”* for consideration in *Nature Neuroscience*.

As you will know Gustavo recently gave a keynote at the Human Brain Mapping conference where he presented the novel ideas and results contained in the enclosed ms. The invitation was based very much on the current excitement within the field of neuroscience with the new possibilities to combine neuroimaging with causal whole-brain modelling that we have pursued in our on-going research programme which has recently borne remarkable fruits in a number of high impact publications ([Deco *et al.*, 2018](#_ENREF_1); [Deco and Kringelbach, 2016](#_ENREF_3); [Schirner *et al.*, 2018](#_ENREF_6)).

Crucially, these models offer the tantalizing potential to understand the causative mechanisms involved in the transitions between different brain states such as healthy wakefulness and, say, sleep, coma or neuropsychiatric disease.

Until now, the field of therapeutic brain stimulation have been primarily driven by research in other animals which have had spectacular successes such as using DBS to treat the debilitating symptoms of Parkinson’s Disease ([Kringelbach *et al.*, 2007](#_ENREF_5)). However, neuropsychiatric disorders are not easily studied with animal models and real progress in rebalancing the diseased brain has not been forthcoming ([Holtzheimer and Mayberg, 2011](#_ENREF_4)).

Nevertheless there are great expectations that brain stimulation (using e.g. TMS or DBS) could be guided by careful neuroimaging and whole-brain modelling which could provide much needed progress in alleviating the suffering ([Deco and Kringelbach, 2014](#_ENREF_2)).

In this paper, we provide a theoretical and experimental framework to predict exactly how to force a transition between brain states; and show specifically how to ‘awaken’ a sleeping brain. This is made possible by showing the fundamental mechanisms of how to force a transition between two brain states by external stimulation. In particular the novel framework opens up for radical translational applications; potentially honing the precision and power of stimulation technologies (e.g. DBS and TMS) to allow the re-establishment of healthy brain states from neuropsychiatric disease such that they can promote a profound reconfiguration of the dynamical landscape necessary for recovery.

For these reasons, we believe our findings are rather exciting and could have broad and general interest for the readership of *Nature Neuroscience*.

Yours,

Morten and Gustavo

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