Mechanisms of the non-linear interactions between the neuronal and neurotransmitter systems explained by causal whole-brain modeling

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Abstract

Although a variety of studies have shown the role of neurotransmitters at the neuronal level, their impact on the dynamics of the system at a macroscopic scale is poorly understood. Here, we provide a causal explanation using the *first* whole-brain model integrating multimodal imaging in healthy human participants undergoing manipulation of the serotonin system. Specifically, we combined anatomical and functional data with a detailed map of the serotonin 2A receptor ($5\text{-}HT_{2A}R$) densities obtained with positron emission tomography (PET). This allowed us to model the resting state and mechanistically explain the functional effects of $5\text{-}HT_{2A}R$ stimulation with lysergic acid diethylamide (LSD). The whole-brain model used a dynamical mean-field quantitative description of populations of excitatory and inhibitory neurons as well as the associated synaptic dynamics, where the neuronal gain function of the model is modulated by the $5\text{-}HT_{2A}R$ density. The results show that the precise distribution of $5\text{-}HT_{2A}R$ is crucial to predict the neuromodulatory effects of LSD. The model identified the causative mechanisms for the non-linear interactions between the neuronal and neurotransmitter system, which are uniquely linked to the underlying neuroanatomical network, the modulation by the specific brain-wide distribution of neurotransmitter receptors, and the non-linear interactions between the two.

Keywords: Whole-Brain Model; Mean Field Model; Neurotransmitters; Serotonin; Psychedelics.

Introduction

Understanding the underlying mechanisms of the human brain in health and disease will require models with necessary and sufficient details to explain how function emerges from the underlying anatomy and is shaped by neuromodulation. Neuromodulators are originated subcortically and project to many different target areas where not only they regulate the neuronal activity but also are recurrently modulated by the neuronal activity itself. Here, we analyze the functional implications of this double interaction and provide a detailed mechanistic explanation of how neuromodulation is coupled with the neuronal system at the whole-brain level.

Multimodal Whole-Brain Model

We integrated a whole-brain density map of the 5-HT_{2A}R (Beliveau et al., 2017) with traditional anatomical and functional connectivity representations from 15 participants obtained by means of diffusion magnetic resonance imaging (dMRI) and functional magnetic resonance imaging (fMRI), respectively (Deco et al., 2018). The whole-brain model was composed of 90 anatomically delineated brain regions linked by the structural connectivity (SC) matrix of fiber densities obtained by tractography (Cabral, Kringelbach, & Deco, 2014; Hagmann et al., 2008). The activity of each region was represented by a dynamic neuronal mean-field model derived from the collective behavior of empirically validated integrate-and-fire (80% excitatory and 20% inhibitory) neurons (Brunel & Wang, 2001; Deco et al., 2014). The population responses for pools of excitatory neurons were given by independent sigmoid functions, regulated by a gain parameter s_E common in all brain regions and initially set to zero. Notably, the model only uses two parameters: a neuronal parameter scaling the global coupling of neuronal populations, G, and a neuromodulator parameter scaling the effects of neurotransmitters on the neuronal gain function weighted by the empirical regional receptor density. To take into account the spatiotemporal fluctuations in functional brain dynamics over time, the model was fitted to the spatiotemporal dynamics of the data (i.e., to the functional connectivity dynamics [FCD]) rather than to the static grand-average functional connectivity (FC) (Allen et al., 2014; Deco & Kringelbach, 2016; Hansen, Battaglia, Spiegler, Deco, & Jirsa, 2015). To find the causal mechanisms linking neuromodulation and neuronal activity, the model was first fitted to the placebo condition using the same fixed gain-value parameters for all regions and adapting only the G coupling parameter. Subsequently, the optimal global coupling parameter value was used to explain the functional dynamics in the LSD condition by selectively changing the gain of each region according to the empirical measured 5-HT_{2A}R density. Specifically, we defined a global gain-scaling parameter, s_E, which was added to the original fixed gain parameters (same for all regions) and thus could serve for scaling of the regional 5-HT_{2A}R values, potentially signaling the influence of the receptors on the recursive circuits of excitatory and inhibitory neurons. Zero values of s_E yield the original gain values, fitting the model to the placebo condition but *not* the LSD condition. The role of the empirical 5-HT_{2A}R was ultimately assessed by comparing the LSD maps with neuromodulatory maps of randomly shuffled 5-HT_{2A}R densities.

Results of Fitting the Whole-Brain Neuromodulation Model to Empirical Data

To find the causal mechanisms linking neuromodulation and neuronal activity, we first estimated the optimal coupling parameter G such that the whole-brain model (with original gain values, i.e., s_E = 0 for all regions) optimally fits the placebo condition. Fig. 1A shows the dependency for G of the fitting in terms of the FC and the FCD. The neuromodulatory effects in the LSD condition were then modeled by estimating the neuronal gain function, namely by scaling the parameter s_E and the corresponding regional empirical 5-HT_{2A}R data.

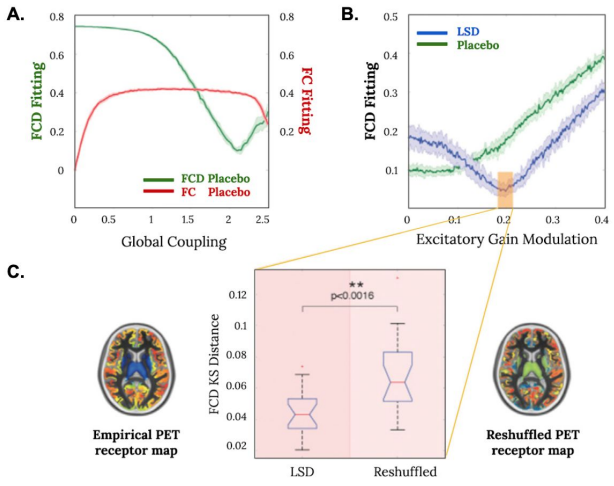

Figure 1. Results of Whole-Brain Model of Placebo and Explaining the Effects of LSD with 5HT_{2A} Modulation of Gain Function

For the LSD condition, when using the optimal coupling point of the placebo condition and systematically scaling the excitatory gain function in each region with the empirical 5-HT_{2A}R data, we find that there is an optimum of the FCD fitting at around (0.2,0.045) (Fig. 1B). In contrast, varying the scaling of the neuronal gain for the placebo condition does not yield an optimum, and thus the fit is not improved by changing the scaling of the neuronal gain by 5-HT_{2A}R density. The finding clearly demonstrates that the brain-activity profiles, induced by the 5-HT_{2A}R agonist LSD depend on the precise 5-HT_{2A}R density distribution map. Furthermore, by randomly shuffling the empirical 5-HT_{2A}R densities we demonstrate that the precise distribution of 5-HT_{2A} is very important for how LSD affects the brain state (Fig. 1C).

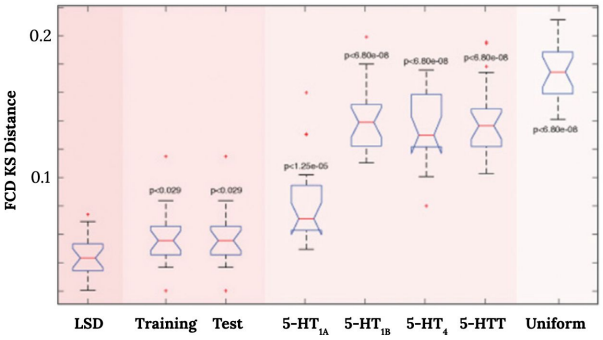

Figure 2. Robustness of the whole-brain modeling approach.

Finally, to test the robustness of our whole-brain modeling approach, we tested the specificity of other receptor-binding maps. Fig. 2 shows a boxplot of the results of the generalization capability of our model by training and testing the 5-HT_{2A}R maps on 50% subset of participants (columns 2 and 3). The results are remarkably similar to using the full set of participants, attesting to the robustness of our results. We also show the results of using other serotonin receptor-binding maps (5-HT_{1A}, 5-HT_{1B}, 5-HT_4, and 5-HTT, columns 4–7), which all perform significantly worse than 5-HT_{2A}, confirming the main role of this receptor to the effects of LSD (Nichols, 2016). Interestingly, however, 5-HT_{1A} receptor-binding map performs slightly better than the 5-HT_{1B}, 5-HT_4, and 5-HTT receptor maps. In the last column, we show the results of using a uniform receptor-binding distribution which is significantly worse than all other receptor-binding distributions.

Conclusions

We demonstrated how the anatomical brain-wide distribution of neuromodulatory activity can be integrated into a whole-brain computational model to provide new causative insights into the non-linear interactions between anatomy, neuronal activity, and more importantly, specific neurotransmitter receptor density. These novel insights are only possible when using a whole-brain model given the fact that it is not possible to scramble the neurotransmitter receptor density in vivo. With time, this new approach could eventually lead to fundamental insights into human brain function in health and disease and be used for drug discovery and design in neuropsychiatric disorders.

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References

Allen, E. A., Damaraju, E., Plis, S. M., Erhardt, E. B., Eichele, T., & Calhoun, V. D. (2014). Tracking whole-brain connectivity dynamics in the resting state. *Cerebral cortex, 24*(3), 663-676.

Beliveau, V., Ganz, M., Feng, L., Ozenne, B., Hojgaard, L., Fisher, P. M., . . . Knudsen, G. M. (2017). A High-Resolution In Vivo Atlas of the Human Brain's Serotonin System. *J Neurosci, 37*(1), 120-128. doi:10.1523/JNEUROSCI.2830-16.2016

Brunel, N., & Wang, X.-J. (2001). Effects of neuromodulation in a cortical network model of object

working memory dominated by recurrent inhibition. *Journal of computational neuroscience, 11*(1), 63-85.

Cabral, J., Kringelbach, M. L., & Deco, G. (2014). Exploring the network dynamics underlying brain activity during rest. *Prog Neurobiol, 114*, 102-131. doi:10.1016/j.pneurobio.2013.12.005

Deco, G., Cruzat, J., Cabral, J., Knudsen, G. M., Carhart-Harris, R. L., Whybrow, P. C., . . . Kringelbach, M. L. (2018). Whole-brain multimodal neuroimaging model using serotonin receptor maps explains non-linear functional effects of LSD. *Current biology, 28*(19), 3065-3074. e3066.

Deco, G., & Kringelbach, M. L. (2016). Metastability and coherence: extending the communication through coherence hypothesis using a whole-brain computational perspective. *Trends in neurosciences, 39*(3), 125-135.

Deco, G., Ponce-Alvarez, A., Hagmann, P., Romani, G. L., Mantini, D., & Corbetta, M. (2014). How local excitation–inhibition ratio impacts the whole brain dynamics. *Journal of neuroscience, 34*(23), 7886-7898.

Hagmann, P., Cammoun, L., Gigandet, X., Meuli, R., Honey, C. J., Wedeen, V. J., & Sporns, O. (2008). Mapping the structural core of human cerebral cortex. *PLoS Biol, 6*(7), e159. doi:10.1371/journal.pbio.0060159

Hansen, E. C., Battaglia, D., Spiegler, A., Deco, G., & Jirsa, V. K. (2015). Functional connectivity dynamics: modeling the switching behavior of the resting state. *Neuroimage, 105*, 525-535.

Nichols, D. E. (2016). Psychedelics. *Pharmacol Rev, 68*(2), 264-355. doi:10.1124/pr.115.011478