The FEBS Journal

FEBS PRESS science publishing by scientists

STATE-OF-THE-ART REVIEW

Bridging the gap between single receptor type activity and whole-brain dynamics

Dirk Jancke[1,2], Stefan Herlitze[3], Morten L. Kringelbach[4,5,6,7] and Gustavo Deco[8,9,10,11]

1 Optical Imaging Group, Institut für Neuroinformatik, Ruhr University Bochum, Germany
2 International Graduate School of Neuroscience (IGSN), Ruhr University Bochum, Germany
3 Department of General Zoology and Neurobiology, Ruhr University, Bochum, Germany
4 Department of Psychiatry, University of Oxford, UK
5 Center for Music in the Brain, Department of Clinical Medicine, Aarhus University, Denmark
6 Life and Health Sciences Research Institute, School of Medicine, University of Minho, Braga, Portugal
7 Centre for Eudaimonia and Human Flourishing, University of Oxford, UK
8 Center for Brain and Cognition, Computational Neuroscience Group, Universitat Pompeu Fabra, Barcelona, Spain
9 Institució Catalana de la Recerca i Estudis Avançats, Barcelona, Spain
10 Department of Neuropsychology, Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany
11 School of Psychological Sciences, Monash University, Clayton, Melbourne, Australia

Keywords
5-HT1A; 5-HT2A; molecular & cellular neuroscience; neurotransmitter; PET; protein design; receptor trafficking; serotonin; visual cortex; whole-brain modelling

Correspondence
D. Jancke, Optical Imaging Group, Institut für Neuroinformatik, Ruhr University Bochum, Universitätstr. 150, D-44780 Bochum, Germany
Tel: +49 234 32 27845
E-mail: dirk.jancke@rub.de
Website: https://jancke-lab.de/

G. Deco, Center for Brain and Cognition, Computational Neuroscience Group, Universitat Pompeu Fabra, 08018 Barcelona, Spain
Tel: +34 935 421 855
E-mail: gustavo.deco@upf.edu
Website: https://barccsyn.org/groups/computational-neuroscience-group

(Received 14 January 2021, revised 15 March 2021, accepted 31 March 2021)

doi:10.1111/febs.15855

What is the effect of activating a single modulatory neuronal receptor type on entire brain network dynamics? Can such effect be isolated at all? These are important questions because characterizing elementary neuronal processes that influence network activity across the given anatomical backbone is fundamental to guide theories of brain function. Here, we introduce the concept of the cortical 'receptome' taking into account the distribution and densities of expression of different modulatory receptor types across the brain's anatomical connectivity matrix. By modelling whole-brain dynamics *in silico*, we suggest a bidirectional coupling between modulatory neurotransmission and neuronal connectivity hardware exemplified by the impact of single serotonergic (5-HT) receptor types on cortical dynamics. As experimental support of this concept, we show how optogenetic tools enable specific activation of a single 5-HT receptor type across the cortex as well as *in vivo* measurement of its distinct effects on cortical processing. Altogether, we demonstrate how the structural neuronal connectivity backbone and its modulation by a single neurotransmitter system allow access to a rich repertoire of different brain states that are fundamental for flexible behaviour. We further propose that irregular receptor expression patterns—genetically predisposed or acquired during a lifetime—may predispose for neuropsychiatric disorders like addiction, depression and anxiety along with distinct changes in brain state. Our long-term vision is that such diseases could be treated through rationally targeted therapeutic interventions of high specificity to eventually recover natural transitions of brain states.

Abbreviations
5-HT, 5-hydroxytryptamine, serotonin; CaMello, Ca^{2+}-melanopsin-local-sensor; dMRI, diffusion magnetic resonance imaging; FC, functional connectivity; FCD, functional connectivity dynamics; fMRI, functional magnetic resonance imaging; GABA, *gamma*-Aminobutyric acid; GluR, glutamate receptor; GPCR, G protein-coupled receptor; KLD, Kullback–Leibler distance; MEG, magnetoencephalography; PET, positron electron tomography; PMS, probabilistic metastable substates; Pvalb, parvalbumin; Rs, receptors; Src, Sarcoma; V1, primary visual cortex.

Introduction

At the heart of neuroscience, there is a deep conundrum which is how to explain the paradoxical flexibility of human brain function to create a rich palette of multiple behaviours despite using the same underlying anatomical connectivity, also called the 'connectome'. In other words, how can the brain's structure provide the grounds for a rich dynamical repertoire of neuronal brain processes? Here, we propose that this system-wide flexibility is brought about by the entanglement between modulatory neurotransmission and neural network activity. In particular, we show how this intricate interplay allows the brain to reconfigure its effective functional connectivity (FC; e.g. changing its operating point) on top of a fixed connectome.

In support of this perspective, we here survey recent literature, strongly suggesting that this is made possible through the specific action of neuronal plasma membrane receptors and their reciprocal impact on macroscopic whole-brain networks. To put it in a nutshell: We here try bridging the explanatory gap between effects at the level of individual neurochemical afferents ('receptome') and whole-brain activity patterns. We illustrate these ideas by focussing on the serotonin (5-hydroxytryptamine; 5-HT) system [1], which has been studied at all functional levels and has been shown to play a key role in health and disease [2]. It should be noted however that, rather than reviewing the extensive current knowledge of serotonergic receptors and the serotonergic system *per se*, we here concentrate on recent studies that speciInE = WEI0 + w + JNMDASnE + GJNMDA∑pCnpSpE-JnSnI + WSERnMn6fically address our new concepts.

Investigations in human and animals have used a large variety of techniques to demonstrate that whole-brain activity depends both on effective connectivity and brain states, reflecting system-properties such as anatomical organization, dynamic thalamocortical loops and the function of ascending arousal systems [3]. The resulting activity patterns can be intricately affected by disease. In turn, subtle changes in activity patterns can be used to predict transitions from health to disease since phase transitions are often preceded by robust gradual reorganization of complex systems in general [4].

Despite some progress, a commonly agreed definition of a brain state is still contentious. To begin with, it is therefore crucial to have a definition that can be used to classify broad states of, for example, wakefulness, sleep and anaesthesia [5–9]. However, rather than characterizing brain states on such phenomenological levels we here define brains states in terms of statistics, that is, as transition probabilities across an ensemble of metastable substates (probabilistic metastable substates, PMS). Such approach allows different substates to be detected and characterized as their probability of occurrence together with their fluctuation profiles (for details see [10]). We further propose that using the combined perspective from cellular receptor levels to whole-brain levels can offer a mechanistic framework for characterizing brain states in terms of their underlying causal mechanisms and dynamical complexity. A global understanding of brain function may emerge from the integration of causal mechanistic whole-brain models that combine anatomy with local dynamics and predict empirical functional data from a variety of sources including human neuroimaging [11–13]. In fact, there has been recent significant progress in constructing such models, describing the complex interplay between neurotransmission and neural activity [14]. In these models, standard anatomical and functional maps of the human brain were combined with a detailed map of serotonergic receptor-density, obtained from a new high-resolution human brain *in vivo* atlas [15]. In particular, adding receptor maps to the whole-brain model allowed to scrutinize how gain values can be adapted by the local regional values of positron electron tomography (PET)-based empirical values of receptor densities. By applying this paradigm in a study where healthy participants were affected by intake of lysergic acid diethylamide, it was found that neurotransmitter modulation of whole-brain activity dynamics can quantitatively be ascribed to one type of receptor binding, namely of 5-HT2A.

By extending this approach, a novel mutually coupled whole-brain model was additionally able to capture the bidirectional interplay between modulatory neurotransmission and the neuronal system dynamics [16]. Such overall coupled system was modelled using a balanced dynamic mean-field approach [17,18] where the neuromodulator system incorporated the dynamics of the neurotransmitter concentration levels (measured *in vivo* using PET) including the well-known Michaelis–Menten release-and-reuptake dynamics [19–21]. In a proof of principle, the modelling considered the effects of psilocybin [22,23], another powerful psychedelic drug on the serotonin transmitter system. To couple the two (i.e. neuronal and transmitter) systems, the anatomical connectivity between the raphe nucleus and its projections throughout the brain was modelled. Overall, the results revealed that the interaction between both dynamical systems is fundamental for explaining the empirical data. Thus, rather than simply relying on changing the gain of only the local neuronal dynamics, the mutual interaction between

neuronal and neuromodulator systems at the whole-brain level was crucial to fully explain the functional modulation of brain activity by psilocybin. These findings are especially important given the demonstrated ability of psilocybin to rebalance the human brain in treatment-resistant depression [24].

To directly visualize the effects of single 5-HT receptor types on the brain's activity dynamics, we further present studies from *in vivo* animal experimental settings. Here, we show with real-time measurements how two different 5-HT receptor types (i.e. 5-HT1A and 5-HT2A) modulate two basic entities of whole-brain processes. That is, ongoing brain activity (reflecting state-dependent whole-brain internal communication processes) and activity evoked by sensory input (reflecting external drive). The results suggest indeed global whole-brain changes in cortical state induced by 5-HT input with balanced effects on internal ongoing activity and sensory drive [25,26]. Specifically, we find that 5-HT1A scales predominantly the weight of internal communication, while 5-HT2A largely scales the weight of external sensory input. Importantly, such modulation is divisive, hence, leaving transferred information contents intact. We exemplify these characteristics by imaging population activity in the mouse visual cortex during optogenetic activation of neurons in the raphe nuclei [27,28] to precisely trigger the release of 5-HT in the cortex. Finally, we demonstrate how the use of optogenetics enables direct and specific stimulation of the 5-HT2A receptor across the cortex by light [29]. Thus, using optical techniques we show how distinct activation of a single receptor type triggers the scaling of visual activity in the cortex.

Altogether, our presented modelling and experimental approaches could pave the way towards new concepts of describing whole-brain activity and its dynamic changes. In fact, neuropsychiatric disorders are often accompanied by changes in brain state and associated with malfunction of specific neurotransmitter systems [30]. Here, we propose how it is possible to disentangle distinct neuronal receptor-specific roles of the neurotransmitter receptome in modulating functional brain dynamics. In turn, the further development of such approaches may help to disentangle the distinct roles of the receptome in psychiatric diseases and to develop more specific therapeutic interventions.

Principles of whole-brain modelling

To noninvasively measure neuronal activity in humans, neuroimaging methods such as functional magnetic resonance imaging (fMRI), magnetoencephalography (MEG) and electroencephalography are typically used. These measures capture whole-brain activity at different spatial and temporal scales. Whole-brain models aim to balance between complexity and realistic (i.e. feasible) levels of such experimental descriptions including the most important functional features of the brain *in vivo* [31,32]. Thus, the fundamental principle of the modelling framework is to link anatomical structure with functional dynamics [11,33] under the given temporal and spatial constraints of the measurements (Fig. 1A). In the model, the emergence of the functional global dynamics arises from the mutual interactions of local node dynamics coupled through the underlying empirical anatomical connectivity. This framework has been especially successful for explaining resting-state networks captured by fMRI [32,34–39].

The underlying structural connectivity needed in the whole-brain model can be obtained in many ways, ideally reflecting the underlying directional anatomical connectivity through large-scale tract tracing [40,41]. Note that cortical connectivity can also be subject to specific plastic changes on longer time scales upon behavioural demands and training, as firstly shown using extra-cellular electrode recordings in somatosensory cortex of adult nonhuman primates [42]. To estimate individual connectivity noninvasively in humans, unidirectional connectivity is nowadays measured using *in vivo* diffusion magnetic resonance imaging (dMRI) combined with probabilistic tractography [43–46].

Next, the complexity of whole-brain modelling can be reduced by adopting meaningful parcellations based on structural and functional brain information and are typically on the order of 80–150 nodes [47,48]. Each node in the whole-brain model consists of an approximation of the local neuronal dynamics of which many different approximations have been used from a spiking neuronal network [37,49], mean-field model [17,38] to mesoscopic models (for instance the Hopf model [13,50]). Such models typically fit the empirical data [51] by optimizing the global coupling parameter scaling of the underlying structural connectivity, which assumes that the conductivity is uniform across brain. Potential heterogeneity in conductivity can also be modelled by adapting the effective connectivity to the empirical data [52]. Interestingly, the emergent collective macroscopic behaviour of brain models has been shown to depend only weakly on the behaviour of individual neurons rather than on activity of populations [31,53,54].

In terms of fitting, whole-brain models are able to describe not only static FC (averaged over all time

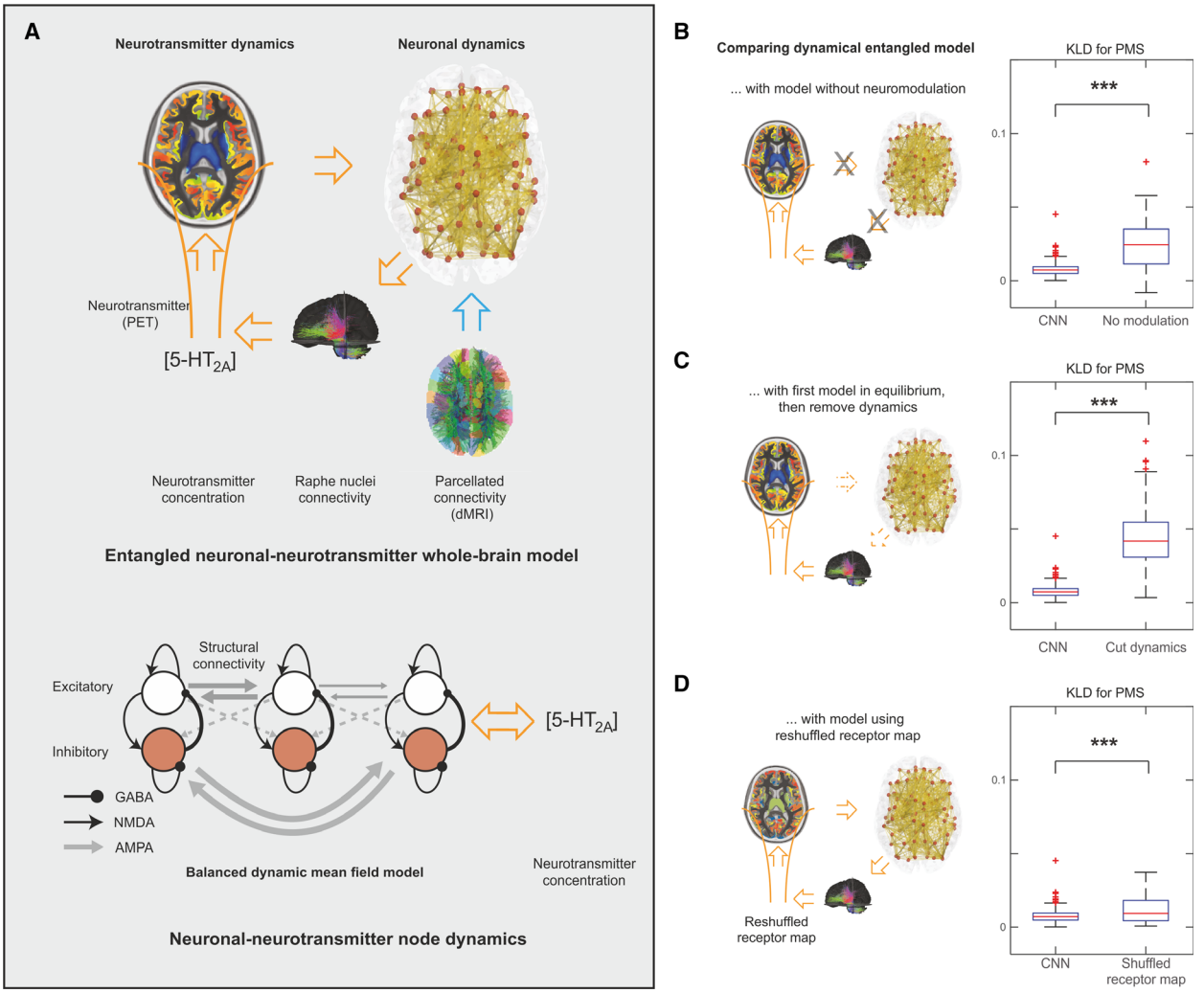

Fig. 1. Entangled whole-brain model. (A) The figure shows the coupling of two different mutually coupled dynamical whole-brain systems (neuronal and neurotransmitter). This was achieved by adding a coupled neurotransmitter system to modulate and interact with the neuronal system, which was modelled using a balanced dynamic mean-field model that expresses consistently the time evolution of the ensemble activity of the different neural populations building up the spiking network [17,18]. (B) The underlying dynamics of neuromodulation involved in psilocybin were obtained by comparing the KLD for the PMS between the empirical data and the whole-brain model undergoing various manipulations. For the optimal fit of the mutually coupled whole-brain model, a very significant difference was found between the optimal fit and the uncoupled system (i.e. without neuromodulation) ($P < 10^{-6}$). (C) A significant difference was also found when removing the feedback dynamics ($P < 10^{-6}$). The optimal model coupling was allowed until steady state, at which point just the average of the neurotransmitter variables was kept while cancelling all feedback dynamics. (D) Finally, a significant difference was found between using the empirical 5-HT2A receptor densities across the regions at the optimal fit compared with randomly shuffling the receptor densities ($P < 10^{-4}$). The applied test was a permutation-based paired *t* test (1000 permutations). The error bars for the KLD data follow the MATLAB convention where the central mark indicates the median, and the bottom and top edges of the box indicate the 25th and 75th percentiles, respectively (across 50 simulations). The whiskers extend to the most extreme data points not considered outliers, and the outliers are plotted individually using the '+' symbol. Figure and accompanying figure legend modified and reproduced from [16].

points) [13], but also dynamical measurements like the temporal structure of the activity fluctuations in FC dynamics (FCD) [55] and PMS [10]. Besides, our model is not restricted to the relatively slow dynamics obtained with fMRI but can be enriched using spectra of recording methods such as MEG [56,57]. Hence, the model can be used to bridge the gap between different timescales from milliseconds to tens of seconds, offering unparalleled mechanistic insights into the multi-scale nature of whole-brain activity [58].

Creating an entangled whole-brain model coupling neurotransmitter and neuronal systems

Recent studies have created whole-brain models integrating serotonergic transmission and neuronal dynamics using human neuroimaging (dMRI, fMRI and PET) from experiments where the serotonin system is modulated by the action of psychedelics, which are remarkably precise in eliciting responses of specific 5-HT receptors [14,16]. Here, we briefly review our entangled whole-brain model (shown in Fig. 1A). It basically consists of a mutually coupled neuronal and neurotransmitter systems of equations, which are described in details in Box 1. The neuronal system uses the dynamics of local nodes which are mathematically defined as balanced mean fields. The spiking output of the network reflects the suprathreshold evolution of ensemble activity across different neural populations [17,18]. Spontaneous (ongoing) activity across different brain regions emerges from the network of excitatory and inhibitory pools of neurons [17,60].

Box 1. Entangled whole-brain model of neuronal and neurotransmitter systems.

The neuronal system uses a balanced dynamic mean-field model with local node dynamics described by expressing the evolution over time of the ensemble activity of the different neuronal populations creating the spiking network [17,18]. The spontaneous activity of each brain region can be described by the following equations governing the dynamics of network consisting of two pools of excitatory and inhibitory neurons:

$$I_n^{(E)} = W_E I_0 + w_+ J_{\mathrm{NMDA}} S_n^{(E)} + G J_{\mathrm{NMDA}} \sum_p C_{np} S_p^{(E)} - J_n S_n^{(I)} \quad (1)$$

$$I_n^{(I)} = W_I I_0 + J_{\mathrm{NMDA}} S_n^{(E)} - S_n^{(I)} \quad (2)$$

$$r_n^{(E)} = H^{(E)}\left(I_n^{(E)}\right) = \frac{g_E\left(I_n^{(E)} - I_{thr}^{(E)}\right)}{1 - \exp\left(-d_E g_E\left(I_n^{(E)} - I_{thr}^{(E)}\right)\right)} \quad (3)$$

$$r_n^{(I)} = H^{(I)}\left(I_n^{(I)}\right) = \frac{g_I\left(I_n^{(I)} - I_{thr}^{(I)}\right)}{1 - \exp\left(-d_I g_I\left(I_n^{(I)} - I_{thr}^{(I)}\right)\right)} \quad (4)$$

$$\frac{dS_n^{(E)}(t)}{dt} = -\frac{S_n^{(E)}}{\tau_{\mathrm{NMDA}}} + \left(1 - S_n^{(E)}\right)\gamma r_n^{(E)} + \sigma \upsilon_n(t) \quad (5)$$

$$\frac{dS_n^{(I)}(t)}{dt} = -\frac{S_n^{(I)}}{\tau_{\mathrm{GABA}}} + r_n^{(I)} + \sigma \upsilon_n(t). \quad (6)$$

For each population of inhibitory (I) or excitatory (E) neurons in each brain region n, the vector $I_n^{(E,I)}$ provides the total input current (in nA), the firing rate is denoted by the vector $r_n^{(E,I)}$ (in Hz), while the synaptic gating is denoted by the vector $S_n^{(E,I)}$. The total input currents received by the E and I pools is converted by the neuronal response functions, $H^{(E,I)}$ into firing rates, $r_n^{(E,I)}$ using the input–output function of [59], where the gain factors g_E and g_I determine the slope of H. Above the threshold currents of $I_{thr}^{(E)}$ and $I_{thr}^{(I)}$, the firing rates are increasing linearly with the input currents. The curvature shape of H around I_{thr} is provided by the constants d_E and d_I. gamma-Aminobutyric acid (GABA) receptors with τ_{GABA} controls the average synaptic gating in inhibitory pools. NMDA receptors with a decay time constant τ_{NMDA} and γ control the synaptic gating variable of excitatory pools, $S_n^{(E)}$. The variable J_{NMDA} is weighting the excitatory synapses, while the weight of recurrent excitation is given by w_+. The overall effective external input is given by I_0 with associated weight functions W_E and W_I. It is important to note that in Eqns (5,6) there is a fixed amplitude of σ for the uncorrelated standard Gaussian noise, υ_n.

We used parameters in the dynamic mean field model based on Wong and Wang (2006) [60] such that each isolated node exhibited the typical noisy spontaneous activity with low firing rate ($r^{(E)} \sim 3$Hz) observed in electrophysiology experiments [61–64]. Furthermore, similar to [17], for each node n, the inhibition weight, J_n, was adjusted such that the firing rate of the excitatory pools $r_n^{(E)}$ remained clamped at 3 Hz—even when receiving excitatory input from connected areas. The algorithm for achieving Feedback Inhibition Control (FIC) is described in [17], improving the fit to the resting-state FC with more realistic evoked activity. All of the parameter values can be found in [16].

The neurotransmitter system is described by the canonical Michaelis–Menten release-and-reuptake dynamics [19–21] governing the dynamics of the neurotransmitter concentration level:

$$\frac{d[s_n]}{dt} = \alpha C_{BR} r_n^{(E)} - \frac{V_{\max}[s_n]}{(K_m + [s_n])} \quad (7)$$

where $[s_n]$ denotes the dynamics of the neurotransmitter concentration level in a brain region n. The corresponding density of a given serotonin receptor R_n has been acquired with PET. This equation is defining the interactions between the neurotransmitter and neuronal system through the brain raphe coupling. The outer product of the fibre density connectivity vector, C_{BR}, between the whole brain and the raphe nucleus, is obtained through dMRI probabilistic tractography. The factor α normalizes the activity such that the current generated by the neurotransmitter (in Eqns 8–10) is adjusting the nonlinear central sigmoidal part of the equation. The second term in Eqn (7), $V_{\max}$ provides the maximum reuptake rate while K_m is the substrate concentration at which the uptake proceeds at half of the maximum rate [19–21].

The effect of the neurotransmitter system on the neuronal system is described in Eqns (8–10). Equations (8,9) are a coupled variation of Eqns (1,2), which model the neuronal activity is a dynamical system by generating an extra current on inhibitory GABAergic neurons and the excitatory pyramidal and:

$$I_n^{(E)} = W_E I_0 + w_+ J_{\mathrm{NMDA}} S_n^{(E)} + G J_{\mathrm{NMDA}} \sum_p C_{np} S_p^{(E)} - J_n S_n^{(I)} + W^S{}_E R_n M_n \quad (8)$$

$$I_n^{(I)} = W_I I_0 + \mathrm{J}_{\mathrm{NMDA}} S_n^{(E)} - S_n^{(I)} + W^S{}_I R_n M_n \quad (9)$$

where the excitatory and inhibitory feedback coupling parameters, $W^S{}_E$ and $W^S{}_I$, describe the coupling from the neurotransmitter system to the neuronal activity. PET measures the density of a serotonin receptor R_n which is weighting the serotonin modulated current vector M_n (current for each brain region). This is given by the standard sigmoid-like function used in pharmacology [20]:

$$\tau_s \frac{d\boldsymbol{M_n}}{dt} = -M_n + \frac{J}{\left(1 + e^{-\beta(\log_{10}[s_n]+1)}\right)} \quad (10)$$

where $\beta = 10$, $J = 0.1$ and $\tau_s = 120\,\mathrm{ms}$ [20]. The coupling of the neuronal to the neurotransmitter system is described by the last terms on the right hand side of Eqns (8,9). Both neuronal and neurotransmitter dynamical system are thus mutually coupled.

The neurotransmitter system uses a separate set of differential equations describing the dynamics of the neurotransmitter concentration level, given by the canonical Michaelis–Menten release-and-reuptake dynamics [19–21], using the dynamics of the neurotransmitter concentration level in a brain region measured with PET. This is defining the interaction between the neuronal and neurotransmitter system through the coupling of the raphe nuclei. The reverse coupling, that is the effect of the neurotransmitter system on the neuronal system, is modelled as a dynamical system of neuronal activity. In this way, both neuronal and neurotransmitter dynamical system are explicitly expressed and mutually coupled. Please note that this is of course a simplified version of several mechanisms regulating the number/density of receptors at the synaptic level, of which some are in response to synaptic activity. However, the excellent fitting to the empirical data suggests that this level of abstraction is highly effective.

Overall, the study of the mutually coupled model showed that it is the entangled dynamics that precisely explain neuroimaging data; in this case the specific modulation of the serotonin system by psilocybin (administered intravenously in healthy participants). First, the entangled whole-brain model was created by fitting to a sensitive measure of the neuronal activity, using PMS space for the empirical psilocybin data (placebo and active condition) and the Leading Eigenvector Dynamics Analysis method [65]. Testing the entangled model by uncoupling the neuromodulators from the neuronal systems showed that this produced highly significant breakdown in fitting the empirical data (Fig. 1B). In further simulations, we tested the role of particular parts of the coupling dynamics. First, the simulations were run until dynamics reached a steady state. The feedback dynamics from neuromodulators to the neuronal system were then halted by decoupling the input from the raphe nucleus. This resulted again in a significant breakdown of the fits to the empirical data (Fig. 1C). Next, to explore the role of the receptor distribution, further simulations were run in which local 5-HT2A receptor densities were randomly shuffled (Fig. 1D) and replaced by other serotonin receptors, known to be much less sensitive to psilocybin (5-HT1A, 5-HT1B and 5-HT4, not shown).

In this study, we tested the effect of each of the single 5-HT receptor types against each other. We assumed in all cases that this source of heterogeneity is adjusting the gain of the neuronal response, which can be interpreted as the balance of excitation/inhibition. Future work could include investigations of multiple interacting 5-HT receptors. One way to do this is by setting the source of heterogeneity as the linear, simultaneous combination of multiple 5-HT receptors, which can be optimized using global techniques to find the best weighting of the receptors optimally fitting the

empirical results. In this way, the role of each receptor type is adapting the gain (level of excitation/inhibition) independently and the contribution of each receptor can then be ascertained.

As can be appreciated, these results demonstrate the relevance of using a biophysically realistic dynamic neuromodulator system, allowing for full entanglement between the dynamics of both neuronal and neuromodulation systems. Overall, the entangled whole-brain framework is therefore likely to be essential for accurately modelling and explaining mechanisms of human brain function in health and disease.

Gain matters - Receptor-specific scaling of internal brain communication processes and external sensory drive

A given brain state is constituted by whole-brain network activity shaped by the dynamical landscape of the brain. Changes between brain states come about when the effective connectivity changes as a function of for example neuromodulation of the local excitation-inhibition ratio in distributed brain regions [17]. In turn, this changes the information transfer across the brain [66]. For example, a large body of literature has shown that cortical state changes affect ongoing activity and its interaction with sensory-driven activity [67–83]. Importantly, as in particular neuromodulators affect the state of cortical networks [84], modulatory receptor-mediated changes in whole-brain dynamics may alter the balance between ongoing ('top-down') and evoked ('bottom-up') communication processes (see Fig. 2 for a sketch of effects of unbalanced scaling of internal ongoing and sensory-evoked activity) and therefore affect broadcasting across the brain. Consequently, neuromodulators crucially impact on the formation of sensory perception [85–87] and higher cognitive functions [88–93].

That 5-HT is one of the prominent neuromodulators involved in the modulation of cortical state [94] becomes apparent by measuring 5-HT-induced changes of the frequency spectrum of cortical activity [95–97]. As also implemented in our whole-brain model, 5-HT is centrally released from neurons in the median raphe and the dorsal raphe nuclei [98–102]. Additionally, and as also largely incorporated in our model, the 5-HT system consists of widespread projections that innervate subcortical areas and all cortical areas [101,103–106], where different types of 5-HT receptors (depolarizing or inhibitory) are co-distributed across different cortical cell types [107–109]. This makes 5-HT indeed a good candidate for the participation in fine-tuned scaling of evoked and ongoing components of cortical activity [110] and their integration across brain-wide networks [30,111,112].

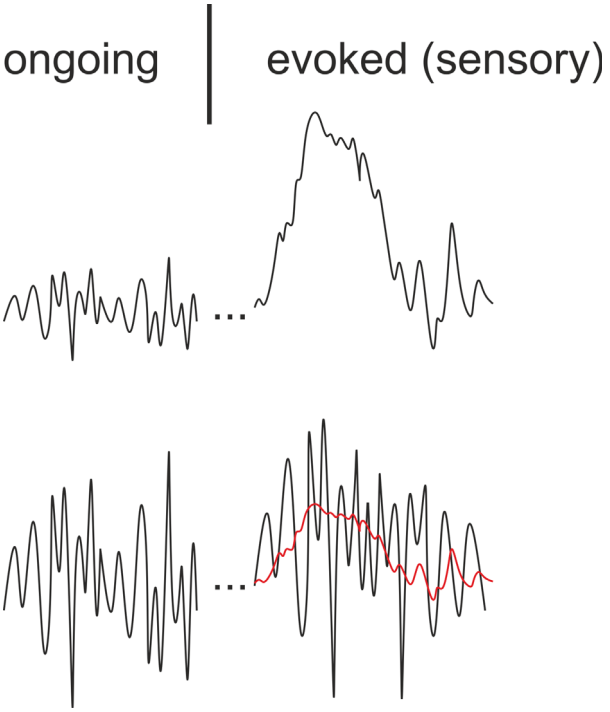

Fig. 2. Effects of unbalanced scaling of internal ongoing activity and sensory-evoked input. Upper: Separate downscaling in amplitude of ongoing activity (left) leads to emphasis of sensory-evoked activity (right). Hence, cortical processes are biased towards external events. Bottom: Conversely, upscaling of ongoing activity (left) while reducing the gain of sensory drive (right, red trace depicts mean amplitude) leads to emphasis of internal brain broadcasts. Hence, cortical processes are biased towards internal communications that overwrite external sensory processing.

However, could the function of single 5-HT receptor types factually be attributed to distinct and separable effects on either sensory-evoked or internally ongoing activity as our whole-brain model implicates? To address this question experimentally, we used an ePet-Cre mouse line [27] that allowed controlled release of 5-HT by photostimulation of Channelrhodopsin2 expressing 5-HT neurons in the raphe nuclei [25,26]. In parallel we used optical imaging of Ca^{2+} fluorescent indicators to track 5-HT-induced modulations of neuronal activity in the visual cortex *in vivo* (Fig. 3).

Upon photostimulation, a pronounced downscaling of activity was found that affected both spontaneous baseline levels and the magnitude of visually driven (i.e. sensory evoked) responses (Fig. 3, right middle plot). This suggests fine-tuned changes in the operating point of the cortex with balanced suppressive 5-HT effects on both sensory evoked an internally ongoing

activity. Crucially, to test for different contributions of different 5-HT receptor types we applied specific 5-HT receptor blockers by microiontophoresis into the cortical tissue [26]. The experiments revealed a prominent role of 5-HT1A receptors in reducing ongoing brain activity (i.e. downscaling the weight of internal communication processes, Fig. 3, left), whereas 5-HT2A receptors contributed to suppression of sensory input and therefore reduce the weight of external drive (Fig. 3, bottom right).

A similar 5-HT-induced modulatory scaling of either spontaneous [114] or evoked activity [115] has been reported for the primary olfactory cortex of mice. Whereas in the anaesthetized state solely spontaneous activity was affected and sensory-driven firing was spared following raphe stimulation [114], in awake animals solely evoked sensory activity was suppressed [115]. These results also support the view that the strength of 5-HT-induced scaling effects and 5-HT targeting of different components of brain activity depends reciprocally on current brain states [26]. Interestingly, in the olfactory cortex the reduction in evoked sensory activity was again exclusively provided by a single 5-HT receptor type, in this case, by the Gq-pathway activating 5-HT2C receptor [115].

Altogether, based on our results, we speculate that an imbalance [116] in the recruitment of 5-HT receptors (e.g. through specific agonist intake or disordered receptor expression pattern) may affect whole-brain information flow, leading to overemphasis of internally generated expectations (i.e. favouring 'priors' [71,117], similarly as proposed for hallucinations [85,118–120]) relative to sensory input and vice versa [114]. Consequently, long-term malfunction of such interplay might trigger psychiatric diseases. Indeed, as the 5-HT2A receptor is widely expressed throughout the brain it is assumed to be specifically implicated in a number of psychiatric disorders such as depression, anxiety and schizophrenia [119,121–128]. The receptor is therefore a prominent drug target for various anxiolytics,

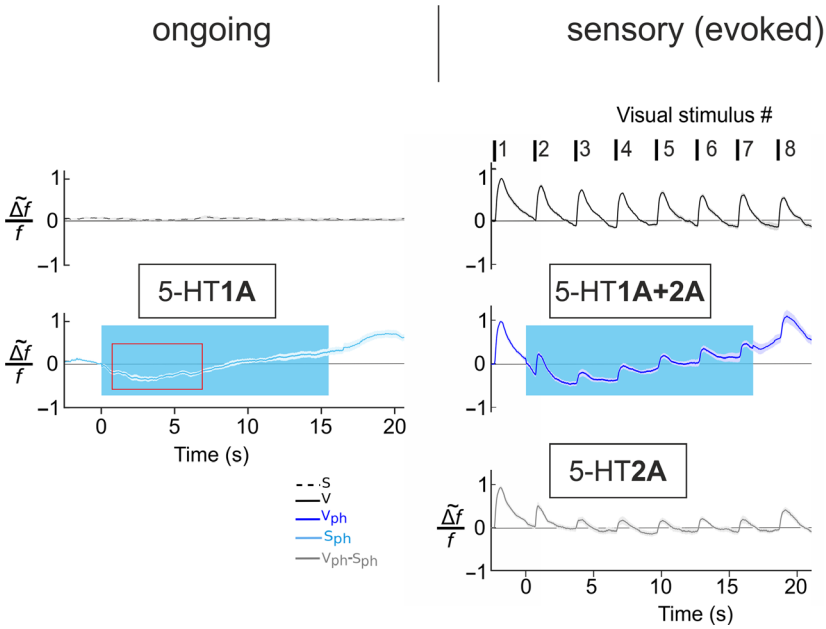

Fig. 3. Separable scaling of brain activity by different 5-HT receptors: Whereas 5-HT1A reduces ongoing internal drive, 5-HT2A reduces evoked sensory activity. Left: Ongoing spontaneous cortical activity (upper plot, stippled black trace, S) in the visual cortex is reduced (red rectangle) by increased 5-HT input (lower plot, light blue trace, S_{ph}). Release of 5-HT in the cortex was triggered by photostimulation of neurons in the raphe nuclei (blue area sketches time of light on). Right top: Controls, evoked responses to repetitive presentation of a visual grating stimulus (V, timing shown on top). Same during photostimulation (dark blue trace, middle plot, V_{ph}). Note the strong downscaling of response gain (i.e. response magnitude). Note also that this reduction was independent of the baseline reduction. This becomes evident after subtraction of the spontaneous component during photostimulation ($V_{ph} - S_{ph}$): Compare nonphotostimulated controls (black trace in upper plot) with grey trace at bottom [= dark blue trace after subtraction of spontaneous component (light blue trace in left plot)]. Specific receptor blocking by iontophoresis revealed that the reduction in each of the activity components was majorly attributed to 5-HT1A (scaling of ongoing activity) and 5-HT2A (scaling of evoked activity). Cortical responses were captured using wide-field Ca^{2+} imaging. The later rise of the signals suggests accumulation of intracellular calcium [113]. Traces are averages across V1 ($n = 8$ mice), shaded areas represent SEM. Figure modified and reproduced from [26].

antidepressants and antipsychotics and is also activated by hallucinogens [129,130]. In fact, on a longer time scale, activation of 5-HT-controlled pathways have been associated with changes in ion channel function and trafficking and formation or collapse of new synapses leading to a reconstruction of neuronal networks, which for example can have deleterious effects such as in anxiety disorders or depression [131–133].

Activating a single receptor type in the cortex through optogenetics

How close can we get in terms of experimental capabilities to demonstrate the specific contribution of a single receptor type, in this case the 5-HT2A receptor, to the scaling of evoked cortical activity? Thus far, the simultaneous measurement of cortical activity *in vivo* and the specific control of a single cortical receptor type —with precise timing and without unspecific activation of other receptor types— appeared out of experimental reach. We recently engineered therefore a construct for the visualization and control of traffic-dependent Ca^{2+} signals in 5-HT2A-R domains, which we called Ca2+-melanopsin-local-sensor (CaMello)-5HT2A [29]. This construct combines the light-activated Gq/11 coupled melanopsin, mCherry and GCaMP6m for visualization of Ca^{2+} signals and receptor trafficking and also uses the 5-HT2A C terminus for targeting the receptor construct into 5-HT2A-R-specific domains. In general, targeting G protein-coupled receptor (GPCR)-specific micro-domains is important for an understanding of the functions of GPCRs in their native cellular environment. It is also necessary in order to understand how electrochemical signals are shaped by GPCR trafficking and internalization, how they contribute to neuronal excitation and plasticity and how these signals are altered under pathological conditions. For example, increased activity of 5-HT2A-Rs might be responsible for some of the psychotic symptoms in schizophrenia [122]. Moreover, atypical antipsychotic agents may antagonize the hyperactivity and membrane targeting of 5-HT2A-Rs [134]. Furthermore, besides the Gq-phospholipase pathway, 5-HT2A-Rs also stimulate G12/13-PLA2 and Gi/o-Src pathways depending on cell-type [118,135]. Again, these observations corroborate that alterations in 5-HT2A-R trafficking and G protein signalling contribute to the development and manifestation of neuropsychiatric disorders.

In our experiments (Fig. 4), CaMello-5HT2A constructs were expressed (by means of viral transfection) in the mouse visual cortex (both in pyramidal cells and interneurons, Fig. 4B) and activated and imaged simultaneously (Fig. 4A,C). Two different constructs were injected, each in a different hemisphere. In one of the hemispheres, the construct with C-terminal, 'CaMello-5-HT2A' (Fig. 4A, blue), was used, where the C-terminal ensures that the receptor is expressed at the 5HT-2A-specific micro-domains. In the other hemisphere, the construct without C-terminal, 'CaMello' (Fig. 4A, red), was injected. Note that without the C-terminal the 5-HT2A pathway is activated but the receptor is nonspecifically expressed throughout the cell body.

Parallel imaging and receptor activation revealed that sensory-evoked activity in the hemisphere containing CaMello-5-HT2A was profoundly suppressed (Fig. 4C). This effect could repeatedly be demonstrated in the dynamics of activity following consecutive visual stimulation (Fig. 4D, left, compare blue and red traces). Importantly, suppression of evoked activity occurred in a divisive manner, as shown by the overlap of the time traces of each hemisphere after normalization (Fig. 4D, right). This means that despite the 5-HT2A-induced downscaling of activity information content itself seems not affected. It should be noted however that the method does not permit detection of possible additional effects on baseline activity levels, as receptor activation and the measurement of neuronal activity occur instantaneously. It would therefore be beneficial to develop constructs that allow activation and optical measurements with nonoverlapping wavelengths in future studies.

Taken together these experiments suggest that it is now possible to simultaneously activate and image the effects of a single receptor type in the cortex by light. Our experiments demonstrate that the 5-HT2A receptor, if expressed in receptor-specific cell domains, can specifically be attributed to a significant reduction in cortical response gain. Moreover, these observations further verify that gain control by the cortical 5-HT2A receptor has substantial and distinct effects at the level of neuronal population dynamics. Our proposed whole-brain model substantiates how such receptor type-specific activation exerts influence on entire network dynamics along with predictable modulations in brain state.

Conclusions

Our current knowledge about basic functioning of the most abundant neuronal receptor types is extensive at the level of single receptor characteristics. In most cases, we have a detailed picture regarding their individual kinetics, sensitivity to ligands and the triggered downstream intracellular cascades. This is particularly true for 5-HT receptors [113], belonging to the class of GPRCs as the largest superfamily of the human

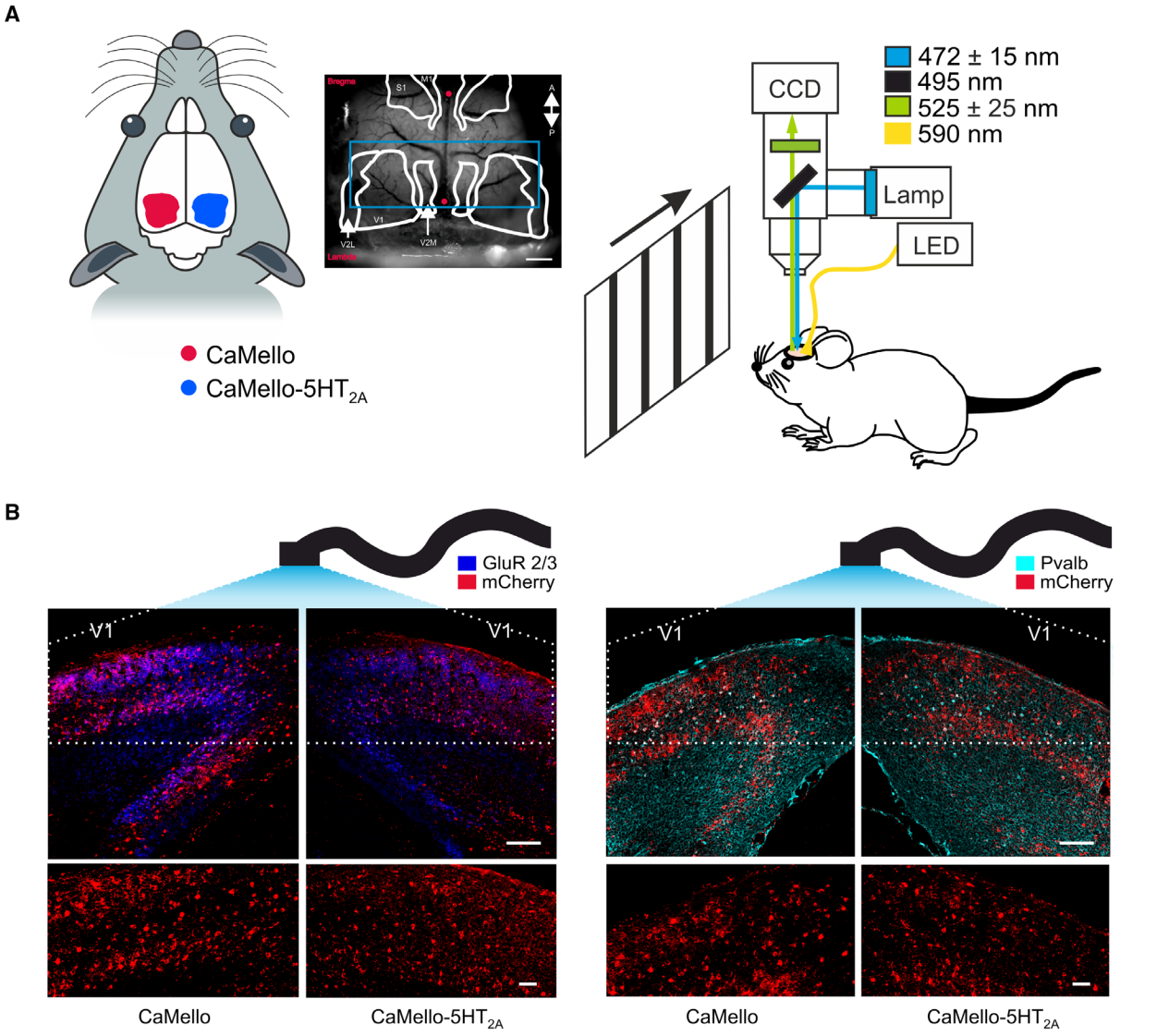

Fig. 4. Experimental visualization of changes in neuronal activity in the mouse visual cortex after activation of a single receptor type: 5-HT2A. (A) Scheme of the experimental setup. Visual stimuli were presented on a monitor at 20 cm in front of the mouse. Between recording (and photostimulation) sessions, yellow light (590 nm) was used to deactivate the constructs. Mice were anaesthetized and head-fixed. Vascular pattern of the cortex overlaid with schematics showing different cortical regions (V1, primary visual cortex). Scale bar, 1 mm. (B) Coronal images depicting brain sections of the visual cortex expressing CaMello and CaMello-5HT2A. Pyramidal neurons were antibody-stained against GluR2/3, while Pvalb^{+} neurons were stained against Pvalb (GluR: glutamate receptor; Pvalb: parvalbumin). Scale bar, 150 μm overview, 50 μm zoom (bottom). (C) Depiction of the imaged area. Top: Vascular pattern of the imaged cortical region. Middle: Activation across V1 and neighbouring visual areas after visual stimulation. Changes in activity are shown as relative change in fluorescence ($\Delta F/F$). Bottom: Overlay of the two images above. (D) Left: Traces depict the time course of spatial averages across V1 ($n = 4$ animals) for CaMello and CaMello-5HT2A in response to visual stimulation (black bars on top show stimulus timing). Right: Comparison of the normalized responses of both constructs. Figure and accompanying figure legend modified and reproduced from [29], licensed under a Creative Commons Attribution 4.0 International License.

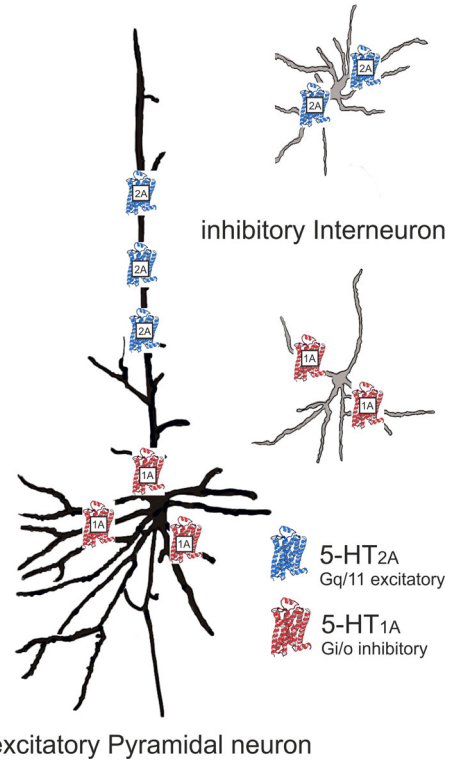

Fig. 5. Expression of 5-HT1A and 5-HT2A receptors across different cell types in cortical neurons. Note that Pyramidal neurons (black) co-express 5-HT1A/2A, which causes biphasic 5-HT responses, whereas these receptors are separately expressed in different types of interneurons (grey). In general, 5-HT1A receptors couple to the Gi/o pathway and mediate slow hyperpolarization responses, while 5-HT2A couple to the Gq/11 pathway and mediate slow depolarization responses.

genome of plasma membrane receptors (coined as 'receptorome' [136,137]), where however, still a substantial proportion termed orphan GPCRs, is awaiting basic screening [138]. 5-HT receptors are divided into subclasses, primarily dependent on whether their activation enfolds excitatory or inhibitory cascades. A plethora of perceptual effects and diseases has been associated with 5-HT receptors and therefore with potential irregularities in 5-HT impact on cortical processing.

There is, however, still a gap of knowledge regarding the neuronal function of distinct 5-HT receptors and their causal perturbative effects on whole-brain dynamics. On the one hand, the difficulty in closing this gap arises from the fact that 5-HT interacts at the same time with different types of 5-HT receptors, that are partly co-expressed and located in different types of neurons (Fig. 5). Analysis of the expression pattern in the cortex using electrophysiological and histochemical approaches suggest that 80% of the pyramidal neurons co-express 5-HT1A and 2A receptors. In fact, all pyramidal neurons in the cortex seem to express 5-HT2A receptors [108]. The modulation of cortical activity is even more complex since both receptor types in combination with other 5-HT receptors are also expressed on GABAergic interneurons [96]. It has been suggested that the differential subcellular distribution of 5-HT1A and 5-HT2A receptors determine their neuronal function, that is that 5-HT1A receptors are localized on the initial segment of pyramidal neurons to shunt action potential generation, while 5-HT2A receptors are localized to apical dendrites to amplify/support excitatory currents [96]. Back tracing the impact of individual receptor types on overall changes in cortical activity cannot easily be achieved because available agonists and antagonists are often not specific enough. Thus, so far, it remains challenging to characterize and quantify contributions of single receptor-induced changes in whole-brain dynamics and eventually, to specify their role in specific psychiatric disorders.

As an attempt to fill this explanatory gap, we here put forward the idea to use the brain's structural connectivity as a prior to estimate modes of FCD that such a system can perform. In animal experiments, we

demonstrate how different cortical receptor types, in our case embedded in the 5-HT structural system, produce distinct effects on the functional cortical dynamics in the visual cortex. To further broaden this picture, from single receptor type effects towards changes of entire brain dynamics, we introduce a new brain model that incorporates mutual interactions between the modulatory neurotransmitter system and neuronal population dynamics.

In this model the subjects' individual 'receptome' is used, that is, the unique expression patterns of density and localization of different receptor types (accounting for basic excitatory or inhibitory characteristics) to estimate their modulatory impact on whole-brain dynamics connected to various modes in brain state. We show that such approach is capable to explain single receptor-related alterations of whole-brain dynamics in individual subjects. Furthermore, we propose that this approach opens the door for biomarkers, as modulatory changes in cortical state relate to changes in sensory processing and consequently, to specific changes in perception and behaviour.

We also would like to point out important current limitations of our outlined approaches. Evidently, due to their invasive nature optogenetic applications are restricted to animal experiments, even though optogenetic therapies (e.g. for retinal diseases [139]) are in progress. Another substantial gap to be crossed in the future is to adapt and expand our whole-brain model towards evoked sensory and motor processes that involve natural behavioural tasks.

Finally, the gap between microscopic single receptor activity and its effects on large-scale whole-brain activity that we try to bridge here, must further be filled at the level of mesoscopic circuitry dynamics (Fig. 5, sketch of the distribution of 5-HT1A and 5-HT2A receptors across different cell types). As pointed out above, receptor function is crucially dependent on its domain-specific implementation at cellular levels. There is indeed a large body of literature dealing with receptor-specific modulations of activity in cortical micro-circuitries at cellular levels that we did not address here. However, our model approach may generally be applicable also in this case. That is, to obtain a full picture across different spatial and temporal scales, future studies may zoom-in to local interactions by combining structural knowledge of cortical cellular micro-circuitries [140] with the expression patterns of individual modulatory receptor types across different cell types. Used together with an entangled whole-brain model, this would provide a powerful tool for investigating and predicting local-global interactions that could transform the potential for developing novel pharmacological interventions. This local-global integration would provide the how and where of such interventions.

Prognostic, diagnostic and therapeutic potentials

The ideas outlined in this review provide a roadmap to obtaining a causal mechanistic understanding of neuropsychiatric disorders, specifically those that have been found to be accompanied by imbalances across both local and global whole-brain levels [36]. As such, this might help discovering novel ways to develop therapeutic brain interventions that are effectively rebalancing brain networks. Our approaches may also help to find biomarkers that allow deviding out broad-illness phenotypes by a finite number of treatment-relevant subgroups [141–144]. Hence, causal systematic studies of neuromodulation and its characteristic effects on local and global changes in brain activity may broaden our knowledge of pathological states. Moreover, the development and optimization of whole-brain models with simulations of drug effects may serve deriving concrete starting-points for treatment strategies. Taken together, the current model-based framework offers a rational way to integrating structural, functional and neurotransmitter neuroimaging data for modelling brain states. Once the global influence of heterogeneity of the local dynamics (here the level of local excitability) has been established, the use of animal models will additionally help to identify regional drug receptor modulation. In this way, our depicted approaches will bridge multiple levels: local and global; human and animal; and health and disease. The resulting evidence could guide direct brain manipulations in conjunction with environmental manipulations, for example in drug-assisted psychotherapy [145], which has been shown promising for the treatment of psychological distress, mood disorders and addiction [146].

Acknowledgements

Deutsche Forschungsgemeinschaft (DFG): Dirk Jancke, JA 945/5-1; JA 945/4-1; Deutsche Forschungsgemeinschaft (DFG): Stefan Herlitze, HE 2471/12-1; 2471/18-1; Deutsche Forschungsgemeinschaft (DFG): Stefan Herlitze, Dirk Jancke, Project ID 122679504 - SFB 874, (project part A2, DJ and project part B10, SH); Deutsche Forschungsgemeinschaft (DFG): Dirk Jancke, JA 945/3-1 and Hamutal Slovin SL 185/1-1, German-Israeli Project Cooperation (DIP); Deutsche Forschungsgemeinschaft (DFG): Melanie D Mark, MA 5806/1-2; MA 5806/2-1; Deutsche Forschungsgemeinschaft (DFG): Stefan Herlitze, SFB 1280, DFG project no. 316803389; GD is supported by a Spanish national

research project (ref. PID2019-105772GB-I00 MCIU AEI) funded by the Spanish Ministry of Science, Innovation and Universities (MCIU), State Research Agency (AEI); HBP SGA3 Human Brain Project Specific Grant Agreement 3 (grant agreement no. 945539), funded by the EU H2020 FET Flagship programme; SGR Research Support Group support (ref. 2017 SGR 1545), funded by the Catalan Agency for Management of University and Research Grants (AGAUR); Neurotwin Digital twins for model-driven noninvasive electrical brain stimulation (grant agreement ID: 101017716) funded by the EU H2020 FET Proactive programme; euSNN European School of Network Neuroscience (grant agreement ID: 860563) funded by the EU H2020 MSCA-ITN Innovative Training Networks; CECH The Emerging Human Brain Cluster (ID: 001-P-001682) within the framework of the European Research Development Fund Operational Program of Catalonia 2014-2020; Brain-Connects: Brain Connectivity during Stroke Recovery and Rehabilitation (ID: 201725.33) funded by the Fundacio La Marato TV3; Corticity, FLAG–ERA JTC 2017, (ref. PCI2018-092891) funded by the Spanish Ministry of Science, Innovation and Universities (MCIU), State Research Agency (AEI). The funders had no role in study design, decision to publish, or preparation of the manuscript.

Conflicts of interest

The authors declare no conflict of interest.

Author contributions

DJ and GD drafted the initial version of the manuscript. All authors edited and revised the final manuscript.

Ethics statement

The cited research involving human subjects was performed in accordance with the standards set by the Declaration of Helsinki where participants gave written informed consent. The cited research reporting *in vivo* animal experiments was approved by the appropriate review ethics committees in accordance with the relevant institutional and national guidelines and regulations. Further information is provided in the referenced original publications.

References

1 Rapport MM, Green AA & Page IH (1948) Serum vasoconstrictor, serotonin; isolation and characterization. *J Biol Chem* **176**, 1243–1251.
2 Deneris ES & Wyler SC (2012) Serotonergic transcriptional networks and potential importance to mental health. *Nat Neurosci* **15**, 519–527.
3 Coimbra B, Soares-Cunha C, Borges S, Vasconcelos NA, Sousa N & Rodrigues AJ (2017) Impairments in laterodorsal tegmentum to VTA projections underlie glucocorticoid-triggered reward deficits. *Elife* **6**, e25843.
4 Atasoy S, Roseman L, Kaelen M, Kringelbach ML, Deco G & Carhart-Harris RL (2017) Connectome-harmonic decomposition of human brain activity reveals dynamical repertoire re-organization under LSD. *Sci Rep* **7**, 17661.
5 Tononi G, Sporns O & Edelman GM (1994) A measure for brain complexity: relating functional segregation and integration in the nervous system. *Proc Natl Acad Sci USA* **91**, 5033–5037.
6 Northoff G (2013) What the brain's intrinsic activity can tell us about consciousness? A tri-dimensional view. *Neurosci Biobehav Rev* **37**, 726–738.
7 Kringelbach ML & Deco G (2020) Brain states and transitions: insights from computational neuroscience. *Cell Rep* **32**, 108128.
8 Gervasoni D, Lin SC, Ribeiro S, Soares ES, Pantoja J & Nicolelis MA (2004) Global forebrain dynamics predict rat behavioral states and their transitions. *J Neurosci* **24**, 11137–11147.
9 Tantirigama MLS, Zolnik T, Judkewitz B, Larkum ME & Sachdev RNS (2020) Perspective on the multiple pathways to changing brain states. *Front Syst Neurosci* **14**, 23.
10 Deco G, Cruzat J, Cabral J, Tagliazucchi E, Laufs H, Logothetis NK & Kringelbach ML (2019) Awakening: predicting external stimulation to force transitions between different brain states. *Proc Natl Acad Sci USA* **116**, 18088–18097.
11 Jirsa VK, Jantzen KJ, Fuchs A & Kelso JA (2002) Spatiotemporal forward solution of the EEG and MEG using network modeling. *IEEE Trans Med Imaging* **21**, 493–504.
12 Breakspear M (2017) Dynamic models of large-scale brain activity. *Nat Neurosci* **20**, 340–352.
13 Deco G, Kringelbach ML, Jirsa VK & Ritter P (2017) The dynamics of resting fluctuations in the brain: metastability and its dynamical cortical core. *Sci Rep* **7**, 3095.
14 Deco G, Cruzat J, Cabral J, Knudsen GM, Carhart-Harris RL, Whybrow PC, Logothetis NK & Kringelbach ML (2018) Whole-brain multimodal neuroimaging model using serotonin receptor maps explains non-linear functional effects of LSD. *Curr Biol* **28**, 3065–3074.
15 Beliveau V, Ganz M, Feng L, Ozenne B, Hojgaard L, Fisher PM, Svarer C, Greve DN & Knudsen GM (2017) A high-resolution *in vivo* atlas of the human brain's serotonin system. *J Neurosci* **37**, 120–128.

16 Kringelbach ML, Cruzat J, Cabral J, Knudsen GM, Carhart-Harris R, Whybrow PC, Logothetis NK & Deco G (2020) Dynamic coupling of whole-brain neuronal and neurotransmitter systems. *Proc Natl Acad Sci USA* **117**, 9566–9576.
17 Deco G, Ponce-Alvarez A, Hagmann P, Romani GL, Mantini D & Corbetta M (2014) How local excitation-inhibition ratio impacts the whole brain dynamics. *J Neurosci* **34**, 7886–7898.
18 Deco G, Ponce-Alvarez A, Mantini D, Romani GL, Hagmann P & Corbetta M (2013) Resting-state functional connectivity emerges from structurally and dynamically shaped slow linear fluctuations. *J Neurosci* **33**, 11239–11252.
19 John CE, Budygin EA, Mateo Y & Jones SR (2006) Neurochemical characterization of the release and uptake of dopamine in ventral tegmental area and serotonin in substantia nigra of the mouse. *J Neurochem* **96**, 267–282.
20 Joshi A, Youssofzadeh V, Vemana V, McGinnity TM, Prasad G & Wong-Lin K (2017) An integrated modelling framework for neural circuits with multiple neuromodulators. *J R Soc Interface* **14**, 20160902.
21 Michaelis L & Menten ML (1913) Die Kinetik der Invertinwirkung. *Biochem Z* **49**, 333–369.
22 Varley TF, Carhart-Harris R, Roseman L, Menon DK & Stamatakis EA (2020) Serotonergic psychedelics LSD & psilocybin increase the fractal dimension of cortical brain activity in spatial and temporal domains. *NeuroImage* **220**, 117049.
23 Lord LD, Expert P, Atasoy S, Roseman L, Rapuano K, Lambiotte R, Nutt DJ, Deco G, Carhart-Harris RL, Kringelbach ML *et al.* (2019) Dynamical exploration of the repertoire of brain networks at rest is modulated by psilocybin. *NeuroImage* **199**, 127–142.
24 Carhart-Harris RL, Bolstridge M, Rucker J, Day CM, Erritzoe D, Kaelen M, Bloomfield M, Rickard JA, Forbes B, Feilding A *et al.* (2016) Psilocybin with psychological support for treatment-resistant depression: an open-label feasibility study. *Lancet Psychiatry* **3**, 619–627.
25 Azimi Z, Spoida K, Barzan R, Wollenweber P, Mark DM, Herlitze S & Jancke D (2018) Subtraction and division of visual cortical population responses by the serotonergic system. *bioRxiv* 444943 [PREPRINT].
26 Azimi Z, Barzan R, Spoida K, Surdin T, Wollenweber P, Mark MD, Herlitze S & Jancke D (2020) Separable gain control of ongoing and evoked activity in the visual cortex by serotonergic input. *Elife* **9**, e53552.
27 Scott MM, Wylie CJ, Lerch JK, Murphy R, Lobur K, Herlitze S, Jiang W, Conlon RA, Strowbridge BW & Deneris ES (2005) A genetic approach to access serotonin neurons for *in vivo* and in vitro studies. *Proc Natl Acad Sci USA* **102**, 16472–16477.
28 Spoida K, Eickelbeck D, Karapinar R, Eckhardt T, Mark MD, Jancke D, Ehinger BV, Konig P, Dalkara D, Herlitze S *et al.* (2016) Melanopsin variants as intrinsic optogenetic On and Off switches for transient versus sustained activation of G Protein pathways. *Curr Biol* **26**, 1206–1212.
29 Eickelbeck D, Karapinar R, Jack A, Suess ST, Barzan R, Azimi Z, Surdin T, Grommke M, Mark MD, Gerwert K *et al.* (2019) CaMello-XR enables visualization and optogenetic control of Gq/11 signals and receptor trafficking in GPCR-specific domains. *Commun Biol* **2**, 60.
30 Conio B, Martino M, Magioncalda P, Escelsior A, Inglese M, Amore M & Northoff G (2019) Opposite effects of dopamine and serotonin on resting-state networks: review and implications for psychiatric disorders. *Mol Psychiatry* **25**, 82–93.
31 Breakspear M, Jirsa V & Deco G (2010) Computational models of the brain: from structure to function. *NeuroImage* **52**, 727–730.
32 Deco G, Jirsa VK & McIntosh AR (2011) Emerging concepts for the dynamical organization of resting-state activity in the brain. *Nat Rev Neurosci* **12**, 43–56.
33 Deco G, Jirsa V, McIntosh AR, Sporns O & Kotter R (2009) Key role of coupling, delay, and noise in resting brain fluctuations. *Proc Natl Acad Sci USA* **106**, 10302–10307.
34 Breakspear M (2004) "Dynamic" connectivity in neural systems: theoretical and empirical considerations. *Neuroinformatics* **2**, 205–226.
35 Deco G, Jirsa VK & McIntosh AR (2013) Resting brains never rest: computational insights into potential cognitive architectures. *Trends Neurosci* **36**, 268–274.
36 Deco G & Kringelbach ML (2014) Great expectations: using whole-brain computational connectomics for understanding neuropsychiatric disorders. *Neuron* **84**, 892–905.
37 Ghosh A, Rho Y, McIntosh AR, Kotter R & Jirsa VK (2008) Cortical network dynamics with time delays reveals functional connectivity in the resting brain. *Cogn Neurodyn* **2**, 115–120.
38 Honey CJ, Kotter R, Breakspear M & Sporns O (2007) Network structure of cerebral cortex shapes functional connectivity on multiple time scales. *Proc Natl Acad Sci USA* **104**, 10240–10245.
39 Goni J, van den Heuvel MP, Avena-Koenigsberger A, de Velez MN, Betzel RF, Griffa A, Hagmann P, Corominas-Murtra B, Thiran JP & Sporns O (2014) Resting-brain functional connectivity predicted by analytic measures of network communication. *Proc Natl Acad Sci USA* **111**, 833–838.
40 Kotter R (2004) Online retrieval, processing, and visualization of primate connectivity data from the CoCoMac database. *Neuroinformatics* **2**, 127–144.

41 Markov NT, Vezoli J, Chameau P, Falchier A, Quilodran R, Huissoud C, Lamy C, Misery P, Giroud P, Ullman S *et al.* (2014) Anatomy of hierarchy: feedforward and feedback pathways in macaque visual cortex. *J Comp Neurol* **522**, 225–259.
42 Recanzone GH, Merzenich MM, Jenkins WM, Grajski KA & Dinse HR (1992) Topographic reorganization of the hand representation in cortical area 3b owl monkeys trained in a frequency-discrimination task. *J Neurophysiol* **67**, 1031–1056.
43 Basser PJ & Pierpaoli C (1996) Microstructural and physiological features of tissues elucidated by quantitative-diffusion-tensor MRI. *J Magn Reson B* **111**, 209–219.
44 Beaulieu C (2002) The basis of anisotropic water diffusion in the nervous system - a technical review. *NMR Biomed* **15**, 435–455.
45 Hagmann P, Cammoun L, Gigandet X, Gerhard S, Grant PE, Wedeen V, Meuli R, Thiran JP, Honey CJ & Sporns O (2010) MR connectomics: principles and challenges. *J Neurosci Methods* **194**, 34–45.
46 Johansen-Berg H & Rushworth MF (2009) Using diffusion imaging to study human connectional anatomy. *Annu Rev Neurosci* **32**, 75–94.
47 Eickhoff SB, Constable RT & Yeo BTT (2018) Topographic organization of the cerebral cortex and brain cartography. *NeuroImage* **170**, 332–347.
48 Eickhoff SB, Yeo BTT & Genon S (2018) Imaging-based parcellations of the human brain. *Nat Rev Neurosci* **19**, 672–686.
49 Deco G & Jirsa VK (2012) Ongoing cortical activity at rest: criticality, multistability, and ghost attractors. *J Neurosci* **32**, 3366–3375.
50 Freyer F, Roberts JA, Ritter P & Breakspear M (2012) A canonical model of multistability and scale-invariance in biological systems. *PLoS Comput Biol* **8**, e1002634.
51 Markounikau V, Igel C, Grinvald A & Jancke D (2010) A dynamic neural field model of mesoscopic cortical activity captured with voltage-sensitive dye imaging. *PLoS Comput Biol* **6**, e1000919.
52 Gilson M, Moreno-Bote R, Ponce-Alvarez A, Ritter P & Deco G (2016) Estimation of directed effective connectivity from fMRI functional connectivity hints at asymmetries of cortical connectome. *PLoS Comput Biol* **12**, e1004762.
53 Dinse HR & Jancke D (2001) Time-variant processing in V1: from microscopic (single cell) to mesoscopic (population) levels. *Trends Neurosci* **24**, 203–205.
54 Onat S, König P & Jancke D (2011) Natural scene evoked population dynamics across cat primary visual cortex captured with voltage-sensitive dye imaging. *Cereb Cortex* **21**, 2542–2554.
55 Hansen EC, Battaglia D, Spiegler A, Deco G & Jirsa VK (2015) Functional connectivity dynamics: modeling the switching behavior of the resting state. *NeuroImage* **105**, 525–535.
56 Cabral J, Luckhoo H, Woolrich M, Joensson M, Mohseni H, Baker A, Kringelbach ML & Deco G (2014) Exploring mechanisms of spontaneous functional connectivity in MEG: how delayed network interactions lead to structured amplitude envelopes of band-pass filtered oscillations. *NeuroImage* **90**, 423–435.
57 Deco G, Cabral J, Woolrich MW, Stevner ABA, van Hartevelt TJ & Kringelbach ML (2017) Single or multiple frequency generators in on-going brain activity: a mechanistic whole-brain model of empirical MEG data. *NeuroImage* **152**, 538–550.
58 Deco G, Cruzat J & Kringelbach ML (2019) Brain songs framework used for discovering the relevant timescale of the human brain. *Nat Commun* **10**, 583.
59 Abbott LF & Chance FS (2005) Drivers and modulators from push-pull and balanced synaptic input. *Prog Brain Res* **149**, 147–155.
60 Wong KF & Wang XJ (2006) A recurrent network mechanism of time integration in perceptual decisions. *J Neurosci* **26**, 1314–1328.
61 Burns BD & Webb AC (1976) The spontaneous activity of neurones in the cat's cerebral cortex. *Proc R Soc Lond B Biol Sci* **194**, 211–223.
62 Koch KW & Fuster JM (1989) Unit activity in monkey parietal cortex related to haptic perception and temporary memory. *Exp Brain Res* **76**, 292–306.
63 Shadlen MN & Newsome WT (1998) The variable discharge of cortical neurons: implications for connectivity, computation, and information coding. *J Neurosci* **18**, 3870–3896.
64 Softky WR & Koch C (1993) The highly irregular firing of cortical cells is inconsistent with temporal integration of random EPSPs. *J Neurosci* **13**, 334–350.
65 Cabral J, Vidaurre D, Marques P, Magalhaes R, Silva MP, Miguel SJ, Deco G, Sousa N & Kringelbach ML (2017) Cognitive performance in healthy older adults relates to spontaneous switching between states of functional connectivity during rest. *Sci Rep* **7**, 5135.
66 Deco G, Tononi G, Boly M & Kringelbach ML (2015) Rethinking segregation and integration: contributions of whole-brain modelling. *Nat Rev Neurosci* **16**, 430–439.
67 Arieli A, Sterkin A, Grinvald A & Aertsen A (1996) Dynamics of ongoing activity: explanation of the large variability in evoked cortical responses. *Science* **273**, 1868–1871.
68 Deneux T & Grinvald A (2017) Milliseconds of sensory input abruptly modulate the dynamics of cortical states for seconds. *Cereb Cortex* **27**, 4549–4563.
69 Ferezou I & Deneux T (2017) Review: How do spontaneous and sensory-evoked activities interact? *Neurophotonics* **4**, 031221.

70 Ferezou I, Haiss F, Gentet LC, Aronoff R, Weber B & Petersen CCH (2007) Spatiotemporal dynamics of cortical sensorimotor integration in behaving mice. *Neuron* **56**, 907–923.
71 Fiser J, Berkes P, Orban G & Lengyel M (2010) Statistically optimal perception and learning: from behavior to neural representations. *Trends Cogn Sci* **14**, 119–130.
72 Fox MD, Snyder AZ, Zacks JM & Raichle ME (2006) Coherent spontaneous activity accounts for trial-to-trial variability in human evoked brain responses. *Nat Neurosci* **9**, 23–25.
73 Haider B, Duque A, Hasenstaub AR, Yu Y & McCormick DA (2007) Enhancement of visual responsiveness by spontaneous local network activity *in vivo*. *J Neurophysiol* **97**, 4186–4202.
74 He BJ (2013) Spontaneous and task-evoked brain activity negatively interact. *J Neurosci* **33**, 4672–4682.
75 Kasanetz F, Riquelme LA & Murer MG (2002) Disruption of the two-state membrane potential of striatal neurones during cortical desynchronisation in anaesthetised rats. *J Physiol* **543**, 577–589.
76 Kenet T, Bibitchkov D, Tsodyks M, Grinvald A & Arieli A (2003) Spontaneously emerging cortical representations of visual attributes. *Nature* **425**, 954–956.
77 Luczak A, Bartho P & Harris KD (2009) Spontaneous events outline the realm of possible sensory responses in neocortical populations. *Neuron* **62**, 413–425.
78 McGinley MJ, Vinck M, Reimer J, Batista-Brito R, Zagha E, Cadwell CR, Tolias AS, Cardin JA & McCormick DA (2015) Waking state: rapid variations modulate neural and behavioral responses. *Neuron* **87**, 1143–1161.
79 Niell CM & Stryker MP (2010) Modulation of visual responses by behavioral state in mouse visual cortex. *Neuron* **65**, 472–479.
80 Raichle ME (2015) The restless brain: how intrinsic activity organizes brain function. *Philos Trans R Soc Lond B Biol Sci* **370**, 20140172.
81 Schölvinck ML, Saleem AB, Benucci A, Harris KD & Carandini M (2015) Cortical state determines global variability and correlations in visual cortex. *J Neurosci* **35**, 170–178.
82 Shimaoka D, Steinmetz NA, Harris KD & Carandini M (2019) The impact of bilateral ongoing activity on evoked responses in mouse cortex. *Elife* **8**, e43533.
83 Brickwedde M, Krüger MC & Dinse HR (2019) Somatosensory alpha oscillations gate perceptual learning efficiency. *Nat Commun* **10**, 263.
84 Marder E (2012) Neuromodulation of neuronal circuits: back to the future. *Neuron* **76**, 1–11.
85 Cassidy CM, Balsam PD, Weinstein JJ, Rosengard RJ, Slifstein M, Daw ND, Abi-Dargham A & Horga G (2018) A perceptual inference mechanism for hallucinations linked to striatal dopamine. *Curr Biol* **28**, 503–514.
86 Pinto L, Goard MJ, Estandian D, Xu M, Kwan AC, Lee SH, Harrison TC, Feng G & Dan Y (2013) Fast modulation of visual perception by basal forebrain cholinergic neurons. *Nat Neurosci* **16**, 1857–1863.
87 Yu AJ & Dayan P (2005) Uncertainty, neuromodulation, and attention. *Neuron* **46**, 681–692.
88 Vertechi P, Lottem E, Sarra D, Godinho B, Treves I, Quendera T, Oude Lohuis MN & Mainen ZF (2020) Inference-based decisions in a hidden state foraging task: differential contributions of prefrontal cortical areas. *Neuron* **106**, 166–176.
89 Doya K (2008) Modulators of decision making. *Nat Neurosci* **11**, 410–416.
90 Hesselmann G, Kell CA, Eger E & Kleinschmidt A (2008) Spontaneous local variations in ongoing neural activity bias perceptual decisions. *Proc Natl Acad Sci USA* **105**, 10984–10989.
91 Hurley LM, Devilbiss DM & Waterhouse BD (2004) A matter of focus: monoaminergic modulation of stimulus coding in mammalian sensory networks. *Curr Opin Neurobiol* **14**, 488–495.
92 Sadaghiani S, Hesselmann G, Friston KJ & Kleinschmidt A (2010) The relation of ongoing brain activity, evoked neural responses, and cognition. *Front Syst Neurosci* **4**, 20.
93 Lottem E, Banerjee D, Vertechi P, Sarra D, Lohuis MO & Mainen ZF (2018) Activation of serotonin neurons promotes active persistence in a probabilistic foraging task. *Nat Commun* **9**, 1000.
94 Celada P, Puig MV & Artigas F (2013) Serotonin modulation of cortical neurons and networks. *Front Integr Neurosci* **7**, 25.
95 Puig MV, Watakabe A, Ushimaru M, Yamamori T & Kawaguchi Y (2010) Serotonin modulates fast-spiking interneuron and synchronous activity in the rat prefrontal cortex through 5-HT1A and 5-HT2A receptors. *J Neurosci* **30**, 2211–2222.
96 Puig MV & Gulledge AT (2011) Serotonin and prefrontal cortex function: neurons, networks, and circuits. *Mol Neurobiol* **44**, 449–464.
97 Grandjean J, Corcoba A, Kahn MC, Upton AL, Deneris ES, Seifritz E, Helmchen F, Mann EO, Rudin M & Saab BJ (2019) A brain-wide functional map of the serotonergic responses to acute stress and fluoxetine. *Nat Commun* **10**, 350.
98 Dahlstrom A & Fuxe K (1964) Localization of monoamines in the lower brain stem. *Experientia* **20**, 398–399.
99 Descarries L, Watkins KC, Garcia S & Beaudet A (1982) The serotonin neurons in nucleus raphe dorsalis of adult rat: a light and electron microscope radioautographic study. *J Comp Neurol* **207**, 239–254.

100 Ishimura K, Takeuchi Y, Fujiwara K, Tominaga M, Yoshioka H & Sawada T (1988) Quantitative analysis of the distribution of serotonin-immunoreactive cell bodies in the mouse brain. *Neurosci Lett* **91**, 265–270.
101 Mengod G, Vilaro MT, Cortes R, Lopez-Gimenez JF, Raurich A & Palacios JM (2006) Chemical euroanatomy of 5-HT receptor subtypes in the mammalian brain. In The Serotonin Receptors: From Molecular Pharmacology to Human Therapeutics (Roth BL, ed), pp. 319–364.Humana Press, Totowa, NJ.
102 Mengod G, Vilaro MT, Raurich A, Lopez-Gimenez JF, Cortes R & Palacios JM (1996) 5-HT receptors in mammalian brain: receptor autoradiography and in situ hybridization studies of new ligands and newly identified receptors. *Histochem J* **28**, 747–758.
103 Waterhouse BD, Mihailoff GA, Baack JC & Woodward DJ (1986) Topographical distribution of dorsal and median raphe neurons projecting to motor, sensorimotor, and visual cortical areas in the rat. *J Comp Neurol* **249**, 460–481.
104 Hale MW & Lowry CA (2011) Functional topography of midbrain and pontine serotonergic systems: implications for synaptic regulation of serotonergic circuits. *Psychopharmacology* **213**, 243–264.
105 Jacobs BL & Azmitia EC (1992) Structure and function of the brain serotonin system. *Physiol Rev* **72**, 165–229.
106 Vertes RP & Linley SB (2007) Comparison of projections of the dorsal and median raphe nuclei, with some functional considerations. *Internatonal Congress Series* **1304**, 98–120.
107 Santana N, Bortolozzi A, Serrats J, Mengod G & Artigas F (2004) Expression of serotonin1A and serotonin2A receptors in pyramidal and GABAergic neurons of the rat prefrontal cortex. *Cereb Cortex* **14**, 1100–1109.
108 Leysen JE (2004) 5-HT2 receptors. *Curr Drug Targets CNS Neurol Disord* **3**, 11–26.
109 Hannon J & Hoyer D (2008) Molecular biology of 5-HT receptors. *Behav Brain Res* **195**, 198–213.
110 Shimegi S, Kimura A, Sato A, Aoyama C, Mizuyama R, Tsunoda K, Ueda F, Araki S, Goya R & Sato H (2016) Cholinergic and serotonergic modulation of visual information processing in monkey V1. *J Physiol Paris* **110**, 44–51.
111 Berger M, Gray JA & Roth BL (2009) The expanded biology of serotonin. *Annu Rev Med* **60**, 355–366.
112 Lesch KP & Waider J (2012) Serotonin in the modulation of neural plasticity and networks: implications for neurodevelopmental disorders. *Neuron* **76**, 175–191.
113 Andrade R (2011) Serotonergic regulation of neuronal excitability in the prefrontal cortex. *Neuropharmacology* **61**, 382–386.
114 Lottem E, Lorincz ML & Mainen ZF (2016) Optogenetic activation of dorsal raphe serotonin neurons rapidly inhibits spontaneous but not odor-evoked activity in olfactory cortex. *J Neurosci* **36**, 7–18.
115 Wang D, Wang X, Liu P, Jing S, Du H, Zhang L, Jia F & Li A (2020) Serotonergic afferents from the dorsal raphe decrease the excitability of pyramidal neurons in the anterior piriform cortex. *Proc Natl Acad Sci USA* **117**, 3239–3247.
116 Buchborn T, Schroder H, Hollt V & Grecksch G (2014) Repeated lysergic acid diethylamide in an animal model of depression: Normalisation of learning behaviour and hippocampal serotonin 5-HT2 signalling. *J Psychopharmacol* **28**, 545–552.
117 Berkes P, Orban G, Lengyel M & Fiser J (2011) Spontaneous cortical activity reveals hallmarks of an optimal internal model of the environment. *Science* **331**, 83–87.
118 Gonzalez-Maeso J, Weisstaub NV, Zhou M, Chan P, Ivic L, Ang R, Lira A, Bradley-Moore M, Ge Y, Zhou Q *et al.* (2007) Hallucinogens recruit specific cortical 5-HT(2A) receptor-mediated signaling pathways to affect behavior. *Neuron* **53**, 439–452.
119 Jardri R, Hugdahl K, Hughes M, Brunelin J, Waters F, Alderson-Day B, Smailes D, Sterzer P, Corlett PR, Leptourgos P *et al.* (2016) Are hallucinations due to an imbalance between excitatory and inhibitory influences on the brain? *Schizophr Bull* **42**, 1124–1134.
120 Riga MS, Bortolozzi A, Campa L, Artigas F & Celada P (2016) The serotonergic hallucinogen 5-methoxy-N, N-dimethyltryptamine disrupts cortical activity in a regionally-selective manner via 5-HT(1A) and 5-HT(2A) receptors. *Neuropharmacology* **101**, 370–378.
121 Geyer MA & Vollenweider FX (2008) Serotonin research: contributions to understanding psychoses. *Trends Pharmacol Sci* **29**, 445–453.
122 Jakab RL & Goldman-Rakic PS (1998) 5-Hydroxytryptamine2A serotonin receptors in the primate cerebral cortex: possible site of action of hallucinogenic and antipsychotic drugs in pyramidal cell apical dendrites. *Proc Natl Acad Sci USA* **95**, 735–740.
123 Maroteaux L, Ayme-Dietrich E, Aubertin-Kirch G, Banas S, Quentin E, Lawson R & Monassier L (2017) New therapeutic opportunities for 5-HT2 receptor ligands. *Pharmacol Ther* **170**, 14–36.
124 Friston K (2005) Disconnection and cognitive dysmetria in schizophrenia. *Am J Psychiatry* **162**, 429–432.
125 Lucki I (1998) The spectrum of behaviors influenced by serotonin. *Biol Psychiatry* **44**, 151–162.

126 Soubrié P (1986) Reconciling the role of central serotonin neurons in human and animal behavior. *Behav Brain Res* **9**, 319–364.
127 Urban DJ, Zhu H, Marcinkiewcz CA, Michaelides M, Oshibuchi H, Rhea D, Aryal DK, Farrell MS, Lowery-Gionta E, Olsen RH *et al.* (2016) Elucidation of the behavioral program and neuronal network encoded by dorsal raphe serotonergic neurons. *Neuropsychopharmacology* **41**, 1404–1415.
128 Zhang G & Stackman RW Jr (2015) The role of serotonin 5-HT2A receptors in memory and cognition. *Front Pharmacol* **6**, 225.
129 Darmon M, Al AS, Emerit MB & Masson J (2015) Insights into serotonin receptor trafficking: cell membrane targeting and internalization. *Prog Mol Biol Transl Sci* **132**, 97–126.
130 Michaiel AM, Parker PRL & Niell CM (2019) A hallucinogenic serotonin-2A receptor agonist reduces visual response gain and alters temporal dynamics in mouse V1. *Cell Rep* **26**, 3475–3483.
131 Doze VA & Perez DM (2012) G-protein-coupled receptors in adult neurogenesis. *Pharmacol Rev* **64**, 645–675.
132 Farb DH & Ratner MH (2014) Targeting the modulation of neural circuitry for the treatment of anxiety disorders. *Pharmacol Rev* **66**, 1002–1032.
133 Meunier CN, Chameau P & Fossier PM (2017) Modulation of synaptic plasticity in the cortex needs to understand all the players. *Front Synaptic Neurosci* **9**, 2.
134 Meltzer HY (1999) The role of serotonin in antipsychotic drug action. *Neuropsychopharmacology* **21**, 106S–115S.
135 Marin P, Becamel C, Dumuis A & Bockaert J (2012) 5-HT receptor-associated protein networks: new targets for drug discovery in psychiatric disorders? *Curr Drug Targets* **13**, 28–52.
136 Setola V, Hufeisen SJ, Grande-Allen KJ, Vesely I, Glennon RA, Blough B, Rothman RB & Roth BL (2003) 3,4-methylenedioxymethamphetamine (MDMA, "Ecstasy") induces fenfluramine-like proliferative actions on human cardiac valvular interstitial cells in vitro. *Mol Pharmacol* **63**, 1223–1229.
137 Rothman RB, Vu N, Partilla JS, Roth BL, Hufeisen SJ, Compton-Toth BA, Birkes J, Young R & Glennon RA (2003) In vitro characterization of ephedrine-related stereoisomers at biogenic amine transporters and the receptorome reveals selective actions as norepinephrine transporter substrates. *J Pharmacol Exp Ther* **307**, 138–145.
138 Strachan RT, Ferrara G & Roth BL (2006) Screening the receptorome: an efficient approach for drug discovery and target validation. *Drug Discov Today* **11**, 708–716.
139 McClements ME, Staurenghi F, MacLaren RE & Cehajic-Kapetanovic J (2020) Optogenetic gene therapy for the degenerate retina: recent advances. *Front Neurosci* **14**, 570909.
140 Paquola C, Seidlitz J, Benkarim O, Royer J, Klimes P, Bethlehem RAI, Lariviere S, de Vos WR, Rodriguez-Cruces R, Hall JA *et al.* (2020) A multi-scale cortical wiring space links cellular architecture and functional dynamics in the human brain. *PLoS Biol* **18**, e3000979.
141 Trusheim MR, Berndt ER & Douglas FL (2007) Stratified medicine: strategic and economic implications of combining drugs and clinical biomarkers. *Nat Rev Drug Discov* **6**, 287–293.
142 Cuthbert BN & Insel TR (2013) Toward the future of psychiatric diagnosis: the seven pillars of RDoC. *BMC Med* **11**, 126.
143 Stephan KE, Bach DR, Fletcher PC, Flint J, Frank MJ, Friston KJ, Heinz A, Huys QJM, Owen MJ, Binder EB *et al.* (2016) Charting the landscape of priority problems in psychiatry, part 1: classification and diagnosis. *Lancet Psychiatry* **3**, 77–83.
144 Stephan KE, Binder EB, Breakspear M, Dayan P, Johnstone EC, Meyer-Lindenberg A, Schnyder U, Wang XJ, Bach DR, Fletcher PC *et al.* (2016) Charting the landscape of priority problems in psychiatry, part 2: pathogenesis and aetiology. *Lancet Psychiatry* **3**, 84–90.
145 Carhart-Harris RL, Roseman L, Haijen E, Erritzoe D, Watts R, Branchi I & Kaelen M (2018) Psychedelics and the essential importance of context. *J Psychopharmacol* **32**, 725–731.
146 Carhart-Harris RL & Goodwin GM (2017) The therapeutic potential of psychedelic drugs: past, present, and future. *Neuropsychopharmacology* **42**, 2105–2113.