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Local inhibitory plasticity tunes macroscopic brain dynamics and allows the emergence of functional brain networks

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Abstract

Rich, spontaneous brain activity has been observed across a range of different temporal and spatial scales. These dynamics are thought to be important for efficient neural functioning. A range of experimental evidence suggests that these neural dynamics are maintained across a variety of different cognitive states, in response to alterations of the environment and to changes in brain configuration (e.g., across individuals, development and in many neurological disorders). This suggests that the brain has evolved mechanisms to maintain rich dynamics across a broad range of situations. Several mechanisms based around homeostatic plasticity have been proposed to explain how these dynamics emerge from networks of neurons at the microscopic scale. Here we explore how a homeostatic mechanism may operate at the macroscopic scale: in particular, focusing on how it interacts with the underlying structural network topology and how it gives rise to well-described functional connectivity networks. We use a simple mean-field model of the brain, constrained by empirical white matter structural connectivity where each region of the brain is simulated using a pool of excitatory and inhibitory neurons. We show, as with the microscopic work, that homeostatic plasticity regulates network activity and allows for the emergence of rich, spontaneous dynamics across a range of brain configurations, which otherwise show a very limited range of dynamic regimes. In addition, the simulated functional connectivity of the homeostatic model better resembles empirical functional connectivity network. To accomplish this, we show how the inhibitory weights adapt over time to capture important graph theoretic properties of the underlying structural network. Therefore, this work presents suggests how inhibitory homeostatic mechanisms facilitate stable macroscopic dynamics to emerge in the brain, aiding the formation of functional connectivity networks.

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Keywords

Homeostasis; plasticity; neural dynamics; intrinsic connectivity networks

Introduction

Activity in the human brain is frequently characterized in terms of spontaneous neural fluctuations that are present, even in the absence of an explicit task. Evidence for such ceaseless dynamics has been reported across spatial and temporal scales and contain both spatial and temporal structure (Beggs and Plenz, 2003; Beggs and Plenz, 2004; Haimovici, 2013; Kitzbichler et al., 2009; Meisel et al., 2013; Meisel et al., 2012; Shew et al., 2009; Shew et al., 2011; Tagliazucchi et al., 2012; Yang et al., 2012). A number of theoretical frameworks have been developed to describe these dynamics (e.g., metastability (Bressler and Kelso, 2001; Friston, 1997; Kelso, 2012; Shanahan, 2010b; Tognoli and Kelso, 2014) and the notion of criticality (Beggs, 2008; Beggs and Timme, 2012; Plenz, 2014; Shew and Plenz, 2013)): broadly, brain activity exists in a highly flexible state, simultaneously maximising both integration and segregation of information, with optimised information transfer and processing capabilities (Bressler and Kelso, 2001; Friston, 1997; Kelso, 2012; Shew and Plenz, 2013; Tognoli and Kelso, 2014). One remarkable feature of spontaneous neural dynamics is that they are present in all but the most extreme of brain states (e.g., deep anaesthesia) (Brefel-Courbon et al.) and have been observed across many different brain configurations (e.g., consistent resting state networks have been reported across ontogeny and phylogeny) (Doria et al., 2010; Mantini et al., 2013).

At the macroscopic scale, a range of theoretical models have aimed to simulate brain activity and understand how neural dynamics emerge (Cabral et al., 2011; Deco and Corbetta, 2011; Deco et al., 2009; Hellyer et al., 2014; Messe et al., 2014a; Messe et al., 2014b). These models demonstrate the primary importance of the underlying structural network topology but also other factors such as, neural noise, time delays, the connectivity strength of connectivity as well as the balance of local excitation and inhibition (Deco et al., 2014). Typically, the desired characteristics of the network (e.g., spontaneous dynamics) only occur within a narrow window of parameters. Outside of the narrow parameter window these models will often fall into a pathological state: (i) no dynamics where global (activity is at ceiling or floor); or, (ii) random activity with little or no temporal or spatial structure. This is in contrast to the actual brain, which (at least approximately) maintains some degree of dynamics in the face of changing external environment as well as with many structural changes (e.g., the configuration of the brain's structural connectivity or neurotransmitter levels changing during aging) and across development and different species. Although at a coarse level, dynamics are maintained across states, at a finer level of description, dynamical regimes are not themselves static and accumulating empirical evidence suggests that how close the brain is to a critical regime varies with arousal and cognitive state (e.g., Fagerholm et al., 2015; Scott et al., 2014): being most critical in the awake resting state. Therefore, theoretical accounts of spontaneous neural dynamics must include mechanisms that maintain those dynamics in general, as well as mechanisms that can tune the dynamic regime in a more subtle way depending on cognitive state.

Homeostatic plasticity has been proposed as a potential tuning mechanism for maintaining neural dynamics based on microscopic neuronal models. At the neural level, homeostatic regulation of neuronal activity was long proposed to be mediated by excitatory neurons (Turrigiano and Nelson, 2004). However, recent work suggests that homeostasis may alternatively be regulated by the activity of inhibitory interneurons, mediated by balanced excitatory and inhibitory activity (E/I) (Vogels et al., 2011). Moreover, E/I mediated homeostasis has been shown to induce critical dynamics within a simple model with mean-field approximations of coupled excitatory and inhibitory neurons (Cowan et al., 2013; Magnasco et al., 2009). (Other adaptive mechanisms have been proposed to facilitate neural dynamics to emerge in models of microscopic neuronal networks models (Levina et al., 2007; Levina et al., 2009; Magnasco et al., 2009; Meisel and Gross, 2009; Meisel et al., 2012)).

These theoretical results (at the microscopic level) suggest that inhibitory homeostatic plasticity may provide a mechanism to stabilize brain dynamics at the macroscopic level, that this plasticity will adapt to the underlying structural topology and will be important for understanding macroscopic patterns of brain activity.

We investigate this using a mean field model of macroscopic brain activity, adapted from the Wilson-Cowan model (Wilson and Cowan, 1972) (Figure 1). The model is based on an empirically-defined white-matter network between 66 cortical regions (Cabral et al., 2011; Deco et al., 2009; Hagmann et al., 2008; Hellyer et al., 2014; Messe et al., 2014a). Each node of the model contains a pool of inhibitory and a pool of excitatory neurons; nodes receive input from other excitatory nodes weighted by the strength of long-distance white matter tracts. We adapt the model by adding a simple local learning rule that adjusts the inhibitory weight within each node such that summed excitation of the node equals a target value. We show that adding this learning rule leads to the following results: 1) it regulates the E/I balance, both locally and globally; 2) it enhances dynamics (resulting in, e.g., dynamics consistent with criticality); 3) inhibitory weights adapt over time to capture higher-order graph theory measures; 4) in the homeostatic model there is an improved correspondence between simulated and empirically-measured functional connectivity from resting state fMRI in humans. Therefore, this local inhibitory learning rule provides a mechanism whereby the underlying brain network topology can shine through while also ensuring rich, spontaneous dynamics.

Methods

Computational Modelling

We construct a macroscopic computational model of the brain, where each node represents one of 66 brain regions, modelled by Wilson-Cowan equations (Figure 1, also see “Wilson-Cowan Model” below). We used the relatively simple Wilson-Cowan model, following other researchers (Deco et al.; Messe et al.; Messe et al.), because it is computationally feasible and contains relatively few parameters making the model design phase more tractable. Although the Wilson-Cowan model is relatively simple, it does contain many key features necessary for exploring the types of macroscopic dynamics of interest. Whilst computational models can be made extraordinarily complex (with the order modelling 1000s of individual

neurons) for the sake of ‘biological realism’ often very similar dynamics are achieved by a much simpler representation of the underlying neural architecture (Bhowmik and Shanahan; Deco et al.).

In our model, each node consists of an excitatory component and an inhibitory component, approximating the mean-field of pools of excitatory and inhibitory neurons (Figure 1B). Excitatory to excitatory connectivity is defined using a well-validated atlas of structural connectivity according to tractography (Hagmann et al., 2008). There is no inhibitory to inhibitory coupling, mimicking the fact that long-range connections are excitatory. Here, the excitatory to inhibitory coupling is scaled by a constant. In this study, we also include a local inhibitory – excitatory interneuron component (Figure 1B, Red). The local weight of this excitatory – inhibitory connection follows a simple local rule, where the inhibitory-excitation coupling weight w^I adjusts such that the local excitatory activation match a target activation rate ρ (see below).

Empirical Structural Connectivity—The computational simulation is constrained according to empirical structural connectivity between 66 cortical regions defined using tractography of diffusion spectrum imaging to describe a matrix for the strength $\langle C \rangle$ and length $\langle L \rangle$ of each connection (Hagmann et al., 2008). The network constructed by these matrices is illustrated in (Figure 1A). These matrices, published by Hagmann et al. (2008), have been extensively validated in a range of different computational model regimes to demonstrate emergent properties of resting state functional connectivity (Cabral et al., 2011; Hellyer et al., 2014; Messe et al., 2014a). Briefly, average measures of length and strength of stream-line based connectivity were estimated in 5 healthy control subjects using deterministic tractography of DSI datasets (TR=4.2s, TE=89s, 129 gradient directions max b-value 9000s/mm²). Deterministic tractography was performed between 998 equal sized, and arbitrary regions of interest (ROIs) of the cortex (Hagmann et al., 2008; Hagmann et al., 2006; Hagmann et al., 2003). Measures of connectivity strength and mean streamline length between these 998 regions were then down-sampled to 66 regions according to the Desikan-Killianey atlas in Freesurfer (FreeSurfer <http://surfer.nmr.mgh.harvard.edu/>), such that C_{ij} is the number of effective streamlines which connect nodes i and j , and L_{ij} is the mean length traversed by the set of streamlines comprising C_{ij} in millimeters (mm).

Wilson-Cowan Model—To model resting state connectivity, we used a model which simulates the activity of each of the 66 cortical regions using the computationally simple Wilson-Cowan model (Wilson and Cowan) (Figure 1A). The 66 regions are modelled as a pool of coupled excitatory, inhibitory and inter neurons. The excitatory pools are recurrently connected through a weight matrix w^E derived as a scaled version of the empirical matrix such that $w^E = S\langle C \rangle$ with an empirical delay denoted by a version the $\langle L \rangle$ matrix defined above (Figure 1B, also see “Empirical Structural Connectivity” above). For each node, the activity of each pool of neurons is described by the following terms for the excitatory $E_k(t)$ pool:

$$\tau^E \frac{\partial E_k(t)}{\partial t} = -E_k(t) + \phi \left(\sum_j w_{kj}^E E_k(t - \tau(L_{kj})) - w_k^I I_k(t) + v_k(t) \right), k = 1 \dots 66$$

and the inhibitory $I_k(t)$ pool:

$$\tau \frac{\partial I_k(t)}{\partial t} = -I_k(t) + \phi(\vartheta E_k(t) + v_k(t))$$

In each pool, the nonlinearity $\phi(x)$ is defined as:

$$\phi(x) = \frac{1}{1 + e^{-ax}} - 0.5$$

$v_k(t)$ is random additive noise, independent for each node k , taken from a normal distribution with the standard deviation of $\beta = 0.25$ except where stated otherwise. $\tau^E = 20$ and $\tau^I = 20$ are the time constants for the excitatory and inhibitory nodes respectively, $a = 5$ is a constant for the nonlinearity, and ϑ is a constant E_k to I_k coupling = 0.5. Values of $\phi(x) < 0$ were set to 0, to ensure that excitatory pools could not have inhibitory effects and inhibitory pools could not have excitatory effects. Finally, the weight of the I_k to E_k coupling (Figure 1A Red) is defined by the vector w_k^I which in the case of non-homeostatic models, is a constant = 1, or in the case of homeostasis is changing according to the rule defined below. The delay term between regions of the model, controlled by the scaled $\langle L \rangle$ matrix, accounts for the delay in communication between regions imposed by neuronal conductance. The magnitude of each delay is controlled by a single factor τ which modulates the conduction velocity of excitatory to excitatory connections within the cortex. The effect of delays on neural dynamics has been well explored within similar dynamical systems models e.g., (Cabral et al.; Deco et al.). For simplicity, we set τ such that the mean velocity of delays imposed by the model is within a biologically plausible range of $\sim 11 \text{ ms}^{-1}$. The model was adapted from the code kindly provided by (Messe et al., 2014a). Where possible, parameter values were left as in the original code.

Homeostatic Inhibitory plasticity—In order to examine the effect of modulating I_k to E_k coupling according to a homeostatic rule, the weight vector w_k^I is allowed to vary online according to the rule introduced in (Vogels et al., 2011) for rate-based nodes, based on experimental data (Haas et al., 2006; Woodin et al., 2003).

The weight matrix from the inhibitory pool to the excitatory pool is determined by an inhibitory plasticity rule defined by (Figure 1A, Red):

$$\frac{\partial w_k^I}{\partial t} = \alpha I_k(t)(E_k(t) - \rho)$$

where α is the learning rate and ρ is the target activation value. It means that when the weights have converged, $\frac{\partial w_k^I}{\partial t} = 0$, the excitatory pool is activated at the value ρ , $E_k(t) = \rho$.

We first let the model recover from its initial state so that that all assessments of model dynamics were calculated after the model had run for a set period of time, the model was

then run continuously to simulate dynamics over a set number of seconds (see results), before measures of complex network dynamics were assessed. In the case of time-dependent experiments (e.g., Figures 2-4), models were run for the same amount of time (i.e., 100 seconds) in order that the noise characteristics of each model were identical. The inhibitory weights were tuned in the presence of varying amounts of noise (Figures 4, 5 and 6). However, the homeostatic weights were ‘frozen’ at the epoch described. This was done so that measures of complex dynamics were dependent on the amount of homeostatic plasticity alone, and not dependent on either on-going weight changes, or differences in model noise. However, results were qualitatively very similar if the weights were not frozen at any point.

Empirical Functional Connectivity

In order to validate the model, we compared its output with previously published empirical functional connectivity data by Honey and colleagues (2009), with an equivalent parcellation scheme to the structural connectivity dataset (Honey et al., 2009). Briefly, functional MRI data (EPI, TR=2s, TE=30ms) in the same 5 healthy control subjects as the DSI. All participants were scanned twice on separate days (scan 1 = 20 min, scan 2 = 15 min). EPI data were registered and resampled onto the b0 image of the DSI acquisition, and time series for each of the 998 ROIs were extracted. Linear de-trending of the functional data was implemented in consecutive 50-second time-windows for each ROI. The residuals of linear regression of the mean cortical, ventricular and white matter with mean BOLD signals from each ROI were used to calculate pairwise measures of resting state functional connectivity using Pearson correlation. Correlation coefficients were fisher transformed, down-sampled to the 66-region space and averaged across all 5 subjects.

Measuring critical dynamics

Avalanche dynamics—A network at criticality will exhibit population events with a probability distribution that follows a power-law function. Such an event – often termed a ‘neuronal avalanche’ is a cascade of bursts of activity in a neuronal network (Beggs and Plenz, 2003). The classical definition of neuronal avalanches, describes bursting within a neural system, bounded by periods of quiescence. Here we define bursting activity within our computational model using a point-process approach. First we identify large amplitude positive and negative excursions beyond a threshold, for each excitatory time course E_i . First we transform the data across time to zero-mean and absolute unit variance:

$$E_i(t) = \frac{1}{\sigma_{E_i}} |E_i(t) - \bar{E}_i|. \text{ Excursions of } \pm 2.3 \text{ SD were defined as a period of interest, whilst}$$

essentially an arbitrary threshold, 2.3SD represents the position within the normal Gaussian distribution, where an individual event is distinct from noise with a nominal probability of $p < 0.01$. However, qualitatively similar results are obtained with a range of smaller values of this threshold. Periods of interest were then discretised, by placing an event at the ‘trigger point’ where the signal first crossed the threshold i.e. the first time point of the period. Discretised activity across the entire system was then (optionally) re-sampled temporally into bins of Δt . Avalanches were defined as a continuous sequence of time-bins within which an event occurred somewhere within the system, bounded by time-bins where network activity was silent. The size of the cascade (S) was defined as the number of individual events that occur within each avalanche. It has been repeatedly observed using this approach

that the probability distribution of the cascade size $P(S)$ within a critical system is scale free, distributed as power law where $P(n) \sim n^{-3/2}$ (Beggs and Plenz, 2003; Beggs and Plenz, 2004; Plenz, 2012; Plenz, 2014; Plenz and Thiagarajan, 2007; Shew et al., 2009; Shriki et al., 2013; Stewart and Plenz, 2006).

Power Law Fitting—To assess the ‘goodness of fit’ of power-law distributed probability distributions, to a reference distribution, we use the previously defined measure of κ (Shew and Plenz, 2013) to compare any given distribution (F) to a probability density function with a known distribution (F^{NA}), by calculating the average distance the two distributions at logarithmically distributed points along the distribution:

$$\kappa = 1 + \frac{1}{m} \sum_{k=1}^{m=10} (F^{NA}(\beta_k) - F(\beta_k))$$

where m is the number of equally spaced comparison points for β_k , spacing the burst sizes logarithmically. If the distribution follows a power-law with a known exponent then $\kappa \approx 1$, which indicates that the network is consistent with being in a critical state. $\kappa > 1$ and $\kappa < 1$ indicate supercritical and subcritical behaviour respectively (Yang et al., 2012). We also present results using an absolute version of this measure, which provides an objective ‘goodness of fit’ to a known power-law distribution rather than describing sub or super critical activity, where:

$$\bar{\kappa} = 1 - \frac{1}{m} \sum_{k=1}^{m=10} |F^{NA}(\beta_k) - F(\beta_k)|$$

In this case, $\bar{\kappa}$ takes a value of between 0 and 1, where 1 is a perfect fit to the reference distribution, and 0 is a poor fit.

Other measures of dynamics

Coefficient of variation—In order to quantify the temporal noise properties of individual nodes in the model, we estimate the average coefficient of variation across all excitatory signals within the model, defined as the ratio of standard deviation and mean of each excitatory time-course:

$$CV = \frac{1}{N} \sum_{k=1}^{N=66} \sigma_{E_k} / \overline{E_k}$$

Where N is the total number of regions within the model.

Variability of global synchrony—To evaluate the variability of the global synchrony within the model, the output from the model was re-represented in phase space by Hilbert transforming activity in the excitatory layer over time. We note that this definition of phase of the time series is meaningful only for narrowband signals (see Glerean et al, 2012), often

assumed to be the case for resting state fMRI. We evaluated the phase history of the all time courses using the order parameters $R(t)$ and $\Phi(t)$, jointly defined by:

$$R(t)e^{i\Phi(t)} = \frac{1}{N} \sum_{n=1}^{N=66} e^{i\Theta_n(t)}$$

Where N = the total number of regions within the model. The level of synchrony between phase time-courses is described by $R(t)$, in terms of how coherently phase changes over time (Bhowmik and Shanahan, 2013; Cabral et al., 2011; Hellyer et al., 2014; Shanahan, 2010b). During fully synchronous behaviour, $R(t) = 1$ and 0 where phase across all phase time series is fully asynchronous. The global phase of the entire population of phase time series is described by $\Phi(t)$. We measure global dynamics in terms of mean global synchrony across the entire simulated timeseries ($\bar{R}$), variance σ_R as a measure of global network synchrony across the same period.

Results

Homeostatic inhibitory plasticity leads to stable E/I activity (Figure 2)

Figure 2 illustrates how a model implementing the inhibitory plasticity rule adapts over time. We consider two scenarios: (i) with a high coupling constant, $S=2.5$, (S scales the strength of between node connections); and, (ii) with a low coupling constant, $S=0.8$. In the strongly coupled scenario, the initial mean excitation is greater than the target excitation level. Over time, both excitation (Figure 2A, red) and inhibition (Figure 2B, red) decrease, with excitation and inhibition becoming more balanced (Figure 2C) and mean excitation approximating the target level, and mean inhibition slightly lower. This is accomplished by a rapid increase in the strength of local inhibitory connections, w^I , (Figure 2D, red) such that inhibition balances the strong excitatory input into each node from other nodes. In contrast, for the weakly coupled case, we see the opposite pattern (Figure 2, blue), with an increase in excitatory and inhibitory activity to the target level, and a decrease in w^I in order to balance the weak long distance excitatory input into each node.

The local inhibitory plasticity rule shapes the inhibitory weights in response to the underlying network structure (Figure 3)

The homeostatic rule attempts to match local inhibition with incoming excitation by adapting the inhibitory weights w^I . Since at each node, the incoming excitation is in part determined by the long distance excitatory to excitatory interactions constrained by the network topology of $\langle C \rangle$, we explored the extent to which the tuning of w^I is controlled by network topology. We assessed how the weights of w^I relate to a range of graph theoretical descriptions of $\langle C \rangle$ over learning. We used the following common node-based graph theoretic measures: degree (the number of connections at each node), strength (the mean weight of connections at each node), clustering coefficient (how clustered a node's neighbours are); betweenness-centrality (a measure of how many paths across the whole network pass through each node); local efficiency (length of paths between neighbouring nodes); and participation coefficient (a measure of how diverse interconnections between a

node and sub-modules with the network). For each length of active plasticity, we evaluated the correlation between each graph metric across nodes and the inhibitory weights across nodes.

Figure 2D demonstrates that immediately after enabling homeostatic-plasticity there is an initial period where the inhibitory weights, w^I , adapt rapidly followed by a stable phase where w^I plateau. During the adaptive phase, the correlation with all graph theory measures increases rapidly. However, over time some measures show a subsequent decline in favour of other measures, such as local efficiency (red) and clustering coefficient (blue). These measures reflect the connectivity of the neighbourhood connected to each node. This suggests that the inhibitory weights may be detecting higher-order statistics reflecting local community structure, rather than purely local measures (e.g., degree or strength) or measures related to how a node interacts with the whole-network (e.g., betweenness centrality). The same relationship with network structure was observed for both weakly and strongly coupled networks.

Homeostatic inhibitory plasticity enhances network dynamics (Figure 4)

The local inhibitory weights strongly affect the network's dynamics (Figure 4A). We assess network dynamics primarily using a measure from the criticality literature that based on the idea of "neuronal avalanches" (Beggs and Plenz, 2003; Beggs and Plenz, 2004). Avalanches occur when activity in nodes passes a threshold, and the avalanche size (in number of nodes affected) and duration are calculated. When dynamics are in a critical regime, the distribution of avalanche sizes should follow a power law. To assess whether dynamics were consistent with criticality, we used a measure, κ , which compares the probability distribution of sizes of simulated avalanches with a canonical power law distribution. $\kappa=1$ is consistent with a power law, and $\kappa<1$ is consistent with subcritical dynamics with relatively few large avalanches and $\kappa>1$ with supercritical dynamics with a larger number of large avalanches.

In Figure 4, we observe that the strongly and weakly coupled models are initially very different in their dynamics. The weakly coupled model is in a supercritical state with many large avalanches, whereas the more strongly coupled model has a reduced number of large avalanche events, consistent with being in a subcritical regime. However, after learning, both models converge on a dynamical regime where the distribution of avalanche sizes is near a power law, consistent with critical dynamics.

The level of the learning target rate (ρ) determines how the model adapts over time and whether it displays dynamics consistent with criticality. Figure 4B shows how κ depends on the target activation ρ , when all other model parameters are kept constant for two different levels of noise ($\beta=0.25$ solid lines, $\beta=0.01$ dotted lines). As the target rate ρ is increased, there is a continuous shift in the model dynamics from $\kappa > 1$ (indicating supercritical dynamics), passing through $\kappa=1$ (consistent with critical dynamics) before becoming $\kappa<1$ (subcritical). Of course, if the target activity is set too high, $\rho>0.2$, the model displays a pathological state, failing to adapt appropriately; since the local inhibitory weights cannot become negative, they hit their zero lower bound, and not enough excitation can be generated to match this very high ρ . In Figure 4B we also show the absolute value of κ (green line) that displays a clear peak, in this case around $\rho=0.1$, indicating that at this target

rate, the model will be in a dynamic regime closest to $\kappa = 1$. There is therefore an optimal target rate that maximises criticality. The optimal target rate depends on the level of noise of the system, consistent with previous theoretical models (Kuehn). Intuitively, if the noise is low, a low target rate is optimal whereas, with high noise, a larger target rate is required for the emergence of critical dynamics. Finally, for completeness, in figure 4C, we describe the mean absolute cross-correlation of all excitatory nodes within the model as a function of ρ .

Homeostatic inhibitory plasticity leads to robust dynamics (Figure 5)

In order to explore how the homeostatic inhibitory plasticity is able to tune model dynamics over a wide range of different starting conditions (see materials and methods), we evaluated the effect of changing noise (β) and coupling strength (S) by evaluating across the plane of $\langle S, \beta \rangle$, both without and with the homeostatic rule enabled (Figure 5). By incorporating local inhibitory plasticity, the model remains in dynamical regimes that are relatively robust to parameter values. Figure 5 presents how κ (Figure 5A) and $\bar{\kappa}$ (Figure 5B) vary across the parameter space, explicitly comparing the model with and without inhibitory plasticity (top, middle). For the non-homeostatic model (Figure 5A, top) with a low coupling constant, the model is supercritical, but as the coupling constant is increased, there is only a narrow band where $\kappa = 1$ before the model becomes subcritical. After the coupling constant becomes greater than $S \approx 5$, the non-homeostatic model breaks (the cross-hatched region in Figure 5A); above this level, excitatory input to each node reaches ceiling levels of activity, with no variation across node time courses, and consequently no dynamics. In contrast, the adaptive model (Figure 5A, middle, and Figure 5A, bottom, for a direct contrast of adaptive versus non-homeostatic) maintains an approximately similar dynamical regime (as measured by κ) across the parameter space, with $\kappa \approx 1$ for most values of noise or coupling constant, and no area where the model enters pathological states. The direct contrast between adaptive and non-homeostatic models (bottom line) shows that the adaptive model almost always shows a κ closer to 1 across the parameter space, except in the very narrow band on the left of the figure (yellow ellipse), where there is very little difference between the two types of models. As expected, analysis of $\bar{\kappa}$ across a portion of the parameter space where meaningful statistical comparisons can be made (i.e. ignoring the unstable zone where $S > 4$ and non-homeostatic dynamics disappear, shown crosshatched in figure 5), using repeated measures ANOVA using S and β as predictor variables, and the presence or absence of the homeostatic learning rule as the repeated measure, there was a main effect, of Homeostasis ($F_{1,695} = 41.14$, $p < 0.0001$). There was also a significant interaction between S and Homeostasis ($F_{1,695} = 12.29$, $p < 0.001$). This suggests that in general across the parameter space, there was a significant increase in $\bar{\kappa}$, indicative of an enhanced power-law fit of the model across a broad range of parameters.

We also calculated two other statistics of complex functional dynamics in addition to the avalanche based κ measures, to demonstrate the existence of broad changes in network dynamics: 1) the coefficient of variation over time; and, 2) the variability of synchrony of the whole network (see Methods);

The coefficient of variation is a unit-free measure of nodal variability over time, assessed by dividing the standard deviation by the mean of the timecourse (CV, Supporting Figure 1).

Across most of the parameter space, CV is greater for the adaptive rather than non-homeostatic model. CV in the non-homeostatic model has a wide range of values, depending on the coupling strength and amount of noise in the system (mean=0.17±0.44). In contrast, the adaptive model shows highly consistent levels of high variability, robust across the parameter space (mean=1±0.18). Similar to the $\bar{\kappa}$ measure, repeated measures ANOVA, demonstrated a significant effect of Homeostasis ($F_{1,695}=1782.7$, $p<0.0001$) alongside an interaction between homeostasis, S ($F_{1,695}=3674$, $p<0.0001$) and β ($F_{1,695}=55.79$, $p<0.0001$) and CV. The difference between the homeostatic and non-homeostatic model is highly correlated with change in κ between the two conditions (Pearson's correlation, $r=0.89$, $p<0.001$), suggesting that when there are dynamics consistent with criticality, the node variability will also be high.

The variability of global synchrony (M, Supporting Figure 1) measures how the synchrony of the nodes of the network changes over time. High values are expected to reflect more interesting dynamical regimes, since the model transitions from periods of more globally synchronous states to globally asynchronous states. Repeated measures ANOVA demonstrated a significant effect of Homeostasis ($F_{1,695}=216.19$, $p<0.0001$) alongside an interaction between homeostasis, S ($F_{1,695}=82$, $p<0.0001$) and β ($F_{1,695}=387$, $p<0.0001$) and the variability of global synchrony. The difference between the variability of global synchrony in the homeostatic condition versus non-homeostatic model, correlated strongly with the difference in both κ , (Pearsons correlation, $r=0.59$, $p<0.001$) and $\bar{\kappa}$ (Pearsons correlation, $r=0.23$, $p<0.001$). In order to evaluate how the variability of global synchrony related to correlation within the model – for example, decreased variability may be determined by increased global correlation, we correlated the mean correlation coefficient of the model, with the measure of variability. Without homeostasis, there was a significant relationship between mean absolute global correlation, and variability of synchrony (Pearsons correlation, $r=0.49$, $p<0.001$). This correlation was improved in the optimal-homeostatic ($\rho=0.1$) model (Pearsons correlation, $r=0.92$, $p<0.001$). The relationship between absolute global correlation and variability of synchrony, remained significant, albeit weaker for two alternative values of ρ , 0.025 (Pearsons correlation, $r=0.23$, $p<0.001$) and 0.2 (Pearsons correlation, $r=0.48$, $p<0.001$) in the sub-critical and supercritical regimes respectively. The same result was present when considering time-lagged cross correlation.

Homeostatic inhibitory plasticity improves the model fit to experimental data (Figure 5)

Previous work has suggested that models of the brain based on network structure show optimal similarity with empirically-measured functional connectivity (from fMRI) when the model is in a rich, dynamical regime (Cabral et al., 2011; Deco and Corbetta, 2011). We evaluated how well the model could replicate empirical measures of functional connectivity (FC) (Honey et al., 2009); we first calculated the pairwise correlation between pairs of E_k timecourses, compared these correlation values with a empirically derived FC values from fMRI, between the same brain regions (see materials and methods). For each of the positions in the $\langle S, \beta \rangle$ model parameter plane, we evaluated the effect of adding inhibitory plasticity on the fit of the model to empirical data. In the case of the non-homeostatic model, there is a small region of parameter space, with low coupling, where the model is able to reproduce empirical measures of FC with relatively high accuracy (Figure 5C, green ellipse). However,

with the application of the adaptive rule, similar or higher levels of similarity are found across the majority of the parameter space. Repeated measures ANOVA, demonstrated a significant effect of Homeostasis ($F_{1,695}=996.96$ $p<0.0001$) alongside an interaction between homeostasis, S ($F_{1,695}=1153.6$, $p<0.0001$) and β ($F_{1,695}=74.662$, $p<0.0001$) and the correlation between simulated and empirical measures of functional connectivity. This suggests that in general across the parameter space, the average fit of simulated functional connectivity was higher in the homeostatic model compared to the non-homeostatic model.

The regions where there is a strong correspondence between the empirical and simulated FC are also where the model shows higher values of κ (Figure 5C middle, red ellipse). This suggests that the adaptive model does not just show rich dynamics robustly across a range of situations, but also adapts to reflect functional connectivity, and therefore is more representative of empirical brain activity. Note that the level of maximum correspondence between simulated and empirical functional connectivity is of a similar magnitude to that reported previously (e.g., (Messe et al., 2014a)). There are regions in the parameter space where the non-homeostatic model performs approximately equivalent to the adaptive model. This is consistent with the results from previous non-homeostatic models which present results from a “sweet-spot” in the parameter space where κ values are close to 1 (Shew and Plenz, 2013; Shew et al., 2009). However, there are also narrow regions in the parameter space (with high noise and low connectivity, green ellipse) where the non-homeostatic model outperforms the adaptive model; these regions, though are not where the maximum correspondence between simulated and empirical data are located and are in regions with limited, subcritical dynamics for the non-homeostatic model.

Note that the results presented for the homeostatic model use the same value of ρ . P does not recalculated for every pairing of S and β , but instead a single value is robust to different noise values, outperforming the non-homeostatic model across the majority of the parameter space.

Homeostatic plasticity, activity level and periodicity of the signal (Figure 6)

To characterize how homeostatic plasticity drives the model into a rich dynamical regime, it is important to explore how it relates to the level of activation of the model and to explore whether the model express oscillations. Figure 6 shows the bifurcation analysis of the non-homeostatic computational model within the explored parameter space presented in Figure 5, showing the regions of low versus high activity and the region of periodicity. Periodicity was approximately quantified by performing a Fourier transform on each node's time course, finding the maximum magnitude and dividing this by the mean magnitude (the same results were found using the standard deviation of the magnitudes instead of the maximum) and then taking the mean across all 66 nodes. For the non-homeostatic model, the results show a clear bifurcation between low and high activity that depends on the level of coupling in the model. Similarly, we show a transition to oscillations with higher coupling constants and low levels of noise, consistent with a Hopf bifurcation.

When Figure 6 is compared to Figure 5, we see that non-homeostatic models with dynamics most consistent with criticality, lie in the low-activity non-oscillatory regime. When homeostatic plasticity is enabled in the model (arrows in Figure 6 and Supplementary Video

1), the model rapidly adapts into a similar dynamic regime across most of the parameter space; the system moves into a low activity state to the left of the high-low activity bifurcation, with a low level of periodicity.

Discussion

It has traditionally been thought that homeostatic balance within microscopic networks of neurons was maintained through the regulation of excitatory connections (Turrigiano and Nelson, 2004). However, recent experimental and theoretical work suggests that the balance of excitatory and inhibitory activity in the cortex (E/I) may be mediated by short-term plasticity (or adaptation) of inhibitory-excitatory interneurons (Vogels et al., 2011). Whilst this has been theoretically demonstrated within microscopic networks of neurons, it is unclear how these principles adapt to the macroscopic network of long distance connections at the whole brain level and how they affect neural function. We hypothesised that such a regime may be important for the emergence of functionally useful dynamics in the brain. We tested this by simulating a macroscopic model of the brain where nodes are brain regions coupled by white matter tracts (defined by diffusion imaging). We showed that: (1) local inhibitory plasticity can maintain the balance between excitation and inhibition, through a homeostatic mechanism that sets activation within a node to a target value; (2) the level of the target activation constrains the resulting dynamics that emerge across the network, determining whether the model shows dynamics that are sub- or supercritical or consistent with criticality; further across the parameter space, the homeostatic model showed consistent dynamics unlike the non-homeostatic model, which showed interesting (i.e., non-pathological dynamics) only in a narrow range of parameter values; (3) the inhibitory weights at each node evolve with learning to reflect higher-order graph theory measures such as local efficiency, showing; (4) across most of the parameter space, the homeostatic model showed a good match with empirically-defined functional connectivity, suggesting that inhibitory plasticity both improves the brain dynamics and the fit with the actual brain. The inhibitory learning rule operates locally, and yet it can tune the whole system to critical-like dynamics. Note, that the use of a local learning rule in our network is highly biologically plausible since experimental work has demonstrated local inhibitory plasticity at the neural level (Haas et al., 2006; Sprekeler et al., 2007; Woodin et al., 2003).

Interestingly, we showed that this homeostatic mechanism leads to a state, where the dynamics of the network are enhanced. In particular, there is an optimal target activation (ρ) that leads to a network expressing dynamics consistent with critical behaviour. This is broadly consistent with the theoretical accounts that demonstrate that inhibitory plasticity can bring a network of randomly connected excitatory and inhibitory neurons into a state of criticality (Cowan et al., 2013). Cowan et al. consider the case of two coupled pools of neurons (excitatory and inhibitory) that can be thought of as corresponding to one of our brain regions. Our work explores whether this behaviour can also be obtained with a much more complex architecture (involving 66 interacting pools of inhibitory/excitatory populations, whose topology is taken directly from empirical data) which cannot be simplified to a neural field approximation with homogeneous coupling.

By considering the bifurcation plots, we see that with plasticity the system moves into low activity regime close to the bifurcation and therefore the system inherits behaviour (e.g., power law avalanche distribution) consistent with criticality. As the target value ρ changes, the κ value (which is a function of how close the system is to the bifurcation) changes, and the system moves into super- or sub-critical regimes. We also see that the optimal non-homeostatic model exists in a non-oscillatory regime, and that the homeostatic plasticity moves the model into a non-oscillatory regime. This is true regardless of the starting position in the parameter space described in the bifurcation diagram (Figure 6). For example, we expect that even with a start in the oscillatory, the system would tune itself towards a non-oscillatory regime controlled by target value ρ . This is broadly consistent with the fMRI BOLD signal, which is not obviously oscillatory, and may be consistent with the presence of non-oscillatory underlying electrical potentials relating to the BOLD signal (He & Raichle, 2009).

The value of ρ by which the network is brought into a rich dynamic state is likely to be determined by biological constraints; for example, at the neuronal level, the target firing rate ρ can be measured from inhibitory plasticity experiments (Woodin et al.) in rats and is a low value (about 5Hz). In addition, the target rate, ρ , provides a way to modulate the dynamical regime, and may be a mechanism for actively controlling the dynamics in the system: e.g., moving them from near critical to slightly super- or slightly sub-critical depending on what is more functionally beneficial. This firing rate could be altered over short and medium timescales by neuromodulators such as dopamine, thereby varying the dynamics as required. Finally, it is worth mentioning that a given value of ρ allows the model to adapt to a wide range of noise and coupling values, outperforming non-homeostatic models (see Figure 5, below). Therefore, although ρ determines the extent to which the system demonstrates scale free activity, the value of ρ is relatively robust to different parameters; a single value of ρ allows the system to maintain approximate criticality in the face of changing coupling and noise. Further experimental and analytical work is required to understand precisely how this relationship may evolve in an empirical organism – for example, local values of ρ may be directly related to the deposition of specific receptor subtypes, or gene expression patterns within the brain.

We show that several different measures of flexible dynamics are enhanced across the entire parameter space with the homeostatic mechanism: flexible dynamics are thought to be functionally important to the brain as they maximise functional properties such as maximizing the dynamic range of responses of the network to inputs as well as maximizing the information capacity and transmission of the network (Shew and Plenz, 2013). By considering simulated neuronal avalanches, we demonstrate that there is a specific target that results in avalanche size distributions with a heavy tail, consistent with a power-law distributed critical dynamics. We also describe the variability of the global synchrony of the network over time (Hellyer et al., 2014; Shanahan, 2010a; Tognoli and Kelso, 2014) that has been proposed to reflect the competing desirable qualities of segregation and integration of information processing, and facilitates exploration. Finally, we show that the average amount of variation in activity over time (the coefficient of variation, supporting figure 1) is highly consistent across the parameter space in the homeostatic model (approximately balancing signal and noise), despite the fact that the amount of intrinsic noise in the model is highly

variable across different network configurations. It is increasingly well recognised that some level of noise aids optimal information processing (Faisal et al., 2008) and we find that the homeostatic rule ensures elevated but not pathological level of noise across the parameter space.

Whether the model displays enhanced dynamics (e.g., displaying regimes consistent with criticality and highly variable levels of global synchrony) depends on the target rate chosen. Although, we have assumed that approximately critical dynamics are optimal, this need not be the case. The same homeostatic mechanism can be used to constrain the network into either super- or subcritical states. For example, there may be benefits to being near a critical state but slightly sub-critical (Fagerholm et al.; Priesemann et al., 2014). If so, then a different target rate could be chosen to achieve this. In addition, there is no requirement for all nodes of the network (i.e., different brain regions) to have the same target rate. This could vary depending on the functional role of a specific brain region (e.g., (Brefel-Courbon et al.)) or depending on regional differences density of inhibitory interneurons or intrinsic or extrinsic levels of noise or the presence of neurotransmitters. For example, the neurotransmitter dopamine has been shown to alter the balance of E/I and modulate criticality (Stewart and Plenz) and be important for cognitive performance and implicated in many neuropsychiatric conditions. Macroscopic models incorporating dopamine pathways and variation in receptor densities, could be used to understand how dopamine modulates plasticity resulting in altered dynamics. For example, one speculative example is that the level of regional dopamine may modulate the level of ρ and so provide a mechanism to alter the richness of the dynamical regime. Future work could focus on the spatial variability of the regional availability of neuromodulators such as dopamine to explore how these could titrate ρ and so allow active control of how critical neural dynamics are. Better understanding these relationships may allow the development of better pharmacological or neuromodulatory interventions to optimize neural dynamics.

One of the strengths of the local inhibitory plasticity mechanism is that, in general across the parameter space, it results in a good fit with the empirical data from fMRI functional connectivity. This is in accordance with previous work, which demonstrated that a similar feedback mechanism which clamped excitatory firing to a pre-determined set level enhanced the fit of the model to empirical measures of functional connectivity (Deco, 2014), where the homeostatic rule employed may be thought of as an integrated version of the differential equation used here. Previous modelling approaches have also demonstrated that the best fit with empirical data is maximized near to criticality (Haimovici, 2013)). The benefits of this mechanism are two fold. First, it can be used as an automatic way to tune a model on-line such that it maintains good dynamics (i.e., dynamics consistent with criticality) while also letting important network structural information shine through (i.e., maximising the fit with empirical functional connectivity patterns). We see how responsive the homeostatic model is to the underlying structure, by observing that the best fit between adapted weights and graph theory metrics are with more complex measurements of clustering and local efficiency, which reflect higher-order structural information. The ability of the homeostatic plasticity to automatically tune itself means that phylogenetic (across evolution) and ontogenetic (across development) processes could potentially take advantage of these mechanisms to allow enhanced dynamics to emerge without the computationally expensive optimization

otherwise required. Second, and more importantly, it suggests that the brain is using this mechanism to stay in a “healthy regime” that: a) avoids runaway activity and therefore epileptic seizure due to the balance of excitation and inhibition; and, b) guarantees rich dynamics by bringing the network to states close to criticality, relatively immune to the noise level or the global excitatory coupling. This robustness might be important during normal brain function: for example, after learning, the excitatory to excitatory weights could be strengthened, but due to the inhibitory plasticity, the network keeps its dynamical properties. This might also be a reason why brain dynamics appear relatively preserved (although there are also important differences) across developmental stages and across individuals. There is a growing interest in understanding psychiatric syndromes such as Schizophrenia and Autism in terms of altered cortical gain control mediated by excitation – inhibition balance (Jardri and Deneve). The mechanism we define here therefore may be important in fine gain control. From a computational perspective, gain control is likely important in predictive coding of neural dynamics over time, where cortical excitability can be understood in terms of precision or salience. The disorder of excitation-inhibition balance in such disorders may therefore lead to aberrant precision in coding of neural information and thus go some way to explain false inference characteristics in disorders such as Autism and Schizophrenia (Adams et al.; Van de Cruys et al.). On the other hand, inhibitory plasticity might actually act to avoid or restrict the extent of pathological states in neurological or psychiatric disorders, e.g., following stroke or traumatic brain injuries, and may facilitate recovery over time. As such, it may be a reason why despite quite serious pathology, e.g., following a stroke, many macroscopic functional connectivity networks may appear surprisingly intact when measured using fMRI.

Future work will extend and further validate the role of homeostatic plasticity in macroscopic brain models. In particular, we can explore whether the same local inhibitory rule can maintain the dynamics as the computational model becomes more complex, incorporating more brain regions, with more realistic dynamical models (Deco et al., 2014) as well as information about neurotransmitters and different cell types (e.g., interneurons) and their regional distributions. Finally, our work is consistent with previous computational work demonstrating that in the presence of external stimuli, measures of information transmission and integration such as entropy and fisher information are enhanced by the presence of regulatory inhibition (Deco, 2014). Further work should explore how plasticity affects dynamics not just with a “resting” simulation, but also in the context of a simulation that models key cognitive states and behaviours.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

The computational model: (A) Graphical Overview of the 66 region structural connectivity matrices used in the computational model. Thickness of connecting vertices represents the strength of connections according to the connectivity matrices (Right). Hotter colours represent longer connections, according to the distance matrix. B. Schematic of two nodes linked by excitatory connections,; each node consists of coupled excitatory and inhibitory pools. C. Example timecourse of a single node from the fully coupled model ($\beta = 0.3$, $k=3$),

both in the presence (Bold) and absence (Light) of homeostatic plasticity, showing a non-oscillatory signal.

Figure 2.

A. Mean inhibitory activation as a function of simulation time during learning for models with different connectivity constants, $S=0.8$ and $S=2.5$. B. Same as in A. but for excitatory activation. C. Mean excitatory minus inhibitory activation – note that this value will not typically equal the target rate for learning (even after learning), since it is the difference before being entered into the non-linear function. D. Evolution of the mean inhibitory coupling weights with learning. Shaded regions = Confidence intervals across 100 repeats of the model.

Figure 3.

Relationship between inhibitory weights at each node and graph theory measures for the same node as they evolve with learning. We plot the correlation between inhibitory weights across nodes and graph theory measures across nodes.

Figure 4.

A) The measure, κ (assessing distance to power law form), as a function of simulation time for two different coupling strengths. After homeostatic adaptation, B) final critical measure κ (purple curves, left axis) and absolute κ (green curves, right axis) and C) the mean absolute cross-correlation (xCorr) between all excitatory nodes as a function of excitatory target value ρ . The results are shown for two different levels of noise (β).

Figure 5.

A. The measure κ (assessing distance to power law form) across the parameter space. B. Absolute κ , C. correlation (Pearson correlation coefficient of the element-wise upper triangular – excluding the diagonal) between the simulated model and the empirical data as a function of the standard deviation of the external noisy input (y-axis) and the S (x-axis), for top – non-homeostatic model, middle – adaptive-model after learning (with a fixed target rate, $\rho=0.1$), and bottom – the difference between the non-homeostatic and the adaptive model after learning.

Figure 6.

A bifurcation plot showing where there are transitions between high and low activity (red line) and evidence of periodicity in the signals (green line), measured across the parameter space used in Figure 5. The results are presented for the non-homeostatic model; the arrows show how homeostatic model changes the bifurcation plot; these changes are illustrated in more detail in supplementary video 1, where the bifurcation plot changes over learning for the homeostatic model.