Evidence for frequency-dependent cortical plasticity in the human brain

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Abstract

Frequency-dependent plasticity (FDP) describes adaptation at the synapse in response to stimulation at different frequencies. Its consequence on the structure and function of cortical networks is unknown. We tested whether cortical "resonance", favourable stimulation frequencies at which the sensory cortices respond maximally, influenced the impact of FDP on perception, functional topography and connectivity of the primary somatosensory cortex using psychophysics and functional imaging (fMRI). We co-stimulated two digits on the hand synchronously at, above, or below the resonance frequency of the somatosensory cortex, and tested subjects' accuracy and speed on tactile localisation before and after co-stimulation. More errors and slower response times followed co-stimulation at above- or below-resonance, respectively. Response times were faster after at-resonance co-stimulation. In the fMRI, the cortical representations of the two digits co-stimulated above-resonance shifted closer, potentially accounting for the poorer performance. Co-stimulation at-resonance did not shift the digit regions, but increased the functional coupling between them, potentially accounting for the improved response time. To relate these results to synaptic plasticity, we simulated a network of oscillators incorporating Hebbian learning. Two neighbouring patches embedded in a cortical sheet, mimicking the two digit regions, were co-stimulated at different frequencies. Network activation outside the stimulated patches was greatest at above-resonance frequencies, reproducing the spread of digit representations seen with fMRI. Connection strengths within the patches increased following at-resonance co-stimulation, reproducing the increased fMRI connectivity. We show that FDP extends to the cortical level and is influenced by cortical resonance.

Significance statement

We extend the concept of frequency-dependent plasticity, thus far used to describe synaptic selective adaptation in response to stimulation at different frequencies, to the level of cortical networks. We demonstrate selective changes in perception, functional topography and connectivity of the primary somatosensory cortex following tactile stimulation at different frequencies. Simulation of a network of oscillators incorporating Hebbian learning reproduced these changes and confirmed the influence of intrinsic cortical resonance on plasticity. We thus show that frequency-dependent plasticity extends to the cortical level and is influenced by cortical resonance, of potential importance for optimisation of therapeutic stimulation approaches to augment learning and memory.

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Introduction

Neuroplasticity refers to the brain's ability to modify its internal connections in response to external stimuli or following trauma and underpins many cognitive processes involved in learning and memory formation across our lifespan (1, 2). It is generally accepted that information in the brain is stored as patterns of connectivity (3) and therefore that the act of learning, whether achieved through passive stimulation or active engagement in a task, necessitates activity-dependent changes to network connectivity. This is accomplished by altering synaptic efficacy in response to external stimuli, and cellular-level studies have indicated that long-term potentiation (LTP) and long-term depression (LTD) are likely to underlie this process (4). LTP is defined as a strengthening of the synaptic connections, it was first described in the 1970s by Bliss and Lømo in their ground-breaking work on hippocampal cells (5) and has since been observed in many regions of the brain. Animal studies have shown that the frequency of synaptic activation modifies plasticity in both glutamatergic and GABAergic synapses (6-10), with reports that high vs. low-frequency stimulation results in long-term potentiation or depression respectively (4). While stimulation frequency appears to be an important factor in plasticity studies, the consequences of frequency-dependent cellular changes on the structure and function of cortical networks are unknown.

A recent study in humans found distinct frequency-dependent behavioural outcomes after tactile stimulation where low-frequency caused impaired performance, whereas high-frequency stimulation improved performance (11), see (12, 13) for reviews of similar experiments. The primary somatosensory cortex (SI) also shows rapid topographic reorganisation in response to repetitive sensory inputs (14-19). Of particular interest are the perceptual changes that accompany such reorganisation. Tactile acuity improvements following tactile stimulation of a single digit over several hours coincide with increased cortical representation of the stimulated site within SI (16-19). Furthermore, synchronous co-stimulation of two digits has been shown to lead to shifting of the cortical representations of the digit regions towards one another and impaired discrimination performance after stimulation (14, 15). SI therefore appears to be an ideal test-bed in which to study the impact of the frequency of repetitive stimulation on the plasticity of cortical networks, and associated behaviour.

A missing factor in frequency dependent plasticity studies is the notion of resonance. Neurons, neural assemblies and cortical networks all exhibit resonance characteristics, whereby they respond maximally to repetitive input within a specific favoured frequency range. For example, the human primary somatosensory cortex has a resonance frequency of approximately 20-26 Hz (20, 21). Cortical resonance is determined by both the biophysical properties of the individual neurons and the network connectivity architecture (22, 23); thus, stimulating a network near or far from its resonance

frequency may result in different network behaviours which could ultimately affect task performance. A recent computational paper investigating frequency-dependent plasticity (FDP) found that the stimulation frequency responsible for inducing maximum LTP was related to axonal length (24), an anatomical feature of cells which is thought to affect resonance in neural circuits (25, 26). Given this, we wished to examine the effect of repetitive tactile stimulation applied at a range of frequencies, at and away from resonance, on the plastic connectivity properties of the human primary somatosensory cortex.

We tested the effects of FDP on human performance and brain functional topography and connectivity of the primary somatosensory cortex using psychophysics and functional MR imaging (fMRI) in separate studies. We applied repetitive tactile co-stimulation to 2 digits on the right hand at 7 Hz (below-resonance), 23Hz (at-resonance) or 39Hz (above-resonance), and tested subjects' performance on a standard tactile localisation task before and after periods of co-stimulation. Using fMRI, we compared changes in digit region localisation and functional connectivity between the regions before and after co-stimulation at-resonance and above-resonance. To relate the behavioural and imaging results to synaptic plasticity, we implemented a computational model using a network of Wilson-Cowan (WC) oscillators (27, 28) incorporating both Hebbian learning rules and homeostatic scaling mechanisms (29). We stimulated the model with a range of driving frequencies and tested the effect of frequency on the plastic connections, drawing comparisons with our experimental results. The term, "frequency dependent plasticity", has thus far been mostly used to describe the phenomenon at cellular level. Here we extend the concept of spike-timing dependent plasticity to understanding the effects at the systems level and suggest that the phenomenon that starts at the level of the synapse has implications at the macro scale.

Results

Psychophysics: frequency-dependent mislocalisation errors

The human primary somatosensory cortex is known to exhibit resonance characteristics at approximately 20-26 Hz. We stimulated digits 2 (D2) and 4 (D4) of the right hand simultaneously with a tactile stimulator at 7 Hz (below-resonance), 23 Hz (at-resonance) or 39 Hz (above-resonance), (see Materials and Methods). We used a forced-choice tactile localisation task to test mislocalisation rates and reaction times before and after 20, 40 and 60 mins of co-stimulation (see Fig. 1).

Two-way repeated measures ANOVA with factors session (pre/post) and driving frequency (below-resonance/at-resonance/above-resonance) was performed on the mislocalisation scores obtained pre stimulation and after 60 minutes of stimulation in R (Version 3.1, R Foundation for Statistical Computing, Vienna, Austria). We found no effect of frequency, a main effect of session ($p<0.001$, $F=12.3$) and an interaction between frequency and session ($p<0.001$, $F=8.5$). Mislocalisation impairment (scores obtained after 60 minutes of co-stimulation compared to baseline) was significantly greater than zero following above-resonance stimulation only ($p<0.00001$, difference 9.73, 95% CI 6.1, 13.4). Similar statistical analysis was performed for reaction times. We found no main effect of frequency or session but an interaction between frequency and session ($p=0.003$, $F=6.6$). Reaction times (after 60 minutes of co-stimulation compared to baseline) were significantly slower following below-resonance stimulation ($p=0.006$, difference 182 ms, 95% CI 54 ms, 310 ms), and significantly faster following at-resonance stimulation ($p=0.025$, difference -156 ms, 95% CI -292 ms, -21 ms).

In summary, co-stimulation at the resonance frequency of the somatosensory cortex resulted in faster reaction times with no change in accuracy in the mislocalisation test. In contrast, co-stimulation at the above-resonance or below-resonance frequency either deteriorated task performance or slowed down reaction times, respectively.

Imaging results: frequency-dependent functional anatomy and connectivity

In order to understand the changes in the functional anatomy and connectivity associated with observed behavioural changes, we repeated the experimental protocol during an fMRI session to test changes in the cortical representations of digits D2 and D4 before and after 46 mins of co-stimulation. Both digit activation maps and functional connectivity changes were compared using the two driving frequencies ‘at-resonance’ and ‘above-resonance’. These two frequencies were chosen because we hypothesised that impaired mislocalisation (found after co-stimulation above-resonance) and faster reaction times (observed after co-stimulation at-resonance) were a result of altered cortical topography and neuronal connectivity within SI. We calculated the Euclidean distance between the

cortical maps for D2 and D4, as well as functional connectivity strength between the digit regions. The results of a mislocalisation task (identical to that described in the previous section) administered before and after the scan confirmed the results found in the psychophysics experiment reported previously.

Digit Separation

The mean distance between the centre voxel of the cortical regions of D2 and D4 before and after the two stimulation frequencies is given in Fig. 2A. Following 23 Hz co-stimulation there was a small decrease in the mean distance between the digit regions (0.73 mm, SE 0.70 mm), whereas after co-stimulation at 39 HZ there is a greater reduction in digit separation (3.4mm, SE 1.19 mm). This size of reduction is in line with those seen in previous works (14, 15). A two-way repeated measures ANOVA was performed on the digit separation distances with factors session (pre/post) and driving frequency (at-resonance/above-resonance). We found a trend for main effect of frequency ($p=0.08$, $F=3.4$), a main effect for session ($p=0.01$, $F=10.7$) and a trend for a session by frequency interaction effect ($p=0.069$, $F=3.8$). The difference between the digit regions (post compared to pre-stimulation) was significantly less than zero for the above-resonance only ($p=0.003$, difference -3.4 mm, 95% CI -5.5 mm, -1.3 mm) suggesting that the digit representations shifted/expanded towards one another in this case. The fMRI activation maps for a single participant indicating the digit regions for D2 (blue) and digit 4 D4 (red) pre (left) and post stimulation (right) with 39 Hz driving frequency in the sagittal and axial views is given in Fig. 2B.

Functional Connectivity between the Digit Regions

We calculated partial coherence as a measure of functional connectivity (FC) between the digit regions per participant for each experimental condition (30). Fig. 2C shows the average coherence across all participants for each of the 4 conditions; pre and post-stimulation for both of the driving frequencies 23 Hz and 39 Hz. After stimulation with at-resonance driving frequency (23 Hz), FC is increased between the digit regions (pre-stimulation 0.13 SE 0.02, post-stimulation 0.24 SE 0.02), whereas no change is observed in FC after stimulation at above-resonance driving frequency (39 Hz) (pre-stimulation 0.17 SE 0.03, post-stimulation 0.17 SE 0.02).

A two-way repeated ANOVA with factors session (pre/post) and driving frequency (at-resonance/above-resonance) was performed on the FC values. We found a trend towards an effect of session ($p=0.07$, $F=4.4$) no effect of frequency and a significant session by frequency interaction ($p=0.036$, $F=5.2$). FC difference (post-pre) was significantly greater than zero following at-resonance only ($p=0.007$, difference 0.10, 95% CI 0.03, 0.17).

In summary, stimulation at the resonance frequency of the somatosensory cortex resulted in strong functional connectivity, without any change in functional anatomy. In contrast, stimulation at the above-resonance frequency merged the cortical maps of the two stimulated digits but did not change functional connectivity between them.

Computational results: frequency-dependent Hebbian network formation

To link the psychophysics and imaging results to the reported data at the cellular and molecular level on FDP (3-5, 8, 31), we implemented a simulation of the experiment in an adaptive neuronal network model of coupled oscillators. Our aim was to investigate whether network connections are frequency-dependent. A network model of loosely-coupled WC oscillators (27, 28) was implemented with resonance ~15 Hz. Excitatory connections between the units were designed to exhibit Hebbian plasticity (see Materials and Methods for details of the learning rule), and inputs to all units (excitatory and inhibitory), were subject to homeostatic scaling, a mechanism by which individual neuronal units can modulate their incoming activity via their own subcellular structures (32). Two circular patches of size 156 units (radius 350 μm) embedded in a 50x50 network of loosely-coupled WC oscillators (Fig. 3A) were co-stimulated with external driving frequencies between 5 and 50 Hz.

Propagation of the signal through the network

We measured propagation of the driving frequency from the activated patches to the rest of the network by calculating the proportion of units outside the stimulated patches activated above baseline at each frequency (see Materials and Methods).

The relative power (compared to a network driven by white noise) of each unit in the network in response to below- or above-resonance stimulation of the two patches (dark red) is shown in Fig. 3B. The proportion of units external to the activated patches that were activated by each of the driving frequencies is shown in Fig. 3C. Driving frequencies below the network resonance frequency (~15 Hz) do not propagate. Stimulation propagates through the network as the frequency of stimulation increases above the resonance frequency.

Evolution of excitatory connections within the network

We evaluated connection strengths for every pair of units in the network at each driving frequency. There are three types of connections: between units within the stimulated patches (Fig. 3D left); between units within to outside (Fig. 3D middle); and between units outside the patches (Fig. 3D right). Connection strengths between units inside the patches were maximal when the stimulation frequency was close to the resonance frequency of the network. This result mirrors the increase in functional connectivity that was observed in the fMRI data previously (see Fig. 2C) and may account for the faster response time in the behavioural data. Connection strengths between units inside to

outside the stimulated patch increased with increasing driving frequency. This mirrors the expansion of the digit representations observed in the fMRI, and may account for the poor performance observed in the psychophysics test. Connection strengths between units outside the stimulated patch were unaffected by stimulation frequency.

In summary, these findings indicate that in our model there is a frequency dependence of the connectivity strengths.

Discussion

In this study, we combined psychophysics, neuroimaging and neurocomputational modelling to better understand the neural changes underlying frequency-dependent plasticity. We used an established method of digit co-stimulation (33) to induce plasticity in the human primary somatosensory cortex. We observed that plastic changes were not only modulated by the driving frequency of stimulation, but also depended on whether this frequency was at, above or below the resonance frequency of the primary somatosensory cortex (20-26 Hz) (20, 21).

Initially, the influence of frequency-specific stimulation on perceptual discrimination was tested by co-stimulation of digits 2 and 4 at one of the three driving frequencies for 1 hour. We found that co-stimulation above-resonance substantially impaired the ability to localise stimuli to one of the digits, probably due to a spreading, expanding or shifting of the digit representations within SI, a process which has previously been shown to correlate with the observed perceptual changes (15). In contrast, co-stimulation at-resonance did not affect mislocalisation, but participants were significantly faster. We hypothesised that close to its resonance frequency, there is a strengthening of the synapses within the stimulated region, resulting in greater efficiency in the Hebbian sense. Co-stimulation below-resonance did not significantly affect performance but slowed reaction times, perhaps reflecting fatigue, and indicating that plastic changes were minimal in this condition (see Fig. 1).

To validate this interpretation, we performed fMRI prior to and immediately following 46 minutes of the same co-stimulation paradigm using the two driving frequencies at- and above-resonance as both of these cases resulted in a significant change to either performance or reaction time which we hypothesised was attributable to measurable plastic change within SI. We confirmed that the digit regions shift/expand following above-resonance co-stimulation and result in a reduced separation of their centre voxel. Previous studies using similar experimental protocols but using non-continuous co-stimulation over a longer period (3 hours) reported digit shifts comparable to ours and in one case reported that these were associated with worsening task performance (14-16). We also confirmed an increase in functional connectivity between the digit regions following the at-resonance co-stimulation which was not observed for the above-resonance case.

Given that much of the prior work on FDP is carried out at the microscopic scale, we set out to link our macroscopic psychophysics and imaging observations to previous reports using computational modelling. We implemented a network model of loosely coupled WC oscillators with plastic Hebbian connections to further understand the experimental findings. We selectively stimulated two small patches within the network at a range of driving frequencies and observed the effect on signal propagation and connectivity strength within the stimulated patches and throughout the network. We

found that connections in the model behaved differently according to whether they were connecting units inside the patches (Fig. 3D left), or units inside the patches to units outside (Fig. 3D middle), or only connecting units outside the patches (Fig. 3D right). Specifically, we found i) the highest excitatory connection strengths occurred within the patches when driven at close to the resonance frequency and ii) that propagation of the signal was strongest following stimulation above the resonance frequency (Fig. 3B and C). Driving the network at frequencies below its resonance resulted in excitatory connection strengths that were weaker than in the other two conditions and this applied to connections both between network units within the stimulated patches as well as units from the patches to outside. As a result, there was also less propagation of the driving signal across the network (Fig. 3B and C).

To summarise, we found that **at-resonance** co-stimulation strengthened functional connectivity between the digit regions and speeded up reaction times. Modelling work supported the observations in that the greatest connection strengths within the stimulated patches occurred in this regime. **Above-resonance** co-stimulation impaired performance, but did not affect reaction times. Neuroimaging showed no change in FC between the digit regions but indicated that the digit regions had shifted or expanded closer together. Modelling results supported these findings in that connections from the patches to external regions (and therefore signal propagation) were greatest at higher frequencies. Previous experimental work has also shown that repetitively paired pre and postsynaptic spikes at low inter-stimulus intervals result in greater synaptic modification than for larger intervals (34). **Below-resonance** co-stimulation did not affect performance but slowed reaction times. Evidence from our modelling work indicated that at lower stimulation frequencies, connectivity within the activated patches, and from the patch to external regions, was lower than the two other stimulus conditions.

Although we do not account explicitly for plasticity of the inhibitory connections in our model, these results indicate that inhibitory processes at the border of the activated patch may be strengthened maximally during co-stimulation at-resonance, preventing the digit regions from expanding or shifting which would result in impaired performance of the mislocalisation task. There is evidence that during low frequency stimulation, GABA activity restricts excitatory synaptic potentiation, whereas at higher frequencies, the inhibitory connections are weakened (10). This phenomenon may account for the movement of the digit regions and the deterioration in performance that we observed following above-resonance stimulation. In future work, perhaps with higher resolution imaging at higher field strength, it would be interesting to determine whether the observed shift in digit regions is driven by the voxels that respond most strongly to the stimuli, or those with a weaker response, on the edge of the digit regions, corresponding to more sub-threshold activity. Previous studies have found increased coherence between neural regions correlates with faster reaction times (35) which may account for the behavioural changes observed following at-resonance stimulation. It has been suggested that

increased coherence allows optimal processing of stimulus input due to synchronised timing of the ongoing neural activity (see (36) for a review). Inclusion of reaction time mechanisms and plastic inhibitory connections are areas for further model development.

The nature of our co-stimulation (continuous repetitive stimulation at fixed frequency) is somewhat different than has been used in previous work. The majority of studies use intermittent synchronous stimulation at ~1Hz (15, 18, 19, 37), making it difficult to draw comparisons with our study. However, overall, these studies show synchronous stimulation leads to improved 2-point discrimination on the stimulated digits, yet, increased mislocalisation between co-stimulated digits. It is suggested (37) that this is due to an enlargement of cortical representations (leading to poorer localisation), yet also a strengthening of connections within those representations (leading to improved 2-point discrimination). Our results support this notion, in so much that we see spreading of representations underlying poorer mislocalisation (at above-resonance frequencies), yet stronger connections within regions leading to faster reaction times (at-resonance). It would be informative to see if at-resonance continuous stimulation improves 2-point discrimination on a single digit, as would be predicted by the model. Work by Ragert *et al* used pulsed stimulation at 20Hz (1s stimulation every 5s) and found improved 2-point spatial discrimination, but neither mislocalisation nor reaction time was reported, again making it hard to draw comparisons with our work (11). It would be interesting to consider the impact of asynchronous stimulation on our test system. Our previous work (14) shows that asynchronous stimulation results in digit separation, with similar results reported in other human (15) and animal studies (38), and so and it might be predicted that this would also be the case here. It is also important to note that while we apply peripheral stimulation, there is abundant evidence from the somatosensory steady-state response literature (20) that the temporal structure of the stimulation will be reproduced in the cortex.

Hebbian learning is thought to underlie many forms of memory formation and learning (39). In our model, we developed a Hebbian learning rule, designed to use proportional firing rates as its input so as to be suitable for use with a neural mass model that does not output spikes explicitly. In addition, input to each cell was modulated via homeostatic scaling (29). In this way, units can modulate their excitation levels allowing them to remain within suitable limits such that they are optimally responsive to their dynamic synaptic input levels (40), and remain stable. Other mechanisms of plasticity include long-term depression (41) and short-term potentiation (42), however, these were not included in the current model to simplify the calculations. The inclusion of all these biological processes is also an area for future model development.

FDP has already been shown to occur in various animal models (3, 5, 31). Inhibitory GABAergic interneurons appear to underlie this frequency dependence by causing hyperpolarisation of post-

synaptic neurons during low-frequency stimulation prohibiting glutamate binding and synaptic potentiation (43). At higher driving frequencies, GABA release is decreased, allowing synaptic potentiation to occur (10). Pioneering work by Markram and Tsodyks (44) describes the frequency-dependence of signal potentiation in the rat somatosensory cortex. They found that the boundary between potentiation and depression was dependent on properties of the synapses such as recovery rates (45). These same synaptic properties are also thought to be responsible for the resonance properties of cells (23), and therefore high and low frequency are themselves relative terms, dependent on the cell's intrinsic properties. In this work, we attempt to provide a context to better understand high and low-frequency stimulation in relationship to the resonance of the sensory systems under investigation. Indeed, we find a clear effect of stimulation frequency on cortical plasticity, with different behavioural and imaging outcomes depending on whether the stimulation is above-, at-, or below-resonance. This behaviour may be grounded in the frequency-dependence of LTP, but further work is required to improve our understanding of the potential equivalence of these phenomena.

In conclusion, by combining 3 separate experimental modalities; psychophysics, MR imaging and computational modelling, we have been able to interrogate this simple model of plasticity in humans. Translation of these key ideas to more complex methods of stimulation would be of great interest. In this paper, we have shown that the frequency of stimulation is crucial to consider when designing protocols aimed at inducing plasticity. For example, in cases where increased performance of a task that has already been learned is required, then we may wish to present the stimuli at the resonance frequency of the system; such as improving motor or language skills after stroke. Alternatively, if re-mapping of the network topography is the aim, to overcome phantom limb pain for example, then stimulation of adjacent regions using above-resonance driving frequency would be optimal. Finally, it is important to note that we measured changes in cortical organisation and connectivity in a *single scanning session,* which could be key for clinical applications where assessment of the propensity of the brain to undergo plastic change could be of relevance, for example in stroke or dementia. If it is possible to probe synaptic plasticity in a single session, then there is greater potential for it to be used as a marker or predictor of neurological decline or treatment response.

Materials and Methods

This study was approved by the University of Manchester Ethics Committee and fully informed written consent was obtained from all subjects prior to participation. For full details of the experimental procedure and analysis methods, please see SI Materials and Methods.

Psychophysics

Forty-five healthy right-handed subjects were recruited from the student/staff population (9 participants repeated two of the conditions resulting in 54 data sets). Participants were assigned to either the 7 Hz (n=19), 23 Hz (n = 17) or 39 Hz (n = 18) condition. We initially determined participants' sensory threshold of digits 2 and 4 of the right hand using the Presentation system (Neurobehavioural Systems, www.neurobs.com). Participants then completed a mislocalisation test; a two-alternative forced-choice test where subjects had to respond as to which of the two digits had been stimulated, to measure baseline mislocalisation rate. Following this, the two digits were synchronously co-stimulated for three periods of 20 minutes at one of three driving frequencies. Stimulators were driven using Matlab software (http://www.mathworks.com) that constructed a sine wave with the desired frequency (7 Hz, 23 Hz or 39 Hz) delivered in-phase to each digit. Every 20 mins (until a total of 60 mins of stimulation was complete), the subjects' completed a further mislocalisation test.

Functional MRI

MR data was acquired using a Philips 3 T Achieva system and an 8-channel phased array head coil for signal detection. Ten healthy right-handed subjects were recruited from the student/staff population (5 male). Participants attended two separate identical scanning sessions separated by at least 14 days. The scan protocol consisted of a high-resolution T_1-weighted structural image and a baseline fMRI digit localisation scan. These were followed by 46 mins of additional scanning (results not reported here) while digits 2 and 4 of the subject's right hand received constant synchronous co-stimulation at either one of the two stimulation frequencies (23/39 Hz) and a final fMRI digit localisation scan. In addition to this, participants completed a mislocalisation test immediately prior to and following the scan

Computational Modelling

In this study, we used the WC model as the basic unit of our network (27, 28). The network model we use has been described in detail previously (22), full details are given in SI Materials and Methods, but descriptions of the learning rule and simulations are given here.

The Wilson-Cowan Network Model

The WC equations describe a simple unit intended to represent a cortical minicolumn approximately 50 μm^2 in size. Units were fixed onto a two-dimensional lattice with periodic boundary conditions in order to represent a small patch of cortical sheet. All excitatory connections within the network are plastic and evolve according to a Hebbian learning rule. In addition, inputs to all units are subject to homeostatic scaling using methodology developed by Remme and Wadman (29).

Hebbian Learning within the model

Hebbian plasticity in the model is implemented through Eq. 1, which specifies the dynamics of the excitatory connectivity matrix CE. In particular, in the absence of activity from units i and j (that is $E_i = E_j = 0$), or if the product of the firing rates from units i and j is lower than the threshold h, the matrix element CE_{ij} will decay towards zero. Otherwise, if both units are active with the product of the rates E_i and E_j above the threshold h, then then there is a positive contribution to the rate of change of CE_{ij} and the synapse is enhanced. The nonlinear threshold is implemented by the Heaviside function $\theta(x)$, which is zero for $x \leq 0$ and 1 otherwise.

$$\tau_h \frac{dCE_{ij}}{dt} = -CE_{ij} + \gamma E_\mathrm{i} E_\mathrm{j} \theta\left(E_\mathrm{i} E_\mathrm{j} - h\right) \quad (1)$$

Parameters for the plasticity equations are defined as follows τ_h = 2.5 s, $\gamma = 1, h = 0.04$, The parameter h was chosen as the square of the mean firing rate for the excitatory population in response to white-noise. Therefore, in order for the connectivity to increase between two units, at least 50% of the excitatory population of each unit must be firing, the parameters τ_h, γ were chosen so that the slope of the decay (when the two units were not coincidently firing) was equal to that of the increase.

Simulations

Propagation of the signal through the network

We generated a network consisting of 50x50 identical units with parameters and connectivity profiles as described above. Two circular sub-networks (size 156 units each, radius 350 μm) within this network were stimulated with a range of driving frequencies between 5 and 50 Hz in steps of 1 Hz. We generated 100 trials consisting of 30,000 time steps for each condition, as this was the length of time needed for the plastic excitatory connectivity strengths to stabilise. A mean power series was calculated from the squared complex conjugate of the Fourier coefficients, and normalised by the total area under the curve for each unit across all trials. The response power at the driving frequency was recorded per unit per trial and this was then compared to the power of the same unit, calculated in the same way, in response to white noise input only. The response power for each of two driving frequencies, 8 Hz and 26 Hz, was calculated per-unit and given relative to the power of the same frequency in response to white-noise. We used the non-parametric Kruskal-Wallis test to determine

whether the response power at the driving frequency was significantly higher than the power of that frequency at baseline.

Evolution of excitatory connectivity within the network

The excitatory connection strength between each coupled pair was classified according to whether it connected units within the patches, units from inside to outside the patches or units outside of the patches. The final connection strength recorded at the end of each trial was averaged over trials per condition and connection type.

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Figure Legends

Fig. 1 Frequency-dependent mislocalisation errors and reaction times in a tactile discrimination task during ongoing stimulation at the resonance frequency of the somatosensory cortex (23 Hz, blue), below-resonance (7 Hz, black), and above-resonance (39 Hz, red).

Participants completed a forced-choice tactile discrimination task. Mean mislocalisation (and standard error) rates (A) and reaction times (B) at baseline and after 3 periods of 20 mins of simultaneous continuous stimulation of D2 and D4 of the right hand at one of the three frequencies. Stimulation of the digits at the resonance frequency facilitated response time at no cost to performance accuracy; whereas stimulation above or below the resonances frequency either deteriorated performance or increased reaction times, respectively.

Fig. 2 Frequency-dependent plasticity of digit region representations

(A) Digit separation. Mean distance between the cortical regions of digits D2 and D4 within SI before (blue) and after (red) co-stimulation at-resonance (23 Hz) and above-resonance (39 Hz) (n=9), standard error given as bars. The distance between the maps reduced significantly after above-resonance co-stimulation suggesting the digit regions merge together.

(B) Functional imaging of a single participant. fMRI Image from a single participant indicating the digit regions for D2 (blue) and D4 (red), pre (left) and post-stimulation (right) with 39 Hz driving frequency in the sagittal and axial views.

(C) Functional connectivity. Partial coherence averaged across all participants obtained between regions D2 and D4 for each of the 4 conditions; pre (blue) and post-stimulation (red) for both of the driving frequencies 23 Hz (left) and 39 Hz (right) (n=9), standard error given as bars. There is stronger functional coupling between the 2 digits following co-stimulation at 23 Hz.

Fig. 3 Computational Results.

(A) Schematic diagram of the WC model.

Two units are shown, both containing an excitatory (E) and an inhibitory (I) population, the parameters $W_{EE}, W_{EI}, W_{IE}, W_{II}$, describe connectivity within a single unit. Inter-unit connectivity is governed by the connectivity matrices CE and CI. Input to units from other units within the network is subject to homeostatic scaling (see Materials and Methods).

(B) Response power of each unit relative to baseline power for two driving frequencies.

The response power of each unit within the network relative to the power of the same frequency for a network driven by white-noise only is given for two driving frequencies ‘below-resonance’ (8 Hz, top) and ‘above-resonance’ (26 Hz, bottom) applied to the two activated patches (dark red). The scale

has been reduced to show the increased power around the edges and especially around and in-between the activated regions.

(C) Proportion of external units with response power higher than baseline, indicating signal propagation.

The proportion of units within the network that were external to the activated patches that had response power significantly greater than baseline is given for each of the driving frequencies calculated using the non-parametric Kruskal-Wallis test. It can be seen that propagation is low for driving frequencies lower than the resonance frequency of the network (~15 Hz). For driving frequencies above 25 Hz, the signal has propagated to almost the entire network in many cases. This indicates that propagation of the stimulus to neighbouring units is also frequency-dependent.

(D) Connectivity strength within the network as a function of driving frequency

Mean final connection strength for connections between units inside the stimulated patches (left), show maximal connectivity for driving frequency at approximately 15 Hz, the resonance of simulated network. Connections between units inside the stimulated patch and units outside the patch (middle) show maximal connectivity strengths when stimulated above the resonance frequency. Connections that neither originate in nor target the activated patch (right) act as a control and it can be seen that they are unaffected by stimulus frequency.