Catecholamines, not acetylcholine, alter cortical and perceptual dynamics in line with increased excitation-inhibition ratio

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ABSTRACT

The ratio between excitatory and inhibitory neurons (E/I ratio) is vital for cortical

circuit dynamics, computation, and behavior. This ratio may be under the

dynamic control of neuromodulatory systems, which are in turn implicated in

several neuropsychiatric disorders. In particular, the catecholaminergic

(dopaminergic and noradrenergic) and cholinergic systems have highly specific

effects on excitatory and inhibitory cortical neurons, which might translate into

changes in the local net E/I ratio. Here, we assessed and compared their net

effects on net E/I ratio in human cortex, through an integrated application of

computational modeling, placebo-controlled pharmacological intervention,

magnetoencephalographic recordings of cortical activity dynamics, and

perceptual psychophysics. We found that catecholamines, but not acetylcholine,

altered both the temporal structure of intrinsic activity fluctuations in visual and

parietal cortex, and the volatility of perceptual inference based on ambiguous

visual input. Both effects indicate that catecholamines increase the net E/I ratio in

visual and parietal cortex.

INTRODUCTION

Cortical activity fluctuates continuously, even in the absence of changes in

sensory input or motor output (1). These intrinsic fluctuations in cortical activity

are evident from the level of single neurons to large-scale networks of distant

cortical areas (2–4). Fluctuations in cortical mass activity, specifically the

amplitude modulation of ongoing oscillations, exhibit temporal structure

characteristic of so-called "scale-free" behavior: Power spectra that scale as a

function of frequency according to a power law, $P(f) \propto f^{\beta}$ (5,6), and long-range

temporal autocorrelations (7–10). This temporal structure of cortical activity varies

widely across individuals, is partly explained by genetics (11), and it exhibits

marked changes in brain disorders (12,13).

The large variability of cortical activity is not only due to the biophysics of

individual cells (1), but also due to the balance between excitatory and inhibitory

inputs to each neuron (2,14). The ratio between excitatory and inhibitory

interactions in local cortical circuits, henceforth referred to as E/I ratio, is also

essential for the characteristic structure of spontaneous cortical activity (15,16).

For example, structural variations of excitatory and inhibitory connectivity affect

the temporal structure of activity fluctuations in a model of a local cortical circuit

(15). Finally, the E/I ratio is also a key determinant of the computational

properties of individual cortical neurons (17,18) as well as the behavior of the

organism, as shown for perceptual categorization tasks (16,18–21).

This key property of cortical circuits, E/I ratio, might not be a fixed

property of cortex, but rather under dynamic control. One factor in particular

might be key for regulating cortical E/I ration and thus cortical variability as well

as behavior: dynamic variations in neuromodulatory tone (22). Modulatory

systems of the brainstem regulate cortical state through widespread ascending

projections, and they are implicated in most of the major neuropsychiatric

disorders (17,23–26). The modulatory neurotransmitters released from these

systems, such as noradrenaline or acetylcholine, alter specific elements

(pyramidal cells or inhibitory interneurons) of cortical microcircuits (27,28) as well

as the variability of cortical neurons (27,29,30). Critically, whether and how

neuromodulatory systems change the net E/I ratio and ongoing activity

fluctuations within local populations of cortical neurons has remained unknown. A

systematic, empirical assessment of the net effects on cortical E/I ratio in human

cortex would be key for understanding how synaptic and cellular effects of

neuromodulation translate into changes in human cognition and behavior, as well

as into disturbances thereof in brain disorders. However, inferences on cortical

net E/I ratio based on standard "resting-state" measurements of human cortical

population activity have, so far, been challenging.

Here, we aimed to overcome this challenge through the integrated

application of computational modeling, magnetoencephalographic (MEG)

recordings of fluctuations in cortical population activity under different

pharmacological interventions and "steady-state" task conditions, and

psychophysical measurements of bistable perceptual dynamics that are sensitive

to cortical E/I ratio (21,31,32). This integrative approach enabled us to

systematically image and compare the effects on the cortical net E/I ratio of two

major groups of neuromodulatory systems: the catecholaminergic (noradrenergic

and dopaminergic) and cholinergic systems. Importantly, we read out their effects

on cortical net E/I ratio from two separate measurements: changes in the intrinsic

fluctuations in cortical activity and of bistable perceptual dynamics. Both yielded

convergent evidence for an increase of net E/I ratio in visual and parietal cortex

due to catecholamines, but not acetylcholine.

RESULTS

We tested for changes in intrinsic perceptual and cortical dynamics under

placebo-controlled pharmacological manipulations of catecholamine (using

atomoxetine) and acetylcholine (using donepezil) levels (Fig 1A). Importantly,

intrinsic fluctuations in cortical activity were measured during two steady-state

conditions (Fig 1B): (i) fixation of an otherwise gray screen (Fixation), as in most

common studies of human "resting-state" activity; and (ii) silent counting of the

spontaneous perceptual alternations induced by a continuously presented,

ambiguous visual stimulus (Task-counting). In a third condition, subjects

immediately reported the perceptual alternations by button-press (Task-pressing).

Fig 1. Experimental design **(A, B)** Types and time course of experimental sessions. **(A)** Each
subject participated in three sessions, involving administration of placebo, atomoxetine, or
donepezil (session order randomized across subjects). Each session entailed the administration of
two pills, in the order depicted for the different session types. **(B)** Within each session, subjects
alternated between three conditions, Fixation, Task-Counting and Task-Pressing, during which
MEG was recorded (runs of 10 min each). See Materials and Methods for details. **(C)** Group
average power spectrum, averaged across all MEG sensors, for Rest and Task (Placebo condition
only).

This design capitalized on recent insights into the changes in cortical E/I-

ratio under sensory stimulation (33,34) and on the effects of cortical E/I-ratio on

bistable perceptual dynamics (21,31,32). These previous insights and our

experimental data combined, allowed for interpreting the latter in terms

alterations in net cortical E/I ratio under the pharmacological treatments.

To solidify our predictions about the impact on modulations of E/I ratio on

the intrinsic correlation structure of cortical population activity, we also simulated

the population activity of a simplified cortical circuit model made up of recurrently

connected excitatory and inhibitory neurons, under systematic variations of gain

modulation at different synapse types.

The Results section is organized as follows. We first present the effects of

the drugs on perceptual alternation rate. We then show how dynamic variations

of E/I ratio due to synaptic gain modulation alter intrinsic fluctuations in the

amplitude of cortical oscillations of a cortical circuit model. Next, we show how

manipulating catecholaminergic and cholinergic neuromodulation, affects

fluctuations in cortical activity—specifically, the temporal correlation structure of

intrinsic fluctuations in the amplitude of cortical oscillations (Fig 2), during both

steady-state conditions (Fixation and Task-counting). Finally, we discuss the drug

effects on other measures of cortical activity as well as peripheral signals. These

controls support the validity and specificity of our main conclusions.

Atomoxetine increases the rate of perceptual alternations compared to

placebo and donepezil

We used the rate of the reported alternations in perception of the ambiguous

visual structure-from-motion stimulus (Fig 1B) as a behavioral proxy for changes

in cortical E/I ratio in visual cortex. Current models of the neural dynamics

underlying bistable perception postulate that such perceptual alternations emerge

from the interplay between feedforward drive of stimulus-selective neural

populations in sensory cortex, mutual inhibition between them, adaptation, and

noise (31,32). Convergent evidence from model simulations (21) as well as

functional magnetic resonance imaging, magnetic resonance spectroscopy, and

pharmacological manipulation of GABAergic transmission (21,35) indicates that

increases in the ratio between feedforward, excitatory input to, and mutual

inhibition within the cortical circuit give rise to faster perceptual alternation rates.

Fig 2. Quantifying the temporal structure of fluctuations in oscillatory cortical activity
(A) *Top.* Time-frequency representation of MEG power fluctuations during Rest (example subject).
Bottom. Filtered signal (10 Hz; black) and the corresponding amplitude envelope (red). **(B)**
Illustration of detrended fluctuation analysis. See main text (Materials and Methods) for details. *Top.*
Cumulative sum of the amplitude envelope. *Bottom.* Detrending of cumulative sum within segments,
shown for two different window lengths N ($N_1 = 500$ ms and $N_2 = 1200$ ms). **(C)** Root-mean-square
fluctuation function $<F_N>$. In log-log coordinates, $<F_N>$ increases approximately linearly as a
function of N, with a slope that is the scaling exponent α. **(D)** Illustration of power spectrum analysis
of amplitude envelope. In log-log coordinates, the power spectrum can be approximated by a
straight line, with a slope β (power-law exponent) and an area under the curve (gray) that quantifies
the overall variance of the signal.

In this study, atomoxetine increased the rate of perceptual alternations compared

to both, placebo and donepezil (Fig 3A; atomoxetine vs. placebo: *p* = 0.007; *t* =

2.913; atomoxetine vs. donepezil: *p* = 0.001; *t* = 3.632; donepezil vs. placebo: *p* =

0.966; *t* = -0.043; all paired t-tests, pooled across Task-counting and Task-

pressing). This atomoxetine effect on the perceptual dynamics was also

significant for Task-counting *(p = 0.045; t = 2.103;* paired t-test; Fig S1A) and

Task-pressing *(p = 0.018; t = 2.540;* paired t-test; Fig S1B) individually, and the

perceptual alternation rates were highly consistent across both conditions (Fig

S1C).

Fig 3. Atomoxetine, but not donepezil, increases the rate of perceptual alternations **(A)** Number of
perceptual alternations reported by the subjects per 10 min run, pooled across task conditions
(Task-counting and Task-pressing). **(B)** Same as (A), after removing blink and eye movement data
(with linear regression).
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One potential concern is that atomoxetine might have increased the rates

of spontaneous eye blinks or fixational eye movements, inducing retinal

transients and thus fluctuations in visual cortical activity and perception, without

any change in intra-cortical E/I ratio. Three observations rule out this concern.

First, there was no significant increase during atomoxetine compared to placebo

in any of five different eye movement parameters measured here (Fig S2).

Second, none of the eye movement parameters correlated significantly with the

perceptual alternation rate (Fig S2). Third, and most importantly, the effect of

atomoxetine on the perceptual dynamics was also significant after removing (via

linear regression) the individual eye movement parameters (Fig 3B).

In sum, the psychophysical results are consistent with an atomoxetine-

induced increase in the net E/I ratio. This change should have occurred in cortical

circuits within the dorsal visual stream that govern the perceptual dynamics of

ambiguous structure-from-motion signals (36).

Effects of synaptic gain modulation on scaling behavior in a cortical circuit

model

We used the temporal correlation structure of fluctuations in cortical activity as a

separate read-out of changes on cortical E/I ratio, guided by simulations of

cortical circuit models under neuromodulation. The models of bistable perception

discussed above are sufficient for generating perceptual time courses, but are not

sufficiently realistic to generate the features of cortical mass activity evident in

physiological recordings of local field potentials or MEG signals (e.g., alpha-band

oscillations, scale-free amplitude envelope fluctuations). We used a more

complex cortical circuit model that does exhibit these features (15) as a starting

point for our modeling work (Fig 4). The model has previously been used to show

that scale-free intrinsic fluctuations in cortical activity are highly sensitive to

variations in the structural E/I ratio (i.e., the percentage of excitatory and

inhibitory connections) in the circuit (15). This model accounts for the joint

emergence of two empirically established scale-free behaviors, which we

reproduced: (i) neuronal avalanches, activity patterns propagating through the

network as evident in recordings from microelectrode arrays, with an event size

distribution following a power-law (37); and (ii) long-range temporal correlations

of the amplitude envelope fluctuations of the model's local field potential, which

we assessed empirically through MEG recordings. The power-law scaling of

avalanche size distribution was quantified in terms of the kappa-index, which

quantifies the similarity between the measured avalanche size distribution and a

theoretical power-law distribution with an exponent of -1.5 (38); a kappa index of

1 indicates perfect match between the two.

Fig 4. Dynamic modulation of excitation-inhibition ratio alters long-range temporal correlations in model of cortical patch. **(A)** Schematic of the computational model. The network consisted of 2500 excitatory and inhibitory integrate-and-fire units and random, local (within an area of 7x7 units) connectivity (magnified within the red square). **(B)** Neuromodulation was simulated as a gain modulation term multiplied with excitatory synaptic weights (w_{ee} and w_{ie}). **(C)** Detrended fluctuation analysis of model simulation (scaling exponent α of 0.85). **(D)** κ as a function of excitatory and inhibitory connectivity (with a spacing of 2.5%; means across 10 simulations per cell). The region of $\kappa \sim 1$, overlaps with the region of $\alpha > 0.5$ and splits the phase space into an excitation-dominant ($\kappa > 1$) and an inhibition-dominant region ($\kappa < 1$). The black square depicts the network configuration that was chosen for assessing the effects of neuromodulation **(E)** Scaling exponent α as a function of excitatory and inhibitory connectivity. **(F)** Same as (D) and (E), but for mean firing rate. **(F)** κ as a function of independent synaptic gain modulation. **(G)** Same as (D), but for scaling exponent α. **(H)** Same as (G), but for firing rate. Red square, baseline state of critical network before neuromodulation was applied. White line, axis of parameter combinations corresponding to changes in excitation-inhibition ratio re-plotted schematically in Fig 8.

The two phenomena unfold on different scales of spatial resolution (single

neurons vs. mass activity summed across neurons) and different temporal scales

(tens of milliseconds vs. several hundred seconds). Yet, both phenomena have

been found to emerge at the same ratio between structural excitatory and

inhibitory connectivity (15), and we replicated this finding here (Fig 4D-F).

Critically, we extended this model with a modulatory mechanism in order

to assess the impact of dynamic, multiplicative changes in cortical E/I ratio that

might result from catecholamines or acetylcholine. We first determined the

structural connectivity (small squares in Fig 4D-F) and the time scale parameters

such that the network generated intrinsic alpha-band oscillations with amplitude

fluctuations that exhibited robust long-range temporal correlations (with $\alpha \sim 0.85$,

Fig 4C), as well as neuronal avalanches with scale-free size distributions

(Materials and Methods). We then independently modulated synaptic connections

through multiplicative scaling of the weights (as illustrated in Fig 4B).

Two separate versions of the synaptic gain modulation yielded

qualitatively similar effects. In the first version shown in Fig 4, we modulated only

excitatory synapses, but independently on excitatory as well as inhibitory neurons

(EE and IE), thus producing asymmetries in the circuits net E/I ratio as in recent

modeling work on the effects of E/I ratio on a cortical circuit for perceptual

decision-making (18). In the second version (Fig S3A), we co-modulated EE and

IE and independently modulated inhibitory synapses on excitatory neurons (EI).

This was intended to simulate modulations of the GABA receptors in the former

case (mediating the effects of inhibitory neurons on others), as opposed (AMPA

or NMDA) glutamate receptors in both of the latter two cases (mediating the

effects of excitatory neurons on others). N_{EE} and N_{IE} were co-modulated by the

same factor for simplicity, because we did not assume that excitatory

(glutamatergic) synapses would be differentially modulated depending on

whether they were situated on excitatory or inhibitory target neurons.

In both versions of the model, changes in net E/I ratio altered κ (Fig 4G

and Fig S3B) as well as the scaling exponent α (Fig 4H and Fig S3C) and mean

firing rate (Fig 4I and Fig S3D). Importantly, the effect of changes in E/I ratio on

the scaling exponent α were non-monotonic, dependent on the starting point:

increases in excitation led to increases in α when starting from an inhibition-

dominant point, but to decreases in α when starting from an excitation-dominant

point (Fig 4G-I, white line).

The effects of excitatory and inhibitory gain modulation on the temporal

correlation structure of the simulated activity were qualitatively similar to the

effects of (structural) changes in the fraction of excitatory and inhibitory synapses

simulated (as shown in Fig 4D-F). We conceptualize the latter as simulations of

individual differences in cortical anatomical microstructure, and the former as

simulations of within-subject, state-dependent changes in cortical dynamics,

which are the focus of the current study. The new simulation results provided a

solid foundation for the interpretation of the pharmacological effects on

fluctuations of alpha-band amplitude envelope signals in human MEG data,

described next.

Atomoxetine, not donepezil, increases the scaling exponent of cortical

activity

We found a subtle, but robust and highly consistent increase in the scaling

exponent α of fluctuations in human MEG under atomoxetine, but not donepezil

(Fig 5 and Fig 6). We focused our analyses on amplitude envelope fluctuations in

the 8–12 Hz frequency range ("alpha band"), for two reasons. First, as expected

from previous work (39), the cortical power spectra exhibited a clearly discernible

in this frequency range, which robustly modulated with task conditions

(suppressed under Task-counting, Fig 1C). Second, the parameters of the above

model were tuned to produce oscillations in the same range (see above and (15)).

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Fig 5. Scaling exponent α for the pharmacological conditions, pooled across Fixation and Task-
counting conditions. **(A)** Mean scaling exponent across all voxels ($N = 3000$) for all three
pharmacological conditions. Compared to placebo, the exponent exhibits a significant increase
under atomoxetine, but not under donepezil. **(B, C)** Spatial distributions of drug-induced changes
(threshold: at $p = 0.05$, two-sided cluster-based permutation test). **(B)** atomoxetine vs. placebo; **(C)**
donepezil vs. placebo. **(D)** Cross-validation approach, see Results for details.
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The average scaling exponent across cortical patches and participants

during Fixation (placebo only) was $\alpha = 0.67$ ($\sigma = 0.09$) and during Task-counting

(placebo only) $\alpha = 0.64$ ($\sigma = 0.07$), indicative of robust long-range temporal

correlations during both behavioral contexts. Averaged across all cortical voxels

and across Fixation and Task-counting conditions, there was a highly significant

increase in α ($p = 0.0068$; $t = 2.93$; paired t-test) under atomoxetine ($\alpha = 0.67$, σ

$= 0.05$), compared to placebo ($\alpha = 0.65$, $\sigma = 0.05$; Fig 5A). There was no

evidence for any effect of donepezil ($\alpha = 0.66$, $\sigma = 0.05$) compared to placebo (p

$= 0.50$; $t = 0.68$; $bf = 0.68$; paired t-test; Fig 5A). The increase in scaling exponent

α under atomoxetine was widespread, but not homogenous across cortex,

comprising occipital and posterior parietal as well as a number of cortical regions

in the midline (Fig 5B, $p = 0.0022$; cluster-based permutation test).

The atomoxetine effect was, although subtle, highly reproducible across

runs. We tested this using a cross-validation approach. We first obtained a set of

voxels that were significantly increased under atomoxetine compared to placebo

(paired t-test, $p < 0.05$) during run 1 (averaged across the two behavioral

contexts, Fixation and Task-counting). Next, we extracted the average scaling

exponents across subjects for both conditions (atomoxetine and placebo) from

run 2. We repeated the procedure with a set of voxels obtained from run 2 and

extracted the scaling exponents from run 1. This unbiased approach reveals a

highly significant increase in scaling exponent α after the administration of

atomoxetine compared to placebo ($p = 0.0023$; $t = 3.365$; Fig 5D).

Repeating the spatial comparison separately for Fixation and Task-

counting yielded significant effects of atomoxetine on α during both behavioral

contexts (Fig 6A, Fixation: $p = 0.0245$; Fig 6B, Task-counting: $p = 0.0035$; cluster-

based permutation test). The significant atomoxetine effects occurred in largely

overlapping posterior cortical regions (Fig 6C). Conversely, we found no evidence

for a significant interaction between the effects of atomoxetine and task anywhere

in cortex: A direct comparison of the atomoxetine vs. placebo contrast maps

between Fixation and Task-counting yielded no significant clusters ($p > 0.081$ for

all clusters; cluster-based permutation test). Taken together, these results

indicate that the effects of atomoxetine were largely independent of sensory drive

and behavioral context.

By contrast, we found no significant effect of donepezil on α in any

cortical region ($p > 0.22$ for all clusters; cluster-based permutation test; Fig 5C).

Further, no effects were evident for donepezil, when splitting by task conditions

(Fig S4). The control analyses presented below establish clear effects of

donepezil on both cortical activity as well as markers of peripheral nervous

system activity, thus ruling out concerns that the drug may have been less

effective overall than atomoxetine (see Discussion).

Fig 6. Atomoxetine increases long-range temporal correlations irrespective of behavioral condition. Spatial distribution of the atomoxetine-induced changes in scaling exponent α during **(A)** Fixation and **(B)** Task-counting. **(C)** Conjunction of maps in (A) and (B), highlighting (in green) voxels with significant increases in both conditions.

Decreased scaling exponent of cortical activity during Task-counting

The cortex-wide scaling exponent α was significantly larger during Fixation than during Task-counting (p = 0.0062; t = 2.97; paired t-test; placebo condition only). This difference was significant across large parts of cortex ($p < 0.05$; cluster-based permutation test; Fig 7A). The task-related decrease was also observed consistently across all pharmacological conditions (Fig 7A). Importantly, the regions exhibiting significant decreases during Task-counting included the occipital and parietal regions that were driven by the moving stimulus and exhibited atomoxetine-induced changes in scaling behavior. Indeed, when testing for the task-dependent change in scaling exponent specifically in those regions showing a significant atomoxetine effect, the reduction during Task-counting was also highly significant (Fig 7B).

Fig 7. Decreased long-range temporal correlations under Task-counting **(A)** Difference in scaling exponent α between Task-counting and Fixation. *Left:* Contrast only for Placebo condition. *Middle.* Contrast only for Atomoxetine condition. *Right.* Contrast only for Donepezil condition. **(B)** Scaling exponent α for Fixation (purple) and Task-counting (yellow) conditions, averaged across voxels comprising the conjunction cluster depicted in Fig. 6C for placebo only (*Top*), atomoxetine only *(Middle)* and donepezil only *(Bottom).*

Change in scaling exponent under atomoxetine is consistent with increase in net cortical E/I ratio

In our model, the scaling exponent α exhibited a non-monotonic dependence on excitation-inhibition ratio (see the white diagonal line in Fig 4G-I and schematic depiction in Fig 8). Consequently, without knowing the baseline state, any change in α is ambiguous with respect to the direction of the change in E/I ratio (i.e., towards excitation- or inhibition-dominance). Thus, the observed increase in α under atomoxetine during Fixation could have been due to either an increase or a decrease in E/I ratio. However, recent insights into the changes in visual cortical E/I ratio during sensory drive in rodents help constrain the baseline state during the Task-counting condition: In the awake state, counter-intuitively, sensory drive decreases E/I ratio in primary visual cortex (33,34). Assuming that the same holds in human cortex during the Task-counting condition this insight enabled us to infer the change in net cortical E/I ratio induced by atomoxetine during Task-counting.

The rationale is illustrated in Fig 8. The observed decrease in α during

Task-counting compared to Fixation (Fig 7A) was likely due to a shift towards

inhibition-dominance (yellow point in Fig 8A). Then, the atomoxetine-induced

increase in α during this condition was likely due to an increase in net E/I ratio

during Task-counting (Fig 8B) – the same conclusion inferred from the increase

in the rate of perceptual alternations above. Because the effects of atomoxetine

on α were the same during Task-counting and Fixation, it is likely that the same

mechanism was at play during Fixation, where the baseline state was unknown.

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Fig 8. Inferring net E/I ratio from changes in scaling exponent α. Schematic illustration of the
inference from observed change in exponent to (hidden) change in net E:I ratio (see main text for
details). The non-monotonic dependence of scaling exponent α on E:I ratio (white line in Fig 4H) is
replotted schematically. **(A)** The measured scaling exponent α during Fixation (gray) can result
from both, inhibition- or excitation-dominant regimes; the baseline is unknown. We assume that
external drive (Task-counting; yellow dot) does not increase E:I ratio (Shadlen & Newsome, 1998).
Thus, the observed decrease in scaling exponent during Task-counting (yellow) must reflect a shift
towards the inhibition-dominance (blue arrows), consistent with animal physiology (34). **(B)** This
constrains the baseline state for the interpretation of the atomoxetine-induced increase in scaling
exponent during Task-counting (red): The latter increase likely reflects an increase in E:I ratio (red
arrow).
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Distinct, or absent, drug effects on other features of cortical dynamics

The absence of a consistent change in the scaling behavior of cortical activity

fluctuations under donepezil (Fig 5C) was not simply due to a lack of effect on

cortical dynamics per se. During Fixation, atomoxetine and donepezil both

significantly reduced MEG power in the 8-12 Hz range, relative to placebo, in

posterior cortical regions (Fig 9 A/B; *p* < 0.05 for all clusters; two-sided cluster-

based permutation test). This suppression in cortical 8-12 Hz power due to both

catecholamines and acetylcholine during Fixation is largely consistent with

previous pharmacological work (30,40), as well as with correlations of cortical

activity with pupil diameter (41–44), a marker of neuromodulatory brainstem

activity underlying the release of noradrenaline and, to some extent, acetylcholine

(45–48).

Fig 9. Similar effects of atomoxetine and donepezil on 8-12 Hz power. **(A)** Spatial distribution of
drug-related alpha power changes during Fixation, thresholded at *p* = 0.05 (two-sided cluster-based
permutation test). *Left.* Power changes after the administration of atomoxetine. *Right.* Power
changes after the administration of donepezil. **(B)** Same as (A), but for Task-counting.
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The atomoxetine-induced changes on 8-12 Hz power during Fixation had

a different spatial pattern than those of the atomoxetine-induced changes in the

scaling exponent α: within the cluster of the significant main effect of atomoxetine

on α, power did not significantly correlate with the changes in α (group average

spatial correlation between pooled difference maps within cluster; *r* = 0.073; *p* =

0.129, *bf* = 1.065).

During Task-counting, neither drug significantly altered MEG-power (Fig

9B, p > 0.05 for all clusters; two-sided cluster-based permutation test),

presumably due to the already suppressed power in the 8-12 Hz range in that

condition.

In sum, the effects of the drugs on cortical power during both conditions

showed that both were, at the dosages selected for our study, were equally

effective on cortical dynamics, consistently suppressing the power of low-

frequency oscillations during Fixation. This, as well as the lack of spatial

correlation of the atomoxetine-induced effects on power and scaling exponent α

further supports the specificity of the atomoxetine effect on cortical scaling

behavior.

Atomoxetine effect on fluctuations in cortical activity is not due peripheral

confounds

We also controlled for changes in peripheral physiological signals under the

drugs as potential confounds of the effect on cortical scaling behavior (Fig 10). As

expected, atomoxetine increased average heart rate (Fig 10A,B). Donepezil had

no significant effect on average heart rate, during neither Fixation (p = 0.8676; t =

0.16; paired t-test; bf = 0.8676; Fig 10A) nor Task-counting (p = 0.3274; t = 1.0;

paired t-test; bf = 0.3139; Fig 10B). Both drugs, however, significantly altered

heart rate scaling behavior, increasing the scaling exponent α (computed on

inter-heartbeat-interval time series, see Methods) in both behavioral contexts

(Fixation/atomoxetine: p = 0.0012, t = 3.62; Task-counting/atomoxetine: p =

0.0167; t = 2.55; Fig 10C; Fixation/donepezil: p = 0.0076, t = 2.88; Task-

counting/donepezil: p = 0.0049, t = 3.06; Fig 10D; all paired t-tests). Critically, the

atomoxetine-induced changes in heart rate showed no (Task-counting: r = 0.00*; p*

= 0.99; Person correlation; bf = 0.15) or only weak and statistically non-significant

(Fixation: r = 0.24; p = 0.21; Person correlation; bf = 0.31) correlations with the

changes in cortical activity (Fig 10A/B, right). Similarly, the atomoxetine-related

changes in the scaling behavior of inter-heartbeat intervals were only weakly (and

not significantly) correlated with the changes in cortical scaling behavior (Fixation:

$r = 0.22$; $p = 0.26$; $bf = 0.27$; Task-counting: $r = 0.26$; $p = 0.19$; $bf = 0.35$; Fig

10C/D, right).

Fig 10. Drug effect on cortical scaling behavior is not explained by systemic drug effects. **(A)** *Left.*
Heart rate for atomoxetine, placebo and donepezil during Fixation. *Right.* Correlation of
atomoxetine-related changes in heart rate (x-axis) with atomoxetine-related changes in MEG
scaling exponent *a* (y-axis) (within significant cluster during Fixation). **(B)** As (A), but during Task-
counting **(C)** *Right.* Scaling behavior of inter-heartbeat intervals (heart scaling exponent). *Left.*
Heart scaling exponent for all pharmacological conditions during Fixation. *Right.* Correlation of
atomoxetine-related changes in heart scaling exponent (x-axis) with atomoxetine-related changes
in MEG scaling exponent *a* (y-axis). **(D)** Same as (C), but during Task-counting.
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490   Atomoxetine, but not donepezil, significantly decreased spontaneous blink

491   rate during Fixation ($p = 0.034$; $t = 2.24$; paired t-test), but not during Task-

492   counting ($p = 0.112$; $t = 1.645$; $bf = 1.130$; paired t-test; Fig S2B). However, again

493   there was no significant correlation between changes in blink-rate and changes in

494   cortical scaling behavior due to atomoxetine (Fixation: $r = -0.26$; $p = 0.19$; $bf =$

495   0.35; Task-counting: $r = -0.09$; $p = 0.64$; $bf = 0.16$).

496   In sum, drug-induced changes in peripheral physiological signals under

the drugs, if present, did not account for the atomoxetine-induced changes in the

scaling behavior of the fluctuations in cortical activity (Figs 5 and 6). These

controls support our interpretation in terms of a specific effect on cortical net E/I

ratio rather than non-specific secondary effects due to the systemic drug effects

or changes in retinal input due to blinks.

DISCUSSION

Cortical circuits maintain a tight balance between excitation and inhibition. The

E/I ratio shapes the computational properties of cortical neurons and circuits (49),

and thereby the behavior of the organism (18–20). Deviations from this balance

have been linked to schizophrenia and autism and might also be at play in

various other neuropsychiatric disorders (50–53). Even in the absence of

changes in sensory input, the ratio between excitation and inhibition changes

continuously in cortex (17,54), presumably due to the effects of neuromodulators,

such as noradrenaline and acetylcholine (20,27–29,55,56). Neuromodulators also

regulate ongoing changes in the operating mode of behavior (23,25,57,58). Here,

we unraveled the effect of neuromodulatory-controlled microcircuit level changes

on the net cortical E/I ratio, as manifest in perception and behavior as well as in

local cortical population dynamics. Catecholamines, but not acetylcholine, altered

both, the dynamics of perceptual inference in the face of ambiguous input, and

intrinsic fluctuations in cortical activity. Both effects provided independent and

convergent evidence for an increase in E/I ratio due to catecholamines.

Convergent evidence for catecholaminergic disinhibition in cortical circuits

Our simulations indicated that the long-range temporal correlation of neural

population activity, as measured with the scaling exponent α, was highly

sensitive to changes in E/I ratio, produced through different regimes of

asymmetric synaptic gain modulation (see the white line in Fig 4H). In both

versions of our model, the neuromodulatory effects were not perfectly symmetric

(see the deviations of peak scaling exponents from main diagonal in Fig 4H).

While the latter effect was small and may be specific to the particular details of

the model, it remains possible that the subtle changes in scaling exponents we

observed were produced through symmetric gain modulations that maintained

the net E/I balance (i.e., along the main diagonal). However, two additional lines

of evidence converge on our conclusion that catecholamines (in particular

noradrenaline) boosted the cortical E/I ratio.

The first line of evidence is the specific and consistent effect of the

cathecolaminergic manipulation on perceptual switch rate in same group of

participants. Building on a well-documented link between the volatility of

perceptual inference on cortical net E/I-balance (21,31,32), this behavioral effect

sits well with the notion of an effective net disinhibition in the circuits of visual

cortex that determine the dynamics of perceptual inference in the face of

ambiguous motion signals.

Second, a mounting body of evidence from recent invasive rodent work

also supports an overall increase in net cortical E/I ratio due to catecholamines,

specifically noradrenaline (17). One study established that noradrenaline

decreases tonic, ongoing inhibition of neurons in auditory cortex, with the

excitatory inputs unaffected (56). Another study showed that noradrenaline (but

not acetylcholine) mediated a locomotion-related, tonic depolarization of visual

cortical neurons (including pyramidal cells) (27). Both studies indicated a non-

selective (i.e. broadband) gain increase of neuronal responses, irrespective of the

features of presented stimuli, which is different from the more subtle disinhibitory

effects of acetylcholine (17,55).

Cortical distribution of catecholaminergic effects on activity fluctuations

The atomoxetine effects on the scaling exponent were widespread across cortex,

but not entirely homogenous. They were pronounced across occipital and parietal

cortex, but not robust in frontal cortex (see Fig 5B). This distribution might point to

a noradrenergic, rather than dopaminergic origin. Atomoxetine increases the

levels of both catecholamines, noradrenaline and dopamine (59), but the

dopaminergic system mainly projects to prefrontal cortex (60) but only sparsely

projects to occipital areas (61), whereas the noradrenergic projections are more

widespread and strong to occipito-parietal cortex (62). Alternatively, this

distribution may reflect the different receptor composition of across cortical

regions (63,64): The relative frequency of different adrenoceptors (α1-, α2 or β-

adrenoceptor) differs strongly between frontal and posterior cortex, which, in turn,

can result in distinct effects of noradrenaline on the dynamics of neural activity in

these different cortical regions (63), in particular persistent activity. Future studies

should investigate whether the observed differences of noradrenergic effects on

long-range temporal correlations in cortical activity are due to these differences in

adrenoceptor composition across cortex.

No evidence for cholinergic effects on net E/I ratio

In contrast to atomoxetine, we observed no robust effect of increased

acetylcholine levels on cortical long-range temporal correlations. This absence of

an effect was unlikely due to an ineffective pharmacological manipulation through

donepezil: the latter had equally strong effects as atomoxetine on alpha-band

power in some cortical regions, as well as on heart rate variability. Rather, the

absence of robust donepezil effects might reflect specific properties of cholinergic

action, which may leave the cortical net excitation-inhibition ratio largely

unchanged. Substantial evidence points to the rapid disinhibition of (excitatory)

pyramidal cells by acetylcholine, by activating a circuit made up of a chain of two

inhibitory interneurons (VIP+ and SOM+) (28,65,66). The cholinergic activation of

this disinhibitory circuit would be expected to shift the net excitation-inhibition

ratio towards excitation, just as we inferred for catecholamines. However, this

disinhibitory circuit seems to mainly affect transient, stimulus-evoked responses

(55), whereas noradrenaline also alters the tonic levels of inhibition (56). This

may explain the relative lack of donepezil effects during the steady-state

conditions (blank fixation and continuous task drive) employed in our present

study. In general, cholinergically mediated disinhibitory effects on cortical

neurons might be subtler as well as more selective than the ones mediated by

noradrenaline (17).

Decrease of long-range temporal correlations during task and sensory

drive

Consistent with our current results, previous studies also found a decrease in

temporal autocorrelations of cortical activity due to external drive, even during

intermittent presentation of stimuli and tasks, entailing more external transients

than the steady-state task condition used here (8,67). The observation is

consistent with the insight from intracellular recordings of cortical neurons in

animals, that cortical responses to sensory stimulation in the awake state are

dominated by inhibition (33,34). One candidate source of this sensory-driven

state change is thalamocortical inhibition (68), but intracortical feedback inhibition

might also contribute (69).

Simulations of large-scale biophysical models of cortical networks show

that the driven state is associated with shortened temporal autocorrelations as

well as a decrease in the entropy of activity states in the network (70).

Correspondingly, the increase in long-range temporal autocorrelations under

catecholaminergic modulation observed presently may be associated with an

increase in entropy, in other words, a tendency of the cortex to explore a larger

set of activity states. This greater exploration of cortical state space may in turn

be linked to a prominent idea about the function of noradrenaline, which

postulates that high tonic noradrenaline levels promote exploratory, and more

distractible, behavior (23).

Functional consequences of changes in net cortical E/I ratio

We observed a selective increase in the rate of spontaneous perceptual

alternations under catecholaminergic but not cholinergic boost, adding to

evidence that these dynamics are under neuromodulatory control (71). Such a

change could be due to an increase in cortical "noise" defined as the amplitude of

spontaneous fluctuations in activity (31). Future invasive studies should relate

chatecholaminergic changes in the variability of spiking activity (72) to bistable

perception.

The selective increase of perceptual alternation rate under atomoxetine is

consistent with the relative decrease of intra-cortical inhibition (21) that was also

inferred from the changes in the long-range temporal correlation structure of

cortical activity. A net increase in excitation will likely have particularly strong

effects on the dynamics of parietal and prefrontal cortical circuits involved in

working memory and decision-making (19). These circuits are characterized by

slow intrinsic fluctuations of activity (73–75). The catecholaminergic increase in

long-range temporal correlations of intrinsic activity fluctuations in parietal circuits

that we observed in the current study may reflect a relative increase specifically

in the recurrent excitation in 'accumulator' circuits. Recurrent excitation, in turn, is

essential for both the computational capacities (76) as well as the timescale of

intrinsic activity fluctuations of these circuits (74,75). Simulations of synaptic gain

modulation of such 'accumulator' circuits indicate that the most robust behavior

emerges from co-modulation of both excitatory and inhibitory synapses, but with

different factors (20). It will be important to test these predictions in future work,

using tasks tailored to probing into these circuits of association cortex.

Catecholamines: a control parameter for critical network dynamics

Long-range temporal correlations in the fluctuations of neural mass activity (i.e.,

activity summed across the entire local network) (7) and avalanches within the

neuronal network (37) jointly emerge at the same ratio between excitatory and

inhibitory connectivity in the simplified cortical patch model used here. Both

phenomena, long-range temporal correlations and neuronal avalanches, are

commonly interpreted as hallmarks of "criticality" (7,10,37,77). Criticality refers to

a complex dynamical system poised between order and chaos (78–80).

The cortex might operate in a narrow regime around this critical point

(80,81). This operating mode, in turn, might yield computational modes superior

to those of the "sub-" or "supercritical" modes (38,77,82–84). A number of recent

reports have indicated that cortical dynamics may fluctuate around the critical

state (85–88), but these fluctuations have, so far, been spontaneous. Here, we

identified two key factors (task drive and catecholaminergic neuromodulation) to

bring these changes under experimental control. Complex systems can self-

organize towards criticality (78), e.g., through plasticity and/or feedback

connections. However, critical dynamics can also be achieved through an

external control parameter that fine-tunes the system. The tuning of temperature

in the Ising model of spin magnetization is a common example (80).

Noradrenaline may serve as such a control parameter in the cerebral cortex.

In sum, combining measurements of perceptual dynamics as well as

intrinsic fluctuations in cortical population activity under steady-state perceptually

ambiguous stimulation provides a novel non-invasive read-out of pharmacological

effects on cortical net E/I ratio in humans. This read-out might be useful for

addressing fundamental questions about the state dependence of cortical

computation and for inferring changes in cortical E/I ratio in neuropsychiatric

disorders, or pharmacological treatments of these disorders.

METHODS

Pharmacological MEG experiment

Participants

30 healthy human participants (16 females, age range 20-36, mean 26.7)

participated in the study after informed consent. The study was approved by the

Ethical Committee responsible for the University Medical Center Hamburg-

Eppendorf. Two participants were excluded from analyses, one due to excessive

MEG artifacts, the other due to not completing all 3 recording sessions. Thus, we

report results from N=28 participants (15 females).

General design

We pharmacologically manipulated the levels of catecholamines (noradrenaline

and dopamine) and acetylcholine in a double-blind, randomized, placebo-

controlled, and cross-over experimental design (Fig 1A, B). Each participant

completed three experimental sessions, consisting of drug (or placebo) intake at

two time points, a waiting period of 3 hours, and an MEG recording. During each

MEG session, participants were seated on a chair inside a magnetically shielded

MEG chamber. Each session consisted of 6 runs of different tasks, each of which

was 10 minutes long and followed by breaks of variable duration.

Pharmacological intervention

We used the selective noradrenaline reuptake inhibitor atomoxetine (dose: 40

mg) to boost the levels of catecholamines, specifically noradrenaline and (in

prefrontal cortex) dopamine (59). We used the cholinesterase inhibitor donepezil

(dose: 5 mg) to boost acetylcholine levels. A mannitol-aerosil mixture was

administered as placebo. All substances were encapsulated identically in order to

render them visually indistinguishable. Peak plasma concentration are reached

~3-4 hours after administration for donepezil (89) and 1-2 hours after

administration for atomoxetine (90), respectively. We adopted the following

procedure to account for these different pharmacokinetics (Fig 1A): participants

received two pills in each session, one 3 h and another 1.5 h before the start of

MEG recording. In the Atomoxetine condition, they first received a placebo pill (t

= -3 h) followed by the atomoxetine pill (t = -1.5 h). In the Donepezil condition,

they first received the donepezil pill (t = -3 h), followed by placebo (t = -1.5 h). In

the Placebo condition, they received a placebo at both time points. The half-life is

~ 5 h for atomoxetine (90) and ~ 82 h for donepezil, respectively (89). In order to

allow plasma concentration levels to return to baseline, the three recording

sessions were scheduled at least 2 weeks apart. This design ensured maximum

efficacy of both pharmacological manipulations, while effectively blinding

participants as well as experimenters.

Stimuli and behavioral tasks

In each session, participants alternated between three different task conditions (2

runs à 10 minutes per condition) referred to as Fixation, Task-counting, and

Task-pressing in the following (Fig 1B). All conditions entailed overall constant

sensory input. Fixation and Task-counting also entailed no overt motor responses

and are, therefore, referred to as "steady-state" conditions in the following. We

used these steady-state conditions to quantify intrinsic fluctuations in cortical

activity. Task-pressing entailed motor responses and was used for reliable

quantification of perceptual dynamics. All instructions and stimuli were projected

onto a screen (distance: 60 cm) inside the MEG chamber. The individual

conditions are described as follows.

Fixation. Participants were asked to keep their eyes open and fixate a

green fixation dot (radius = 0.45º visual angle) presented in the center of an

otherwise gray screen. This is analogous to eyes-open measurements of

"resting-state" activity widely used in the literature on intrinsic cortical activity

fluctuations.

Task-counting. Participants viewed a seemingly rotating sphere giving rise

to the kinetic depth effect (91,92): spontaneous changes in the perceived rotation

direction (Fig 1B). The stimulus subtended 21º of visual angle. It consisted of

1000 dots (500 black and 500 white dots, radius: 0.18º of visual angle) arranged

on a circular aperture presented on a mean-luminance gray background, with the

green fixation dot in the center. In order to minimize tracking eye movements, the

sphere rotation was along the horizontal axis, either "forward" (towards the

observer) or "backward" (away from the observer), and the dot density decreased

along the horizontal axis towards the center of the stimulus. Participants were

instructed to count the number of perceived changes in rotation direction and

report the total number of perceived transitions at the end of the run. Just like

during Fixation, Task-counting minimized any external (sensory or motor)

transients. Subjects silently counted the alternations in perceived rotation

direction and verbally reported the total count after the end of the 10 min run.

Task-pressing. This condition was identical to Task-counting, except that

participants were instructed to press and hold one of two buttons with their index

finger to indicate the perceived rotation direction of the sphere. Thus, each

perceptual alternation was accompanied by a motor response leading to change

in the button state. This allowed for a more reliable quantification of participants'

perceptual dynamics. On two sessions (atomoxetine condition), button presses

were not registered. Hence, the corresponding analyses were performed on 26

participants.

Data acquisition

MEG was recorded using a whole-head CTF 275 MEG system (CTF Systems,

Inc., Canada) at a sampling rate of 1200 Hz. In addition, eye movements and

pupil diameter were recorded with an MEG-compatible EyeLink 1000 Long

Range Mount system (SR Research, Osgoode, ON, Canada) at a sampling rate

of 1000 Hz. In addition, electrocardiogram (ECG) as well as vertical, horizontal

and radial EOG were acquired using Ag/AgCl electrodes (sampling rate 1200 Hz).

Data analysis

Eye data

Eye blinks were detected using the manufacturer's standard algorithm with

default settings. Saccades and microsaccades were detected using the saccade

detection algorithm described in (93), with a minimum saccade duration of 4

samples (= 4 ms) and a threshold velocity of 6. For 18 out of 28 participants, only

horizontal eye movements were recorded.

EOG data

EOG events (blinks and saccades) were extracted using semi-automatic artifact

procedures as implemented in FieldTrip (94). In short, EOG traces were

bandpass filtered using a third-order butterworth filter (1 – 15 Hz) and the

resulting signal was z-scored. All time points where the resulting signal exceeded

a z-score of 4 were marked as an EOG event.

MEG data

Preprocessing. First, all data were cleaned of strong transient muscle artifacts

and squid jumps through visual inspection and manual as well as semi-automatic

artifact rejection procedures, as implemented in the FieldTrip toolbox for MATLAB

(94). To this end, data segments contaminated by such artifacts (+/- 500 ms)

were discarded from the data (across all channels). Subsequently, data were

downsampled to 400 Hz split into low (2-40 Hz) and high (>40 Hz) frequency

components, using a 4th order (low- or high-pass) Butterworth filter. Both signal

components were separately submitted to independent component analysis (95)

using the FastICA algorithm (96). Artifactual components (eye blinks/movements,

muscle artifacts, heartbeat and other extra-cranial artifacts) were identified based

on three established criteria (97): power spectrum, fluctuation in signal variance

over time (in bins of 1s length), and topography. Artifact components were

reconstructed and subtracted from the raw signal and low- and high frequencies

were combined into a single data set. On average, 20 (+/- 14) artifact

components were identified for the low frequencies and 13 (+/- 7) artifactual

components were identified for the high frequencies.

Spectral analysis. Sensor-level spectral estimates (power spectra and cross

spectral density matrices) were computed by means of the multi taper method

using a sequence of discrete prolate Slepian tapers (98). For the power spectrum

shown in Fig 1C, power spectra were computed using a window length of 5s and

a frequency smoothing of 2 Hz, yielding 19 orthogonal tapers. The focus of this

paper was on the fluctuations of the amplitude envelopes, rather than on the

(oscillatory) fluctuations of the carrier signals *per se*. The temporal correlation

structure of the amplitude envelope fluctuations of cortical activity seems similar

across different carrier frequency bands (10). We focused on amplitude envelope

fluctuations in the alpha-band because (i) the cortical power spectra exhibited a

clearly discernible alpha-peak, which robustly modulated with task, as expected

from previous work (39) (Fig 1C); and (ii) the computational model used to study

the effect of synaptic gain modulation on cortical activity fluctuations was tuned to

produce alpha-band oscillations (see above and (15)).

Source reconstruction: general approach. The cleaned sensor level signals (*N*

sensors) were projected onto a grid consisting of *M = 3000* voxels covering the

cortical surface (mean distance: 6.3 mm) using the exact low-resolution brain

electromagnetic tomography (eLORETA; (99) method. The magnetic leadfield

was computed, separately for each subject and session, using a single shell head

model constructed from the individual structural MRI scans and the head position

relative to the MEG sensors at the beginning of the run (100). In case no MRI

was available (4 subjects), the leadfield was computed from a standard MNI

template brain transformed to an estimate of the individual volume conductor

using the measured fiducials (located at the nasion, the left and the right ear).

Source level estimates of amplitude envelopes and power. For comparing

amplitude envelope and power estimates between experimental conditions in

source space we aimed to select a single direction of the spatial filter for each

voxel across pharmacological conditions (i.e., MEG sessions), but separately for

Fixation and Task-Counting conditions. The rationale was to avoid filter-induced

biases in the comparisons between the pharmacological conditions, while

allowing that external task drive might systematically change the dipole

orientations.

To this end, we first computed the mean source-level cross-spectral

density matrix $C(r, f)$ for each frequency band, f, averaged across the three

MEG sessions, as follows:

$$C(r,f) = \tfrac{1}{3}\sum_{i=1}^{3}\left(A_i^T(r)C_i(f)A_i(r)\right) \qquad (1)$$

whereby i indicated the MEG session, $C_i(f)$ was the (sensor-level) session- and

frequency-specific cross-spectral density matrix and A_i is the spatial filter for

session i. We then extracted the first eigenvector $u_1(r, f)$ of the session-average

matrix $C(r, f)$ and computed the unbiased filter selective for the dominant dipole

orientation, $B_i(r, f)$, as:

$$B_i(r,f) = A_i(r)u_1(r,f) \qquad (2)$$

Please note that this filter was now frequency-specific, whereas the

previous filters, $A_i(r)$, were not. To obtain instantaneous estimates of source-

level amplitudes, the sensor-level signal for session i, $X_i(t)$, was band-pass

filtered (using a finite impulse response filter) and Hilbert-transformed, yielding a

complex-valued signal $H_i(f, t)$ for each frequency band. This signal was

projected into source space through multiplication with the unbiased spatial filter,

$B_i(r, f)$, and the absolute value was taken:

837
$$Env_i(r, f, t) = |(H_i(f, t)\, B_i(r, f))| \qquad (3)$$

where $Env_i(r, f, t)$ was the estimated amplitude envelope time course of source

location r and frequency f. Next, for each session, unbiased source-level cross

spectral density estimates were obtained from the sensor-level cross-spectral

density matrix $C_i(f)$ and the frequency-specific, unbiased spatial filter $B_i(f)$. The

main diagonal of the resulting matrix contains source-level power estimates for all

source locations:

844
$$S_i(f) = diag(B_i^T(f)_i C_i(f) B_i(f)) \qquad (4)$$

These computations where repeated separately for the Task-counting and

Fixation conditions, session by session. The differences in amplitude envelope

fluctuations and power estimates between pharmacological and task conditions

reported in this paper were robust with respect to the specifics of the analysis

approach. In particular, we obtained qualitatively similar pharmacological effects

in sensor space, as reported in an earlier conference abstract (101).

Detrended fluctuation analysis. The source-level amplitude envelopes

$Env_i(r, f, t)$ were submitted to detrended fluctuation analysis (102,103) in order

to quantify long-range temporal correlations. Detrended fluctuation analysis

quantifies the power law scaling of the fluctuation (root-mean-square) of a locally

detrended, cumulative signal with time-window length. Different from the analysis

of the more widely known autocorrelation function (73,74), detrended fluctuation

analysis provides robust estimates of the autocorrelation structure for stationary

and non-stationary time series. The procedure of the detrended fluctuation

analysis is illustrated in Fig 2.

For simplicity, in the following, we re-write the amplitude envelope

$Env_i(r, f, t)$ as x of length T. First, we computed the cumulative sum of the

demeaned x, (Fig 2B):

$$X(t) = \sum_{t'=1}^{t}(x(t') - \langle x \rangle) \qquad (5)$$

where t' and t denote single time points up to length T. The cumulative signal X

was then cut into $i = 1 \dots k$ segments Y_i of length N (overlap: 50%), where $k =$

$floor[(T - N)/(0.5\,N)]$ (Fig 2B, top). Within each segment Y_i of equal length N,

the linear trend Y_{i_trend} (least squares fit) was subtracted from Y_i (Fig 2B, bottom,

blue vs. red lines), and the root-mean-square fluctuation for a given segment was

computed as:

$$F_{N\_i} = \left[\frac{1}{N}\sum_{n=1}^{N}(Y_i(n) - Y_{i\_trend}(n))^2\right]^{\frac{1}{2}} \qquad (6)$$

872 where n indicates the individual time points. The fluctuation was computed for all

873 k segments of equal length N and the average fluctuation was obtained through:

$$< F_N > = \frac{1}{k}\sum_{i=1}^{k} F_{N\_i} \qquad (7)$$

875 The procedure was repeated for 15 different logarithmically spaced window

876 lengths N, ranging from 3 s to 50 s, which yields a fluctuation function (Fig 2C).

877 As expected for scale-free time series (103), this fluctuation function follows a

878 power-law of the form:

$$< F_N > \propto N^\alpha \qquad (8)$$

The "scaling exponent" α was computed through a linear regression fit in log-log

coordinates (Fig 2C). The longest and shortest window lengths were chosen

according to guidelines provided in (103).

A scaling exponent of $\alpha \sim= 0.5$ indicates a temporally uncorrelated ("white

noise") process. Scaling exponents between $0.5 < \alpha < 1$ are indicative of scale-

free behavior and long-range temporal correlations (103), whereas exponents of

$\alpha < 0.5$ indicate long-range anti-correlations ("switching behavior") and $\alpha > 1$ are

indicative of an unbounded process (103). The scaling exponents for alpha-band

MEG amplitude envelopes estimated in this study ranged (across experimental

conditions, MEG sensors and participants) from 0.40 and 1.04, with 99.4% of all

estimates in the range from 0.5 to 1. This is indicative of scale-free behavior and

consistent with previous human MEG work (7–10,12,13).

Relationship between measures of cortical variability. Scale-free behavior of

neural time series has also been quantified via analysis of the power spectrum

(5,6,73). There is a straightforward relationship between both approaches, which

we explain below, to help appreciate our results in the context of these previous

studies. The power spectrum of the amplitude envelope of cortical activity is

typically well approximated by the power law $p(f) \propto f^{-\beta}$, where β is referred to

as the power-law exponent (Fig 2D). For power-law decaying autocorrelations,

the relationship between the power-law exponent β and the scaling exponent α

(estimated through DFA) of a time series is:

$$\beta = 2\alpha - 1 \qquad (9)$$

Analysis of ECG data. ECG data were used to analyze two measures of

peripheral autonomic activity: average heart rate and heart rate variability. For

both measures, we used an adaptive threshold to detect the R-peak of each

QRS-complex in the ECG. Heart rate was then computed by dividing the total

number of R-components by time. Heart rate variability was quantified by means

of the detrended fluctuations analysis described for MEG above, but now applied

to the time series of the intervals between successive R-peaks (9,10). In line with

the MEG analyses, we used windows ranging from 3 to 50 heartbeats (roughly

corresponding to 3–50 s).

Statistical tests

Statistical comparisons of all dependent variables between conditions were,

unless stated otherwise, performed using paired t-tests.

Null effects are difficult to interpret using regular null hypothesis

significance testing. The Bayes Factor addresses this problem by quantifying the

strength of the support for the null hypothesis over the alternative hypothesis

provided by the data, taking effect size into account. Wherever null effects were

conceptually important, results obtained from a regular (paired) t-test (104) and

Pearson correlations (105) were converted into corresponding Bayes Factors.

To map significant changes of scaling exponents α on the cortical surface,

we computed a non-parametric permutation test based on spatial clustering

(106,107). This procedure has been shown to reliably control for Type I errors

arising from multiple comparisons. First, a paired t-test was performed to identify

voxels with significant changes (voxel with $p < 0.05$). Subsequently, significant

voxels are combined into clusters based on their spatial adjacency. Here, a voxel

was only included into a cluster when it had at least two significant neighbors.

Subsequently, the t-values of all voxels comprising a cluster were summed,

which yields a cluster statistic (i.e., a cluster t-value) for each identified cluster.

Next, a randomization null distribution was computed using a permutation

procedure (N = 10.000 permutations). On each permutation, the experimental

labels (i.e., the pharmacological conditions) were randomly re-assigned within

participants and the aforementioned procedure was repeated. For each iteration,

the maximum cluster statistic was determined and a distribution of maximum

cluster statistics was generated. Eventually, the cluster statistic of all empirical

clusters was compared to the values obtained from the permutation procedure.

All voxels comprising a cluster with a cluster statistic smaller than 2.5% or larger

than 97.5% of the permutation distribution were labeled significant, corresponding

to a corrected threshold of $\alpha = 0.05$ (two-sided).

Model simulations

To simulate the effects of synaptic gain modulation on cortical activity fluctuations,

we extended a previously described computational model of a local cortical patch

(15) by means of multiplicative modulation of synaptic gain. All features of the

model were identical to those of the model by (15), unless stated otherwise. The

model consisted of 2500 integrate-and-fire neurons (75% excitatory, 25%

inhibitory) with local connectivity within a square (width = 7 units) and a

connection probability that decayed exponentially with distance (Fig 4A). The

dynamics of the units were governed by:

$$I_i = I_i + \sum_j N_{ij} W_{ij} S_j \qquad (10)$$

$$\tau_i \frac{dI_i}{dt} = I_0 - I_i \qquad (11)$$

where subscripts i, j indicated different units, N_{ij} was a multiplicative gain factor,

W_{ij} were the connection weights between two units, and S_j a binary spiking

vector representing whether unit *j* did or did not spike on the previous time step,

and $I_0 = 0$. The connection weights were $W_{EE} = 0.0085$, $W_{IE} = 0.0085$, $W_{EI} =$

-0.569 and $W_{II} = -2$ whereby subscript E indicated excitatory, subscript I

indicated inhibitory, and the first and second subscript referred to the receiving

and sending unit, respectively.

On each time step (*dt* = 1 ms), I_i was updated for each unit *i*, with the

summed input from all other (connected) units *j* and scaled by a time constant

$\tau_i = 9 \text{ ms}$, which was the same for excitatory and inhibitory units. The probability

of a unit generating a spike output was given by:

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$$P_{si} = P_{si} + I_i \qquad (12)$$

966
$$\tau_P \frac{dP_{si}}{dt} = P_0 - P_{si} \qquad (13)$$

with the time constant for excitatory units $\tau_P = 6\ ms$ and for inhibitory $\tau_P = 12\ ms$.

P_0 was the background spiking probability, with $P_0(exc.) = 0.000001\ [1/ms]$ and

$P_0(inh.) = 0\ [1/ms]$. For each time step, it was determined whether a unit did or

did not spike. If it did, the probability of that unit spiking was reset to

$P_r(excitatory) = -2\ [1/ms]$ and $P_r(inhibitory) = -20\ [1/ms]$.

We used this model to analyze the dependency of two quantities on E/I

ratio: (i) the power-law scaling of the distributions of the sizes of neuronal

avalanches (37) estimated in terms of the kappa-index κ which quantifies the

difference between an empirically observed event size distribution and a

theoretical reference power-law distribution with a power-law exponent -1.5 (38),

and (ii) the scaling behavior (scaling exponent α) of the amplitude envelope

fluctuations of the model's local field potential. To this end, we summed the

activity across all (excitatory and inhibitory) neurons to obtain a proxy of the local

field potential. We band-pass filtered the local field potential in the alpha-band (8–

12 Hz) and computed long-range temporal correlations in the alpha-band

amplitude envelopes following the procedure described above (see *Detrended*

fluctuation analysis of MEG data), using windows sizes ranging from 5 s to 30 s.

For all simulations reported in this paper, we optimized the connection weights

using Bonesa, a parameter tuning algorithm (108), such that the network

exhibited alpha-band oscillations, long-range temporal correlations, and neuronal

avalanches (see Discussion).

In order to assess the influence of structural excitatory and inhibitory

connectivity on network dynamics (Figs 4D-F), we varied the percentage of units

(excitatory and inhibitory) a given excitatory or inhibitory unit connects to within a

local area (7 units x 7 units; Fig 4A). These percentages were varied

independently for excitatory and inhibitory units with a step size of 2.5%.

The gain factor N_{ij} was the main difference to the model described by

(15). It was introduced to simulate the effects of neuromodulation on synaptic

interactions in the cortical network (20). With all the above parameters fixed

(42.5% excitatory connectivity, 75% inhibitory connectivity; small square in Figs

4D-F), we systematically varied the synaptic gain factors, in two different ways. In

the first version, we only varied N_{EE} and N_{IE} to dynamically modulate the circuit's

net E/I ratio (Fig 4B), in a way consistent with recent modeling of the effects of E/I

ratio on a cortical circuit for perceptual decision-making (18). In the second

version, we varied N_{EE}, N_{IE}, and N_{EI} (Fig S3A). Here, N_{EI} was modulated

independently from N_{EE}, and N_{IE}, which in turn were co-modulated by the same

factor.

Per parameter combination, we ran 10 simulations, using the Brian2

spiking neural networks simulator (109). Each simulation was run for 1000

seconds, with a random initialization of the network structure and the probabilistic

spiking. In this paper, we focus on the effects of neuromodulation on the scaling

exponent α, which served as a reference for interpretation of the MEG effects.

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Conceptualization: T.P., A.K.E., and T.H.D.; Experimental design: T.P. and

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Formal analysis: T.P.; Model simulations: A.-E.A.; Writing - Original draft: T.P.

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1029 The authors declare no competing financial interests.

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SUPPLEMENTARY FIGURES

S1 Fig. Similar atomoxetine-related effects in both Task-counting and Task-resting conditions. **(A)** Number of perceptual alternations reported by the subjects per 10 min run for Task-counting condition. **(B)** Same as (A), but for Task-pressing condition. **(C)** Relation between the number of reported alternations during Task-counting (x-axis) and Task-pressing (y-axis). The blue line depicts a linear relation with slope 1 as a reference.

S2 Fig. Change in perceptual alternation rate is not due to change in blinks or fixational eye movements. **(A)** Number of EOG events for during Task-counting (left), Task-pressing (middle) and pooled across both conditions (right). Scatter plots depict the relation between the number of EOG events (x-axis) and the number of reported perceptual alternations (y-axis). **(B)** Same as (A), but for the number of detected eye blinks. **(C)** Same as (A) and (B), but for the number of saccades (horizontal and vertical). **(D)** Same as (C), but for horizontal saccades only. **(E)** Same as (D), but for vertical saccades only.

A

S3 Fig. Different version of modulation of E/I ratio in cortical patch model **(A)** Neuromodulation was simulated as a gain modulation term multiplied with excitatory (EE and IE) and/or inhibitory (EI only) synaptic weights. **(B)** κ as a function of excitatory and inhibitory connectivity (with a spacing of 2.5%; means across 10 simulations per cell). The region of $\kappa{\sim}1$, overlaps with the region of $\alpha > 0.5$ and splits the phase space into an excitation-dominant ($\kappa{>}1$) and an inhibition-dominant region ($\kappa{<}1$). **(C)** Same as (B), but for scaling exponent α. **(D)** Same as (B) and (C), but for firing rate.

S4 Fig. No donepezil-related changes in scaling exponent in neither behavioral contexts. **(A)** Spatial distribution of donepezil-induced changes in scaling exponent α during Fixation, thresholded at p = 0.05 (two-sided cluster-based permutation test). **(B)** As (A), but for Task-counting.