

To examine this idea theoretically, we constructed a functional connectivity graph (Eguíluz et al., 2005) for each of the random 1000-unit networks described above. Each of the graphs' nodes represented a unit and two units were connected by an edge if the correlation of activity between them was in the top 1% of all such correlations. The clustering coefficient (Luce & Perry, 1949) of such a graph indicates the degree to which functional connectivity is tightly clustered in the network. As predicted, higher gain was associated with higher clustering coefficients (Figure 3.2D; $r = 0.99$, $p < 10^{-12}$).

To test the degree to which functional connectivity was tightly clustered in the brain, we similarly constructed a functional connectivity graph for each participant and each game (18 graphs per participant). The graphs were constructed as done for the simulated networks, except that in this case each of the graphs' nodes represented a voxel, and connectivity was determined by the correlation between voxels' time series (see Figure 3.6 A and B for example graphs). As predicted, we found a significant game-by-game correlation between the clustering coefficient of these graphs and baseline pupil diameter (mean $r = 0.14$ across participants, $t_{27} = 1.82$, $p < 0.05$ one tailed; Figure 3.6C). That is, when participants' pupil diameter indicated high gain, their neural functional connectivity tended to be more tightly clustered. Moreover, we found a similar correlation when the analysis was restricted to prefrontal cortex, an area that is not involved in primary visual processing (mean $r = 0.14$ across participants, $t_{27} = 2.05$, $p < 0.05$), suggesting that the relationship between pupil diameter and clustering was indeed due to global fluctuations in gain and not due to differences in activation to the visual stimuli.

Seeded Content – **Brain** – Wikipedia
<https://en.wikipedia.org/wiki/Brain>

The **brain** is an [organ](#) that serves as the center of the [nervous system](#) in all [vertebrate](#) and most [invertebrate](#) animals. The brain is located in the head, usually close to the sensory organs for [senses](#) such as [vision](#). The brain is the most complex organ in a vertebrate's body. In a human, the [cerebral cortex](#) contains approximately 15–33 billion [neurons](#),^[1] each connected by [synapses](#) to several thousand other neurons. These neurons communicate with one another by means of long [protoplasmic](#) fibers called [axons](#), which carry trains of signal pulses called [action potentials](#) to distant parts of the brain or body targeting specific recipient cells.

[Physiologically](#), the function of the brain is to exert centralized control over the other organs of the body. The brain acts on the rest of the body both by generating patterns of muscle activity and by driving the secretion of chemicals called [hormones](#). This centralized control allows rapid and coordinated responses to changes in the [environment](#). Some basic types of responsiveness such as [reflexes](#) can be mediated by the spinal cord or peripheral [ganglia](#), but sophisticated purposeful control of behavior based on complex sensory input requires the information integrating capabilities of a centralized brain.

The operations of individual brain cells are now understood in considerable detail but the way they cooperate in ensembles of millions is yet to be solved.^[2] Recent models in modern neuroscience treat the brain as a biological [computer](#), very different in mechanism from an electronic computer, but similar in the sense that it acquires information from the surrounding world, stores it, and processes it in a variety of ways.

This article compares the properties of brains across the entire range of animal species, with the greatest attention to vertebrates. It deals with the [human brain](#) insofar as it shares the properties of other brains. The ways in which the human brain differs from other brains are covered in the human brain article. Several topics that might be covered here are instead covered there because much more can be said about them in a human context. The most important is [brain disease](#) and the effects of [brain damage](#), that are covered in the human brain article.

Functions

Information from the sense organs is collected in the brain. There it is used to determine what actions the organism is to take. The brain [processes](#) the raw data to extract information about the structure of the environment. Next it combines the processed information with information about the current needs of the animal and with memory of past circumstances. Finally, on the basis of the results, it generates motor response patterns. These signal-processing tasks require intricate interplay between a variety of functional subsystems.^[83]

The function of the brain is to provide coherent control over the actions of an animal. A centralized brain allows groups of muscles to be co-activated in complex patterns; it also allows stimuli impinging on one part of the body to evoke responses in other parts, and it can prevent different parts of the body from acting at cross-purposes to each other.^[83]

Perception

The human brain is provided with information about light, sound, the chemical composition of the atmosphere, temperature, head orientation, limb position, the chemical composition of the bloodstream, and more. In other animals additional senses are present, such as the infrared heat-sense of snakes, the [magnetic field sense](#) of some birds, or the electric field sense of some types of fish.

Each sensory system begins with specialized receptor cells,^[7] such as light-receptive neurons in the [retina](#) of the eye, or vibration-sensitive neurons in the [cochlea](#) of the ear. The axons of sensory receptor cells travel into the spinal cord or brain, where they transmit their signals to a [first-order sensory nucleus](#) dedicated to one specific [sensory modality](#). This primary sensory nucleus sends information to higher-order sensory areas that are dedicated to the same modality. Eventually, via a way-station in the [thalamus](#), the signals are sent to the cerebral cortex, where they are processed to extract the relevant features, and [integrated](#) with signals coming from other sensory systems.^[7]

Motor control

[Motor systems](#) are areas of the brain that are involved in [initiating body movements](#), that is, in activating muscles. Except for the muscles that control the eye, which are driven by nuclei in the midbrain, all the voluntary muscles in the body are directly innervated by [motor neurons](#) in the spinal cord and hindbrain.^[7] Spinal motor neurons are controlled both by neural circuits intrinsic to the spinal cord, and by inputs that descend from the brain. The intrinsic spinal circuits implement many [reflex](#) responses, and contain [pattern generators](#) for rhythmic movements such as walking or swimming. The descending connections from the brain allow for more sophisticated control.^[7]

The brain contains several motor areas that project directly to the spinal cord. At the lowest level are motor areas in the medulla and pons, which control stereotyped movements such as walking, breathing, or swallowing. At a higher level are areas in the midbrain, such as the [red nucleus](#), which is responsible for coordinating movements of the arms and legs. At a higher level yet is the [primary motor cortex](#), a strip of tissue located at the posterior edge of the frontal lobe. The primary motor cortex sends projections to the subcortical motor areas, but also sends a massive projection directly to the spinal cord, through the [pyramidal tract](#). This direct corticospinal projection allows for precise voluntary control of the fine details of movements. Other motor-related brain areas exert secondary effects by projecting to the primary motor areas. Among the most important secondary areas are the premotor cortex, basal ganglia, and cerebellum.^[7]

In addition to all of the above, the brain and spinal cord contain extensive circuitry to control the [autonomic nervous system](#), which works by secreting hormones and by modulating the "smooth" muscles of the gut.^[7]

Arousal

See also: [Sleep](#)

Many animals alternate between sleeping and waking in a daily cycle. Arousal and alertness are also modulated on a finer time scale by a network of brain areas.^[7]

A key component of the arousal system is the [suprachiasmatic nucleus](#) (SCN), a tiny part of the hypothalamus located directly above the point at which the [optic nerves](#) from the two eyes cross. The SCN contains the body's central biological clock. Neurons there show activity levels that rise and fall with a

period of about 24 hours, [circadian rhythms](#): these activity fluctuations are driven by rhythmic changes in expression of a set of "clock genes". The SCN continues to keep time even if it is excised from the brain and placed in a dish of warm nutrient solution, but it ordinarily receives input from the optic nerves, through the [retinohypothalamic tract](#) (RHT), that allows daily light-dark cycles to calibrate the clock.^[89]

The SCN projects to a set of areas in the hypothalamus, brainstem, and midbrain that are involved in implementing sleep-wake cycles. An important component of the system is the [reticular formation](#), a group of neuron-clusters scattered diffusely through the core of the lower brain. Reticular neurons send signals to the thalamus, which in turn sends activity-level-controlling signals to every part of the cortex. Damage to the reticular formation can produce a permanent state of coma.^[7]

Sleep involves great changes in brain activity.^[7] Until the 1950s it was generally believed that the brain essentially shuts off during sleep,^[90] but this is now known to be far from true; activity continues, but patterns become very different. There are two types of sleep: [REM sleep](#) (with dreaming) and [NREM](#) (non-REM, usually without dreaming) sleep, which repeat in slightly varying patterns throughout a sleep episode. Three broad types of distinct brain activity patterns can be measured: REM, light NREM and deep NREM. During deep NREM sleep, also called [slow wave sleep](#), activity in the cortex takes the form of large synchronized waves, whereas in the waking state it is noisy and desynchronized. Levels of the neurotransmitters [norepinephrine](#) and [serotonin](#) drop during slow wave sleep, and fall almost to zero during REM sleep; levels of acetylcholine show the reverse pattern.^[7]

Homeostasis

For any animal, survival requires maintaining a variety of parameters of bodily state within a limited range of variation: these include temperature, water content, salt concentration in the bloodstream, blood glucose levels, blood oxygen level, and others.^[91] The ability of an animal to regulate the internal environment of its body—the [milieu intérieur](#), as pioneering physiologist [Claude Bernard](#) called it—is known as [homeostasis](#) ([Greek](#) for "standing still").^[92] Maintaining homeostasis is a crucial function of the brain. The basic principle that underlies homeostasis is [negative feedback](#): any time a parameter diverges from its set-point, sensors generate an error signal that evokes a response that causes the parameter to shift back toward its

3.3 Pharmacological manipulation

In studying the effects of LC-NE function and neural gain, pupil diameter measurements only provide correlational evidence. Causal evidence, however, can be obtained using pharmacological manipulation. Thus, we next examined variations in functional connectivity strength and clustering in response to the norepinephrine-specific reuptake inhibitor reboxetine.

Reboxetine has been in use for the treatment of depression, anxiety and attention deficit hyperactivity disorder (Hajós et al., 2004). Its binding affinity is highly selective to the norepinephrine transporter, and both acute and chronic administration of the drug have been shown to raise extracellular levels of norepinephrine in frontal cortex and hippocampus (Hajós et al., 2004; Millan et al., 2001; Sacchetti et al., 1999). However, reboxetine does suppress LC-NE activity, and thus reduces physiologic norepinephrine function (Szabo and Blier, 2001). Still, since reboxetine increases cortical extracellular norepinephrine levels, we predicted that its administration would be associated with signs of increased gain in fMRI – that is, with stronger and more tightly clustered functional connectivity networks.

To test this prediction, we analyzed a pharmacological fMRI data set that was shared with us by Andrea Reinecke and Catherine Harmer from the University of Oxford (Papadatou-Pastou et al., 2012). Half of the participants received reboxetine, and half received placebo, 2 hours before performing an autobiographical memory task in the MRI scanner for a period of 9 minutes. In analyzing the fMRI data, we used the same methods as in the pupillometry study. That is, absolute functional connectivity was measured throughout the brain, and graph-

theoretic analysis was used to compute for each participant the degree to which functional connectivity was clustered.

3.3.1 Functional connectivity strength and clustering

Salivary cortisol levels, which are indicative of the efficacy of reboxetine, were similar in the two study groups at baseline (reboxetine group: 15.71 ± 1.80 mmol/L; placebo group: 15.08 ± 1.75 mmol/L), but higher in the reboxetine group before entering the scanner (reboxetine group: 17.48 ± 1.93 mmol/L; placebo group: 11.57 ± 1.36 mmol/L) and at the end of the study (reboxetine group: 14.85 ± 1.53 mmol/L; placebo group: 9.29 ± 1.09 mmol/L; $F_{1,20} = 6.62$, $p < 0.05$, ANOVA).

In contrast to our prediction, mean whole-brain functional connectivity strength was *lower* in the reboxetine group compared to the placebo group ($t_{20} = -2.2$, $p < 0.05$; Figure 3.7A, left).

Furthermore, graph-theoretic analysis showed that functional connections were less clustered in the reboxetine groups ($t_{20} = -3.1$, $p < 0.01$; Figure 3.7A, right) as compared to controls. Both of these results are consistent with lower rather than higher neural gain in response to reboxetine.

Functional connectivity and clustering coefficient were strongly correlated across participants ($r = 0.65$, $t_{20} = 3.8$, $p < 0.005$; Figure 3.7B), suggesting that low clustering in the reboxetine group might have simply reflected weaker functional connectivity. However, clustering was still lower in the reboxetine group after the effect of mean functional connectivity was regressed out ($t_{20} = -1.82$, $p < 0.05$ one tailed). The same result was found when clustering was compared between the reboxetine group and those participants in the placebo group whose

mean functional connectivity was in the same range (functional connectivity < 0.07 ; $t_{15} = -2.06$, $p < 0.05$ one tailed). Thus, the effect of reboxetine on the clustering of functional connections was only partially predicted by its effect on mean functional connectivity.

Notably, reboxetine administration seemed to restrict mean functional connectivity and clustering coefficients to a specific range (0.06 to 0.07 for the former, 0.004 to 0.012 for the latter), as compared to the more varied measurements in the placebo group (Figure 3.7B). To gain further insight into these results, we examined the number of strong connections made by each voxel (i.e. its cardinality) in participants' functional connectivity networks. In participants with strong mean functional connectivity (FC > 0.07), all of which belonged to the placebo group, connectivity mostly involved relatively few densely connected voxels (cardinality > 500), while most voxels were sparsely connected (cardinality < 100 ; variance of cardinality: 17026 ± 2024 ; Figure 3.7C). Densely connected voxels were not limited to particular brain regions, but rather, were scattered throughout the brain (Figure 3.7D). In contrast, in participants from both study groups whose mean functional connectivity was weaker (FC < 0.07), connectivity involved a large number of voxels with an intermediate number of connections (100 to 500; variance of cardinality: 7588 ± 754 ; difference from high FC participants: $t_{20} = 4.9$, $p < 10^{-5}$). Seemingly, without pharmacological intervention (i.e., in the placebo group) participants functioned in one of two modes: either few voxels were significantly involved in neural communication, or almost all voxels were. In contrast, only the latter mode was evident in participants who received reboxetine suggesting that reboxetine restricted whole-brain neural communication to this specific mode.

3.3.2 Signs of decreased gain?

While weaker and more distributed functional connectivity is suggestive of low gain, it can also result from an *increase* in norepinephrine and gain that exceeds physiological levels. This can be demonstrated in our neural network models: when gain was increased in the model to such a degree that, on average, half of the model's units were at saturation levels of activity, unit-to-unit correlations started decreasing with increasing gain (Figure 3.8A). However, this decrease in correlations was not coupled with a decrease in the clustering coefficient as was the case in our fMRI data. Nevertheless, clustering coefficients are sensitive to the underlying structure of the network, prompting us to examine these effects in a more structured network. Our simulations showed that in a network composed of multiple groups of units with strong within-group connections and weak between-group connections the clustering coefficient did drop with the weakening of correlations at high levels of gain (Figure 3.8B).

To determine whether weaker functional connectivity in the reboxetine group resulted from low gain or from exceedingly high levels of gain, we thus examined the absolute mean-corrected blood-oxygen-level dependent (BOLD) signal. By definition, increased gain should always drive activations towards maximal or minimal levels (Figure 1.2), regardless of network structure. Thus, provided that activations are mean corrected, absolute activation levels should increase monotonically with gain (Figure 3.8, mean activation level). Indeed, we have seen previously that pupillary indices of high norepinephrine are associated with a higher mean BOLD signal (see section 3.1). Here, however, mean BOLD signal was similar in the reboxetine group and in participants from the placebo group with similarly low functional connectivity levels ($FC < 0.07$; $t_{15} = 0.3$, $p = 0.73$), but higher in participants from the placebo group that

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