Brain activity should neither be completely random nor completely ordered. If the brain were to react with random activity every time it received an incoming stimulus, the interaction with the outside world would likely be incoherent and unpredictable. Similarly, if brain activity were completely ordered or synchronous all the time, there would be no variability in the ways to react and interact with the environment. It is easy to see that both extremes are clearly not appropriate to describe cortical brain function and should be dismissed.

What is more interesting is how exactly networks of neurons such as in the cortex transition from disorder to order. Previous computational and in vitro network studies have pointed to effective connectivity, i.e. the degree to which neurons are interconnected and “excite” each other, as a critical player controlling the level of order and disorder in cortical networks. When connectivity is low, network activity is disordered; as neurons become more and more interconnected, a point is reached where order abruptly emerges (Figure 1). Such a rapid change is well described by what is called a phase transition in physics. For network activity to be neither completely disordered nor completely ordered, neuronal networks have to be operating near such a phase transition — at the transition between an ordered and a disordered phase which is controlled by effective connectivity.

In a recent study, we provided evidence that this is actually the case in living human brains. Specifically, we analyzed the amount of order by quantifying the synchrony in cortical networks of epilepsy patients while the number and dosage of antiepileptic drugs (AEDs) were varied. Most AEDs reduce the ways neurons can excite each other by decreasing the excitability of individual neurons, enhancing inhibitory synaptic transmission or inhibiting excitatory synaptic transmission, and therefore essentially reduce the effective connectivity in similar ways as reported before. We found that when no AEDs were administered, networks would, on average, settle somewhere in the middle between order and disorder (Figure 1, black histogram). When effective connectivity was reduced by AEDs, networks shifted more toward the disordered, asynchronous state (Figure 1, blue histogram).

These histograms also provide evidence that cortical network activity alternates to some degree between different levels of synchrony (or order). Even when no AEDs were administered, networks fluctuated between states with higher and states with lower synchrony, but on average remained in the vicinity of the transition from low to high order. There has been considerable debate related to the question whether cortical networks are poised at or near a critical phase transition. In this context, the variability to be observed in the histograms in our work can be...
interpreted as some indication that physiological cortical networks do not operate at one particular point, such as a critical point in phase space, all the time. Instead they fluctuate while maintaining a certain mean value. In the language of dynamical systems, network dynamics constantly fluctuates and thereby visits sub- and supercritical states while, on average, remains in the vicinity of the transition disorder to order. Without antiepileptic drugs, networks are consequently on average closer to the phase transition, while antiepileptic drugs, on average, drive networks toward the subcritical, disordered regime.

**Figure 1.** Increasing evidence from computational, cell culture and human studies suggests a close link between cortical network synchrony and effective connectivity. As connectivity, or more generally excitability, is increased, network synchrony increases rapidly (schematically depicted by purple line). Long-term monitoring indicates that human cortical networks reside in the vicinity of this synchronization transition (black histogram) whereas AED, on average, shift networks toward lower synchrony (blue histogram). The link between synchrony and excitability allows an approximate mapping of these synchronization changes to excitability (black dotted lines). AEDs shift cortical excitability to lower levels. Conversely, wake moves cortical networks to higher excitability (and synchrony) which is recovered by sleep.
The observed ability of AED to gradually shift network dynamics to different mean synchronization values in human cortical networks can potentially provide further insights as to the particular type of transition governing the progression from disorder to order. An interesting candidate is a transcritical bifurcation. A transcritical bifurcation is characterized by 2 fixed points which interchange stability upon variation of a control parameter. In our report, the 2 fixed points would correspond to the asynchronous and the synchronous network states, and the control parameter is the effective connectivity or, more generally, excitability. The transition between them can be expected to be comparatively gradual in a transcritical bifurcation which could explain the relatively gradual changes in synchrony upon administration or reduction of AEDs.

Pathological changes in excitability of cortical tissue commonly underlie the initiation and spread of seizure activity in epilepsy patients; monitoring of excitability and controlling its degree using AEDs is of prime importance for clinical care and treatment. To date, however, reliable measures of cortical excitability have been difficult to obtain. Quantitative markers of excitability can potentially guide more objective and individualized treatment approaches and give reliable feedback on the effect of antiepileptic drug treatment in epilepsy patients. The measure of network synchrony provides a step toward such an excitability biomarker. By monitoring spontaneous brain activity, the amount of order in the brain can be quantified, providing information about the underlying excitability of brain networks (Figure 1). Discovery of this mapping between network synchrony and excitability in human brain networks was largely guided by interpreting previous work on computers and cell cultures in the context of dynamical systems theory. It therefore provides a good example of how a theoretical framework such as phase transitions can help uncover findings with interesting implications for the neurological treatment of epilepsy patients as well as for the understanding of the role of sleep.

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