Brain connectivity reduction reflects disturbed self-organisation of the brain: Neural disorders and General Anesthesia

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Abstract The neurophysiological correlate of functional neural impairment is an open problem. Functional impairment may be observed as mental disorder, seizures or modification of consciousness level. The latter include loss of responsiveness under general anaesthesia, sleep or even trance in hypnosis. This chapter points out the relation between reduced brain connectivity as a possible correlate of neural functional impairment and self-organisation in the brain. A first numerical example demonstrates how neural noise disturbs self-organisation in the brain. Estimators of self-organisation such as global phase synchrony or information transfer quantify the degree of self-organisation. The chapter shows up by a brief literature review how these estimators indicate brain connectivity modifications in neural disorders and under general anaesthesia.

Key words: unconsciousness, Alzheimer disease, Parkinson disease, multiple sclerosis, noise-induced transition

Introduction

The healthy normal brain can be regarded as an optimally tuned self-organised complex system [Singer (1986), Haken (1996), Kelso (1995)]. It decodes sensory stimuli and encodes them to trigger responsive action. Multiple functional areas are known to transfer and share information. These properties result from a very high degree of self-organisation in and between functional areas, whose interactions enables the brain to process information. If these interactions are disturbed, then the brain can exhibit abnormal functions. Dependent on the degree of disturbed interactions, these abnormal functions are observed clinically as abnormal behaviour or even patholo-

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gies. The present chapter discusses diseases and reduced consciousness emerging under drug administration, e.g. in hospital under general anesthesia. The chapter reviews the role of brain connectivity in neural disorders and demonstrates how brain network fragmentation may explain loss of behavioral responsiveness in patients under general anesthesia and why this reflects the partial breakdown of brain self-organisation.

Self-organisation in the brain

Complex systems exhibit a hierarchical structure of subunits that interact with each other [Haken (2004), Nicolis and Prigogine (1977)]. For weak interactions, the system dynamics is more or less given by the sum of the single subunits. However, for stronger interactions, subunits merge and generate new subunits on a higher hierarchical level. These higher level units show dynamical behaviour that is not the sum of the subunits it emerged from but have new properties. Again, these new subunits on a higher hierarchical level interact with other new subunits generating together units on even higher hierarchical levels and so on. This merge of subunits is called self-organisation. The higher level subunits can be observed as cooperative phenomena, such as cognitive functions [Singer (1986)], synchronisation [Singer (1993), Hutt and Munk (2006)] or motor behavior [Kelso (1995)]. The enhanced interactions between subunits may indicate merged subunits and self-organisation. Hence a reasonable approach to reveal underlying neural mechanisms is the data analysis of neural activity that aims to quantify and identify interactions between subunits.

On a microscopic scale, single neurons or small neuron populations represent subunits and a well-established data analysis approach is to extract synchronisation measures between these subunits from experimental data. For instance, enhanced synchronisation between single visual cortex neurons in visual perception tasks indicated cooperative interactions [Koenig et al (1995), Singer and Gray (1995)]. This leads to the hypothesis [Singer (1993)] that the brain solves the visual binding problem by synchronisation or self-organisation.

On a macroscopic scale applying spatial mode analysis of electroencephalographic data [Uhl et al (1998), Seifert et al (2018), Hutt (2004), Hutt and Riedel (2003), Fuchs et al (2000), Lehmann and Skrandies (1980), Pascual-Marqui et al (1995), Hutt and Schrauf (2007)] extracts spatial patterns that are supposed to reflect underlying interacting subunits. For instance, it has been shown that the spatio-temporal dynamics of middle-latent auditory evoked potentials is low-dimensional reflecting highly ordered neural activity [Hutt and Riedel (2003)]. This indicates neural self-organisation on a larger spatial and temporal scale.

To understand neural mechanisms and quantify the degree of self-organisation, brain connectivity has attracted much attention in recent years [Jirsa and McIntosh (2007), Sporns (2010)]. For instance, [Friston (1994)] distinguished structural, effective

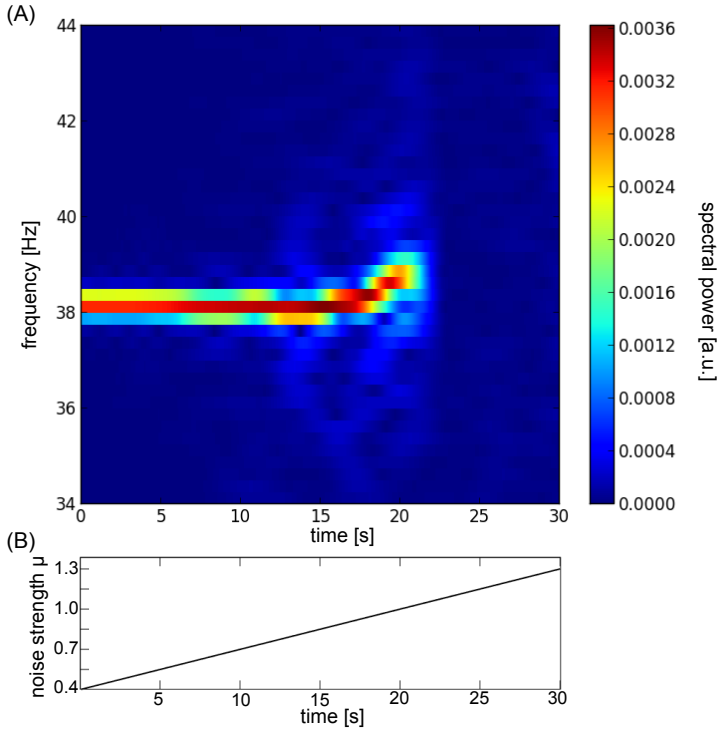

Fig. 1 Additive noise destructs coherent network activity. (A) Time-frequency distribution of the network mean $\bar{V}(t)$ gained from a Morlet wavelet analysis. (B) Noise strength μ with respect to time. The transfer function is chosen to $S(V) = 100/(1 + \exp(-100V))$.

and functional connectivity describing connections by fiber pathways, by correlations and by information flow, respectively. Other approaches aim to quantify influences of model variables [Friston et al (2003)] or brain regions or systems [Tononi and Sporns (2003)] on each other, e.g. by computing correlation coefficients or spectral or phase coherence.

An illustrative example

For illustration of self-organisation and how this can be quantified, let us consider a sparsely-connected network of $N = 100$ nodes that is driven by additive random noise

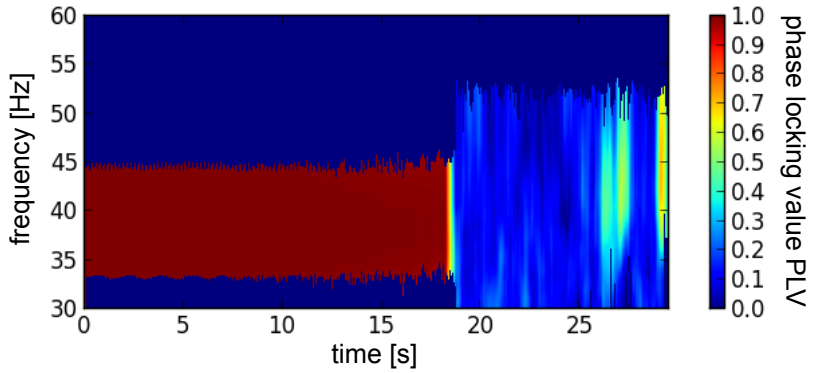

Fig. 2 Global phase locking for small noise and its destruction by large noise. This phase coherence is quantified by the Phase Locking Value PLV [Lachaux et al (1999)] and reflects the coherence in the system. Phase values are derived implicitly from wavelet transforms [Lachaux et al (1999)] and are defined for non-zero spectral only. To this end, we set PLV= 0 at time-frequency pairs where the spectral power $< 0.5 P_{max}$ with the maximum instantaneous spectral power P_{max} [Hutt et al (2018)].

$$dV_i = \left(-V_i + \frac{g}{N} \sum_{j=1}^{N} W_{ij} S[V_j(t-\tau)] \right) dt + \alpha \xi(t) \quad , \quad i = 1, \ldots, N \tag{1}$$

with $\alpha = 170/\sqrt{60}, g = 0.02$, the nonlinear transfer function S and Gaussian zero-mean i.i.d noise with $\langle \xi(t)\xi(t') \rangle = \mu^2 \delta(t-t')$. The parameter $\tau = 8$ms is a delay time and μ denotes the noise strength of the driving force. The network is sparse with connectivity probability 0.8 and the connection strength $W_{ij} = 1 \; \forall \; |i-j| \leq 4, W_{ij} = -1$ otherwise, i.e. the network exhibits local excitation and lateral inhibition. Previous studies [Lefebvre et al (2015), Hutt et al (2016)] show that additive noise in such a network tunes the systems power spectrum and destructs coherent rhythmic activity for large noise levels. To gain the numerical solution of Eq. (1), we apply an Euler-Maryuama method [Buckwar et al (2008)] with discrete time step $\Delta t = 1$ms.

Figure 1(A) shows the time-frequency distribution of the network mean $\bar{V}(t) = \sum_{i=1}^{N} V_i(t)/N$ and Fig. 1(B) gives the noise strength μ that changes with respect to time. We observe an oscillation of the network mean with a single frequency for low noise levels and a destruction of this rhythm by additive noise. The different elements in the network are coherent at low noise levels as seen in Fig. 2, whereas coherence breaks down abruptly at larger noise levels. Since coherence reflects self-organisation in the network, we conclude that large noise destructs self-organisation. It is important to note that this destruction does not happen by weakening the direct coupling between elements but by rendering the interaction of network elements more noisy, see the discussion in [Lefebvre et al (2015), Hutt et al (2016)].

Besides coherence measures, brain connectivity may be quantified by information theoretic measures [Wibral et al (2014b), Lizier (2014)]. Figure 3 shows the Transfer Entropy (TE) [Wollstadt et al (2014)] between two arbitrarily chosen time series

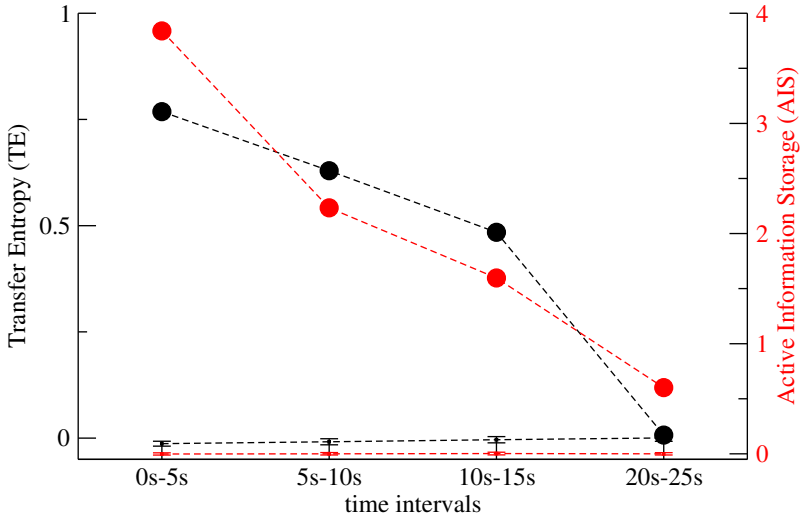

Fig. 3 Increasing noise decreases Transfer Entropy (TE) and Active Information Storage (AIS) between and in two arbitrarily chosen network nodes, respectively. Thick dots mark the values for the signals, small dots with error bars represent results for 1000 surrogate data [Lizier (2014)]. The estimates of TE and AIS have been computed with the open toolbox JIDT [Lizier (2014)] with standard parameters and delay time τ = 8ms.

$V_i(t)$ and $V_j(t)$ and the Active Information Storage (AIS) [Wibral et al (2014a)] in $V_i(t)$ in different time windows. Since the noise level increases with time, Fig. 3 reveals that TE and AIS decrease with increasing noise level. Hence less information is passed between elements with increased noise level and less information is stored in them. Since AIS reflects the degree of predictability from the corresponding time series, decreasing AIS is consistent with increased system randomness. Both measures may reflect the degree of self-organisation in the system, while typically TE is also interpreted as a brain connectivity measure.

The next section illustrates by selected literature examples that brain connectivity and neural disorders are strongly related. Then the subsequent section points out that modifications of brain connectivity during sedation and unresponsiveness under general anesthesia resemble well findings in neural disorders. In sum, this resemblance indicates that deterioration of connections (being structural or functional or effective) yields impairment of mental abilities as a consequence of a self-organisation deterioration.

Brain connectivity in neural disorders

It is trivial to state that brain areas do not interact directly with each other if there are no fiber pathways between them. Consequently, in the following we assume present fiber pathways in the network if not stated otherwise. As already stated, enhanced brain connectivity may yield self-organisation. Such a well-balanced and self-organised brain state ensures normal information processing and good cognitive abilities. In turn weakened brain connectivity may yield abnormal functions, such as cognitive impairment, attentional deficits, unconsciousness or even diseases. This insight promises to contribute to early diagnostic examinations based on Magnetic Resonance Imaging. Here the state of the art is the detection of structural abnormalities, e.g. in Alzheimer disease [Scheltens et al (1992)], Parkinson disease [Yekhlef et al (2003)] or multiple sclerosis [Sbardella et al (2015)].

Beyond the detection of structural pathologies, functional connectivity modifications appear to correlate well with structural pathologies and cognitive impairment. For instance, multiple sclerosis (MS) patients are found to exhibit a functional fragmentation of the cerebellum [Dogonowski et al (2014)] and the white-matter integrity [Hawellek et al (2011)]. Interestingly, the latter study also shows enhanced functional connectivity in modules of the default-mode network in early multiple sclerosis patients. The corresponding authors provide two explanations. The enhanced functional connectivity may represent a compensatory effect of the brain to solve given tasks what is more difficult for the brain with loss of white-matter integrity. Moreover, the finding could be explained by the loss of diversity in large-scale cortical dynamics due to white-matter integrity loss. This missing ability of large-scale diverse cortical patterns may enhance local patterns increasing local functional connectivity. This latter line of argumentation resembles the finding of a recent work on enhanced effective connectivity in local areas under general anesthesia, see the subsequent section for more details.

These findings in multiple sclerosis resembles qualitatively in some respect to the brain connectivity in Alzheimer's disease (AD). Resting-state functional Magnetic Resonance Imaging studies have revealed that AD patients exhibit a fragmentation of the brain network [Wang et al (2007)], e.g. within the default-mode network [Greicius et al (2004)] as in multiple sclerosis [Hawellek et al (2011)]. A further common feature to brain connectivity in multiple sclerosis patients is the enhanced functional connectivity in intralobe connections [Wang et al (2007)], such as in prefrontal lobe [Horwitz et al (1987)] or in parietal lobe [Bokde et al (2006)].

In Parkinson disease (PD) dynamic functional brain deteriorations has been found in patients with mild cognitive impairment [Diez-Cirarda et al (2018)] and in idiopathic PD patients [Hacker et al (2012)]. Similar to MS and AD, also enhanced correlations in certain brain areas have been found, e.g. in the prefrontal cortex [Hacker et al (2012)] and in the default-mode network [Disbrowa et al (2014)].

Summarising, there is strong indication that modification of functional connectivity is strongly related to brain disorders, be it reduction of functional connectiv-

ity in global networks or enhanced function connectivity in more local structures. Consequently, these disorders may result from strong reduction of network self-organisation.

Brain connectivity under general anesthesia

Arousal is an important action in the brain setting the level of excitation and hence controlling brain functions [Quinkert et al (2011)]. The ascending arousal system (ASS) [Moruzzi and Magoun (1949)] is a neural distributed network that sets the level of arousal via two major branches [Saper et al (2005)]. One branch is an ascending pathway from brainstem to the thalamus that inputs to the reticular nucleus and activates thalamic relay cells. Fast firing in cells in the upper brain stem areas peunculopontine and lateral tegmental nuclei is present during wakefulness and Rapid Eye Movement (REM)-sleep and low activity marks non-REM sleep stages. The other branch ascends, inter alia, from the brain stem and caudal hypothalamus, bypasses the thalamus projecting to the lateral hypothalamus, the basal forebrain and the cerebral cortex. Lesions along this pathway induce sleepiness and coma.

It is well-known that general anesthetics alter neurotransmission in the cerebral cortex, thalamus and brain stem [Alkire et al (2008), Brown et al (2010)]. Sedative and hypnotic anesthetics diminish cortical activity in ferrets [Sellers et al (2013)] and humans [Purdon et al (2012), Murphy et al (2011)]. This decrease of neural activity has been found by several experimental techniques, such as Positron Emission Tomography (PET) as reduced metabolic activity [Fiset et al (1999)], functional Magnetic Resonance Imaging (fMRI) as reduced BOLD-response and by electroencephalography (EEG) as reduced voltage amplitude [Purdon et al (2009)]. For some general anesthetics, this reduced activity can be explained by anesthetics-enhanced inhibitory action of GABAergic receptors and anesthetic-diminished excitatory action of NMDA receptors [Franks and Lieb (1994)].

Taking a closer look at the AAS, its cortical and subcortical structures play different roles in arousal regulation. The brain stem projects along the two AAS pathways, activates or de-activates various AAS-structures setting the excitation level of the cerebral cortex and controls respiratory and cardio-vascular functions [Brown et al (2010)]. The brain stem is also supposed to largely influences thalamo-cortical oscillations that are observed in EEG [Scheib (2017)]. A further major target structure in the AAS is the central thalamus that regulates the level of consciousness and lesions in this area may produce neurological disorders of consciousness [Schiff (2008)]. The hypothalamus may also promote awake state, while it primarily plays an important role in sleep regulation [Saper et al (2005)].

Anesthetics affect the cortex and the functional structures in the AAS and primarily reduce their activity. This reduction may explain the interruption of information processing in the brain during anesthesia. However, various experimental studies in the recent decade and the corresponding hypothesis of Tononi et

al. [Tononi and Sporns (2003), Tononi (2004), Pillay et al (2014)] indicate that it is less the reduced neural activity that is the major marker of the anesthetic state but rather the connectivity between neural structures. Various electrophysiological and modelling studies have shown that anesthetics reduce the global connectivity in the brain [Hudetz and Mashour (2016)] accompanied by a characteristic change of the activity power spectra [Boly et al (2012), Vizuete et al (2014), Lewis et al (2012), Hashemi et al (2015)]. These findings are partially consistent with experimental evidence from fMRI [Huang et al (2018)] revealing that global connectivity and the mean frequency of neural rhythms decreases with the level of sedation. A recent study on the information flow between ferret prefrontal cortex and visual cortex has revealed a decreasing transfer entropy between both areas under isoflurane sedation [Wollstadt et al (2017)]. In the clinical context, patients with consciousness disorder show strong functional disconnections as well [Huang et al (2018)].

However this view is challenged by experimental evidence that, at surgery anesthetic level that is deeper than for sedation, faster neural activity becomes more pronounced again [Huang et al (2018)] and hence the frequency shows a multiphasic relation to the level of anesthesia. This multiphasic modification has been found in functional connectivity as well [Liu et al (2013)]. Some cortical and subcortical areas exhibit a first connectivity reduction while increasing anesthetic concentration before their connectivity was recovered at even deeper anesthesia.

Moreover, anesthetic sedation may even yield connectivity enhancement between certain structures, such as the increased connectivity between the precuneus and cortical areas in humans [Liu et al (2014)] or between the posterior cingulate cortex and, e.g., the sensorimotor cortices [Stammatakis et al (2010)]. In an information entropy study of Local Field Potentials in ferret prefrontal cortex and visual cortex, [Wollstadt et al (2017)] found decreasing TE between prefrontal cortex and visual cortex, an increase in intra-area AIS and a decrease in intra-area entropy (H) with anesthetic level in both areas. The authors of that study argue that less available information H in each area yields less information that can be transferred (TE). Synchronously, the increase of AIS reflects an increased predictability of the corresponding neural activity reflecting enhanced coherence. This is in line with the onset of coherence in the $\alpha-$EEG frequency band at the point of loss of consciousness during propofol anesthesia [Cimenser et al (2011), Supp et al (2011)].

A recent study of [Lee et al (2017)] further reveals that the onset of enhanced $\delta-$power in EEG reflects well the point of loss of consciousness and that parietal and fronto-parietal connectivity in this frequency range increases. Together with previous studies on EEG-power spectra under general anesthesia, this latter study indicates that connectivity may also depend on frequency range. Future studies will elicit whether brain connectivity is frequency-dependent.

In sum, this line of evidence suggests that an increased coherence in local areas by anesthetic action induces the fragmentation of the global network. [Huang et al (2018)] bring up the hypothesise that, at first, sedation enhances local connections while the global network remains unchanged, before global connections

are reduced at deeper sedation levels. Then, in deep anesthesia or in disorders of consciousness local networks are fragmented as well.

Conclusion

Self-organisation in the brain is the condition for normal neural information processing in healthy patients. The reduction or removal of neural self-organisation is reflected, e.g., as neural disorders in diseases or loss of consciousness under anesthesia. In these cases, the brain connectivity is affected in a similar manner. Local areas enhance their synchronisation and hence their connectivity whereas global connections are reduced. These common features in neural disorders and anesthesia (and even in sleep) point to the important role of connectivity in neural processing of information. Here, it is important to mention a line of evidence on the self-organisation in epileptic seizures [Jiruska et al (2013)]. It has been found experimentally that epileptic seizures exhibit high-frequency activity in local patches in the seizure onset zone [Schevon et al (2010)], while desynchronization has been observed at the seizure onset[Netoff and Schiff (2002)]. These, at a first glance contradictory findings, can be explained easily by spatial subsampling of electrodes detecting desychronization between low - and high-frequency spatial patches.
Future research will reveal whether these connections are strongly frequency-dependent. The distinction of connectivity in certain frequency bands may advance the understanding of diseases and general anesthesia.

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