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Operational Architectonics Methodology for EEG Analysis: Theory and Results

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Abstract:

This chapter discusses various aspects of operational architectonics methodology for EEG analysis that have been developed over the course of last 17 years in relation to nonstationarity of brain functioning. At first we detail the peculiarities and evidence for a spatial and temporal nonstationarity in the EEG signal, then we review a theoretical framework that could integrate the existing data with a focus on theoretical advantages provided by an operational architectonics framework, and finally we describe the experimental results related to methodology. In the last part of the chapter we outline the application of OA methodology to clinical, pharmacological, cognitive, and neurophilosophical studies.

Key Words:

Electroencephalography (EEG); nonstationarity; spontaneous brain activity; neuronal assemblies; brain operations; operational module (OM); rapid transitional process (RTP); operational synchrony (OS); functional synchrony; operational architectonics (OA).

> *"We will have to face the fact that our models*
> *will have to be much more complex if we take into account*
> *the topographical differentiation and the temporal variability,*
> *i.e. the dynamics of the EEG. And as long as we are not able to do this we*
> *cannot claim to be talking about a model that can even remotely describe EEG activity"*
> Kunkel ***(1)***

1. Introduction

Ongoing spontaneous brain activity at the cortical level (electroencephalogram – EEG) is the result of dendritic and postsynaptic currents of many cortical neurons[1] firing in nonrandom partial synchrony ***(8, 9)***. It was demonstrated that neural activity patterns measurable at the macro-level by EEG are correlated with underlying neural computations ***(10-15)*** and accompany specific behaviour and cognition ***(16, 17)***. These studies suggest that EEG provides a direct measure of cortical activity with millisecond temporal resolution.

EEG studies in their totality revealed the following important features of the EEG signal:

- EEG characteristics were found to be independent from cultural and ethnic factors ***(18)*** which may reflect a common genetic heritage of the human brain development.
- EEG is characterised by high inherent stability. Indeed, it was reported that repeated 20-second samples of EEG were about 82% reliable, 40 seconds samples were about 90% reliable and 60 seconds were approximately 92% reliable ***(19)***.
- EEG is highly reproducible ***(20-26)***. For example, Burgess and Gruzelier ***(22)*** reported average reliabilities of 0.81 and 0.86 for theta and alpha bands[2] in resting, eyes open EEG with a test–retest interval of about 1 h. Test–retest correlation coefficients for EEG power, after a 12–16-week interval between measurements, are also high ~0.8 for both absolute

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[1] One also needs to consider the possible role of glial cells as sources of extracellular currents, especially since these cells are known to be sensitive to changes in extracellular ions ***(2, 3)***. Therefore some researchers suggest that glial cells might "convert" ongoing spike activity into wave potentials. However, glial cells have an extremely slow time course, requiring several seconds to reach their peak. For this reason, it appears likely that the major glial contribution is to "steady cortical potentials", rather than to the EEG from which potentials under 1 Hz are generally excluded ***(4)***. There is another drawback with such a suggestion: extracellular potassium concentrations determine the membrane potential of astrocytes ***(5)***; however, during spontaneous activity it is very unlikely that changes in extracellular potassium concentration would be sufficient to produce any glial potentials; in fact, glial activity reveal no wave activity at all ***(6, 7)***. These, and pharmacological data ***(4)*** indicate that it is the activity of neurons that is essential and critical for EEG activity.

[2] EEG bands represent electromagnetic oscillations in different frequency ranges arising from synchronous and coherent electrical activity of neurons in the brain: delta: 1.5-3.5 Hz, theta: 4-7.5 Hz, alpha: 8-13 Hz, beta: 13-30 Hz and gamma: > 30 Hz.

and relative power ***(19, 21, 27)***. For longer intervals (with an average 10-month interval), the test–retest reliability stays ~0.7 ***(20)***. Even over a time period of 5 years the EEG parameters demonstrated very high stability ***(28)***.

- EEG characteristics are mostly explained by heritability ***(29, 30)*** (for a review and meta-analysis, see ***(31)***). The authors conclude that EEG is one of the most heritable characteristics in humans.
- The existence of EEG phenotypes has been demonstrated ***(32)***. EEG phenotypes are clusters of commonly occurring EEG patterns found in the general population that are believed to be the result of underlying genetics. Several studies have begun to identify genes associated with certain EEG phenotypes (for the review see ***(33)***).
- EEG oscillations are phylogenetically preserved ***(34)*** and provide basic links to brain functions, especially for communication and associative functions ***(35)***. EEG oscillations define short temporal windows for flexible communication between widely distributed neuronal ensembles, which are associated with different types of sensory and cognitive processes ***(11, 36-39)***.
- EEG oscillations are causally implicated in cognitive functions: transcranial-magnetic stimulation at physiologically meaningful rhythms has domain-specific effects on cognitive activities ***(40-42)***.
- As a field, EEG may act (top down) on networks (neuronal assemblies) ***(17)***: an electric field may induce electrophoretic redistribution of charged ions both intracellularly and extracellularly and thereby directly modulate neuronal physiology; additionally, various structures in the brain are sensitive to electromagnetic fields ***(43)***. Indeed, it was demonstrated that the firing rate of a spontaneously active single neuron depends strongly on the instantaneous spatial pattern of ongoing population activity in a large cortical area ***(44)*** (for the review see ***(45)***). Here EEG characteristics may be considered as order parameters which modulate the behaviour of neurons or neuronal assemblies ***(46)***.

Thanks to these important features, EEG is extensively used in brain research and for clinical purposes. It appears that *as a neurophysiological phenomenon EEG has its own structure, regularities and rules of organization* ***(16, 47-50)*** (for the reviews see ***(51-57)***). Only when one knows the structural peculiarities of an EEG signal, it is possible to make proper use of EEG as a tool and provide adequate data interpretation. In fact, it is impossible to design a cognitive EEG experiment that is not biased by assumptions (explicit or implicit) regarding brain dynamics and the statistical characteristics of EEG, particularly with respect to its temporal and spatial dynamics.

Therefore, a much deeper understanding of brain spatio-temporal dynamics (which is reflected in EEG) is essential for genuine long-term progress in psychophysiological, cognitive and medical sciences.

A great number of EEG studies have been accumulated since the first EEG report published by Berger in 1929 ***(58)*** with a remarkably consistent fact emerging: *the spatio-temporal dynamics of EEG is hidden in its nonstationary structure*.

2. EEG nonstationarity

The available evidence suggest that neurons self-organize into transient networks (neuronal assemblies) that synchronize in *time* and *space* to produce a mixture of short bursts of oscillations that are observable in the EEG signal ***(11, 38, 39, 59)***. The dynamics of EEG spatio-temporal variability is characterized by abrupt alteration of relatively stable periods, the duration and size of which are significantly different from the respective characteristics of a random process ***(51, 56, 57, 60-67)***.

In this context EEG nonstationarity is expressed in both temporal (*temporal nonstationarity*) and spatial (*spatial heterogeneity*) dimensions. In the following two subsections we will consider these two features separately.

2.1. Temporal nonstationarity of EEG

At present it is well established that an EEG is a highly nonstationary signal ***(48, 51, 53, 56, 64, 65, 68-77)***. This means that EEG signal has different characteristics in various points in time. It was demonstrated that in the phenomenon of EEG temporal variability, not only the stochastic (noise) fluctuations of the EEG parameters, but also the *temporal structure* of the signal itself are reflected ***(48, 78, 79)*** (for a review see ***(52, 53, 56)***). It is assumed that EEG variability or nonstationarity is the reflection of structural or piecewise stationary organization of the signal. Piecewise stationary structure of EEG is considered to be the result of “gluing” of short-term stationary casual processes with different probability characteristics ***(61, 64, 65, 80-82)*** (for the reviews see ***(52-54, 56, 67)***).

Considering that each local EEG signal (registered from a given cortical area) is characterized by three major components (amplitude, frequency and phase), one may assume that each of them can exhibit nonstationary behaviour in relation to time. Indeed, it has been demonstrated that all three EEG characteristics change *abruptly* (not necessary simultaneously) with the progression of time (for EEG amplitude see ***(53, 56, 83-86)***; for EEG frequency see ***(49, 50)***; for EEG phase see

(62, 87-90)). In other words, the values of EEG amplitude, frequency and phase persist for some time around some stable average, then abruptly "jump" up or down to a new stable average which after some time is replaced by another average level. These "jumps" in separate local EEG characteristics mark the discontinuities of relatively stable functioning of local neuronal networks. It has been proposed that during these stationary periods a particular brain system executes separate operations ***(51, 81, 82)*** (for a review see ***(91)***). This suggests that ongoing brain activity occurs in discrete steps ***(62, 64, 85, 87, 89, 92)*** and confirms the view that the cerebral cortex is always active, even during rest ***(44, 57, 93-98)***.

The functional significance of EEG temporal structure was confirmed by numerous studies where it was demonstrated that different EEG temporal structures were associated with (a) different degree of psychophysiological and social adaptivity of individuals ***(99-101)***, (b) different cognitive loading ***(26, 49-52)***, and (c) different psychopathologies (for schizophrenia ***(102)***; for epilepsy ***(103)***; for major depression disorder ***(104)***; for opioid dependence ***(105)***; for a review see ***(106)***).

In this context each local EEG signal can be reduced to a temporally organised sequence of nearly-stationary segments of various types. It can be suggested that the EEG activity within each type (or class) of segment is generated by the same or similar dynamics and driving force ***(51, 81, 82, 107)***. However, EEG activity from different classes of segments, has, in effect, different driving forces and is therefore being generated by different dynamics. In their turn, consecutive EEG segments comprise a new sequence in a particular time-scale. Such functional EEG structure comprises hierarchical multivariability which reflects the poly-operational structure of brain activity ***(55, 108)***.

2.2. Spatial heterogeneity of EEG

Besides the temporal nonstationarity of EEG signal there is another striking feature of EEG which is the spatial difference in electrical activity from electrode to electrode ***(109)*** indicating that the brain generates a highly structured in space extracellular electric field ***(85, 87)***.

Experimental findings suggest the existence of statistical *heterogeneity* (anisotropy) of the electromagnetic field in relation to local field potential (LFP) processes ***(110)*** and local EEGs ***(53, 56, 57, 64, 111, 112)***. It was demonstrated that such electromagnetic spatial heterogeneity relates to large-scale morpho-functional organization of the cortex:

- Dynamic baseline of intrinsic (not stimulus- or task-evoked) brain activity during resting wakefulness is topographically organized in discrete brain networks – resting state networks ***(57, 113, 114)***. Each of these functional networks is characterized by a specific electrophysiological signature that involves a combination of different EEG rhythms. Thus, topographic EEG structure is frequency specific ***(115)***.

- Each local EEG recording or small group of local EEG recordings has its own activity (indexed by a set of spectral patterns of different types) ***(49)***.
- The same type of EEG activity (indexed by spectral pattern of a given type) occurs in approximately 70% of all observations in no more than two functionally homologous EEG locations: for example O1-O2 ***(106)***, thus suggesting functionally heterogeneous topology of EEG.
- Topographic variability of different types of EEG short-term spectral patterns revealed that spatial EEG map is expressed as a mosaic of cortical structures that are functionally integrated into clusters of different size ***(57, 63, 66)***.
- A high number of mutual intercorrelations between various piecewise descriptors of EEG when all local EEG recordings are accounted for and, at the same time, the absence of such intercorrelations when each local EEG recording was taken in isolation suggests that functional dynamics of neuronal assemblies (indexed by various piecewise EEG descriptors) take place within a rigid and narrow morpho-functional range, which constrains topological (among locations) relations between these piecewise descriptors of EEG ***(53)***.
- Spatial heterogeneity of neuronal synchrony has been repeatedly demonstrated at the level of LFP ***(110)*** as well as at large-scale level of EEG ***(55-57, 116-122)***.
- Cortical areas separated by distances exceeding the diameters of 'wave packets'[3] have differing wave forms and therefore different spectral pattern types ***(85, 87)***.
- Covariance between neighbouring electrodes across cortex functional boundaries (e.g., parietal to temporal areas) is much higher than covariance within functional regions (e.g., left parietal to midline parietal area), indicating that multiple functionally distinct areas are reliably assessed by EEG topographic heterogeneity ***(124, 125)***. This morpho-functional heterogeneity of EEG was also confirmed in an independent study in which the spatial heterogeneity of scalp-recorded EEG synchronicity was measured along longitudinal (anterior-to-posterior and posterior-to-anterior directions) and transversal (right-to-left anterior and right-to-left posterior directions) electrode arrays with scalp electrodes equally spaced in all these arrays ***(53, 73)***. Data from actual EEG was compared with so-called

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[3] The coordinated activity manifests a "wave packet" that requires synchronization of a shared carrier wave of the outputs of a large number of neurons over the area ***(85, 87, 123)***.

"surrogate" EEG in which a mixing of actual local EEG recordings was done so that the natural time relations between all local EEG recordings were completely destroyed, but the number, duration and sequence of segments within each local recording remained the same as in the natural EEG. For longitudinal electrode arrays (despite all testing pairs of EEG electrodes having the exact same interelectrode distance) the synchronicity index exhibited a notable topological landscape: significantly decreasing ($p < 0.05$) in locations of EEG electrode pairs on the head that crossed functional cortex boundaries ***(53, 73)***. This data clearly indicates that temporal consistency of segmental architectonics of the electrical field becomes weak at the boundaries of well-outlined functional cortical areas.

Additionally (a) the relationship between synchronicity index and interelectrode distance was not monotonous for both longitudinal electrode arrays: step-wise dependency was observed and (b) forward (posterior-to-anterior) and backward (anterior-to-posterior) dependences of synchronicity index from the interelectrode distance varied significantly from each other ***(56)***. These results suggest that in such conditions the contribution of volume conduction is insignificant.

For transversal electrode arrays it was demonstrated that (a) anterior and posterior cortex areas had opposite tendencies in the dynamics of synchronicity index (notice that anterior and posterior cortex areas have different morpho-functional organisation) and (b) maximal synchronicity index values in the posterior cortical areas were obtained for homological lateral EEG locations (which have similar morpho-functional organisation) despite the largest interelectrode distance in the electrode array ***(56)***.

Summarising, these findings suggest notable topological peculiarities of the EEG signal along the cortex, thus reflecting a morphologically and functionally heterogeneous organization of the cortex.

Taking together the aforementioned findings, one may suggest the existence of statistical heterogeneity (anisotropy) of the electromagnetic brain field in regard to neurodynamics within and between regional EEGs, which is best described by so-called clustered functional networks ***(57, 126)***. Simulations of clustered networks suggested that such spatial heterogeneity of EEG may have a number of advantages when compared to a random or homogeneous structure. It was demonstrated that clustered networks are more easily activated than random networks of the same size ***(126)***. This is due to the higher density of connections within the clusters which facilitated local activation. At the same time, the sparser connectivity between clusters prevents the spreading of activity across the whole network. Thus, in contrast to random networks, clustered networks possess an expanded critical functional range for which initial activations resulted in persistent but nonglobal network activity ***(126-128)***. Such topology is consistent with so called "*small world*" networks ***(129-134)***, which are characterised by predominantly local coupling with a small number of long-range connections ***(130, 135)***.

Functional significance of spatial heterogeneity of EEG was also confirmed by numerous studies where it was demonstrated that different EEG spatial structures were associated with (a) encoding of various sensory information and the meaning of this information ***(73, 136)***, (b) different levels of complexity in conscious thinking ***(61, 137, 138)***, (c) different cognitive loading ***(61, 73, 86, 139-141)***, (d) reconfiguration between rest and task conditions ***(142)***, (e) changes across age ***(143)***, and (f) different psychopathologies ***(86, 144)*** (for Alzheimer's disease ***(145)***; for epilepsy ***(66, 146)***; for major depression disorder ***(147, 148)***; for drug intake ***(83, 84, 149-154)***; for schizophrenia ***(155-157)***).

Summarising this subsection we can conclude that as opposed to being a continuous process, the EEG (within each local signal/channel and as a global whole-cortex field) represents a series of consecutive short-term segments, each of which is produced from synchronized activity of a different group of cells – neuronal assemblies (for a review see ***(57, 158)***). Surprisingly, even though such knowledge about the structure of EEG signal has been available for decades ***(159)***, it has been largely neglected in most methods used for modern day EEG analysis ***(51, 63)***. Usually, manifestations of nonstationarity in the EEG signal are either carefully eliminated, or are considered as an unavoidable "noise", which should be diminished ***(53)***. To minimize this so-called "noise", various mathematical procedures of smoothing and averaging are applied to the raw data. The key assumption underlying such statistical analyses is the "stationarity" of the EEG signal. At the same time, in view of the overwhelming evidence for the disjointed nature of EEG activity presented above, it would be unwise to treat the EEG as a stationary statistical process ***(53, 63)***. Since we are essentially dealing with a sequence of discrete processes (short-term segments), methods presupposing a continuous process are likely to have a rather limited application in EEG analysis ***(4, 48, 53, 56, 60, 68, 69)***.

Even though approaches based on the assumption of EEG stationarity have revealed some important signal characteristics (for example, the functional significance of different EEG frequency bands ***(35, 160, 161)***), the initially rapid temporal resolution of the EEG signal is usually lost under such conditions. In the meantime, it is obvious that regardless of how powerful or statistically significant the different estimations of averaged EEG characteristics may be, there might be substantial difficulties in arriving at a meaningful neurophysiological interpretation of these if they are not matched to their inherent piecewise stationary structure ***(4, 50, 53, 63, 162)***. For example, invariants such as the mean power/amplitude spectrum, average ERP and ERD/ERS, coherency, fractal dimensions, Lyapunov exponents, and many other indexes have an interpretation only for stationary dynamics ***(163)***. Furthermore, the nonstationarity of the EEG signal usually does not allow researchers to construct a global dynamical model for the whole observable phenomenon ***(164)***. Therefore, there is a need for a *novel methodology of EEG analysis* that is sensitive to the underlining quasi-stationary nature of EEG signal (in both temporal and spatial dimensions) and plausible for a better understanding of the functional organization of the neocortex and its relation to a cognition and eventually consciousness.

One of such novel methodologies for EEG analysis is an *operational architectonics (OA)* framework[4] which (a) considers the nonstationarity of EEG (is sensitive to spatial-temporal structure of EEG), (b) does not contain temporal averaging procedures, (c) is model-independent, (d) has special tests for non-random and non-occasional nature of the results, (e) produces results which are easy to interpret in terms of their neurophysiological correlates and (f) permits to measure postulated entities in practice ***(55, 56)***.

3. Brief introduction to the Operational Architectonics methodology

In this subsection we will overview the main concepts of *operational architectonics* (OA) theory and the related methodological approaches to EEG analysis. The basic operational units of brain activity within OA theory are presented by the local field activity of neuronal assemblies "*hidden*" in the complex nonstationary structure of brain EEG field ***(53, 56, 63, 91)***. Such local fields are organised spatially and temporally within a *nested hierarchy*[5] of increasing in complexity discrete metastable states that serve as the basis for functioning of such a multivariable and complex system like the brain ***(108)***.

3.1. Neuronal assemblies and EEG signal

A neuronal assembly is generally defined as a set of neurons that are able to synchronise their sub-threshold oscillations (excitatory/inhibitory postsynaptic potentials — EPSPs/IPSPs), leading to a

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[4] For other major methodologies of EEG analysis which explicitly utilize EEG nonstationarity see the work of Lehman and coworkers ***(60, 61, 67, 80, 138, 147, 149, 150, 165)***, Freeman and coworkers ***(62, 64, 65, 85, 87, 89, 90, 112, 123, 158, 166)***, and Breakspear and Stam with coworkers ***(75, 134, 145, 167-169)***.

[5] According to Feinberg ***(170-172)***, in a non-nested hierarchy the entities at higher levels of the hierarchy are physically independent from the entities at lower levels and there is strong constraint of higher levels upon the lower levels, whereas in a nested hierarchy the higher levels are physically composed of lower levels, and there is no central control of the system resulting in weak high-to-low levels constraint.

coherent activity of the whole assembly ***(16, 34)*** in order to perform a specific physiologic or cognitive operation ***(173, 174, 175)***. Historically, this notion goes back to Hebb ***(176)***, though the classical (Hebbian) neuronal assemblies are too slow and rigid, and therefore would not be suitable for fast cognitive operations (for a discussion, see ***(55)***).

A modern understanding of neuronal assemblies stresses their functional and highly transient nature, which is at scales both coarser (for *spatial* dimension) and finer (for *temporal* dimension) compared to classical assemblies ***(177)***. The idea is that large masses of individual neurons can quickly become functionally self-organised (associated or disassociated), thus giving rise to *transient* assemblies ***(178, 179)***. The overall pattern of emergent neuronal assembly's correlated activity – local field or wave-packet ***(65)*** – persists over some temporal interval, during which it is thought to execute the basic physiologic or cognitive operation ***(180, 181)*** which may also be subjectively experienced as a presence of simple phenomenal feature/qualia[6] ***(54, 91)***. This pattern is very sensitive to fluctuations and it can be swiftly rearranged during rapid transitional period ***(91, 186, 187)***. As has been demonstrated in vitro, such intervals of correlated activity are manifested in oscillatory waves ***(34, 188)*** accessible through local EEG measurements ***(59, 85, 87, 189)***. Thus, the behaviour of neuronal assemblies is highly dynamic and nonlinear ***(53, 65, 158, 169)***, and arises as a consequence of propagating local synchrony in the form of avalanches of neuronal activity ***(190, 191)*** (for a brief explanation of avalanches see below).

EEG waves recorded from the scalp are integrated excitatory and inhibitory postsynaptic potentials (EPSPs/IPSPs) of neuronal membranes ***(85, 87, 189)***. Since they reflect extracellular currents caused by synchronized neural activity within a given brain volume ***(192)***, the local EEG signal within quasi-stationary (nearly stable) segments represents an envelope of the probability of non-random coherence (so-called a "common mode" or a "wave packet" ***(65)***) in the neuronal assemblies near to the recording electrode ***(158, 169)***. Even though the neuronal cells that comprise an assembly under the electrode may be spatially intermixed with neuronal cells from other neuronal assemblies performing different computational tasks, they are separated by different temporal scales reflected in a set of particular narrow EEG frequencies[7] ***(39, 193)***. Therefore, it is possible to consider each local EEG quasi-stationary segment of particular type as the single event

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[6] Indeed, it has been shown that distinct neuronal assemblies display preferential processing for certain features such as color, shape, motion, smell, etc. ***(182)***. Moreover, it has been documented that the local fields of various neuronal assemblies correlate with different conscious percepts ***(158, 183, 184)*** and if cognitive processing does not take place, such transient neuronal assemblies do not form ***(185)***.

[7] Experimental studies have shown that different frequencies appear to be related to the timing of different neuronal assemblies, which are associated with different types of sensory and cognitive processes (for a detailed overview, analysis and discussion see ***(91)***).

in the EEG-phenomenology, which reflects the particular operation of a related neuronal assembly ***(54, 56, 106)***.

Of course, there is no simple (one-to-one) relation between an EEG quasi-stationary segment of particular type and the actual state of the neurons in the underlying network: many different configurations of firing neurons can give rise to the same type of short-term EEG activity (many-to-one relation). At the same time, the same configuration of firing neurons cannot give rise to two (or more) different types of short-term EEG activity. Thus, two different types of short-term EEG activities are likely to originate from two different configurations of firing neurons ***(107)***. Consequently, short-term EEG activity of a particular type reflects a specific class of neuronal activity, where each of the activities has something common with the others within the same class (one-class–to–one relation). Moreover, two classes of neuronal activities do not overlap (otherwise the same configuration of firing neurons could give rise to two or more different short-term EEG activities). Thus, a given type of short-term EEG activity may be considered as a single event (which reflects a particular class of neuronal activity) in EEG phenomenology. Additionally, considering the aforementioned spatial heterogeneity of EEG (see section 2.2 above) one may suggest that local EEG short-term activity is mainly determined by underlying neurodynamic (functional state) and that this type of activity mainly reflects the large-scale morpho-functional organization of the cortex rather than the effect of volume conduction, at least for the 10/20 System (used in the majority of EEG studies) which measures the main cortex lobes.

Within the duration of one quasi-stationary EEG segment, the neuronal assembly that generates the oscillations is supposed to be in a steady quasi-stationary state ***(51, 73, 81)***. The *rapid transition processes* (RTPs) occurring in the continuous EEG activity mark the boundaries between quasi-stationary segments for this activity. The transition from one segment to another reflects the changes of the neuronal assembly microstate or, if multiple frequencies are considered, changes in the activity of several neuronal assemblies ***(53-56, 65)***. This is the first (*low*) level of operational architectonics framework of brain functioning (for a complete description see ***(55, 56, 91)***).

3.1.1. EEG signal segmentation approach – RTP estimation

Because the major contributor to temporal modulation of the variance and power of the EEG signal is the sharp change in its amplitude ***(194)***, the identification of RTPs can be reduced to detecting the moments of rapid statistically significant decrease or increase of EEG amplitude ***(56)***. In this sense, RTP is defined as an abrupt change[8] in the analytical amplitude of the local EEG

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[8] In mathematical statistics this phenomenon is known as the change-point problem ***(195)***.

signal above a particular threshold derived from a statistical procedure which was established experimentally for each local EEG in previous modelling and empirical studies ***(56)***.

There are several mathematical approaches to segment a multichannel EEG signal. Unfortunately, the vast majority of them are based on the assumption that an EEG signal can be sufficiently described by using a mathematical model characterised by a finite collection of parameters ***(81)***. In mathematical statistics such methods are known as parametric ***(196)***. One example of such methods used for EEG segmentation is autoregressive moving average modelling ***(69, 197, 198)***. Linear regression modelling is another example of used EEG segmentation method ***(199)***. Even though parametric methods are quite effective if the phenomenological model of the analysed process is known ***(196)***, in case of EEG signal no such generally accepted phenomenological model has been ever suggested ***(81)***. In fact, very different mathematical models can be fitted to the same EEG signal, thus resulting in vastly different estimates of segments. This makes the usage of parametric methods for EEG segmentation unjustified.

Another drawback of nearly all EEG segmentation methods is the fact that they are designed for stationary signals. Such algorithms can be applied correctly only to stationary intervals of the signal, but the presence and location of these stationary intervals are unknown before the procedures are actually applied – a so called vicious circle ***(81)***. Therefore, nonparametric approaches that do not require any model of the signal and *a priori* information about its distribution are needed.

Fingelkurts and Fingelkurts ***(200)*** were among the first who applied such nonparametric segmentation procedure which has been proposed by Brodsky and Darckhovsky to EEG signal. Since then, the initial procedure has been substantially modified and improved reaching its current form ***(56)***. The general statistical principles of it have been described extensively elsewhere ***(54-56)***. Therefore, here we provide only a brief overview of this approach. This adaptive segmentation procedure is used for the parallel automatic segmentation of local EEG signals within a multichannel EEG record. The method is based on an automated algorithm that moves a double window screening along each separate EEG signal/channel. The following steps are taken to estimate RTPs:

(1) Comparisons are made between ongoing EEG amplitude absolute values averaged in two windows – ‘test’ and ‘level’ (duration of test window << duration of level window), both starting from the first data point. The durations of test and level windows are identical across different subjects and EEG channels for each particular frequency band (but different between the bands) to guarantee the best conditions for RTP evaluation.

(2) If the absolute maximum of the averaged amplitude values in the test window is less or equal to the averaged amplitude values in the level window, then the hypothesis of EEG homogeneity is accepted.

(3) If the absolute maximum of the averaged amplitude values in the test window exceeds the averaged amplitude values in the level window, according to the threshold of “false alerts” (first condition – the Student criteria), its time instant becomes the preliminary estimate of the RTP.

(4) A second condition must be fulfilled to eliminate “false alerts” associated with possible anomalous peaks in the amplitude: several points of the digitized EEG recording following this preliminary RTP must have a statistically significant difference between averaged amplitude values in the test and level windows (Student’s *t*-test).

(5) If these two criteria are met, the preliminary RTP is considered real.

(6) Thereafter, both windows are shifted from this RTP to the next time-point, and the procedure is repeated to detect the next RTP.

With this technique, the sequence of RTPs with statistically proven ($p < 0.05$, Student’s *t*-test) time coordinates is determined individually for each EEG channel and for each epoch of analysis (Fig. 1, upper panel).

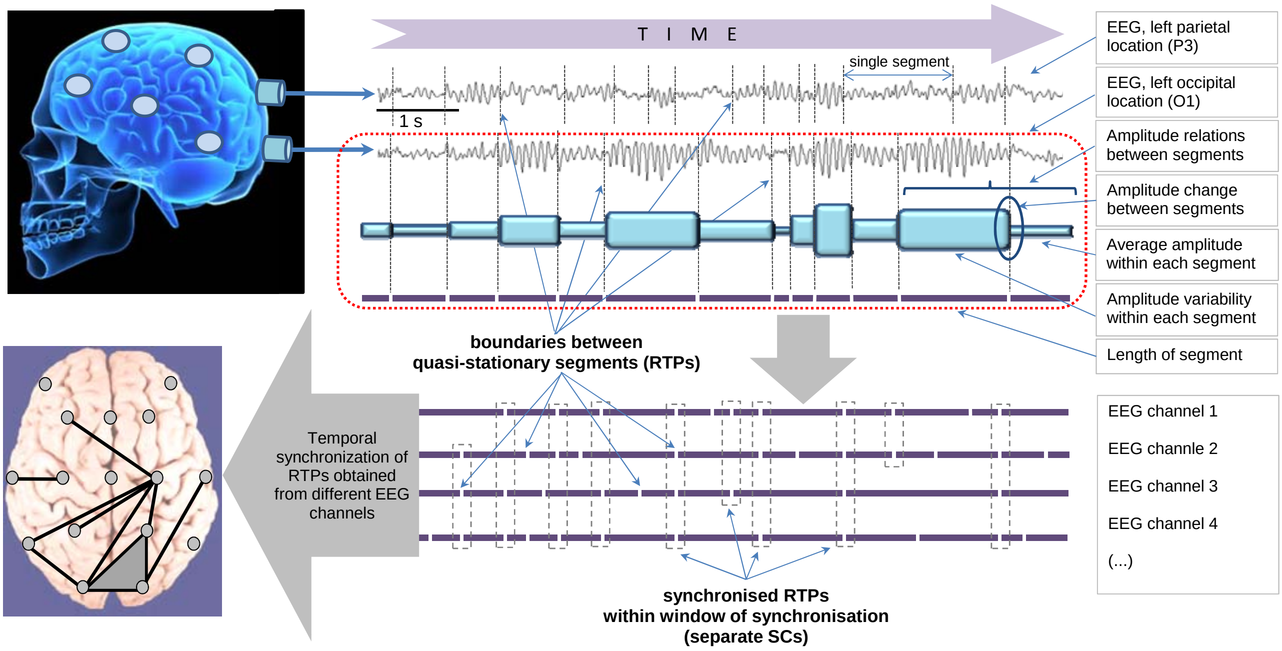

Figure 1. Schematic illustration of the Operational Architectonics methodology including steps for EEG segmentation, extraction of segments’ features and synchronization of segments. Further explanations are provided in the text. RTP—rapid transitional processes (boundaries between quasi-stationary EEG segments); SC—momentary synchro-complexes (synchronization of RTPs between several but always the same local EEGs at the particular time instants).

The choice of window durations and of the ‘false alerts’ rule was made during a few preliminary modelling studies (for a review see ***(56)***) to guarantee the following two goals: (a) to detect as many of real RTPs as possible and (b) to keep the level of ‘contamination’ by ‘false’ RTPs in the results reasonably low.

The identified quasi-stationary segments of EEG activity could be characterized by several attributes that reflect different characteristics of transient neuronal assemblies ***(83, 86)***. These attributes are (Fig. 1, middle panel):

(1) Average amplitude within each segment (microvolts), – as generally discussed above, mainly indicates volume or size of the neuronal assembly; the more neurons recruited into an assembly through local synchronization of their activities, the higher the amplitude corresponding to this assembly’s oscillation in the EEG ***(16, 201)***.

(2) Average length of segments (milliseconds) – illustrates the functional life-span of a neuronal assembly or the duration of operation produced by this assembly; because a transient neuronal assembly functions during a particular time interval, this period is reflected in EEG as a stabilized interval of quasi-stationary activity ***(180)***.

(3) Coefficient of amplitude variability within segments (%) – shows the stability of local neuronal synchronization within a neuronal assembly ***(194)***.

(4) Average amplitude relation among adjacent segments (%) – indicates neuronal assembly growth (recruitment of new neurons) or disassembling (functional elimination of neurons) ***(180)***.

(5) Average steepness among adjacent segments, estimated in the close area of RTP (%) – shows the speed of neuronal assemblies growing or disassembling ***(180)***.

3.1.2. Methodological results related to EEG segmentation

Experimental results revealed a relatively large number of EEG segments per minute for nearly all narrow frequency bands ***(73, 83, 139, 180, 200, 202)***. For example, there are about 60 quasi-stationary segments for delta activity (~1000 ms average duration), 120 quasi-stationary segments for theta activity (~500 ms), 200 quasi-stationary segments for alpha activity (~300 ms), 250 quasi-stationary segments for beta-1 activity (~250 ms), 300 quasi-stationary segments for beta-2 activity (~200 ms), and 350 quasi-stationary segments for gamma activity (~ 170 ms) per each one-minute local EEG during restful wakefulness with closed eyes. Similar relations between durations of quasi-stable states within different frequency bands have been shown in independent research ***(57)***. This range of temporal durations fits very well with the biophysical processes underlying the assemblies’ formation, often iteratively on timescales corresponding to 100-900 ms range ***(34)***. As it has been pointed out by David et al. ***(203)*** a neuronal assembly's operation should be longer than the time for spike transmission between neurons either directly or through a small number of synapses (from few milliseconds to several tens of milliseconds) and it must be shorter than the time it takes for a cognitive act to be completed (which is from several hundreds of milliseconds to a few seconds).

Within such segments, the degree of synchronization (alignment of EPSPs/IPSPs times in multiple neurons making up the neuronal assembly) can vary in time, so it is important to consider how much variability can be tolerated and still be able to consider assembly member neurons to be "acting together" ***(204)***. Our data have shown that the coefficient of within-segment amplitude variability was relatively low for all studied frequency bands (thus indicating the formation of neuronal assemblies ***(91)***; rest with closed or open eyes), and it was substantially higher (up to 30%) for the randomly altered EEG[9] (see also ***(139)***). Such a considerable increase in the values of within-segment amplitude variability in the 'random' EEG indicates the absence of stabilised epochs and thus lack of neuronal assembly formation ***(56)***. More precisely it represents an estimation of the maximum possible rate of relative alterations in the amplitude variability for a given EEG ***(53)***.

Additionally, it has been shown that average amplitude relations among adjacent segments was substantially lower for the randomly altered EEG when compared to real EEG (rest with closed or open eyes; for an example, see ***(139)***), thus indicating that RTPs are true authentic boundaries of EEG quasi-stationary segments which reflect the episodes of relative stabilization of neuronal activity within separate neuronal assemblies separated by such RTPs ***(53, 56, 139)***.

OA theory proposes that the simple operations of neuronal assemblies that we experience subjectively as simple patterns/features of complex thought/image/scene and/or observe objectively as elemental operations of behaviour are created and executed in emergent neural fields of self-organized activity of neuronal assemblies ***(91)***. If this is so, then one should observe a RTP in local EEGs (reflecting a reset of a new operation) every time a novel task (or experimental input) is induced. In other words, if RTPs are true EEG markers of transitional moments between local neuronal assembly operations (indicating their start and end), than under experimental conditions the number of RTPs should be much higher at the exact moment of systematic change from one cognitive/mental operation to another (induced start of a new task) when compared to other task-free time-coordinates within the same condition or a control condition that does not include systematic change of operations according to an experimental protocol. Indeed, experimental

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[9] The procedure of random mixing of amplitude values within each local EEG signal for a multichannel EEG recording was used ***(73)***.

studies have confirmed this hypothesis ***(73, 200)*** (for illustration see Fig. 4 in ***(56)***). These findings clearly indicate that RTPs are the true markers of beginnings and ends of brain-mind operations.

Generally, it has been shown that segmental description of local EEG signals within the multichannel EEG recording is very sensitive to a both spontaneous (stimulus independent) and induced (stimulus dependent) brain states ***(73, 139, 180, 200, 205, 206)*** (for a review see ***(86)***) as well as pharmacological influence ***(83, 151, 153, 154)*** and various pathological conditions ***(73, 102, 152)*** (for a review see ***(86)***).

Summarising this subsection we would like to stress that application of OA methodology to an EEG signal allows researchers to monitor local electric fields of transient neuronal assemblies with millisecond time resolution via extracellularly placed (at the scalp) electrodes[10] and can be used to interpret many facets of neuronal communication and computation ***(180)***. For example, such parameters as size, life-span, stability, and speed of neuronal assemblies growth or disassembly can now be studied robustly as a function of subject's states, behavioural acts, pharmacology usage and neurological or psychiatric pathology (for a review see ***(86)***). The main advantage of such methodology over others, used for the investigation of EEG activity, is that not only are the underlying biophysical mechanisms taken into account but also the neurophysiologic processes related to the EEG and reflected in its spatial and temporal nonstationarity are considered ***(91)***.

From the first studies of RTPs dynamics ***(52, 73, 139, 200, 208)*** it has been noticed that when a RTP in EEG amplitude occurs at any one site (separate EEG channel), it tends to simultaneously occur at several sites of the multichannel EEG recording, marking the onset of a spatio-temporal EEG pattern[11]. Peculiarities of such synchronisation will be discussed in the following subsection.

3.2. Synchronisation of operations of neuronal assemblies and EEG signals

The second (*high*) level of OA theory describes the temporal synchronization of different brain operations (*operational synchrony*) that are executed simultaneously by different local and transient neuronal assemblies ***(91)***. Indeed, as it has been observed in the previous subsection, individually each neuronal assembly presents only a partial aspect of the whole object/scene/concept ***(211)***, while the wholeness of "perceived" or "imagined" is brought into existence by joint (synchronized) operations of many functional and transient neuronal assemblies

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[10] When recorded from the scalp it is referred to as an electroencephalogram (EEG), an electrocorticogram (ECoG) when recorded by electrodes on the cortical surface, and as the local field potential (LFP) when recorded by a small-size electrode in the brain ***(189)***. The magnetic field induced by the same activity is referred to as magnetoencephalogram (MEG) ***(207)***.

[11] Similar dependence has also been found in the phase ***(166, 209)*** and frequency ***(210)*** characteristics of EEG signals.

in the brain[12] (for a thorough discussion see ***(91, 217)***; see also ***(218)***). The recombination of neuronal assemblies in new configurations makes it possible to present subjectively a nearly infinite number of different qualities, patterns, objects, scenes and concepts – even those, with which we have never been acquainted before.

Such synchronization of operations gives rise to a completely new level of brain abstractness – *metastable* brain states[13] ***(108)***. These metastable brain states or functional *Operational Modules* (OM), as we name them, accompany the realization of brain complex (and composite) macro-operations (e.g., cognitive percepts, phenomenal objects, and reflective thoughts; for a review see ***(91, 217)***), whereas each of them is instantiated by the particular volumetric spatial–temporal pattern in the electromagnetic field ***(54-56)***. Within the OA theory, the complex operation or operational act has internal structure where each element in its turn also has its own internal structure and so on until the simplest elemental operations are reached (Fig. 2). In other words, there is a more complex operation/operational act that subsumes the simplest ones. It is critical that any complex operation/operational act is not just a conjunction of simplest operations (or operational acts) – it is an operation (or operational act) in its own right with emergent properties that are not evident in the subordinate constituents. Such architecture has a clear *nested hierarchy* ***(224)*** and thus could serve as the needed ingredient of brain organization that would allow a conscious mind to be expressed and present the features of consciousness (referred to as neural states, mental unity, qualia, and mental causation), which are discussed in detail elsewhere ***(54, 91, 217)*** (see also ***(170-172)***).

3.2.1. Synchronisation of EEG segments – Structural Synchrony measure

Because the beginning and end of discrete operations of local neuronal assemblies are marked by the sharp changes in local EEG amplitude (RTPs), the simultaneous occurrence of these RTPs found in different local EEG signals within the multichannel EEG recording could provide evidence of neuronal assemblies synchronisation (located in different brain areas) that participate

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[12] The idea that synchrony of EEG potentials reflects functional connectivity at the neuronal assemblies level has been proposed by Livanov ***(212)*** and later proven by him in a direct neurophysiological experiment ***(213)***. In this experiment the correlation coefficient between EEGs in visual and motor cortical areas of the rabbit was estimated. It appeared that, if the correlation coefficient exceeded a particular level, the visual signal triggered paw movements, and if this coefficient was lower than the established level, no motor reaction occurred. Further important work in this domain was developed by Lazarev with co-workers ***(214-216)***.

[13] Metastability in the brain ***(108)*** refers to competition of complementary tendencies of cooperative integration and autonomous fragmentation among many distributed brain areas ***(219-221)***. The interplay of these two tendencies (autonomy and integration) constitutes the metastable regime of brain functioning ***(108, 219)***, where local (autonomous) and global (integrated) processes coexist as a complementary pair, not as antagonists ***(222, 223)***. The OMs are metastable because of intrinsic differences in the activity between neuronal assemblies, which constitute OMs, each doing its own job while at the same time still retaining a tendency to be coordinated together within the same OM in order to execute the macro-operation ***(91)***.

in the same functional act as a *group* (Fig. 1, bottom panel), e.g. executing a particular complex operation responsible for a subjective presentation of complex objects, scenes, concepts or thoughts ***(54, 91, 217)***. Fingelkurts and Fingelkurts ***(200)*** were the first who came up with this hypothesis as well as suggested the quantitative method for estimation of such unique type of brain synchrony. The method is named "*Structural Synchrony*" (or index of structural synchrony, ISS) since it refers to a synchrony between structures of local EEG signals, though qualitatively it estimates the synchrony among operations of multiple neuronal assemblies, thus it corresponds to an "*Operational Synchrony*" ***(73)***. Later this method has been modified to expand its functionality ***(56)***.

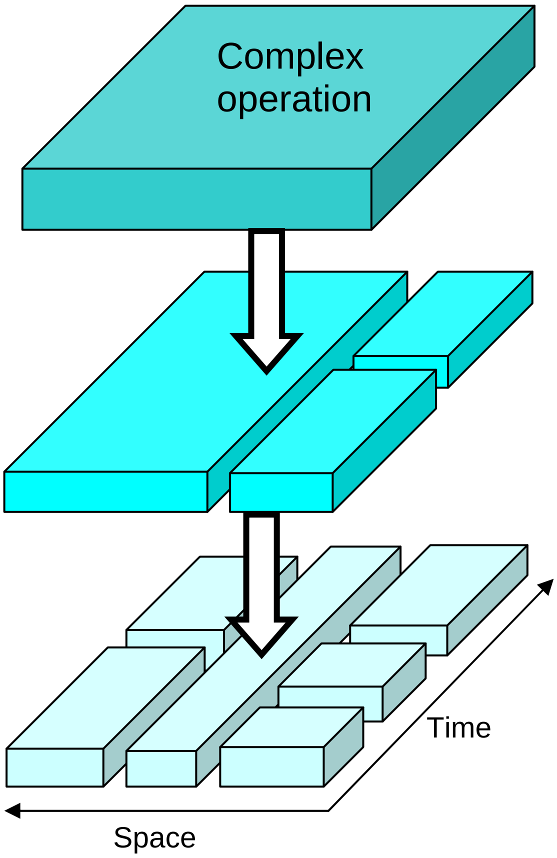

Figure 2. Schematic presentation of the compositionality of operations. Further explanations are provided in the text.

The details of this technique are beyond the scope of this article therefore we will concentrate on the essential aspects only. In brief, each RTP in the reference EEG channel (the channel with the minimal number of RTPs from any pair or set of EEG channels) is surrounded by a short "window" (Δt, ms). Any RTP from another (test) EEG channel is considered to coincide if it fell within this window (Fig. 1, bottom panel). It is important to note that such coincidence of RTPs is related to a specific type of signal coupling – the *structural synchronization of discrete events* –

which completely ignores the level of signal synchronization in the intervals (segments) between the coinciding RTPs[14] ***(122, 200)***. Therefore, this approach explicitly uses the definition of functional connectivity agreed upon in neuroimaging community ***(226)***: Functional connectivity is defined as the temporal correlation between spatially remote neurophysiological *events* ***(227)***. As it has been noted by Plenz ***(191)***, such measure would in fact represent an unbiased estimate of synchronization, because in the absence of any knowledge about the underlying spatial organization of the involved neuronal assemblies, it uses temporal proximity of RTPs to estimate non-random interaction ***(56)***. Importantly, ISS could capture both the near instantaneous synchronous RTPs, comparable to zero-phase locked synchronisation between two sites, as well as successively synchronized RTPs, comparable with delayed phase-locked synchronization ***(122)***.

To arrive at a direct estimate at the 5% level of statistical significance ($p < 0.05$) of the ISS, computer simulation of RTPs coupling is undertaken based on random shuffling of time segments marked by RTPs (500 independent trials). As a result of this procedure, the stochastic (random) levels of RTP coupling ($\mathrm{ISS}_{\mathrm{stoch}}$), together with the upper and lower thresholds of $\mathrm{ISS}_{\mathrm{stoch}}$ significance (5%) are calculated. The ISS tends towards zero if there is no synchronization between EEG segments derived from different EEG channels and has positive or negative values where such synchronization exists. Positive values (higher than upper stochastic level) indicate ‘active’ coupling of EEG segments where synchronization of EEG segments is observed significantly more often than expected by chance (as a result of random shuffling during a computer simulation), whereas negative values (lower than low stochastic level) mark ‘active’ decoupling of segments where synchronization of EEG segments is observed significantly less than expected by chance (as a result of random shuffling during a computer simulation). Dynamics of ISS and its positive and negative levels are shown in Fig. 3. The strength of EEG structural synchrony is proportional to the actual value of ISS: the higher this value, the greater the strength of functional connection.

Since most methods that estimate synchronization look at pairs of recording channels only, a global picture of synchronization in multichannel EEG recording is usually obtained by averaging the pairwise synchronization between every possible pair of channels. The main problem with such an approach is its inability to detect the naturally arising synchronization patterns across space and time ***(228)*** (for a review see ***(91)***). In contrast to the majority of other synchronization methods

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[14] It should be noted here that the original rather narrow neurophysiological definition of synchronization as two or many subsystems sharing specific common *continuous* frequencies is replaced here by the broader notion of a process, whereby two or many subsystems adjust some of their time-varying properties to a common temporal scale due to *coupling of events* or common external forcing ***(225)***.

(that have a number of other limitations[15]) the OA methodology uses algorithmic instruments that permit it to estimate synchrony of events in more than two EEG channels.

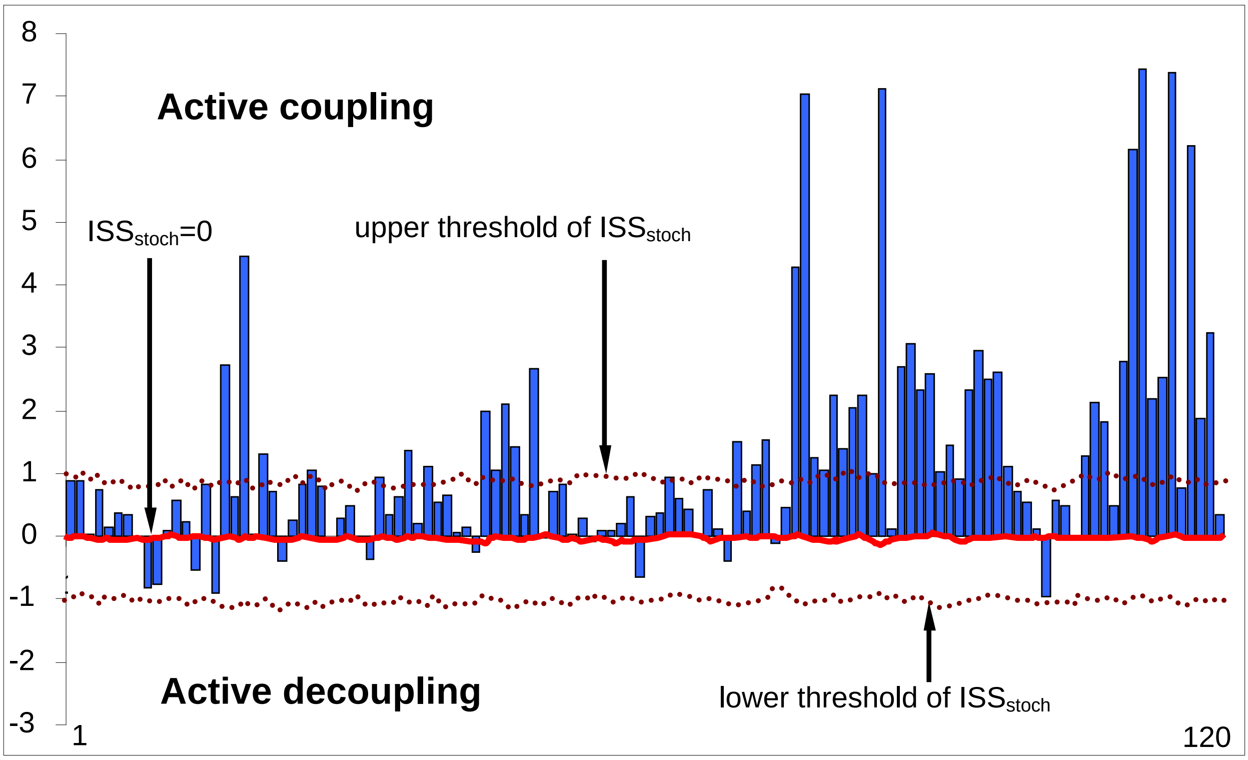

Figure 3. Schematic illustration of the index of structural synchrony (ISS) and its stochastic levels. As an example, the calculations of ISS are shown for 16 EEG channels. The *Y*-axis displays the ISS values found in the experiment (illustrated as bars). The *X*-axis displays the 120 possible pair combinations of 16 EEG channels. The data presented for a healthy subject in a rest condition with eyes closed.

Structural synchrony can be identified in several (more than two) EEG channels, thus identifying synchrocomplexes (SC). A SC is a set of EEG channels in which each channel forms a paired combination (with valid values of ISS) with all other EEG channels within the same SC; meaning that all pairs of channels in an SC have to have statistically significant ISS values linking them together (Fig. 1, bottom panel). The number of cortical areas (indexed by the synchronised EEG channels) recruited in a SC is described as "the order of areas recruitment" ***(73, 200, 210)***. Therefore, all SCs could be divided into a set of categories based on the number of cortex areas

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[15] Such methods (1) are predominantly designed for EEG analysis only in pairs of derivations, (2) do not take into consideration the non-stationary nature of the signal, (3) indicate only the linear statistical link between time-series curves in a frequency band, (4) require long time epochs of analysis, (5) can only be applied to a homogeneous medium, which is an unrealistic assumption for the brain, (6) borrow complex methodologies and conceptual frameworks from physics, mathematics, and engineering, but use them loosely when applying to the analysis of physiological signal, (7) being averaged indices lose a substantial part of their diagnostic value for studying discrete functional states of the brain, (8) use local EEGs that participate in the formation of the resultant dipole vector far from equally, and this is unjustified from the viewpoint of indubitable neurobiological equivalence of cortical areas, (9) are often difficult to interpret in terms of their physiological correlates, (10) do not directly estimate metastability in the brain (see also ***(56, 122, 210)***).

involved: SC_2 – SC with 2nd order of areas recruitment, SC_3 – SC with 3rd order of areas recruitment, SC_4 – SC with 4rd order of areas recruitment, and so on. Notice that any given SC is considered as a member of its own category (for example, SC_3) only if the correspondent RTPs coincided in time among correspondent number of EEG channels (in this example, 3). However, any three SCs_2 which could comprise the particular SC_3 but which do not coincide in time between each other are not considered as producing SC_3 type and, therefore are not counted as SC_3, but instead as SC_2. The same logic is applied to any other SC category larger than SC_2.

Notice that synchronised RTPs mark transitions between different segments in the EEG signal, which are usually of different type in the various EEG channels. Therefore, the described RTPs-based measure of functional connectivity, in contrast to conventional approaches, is free from similarities of the EEG signals in different channels. In this context, the simultaneous stabilization of RTPs across several cortical areas is supposed to reflect the formation of a steady cooperation of operations among scattered in different cortical areas neuronal assemblies independent of the particular characteristics of these operations ***(91)***. At the more conceptual level, such synchrony presents the relevant sub-operations or phenomenal qualia about the external objects (or scenes) reflected in the wave packets of quasi-stationary EEG segments derived from different cortical areas for integration and formation of a unified macroscopic (complex) phenomenal object, scene or thought as the culminating act of perception, imagination or thinking (for a detailed discussion see ***(91, 217)***). In this context SCs have a direct relation to the OM estimation.

3.2.2. Operational Module (OM) estimation

The criterion for defining an OM is a sequence of the same type SCs of the same category during given epoch of analysis. In other words, the constancy and continuous existence of each OM persist across a sequence of discrete and concatenated segments of stabilized (coupled) local EEG activities (indexed by the same SCs) that constitute that particular OM (Fig. 4; ***(55, 56)***). Conceptually, *the continuity of any given OM exists as long as the set of neuronal assemblies located in different brain areas maintains synchronicity between their discrete operations*[16]. Analogous to SCs, OMs can be of different order of areas recruitment (indexed by the number of synchronised EEG channels).

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[16] The presented concept of the OM suggests that both parallel and serial processing may be just different sides of the same one underlying mechanism—synchrony of operations of neuronal assemblies. Parallel processing is performed by individual neuronal assemblies, while serial processing emerges as a result of formation of OMs and their changes along with shifts in the process of actualization of objects in the physical or mental world ***(122)***.

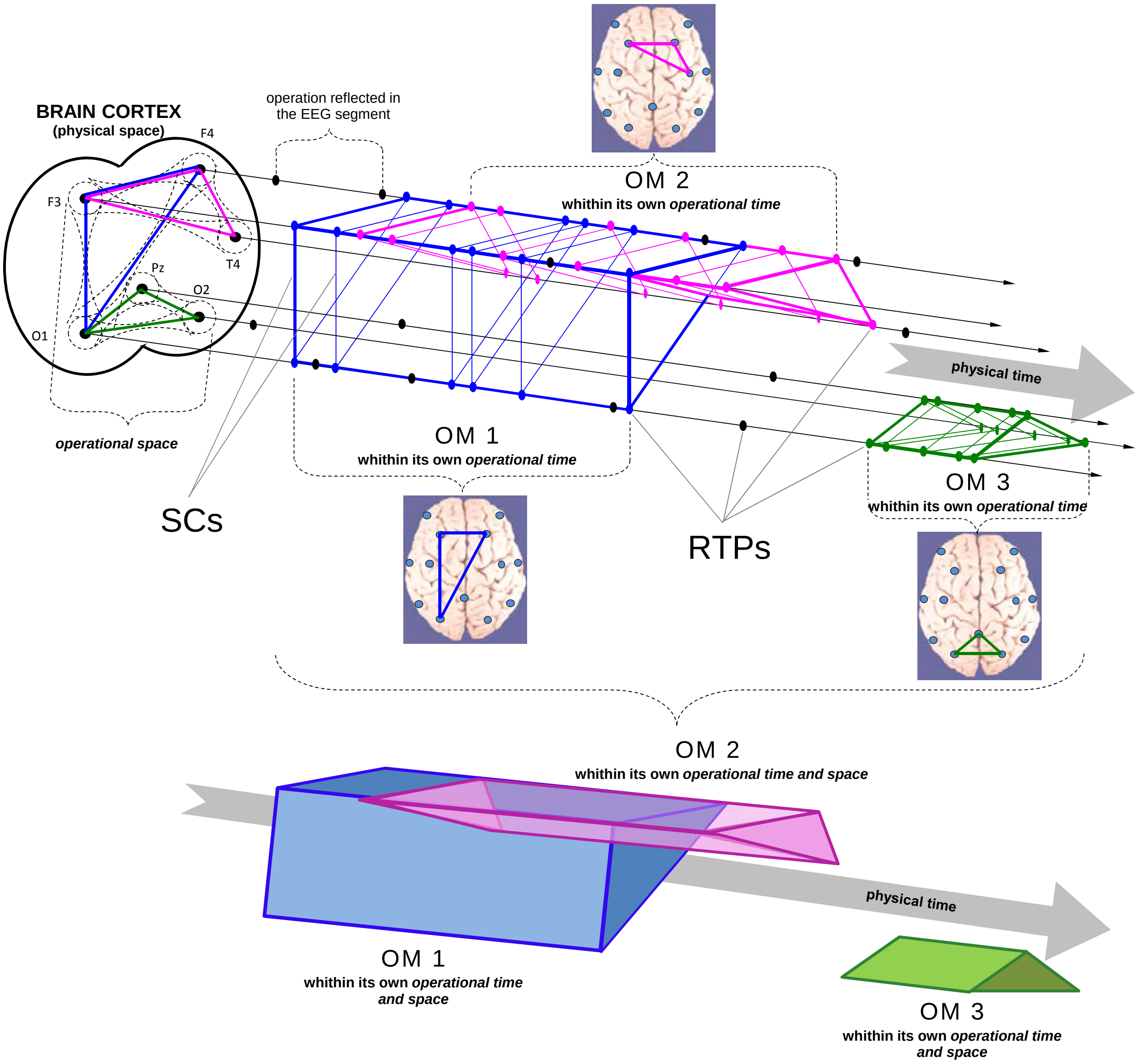

Figure 4. Schematic illustration of Operational Modules (OMs) and Operational Space–Time (OST). Each OM exists in its own OST, which is "blind" to other possible time and space scales present simultaneously in the brain "system": all neural assemblies that do not contribute to a particular OM are temporarily and spatially "excluded" from the OST of that particular OM. Further explanations are provided in the text. RTP—rapid transitional processes (boundaries between quasi-stationary EEG segments); SC—momentary synchro-complexes (synchronization of RTPs between several but always the same local EEGs at the particular time instants); F3 — the left frontal cortical area; F4 — the right frontal cortical area; O1 — the left occipital cortical area; O2 — the right occipital cortical area; T4 — the right temporal cortical area; Pz — the central parietal cortical area. As an example, it is shown that neural assemblies in these areas could synchronize their operations on three different (even though partially intertwined) spatial–temporal scales, thus forming three separate OMs each having its own operational space–time (bottom panel, 3D-objects).

The notion of *Operational Space–Time* (OST) applies here ***(229)***. Intuitively, OST is the abstract (*virtual*) space and time which is "self-constructed" in the brain each time a particular OM emerges[17]. Formally, the OST concept holds that for a particular complex operation, the spatial distribution of the locations of a *particular set* of neuronal assemblies together with their synchronous activity at repetitive instants of time (indexed by SCs) comprises the OM. These distributed locations of that set of neuronal assemblies are discrete, and their proximity as well as the activity in the "in-between area(s)", delimited by the known locations of neuronal assemblies, are not considered in the definition (only the exact locations of a particular set of neuronal assemblies are relevant). Also, between the moments in time that particular locations of the neuronal assemblies synchronize, there can be smaller subset(s) of these locations synchronized between themselves or with other neural locations, though these do not relate to the same space–time of the same OM (although they may relate to some other OM). Therefore several OMs each with its own OST can coexist at the same time within the same volumetric electromagnetic field ***(91)***. The sketch of this general idea (based on experimental data) is presented in Fig. 4.

According to OA theory, the metastable OMs at an OST level somehow "freeze", and "classify" the ever changing and multiform stream of our cognition and conscious experiences ***(91)***. In this sense, the succession of complex cognitive operations, phenomenal images or thoughts is presented by the succession of discrete and relatively stable OMs, which are separated by rapid transitive processes (RTPs), i.e. abrupt changes of OMs[18] (see Fig. 5). As it has been shown experimentally ***(52, 83, 84, 139, 148, 153, 202, 208, 232)***, at the critical point of transition in a mental state, e.g. during changes from one task/thought to another, the OM undergoes a profound reconfiguration which is expressed through the following process ***(91)***: A set of local bioelectrical fields (which constitute an OM) produced by transient neuronal assemblies located in several brain areas, rapidly loses functional couplings with one another and establishes new couplings within another set of local bioelectrical fields; thus demarcating a new OM in the volumetric OST continuum of the brain. Using this mechanism the brain determines who "talks" to whom at any particular moment. In this sense, the brain can "rewire" itself dynamically and functionally on a milliseconds time scale without changing the synaptic hardware[19] ***(57, 235)***.

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[17] In this way, OMs lie, in some sense, between classical, connectionist and process architectures. They resemble connectionist networks ***(230)*** in many respects: they may serve as associative, content addressable memories, and they are *distributed* across many neural assemblies. Yet, the specific spatial–temporal patterns (OMs) per se are *unitary*, like symbols of classical logics ***(231)***. And yet, each OM is a *process*, since it lasts as long as several operations that have some continuity in time (and which are produced by different neuronal assemblies) are synchronised among each other during a given temporal interval ***(91)***.

[18] First substantial experimental support for this formulation was obtained within the framework of the brain microstates concept: it has been shown that momentary cortical electric field distributions are abruptly upgraded and constantly replaced ***(61, 80, 138, 165)***.

[19] This is why an OM is relatively independent from the underlying small-scale neurophysiological processes in the brain ***(91)***. More specifically it is independent from intrinsic brain anatomical topology that determines which single

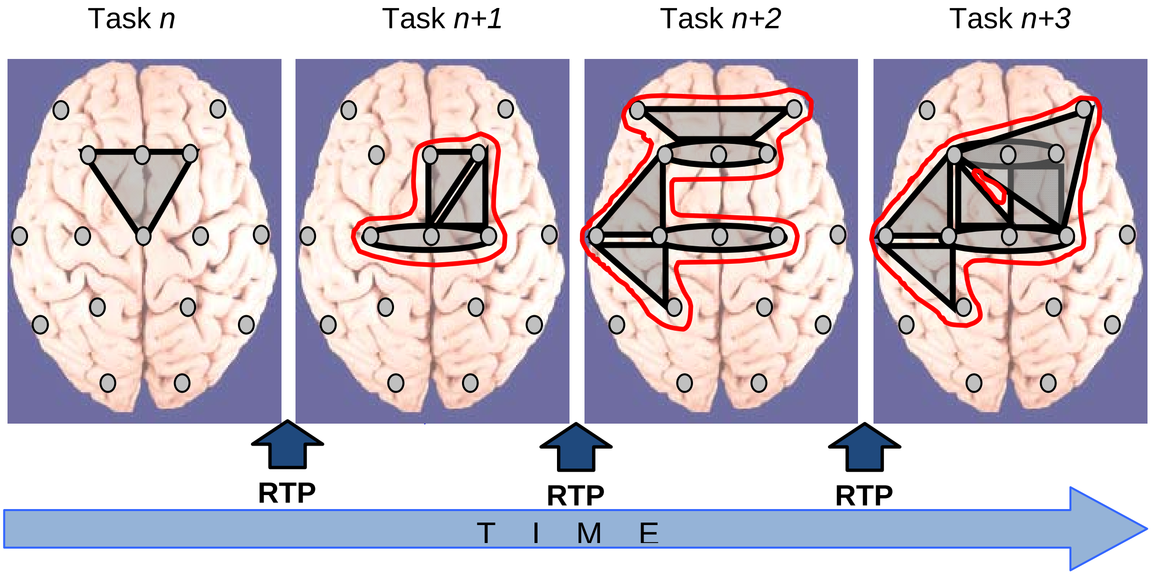

Figure 5. Schematic diagram depicting dynamics of operational modules (OMs). Relatively stable complex OMs (outlined by the red line) undergo abrupt changes simultaneously with changes in cognitive task. Such abrupt changes marked as rapid transitional periods (RTPs). Grey shapes illustrate individual OMs. Red line illustrates complex OMs. For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article. This scheme is based on data published in the Ref. ***(247)***.

3.2.3. Methodological results related to EEG structural synchrony

Already first experimental studies ***(52, 73, 139, 200, 208, 232)*** had shown that OMs (specific spatio-temporal configuration of stabilized segments among local EEG fields) indeed exist, thus confirming the discovery of a new and previously unknown type of brain functional connectivity. It was found that such OMs are characterized by different order of recruitment of cortical areas: from any two to the whole cortex. Surprisingly, analysis has shown ***(200, 232)***, that independently from the condition or functional state all independent OMs of second order of cortical areas recruitment that do not participate in any OM of a higher order of areas recruitment have negative ISS values. This means that any two cortical sites tend to actively de-couple their operations if they are not bound to a third site or several other areas concurrently. In other words, if two areas of the cortex are operationally synchronized, they also tend to be synchronized with some other area(s).

Recent calculations showed that the power-law statistics governs the probability that a particular number of cortical areas is recruited into an OM (defined as the temporal RTP coincidences among different EEG channels). This ubiquitous dependency is characterized by a fractal relation between different levels of resolution of the data, a property also called self-

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neuron of a given anatomical circuit produces a particular spike pattern of a given temporal signature (for similar argumentation see ***(43, 233, 234)***).

organized criticality ***(236)***. Thus, it has been shown that OMs are indeed driven by a renewal process with power index $\mu\approx 2$ ***(237-239)***[20], which is in line with Beggs and Plenz's ***(244)*** avalanche research. An avalanche is defined as a spontaneous and abrupt burst of activity observed on variable numbers of electrodes for different periods of time separated by silent or quasi-stable periods ***(191)***. Neuronal avalanche behaviour is an indication that the cortex is working in a critical condition. Critical systems exhibit scale-free, power-law dynamics at many levels of description during transitions between order and disorder and their universal behavior is independent of the specific realization of system components ***(245)***.

It has been shown that independent OMs of the second order of areas recruitment which have negative ISS values, constitute only 14% from total number of all possible OMs formed by two cortical areas, that are part of triple, quadruple and higher degree OMs ***(73, 200)***. These higher degree OMs have only positive values of ISS. Thus, one may conclude that the brain "prefers" to synchronise three or more cortical areas in order to execute on-going complex operations, otherwise neuronal assemblies tend to work autonomously. Our analysis also revealed that such stabilized spatio-temporal OM configurations have transient dynamics which is expressed as a series of sudden transitions between OMs ***(73, 139, 200, 208)***. What is the life-span of OMs with different order of areas recruitment?

From an information-theory point of view, one may suppose that large (covering most or the whole cortex) long-lasting OMs are not efficient in the healthy brain ***(178)*** because context-dependent information transfer is necessarily more transitory and would require dynamic reconfiguration of OMs as well as existence of many OMs. This intuition has been confirmed experimentally ***(73)***: it has been shown that the average life-span of OMs is longest for OMs with 2nd order of areas recruitment (~30 sec in average) and shortest for OMs that span most or the whole cortex (~100 ms in average)[21]. Thus, one may conclude that the brain operates as a highly dynamic system where large spatial-temporal patterns of stabilised activity (indexed as OMs) are formed only for a very brief episodes and quickly dissolve allowing the brain (as a whole) to have more degrees of freedom to form new OMs needed to execute newly immediately emerged and ever changing operations. Therefore, the dynamics of cortex functional organization is usually

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[20] In physics the value $\mu=2$ indicates a transition between two kinds of ergodicity breakdown, stationary and nonstationary, respectively ***(240, 241)***. Moreover, it has been shown that having complex networks at $\mu\approx 2$ provides ideal conditions for transmitting and receiving information ***(242)***. Recently it has been confirmed that neuronal avalanches provide optimal condition for the mutual information transfer between stimulus and response ***(243)*** and allow the realization of a large diversity of activity patterns ***(191)***.

[21] These life-span accounts of OMs, including variations in duration, are consistent with known estimates of cognitive processes, and of highly dynamic "moments of experience" or "thoughts", which may vary between ~100 milliseconds and several seconds depending on circumstances ***(246)***. These values are also consistent with independent EEG studies applying different methods of data analysis ***(57, 67, 80)***.

dominated by local interactions between brain regions. Here it is important to note, that some types of OMs of particular categories are surprisingly stable and persist across all studied experimental conditions in all studied subjects ***(73, 232, 247)***. Initially we have interpreted such OMs as responsible for long-lasting, complex brain operations and body "housekeeping" tasks ***(229)***. However, it later became evident ***(98)*** that, as a whole, these highly stable OMs constituted a set of cortical areas that has been named the "Default Mode Network" (DMN) ***(248)***. Nowadays researchers tend to associate the DMN either with stimulus-independent thought ***(249, 250)*** or with the "autobiographical" self ***(249, 251)***, or being a "self", or having self-consciousness ***(170, 252)***. Indeed, as we have discussed in other work ***(98)***, a subject that experiences phenomenal self-consciousness always feels directly present in the centre of an externalized multimodal perceptual reality ***(253, 254)***. This is why the set of particular OMs that constitute a DMN and altogether specify the sense (probably in an implicit form) of 'being a self' is always active, even during realization of some cognitive (or other) tasks and conditions (including dreaming), independently of their complexity ***(98)***.

Coupling of neuronal assemblies is usually examined within single frequency bands (meaning on a particular temporal scale). At the same time, as noted by Buzsáki and Draguhn ***(34)***, different oscillatory frequencies might carry different dimensions of brain integration, and the coupling of operations of neuronal assemblies between two or more temporal scales (frequency bands) could provide enhanced combinatorial opportunities for storing/processing/presenting complex spatio-temporal patterns ***(91, 255)***. The central assumption behind such a view is that oscillations within different frequency bands reflect different types of cognitive processes ***(11, 39, 106, 256)*** and that different oscillations become synchronized if the task (or condition) demands require a co-activation or integration of the respective cognitive processes ***(256, 257)***.

Considering the polyphonic character (mixture of different frequency oscillations) of the EEG field ***(11, 16, 39)*** and the hierarchical nature (different time-scales) of segmental descriptions of local EEG fields ***(52-54, 56)***, OMs could co-exist on and between different temporal (frequency oscillations) scales. In addition to topographical relationships, cross-frequency synchronization is capable of describing synchronous activity between different neuronal assemblies that may spatially overlap under the same EEG electrode.

The OA methodology enables researches to study such cross-frequency coupling in a direct manner[22] ***(56)***. In contrast to many other methods (for a critique see ***(258)***), it (a) requires no *a*

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[22] It is worth noting that within the OA framework there are no methodological restrictions for relations between frequency bands, that is because the ISS measure is not associated with phase relations of the EEG signal as it is the case for more conventional methods of estimating EEG synchronization ***(56, 255)***.

priori assumptions about which frequency bands should be synchronized, but rather relies on the natural statistical properties of the data to reveal cross-frequency synchronization; (b) is sensitive to transient changes in cross-frequency coupling over both time and frequency; (c) can simultaneously assess multiple cross-frequency synchronizations (i.e., different synchronizations in different frequency bands), and (d) is well-suited for investigating possible cross-frequency coupling during dynamic and/or brief cognitive or perceptual events ***(210)***.

From the first studies in this field ***(73, 200, 255)*** it became evident that segmental flows among the EEG frequency components are more or less synchronized and depend on the character of information-processing of brain activity. Interestingly, such synchrony is independent of narrow frequency bands' closeness within broad EEG spectral pattern ***(73, 255)***. For example, the ISS is not always higher in the alpha1-alpha2 pair of frequency bands (neighbouring oscillations) when compared to delta-beta1 pair of frequency bands (non-neighbouring oscillations). The principal finding is that ISS between basic EEG rhythms (delta, theta, alpha1, alpha2, beta1, beta2) decreases in each local cortical area as cognitive loading increases[23] ***(73)***. Another finding concerns the occipital-frontal gradient: ISS values for the cross-frequency synchrony increase during rest condition in the direction from occipital to frontal cortical areas, while they decrease along the same direction during cognitive activity[24] ***(73)*** (for an illustration see ***(56)***).

Together, these findings pointed to the existence of not only spatially nested neuronal assemblies, but also to a dynamically organised nested structure of OMs between different temporal scales ***(224)*** (see also ***(167, 256)***). In such functionally nested architecture, the on-going brain activity during an *awake resting state* is characterized by (i) increased coupling between operations of neuronal assemblies located within the same cortical area, though performing their operations on different temporal scales, and at the same time by (ii) decreased coupling between operations of neuronal assemblies located in different cortical areas, though performing their operations on the same temporal scale. In response to *cognitive loading* such dependency reverses: local cross-scale synchrony decreases while the topographical same-scale synchrony increases ***(73, 232)***.

Our research has shown ***(73, 200, 255)***, that OMs (being themselves the result of synchronized operations produced by distributed transitive neuronal assemblies) are capable of further operational synchronisation between each other both, within the same, and across different temporal scales, thus forming a more abstract and complex OM which constitute an integrated

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[23] The reader is reminded that the topographical (between different cortex locations) operational synchrony within the single frequency band, on the contrary, increases in response to cognitive loading ***(73, 210, 232)***.

[24] Importantly, this phenomenon does not depend on the EEG alpha-activity expression, since it has been demonstrated that it is identically present in subjects with both, very high and very low ("flat") alpha-activity ***(73)***.

experience ***(91, 217)***. In such operational architecture, each of the complex OMs is not just a sum of simpler OMs, but rather a natural union of abstractions about simpler OMs. Therefore, OMs have a rich combinatorial complexity and the ability to reconfigure themselves rapidly, which is crucially important for the presentation of highly dynamic cognitive and phenomenal (subjective) experience ***(91, 217)***. Yet the opposite process is also possible, where any complex OM can be partitioned into a set of sub-modules, and to that effect each sub-module may be further decomposed into sub-sub-modules, stripping these processes all the way down to basic operations. Such decomposition would be responsible for a segmentation of our subjective experience and focused attention. In other words, such operational architecture has the fractal property of hierarchical modularity, multi-scale modularity or, as Meunier and co-workers called it, “Russian doll” modularity ***(259)***.

Taking into account the hierarchy of segmental description of EEG in different temporal and spatial scales, it could be suggested that the discrete structure of brain activity depicted in the EEG piecewise spatio-temporal stationary structure is the operational framework within which a variety of rapid ‘microscopic’ variables can obey the ‘macroscopic’ operational structure of brain activity ***(91)***. Thus, the spatial and temporal nested hierarchy of discrete metastable states of neuronal assemblies can serve as the basis for functioning of such a potentially multivariable system like the brain ***(108)***.

What are the functional benefits that make such nested hierarchy of virtual modules of brain activity so attractive for brain functioning? One of the earliest propositions formulated by Simon ***(260)***, states that a “nearly decomposable” system that is comprised of multiple and sparsely inter-connected modules allows more rapid adaptation of the system in response to changing environmental conditions (see also ***(261)***). In respect to a central nervous system, there could be several important advantages: (a) Networks of functional and dynamic modules have the property of small-worldness which is advantageous because it favours locally segregated processing (with low wiring cost) of specialized functions (for example visual or auditory detection) due to the high clustering of couplings between nodes in the same module, while at the same time support globally integrated operations of more generic functions (for example working memory) due to the short path length ***(259)***. Such double tendencies intervened within the same modules demonstrate the principle of metastability ***(108)***. (b) The topology of functional and dynamic modules is associated with rich non-linear dynamical behaviour: temporal scales separation due to fast intra-modular processes and slow inter-modular processes ***(262)*** as well as high dynamical complexity due to the coexistence of both segregated and integrated activity ***(108, 211, 263)***. Meunier et al. ***(259)*** observed that the presence of modules allows some neuronal activity to remain locally encapsulated while at the same time maintaining a dynamical balance where dynamical activity is maintained between the extremes of rapidly "dying out" and invading the whole network, as marginally stable modules can be combined or divided while preserving stability ***(264, 265, 266)***. (c) Another advantage of virtual modules is their optimality at performing tasks in a changing environment ***(259)***, where a certain set of simple (basic) operations are required and where a combination (coupling) of these "building operations" is needed to solve complex tasks ***(91, 217)***.

4. Implications of OA methodology

In the previous section we have briefly observed the main tenets and general methodological results of Operational Architectonics framework for EEG analysis. The main advantage of such methodology is the fact that it allows researchers to study the inherent local and global processes in the EEG field at a common level of formal analysis. According to this analysis all multivariability and complexity of brain operations are reflected in the nested hierarchy of dynamic local fields of neuronal assemblies ***(91, 256)***. In the following subsections we will overview the implications of OA methodology for specific domains.

4.1. Implications for cognitive neuroscience

There are several major problems in cognitive neuroscience that attract many resources, with researchers aiming to resolve or clarify them. One such problem is a working memory. Even though it has been understood already for some time that memory (and working memory in particular) reflects a distributed property of large-scale cortical systems ***(35, 218, 267, 268)***, the particular contribution of neuronal assemblies located in different cortical areas during episodic encoding and retrieval processes is still uncertain and only partially understood ***(269)***.

The application of OA methodology to memorising conditions revealed rich data about the neurophysiological mechanisms behind different stages of the memory task ***(73, 139, 200, 208, 232, 247)***. The experiments were designed in such a way that it was possible to test resting, waiting, encoding, keeping-in-mind (retaining), and identification (retrieval) short-term periods of the memory task separately and in their natural chronology.

The most straightforward result was that bursts of abrupt OM formations were observed at the exact moments when one stage of a memory task was switching over to another in a controllable manner, for example, transition from encoding to retention ***(73, 200)***. This finding clearly indicates that formation of virtual OMs is guided by the need to execute complex cognitive or mental operations. Since each complex operation is a coupling of several simpler ones ***(91, 217)***, one may expect to find many OMs of different complexity present within each stage of the memory task. This is indeed the case. The diversity of OMs grows as cognitive loading increases, reaching its maximum at the retention stage (Fig. 6, upper panel). It were OMs with the small and medium order of areas recruitment that contributed the most to such increase in OMs diversity ***(73, 200, 232, 247)***. This observation can be easily interpreted as an increased need for independent brain operations that parallel the need to anticipate, perceive, encode and then keep-in-mind external stimuli during the studied increase of cognitive loading of a memory task. Indeed, in agreement with the general understanding, many neuronal assemblies with distributed parallel processing are active and must synchronise their operations in order to be able to execute the needed cognitive operations as a basis for successful memory performance ***(247)*** (see also ***(16, 257, 270, 271)***).

Interestingly, the increase in diversity of sets of OMs along the increase of cognitive loading is also accompanied by the increase of life-span of respected OMs (Fig. 6, upper panel). For example, the average life-span of OMs was minimal during resting stage (before stimuli presentation) and reached its maximum at the retention stage of the memory task ***(73, 232, 247)***. It can be explained that during an increase in the cognitive loading, the growing number of complex cognitive operations also paralleled by an increase of their durations. Such prolonged duration of complex cognitive operations during encoding and especially retention stages of a memory task is probably an important condition for successful memorisation ***(73, 232, 247)***. However, detailed analysis revealed a more complex picture.

Even though the rate of successfully memorised stimuli in our experiments was quite high (up to 90%) some trials for each subject were not successful – the item was not memorised correctly. Therefore, it was interesting to study the diversity and life-span of OMs as a function of high and low memorability in the same subjects. It has been found that the maximum diversity as well as longest life-span of OMs were found in trials with low memorisation ***(73, 232)***, thus indicating that an excess of couplings of operations and too rigid dynamics of such coupled operations is incompatible with successful memorisation. Interestingly, such an excess in the number and life-span of OMs was already present at the “waiting” stage (before the stimulus has been presented), where subjects only prepare to memorise the future coming stimuli ***(73, 232)***. Thus, such an excess is not an event-related phenomenon but reflects a process mode that most likely can be interpreted in terms of a top-down process, for example the mentation (association thoughts) not related to the current task. The fact that such mentation could directly contribute to the process of forgetting has been documented by Klimesch et al. ***(272)***.

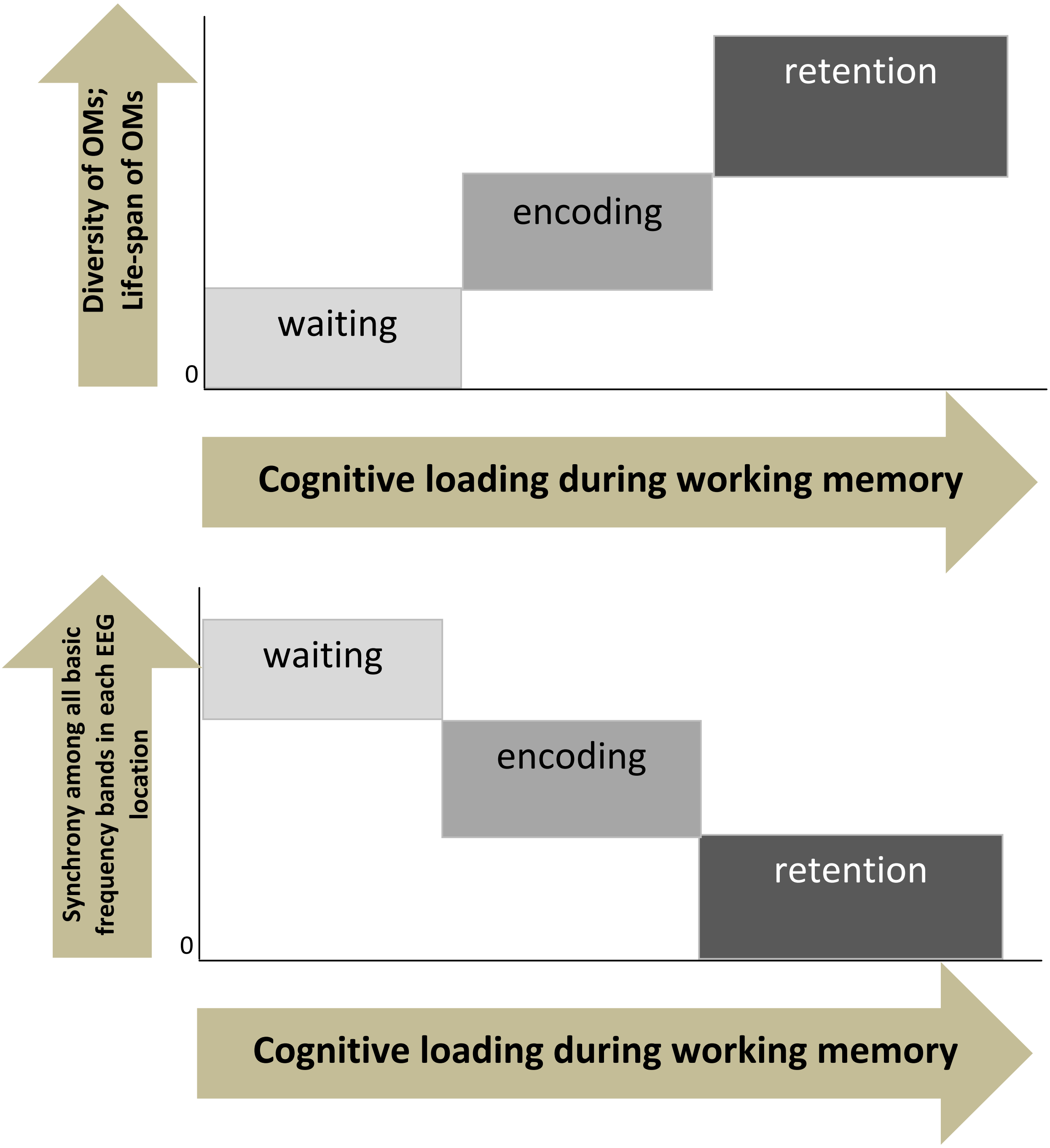

Figure 6. Schematic presentation of the dynamics of diversity and life-span of OMs (upper panel) and average operational synchrony among all basic frequency bands within each EEG channel (bottom panel) as a function of cognitive loading during different stages of working memory task. This scheme is based on data published in the Ref. ***(247)***.

Thus, the findings presented here suggest that a particular number of specific medium-sized and with medium life-span OMs (that "cover" certain cortical areas) seems necessary to achieve successful memorisation ***(73, 232, 247)***. Indeed, although memory encoding, retention and retrieval often share common regions of the cortex, the operational synchrony of these areas is always unique and presented as a mosaic of nested OMs for each stage of the short-term memory task ***(73,***

232, 247). When there are too few or too many OMs and their life-span is either too short or too long, then such conditions lead to cessation of efficient cognitive operation. Such dynamic balance of integrated and segregated processes as a necessary and sufficient condition to produce efficient cognitive activity (and eventually consciousness) is becoming increasingly recognized ***(91, 169, 184, 217, 220-222, 273)***.

As we have discussed above, operational synchrony can exist across a number of functional domains, with different frequency rhythms associated with each domain, thus indicating cross-frequency synchronization ***(256-258, 274, 275)***. Application of OA methodology to different stages of a working memory task reveals the progressive decrease of average values of operational synchrony among all basic frequency bands (delta, theta, alpha1, alpha2, beta1, and beta2) in a cognitive load-dependent manner (Fig. 6, bottom panel) in each cortical location ***(73, 200, 232)***. These data corroborated with the fact of parallel increase of operational synchrony between different cortical locations – spatial synchrony within the same frequency domain (Fig. 6, upper panel). Together these results clearly indicate that the decrease of cross-frequency synchrony in *each cortical location* releases the needed degrees of freedom of the neuronal assemblies (located in such cortical areas), allowing them to perform synchronously their operations on a particular temporal scale (frequency) *between different cortical locations* as a function of cognitive loading ***(73, 232)***.

At the same time, operational synchrony between some particular pairs of EEG frequencies increased as a function of cognitive loading during the various stages of working memory task ***(73, 200, 232)***. These frequencies were mostly alpha1-beta1 and alpha2-beta1, and to a lesser extent delta-theta and theta-beta2 pairs that were positively correlated with memory loading in all frontal, central, temporal, parietal, and occipital regions. On the contrary, operational synchrony in the delta-alpha2 and alpha1-alpha2 pairs decreased as a function of cognitive loading during working memory task. A similar wide-band alpha-beta coupling has been observed using the method of a very narrow-band EEG analysis to characterize the working memory encoding and retention ***(276)*** and also during pharmacological influences ***(277, 278)***. Thus, the current findings support earlier suggestions for complimentary roles of alpha and beta rhythms during working memory and cognitive loading ***(256, 275, 279, 280)***. In line with this understanding, alpha and beta band network topologies (neuronal assemblies) have similar characteristics when compared to other frequency bands: they are more clustered and small-world-like ***(281)***. Hence, operational synchrony between them is much more likely.

Coupling between theta and beta frequency bands has been previously observed in animals ***(282)*** and humans ***(283)*** during states of increased vigilance. These observations are in line with our more resent finding on increased coupling (indexed by operational synchrony) between theta-beta1 frequencies during increased cognitive load of a memory task ***(73, 200, 232)***. The decreased coupling between alpha1 and alpha2 frequency bands during working memory most likely reflects a non-synchronous suppression of both components of alpha activity, which also have different functional meaning ("attention" for slow alpha and "engram consolidation" for the fast alpha; see ***(272, 284)***).

Interestingly, the trials with high memorability were characterised by a very strong coupling between alpha2-beta1 frequency bands, while trials with low memorability (in the same subjects) had strong synchrony in the alpha1-beta1 band pair ***(73, 200, 232)***. These findings are in line with earlier studies of Klimesch ***(272)*** who demonstrated that subjects with faster alpha rhythm performed better on a memory task, compared to subjects with slower alpha activity. An important difference though of data presented here is that the subjects were the same, but when the trial happened to be unsuccessful (subjects failed to memorise a given stimuli) it was alpha1 that was operationally synchronised with beta1, while during the successful trials (subjects memorised well) it was alpha2 that was synchronised with beta1 ***(73, 232)***.

There was also another characteristic feature of the unsuccessful trials: topographical operational synchrony between segmental structure of alpha activity in any given cortical area and segmental structure of theta activity in all other cortical areas had negative values of ISS, thus indicating *unbinding* of operations performed by neuronal assemblies operating on different temporal scales ***(73, 232)***. For the successful trials such topographical alpha-theta operational synchrony on the contrary increased as a function of cognitive loading throughout the working memory task ***(73)***. The reported results suggest that forgetting is associated with some sort of unbinding of operations performed by particular neuronal assemblies (for a similar conclusion see ***(285)***). Most interestingly, such negative values of ISS (that indicate unbinding) between alpha and theta rhythms were observed over the entirety of the unsuccessful trials: pre-stimulus as well as post-stimulus. Thus, one may conclude that such alpha-theta cross-frequency decoupling is not an event-related phenomenon but rather reflects a process that can be interpreted in terms of top-down controlled processes ***(257)***. Other situations, where operational synchrony exhibits negative ISS values include (a) the failing of conscious binding of multisensory features into a coherent mental "object" ***(286)*** and (b) fading of consciousness altogether as in vegetative and to a smaller degree in minimally conscious patients ***(287, 288)***.

To summarise this subsection, findings on OMs dynamics clearly point to the fact that the binding of sensory feature representations into phenomenal (subjective) "objects", active encoding, maintenance and retrieval of these mental "objects" during working memory are critically dependent on dynamic millisecond-range synchronization of multiple operations performed by local neuronal assemblies that operate on different temporal (oscillations) scales nested within the same operational hierarchy ***(91, 256)***.

4.2. Implications for clinical practice

After years of research, modern neuroscience conceptualises the human brain as a complex nested hierarchy of functionally specialised neuronal assemblies that interact with each other in a spatially and temporally coherent fashion ***(170-172, 256)***. By means of such interactions, these neuronal assemblies and their larger synchronised conglomerates (OMs) shape physiological (normal) and pathological (diseased) behaviors ***(86)***. Despite the wide spread of neuropsychiatric disorders ***(289, 290)*** and the progress in the basic neuroscience, there is only little advance in understanding the pathophysiology of such disorders and correspondent to it delay in the development of effective therapies ***(291)***. We believe that this is due to a lack of a consistent paradigm of psycho- and neuro-pathology that would incorporate the novel knowledge from basic neuroscience. At the same time, such a novel paradigm that stresses the dynamic balance between isolated functions of local neuronal assemblies and globally coordinated activity between them is beginning to emerge ***(291)***. It has been suggested that the loss of such a metastable balance in favour of either independent or hyper-ordered processing leads to a pathological states that give rise to neuropsychiatric syndromes constituting a particular disorder ***(86, 151)*** (see also ***(291, 292)***). This subsection reviews current knowledge about OMs' dynamics in different pathologies derived from application of OA methodology in neurological and psychiatric conditions.

4.2.1. Chronic opioid addiction

It has been found that the number of OMs and strength of coupling within such OMs (estimated by an ISS) was significantly lower in chronic opioid abusers than in healthy controls ***(152)***. This dependence was observed in alpha and beta frequency bands. Such disruption in the formation of virtual OMs is consistent with disorganization syndrome of cortex processes (suggested by Bressler ***(292)***). Most likely, the disrupted operational connectivity between local and distributed neuronal assemblies is a candidate mechanism for the well-documented pattern of impairment in addicts, expressed as lack of integration of different cognitive functions for effective problem solving, deficits in abstract concept formation, set maintenance, set shifting, behavioural control, and problems in the regulation of affect and behavior ***(293-296)***. From this perspective then, disorganization in the cortex activity of chronic opioid addicts is in favour of independent processing that was paralleled by increased volume, stability, and life-span of local neuronal assemblies in such addicts ***(152)***. Furthermore, it has been found that the more years the subjects abuse opioids on a daily basis the more disintegration (indexed by ISS) takes place within the posterior section (low central, parietal, low temporal, and occipital areas) of the cortex. Hence, these findings give ground to suppose that longitudinal opioid abuse preferentially impairs the formation of OMs in the posterior cortex section. Areas located in this part of cortex are suggested to be responsible for a number of important functions ***(297)***: perception, differentiation and somatosensory functions, memory functions and autobiographical records, as well as visual perception. Therefore one may suggest that the absence of appropriate relations between all these functions in opioid abuse patients due to a broken mechanism of OMs formation leads such patients to specific maladaptive actions such as those directed at drug-seeking and drug-taking behaviour which characterise addiction ***(152)***.

4.2.2 Opioid withdrawal/abstinence

Based on clinical and cognitive psychology studies it is known that when addicts crave for the drug, anxiety, nervousness, lack of inhibitory control, positive drug related expectancies, and intrusive thoughts related to drugs are all simultaneously present ***(298, 299)***. Consistent with the OA methodology framework, these complex cognitive functions are critically based on the dynamical interactions of operations performed by many cortical neuronal assemblies (see also ***(64, 271, 300, 301)***). Considering that withdrawal/abstinence initiates a widespread parallel activation of cortical regions responsible for the cognitive operations mentioned above, one can expect to see a significant increase in formation of many OMs. Such increased operational synchrony among many transient neuronal assemblies would then explain the strong motivation of abstinent patients for the excessive drug craving, where the dynamics of local brain operations (functions) would be restrained by the large-scale context (removal of the aversive state) of mutually connected cortical areas. Application of OA methodology to EEG of abstinent patients fully confirms this hypothesis: a significant increase in formation of many OMs of different complexity (with a focus in the anterior part of the cortex) was found in opioid-dependent patients during withdrawal as compared to healthy controls ***(153)***. It has also been documented that the complexity of OMs and strength of coupling within OMs (indexed by ISS) have had a predictive force towards the severity of abstinence: patients with strong withdrawal symptoms had higher number and strength of couplings among neuronal assemblies than patients with mild symptoms ***(153)***.

4.2.3. Major depression

Even though the modern model of major depression stresses the key role of anterior asymmetry – the so-called cognitive anterior model of depression ***(302)***, from the point of view of metastable balance hypothesis outlined above, major depression could generally be viewed as a disorder of disturbed neuronal assemblies' plasticity, leading to an inadequate relationship between multiple operations produced by these neuronal assemblies. Application of OA methodology to EEG of medication-free patients with major depression reveals a widespread and significant increase in formation of OMs when compared to healthy subjects, with greater number of small OMs in the left hemisphere and large OMs in the right hemisphere ***(148)***. Such peculiarities of operational synchrony could be interpreted as signs of adaptive (over)compensation of the "depressed" brain in an attempt to achieve more adequate semantic context which is presented differently in left and right hemispheres ***(303)*** through establishing a new overall metastable brain state ***(108)***. It has been suggested that in the process of such overcompensation, connections between neuronal representations of negative affect and different semantic concepts become strongly activated ***(148)***. This hypothesis found confirmation in a semantic network model studies ***(304, 305)*** in which both semantic and affective features are represented as nodes in the network. It was found that people who are depressed suffer from strongly activated connections between negative affective nodes and multiple semantic concepts, creating feedback loops that maintain depressive affect and mentation ***(306-308)***. This is why depressed individuals tend to see even positive information as negative because it becomes associated with personally relevant negative information ***(309)***. The observed type of a new metastable brain state with increased operational synchrony could be a possible mechanism underlying the maintenance of a depressive state ***(148)***.

4.2.4. Schizophrenia

Schizophrenia is another mental disorder whose pathophysiological mechanisms could be better understood if it viewed as a disorder of metastable balance between large-scale integration (formation of OMs) and independent processing (local transient neuronal assemblies) in the cortex, favouring independent operations ***(156, 157, 291, 292)***. Application of OA methodology to patients with schizophrenia ***(155)*** reveals a significant decrease of operational synchrony among remote neuronal assemblies (indexed as OMs formation) in schizophrenic patients when compared to healthy subjects ***(86)***. Such low level of operational synchrony may signify a well-documented pattern of mental impairment in schizophrenics that expresses a lack of integration of different cognitive functions for effective problem solving, deficits in abstract concept formation, set maintenance, set shifting, behavioural control and problems in the regulation of affect and behaviour ***(310, 311)***. Since in this study negative and positive symptomology were mixed, one could not make a firm conclusion how different symptomology would be reflected in the operational architectonics of EEG. One may suppose though that high values of positive symptomology in patients with schizophrenia would be paralleled by rather increased level of OMs formation; this hypothesis needs to be tested in a separate study.

4.2.5. Epilepsy

The epileptic brain presents a unique pathological condition that, despite the fact that it is the most common disorder of the nervous system ***(312)***, is still poorly understood. A recently emerging view that brain disorders and associated psychiatric problems are accompanied by disruption in the spatio-temporal structure of integrative brain activity ***(313)***, where this structure is either more irregular (uncorrelated randomness) or more regular (excessive order) than in normal healthy brain, could be of a particular help ***(151)***. Application of OA methodology to an epileptic brain during the interictal (without signs of epileptiform abnormalities) periods in medication-free patients with chronic idiopathic generalized epilepsy reveals that (a) interictal EEG is characterized by OMs which contain more cortex areas than healthy control EEG and that (b) brain oscillations of cortex regions involved in such OMs tend to have longer periods of temporal stabilization in interictal EEG when compared with control EEG ***(66)***. Both findings suggest less dynamic performance of cooperative brain operations (dynamic rigidity) in patients with chronic epilepsy than in healthy subjects. Generally these findings pointed to a conclusion that chronic epilepsy should be determined not by a focus of pathological activity, but rather by an epileptic system, that contains a set of coupled distributed oscillatory states (or resonances) involved in a common activity ***(66)***.

Summarising this subsection we could express the hope that the effort to look at many chronic disabling mental or neurological disorders as conditions with dynamical disruption in the spatio-temporal functional structure of integrative brain activity ***(64, 271, 291, 292, 300, 301, 313)*** would result in a new generation of evidence-based diagnosis and treatment strategies ***(314, 315)***.

4.3. Implications for somnology studies

In mammals sleep is associated with specific cortical EEG patterns, generally divided into rapid eye movement (REM) and non-rapid eye movement (NREM)[25] sleep ***(317)***. During REM sleep EEG is desynchronized and hippocampal theta rhythms are present, while during NREM sleep EEG is characterised by presence of slow (delta) waves, sleep spindles and K-complexes ***(318)***. As

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[25] The only known exception so far includes the primitive egg-laying mammals echidnae, in which a REM/NREM mixed state has been observed ***(316)***.

recently observed by Mignot ***(318)***, it is likely that sleep is a distributed process with some neuronal systems being the primary drivers. Interactions between sleep- or wake-specific neuronal assemblies must ensure that the processes occur in synchrony and in exclusion of each other to create stable states of wake, NREM, and REM, with limited time spent in transition states. This view is highly compatible with OA methodology, according to which many transient neuronal assemblies rapidly synchronise their operations in order to present the stability of a particular complex state/operation ***(91)***.

So far the OA methodology has been applied only to EEG from NREM sleep. Results show that during NREM sleep the size of neuronal assemblies gets smaller, while the life-span increased compared to wakefulness state with closed eyes ***(86)***. Furthermore, NREM sleep was characterised with increased formation of OMs; though coupling strength within such modules was not strong ***(86)***. These findings mark a weak communication among neuronal assemblies located in different cortex areas during NREM sleep, allowing some level of flexibility with quick reorganization of synchronized neuronal assemblies into different combinations (OMs) in order to present a large number of possible cognitive operations needed for proper learning and memory consolidation which are posited to take place during NREM sleep ***(319-321)***.

Additionally, dividing NREM sleep on the dream-present and dream-absent epochs reveals that NREM dream condition (which is usually presented with simple, static, isolated image(s) or though(s) and by one modality ***(322)***) is characterised by short-lived small neuronal assemblies, long-lived large neuronal assemblies, and by a significant increase in OMs formation when compared to dreamless NREM condition ***(91)***.

Further studies are needed to detail OA organisation of the brain during REM, NREM conditions as well as during sleep pathologies.

4.4. Implications for neuropharmacology

As we have discussed above, recent research emphasizes that the majority of brain disorders and psychiatric/mental problems are accompanied by disruption in the temporal and metastable structure of brain activity ***(313)***, where this temporal structure could be either more irregular (uncorrelated randomness) or more regular (excessive order) than normal ***(291, 292, 323, 324)***. From this perspective, it has been suggested that the future of psychopharmacology lies in its ability to design psychotropic drugs that can restore the normal temporal structure and metastable structure of brain activity ***(151)***. This approach seems more physiologically adequate to integrative, nonstationary and self-organized nature of brain processes and fits in with a novel understanding of the dynamical nature of brain diseases, where so-called “lesions in time” become more evident especially in the early stages of the disease, than “lesions in structure” ***(325)***. In this context, it is important to study how different psychotropic drugs can modify temporal/metastable structure of brain activity in healthy subjects and patients.

Application of OA methodology to EEGs recorded under the influence of lorazepam ($GABA_A$ agonist) reveals that the number of OMs and the strength of coupling within such OMs significantly increased under the lorazepam administration ***(84)***. It is important to note that it was a randomized, double-blind, cross-over, placebo-controlled study. In the same study, it was found that different-sized neuronal assemblies in alpha and beta frequency bands performed differently under lorazepam when compared with placebo ***(83)***: For the alpha-generated neuronal assemblies, it was observed that large neuronal populations exhibited a total decrease in size, functional life span and stability under lorazepam administration when compared to placebo. In contrast, small neuronal assemblies were very stable. The functional life-span of all beta-generated neuronal assemblies was prolonged ***(83)***. These findings are likely to reflect the prolongation of inhibitory neuronal operations that manifest in the form of slowing of cognitive performance under the lorazepam administration ***(326)***. It has also been suggested that, probably, strong enhancement of $GABA_{ergic}$ function by lorazepam “mimics” the conditions of an immature brain ***(84)***, where excitatory actions of GABA provide most of the initial activity, a primitive signal with poor information content that propagates to all brain structures ***(327)***.

In contrast, heroin imposes a full disruption in the OMs’ formation with a parallel decrease in coupling strength within the OMs ***(152)***. As we have discussed above, such disruption of operational synchrony among neuronal assemblies located in different cortical areas is consistent with cortex disorganization syndrome (suggested by Bressler ***(292)***). It is likely that heroin-induced disruption of operational synchrony may constitute the candidate mechanism for the well-documented pattern of cognitive impairment in heroin users: lack of integration of different cognitive functions, deficits in abstract concept formation and behavioural control, and problems in the regulation of affect and behaviour ***(293, 294, 296)***.

Since methadone is sometimes used as a maintenance treatment for heroin-dependent patients ***(328)***, it was interesting to study its effect on the EEG operational architectonics in such patients. Application of the OA methodology to EEGs of patients who were on methadone treatment during many months showed that methadone restored the normal values of number and coupling strength of OMs ***(154)***, and consequently has normalized the metastable organization of the cortex in all patients (for a discussion see ***(108)***). This conclusion is consistent with the current theoretical view that normal brain function is the product of a large-scale network of coupled neuronal assemblies exhibiting transient and inherently metastable dynamics ***(122, 168, 219, 329)***.

Summarising this subsection we hope that the application of OA approach for EEG analysis will contribute to a current effort in developing a more rational psychopharmacology that takes into consideration the novel views on brain /mental disorders.

4.5. Implications for ontological development research

There are several critical questions in the developmental EEG studies: What is the physiological basis for the synchrony within oscillations in human EEG over the developmental life-span? If oscillations reflect important cognitive processes then do different synchronicity modes within and between oscillations contribute to the development of different aspects of human cognition? In order to get some insight to these questions, we reanalysed results of OA methodology which was applied to EEGs of healthy 12 years old teenagers ***(155)*** and healthy 30 years old adults ***(86)***. The results revealed that the formation of OMs and the strength of coupling within the observed OMs were smaller in teenagers when compared to adults ($p < 0.01$, Wilcoxon test). These findings are in agreement with current understanding that with age the repertoire of the states of individual neuronal assemblies located in different cortical regions become bigger due to increased specialisation; and that at the same time there is increased integration between distributed neuronal populations responsible for different cognitive operations in adults ***(330)***. In general, these findings are in line with modern neo-Piagetian models of cognitive development from childhood to adulthood ***(331-335)***. They are also consistent with previous EEG coherence studies ***(118, 336-338)*** which show that as the number of connections increases with age then there is accompanied increased coherence (synchronicity), and increased stability and decreased "chaos" ***(339)***.

4.6. Implications for personality features studies

The dynamic balance between synchronisation and desynchronisation of cognitive operations is considered essential for normal brain function ***(86, 291, 292)***, as we have discussed above. If this is so, then such balance paralleled by EEG operational architecture balance should (a) have noticeable stability within individuals and (b) exhibit variability between individuals, – thus been the "signature" of personality. This issue has not studied at a proper detail yet, however, some preliminary data is emerging. Applying the OA methodology to EEGs of monozygotic twins and comparing the OA indexes within the monozygotic pairs (genetically related subjects) and between members from different pairs (genetically unrelated subjects) revealed that the formation of OMs, their diversity and types were nearly identical within members of the monozygotic pairs but differ significantly in participants from different monozygotic twin pairs ***(73, 200)***. Specifically, the average Spearman rank correlation in the intra-pair and inter-par similarities of OMs for the resting condition was 0.53 for genetically related and -0.13 for genetically unrelated subjects. These findings point to the existence of particular dynamic OM profiles that are individually predetermined and most likely have high heritability. The possibility of high genetic heritability for EEG functional connectivity has been documented in other independent studies ***(29, 337, 338-340)***.

It has also been shown that such OM profiles correlate significantly with different cognitive, affective styles of subjects and their personality features ***(200)***: for example, verbal type of thinking, normal level of anxiety and neuroticism, and phlegmatic temperament type[26] altogether characterise subjects with a high number of large OMs in the left hemisphere with a focus in anterior part of the cortex. Subjects with nonverbal/abstract type of thinking, diminished level of situational anxiety and neuroticism, and sanguine temperament type were characterised by a diverse set of large OMs in the right hemisphere with a focus in the posterior part of the cortex (Fig. 7, upper plane). Interestingly, such dependence between OM profiles and personality features was “hardwired” during rest condition only. During a particular cognitive task, the given OM profile tends to transform in order to execute a particular task. For example, if the initial personal OM profile was verbal but the cognitive task was visual (non-verbal), then during such visual task the verbal OM profile characteristics became similar to a non-verbal OM profile (Fig. 7, bottom plane); though the efficiency of subjects with such transformed profile during the visual cognitive task was slightly lower than the efficiency of subjects with initially present non-verbal OM profile ***(200)***. These findings have been confirmed in the test-retest study which took place after 2 weeks.

Generally these data suggest that human individual cognitive abilities relate to a particular operational architectonics of the brain resting-state activity that is expressed as a nested spatial and temporal nonstationarity of EEG field which though possesses some degree of freedom, that allow it to reorganise itself in order to execute a particular complex task or operation. Such a view is congruent with the hypothesis of Bekhtereva ***(343)***, who proposed that brain activity during the resting-state may reflect the brain’s potential processing abilities and is correlated with individual differences in the cognitive process (for recent research see ***(344, 345)***).

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[26] For personality features and temperament types see Eysenck and Eysenck ***(341)*** and Diamond ***(342)***.

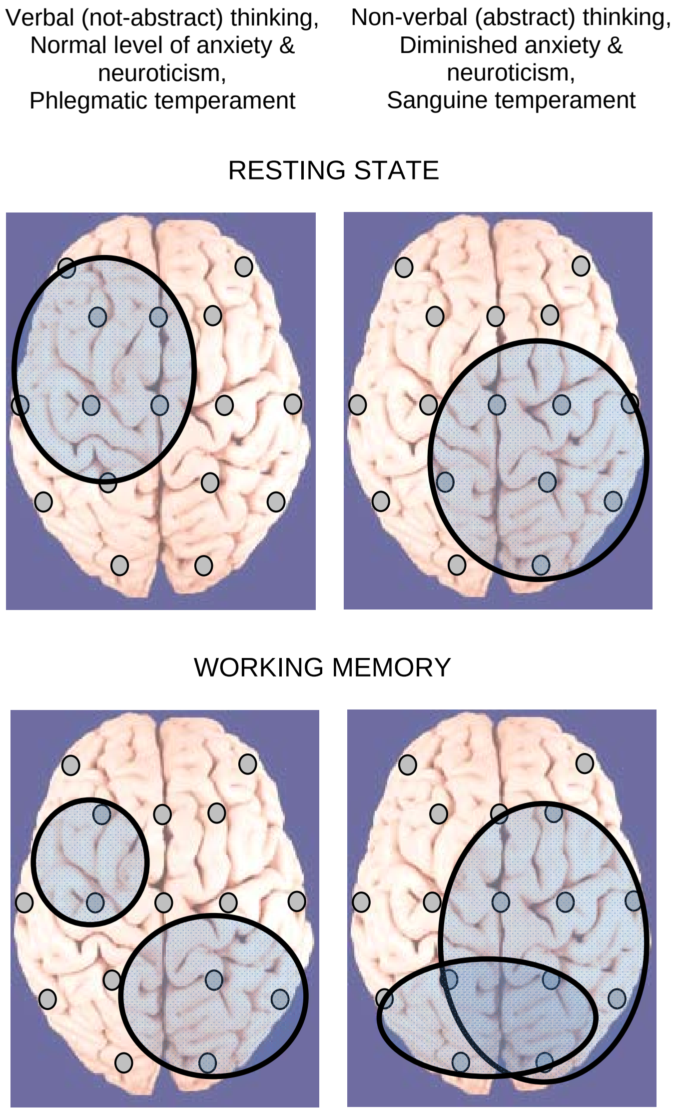

Figure 7. The position of OMs typical for individuals with different personality features. Circles indicate the locations of most frequently found OMs. Further explanations are provided in the text.

4.7. Implications for neurophilosophy

The greatest unresolved theoretical issue that neuroscientists would hope to gain some understanding of is "consciousness" (the entity that none can still easily define, but nearly all accept that it exists ***(346)***) and its neural (brain) constitutes. To date, no one has provided a complete explanation as to how the subjective experience (phenomenality) could arise from the multiple actions of neurons in the brain. Nevertheless, currently, it is agreed that further understanding of phenomenal consciousness will obviously rely upon the view according to which phenomenal consciousness is grounded to material carrier processes that take place in the brain

(43, 54, 55, 158, 301, 347). It is even suggested that phenomenal consciousness is a higher level of biological organization in the brain ***(253)***. OA theory is highly compatible with these views.

The main tenets of the OA theory ***(91)*** are as follows: the brain generates a highly structured and dynamic extracellular electric field in spatial and temporal domains ***(43)*** and over a range of frequencies ***(35)***. This field exists within brain internal physical space-time (IPST) and is best captured by the electroencephalogram (EEG) measurement ***(16)***. Detailed analysis of the structure of EEG's complex hierarchical architecture reveals a specific operational space-time (OST) which literally resides within the IPST and is isomorphic to phenomenal space-time (PST) and, as it has been proposed, may serve as the potential neurophysiological constituent of the phenomenal consciousness' architecture ***(91, 217)***. Therefore, to test whether consciousness is indeed an emergent phenomenon of coherent dynamic binding of operations performed by multiple neuronal assemblies (organized within a nested hierarchical brain architecture), further experimental work was needed to demonstrate that the attributes and operational synchrony of local EEG segments would change in circumstances when awareness expression is either weakened or lost completely. The OA theory predicts that both low and high levels of operational synchrony among neuronal assemblies would result in a dramatic fading of consciousness ***(91)***.

Application of OA methodology to EEGs of patients who are in a permanent vegetative state (VS) or in a minimally conscious state (MCS) pointed to one among the two alternatives predicted by the OA theory in relation to a specific case of (un)consciousness expression in minimally communicated and non-communicated patients with severe brain injuries ***(287, 288)***. Taken together, the results of these studies support the view according to which it is an intact coordinated activity (operational synchrony) among relatively large, long-lived, and stable neuronal assemblies that is important for enabling routine representational processes to be integrated within a coherent phenomenal world from the first-person perspective ***(253, 348, 349)***. Additionally, and as predicted by the OA theory, transient operational integrity of neuronal assemblies allows discrete moments of "phenomenal present" to be bundled in larger units (formation of OMs) making it possible to present mentally a practically infinite number of different qualities, patterns, objects, scenes, concepts and decisions ***(91)***. Impairment in such operational integrity (disruption up to an active decoupling) among neuronal assemblies may underlie the fading of consciousness until its complete absence, if such impairment reaches a critical level as it does in the patients in VS, who have complete unawareness of self and the environment ***(287, 288)***.

Another important model, where subjective experience is presented in a contrasted form (which could be easily manipulated), is hypnosis. In a pure hypnotic state the subject experiences an altered background state of consciousness different from the normal baseline state of consciousness ***(350)***. This subjective state is characterized by some sort of "emptiness" or "absorption" brought about by dissociations in the cognitive system, such that separate cognitive modules and subsystems may be temporarily incapable of normal communication with one another ***(351, 352)***. Additionally, it has been shown that the sensation of time passing is stretched during hypnosis, because internal events are subjectively slowed ***(353, 354)***. Adhering to the tenets of OA framework, these subjective experiences should be reflected in the operational architectonics of the EEG brain field. In a pilot study applying the OA methodology to hypnotic EEG data ***(202)*** it was indeed shown that the functional life-span of all neuronal assemblies (indexed by the EEG quasi-stationary segments) was significantly longer during hypnosis when compared to normal baseline conscious condition of the same subject. It was further found that the number and strength of synchronized operations among different neuronal assemblies were significantly lower during hypnosis than during the baseline, thus limiting the possibility of any OMs with order of areas recruitment higher than two to emerge. As a result they were absent ***(202)***. Since OMs represent the formation of integrated conscious experiences, their absence may explain such unusual subjective experiences during pure hypnosis as amnesia, timelessness, detachment from the self, a "willingness" to accept distortions of logic or reality, and the lack of initiative or wilful movement ***(355)***.

This research program aims to reveal the neural mechanisms of phenomenal consciousness and to evaluate whether such findings are leading toward a neuroscientific explanation of consciousness within the OA framework. Phenomenal consciousness refers to a higher level of organization in the brain ***(253)*** and captures all immediate and undeniable (from the first-person perspective) phenomena of subjective experiences (concerning hearing, seeing, touching, feeling, embodiment, moving, and thinking) that present to any person right now (subjective present) and right here (subjective space) ***(91)***. According to this definition someone possesses phenomenal consciousness if there is any type of subjective experiences that is currently present for him/her. The well-known in the brain-mind research philosophical "hard problem" is the problem of understanding how the brain (or, more generally, any physical system) could produce any subjective, phenomenal experiences at all ***(356)***. To make progress in solving this "hard problem", the neural counterparts directly constituting phenomenal consciousness must be localized and identified. The suggested research program utilising OA methodology may contribute to this goal.

4.8. Implications for artificial intelligence

The idea of machine consciousness first considered by Angel ***(357)*** had recently progressed from being an interesting philosophical diversion to a real possibility ***(358)***. Several researchers, engineers and computer scientists have already began to address the subject by designing and implementing models for artificial consciousness referred to as "machine consciousness" or "synthetic consciousness" ***(359-365)***. However, almost all of them take a more or less conventional computational or low-level neurally inspired (anatomical) approach ***(366)***. At the same time, as noted by Indiveri et al. ***(367)***, such an approach stands before a large conceptual challenge: to bridge the gap from systems (machines) that merely mimic or simulate cognitive processes usually correlated with consciousness (so-called Weak Artificial Consciousness ***(363, 368)***) to ones that are genuinely conscious (Strong Artificial Consciousness ***(363, 368)***). An important practical matter related to this challenge is that a true "conscious machine" should be seen as a man-made artificial system (e.g., robot) that enjoys subjective phenomenal experiences and related rational thinking ***(366)***.

The OA theory of brain and mind functioning offers a conceptual–theoretical architecture that computing system (robot) could implement (after appropriate mathematical formalization and engineering would be achieved) to simulate the operational level in which consciousness and thinking would self-emerge ***(369)***. In this context the problem of producing man-made "machine" consciousness and "artificial" thought is the problem of duplicating all levels of nested OA hierarchy (with its inherent rules and mechanisms) found in the EEG field, which can constitute the neurophysiological basis of phenomenal level of brain organization ***(369)***. The aim should be to abstract and formalize the principles of the nested hierarchy of operations which constitute phenomenal consciousness and thought, rather than attempting to directly mimic the whole diversity of chemical and physiological mechanisms of brain functioning or the whole diversity of consciousness states, which is a quite unrealistic enterprise ***(370)***. In this case one could expect that by reproducing one architecture (brain operational) we can observe the self-emergence of the other (mind phenomenal) ***(369)***.

5. Conclusion

In the 17 years of its existence, OA methodology of EEG analysis has evolved into a valuable technique which can be useful for clinicians, basic researchers and philosophers of mind. It has a set of tool that provide means to examine different features and dynamics of cortical neuronal assemblies and topological coupling of their operations in normal and abnormal human brains as well as in altered states of consciousness. The specific approaches of EEG analysis within the OA methodology ***(56)*** are especially well suited for studies of nonstationary signals and uniquely capable of investigating the dynamic and metastable changes of brain spatial–temporal patterns that are isomorphic with cognitive and phenomenal levels ***(371)***. Essentially these tools take repetitions of spatial–temporal patterns (indexed as OMs) into account at all functional levels, thus capturing both dynamic as well as hierarchical complexities of brain activity which is nested within a multi-scale operational architecture ***(91)***.

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