# Functional Connectivity in the Brain – Is it an Elusive Concept?

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**Abstract:** Even though functional brain connectivity is an influential concept in modern cognitive neuroscience, it is a very controversial notion. This is why further theoretical and methodological clarification are needed to help define precisely what is meant by functional connectivity and to help frame associated issues. In this review we present the neurophysiological concept of functional connectivity, which utilizes in a plausible manner the notion of neural assemblies, as well as local and large-scale levels of description. Here functional connectivity is the mechanism for the coordination of activity between different neural assemblies in order to achieve a complex cognitive task or perceptual process. Our theoretical and empirical findings offer new insights into possible implications of the concept of functional connectivity for cognitive neuroscience.

*Keywords:* Local/Remote functional connectivity; brain synchronization; structural/operational synchrony; binding; neural assemblies; brain operations; EEG/MEG; quasi-stationary segments; metastability; operational modules; mental states.

## 1. Introduction

Framing the issue of brain connectivity has proven to be very difficult, as demonstrated by the recent Workshop on Functional Connectivity (see ref. [1]). Over the years researchers have studied phenomena akin to brain connectivity; however, the data and methods used to evaluate such connectivity have varied enormously. Techniques to assess brain connectivity have different spatial and temporal resolutions (nontomographic xenon-133 inhalation [2], PET [3,4], rCBF [5,6], fMRI [7-9], EEG/MEG [10-18]), and they have focused on different levels of description (activity of individual neurons, activity of neural assemblies, or large-scale activations, see Ref. [19]). The situation is complicated still further by the fact that the actual

computational algorithms and concepts used to define the values of brain connectivity differ between studies and researchers. Most likely different measures of functional connectivity are not related to one another in any kind of simple way. Because of this, some researchers have suggested that brain connectivity is an elusive and even indefinable concept [20]. Nevertheless, functional brain connectivity has become one of the most influential concepts in modern cognitive neuroscience, especially given the current shift in emphasis from studies of functional segregation to studies of functional integration. That is why the concept of brain connectivity needs further theoretical and methodological clarification.

There are three main types of brain connectivity: neuroanatomical, functional and effective connectivity. The modern view of *neuroanatomical connectivity* holds that the boundary between anatomy and function is fuzzy. According to this view the formation of new connections and the elimination of already existing ones are largely biased by functions executed (for review, see Ref. [21]). Indeed, it has been found that more active axons (depending on the functions executed) have a competitive advantage over less active ones [22]. Additionally, studies of brain plasticity can be used as an indicator of functional relevance. These studies include research on changes of local connectivity in sensory cortices [23], in the thalamus and in the brainstem [24]; changes in subcortical connectivity [25]; changes in cortico-cortical feedback [26]; and changes in long-range cortico-cortical connectivity [27].

However, there is a major problem with using such brain plasticity to explain perceptual and cognitive processes. For one thing, it is too slow and it relies on learning by repetition at a low-level (single neurons) organization of the brain. However, a great part of our cognition and perceptions are fast, unique, and singular in a veritable sense [28]. For example, we can perceive individual objects that we see only once, and never again, within a fraction of a second. The coherency of perceptual and cognitive states is achieved rapidly and effortlessly [29]. It is obvious that neuronal representations of such objects and related cognitive processes cannot be based on slow anatomical connectivity [28]. Instead, functional connectivity may be the appropriate mechanism.

*Functional connectivity* is defined as the temporal correlation between spatially remote neurophysiological <u>events</u> [30], expressed as deviation from statistical independence (temporal correlation) across these events in distributed neuronal groups and areas. *Effective connectivity* is a more abstract notion; it is defined as the influence that one neural system exerts over another either directly or indirectly [31]. It is obvious that, conceptually, effective connectivity can be derived directly from the functional connectivity with a model specifying the causal links between the participating units [20]. Thus we conclude that functional connectivity is the

most central and challenging of the three conceptions of brain connectivity for theories about neural interactions, when analyzing functional neuroimaging data and when developing computer simulations. Because of that we will concentrate in this paper specifically on the concept of functional connectivity.

## 2. Measuring functional connectivity in the brain

The further understanding of brain dynamics will obviously rely upon the development of suitable techniques to analyze neural data for evidence of significant functional correlations. Which measure of functional connectivity is the most useful for studying brain functioning? Treating the brain as *a dynamic system* from which we are able to observe certain physiological parameters over time; and since it has been suggested that transient synchronization of neuronal systems is essential for brain operation and conscious performance, a temporal resolution in the order of milliseconds is of special interest [32]. Here, the electroencephalogram (EEG) and magnetoencephalogram (MEG) provide a satisfactory scale for accessing temporal evolution of the brain activity associated with cognitive processes in health and disease [11,33,34]. However, momentary (temporal) changes in brain activity, as reflected in EEG/MEG, are rarely exploited due to lack of analytical tools and methodology (one exception is the research conducted by Prof. Lehmann's group, see ref. [35,36]). Special techniques are required for the detection of such dynamics. That is why we would like to provide a neurophysiological concept of functional connectivity that utilizes, within the same framework, both local and remote neuronal interactions at the millisecond scale of EEG/MEG.

According to the definition of functional connectivity [30], the issue that is central to this concept is correlated neurophysiological *events*, which can be derived directly from EEG/MEG data. The question thus arises: what might these events be (considering that there should be the 'well-defined' and 'well-detected' EEG events)? Modern theoretical and experimental work suggests that these events should reflect the discrete operations of brain activity: elemental operations at the local-scale level and complex operations at the large-scale level [37] (see also Ref. [38]). Here, the notion of a neuronal assembly should be employed, in a functional sense [39,40]. Indeed, neuronal assemblies are critical for particular brain operations (*local functional connectivity*); however, cognitive operations itself arise from combined synchronous actions/operations of many neural assemblies (*remote functional connectivity*) [41]. Thus, the cell assembly theory (which describes the intermediate-level structure of the brain) seems the only plausible concept that bridges the gap between neural and mental dynamics [39].

Now, an additional question arises: which of known EEG/MEG measures of functional connectivity derives the information about operations (discrete events) and estimate the inherent temporal/dynamical correlations among them? Traditionally, coherence and correlation have been the main methods to assess the degree of functional connectivity between brain areas [42]. Over time, initial attempts to describe quantitatively the relationship in activity of cortical areas, has gradually transformed into a direct postulation of the presence of an "interrelation" between different sections of the brain only in the case of a high significance of crosscorrelation and coherency [43]. However, mathematically, the coherence value indicates only the linear statistical link between time-series curves in a frequency band [13]. Meanwhile, it is obvious that, in general, the absence of some types of statistical interrelation between two processes does not mean the absence of any interaction between them at all (for critical discussion see Ref. [14]; see also ref. [13,17]). Show and Simpson (1996-1997) [44] stressed that one must be careful when interpreting coherence (and partial coherence) as an indicator of functional connectivity. For example, he pointed out that EEG signals show a finite correlation even when recorded from separate subjects [43].

Recently, several new methods for detecting functional connectivity between cortical areas have been published: partial directed coherence [18], dynamic imaging of coherent sources [45], and phase synchrony based on wavelet [15] or Hilbert [16] transforms. However, all these methods have limitations. The drawback is that these approaches have one or several of the following: they do not take into consideration the nonstationary nature of the signal; they require long time epochs of analysis; they use averaging and smoothing procedures, and they use linear models which for the brain is not typically the case [46]. For the phase concept to be successfully used, the frequencies of the signal should be locked, otherwise multiple harmonics of these frequencies may overlap and lead to ambiguous phase information [47]. Further, the concept of phase synchronization can be applied only to homogeneous medium [48], which is an unrealistic assumption for the brain. The situation is complicated further by a non-stationary process in the nonlinear phase (de)synchronization measure [49].

Another drawback is that all these approaches borrow complex methodologies and conceptual frameworks from physics, mathematics, and engineering, but use them loosely when applying them to the analysis of physiological activity. Therefore neuroscientists have to make sophisticated assumptions that make sense in one case but not in others, and, in general, have little to do with the original, precise, mathematical definition.

In conclusion, none of the current conventional methods allows the direct reconstruction of operational dynamics at the EEG/MEG level (for a critical discussion, see ref. [14,17,50]).

Most of classical measures describe something else, perhaps some similarities between continuous time-series, rather than the temporal correlation between spatially remote neurophysiological events [20]. Below we will provide a neurophysiological concept of functional connectivity that utilizes explicitly the notion of neurophysiological events (brain operations), as well as local and large-scale levels of description.

## 3. The neurophysiological concept of functional connectivity

It is well established that neurons do not function as isolated units [51]. Large groups of neurons distributed along the cortex can quickly (abruptly) become associated or disassociated thus giving rise to transient assemblies [52]. The emergence of specific neural assemblies is thought to provide the functional elements of brain activity that execute the basic operations of informational processing [41,53-55]. The assembly as a whole has emergent properties that do not exist at the level of individual neurons [51]. In this sense, the representation of information by neuronal assemblies is *ergodic* (the same as the generation of pressure by water molecules in an enclosed volume) and *robust* (i.e., damage to a single cell or cell mortality need not have a catastrophic effect on the total representation of information) [34]. Additionally, neuronal assemblies have other key important properties, such as mechanisms for noise removal, short-term memory, and the instantiation of complex, nonlinear functions [56].

Communication of neurons within an assembly is achieved through the synchronous activity of the participating neurons [33,40,54,57-59]. There are clearly many other aspects of neuronal interactions; however, the temporal synchronization is one of the most important [60]. The fact that neurons are able to synchronize their subthreshold oscillations (excitatory/inhibitory post synaptic potentials, EPSP/IPSP), leading to fixed states in the overall neuronal assembly and rapid transitions between such states, has been shown experimentally and in computational models [61]. Generally, the overall pattern of correlated activity within a neural assembly is very sensitive to fluctuations, and it may be swiftly rearranged during rapid shift of state [62] (for review, see Ref. [63]). This *local functional synchronization* may have a rhythmical nature [33]. As a result, the formation of a neuronal assemble is accompanied by a rhythmical increase in the total potential, whereas a disruption of the neuronal assemble is characterized by a decrease in the total potential [32,34].

According to a relatively new and promising area of electrophysiological research at the EEG/MEG level, brain operations (oscillations of the total potential) might be reflected in the periods of *quasi-stationary segments* that correspond to a temporary stable local microstates in brain activity [17,64,65]. Now it is recognized that the EEG signal is "glued" from several

segments of random stationary processes with different probabilistic characteristics (for a review see Ref. [66]). This idea has its roots in the work of Bodenstein and Praetorius (1977) [67]. In this framework, it is possible to consider one quasi-stationary segment as the *single event* in EEG/MEG-phenomenology. Within the duration of one segment, the neuronal assembly that generated the oscillations is in a steady stationary state [68], where participating neurons are functionally synchronized. The transition from one segment to another reflects the changes in the neuronal assembly state and/or in the neuronal assembly itself. These transitions (rapid transitional processes, RTP) in the EEG/MEG occur abruptly and are the boundaries between EEG/MEG segments (or brain operations at the functional level, see Ref. [38] for a discussion). The transition (RTP) *per se* is not a gap; rather it is a continuous process from one EEG/MEG segment/state to another. It is only the *speed* of the transition – which is extremely fast (approximated as a time point) relative to the time spent in each "segment" – that makes it appear as a rapid shift [17,65]. Such RTPs are obtained using an adaptive segmentation approach [50] (for a review of other segmentation techniques, see Ref. 17). Interested readers not familiar with the procedure may obtain some technical details in the Appendix A of this review.

Neuronal assembly relations have not only a temporal, but also a spatial aspect, whereby many such assemblies interact with each other [34,54,69]. Consistent with this view, complex brain functions require the integration of many operations performed by different neuronal assemblies throughout the whole neocortex [70-72]. Here, a complex function is a pattern of interrelated processes directed toward the performance of a particular task or act that are implemented by functionally related cortical areas [60,70]. At the EEG/MEG level this *remote functional connectivity* among distinct neuronal assemblies is reflected in the synchronization of quasi-stationary segments (estimated by EEG/MEG structural synchrony, SS) between different EEG electrode sites (brain regions) in specific frequency bands [17,65]. The SS index (ISS) reflects systematic temporal relationship between the on-going changes of brain activity (RTPs) in different cortical areas – synchronization of brain operations (events) which is the essence of functional connectivity (for review, see ref. [38,65]). This method is very simple conceptually and does not require the formulation of complicated mathematical concepts as, for example, phase space (the interested reader may consult Appendix B of the present paper for technical details). As a result of such SS process, the *transient metastable states* emerged in the form of operational modules (OMs) [38]. Metastability is an entirely new conception of brain organization [73-75]. In the metastable regime of brain functioning, the individual areas

of the brain exhibit tendencies to function autonomously at the same time as they exhibit tendencies for coordinated activity [72] (for review, see also Ref. [37,65]).

The approach suggested here, thus, explicitly uses the definition of the functional connectivity concept agreed upon in neuroimaging community [20]. Consistent with this definition, quasi-stationary segments in EEG/MEG reflect local functional connectivity processes, while estimated periods of the mutual temporal stabilization of quasi-stationary segments (metastable OMs) in the multichannel EEG/MEG reflect remote functional connectivity. This theoretical framework may offer a plausible link between macroscopic and mesoscopic levels of brain descriptions: it permits analysis of remote (functional synchrony of distributed neuronal assemblies – metastable states) as well as local (transient neuronal assemblies) interactions of neocortex activity simultaneously [76]. What are the implications of this framework of functional connectivity for the neuroscience research and what are the major advantages of this concept?

## 4. Implications of functional connectivity concept for neuroscience

There are several paradigmatic problems in neuroscience that still need to be resolved, or at least clarified. One is the problem of timing. The fundamental question in cognitive neuroscience "as to whether cognition and its neural representations occur in discrete epochs or continuously" has, until now, not been definitely answered one way or the other. As VanRullen and Koch (2003) argue their paper [77], ambiguity is caused in part by experimental paradigms that avoid the temporal structure of the phenomenon under investigation. The unified concept of local and remote functional connectivity seems suitable for bridging the continuous and discrete brain processes that subserve cognition and subjective experience (Fingelkurts and Fingelkurts, forthcoming). In the framework of this concept, local functional connectivity leads to the formation of transient neuronal assemblies with discrete functional (or operational) life-span (like symbols in classical logics, see ref. [78]), while the remote functional binding of several such assemblies organizes the continuous and distributed spatio-temoral pattern – OM (as in a connectionist network theory, see ref. [79]). Thus, *discreteness* of parallel brain operations becomes implemented in the *continuity* of unified metastable OMs [80].

Another major question in neuroscience concerns the problem of parallel or serial processing, especially concerning memory scanning and item recognition [81,82] or serial models of word processing. Although behavioral research has led to the suggestion that memory scanning is serial and exhaustive [83], parallel search models have been proposed also [81]. Within the framework of functional connectivity suggested here the dichotomy between

parallel and serial neural processing (as well as local *vs* global processing) becomes irrelevant, since both ends of the dichotomy can be embodied and observed in the moment-by-moment states of the large-scale network of neural assemblies. Indeed, parallel processing is performed by simultaneously active individual and separate neuronal assemblies, whereas serial processing emerges as a result of formation of OMs and abrupt shifts between them [37,38]. For example, operations may couple in time as a triplet (or quadruplet, and so on) in cortical areas *A*, *B* and *C*, but not as a pair in areas *B* and *C* (without the simultaneous operations in *A*) [84]. This process has been suggested [85] as a kind of fast parallel information processing, because several operational flows in different cortical areas are executed simultaneously [86]. Another possibility is that when the RTP in EEG channel *A* often precedes a RTP in EEG channel *B* with relatively constant time delay, this may be considered as an evidence for serial processing: The operational 'switches' reflected in *A* probably cause those in *B*. Thus, OM may combine two different strategies of information processing that could allow the multiplexing of different memories within the same OM, and thus could enhance the memory capacity. This interpretation is consistent with Townsend's [87] models of rapid information processing involving parallel processing. It is also in line with the well-established viewpoint that encoding and retrieval of information in neuronal tissue requires some sort of binding mechanism that allows the expression of specific relationships between different brain areas (for review, see Ref. [59]).

Memory *per se* is another long-standing unresolved subject in neuroscience. Even though it is the subject of an enormous volume of research, the specific and complementary interrelations between different cortical areas during episodic encoding and retrieval processes are only partially understood. The concept of functional connectivity suggested here predicts that concrete combinations of functionally coupled cortical areas would indicate selective channeling of information to different operations, concurrently executed by different neural assemblies. It has been shown that occipital and parietal cortical areas perform longer operational acts during the waiting, retention and retrieval memory stages, whereas the anterior cortical areas exhibit shorter brain operations [80]. However, during an encoding period, posterior neural assemblies also demonstrated short brain operations. At the large-scale level it has been demonstrated that functionally distinct cortical regions might be preferentially synchronized (remote functional connectivity) and involved in different stages of memory processing such as encoding, retrieval, and retention (for details, see Ref. [17,80]). This was expressed through a gradual increase in EEG structural synchrony process together with a growth of cognitive loading [14,80]. Thus, the principle finding was the existence of systematic

specific functional combinations among cortical areas, which changed significantly through the memory task [80]. Convergent data suggest that working memory is most likely an emergent property of a multiregional network (i.e., remote functional integration), and is not a strictly hierarchical processing based on the convergence of information through association regions. The last three conclusions are in agreement with the works of McIntosh [41], Fuster [88] and Basar [89].

Perceptual multisensory integration is yet another major unresolved problem in modern neuroscience [90]. When and where in the human brain the integration of such multisensory information occurs is not yet known [91]. Most research in humans demonstrates the existence of the phenomenon, but does not reveal the underlying physiological processes (for a review, see ref. [92]). However, the concept of functional connectivity suggested here helps to reveal (using a robust illusion known as the McGurk effect [93]), that the apparent synthesis of information from different modalities may also be achieved through the process of structural synchrony between modality-specific and non-specific cortical areas (for a detail discussion, see Ref. [94]). Thus, the well-timed spatiotemporal synchronization patterns (indexed by structural synchrony in MEG) related to audio-visual integration were obtained. The subjects, who did not display the McGurk illusion (meaning that they lacked multi-sensory integration), in contrast, demonstrated significant uncoupling (negative values of structural synchrony) of particular brain areas [94]. The temporal synchronization of cortical operations processing unimodal stimuli at different cortical sites reveals the importance of temporal features of auditory and visual stimuli for audio-visual speech integration. The main principle lies in the systematic moment-by-moment metastable synchronization of the on-going changes of brain activity among different neural assemblies of the large-scale networks [17,72]. These changes (rapid transition processes) have been shown to be the triggering moments of discrete operations processed in various cortical sites [14,65]. This is in keeping with recent studies (for review, see Ref. [95]), suggesting that multisensory integration is a process that not only facilitates detection of the multisensory stimuli by amplification of the unimodal sensory signals, but also combines these signals to form new, multimodal representational percepts [92].

A final important question in neuroscience is how psychopharmacological agents influence local and large-scale brain functional connectivity. The effects of a single dose (30μg/kg) of lorazepam on the operational activity of neuronal assemblies and on the remote temporal binding between them were examined in a double-blind randomized crossover placebo controlled study [50,76]. The suggested concept of functional connectivity permits researchers

to study large-, medium-, and small-sized neuronal assemblies separately through EEG/MEG measure, and to estimate remote functional interrelations between them. It was found that different-sized neuronal populations within alpha and beta frequency bands perform differently under lorazepam, when compared to placebo groups [76]. Thus, for the alpha-generated neuronal populations large neuronal assemblies exhibited a decrease in total size, functional life span, and stability. Small neuronal assemblies throughout the entire cortex were not as influenced by the inhibition process (lorazepam administration) as large assemblies, and hence were stable. For the beta-generated neuronal populations, none of the neuronal assemblies (large-, medium-, and small-sized) increased the beta-amplitude under lorazepam administration, when compared with placebo (for discussion, see Ref. [76]). These findings suggest that differences in the behavior between neuronal assemblies of different size may vary depending on the strength of internal interactions and the size of neuronal populations. It was also demonstrated that lorazepam leads to a whole cortex significant increase in the number and strength of remote functional connections within both alpha and beta frequency bands [50]. These functional connections correspond to the temporal synchronization of operations processed by local neuronal assemblies within different cortical sites. The fact that such temporal synchronization exists under the lorazepam administration suggests that inhibition may also be an efficient mechanism for synchronizing large populations of neurons (for a detailed discussion, see Ref. [50]).

## 5. Conclusions

We have reviewed a variety of brain connectivity concepts and discussed our proposed neurophysiological concept of functional connectivity. This concept offers a unified methodological and conceptual basis for a possible mechanism whereby the transient synchronization of brain operations may construct unified and relatively stable neural states, which underlie mental states, and conscious states in particular (for details see Ref. [38,65]). Thus, the concept of local and remote functional connectivity, whereby elementary operations are localized in discrete cortical and subcortical regions, and complex brain functions involve synchronous processing in a wide-spread network, is a highly promising framework in modern theories of neuroscience and cognition (a more thorough discussion with full reference to the source papers can be found in Ref. [37]; see also Ref. [33,72,96]).

**Appendix A. Methods of EEG/MEG segmentation and local functional connectivity**

The method of rapid transitional processes (RTP) identification (algorithm SECTION1.0$^\circledR$, Human Brain Research Group, Moscow State University) is based on the automatic selection of level-conditions in accordance with a given level of the probability of "false alerts" and carrying out simultaneous screening of all EEG/MEG channels (for a review see Ref. [65]). In order to estimate RTPs, comparisons are made between the ongoing EEG/MEG amplitude absolute values averaged in the test window and the EEG/MEG amplitude absolute values averaged in the level window (test window << level window). 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/MEG homogeneity is accepted. Otherwise, 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 the false alerts (the Student criteria), its time instant becomes the preliminary estimate of a RTP. Also another condition must be fulfilled in order to eliminate the "false alerts" associated with possible anomalous peaks in the amplitude. The five points of the digitized EEG/MEG following this preliminary RTP must have a statistically significant difference between averaged amplitude values in the test and the level windows (Student's $t$). If these two criteria are met, then the preliminary RTP are assumed as actual. Then, each of the windows shifts on one data-point from the actual RTP and the procedure is repeated. With this technique, the sequence of RTPs with statistically proven time coordinates can be determined for each EEG/MEG channel individually for each epoch (Fig. 1). The details of methodology and theoretical concepts are described elsewhere [65,76]. By varying the parameters of this technique it is possible to obtain the segments corresponding to a more or less detailed structure of the EEG/MEG [75]. This allows the description of the structural EEG/MEG organization as a hierarchy of segmental descriptions on different time scales [17].
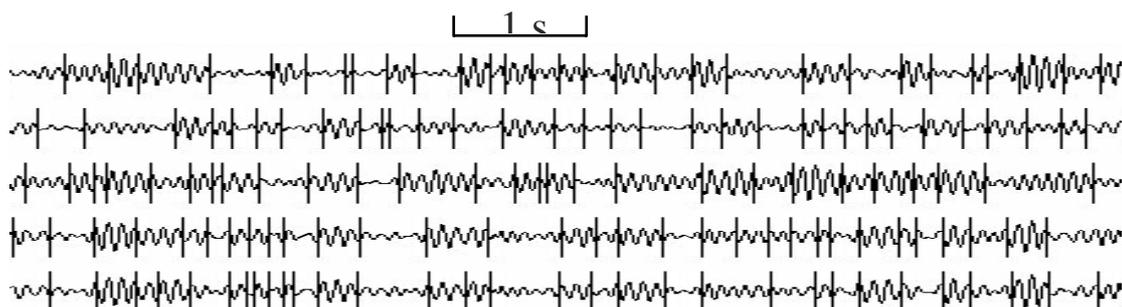
**Fig. 1. Typical example of EEG channels with automatically detected rapid transitional processes (RTP).** Note that the length of RTP is so brief that it appears to have almost zero duration in the figure (shown as vertical lines). Figure illustrates an example of 5 EEG channels (from the bottom: O1, O2, P3, Pz, P4,) filtered in the alpha frequency band. Subject was in rest condition, eyes open. It can be seen that some RTPs in different EEG channels appeared temporally close.

After quasi-stationary segments (indexed by RTP) are obtained, several characteristics (attributes) of segments [55] can be calculated. These attributes reflect different aspects of local processes in the cortex and thus permit assessing the mesolevel description of cortex interactions (local functional interactions within transient neuronal assemblies) through large-scale EEG/MEG estimates. The attributes are the following (for a discussion, see ref. [76]):

1. Average amplitude within each segment ($\mu V^2$) – as generally agreed, indicates mainly the volume or size of neuronal population: indeed, the more neurons recruited into assembly through local synchronization of their activity, the higher will be the amplitude of corresponding to this assembly oscillations in the EEG/MEG.

2. Average length of segments (ms) – illustrates the functional life span of neuronal population or the duration of operations produced by this population: since the transient neuronal assembly functions during a particular time interval, this period is reflected in EEG/MEG as a stabilized interval of quasi-stationary activity.

3. Coefficient of amplitude variability within segments (%) – shows the stability of local neuronal synchronization within neuronal population or assembly.

4. Average amplitude relation among adjacent segments (%) – indicates the neuronal assembly behavior – growth (recruiting of new neurons) or distraction (functional elimination of neurons).

5. Average steepness among adjacent segments (estimated in the close area of RTP) (%) – reflects the speed of neuronal population growth or distraction.

**Appendix B. Synchronization of quasi-stationary segments in multi-channel EEG/MEG as index of remote functional connectivity**

The original technology for estimation of functional brain connectivity through the index of EEG/MEG structural synchrony (ISS) was developed. The ISS is estimated through synchronization of quasi-stationary segments between different EEG/MEG channels. This measure (algorithm JUMPSYN1.0$^{®}$, Human Brain Research Group, Moscow State University) reveals functional (operational) interrelationships between cortical sites different from those measured by correlation, coherence and phase analysis [17]. Each rapid transitional process (RTP) in the reference EEG/MEG channel (the channel with the minimal number of RTP from any pair of EEG/MEG channels) was surrounded by a short "window" (ms). It was taken that any RTP from another (test) channel coincided if it fell within this window. The ISS for pairs of EEG/MEG channels can be estimated using this procedure (for the details, see Ref. [50, 80,94]). To arrive at a direct estimation of a 5% level of statistical significance of the ISS ($P <$ 0.05), computer simulation of RTP synchronization should be undertaken based on random shuffling of time segments marked by RTP (500 independent trials). As a result of this procedure the stochastic level of RTP coupling ($ISS_{stoh}$), and the upper and lower thresholds of $ISS_{stoh}$ significance (5%) would be calculated. The ISS tends towards zero where there is no synchronization between the EEG/MEG segments and has positive or negative values where such synchronization exists. Positive values indicate 'active' coupling of EEG/MEG segments (synchronization of EEG/MEG segments is observed significantly more often than expected by chance), whereas negative values mark 'active' decoupling of segments (synchronization of EEG/MEG segments is observed significantly less than expected by chance) (Fig. 2).
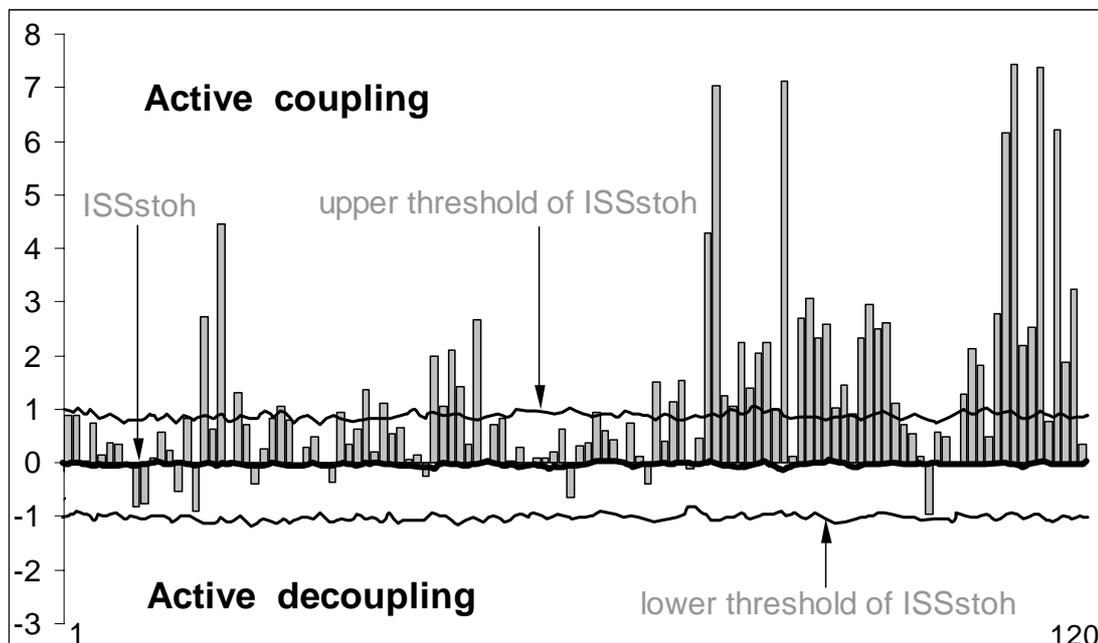
**Fig. 2. Schematic illustration of the index of structural synchrony (ISS) and its stochastic levels.** As an example, the calculations of ISS are shown for 16 EEG channels. The *Y*-axis displays the ISS values found in the experiment (illustrated as gray bars). The *X*-axis displays the 120 possible pair combinations of 16 EEG channels (1 = O1-O2, 2 = O1-P3, 3 = O1-P4, 4 = O1-T5, … 115 = F4-Fz, 116 = F4-F7, 117 = F4-F8, 118 = Fz-F7, 119 = Fz-F8, 120 = F7-F8). Control subject is in rest condition, eyes closed. Figure is reproduced from the Fingelkurts et al. 2004, Human Brain Mapping ©.

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