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Brain and Mind in a Cartesian System of 21st Century.

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Since Descartes, Leibniz and Newton there has been no scientist, who has a full command of all the intellectual activity of his day. Since that time, science has been increasingly the task of specialists, in fields, which show a tendency to grow progressively narrower. This ability of full command cannot be presented by the scientists of the 21st century.

In despite of this, collaboration of scientists bridging continents became possible. Because of powerful computers our memory capacity became larger: new methods and associative algorithm became extremely rich (Feynman diagrams, Heisenberg's S. Matrix, statistical mechanics). Accordingly, the boundary regions of multiple fields of science offered the richest opportunities to qualified investigators.

The brain is the most complex system in the universe known to us. In the present syposium we will try first to understand dynamics of the brain, i.e. a biological system which works and continuously changes. If we assume that the brain is the organ, which also controls our mind and our body the understanding of brain dynamics should help to search the communicative processes between the body and the brain. Additional to the electrical oscillations the brain-body machineries are also controlled by transmitters. It exists also recurrent loops and feedback loops between the body and the transmitters. Furthermore, oscillatory activities in the brain and body are affected by transmitters; the electrical processes also control release of transmitters. According to these facts the understanding of brain mind is a difficult problem in which several processes are involved. The questions (what is mind and what is brain mind?) can be approached only by consideration of the ensemble of machineries and links that are shown in figure 1. In the upper part of figure 1 we schematically describe that the machinery of brain mind cannot be understood by analyzing processes only at the level of the adult brain. Our thesis is this: In order to approach the brain-mind we also have to observe machineries of ganglia and brains during evolution of species and also analyze physiological processes and anatomical changes during maturation of the brain including babies, adults and elder persons. Additional to this we have to analyze pathologies as Alzheimer, Schizophrenia and Bipolar Disorders.

The aimed goal of this symposium consists as a first aim in a big élan to understand machineries of brain-mind, not only by means of philosophical ways but solid empirically. However, another important goal is the trial to indicate some new avenues, how scientists could try to understand general principles of science. From Newton to Einstein and Heisenberg from René Descartes to Bergson all science is developed by searching general principles.

Shouldn't we perform also similar steps in studies to understand brain-mind?

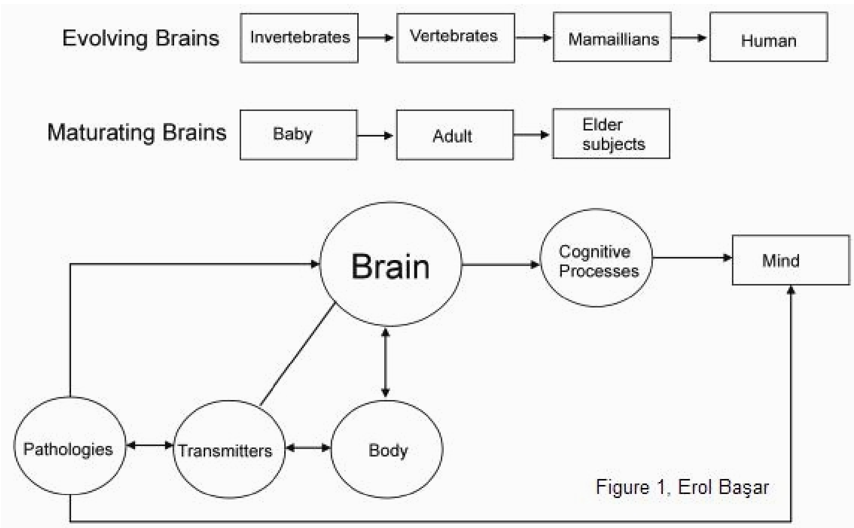

Figure 1, Erol Başar

Figure 1 schematically explains the step proposed for an approach to brain-mind

Norbert Wiener says: If a new scientific subject has real vitality the center of interest in it must and should shift in the course of years. This was the case in the case of the oscillatory dynamics; I hope time has come for a new shift.

Understanding the Mind

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"Mind" is a word that implies multiple functions: we pay attention, we see, we hear, we remember, we feel, we act, we experience, and so forth. These activities rely at least in part on the workings of a physical organ called the brain immersed, as it is, in a complex world that also consists of other human beings**.** Like structure and function, nature and nurture, organism and environment, the contents of mind and the dynamics of mind are inextricably connected. Thoughts are not static: Like the flow of a river, they emerge and disappear as patterns in a constantly shifting dynamic system (Kelso, 1995). Science demands we go beyond metaphor to seek description and explanation. As in other, more mature fields it is crucial to have a theory or at least a conceptual framework of what one is trying to understand. In the context of recent developments in the science of coordination (coordination dynamics) an attempt is made to sketch a theory of mental activity that respects both the contents of thought and the dynamics of thinking. The purpose is to stimulate insight into how mind, brain and behavior might be connected in a unified way. For ease of exposition, the theory is communicated via the following propositions, each of which has varying degrees of empirical support:

1. Although much remains to be clarified, studies of the brain (e.g. fMRI) suggest that the contents of thoughts depend on the neural structures activated. Reciprocally, the neural structures activated influence -- directly or indirectly--the contents of thoughts.
2. Unlike real estate, mind is not only about location. Active, dynamic processes like "perceiving", "attending", "remembering," and "deciding" emerge as *patterns of interaction* among widely distributed neural ensembles, and in general between human beings and their (social) environments.
3. Neuronal ensembles in different parts of the brain oscillate at different frequencies. At least 12 different rhythms from the infraslow (less than 1Hz) to the ultrafast (more than 100Hz) have been identified in the brain and are known to support various sensory, motor and cognitive functions. Such oscillatory activity is a prime example of self-organization in the brain (e.g. Basar, 2004). The nonlinear oscillator is proposed as the basic structural~functional unit or 'coordinating element' of the brain.
4. Oscillation, though necessary is not sufficient. What matters is that oscillations are coupled or "bound" together into a coherent unit or network. This is a dynamic, self-assembling process, parts of the brain engaging and disengaging in time. For example, in-phase and antiphase are just two out of many possible multistable, phase synchronized states that can exist between specialized brain areas depending on their respective intrinsic properties and functional connectivity.
5. Different thoughts correspond to different relative phases between oscillating brain areas. Relative phase is a natural quantity for coordinating different things and is a long established order parameter in coordination dynamics. Phase is also the means by which excitatory and inhibitory neurons communicate with each other in so-called central pattern generators that may be exploited at the level of cortical circuitry. In coordination dynamics, phase relationships carry *functional information* with multiple attractors setting alternatives.
6. The persistence of a thought depends on the *stability* of the brain's relative phase dynamics. Some thoughts persist longer than others because the phase relations underlying them are more stable. Many factors (environmental, intentional, attentional, emotional, learning, forgetting, etc.) have been shown to influence the stabilizing and destabilizing of brain states.
7. What makes thoughts switch? When it comes to the nervous system, it is always tempting to ask (e.g., Abbott, 2006): "where are the switches in this thing?" Merely because there is switching, e.g. in perception, does not necessarily mean there are switches. Considerable experimental evidence shows that switching in both brain and behavior may take the form of a nonequilibrium phase transition. Fluctuations play a key role, testing the stability of states and enabling the system to discover new states. In coordination dynamics, once the system settles into an attractor, a certain amount of noise or a perturbation is required to switch it to another attractor. Or, if internal or external conditions change (e.g. via neuromodulators) a bifurcation or phase transition may occur, causing the system to

switch from being multistable to monostable or vice-versa. Phase transitions constitute a basic form of *selection or decision-making.*

8. Instead of thoughts corresponding to rigid, phase and frequency locked states in the brain, broken symmetry in the coordination dynamics allows a more fluid *metastable* regime. Metastability is characterized by partially coordinated *tendencies* (not states) in which individual coordinating elements are neither completely independent of each other ("locally segregated") nor fully linked in a fixed mutual relationship ("globally integrated"). In experimental brain recordings, metastability is revealed by brief epochs of phase synchrony interspersed in time with phase wandering. Theoretical modeling demonstrates that metastability arises as a result of changes in the dynamic balance between the coupling among neural ensembles (mediated, typically by reciprocal pathways in the brain) and the expression of each individual neural ensemble's intrinsic properties (typically heterogeneous in nature). The metastable regime offers scientific grounds for "reverie": thoughts come and go fluidly as the oscillatory units of the brain express both an interactive integrative dynamic and an individualistic segregative dynamic. Metastable coordination dynamics also rationalizes William James (1890) beautiful metaphor of the stream of consciousness as the flight of a bird whose life journey consists of 'perchings' (phase gathering, integrative tendencies) and 'flights' (phase scattering, segregative tendencies). Both tendencies are crucial: the former to summon and create thoughts; the latter to release individual brain areas to participate in other acts of cognition, emotion and action.

9. In some traditions, it is not the contents of thoughts that matter, but their "stickiness". In the metastable regime of the coordination dynamics, the stickiness of thoughts depends on how close the neural system is to the fixed points of the relative phase dynamics. Sticky thoughts have long dwell times and a high probability density of near perfect phase synchrony between the brain's oscillations. Passing thoughts, as the name suggests, have short dwell times and low probability density. Stickiness means that the coupling interaction between neural populations is stronger than the tendency of these populations to express their individual autonomy and/or to disengage from one neural coalition to participate in others. Very sticky thoughts correspond to phase trapping between the brain's oscillations and may be pathological. Well-known manifestations of too much synchronization in the brain are diseases like Parkinson's disease and epilepsy. On the other hand, it appears that certain diseases such as schizophrenia appear to be characterized by a reduction in oscillatory brain activity and a relative absence of long range phase synchrony (Uhlhaas & Singer, 2006). Like order and chaos, it seems the boundary between health and disease is a fine one and mutable too.

10. Information creation. According to Quantum Mechanics, out of a universe in which quantum indeterminacy rules - the wave function is spread out over all of space - nature selects an alternative. In this way, information is created. For the Nobel Laureate, E. Wigner if we are to explain the appearance of the world as we know it, conscious agency is required to collapse the wave function. In coordination dynamics, information (as a marginally coupled, phase-locked pattern) is created and destroyed in the metastable regime, where the slightest nudge will put the brain~mind into a new coordinated state. The process by which the metastable coordination dynamics of the brain creates new, functionally meaningful information may be called consciousness.

In sum, thought is matter and thinking is matter in motion—the coordination dynamics of the brain. Thinking arises as a low dimensional, coherent pattern in the brain in an extremely high-dimensional system called the human being coupled to its environment. The slightest fluctuation can trigger a thought. Context matters. The coordination dynamics of thinking is essentially nonlinear and contains multistability and switching—both essential for decision-making but debilitating when they lead to polarization. Coordination dynamics is different because it deals primarily in the currency of *functional information*: the two "forces" that drive coordination dynamics deal fundamentally with *information exchange.* One force is the strength of coupling between the coordinating elements; this allows information to be distributed to all participating elements and is a key to integrative, collective action. The other is the ability of individual elements to express their autonomy, and thereby minimize the influence of others. Self-organization in the metastable regime is the interplay of both. This is the architecture of mind. Metastable mind.

Determinants of neuronal network activity in cultured hippocampus.

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Spontaneous network activity is an essential property of a living brain, to the extent that different frequencies, amplitudes, duration and spread of this activity are assumed to underlie different cognitive states in the organism. While the functional relevance of the different forms of spontaneous network activity is being understood, little information exists on the rules that govern the generation, spread and synchronization of spontaneous network activity in the absence of extrinsic afferent drive. A corollary clinically important issue relates to the reasons for why and when does a network break away to become epileptic. Using dissociated cultured hippocampal neurons we are able to begin deciphering these rules. The system is simple enough to allow a more detailed analysis of network activity in general, and of central neurons in particular. Apparently, network activity emerges at several days in vitro (3-7DIV) and its establishment does not actually require either excitatory, inhibitory or even spike discharges. As we cannot identify leader neurons, and cannot trigger the network by producing action potentials in single neurons, it is tentatively believed that the activity is a subtotal of activity of several neurons acting at the same time. The spread of this activity and the synchronicity are dependent on activation of inhibitory GABAergic neurons. Furthermore, the complexity of dendritic arbor of maturing neurons as well as the presence of dendritic spines on these neurons contribute to the complexity of network activity, in a non-linear manner. Finally, ongoing network activity is important for the survival of neurons in culture. These on-going studies are expected to contribute to the understanding the much larger and more complex activity of network of neurons in the brain.

Cellular alpha rhythm mechanisms and their possible association with perceptual timing.

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The classical occipital alpha (α) rhythm (8-13 Hz) is most apparent during relaxed wakefulness but is also linked to several key aspects of perceptual timing. Although it was the first EEG oscillation to be discovered nearly 80 years ago, its precise cellular basis and the mechanisms by which it influences the timing of perceptual processes are unknown. I show here that the α rhythm is primarily driven by a subset (30%) of gap junction (GJ) coupled, high-threshold (HT) bursting thalamocortical (TC) neurons located in the primary visual thalamus (i.e. the lateral geniculate nucleus, LGN). The remaining majority of LGN TC neurons generate action potentials in a traditional tonic or relay mode which are also correlated with the α rhythm. These cells form two distinct coalitions where the average firing occurs as a cyclic step-like increase which is centred on the negative peak of the local field oscillation in one group and on the positive peak in the other. These step-like increases arise from a complex interaction between direct GJ connections from HT bursting cells and phasic inhibition from local GABAergic interneurons which themselves are driven by convergent synaptic input from HT bursting cells. Thus, a specialized network of pacemaker TC neurons generates both local and EEG α activity and creates a dual-clocking mechanism which finely controls action potential output in assemblies of relay mode TC neurons. These results may provide the first definitive link between neuronal dynamics and the α rhythm-associated timing of perceptual processes.

Updating P300: An Integrative Theory of P3a and P3b

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The empirical and theoretical development of the P300 event-related brain potential (ERP) will be reviewed by considering factors that contribute to its amplitude, latency, and general characteristics. The neuropsychological origins of the P3a and P3b subcomponents are outlined, and how target/standard discrimination difficulty modulates scalp topography will be discussed. The neural loci of P3a and P3b generation are highlighted, and a cognitive model is proffered: P3a originates from stimulus-driven frontal attention mechanisms during task processing, whereas P3b originates from temporal-parietal activity associated with attention and appears related to subsequent memory processing. Neurotransmitter actions associating P3a to frontal/dopaminergic and P3b to parietal/norepinephrine pathways are suggested. Neuroinhibition is suggested as an overarching theoretical mechanism for P300, which is elicited when stimulus detection engages memory operations.

Frequency-Dependent Cortical Dynamics and the Optimization of Perception.

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Perception is a dynamic cognitive process that is optimized on millisecond to second time scales to enhance capability. Neural dynamics in primary sensory cortex, such as changes in the sensitivity of cortical neurons to sensory input, may play a key role in this optimization process.

One form of rapid neural transformation my lab focuses on is activity-dependent dynamics, shifts in neural responsiveness as a function of ongoing activity in a local cortical network. To study this problem, we employ animal model systems (rats and monkeys) and human psychophysical and imaging studies.

A specific form of activity-dependent dynamics is frequency-dependent dynamics. Frequency-dependent cortical dynamics can be recruited by changes in the pattern of sensory-driven input—as the ongoing rate of sensory input is varied (for example, how frequently a tone is played or a finger is tapped), the response of the cortical network to new input varies with it. Recording in the 'barrel' cortex that is responsive to deflections of vibrissa on the rodent face, we have shown that stimulation of a vibrissa at 5-15 Hz leads to a decrease in the response amplitude of cortical neurons, and an increase in the precision of sensory tuning in these same neurons. For example, stimulation of a vibrissa at low frequencies (e.g., 1 Hz) will activate several millimeters of cortex, but stimulation at 5-10 Hz leads to a sharpening in the lateral spread of activation across the cortex, so that only a single cortical column (.5 x .5 mm) is effectively activated. As a corollary, the receptive field of any single neuron is also sharpened, and will respond less to all vibrissae, with a specific loss of the initially weaker 'surround' vibrissa inputs. Similar sharpening of responses has been observed in the temporal fidelity of a response—at 5-15 Hz, phase locking of spiking and vibrissa deflection is increased—as is tuning for the direction a vibrissa is deflected. This kind of frequency-dependent transformation is particularly relevant for the vibrissa sensory system because rats choose to actively sample the world by moving their vibrissae at 5-15 Hz, a behavior known as whisking.

We hypothesized that these frequency dependent dynamics represent a shift from a mode optimal for detection of sensory input to one optimal for discrimination. In the non-adapted state, a sensory input will more effectively drive activity in cortical neurons, creating a robust 'alerting' signal that contact has occurred. In contrast, in the adapted state, this response will be relatively suppressed. The increase in the precision of tuning in the adapted state will, however, potentially enhance the specificity of representation, facilitating discrimination between different inputs (e.g., judgments of which vibrissa was stimulated, or judgments of the direction of vibrissa motion). A key prediction of this hypothesis is that when thalamic input is ongoing at 5-15 Hz, the cortex will be suppressed, and detection will be impaired.

These sensory-driven dynamics may in many ways parallel dynamics driven by internal 'state' properties of the thalamo-cortical loop. The 'alpha' state observed in primary somatosensory cortex is an ongoing 5-15 Hz rhythm that (in some cases) originates in thalamic activity at this rate. Our prior studies predict the suppression of sensory input during this ongoing activity. To test this hypothesis, we have conducted magnetoencephalographic (MEG) recording of human primary somatosensory cortex (SI) during performance of detection tasks. To 'decode' the meaning of activity observed in SI recorded external to the head with MEG, we have implemented a full multi-neural model of SI cortex, with biophysically appropriate current flow and fully modeled dendritic compartments. This model can predict the key features of the sensory-evoked SI response up to ~150 msec after stimulus presentation.

We have found (Jones et al., in press) that the detection of a threshold-level perceptual stimulus (a tap) applied to the fingertip is predicted by diminished amplitude of the SI evoked response. Using the model, we can predict specific neural correlates—the timing and intensity of different sources of input to the circuit—that generate this diminished response. We have also found that trials that will be missed showed greater alpha activity prior to stimulus onset, and that alpha levels predict SI evoked response suppression. These findings are consistent with the prediction that alpha-driven adaptation of SI decreases detection probability. We are now testing the hypothesis that alpha is not simply a global 'inattention' signal, but rather that alpha can be selectively deployed to specific representations to suppress uninformative 'distractions,' to enhance performance. This hypothesis is supported by Worden et al. (2000), who showed that alpha power is increased in the hemisphere contralateral to a distracting visual stimulus. To test this hypothesis, in humans we are conducting selective attention tasks (attend hand not foot), and in rats we are testing vibrissa-specific detection capability. Our rat studies will be conducted using intracellular in vivo recording techniques and laminar electrode recordings, providing insight into the cortical cell types (fast-spiking interneuron activity versus regular-spiking neuron activity) and the layers of origin of these dynamics. Further, studies in the rat will allow us to test the hypothesis that alpha can be deployed to block input to the specific barrel column that represents a 'distracting' vibrissa input. We are also using rodent mouse models now, with genetically targeted approaches, to look at how specific sub-types of interneurons may contribute to these activity-dependent dynamics

Memory related EEG oscillations and top-down control.

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An integrative theoretical approach about memory related oscillations will be presented. The basic assumptions are that (i) memory related oscillations are probably confined to theta and upper alpha, (ii) reflect top-down control in two complex memory systems, and that (ii) other frequencies particularly in the gamma range are important for memory probably only in the sense that they become coupled to lower frequencies. This latter view is based on the fact that synchronized gamma activity has been found in many different tasks including motor learning, response execution, and attention driven top-down process.

In contrast to previous studies, where we related theta and upper alpha to a variety of different memory processes, we suggest here that these oscillations are associated with two types of top-down control. Different memory systems, such as WM and (sensory-semantic) LTM may have their own types of top-down processes that control access to and/or manipulation of stored information and our assumption is that theta and upper alpha reflect these processes.

For theta, at least three types of responses can be distinguished that may be related to different types of WM-related top down processes such as central executive, sustained attentional control and control of episodic encoding and retrieval. These ideas appear straight forward for theta, because synchronization is the typical and reliable event- and task-related response of this frequency domain. But alpha shows desynchronization in many tasks and, thus, the traditional interpretation of this frequency domain was (and still is) based primarily on measuring desynchronization and not synchronization. The underlying assumption of this approach was (and still is) that synchronized alpha reflects some sort of resting state which is not related to any specific type of information processing. But a variety of findings document that the specific function of alpha is – as for any other oscillation – related to the synchronized and not to the desynchronized state. As an example, when a task requires that certain operations must be performed with stored information (e.g., stored information must be kept in mind, must not be retrieved or must be manipulated by performing some transformation) alpha reliably exhibits synchronization. We assume that the different tasks that are associated with synchronized alpha reflect different aspects of top-down control in a complex sensory-semantic long-term memory system.

Cortical oscillations and auditory memory.

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Cortical oscillations in humans are involved in a variety of cognitive processes including the perception of familiar or gestalt-like objects, selective attention and both short- and long-term memory. We have used magnetoencephalography to investigate oscillatory signals during different types of sound processing. A non-parametric statistical probability mapping was applied to assess the spectral and topographical properties of oscillatory activity patterns. Passive processing of infrequent sound changes in mismatch paradigms was associated with increased gamma-band activity (GBA) over posterior temporo-parietal areas for auditory spatial deviations, whereas GBA enhancements over anterior temporal and inferior frontal regions accompanied sound pattern changes. This supported the notion of dual auditory dorsal and ventral processing streams, respectively. A similar topography of activations was also observed during the maintenance of auditory spatial or pattern features during the delay phases of short-term memory tasks, probably reflecting the storage of task-specific information in higher sensory networks. In addition, increased coherence and phase synchronisation between these putative higher sensory areas and frontal regions may have indicated increased maintenance-related cortico-cortical coupling. Further evidence for the role of fast oscillations was obtained from studies of audiovisual integration and auditory decision-making.

In a recent study, we have focused on the question whether oscillatory components can be identified that reflect individual stimulus representations during maintenance in short-term memory. 28 adults were assigned to one of two groups who were presented with only right- or left lateralized sounds, respectively. In each group, two sample stimuli were used which differed in their lateralization angles (15° or 45°) with respect to the midsagittal plane. The statistical analysis compared spectral amplitude differences between 15° versus 45° stimuli. Distinct GBA components were found for each sample stimulus in different sensors over parieto-occipital cortex contralateral to the side of stimulation. The amplitude of these components peaked during the middle 200-300 ms of the delay phase. The differentiation between 'preferred' and 'nonpreferred' stimuli during the final 100 ms of the delay phase correlated with task performance. These findings suggest that the observed GBA components reflect the activity of distinct networks tuned to spatial sound features, that are involved in keeping task-relevant information active in short-term memory. In summary, cortical oscillations can be identified in magnetoencephalogram with a good spatial resolution. These oscillations may be interpreted as reflecting the synchronisation of cortical networks underlying the representation of task-relevant stimulus features.

REM Sleep Dreaming, a Frontal Disconnection State.

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Cognitive content of REM sleep dreaming, as assessed by recording of narratives immediately after awakening from REM sleep, is characterized by a mixture of perceptual richness full of details, action and emotional content reflecting an activated state of sensory-motor and emotional systems and at the same time of bizarreness, distortion of reality, discontinuity, incongruities, lack of purpose, rigidly focused attention and lack of awareness of being dreaming together with the sensation that the plot is dictated by someone else.

Perceptual clarity and emotional content in dreaming are compatible with brain electrical activation and metabolic activation of posterior cortical and limbic system regions found during REM sleep. The acceptance of bizarreness and incongruities without questioning if they are consistent with reality are compatible with cognitive alterations found in frontal lobe dysfunction and with metabolic deactivation of this brain region found during REM sleep as compared to wakefulness.

However, what is particular about REM sleep is the simultaneous existence of perceptual and emotional acuity plus a distorted interpretation of ongoing mental content, on the cognitive side, and electrical and metabolic activation of posterior brain regions and metabolic deactivation of anterior regions, on the physiological side, indicating a dissociation between perceptual and action components of the perception-action cycle during REM sleep.
Synchronization of simultaneous electrical activity plays a crucial role in the binding of spatially separated but temporally correlated stimuli into whole events. The analysis of simultaneous ongoing electrical activity during ten minutes prior to dream reports by crosscorrelation methods has revealed a loss of temporal coupling of intrahemispheric activity during REM sleep periods as compared to wakefulness and slow wave sleep between frontal (executive) and posterior (perceptual) regions, whereas intra-hemispheric coherent activity among posterior regions maintains wakefulness values.

The decrease of temporal coupling between frontal and posterior regions during REM sleep indicates a functional dissociation between executive and perceptual regions that provides a distorted binding mechanism resulting in misinterpretation of ongoing perceptual activity, lack of judgment and passive acceptance of bizarreness and loss of voluntary control of thinking sensation, while wakefulness levels in EGG correlation of fast activity among perceptual regions might explain perceptual acuity.

Further analysis of EEG and magnetoencephalographic activity during REM sleep has revealed increased cortical and limbic activation and reorganization of temporal coupling linking large brain regions by phasic events probably related to pontine tonic and phasic incoming activations.

Gender Differences in Event Related Oscillations during Visual Paradigms.

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Analysis of Event Related Oscillations (EROs). had clearly showed the possibility to differentiate changes induced by facial expressions (Güntekin, B., Başar. E., Emotional face expressions are differentiated with brain oscillations. Int. J. Psychophysiol. 2007 Apr;64(1):91-100. Epub 2006 Dec 5). On the other hand, there are only few studies describing gender differences in event related oscillations. In order to understand the gender differences in event related oscillations we demonstrate the results of two different experimental paradigms. In the first experimental paradigm we have used the simple visual stimulation to demonstrate the differences in Event Related Oscillations (EROs) between female and male subjects. The data of 32 (16 males, 16 females) healthy subjects were recorded from thirteen different scalp locations (F_3, F_4, C_z, C_3, C_4, T_3, T_4, T_5, T_6, P_3, P_4, O_1, O_2). Analysis was performed in the delta (0.5–3.5 Hz), theta (5–8.5 Hz), alpha (9–13 Hz), beta (15–24 Hz), and gamma (28–48 Hz) frequency ranges. The results showed that the maximum peak-to-peak delta response amplitudes for women were significantly higher than for men over occipital, parietal, central and temporal electrode locations. There were also differentiations in the beta and gamma oscillatory responses. These gender differences were most pronounced over the electrode site O_2, that is, over primary visual areas.
In the second experimental paradigm three sets of Ekman and Friesens's facial expressions (neutral, angry, and happy) were presented to 26 healthy subjects (13 males, 13 females) while recording from 13 different scalp locations. Analysis was performed in the beta (15–24 Hz) frequency range, Occipital beta response (15–24 Hz) was significantly larger for women than for men during the presentation of face expressions. Accordingly, the results of two experimental paradigms indicate the necessity of introducing standardization between male and female subjects by means of oscillatory dynamics. In turn, this standardization may be useful for cognitive and clinical studies.

Bipolar Pathophysology and Treatment Development.

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Bipolar disorder, recognized by Hippocrates and Aretaeus, has received renewed scientific interest consequent to development of effective, novel treatments over the past 50 years. Certain features of bipolar disorder and its scientific study have facilitated these landmark developments, while others have impeded advances. This presentation focuses on both for purposes of providing a scientific platform that may be useful to basic and clinical scientists to achieve seminal advances in understanding pathophysiology, including inherited and experience based contributors to disease expression. Counterintuitively, the latter are better understood than the former, and include hypothalamic pituitary axis dysregulation, early life psychological and physiological insults, e.g., CNS infections, use of abusable drugs, and vascular or traumatic brain injury at any time. The limited advances to date from genetic studies are in part consequent to the flawed syndromal phenotype currently in vogue. DSM criteria largely resolve problems of criterion variance, but both include false positive cases and exclude true positive ones. The former problem is consequent to treating all identified symptoms as equal and allowing "either/or" variables, rather than having evidence based mandatory illness features. The latter is consequent to allowing only cross sectional symptoms as a basis for diagnosis, at the expense of family history of mood disorders, age of onset, illness course and biological or endophenotypic features not inherently tied to manic or depressive episodes; as well as durational requirements for episodes that are inconsistent with now conclusive evidence. With only slight exaggeration, were similar criteria in place for diabetes, only persons in sustained diabetic ketoacidosis would qualify for the diagnosis of diabetes mellitus.

The scientific unveiling of lithium, valproate and lamotrigine as specifically efficacious treatments for domains of bipolar disorder is instructive in the effective application of inductive logic that has largely been absent in most other drug development efforts for bipolar disorder at the turn of the 21st century. In each instance, astute observations by expert psychiatrists recognized fundamental illness features, which led to hypotheses tied to a single drug tested in open but meticulous observational studies, then refinements of the hypotheses with testing in randomized controlled trials. Additionally, the studies yielded critical information on the fundamental behavioral domains of bipolar disorder and the impact of the 3 drugs on these domains. The attention to domains identified by factor analyses of behavioral items that capture the spectrum of fundamental disturbed behavior clarified that rather than two domains, depression, manic energy and mood, anxiety, irritability, psychosis and somatic distress each contribute to the illness. In turn, these results led to testing neuronal transducing systems associated with the drugs in cellular systems and non-primates. Thereby, a close linkage between phenomenological, pharmacodynamic and efficacy based data was forged. The overlapping effects of lithium and valproate on signal transducing systems, e.g., ERK and PKC, despite differences in their first step actions (distinct from other drugs with utility in bipolar disorders) provide a road map forward for better understanding of pathophysiology and development of novel treatments for bipolar disorders.

Increased Oscillatory Delta and Beta Frequency Responses to Visual Stimuli in Bipolar Disorder Normalizes with Chronic Valproate Use.

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Background: Bipolar disorder involves various cognitive dysfunctions even in euthymic phase of the illness. Dysfunction in GABA/Glutamatergic systems and neural circuits that regulate cognitive processing seem to be involved in the underlying pathology. Event related oscillatory neuroelectrical activity reflects integrative brain functioning. Delta responses (0.5-3.5Hz) to a stimulus represent signal detection and decision making whereas alpha responses (8-13 Hz) are thought to be strongly correlated with attention and memory, overall with working memory and suggested to be the universal operator in the brain. The aim

of the present study was to detect differential oscillatory responses to visual target stimuli during an odd-ball paradigm in patients with bipolar disorder and how they change after chronic valproate monotherapy. Methods: Event Related Potentials (ERPs) to visual odd-ball paradigm in ten euthymic and ten manic medication free, DSM-IV bipolar patients were measured before and after six weeks of valproate monotherapy. Twenty sex and age matched healthy controls were similarly assessed twice with a 6 week interval. Different frequency band responses were obtained by digital filtration of ERPs within the 1000 msec time window for delta, 500 msec window for alpha and 300 msec window for beta responses. Repeated measures and one-way ANOVA, Wilcoxon and Mann Whitney U tests were used where necessary. Results: At baseline, euthymic patients showed higher delta responses to target stimuli in all channels but significantly in the left frontal (F3) (p: =0.03) and left temporal (p. 0.05) channels compared to healthy controls. Patients in the manic phase had significantly higher beta (p: 0.002) and lower alpha responses in the occipital area compared to healthy controls. Six weeks of valproate monotherapy caused a significant reduction high delta responses in Fz (p: 0.04) F3 (p: 0.03), and temporal T3 (p: 0.02), T4 (p: 0.01), T5 (p: 0.01) channels compared to baseline in the euthymic group. In the manic group, high occipital beta responses reduced significantly (p: 0.03) and became similar to those of the normal controls after valproate monotherapy. Alpha response further and significantly reduced (p: 0.04) after valproate but it was still similar to that of the normal controls. Controls did not differ between two assessments with regard to any of the studied frequency band responses. Conclusions: Bipolar patients show different patterns and disturbed oscillatory activity each representing a different cognitive processing during different phases of the illness compared to normal controls. Valproate seems to have a selectively normalizing effect on the altered electrical activity of left frontal and bilateral anterior temporal areas in the euthymic and of the occipital area in the manic patients. This may be through modulation of glutamatergic and GABAergic mechanisms and indicative of medication's neuroprotective effect.

Neural traits and states predict brain responses and behaviour.

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Numerous studies in Psychology, Neurology, and Psychiatry have demonstrated close correlations between brain activity and cognitive functions. In addition, neural traits and states represent a predisposition for specific behaviour. Here, we want to show how genetic polymorphisms and prestimulus EEG oscillations can serve as traits and states, repectively - in order to derive predictions for subsequent brain responses and behaviour. For example, a polymorphism of the the dopamine receptor D4 significantly modulates event-related gamma oscillations. Furthermore, prestimulus alpha and gamma oscillations correlate with poststimulus performance. While many of the studies have so far only established correlations between these parameters, they can in the future be applied to truly predict brain responses and behaviour.

Delta and theta oscillatory activities reflect different aspects in Alzheimer's disease.

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Diagnosis and treatment monitoring are important aspects in the most common form of dementia, Alzheimer's disease. In the present study, event related oscillations of patients with Alzheimer type of dementia (AD) were analyzed by using a visual oddball paradigm. A total of 22 mild probable AD subjects according to NINCDS-ADRDA criteria and 20 age-, gender-, and education-matched *healthy control subjects* were compared. AD group consisted from11 *untreated* patients and 11 patients *treated* with cholinesterase inhibitor. Oscillatory responses were recorded from 13 scalp electrodes. Significant differences in delta frequency range were seen between the groups by using repeated measures of ANOVA analysis

(F(9.120)=2.228, p=0.022). Further, Wilcoxon analysis was performed. Peak amplitudes of delta responses of healthy subjects were significantly higher than either groups of AD at mid- and left central regions, (Cz, C_3). The delta oscillatory responses were not affected by cholinesterase inhibitors. On the other hand, theta oscillatory responses of untreated AD patient group, were different from treated AD or control subjects over left frontal regions (F_3). Our findings imply that the delta oscillatory responses at central locations are highly instable in mild probable AD patients regardless of treatment when compared to the healthy aged controls. Cholinergic drugs seem to modulate theta oscillatory responses, but not delta responses. The theta oscillatory activity improves over left frontal area. This divergence between delta and theta oscillations once more shows the efficacy of the oscillatory dynamics in diagnosis and monitoring treatment.

ERP and ERO Variabilities Due To Genetic Polymorphisms of Glutamatergic and Gabaergic Neurotransmission.

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ERPs as well as event related oscillations are heritable. Recent studies on gene polymorphisms related with specific components of neurotransmitter systems suggest that the inter-individual differences in brain functions within healthy and patient populations can depend on polymorhisms, because of their capability of constituting neurochemical and/or structural differences. Therefore, potential candidates for the genetic determinants of ERPs are genes encoding several most important neurotransmitter receptors. In this study, we aimed to identify associations of functional polymorphisms in dopaminergic, noradrenergic, GABAergic and glutamatergic neurotransmission systems on wave components of auditory and visual ERPs. Three cognitive paradigms were used to derive ERPs: (i) auditory novelty paradigm with 70% standard, 15% target and 15% novel sounds, (ii) visual go/nogo paradigm with 50% go and 50% nogo stimuli, and (iii) a CNV paradigm with a visual S1 and auditory S2 and 1.5 s interval between them. ERPs were derived form 30 channels according to the extended 10/20 system. To avoid confounding effects of gender, age, education, and IQ on ERPs, the study was carried out on 202 healthy male medical students. The differences of amplitudes and latencies of ERP wave components and the evoked and total powers of EROs obtained by means of wavelet transform among various genotypes of these polymorphisms were tested with ANOVA. The results showing significant effects of these polymorphisms on both ERP wave components and on evoked and induced oscillations in various frequency ranges will be reported in this presentation.

Are oscillatory brain responses generally reduced in schizophrenia during long sustained attentional processing?

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Deficits in sustained attention and vigilance are common in schizophrenia. It has recently been suggested, that these impairments are not mainly mirrored in a general reduction of the EEG-response, but are related to specific alterations in oscillatory networks. Following this approach we investigated the oscillatory delta, theta, alpha and gamma EEG activity during an auditory version of the continuous performance test in patients with schizophrenia and healthy controls. To estimate processing differences between schizophrenia patients (n=10) and healthy controls (n=10) maximum peak-to-peak amplitudes were quantified using averaged and single trial data.

Using averaged data to estimate amplitudes, the results indicated significantly reduced amplitudes in schizophrenia patients in all analyzed frequency bands, mainly at anterior locations. However, single trial analysis suggested that the amplitude reductions observed in the averaged delta, theta and alpha response in patients were due to an increased intertrial variability in the phase of the measured maximum amplitudes (i.e., increased processing jitter). For gamma, maximum amplitudes were already reduced at the single trial level. These results demonstrate that, although often postulated, the EEG response in patients is not merely reduced. Schizophrenia can be characterized by multiple impairments in oscillatory networks, which indicates a disturbance in the interplay and temporal integration of all frequency components as well as the intertrial variability.

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