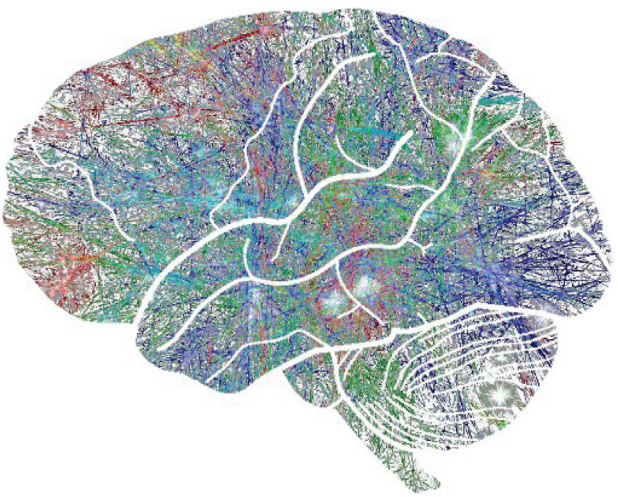
1st INTERNATIONAL SYMPOSIUM ON TRANSIENT DYNAMIC BRAIN STATES – FROM BASIC RESEARCH TO CLINICAL APPLICATIONS

17th–18th March, 2015

University of Tübingen, Germany



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Preface/Introduction

Welcome to the 1st International Symposium on Transient Dynamic Brain States being held at the University of Tübingen in Germany. It's a great pleasure and honor to have you participating in this exciting event!

The human brain undergoes a continuous transition between functional states allowing for fast and efficient adaptation to the environment. These dynamic brain states are essential for normal brain function, but when disturbed can be associated with severe neurological and psychiatric disorders.

Latest advances in neurotechnology can be used to monitor, analyze and modulate dynamic brain states. Implantable and non-invasive brain-machine interfaces (BMIs), for example, use neuronal signals to control external devices and machines. Electric and magnetic brain stimulation is applied in various CNS disorders such as Parkinson's disease, stroke, depression or chronic pain.

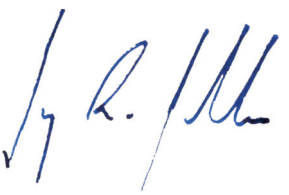
Merging our growing understanding of transient dynamic brain states with most recent developments in neurotechnology will open new doors for more individualized and effective treatment strategies for neurological and psychiatric disorders.

The 1st International Symposium on Transient Dynamic Brain States gathers world-renowned experts from leading research institutes and hospitals to address current topics in this exciting new field and render its future implications for clinical neuroscience.

I would like to take this opportunity to thank the Deutsche Forschungsgemeinschaft (DFG) for their generous support of the symposium, which will most certainly offer an excellent environment for meaningful discussions and fruitful interactions. Furthermore, I'd like to thank Birgit Teufel and the Conventus GmbH for their help and consistent efforts in the preparation of this symposium.

All abstracts will be made available shortly after the symposium at the online publisher "Frontiers" (www.frontiersin.org) whereas video recordings of the talks and discussions will be made available at the conference website (www.neural-dynamics.org).

I hope you will enjoy the symposium and wish you exciting and informative interactions!



Surjo R. Soekadar, MD

Organizer and Symposium Chair

University of Tübingen

Agenda

Tuesday, March 17th, 2015, 6.00 p.m. – 9.30 p.m. (Silchersaal)

Freiheit, Wille und Gehirn/Freedom, Will and the Brain –
with Lüder Deecke, Niels Birbaumer and Johannes Dichgans
Moderator: Steve Ayan, Chief Editor, "Gehirn & Geist"
Music: Olga Šroubková, EMCY Awardee (violin) and Jan Šimandl (piano)

Wednesday, March 18th, 2015, 9.00 a.m. – 5.40 p.m. (Alois Alzheimer Auditorium)

Transient Dynamic Brain States – From Basic Research to Clinical Applications
Chair: Surjo R. Soekadar, MD, Tübingen

9.00–9.30 a.m.	Get together with tea and coffee
9.30 a.m.	Welcome Address and Opening Remarks **Andreas Fallgatter**, MD, University Hospital of Tübingen, Germany **Arnold Mandell**, MD, UCSD, La Jolla, USA
9.50 a.m.	**Niels Birbaumer**, PhD, University of Tübingen & Ospedale San Camillo, IRCCS, Venice, Italy *Transient Dynamic Brain States – From Basic Research to Clinical Applications*
10.30 a.m.	**Hal Weinberg**, PhD, Simon Fraser University, Vancouver, Canada *The Beginning of a New Look in the Understanding of Brain Function*
11.10 a.m.	Coffee Break
11.30 a.m.	**Margot Taylor**, PhD, Hospital for Sick Children, Toronto & University of Toronto, Canada *MEG Indices of Cognitive Development: Focusing on Executive Functions in Children with Autism*
12.10 p.m.	**Stephen E. Robinson**, PhD, National Institute of Mental Health (NIMH), Bethesda, USA *Connectivity Differences among Schizophrenics, Unaffected Siblings, and Normal Control Subjects Revealed by MEG Transfer Entropy Analysis*
12.50–2 p.m.	Lunch Break
2.00 p.m.	**Matthew Brookes**, PhD, University of Nottingham, United Kingdom *Measures of Neural Network Complexity in Neurodevelopment and Schizophrenia*
2.40 p.m.	**Michael Wibral**, PhD, J.W. Goethe University, Frankfurt, Germany *Neural Information Dynamics in Psychiatric and Neurologic Disorders*
3.20 p.m.	**Christian Meisel**, MD, National Institute of Mental Health (NIMH), Bethesda, USA *Sleep, Criticality and Optimal Information Processing in Cortical Networks*
4.00 p.m.	Coffee Break
4.20 p.m.	**Lüder Deecke**, MD, University of Vienna, Austria *Getting Ready for Action – The Course of the Bereitschaftspotential from Limbic to Supplementary and Primary Motor Areas via Motor Loops*
5.00 p.m.	**Surjo R. Soekadar**, MD, University Hospital of Tübingen, Germany *Bereitschaftskomplexität: New Approaches to Image Complexity of Dynamic Brain Activity & Outlook / Concluding remarks*
5.30 p.m.	End of symposium

Alf'ven magnetic and Robinson information waves in the human MEG

Arnold J. Mandell[1,2,3]

1. Fetzer-Franklin Memorial Trust, Kalamazoo, MI, USA
2. Core MEG Facility, NIMH, Bethesda, MD, USA
3. Department of Psychiatry, UCSD School of Medicine, La Jolla, CA, USA

There has been a recent spate of magnetoencephalographic, MEG, studies yielding evidence for both intermittent ("bursting") and continuous ("helical") turbulence in the electromagnetic records of resting (task-free) and task-related records from human subjects. Orbits in MEG-sensor phase space manifest sensitivity to initial conditions (leading Lyapunov exponent, $\Lambda_1 > 0$), mixing (disordering of sequences, $x_i x_j x_k \rightarrow x_j x_i x_k$, fractional Hausdorff dimension ($2 < d_H < 3$), positive topological entropy generation ($\delta h_T > 0$), power law scaling of their frequency spectra, $\rho(\omega)^{-\alpha}$ ($1 < \alpha < 3$) and the relation: $h_T \approx \Lambda \bullet d_H$. Statistical mechanically, the probability distribution of amplitudes may be " stretched exponential," $p_\beta(t) = 1 - e^{-t^\wedge\beta}$ or "algebraic" $p_{\tau,n} = \tau/(\tau^2 + \tau^2/n)$. These are diagnostic manifestations of dynamical chaos, with its relatively high capacity for information generation, transport and reception ("chaotic resonance"). How might this come about in brain magnetic fields in which the usual analyses assumes linear sources and sinks, polarity and the superposition of waves? It is even assumed by many that the brain's magnetic field lines are axiosymmetric and thus cancel. We know that the brain field is *not* axiosymmetric thus emitting net, non-cancelled magnetic fields. How might these brain magnetic fields reflect the information rich dynamics of chaos?

This issue has a natural home in a field that has as its mathematical foundations the convolution of the Navier-Stokes hydrodynamic and the Maxwell's electromagnetic dynamical equations along with the theoretical and experimental methods of magnetohydrodynamics, MHD. The brain has the requisite MHD components: bounded conducting fluids (sodium, potassium, chloride ions containing cerebrospinal and interstitial fluids) in the presence of a continuously changing magnetic field. The evidence for the latter being the MEG record. Although the usual data treated by MHD involves high energy systems such as solar plasmas, the magnetic fields themselves are naturally scale free such that emergent hierarchical dynamical patterns in the large can be realized in the ultra-small as well. The magnetic field dissipative shearing induced turbulence occurs when electrical and magnetic fields are aligned resulting in turbulent transverse Alf'ven magnetic waves. In addition, recent findings describe chaotic dynamics involving magnetic field line "reconnections" resulting in anomalous magnetic field geometries. These mechanisms together help explain the magnetic field lines stretching and then folding in (for example) the Ruelle–Takens route to chaos (fixed point $\rightarrow$ limit cycle $\rightarrow$ ellipse $\rightarrow$ two or more irrationally related quasiperiods (EEG; Δ, θ, α, β, Γ) $\rightarrow$ intermittency $\rightarrow$ continuous chaos. This evolution transiently increases local magnetic field density (folding) followed by its decay much more slowly than the associated electric field. Sometime the magnetic field is described (relative to the electric field) as "frozen." These dynamics together result in the brain's turbulent magnetic fields.

Methods used to characterize this behavior include the invocation of symbolic dynamics encoding of the MEG chaotic signal as an information measure-theoretic object. The results of this treatment manifested a consistently constrained range of values for these "invariant" (from any initial condition) informational measures. Utilizing the discovery of the utility of symbolic dynamic methods and attendant measure theoretic stability, it was natural for Robinson to explore the possible differential brain regionality of these information containing abstractions. His sliding window relative amplitude ranking vectors called the *Rank Vector Entropy, RVE,* was often more sensitive than power, in reflecting function-related brain localization. *Mutual Information*, *MI*, of two regional *RVE*s, *MI*(*RVE*) quantitated the amount of informational sharing between two sites. The kernel of the symbolic dynamic RVE computation is the non-negative, square, symmetric transition matrix, M_T, used in the computation of measures on the densities of sequences of transition-matrix self-maps. Robinson saw the opportunity to extend this M_T self-mapping transition process to paired regions thus quantifying the rate of regional sharing of information in the human MEG.

The results, when the MEG studied during an *n-back task* quantifying memorial "effort" (the comparison of remembering "0-back" to "1 or 2-back" alpha-numeric symbols) demonstrated the expected regional pairings involving the temporal lobe, especially hippocampus. The graded effort, for example, 0 back versus two back, was reflected in Robinson's shared *event related Symbolic Transfer Entropy, efSTE,* seen especially in sensors reporting the entropy-equivalent complexity measures in the dorsolateral-prefrontal cortex, DLPFC.

We suggest that the brain's magnetic fields take the forms of information rich continuous and intermittent chaos, which can be shown to dynamically generate, transport and receive information.

Adaptation of dynamic brain states in paralysis

Niels Birbaumer[1,2]

1. University of Tübingen, Tübingen, Germany
2. Ospedale San Camillo, IRCCS, Venice, Italy

Dynamic adaptation of brain states becomes particular obvious in extreme disease or extreme environmental or psychological affective and cognitive stimulation: we describe data of brain communication in completely locked-in patients using near-infrared-spectroscopy (NIRS)-EEG brain-machine interfaces (BMIs), sleep recordings and quality of life scoring. Despite a continuous a-dynamic slow wave dominant EEG (6 Hz high amplitude dominant frequency during waking) and irregular 2–3.5 Hz sleeping episodes during day and night, quality of life questions are answered positively over long time periods with the BMI. Similar patterns were reported during deep meditation and other forms of muscle paralysis. We present these data and an "extinction of goal directed thinking" model in paralysis.

Acknowledgments

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The beginning of a new look in the understanding of brain function: systems of the brain related to the processing and utilization of information may be different for different individuals

Hal Weinberg

Simon Fraser University, Burnaby, BC, Canada

The history of brain physiology in the last 100 years is actually the history of a pendulum swinging back and forth, from the concept of localized function, to the concept of distributed function, through physically distributed interacting and dynamic systems.

Until recently individual differences in the imaging of brain function were described primarily in terms of deviations from the average variability in measurements. However, recently it has been possible to begin an understanding of how different brain systems change as the result experience, and how these systems, and their changes, are responsible for different people being different people. MEG currently may have the best potential to measure individual differences in the brain, because of its time resolution, and its ability to directly measure the function of neuronal systems in real time, and without the use of high frequency or chemical impositions on that function.

However the increasingly advanced technology of all methods of brain imaging will be able to recognize and document individual differences – and to predict how those differences may impact the current and future life of an individual The implications of this for the treatment of disease and behavioral disorders, and for the prediction and control of individuals, could change our current concept of, and acceptance of, individuality and the diversity of a society.

MEG indices of cognitive development; focussing on executive functions in children with autism

Margot J. Taylor[1,2]

1. Hospital for Sick Children, Toronto, ON, Canada
2. University of Toronto, Toronto, ON, Canda

Executive and social cognitive functions are the abilities that allow one to operate successfully in complex human society. These abilities include working memory, inhibition and understanding the emotions and intentions of others. All of these cognitive functions show protracted maturation over childhood and into adulthood and poor mastery of these abilities has debilitating repercussions on social function. The neural bases of these cognitive functions rely on strong reciprocal connections within frontal cortex, frontoparietal cortical regions and between cortical and subcortical structures. Although neuroimaging work has examined social cognitive function in adults, there is less information on the maturation of the underlying neural substrates and their function and how this maturation proceeds in children with profound social deficits, such as children with autism spectrum disorder (ASD). We have a series of protocols optimized for magnetoencephalography (MEG) for children, including inhibition, emotional inhibition, working memory, emotional face processing, and theory of mind tasks that allow us to explore the neural correlates of these abilities in typically developing children and in those with ASD. Even resting state analyses show significant effects with age and diagnosis. I will present some of these data, highlighting the developmental changes, the sensitivity of MEG with these paradigms, and how the patterns differ in children with ASD.

Connectivity differences among schizophrenics, unaffected siblings, and normal control subjects revealed by MEG transfer entropy analysis

Stephen E. Robinson

National Institute of Mental Health (NIMH), Bethesda, MD, USA

Functional imaging and anatomical evidence, primarily from fMRI and DTI, suggests that schizophrenia is associated with reduced functional connectivity between the prefrontal cortex and the rest of the brain. This study compares information flow between cortical regions as a measure of connectivity by imaging directional information transfer using symbolic transfer entropy. The MEG recordings for schizophrenics ($n = 47$), their unaffected siblings ($n = 48$), and normal control subjects ($n = 43$), selected from a larger MEG sibling study, while performing a working memory (n-back) task, were analyzed. Comparison of the schizophrenic group with the normal subjects revealed hypo-connectivity for long-range connections between the prefrontal cortex and lateral structures including the insula. Hyper-connectivity was observed for short-range connections within the prefrontal cortex – especially connections with rostral prefrontal cortex. By contrast, comparison of the unaffected siblings with the normal subjects revealed hyper-connectivity between the precuneus and prefrontal cortex. These findings were significant at a false discovery rate of <0.002. Differences in effective connectivity for the schizophrenic group between precuneus and prefrontal cortex were not statistically significant. The unaffected sibling group shares a large number of genetic markers with the schizophrenics. This suggests that deficits in functional connectivity in the siblings may be compensated for by increased connectivity with the precuneus.

The disordered brain: measuring neural network complexity in schizophrenia and neurodevelopment

Matthew Brookes

University of Nottingham, Nottingham, UK

In recent years, measurement of signal entropy has been highlighted as a new means to provide novel information about non-linear neural network dynamics in health and disease. In this talk, I will discuss our recent work in this area. I will begin by discussing entropy measurements in brain areas rendered active by cognitive tasks, and I will show that an increase in local neural processing generates localized and transient increases in complexity in the MEG signal. Following this, I will explore the relationship between entropy and more established time-frequency decomposition methods, which elucidate the temporal evolution of neural oscillations. I will show evidence for a direct but complex relationship between entropy and oscillatory amplitude, which suggests that these independent metrics are complementary. Finally, I will show two emerging applications of signal entropy measurements: First, I will use entropic transformation it to shed light on aberrant neurophysiological processing in schizophrenia, including how these metrics are in agreement with a disconnection hypothesis. Second, I will show evidence for changing entropy in well-known large-scale networks, throughout neurodevelopment.

Neural information dynamics in psychiatric and neurologic disorders

Michael Wibral

J.W. Goethe University, Frankfurt, Germany

Information theoretic quantities separate and measure key elements of computation in neural systems, such as the storage, transfer, and modification of information. This way, they help to better understand the computational algorithm implemented in a neural system under investigation. This understanding cannot be reached by detailed biophysical modeling alone, as will be shown in a toy model. Indeed, the missing link between neural dynamics and computational algorithms can be provided by information theoretic methods. Specifically, we introduce measures of active information storage and of information transfer and apply it to two example datasets from MEG. In the first example, we show that local active information storage is reduced in patients suffering from autism spectrum disorder. In the second example, we demonstrate changes in information transfer in multiple sclerosis.

Sleep, criticality and optimal information processing in cortical networks

Christian Meisel

National Institutes of Mental Health (NIMH), National Institutes of Health (NIH), Bethesda, MD, USA

Sleep is crucial for daytime functioning and well being. The importance of sleep is illustrated by the deteriorating effects of chronic sleep restriction or total sleep deprivation on performance. Without sleep optimal brain functioning such as responsiveness to stimuli, information processing, or learning is impaired. Such observations suggest that sleep plays an important role in organizing cortical networks toward states where information processing is optimized. The general idea that computational capabilities are maximized at or nearby critical states related to phase transitions or bifurcations (Langton, 1990) led to the hypothesis that brain networks operate at or close to a critical state. Near phase transitions, a system is expected to recover more slowly from small perturbations, a phenomenon called critical slowing, and observables typically exhibit power-law scaling relationships. Growing experimental evidence on neuronal avalanches (Beggs and Plenz, 2003), i.e., spatiotemporal clusters of synchronous activity in cortex, suggests that the brain under normal conditions resides near a critical state. In the talk I will present results from human and animal studies on changes in signatures of critical brain dynamics during sustained wakefulness and discuss them in the context of recent experimental findings on "critical brain dynamics" on the one hand side and theories about the function of sleep on the other side. Our results suggest a growing deviation from criticality during wakefulness (Meisel et al., 2013) and could provide a network-level framework for the role of sleep: to reorganize cortical dynamics toward a state where information processing is optimized.

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Getting ready for action – the course of the Bereitschaftspotential from limbic to supplementary and primary motor areas via motor loops

Lüder Deecke

Department of Clinical Neurology, Medical University of Vienna, Vienna, Austria

Our knowledge about the abilities of man and his brain rests on classical clinical neurology. The old clinical neurologists, [for example Kleist (1934)], studied their patients with their diseases and their neurological symptoms and followed them over years, and finally on autopsy they studied the brain lesion precisely and highly scientifically under the microscope using cytoarchitectonics of cortical areas. With this they were then able to correlate the clinical picture and its neurological deficits with the lesion. Lesion experiments can be performed in animals, not in man. If one, however, studies the "lesion experiments" that nature does (diseases), one has lesion experiments in man! This large body of classical knowledge of brain function has led to two theories (models, Hal Weinberg calls them concepts) of how the brain functions: (1) *A hierarchical system* of centers ordered side by side or on top of each other – in favor for this system are the specific functional deficits secondary to localized, acute cerebral lesions, also the results of functional magnetic resonance imaging serving as a proof that Kleist (1934) with his map and his contemporaries were basically correct. (2) Since Lashley (1931) "mass action principle," which does not hold for rats only but was confirmed also for man, namely for children (Kornhuber et al., 1985), *a distributed system*, in which, by nerve fibers, most of the brain is connected with many other centers, and this system achieves its performances always by distributed cooperation – in favor for this system are the associative memory and the gradual recovery of function (with the help of active training in neurorehabilitation) after lesions, but also the histology and hodology of cerebral networks. In the past, these two principles were discussed on an *either or*-basis as Hal Weinberg points out and heavy debates and scientific disputes and controversies were fought between scientists and schools of proponents in favor of localized function and those in favor of distributed function ("localizationist" against proponents of distributed function in networks). However, the debates are no longer necessary, since an *as well as*-basis is realistic (Kornhuber and Deecke, 2012), i.e., both principles are obviously realized in higher brains (Mountcastle, 1998). So we are now beyond these century long struggles and controversies.

In its activity the brain can achieve astounding performances, which we are mostly not consciously aware of: For instance the visual perception of a figure on a moving background (e.g., permanently necessary when driving a car) requires numerous multiplications carried out in a decentralized manner in the distributed systems of the brain. On the other hand, our ability to mentally go back vthe way in time of our own acting and experiencing and also the fates of companions in life, i.e., episodic memory, requires self-leadership with the high art of management, and this leadership is organized by the prefrontal cortex within the hierarchical system (Wheeler et al., 1997) – of course with the support of the distributed, associative system.

THE BEREITSCHAFTSPOTENTIAL

In 1964, my mentor Hans Helmut Kornhuber (1928–2009) and I recorded brain activity in the EEG preceding willful (volitional) actions (Kornhuber and Deecke, 1964). The term *readiness potential* was offered but *Bereitschaftspotential* (BP) was preferred (a German word in the English language). The BP was not a serendipitous discovery – we were actively searching for signs of self-active intention and will.

The method of reverse averaging was developed in 1964. Simple movements (rapid flexions of the forefinger) have to be *monophasic*. Using wrist extension and flexion in one flick of the hand is not good, since this employs two movements instead of one.

We found the BP in 1964. The full paper was published in 1965 in Pflügers Archiv – a citation classic (Kornhuber and Deecke, 1965).

In 1978, another citation classic appeared (Deecke and Kornhuber, 1978) with the important finding that the supplementary motor area, SMA is active prior to willful actions and also prior to the activation of motor cortex (M1, Brodmann Area 4). For review of the history cf. Deecke (2014).

In 1982, I was invited as Visiting Professor by Hal Weinberg to the Simon Fraser University Burnaby, Greater Vancouver. Hal had as one of the first an MEG. At that time with one channel only. It has been hard but it has been worth the effort in long nocturnal experiments (because at day time cars caused artifacts) to map the magnetic field lines with voluntary hand and finger movements on the skull and to establish the electrical dipole (Deecke et al., 1982). Then also foot and toe movements were investigated (Deecke et al., 1983), as well as the MEG prior to speech (Weinberg et al., 1983). In our Vienna MEG we intensely investigated the voluntary motor system with MEG, e.g., Kristeva et al. (1991). An important achievement was to prove the SMA activity, which is so nicely seen in the EEG also in the MEG. I was puzzled that we found that the Bereitschaftsmagnetfeld, Bereitschaftsfield (BF) has a later

onset time (about 500 ms prior to movement) than the BP or in other words: while it is relatively easy to record the late readiness field (BF2) in the MEG and map it to nice Penfieldian homunculi (Penfield and Rasmussen, 1950), thereby proving that BF2 is, indeed, generated by Brodmann's area 4 (Cheyne et al., 1991), MEG localization of the early BF1 generator was less readily achieved. The reason is that in the healthy subject, both SMA generators are active even in case of unilateral movement. Due to the anatomical localization of the SMA on the mesial surface of the hemisphere, the two SMAs are facing each other and partially cancel each other out, while the CMA activity is more or less a pure *radial* dipole that escapes MEG detection. The solution was found by two strategies:

(1) We made experiments using the BP paradigm in a patient with a right SMA lesion caused by a stroke (Lang et al., 1991). In this patient having only one remaining SMA (the left) performing voluntary flexions with his right index finger, the results were quite convincing: In the early phase of the readiness magnetic field (1200–800 ms prior to the onset of movement, BF1 corresponding to BP1) field lines were going out of the head at the vertex (Cz) and were going into the head at a frontal position between F3 and Fz. They thus enveloped an electrical dipole on the mesial surface of the left hemisphere in the left (intact) SMA. A similar dipole was found during the period of 800–600 ms prior to the onset of movement, still corresponding to the BP1-SMA system. However, in the late phase of the Bereitschaftsfield (BF2 analogous to BP2), in this case measured between 200 and 0 ms prior to movement onset activity had shifted: Magnetic field lines now left the head at FC3 and entered the head at FCz. This indicated an electrical dipole in the left area 4 hand representation (M1, motor strip). This again supports our finding that the SMA/CMA *leads* the M1 motor cortex activation prior to human voluntary movement. The SMA/CMA system is obviously needed for simple movements as well in order to prepare for the volitional, endogenous movement (it is the self-initiation that requires the SMA!), albeit more so for complicated movements.

(2) The second strategy to try to find the SMA activity prior to movement in the MEG, i.e., the early BP component, BP1 or its MEG equivalent BF1 is that other MEG experts told me it should be possible to detect it in the intact subject as well. Although always both SMAs are normally active even preceding unilateral movement, the *contralateral* SMA activity should be somewhat stronger than the ipsilateral one for unilateral movement. A finger tapping task of the right fingers has been employed in 8 normal volunteers who were recorded in our 143-channel whole scalp MEG system (CTF Inc., Vancouver) at the Department of Clinical Neurology Medical University of Vienna accommodated in a magnetically shielded room (Vacuumschmelze, Hanau, Germany) in the middle of the night, when the strong dipoles of the streetcar overhead contact line has been switched off. Indeed, under these quiet conditions, the pre-movement SMA activity of BF1 between about 1.5 to 0.5 s prior to movement onset was successfully recorded. The left SMA dipole was stronger than the right one: dipole moment contralaterally 2.4 nAm [nano Ampère meters] as compared to 1.6 nAm ipsilaterally (Erdler et al., 2000). The MEG is also very important for epileptology (Pataraia et al., 2005).

In 1984, we used visual tracking movements and found evidence that the frontal cortex is starting and supervising the tracking but not executing it, *delegating* this to the "expert systems" visual cortex and M1 (Lang et al., 1984).

In 1999, Cunnington et al. found event-related fMRI time courses resembling the BP, only having a later onset time (Cunnington et al., 1999). In 2002 and 2003, Cunnington et al. introduced the term *Bereitschafts-BOLD effect* in these event-related fMRI studies (Cunnington et al., 2002, 2003).

In conclusion, we can state that the first component of the BP (BP1 or BP_{early}) is generated by the SMA proper, the pre-SMA and also the CMA (cingulate motor area). The second component (BP2 or BP_{late}) is generated by the primary motor cortex M1. Against previous belief, the intentional activity is not traveling directly from the SMA to M1 but runs via the motor loop. This means that the formation of will has already taken place in the frontal lobe, and the preparation for movement is initially handed over to unconscious routine processes of the basal ganglia which do the groundwork for M1. M1 gives the last command (Deecke and Kornhuber, 2003; Kornhuber and Deecke, 2012). During BP1, we do not yet consciously perceive our own motor planning, but during BP2 we do. From this observation Libet et al. (1983) concluded (incorrectly) that we do not have free will in the *initiation* of the action (BP1) but in its *control* (BP2) we have. Yet we (Kornhuber and Deecke, 2012) show that consciousness is not a prerequisite for *free will*. There are conscious *and* unconscious agendas in the brain and both are important. *Ergo:* Free will is involved in control *and* initiation (Deecke, 2012).

Ross Cunnington with his Brisbane team in Australia has performed further important research on the CMA. He made the impossible possible, i.e., succeeded in recording the EEG during the very session of the subject in the fMRI machine (*concurrent* EEG and fMRI recording). Furthermore he employed *single trial* correlation analysis. The respective paper is already accepted in *J. Neurosci.* (Nguyen et al., 2014). They found that greater amplitude of pre-movement activity associated with the BP is also associated with greater activation in the cingulate cortex, specifically the anterior mid cingulate cortex (aMCC). Ross noted: We have also now added connectivity analysis which has been really interesting. It suggests that the cingulate cortex and supplementary motor area have reciprocal connections that excite each other and therefore sustain each others' activity before movement. It therefore appears that sustained pre-movement activity arises from this reciprocal "self-sustaining system" of the cingulate and the SMA, maintaining each others' activity in a loop in readiness for action, until some other signal comes to initiate movement.

That means we envisage that these loops are running, and a *running loop* exerts a type of *pre-tension* to the structures it influences – makes everything sensitive, sensitizing or priming the preparation of the whole pathway – facilitating it in the way that movement can be elicited "just like that" (flipping a finger). I would like to stress that the system then works quasi threshold-free. Ross answered: I agree completely with that view of motor loops, exciting the system so that it is "primed" or ready for action ("*Handlungsbereitschaft*") so that only a very small impulse is needed to trigger movement onset.

So the newest information on the CMA, specifically the anterior mid cingulate cortex (aMCC) is that there is an additional loop – maybe still more – (re-entrant cycle) between CMA ↔ SMA, the early motor loop, while the cortico-basal ganglia-thalamo-cortical re-entrant cycle is the late motor loop. What I am trying to say: It is not just connectivity, which has to be considered in the frame of Bereitschaftskomplexität, it is this very special connectivity, the re-entrant cycle connectivity. These feed back loops are of utmost importance and will even gain in importance in the future, and I am not exaggerating when saying: The extraordinary fine-tuning of all biological control systems by means of negative feedback loops is a true evolutionary marvel (Bauer, 2015). It is my credo that we have to *think in loops*! For instance Parkinson's disease cannot be understood without looking at it with the motor loop in mind. And also for the "early motor loop," the CMA (aMCC) ↔ SMA-loop, which as a "running loop" primes readiness for action, there is a clinical syndrome: If this loop is downregulated, the consequence is a disturbance of spontaneity. This can be present to the extent of the pathologic condition called "akinetic mutism," which is the medical term describing patients tending neither to move (akinesia) nor speak (mutism), they are not paralyzed though but lack the will to move, they describe this that as soon as they "will" or attempt a movement, a "counter-will" or resistance rises up to meet them (Ziegler et al., 1997).

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Bereitschaftskomplexität: new approaches to image complexity of dynamic brain activity

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Since the discovery of brain oscillatory activity, the ability to decode information from brain oscillations promised a better understanding of the basic principles of brain function. However, partly due to limited computational capacities, most established measures of task-free and task-related brain activity are based on averaged amplitude or source power, while the electric or magnetic signals recorded at the millisecond-to-millisecond range exhibit chaotic and highly complex features related to dynamic state transitions not reflected in these measures. These state transitions, however, can be characterized by entropy measures, e.g., rank vector entropy (RVE), a non-parametric partial symbolic analogue to metric entropy that ignores the absolute signal amplitude in favor of its relative amplitude within a given sampling window, and converts the measurement values of a short sequence of samples into a rank ordered one-dimensional embedding space. We found that the same state change resulting in a slow negative potential shift preceding voluntary movements by up to 2 s (<0.1 Hz) introduced by Kornhuber and Deecke (1964) as Bereitschaftsfield (BF) can be detected by applying the RVE algorithm to broadband beamformer-processed magnetoencephalographic (MEG) data (4–150 Hz). Due to the similarity to the BF, we refer to the RVE waveform associated with voluntary self-paced movements as Bereitschaftskomplexität. While undetectable in these frequency bands (4–150 Hz) using conventional methods based on averaging amplitude or power, our finding indicates that RVE can reveal such information and might be a powerful tool to investigate causal links between dynamic brain states and human behavior that were previously inaccessible.

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The beginning of a new look in the understanding of brain function: systems of the brain related to the processing and utilization of information may be different for different individuals

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SUMMARY

The history of brain physiology in the last 100 years is actually the history of a pendulum swinging back and forth, from the concept of localized function, to the concept of distributed function through physically distributed interacting and dynamic systems.

Until recently individual differences in the imaging of brain function were described primarily in terms of deviations from the average variability in measurements. However, recently it has been possible to begin an understanding of how different brain systems change as the result experience, and how these systems, and their changes, are responsible for different people being different people. Magnetoencephalography currently may have the best potential to measure individual differences in the brain, because of its time resolution and its ability to directly measure the function of neuronal systems in real time without the use of high frequency or chemical impositions on that function.

However the increasingly advanced technology of all methods of brain imaging will be able to recognize and document individual differences – and to predict how those differences may impact the current and future life of an individual. The implications of this for the treatment of disease and behavioral disorders and for the prediction and control of individuals could change our current concept of, and acceptance of, individuality and the diversity of a society.

INTRODUCTION

What I would like to discuss are ideas about brain function that resulted from the developing technology for imaging distributed, dynamic and interacting systems, and how that technology continues to influence the concept of brain systems related to complex information processing, and the implications of this for the diversity and character of the human species.

The history of attempts to understand brain function date back to 1700 BC when Aristotle, thought the heart, not the brain, was the location of intelligence.

Ancient Egyptians were probably the first to distribute written accounts of anatomy of the brain, and that anatomy was considered the primary determinant of human capabilities. Sources of function were defined by anatomy, and as technology progressed, those sources, i.e., areas of the brain, were identified as responsible for complex information processing and behavior.

In the last 50 years, the pendulum was swinging back and forth from the concept of localized function to the concept of broadly distributed function through interacting and dynamic systems, i.e., systems that are always changing.

The early concepts of specific localized functions (Figure 1) for specific areas or parts of the brain has a long history that includes studies of brain stimulation and lesions of specific areas for the treatment disorders like epilepsy, and the

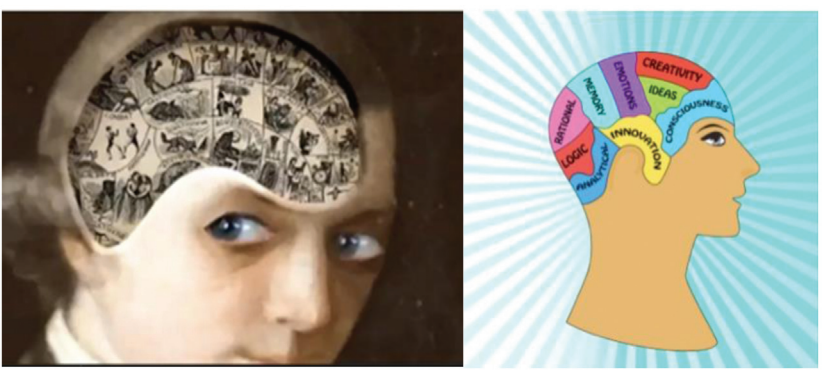

Figure 1: Illustrations that underline the concept of localized brain function.

use of frontal lobotomies to treat behavioral disorders. Lesions of the brain that destroyed large areas were done not because it was assumed there was distributed function within those areas, but rather because of a lack of sophisticated knowledge of how the brain functioned.

Frontal lobotomies, temporal lobectomies and other massive lesions were justified based on changes in complex behavior that resulted from those lesions, without any clear understanding of how the brain functioned, in respect to those behaviors.

In the late 1950s, I was doing "cutting edge research", i.e., the cutting of medial and lateral hypothalamus to study hunger, thirst and sex (it seemed as if hunger, thirst and sex have always been considered to be related to each other, in one way or another, of course).

At that time, in the 1950s, I wondered, to myself of course, whether a complex function like hunger or sex could be attributed to only one part of the brain – when the history of each individual clearly determined, to a large extent, the way in which those functions were individual – to the individual.

Until relatively recently brain imaging was primarily thought of as a method for measuring only localized function. The imaging methodologies for determining function were primarily the methodologies for specifying the place where that function was located in the brain.

We all know about the first measurement of magnetic fields related to brain function, initiated by David Cohen in 1968 – and without a superconducting quantum interference device (SQUID). The recording was done using a copper induction coil as the detector. The idea was that electrical currents produce orthogonally oriented magnetic fields, and the net currents can be modeled of as current dipoles with a location, orientation and magnitude.

This was, I think, the beginning of the idea to use "dipole sources" in the brain for the understanding of different types of information processing. The first SQUID (Figure 2, right panel) was then introduced, using Josephson Junctions, to detect very small magnetic fields.

Magnet resonance imaging (MRI), functional magnet resonance imaging (fMRI), diffusion tensor imaging (DTI), and magnetoencephalography (MEG) all began with the assumption, or hope that the technology would reveal specific places in the brain that were responsible for complex function. The use of MEG to study brain function has a long history (Hari and Salmelin, 2012). MEG began with the assumption that it was a method for detecting dipoles. Dipoles were originally defined as an electrical source with a particular spatial orientation. The idea was that the source of a field was specific to a specific behavior. The initial assumption was that a single current dipole in a homogenous conducting sphere is the appropriate model for many types of brain activity that are responsible for perception, complex information processing and complex response output. One simply had to find the source – and the technology was developed to move the single channel MEG around the brain to discover that source (Figure 3).

The original assumption was an important justification for the use of MEG as distinct from electroencephalography (EEG), i.e., that the use of a homogenous sphere as the model for the head based on the fact that concentric layers of different conductivity in the sphere have no effect on the magnetic field measured outside the sphere, and thus the identification of dipole sources, were not influenced by the physical structure of the brain or skull.

Thus the idea of a single dipole in a homogeneously conducting sphere came to be the model of sources for complex behavior. Of course an argument at that time was, and still is, whether the dipole is the location of an actual source or rather an index of a complex distributed system (Figure 4, left panel).

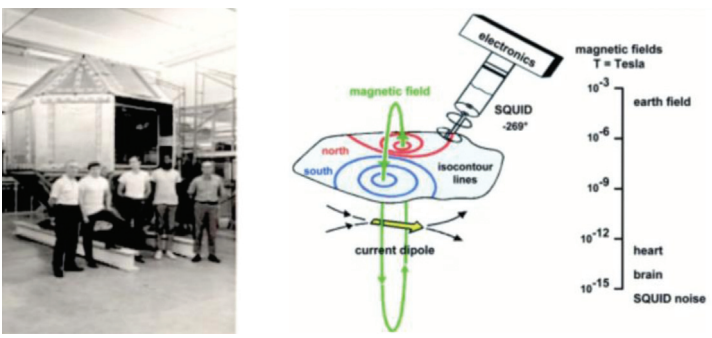

Figure 2: Left panel: photograph of David Cohen amid his colleagues. Right panel: illustration of a superconducting quantum interference device (SQUID).

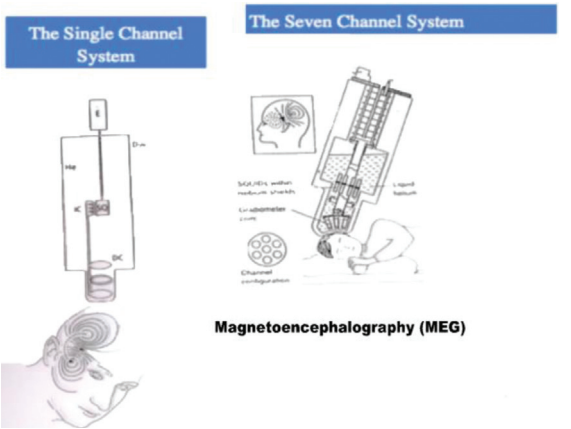

Figure 3: Illustration of a single and seven channel MEG system.

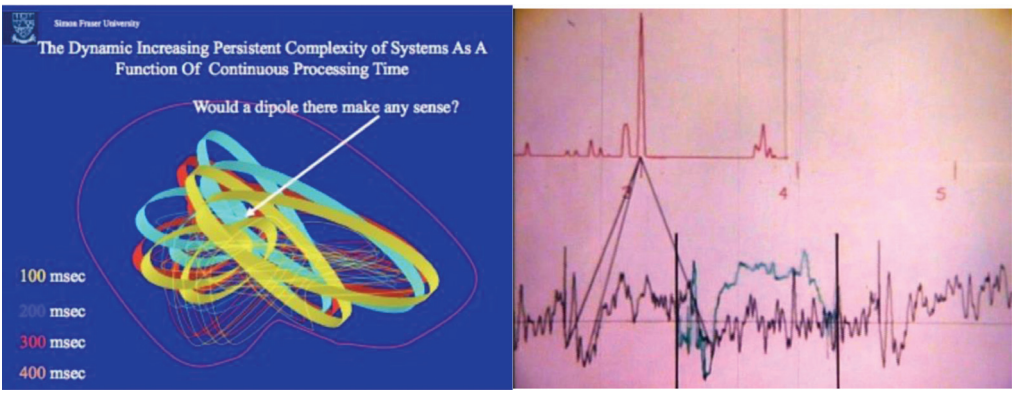

Figure 4: Left panel: increasing complexity of a system as a function of continuous processing time. Right panel: introducing the recognition index.

Later, it became increasingly clear that a single dipole was not a viable explanation of brain function responsible for complex behavior. The dipole then became the "center of gravity" of a system and was, and is now, considered an estimate of, or an average of, multiple dipoles, with respect to both direction and strength of distributed sources.

This idea was the beginning of a change in the direction of the "swinging pendulum" with respect to the definition of localization of function, and brain imaging began to increasingly focus on the distribution of function in the brain. The viability of this approach included all imaging technologies. When I was working at the Burden Neurological Institute with Grey Walter in Bristol England during the late 1960s – a period of social revolution within the Western World – we were doing multifocal stimulation of frontal white, with 64 gold electrodes that were implanted for as long as 6 months. This was to treat obsessive-compulsive disorders. We worked from the midline outward – to lateral structures, and observed behavioral changes specific to individual obsessions after long periods of stimulation (Weinberg et al., 1969).

We thought that we were reorganizing the interaction of subcortical and cortical systems – but of course we really did not know what those systems were. We were doing what most scientists did at that time and what is being done today to a large extent, i.e., trying out a treatment and determining its effectiveness through an observation of brain imaging and behavior. At that time we were using EEG recorded from subcortical sites and we all began to realize that we did not have a real understanding of complex distributed brain function. We began to think about how to measure spontaneous activity of complex systems that were not the immediate result of external stimulation – and so we developed the concept of "emitted cerebral events" – events in the brain that reflected brain activity related to the processing of specific events when those events were not present.

The idea was to develop for each individual a template of the activity that resulted from the presentation of stimuli that originally required a response and then use that template for a match to what was happening in the brain when the

Figure 5: Grey Walter, Rosa Gombi, and Hal Weinberg in 1972.

patient was thinking about an expected but absent event. It was called the Recognition Index (Figure 4, right panel). Of course one thing we found is that the "template" was different in different parts of the brain – but the template presumably reflected what the patient was thinking. Basically the idea was to use pattern recognition as an alternative to signal averaging (Weinberg, 1972).

The reason I mention this now is that it was an example of a methodology that attempted to describe complex distributed brain function using spontaneous activity related to information processing that was different for each individual.

We published some of this in the early 1970s with Grey Walter, Ray Cooper, and with Rosa Gombi who was visiting from, what was then, the Soviet Union (Figure 5).

However, the really important element of this research is that for us it began with the attempt to identify patterns of brain activity related to information processing, that was specific to individuals – the concept that measurement of brain activity related to the processing of the same information may be different for different individuals. I would like to expand on this. I often think of Mozart. Can you imagine how a pianist can remember 10 different concerti – or more – and produce the frequently varied motor output related to those memories, i.e., to produce the same auditory concept? Clearly, a distributed program must exist that includes the use of sensory and motor systems, as well as complex processing and memories that occur when each performance is almost, but not identical to, the last. And of course each musician could have a different pattern of brain activity that results in the same or similar output.

Or think about something "a lot simpler." A person walking from point "a" to point "b." Each person has its own gait, which results from their own input, processing and output systems, although they "perform the same action". As we all know, you can identify someone by their gait – and of course – if one of those legs was amputated would "walking" for that person be located in that leg?

Many of the early studies of brain imaging, and many current studies, continue to be focused on establishing the localized sources of evoked potentials – sources that are described as fixed and stable – and described as an "average" within an individual to deal with observed "variability".

A common example is the P300, occurring 300 ms after an input (Tarkka et al., 1998). Initially P300 was used to identify a location of the processing source, e.g., Hegeri and Frodl-Bauch (1997). It is now clear that the information processing that results in a P300 results from a widely distributed interaction of many areas of the brain between approximately 20 and 300 ms, and is different for different modalities, i.e., that P300 is actually a result of what is going on in widely distributed areas of the brain (Polich, 2007).

Of course a pivotal question related to the degree to which functions of the brain are localized is the definition of localization, i.e., what is meant by localization – and this depends very much on the methodology for recording what is going on in the brain and of course the level of, and characteristics of, the mathematics analysis that determines localization. Here is another analogy. Consider the perspective of someone viewing our earth from distant space. His or her description of its transportation system is different from that of someone who is analyzing the system from the perspective of someone riding on the system. A molecular analysis of brain systems produces a different concept of systems, and therefore the idea of what constitutes a system, and localization of the system, is influenced by the definition of the system.

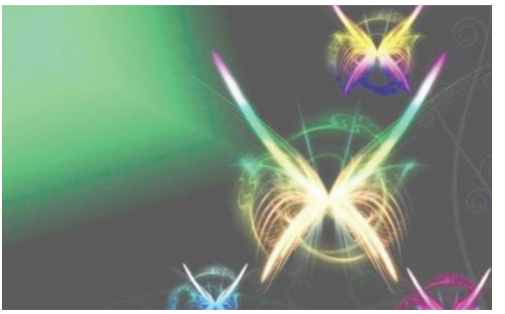

Figure 6: Chaos theory, here illustrated as a high dimensional dynamic system, increasingly influenced neuroscience in the early 90s of the last century.

Invention is of course the demonstration of how ideas drive technology, but in the areas of physiology, although the technology seems to be driving ideas, the technology is still in its discovery stage for the identification of distributed, dynamical systems in the brain, i.e., the measurement of systems in three dimensions of the space, including concurrent measurement of time with the required and defined temporal resolution. The technology is not there yet, but the pendulum is swinging.

The pendulum for EEG was clearly shifting in the late 1990s. For example, Paul Nuñez book on Neocortical Dynamics in 1995 (Nunez, 1995) and Gerald Edelman's book "The Remembered Present" in 1989 (Edelman, 1989), were important in the re-development of ideas of distributed function. Edelman described what he called re-entrant neural networks that were distributed systems, which included the interaction of cortical, thalamic and brain stem activity.

And then there was the application of Chaos Theory as another example (Christine et al., 1990). Chaos theory applied to brain function considers the brain a complex, high dimensional, dynamic system of billions of interacting systems. The underlying idea of using chaos theory to study brain function is that complex function requires an interaction of widespread and spatially distributed parts of the system. The assumption is that everything within the brain is interacting, illustrated by the Butterfly Effect, whereby a single butterfly flapping its wings, e.g., a molecular change in a location of brain, as a result of input, can cause a "tornado" in the rest of the brain (Skarda and Freeman Walter, 1990).

And then of course there is plasticity of the brain. The whole concept of plasticity includes the assumption that fixed and unchanging localization is not a viable understanding of brain function. Therefore the importance of understanding plasticity is critical to an understanding of the interaction of input and output systems and to the processing information.

Brain plasticity is now clearly recognized as normal brain function related to the acquisition of behavior and information processing and it is now known to be a fundamental property of the brain. Brain plasticity has been implicated in various psychiatric and neurodegenerative disorders including obsession, depression, compulsion, psychosocial stress, Alzheimer's, and Parkinson's disease. Plasticity therefore has become a real challenge to the concept of localized sources in the brain.

Now back to brain imaging in the context of distributed dynamic systems that are unique to individuals, and the implications of this for the character of the human species.

Magnetoencephalography introduced of a new approach to the analysis of complex information processing because of its time resolution, and its ability to directly measure function in real time, without the use of any high frequency or chemical impositions on that function.

When I returned from the Burden Neurological Institute, Max Burbank and his group were developing a single channel MEG system, and we began to collaborate in the development of studies of distributed systems – and at that time by multiple recordings using an MEG that mechanically moved around the head. Of course at that time the idea was that there were fixed systems for processing input, which could be identified by the configuration of dipoles that were computed using different locations of the sensor.

The CTF MEG technology began its development in 1970 (Figure 7). At that time, when everyone was initially looking for dipoles in the brain, I remember asking if MEG could discriminate between excitatory and inhibitory systems. Inhibitory functions are of course critical in an understanding of distributed interacting systems, and in the 1970s I organized several symposia through the Canadian Psychological Association to discuss the question of whether the contingent negative variation (CNV) was a unitary potential – what Grey Walter had suggested in the early 1960s.

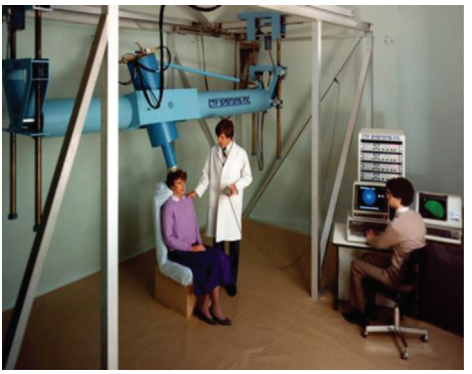

Figure 7: Single channel third gradient MEG system, 1983.

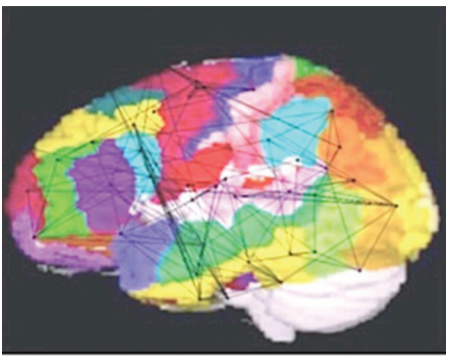

Figure 8: Structure out of chaos: functional brain network [see Van Straaten and Stam (2013)].

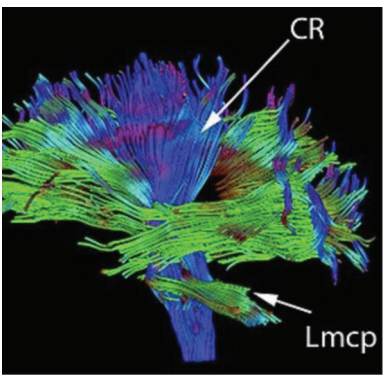

Figure 9: CNS clinical operative monitoring. CR, Corona radiate; Lmcp, left middle cerebral peduncle.

THE NEW LOOK

Current technologies are now focusing on the new look in brain imaging, i.e., a focus is on individual differences in brain systems, and the control and modification of individual's capabilities. Is it time to stop describing an individual with respect to the central tendency, and a standard deviation of a group to which that person is assigned. Each brain is different and that is why we are different people but there is very little known about how to compute or control those different systems of the brain. One of the new efforts to understand individual differences and the use of those differences is the consortium of Washington University, University of Minnesota and Oxford University and others to begin a comprehensive mapping of human brain circuitry in healthy adults using methods of non-invasive neuroimaging to understand brain system connectivity, its relationship to individual differences in circuitry of the brain and the influence of those systems on behavior – i.e., the Connectome Project (Figures 8 and 9).

Figure 10: Illustration of graphic analysis (left panel) applied to children with Down syndrome (right panel).

A primary goal of the Human Connectome Project (https://humanconnectome.org) is to understand individual differences in patterns of connectivity within the brain and how this variability is associated with alterations in the cognitive and behavioral variables that actually "define" the individual (Zhang et al., 2014). Presumably the result will be an understanding and possible control of the relationship between individual brain function and individual behavior, and the personal characteristics of information processing.

An example is the use of 90 cortical and subcortical sources to estimate a connectivity matrix defined by six frequency bands, recorded in patients with Autism and in healthy controls. The data is the degree correlation of activity in different nodes to indicate the extent to which different nodes are connected to each other.

The use of a graphic analysis of correlations of activity in distributed dipole locations is a new methodology for differentiation of systems, e.g., Ye et al. (2014) (Figure 10, left panel). The approach regarding recognition in distributed systems is to reconstruct activity – either resting or task based, and then filter into different frequency ranges and extract regional phase synchrony, calculated between regions. Machine learning is then applied to distinguish between the distributed network characteristics in different experimental groups and with a sensitivity and specificity that can be useful at the single subject level.

When we introduced the MEG to the BC Downs Syndrome Foundation, the funding and enthusiasm we encountered was built around the idea that the MEG could identify the characteristics of specifics of individual information processing, and of motor capabilities for each child who had Down's Syndrome (Figure 10, right panel).

The concept was to individualize training based on brain imaging and to maximize the capabilities and contribution to the society, of each disabled person, and to facilitate their development of themselves – as individuals.

What will this world be like if the new look for brain imaging is to combine imaging with an increasingly complex computational neuroscience, i.e., the study of brain function in terms of the information processing properties of individual dynamics, and of individual distributed systems (Bullmore and Sporns, 2014; Lv et al., 2015) in the individual brain. What are the possible consequences of being able to identify the characteristics of, and potential for, different kinds of behavior and information processing.

Does that dynamic interaction of systems in the brain actually constituted "the individual"? What are the distinctions between individual and societal advantages to this future capability of neuroscience? Will the technology result in the ability to change a brain, of course if the individual "consents" to have his or her brain changed to maximize their potential – I think we can all see the issues that evolve. There are of course positive and negative consequences of a real understanding of the potential of each individual, and the control of that potential for purposes of "what are".

What would be the current response of the society if control were able to stop the killing of people by people – and would that be a good thing? Of course the answer today is no – since the killing of people now is for the purpose of control.

And then there is the question of how these decisions about control are made and is the ultimate consequence of the uses of science to understand the human brain a negative or a positive future for the human race?

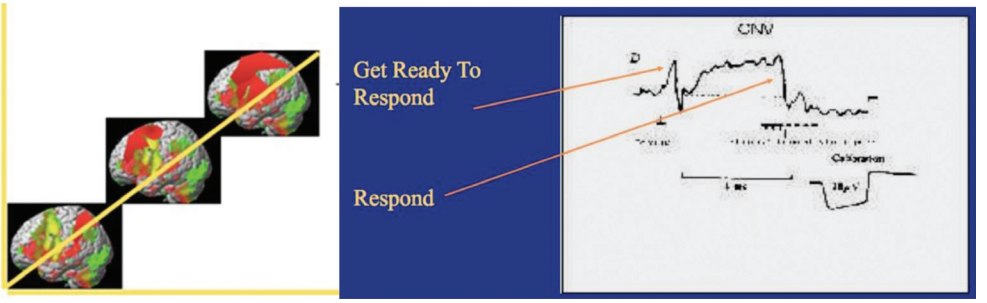

Figure 11: Left panel: increasing complexity. Right panel: illustration of the contingent negative variation (CNV) as described by Walter et al. (1964).

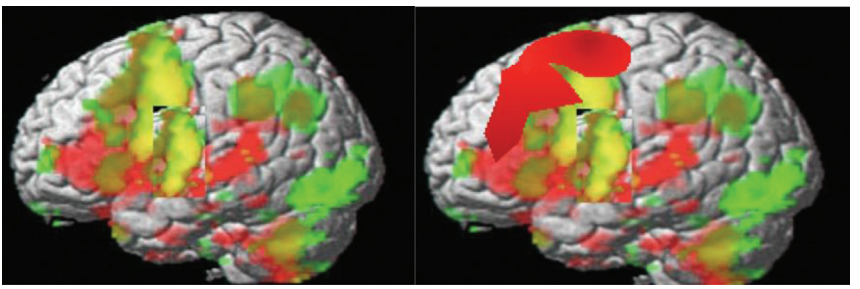

Figure 12: The idea: prediction of future capability based on brain imaging. Different activation patterns predict e.g., capacity to solve problems in different cognitive domains.

The CNV was originally described by Walter et al. (1964) (Figure 11) and was one of the first "event related potentials" (ERP) recorded with EEG and related to the brain process of "expectancy". It was clear however that the CNV had a different configuration for different individuals and changed with experience of the individual with respect to the processing of information that was used to implement the CNV.

The technology now is close to being able to identify different system configurations for the same external information that are unique to different individuals receiving that information. What would be the consequences if there was a recognition index of each person for different types of information? What could be the consequences if brain imaging could predict an individual's future learning, their future criminality, health-related behaviors and potential response to drug or behavioral treatments, i.e., the personalization of educational and clinical applications?

An example is the studies of Dr. John Gabrieli (Gabrieli et al., 2015) of the Massachusetts Institute of Technology (MIT) in Cambridge and his colleagues who describe the predictive power of brain imaging across a variety of different future behaviors, including infants' later performance in reading, students' later performance in math, criminals' likelihood of becoming repeat offenders, adolescents' future drug and alcohol use, and addicts' likelihood of relapse (Figure 12).

"Presently, we often wait for failure in school or in mental health to prompt attempts to help, but by then a lot of harm has occurred," says Dr. Gabrieli. "If we can use neuroimaging to identify individuals at high risk for future failure, we may be able to help those individuals avoid such failure altogether." The authors also point to the clear ethical and societal issues that are raised by studies attempting to predict individuals' behavior. "We will need to make sure that knowledge of future behavior is used to personalize educational and medical practices and not be used to limit support for individuals at higher risk of failure. For example, rather than simply identifying individuals to be more or less likely to succeed in a program of education, such information could be used to promote differentiated education for those less likely to succeed with the standard education program."

Koene (2012) has been making the argument for some time that computational science will be able in the future to upload brain systems of the individuals into a computer through an analysis of real time imaging of distributed interacting and dynamic systems – basically that a computer will be able to "read the mind" of the individual. Of course the ultimate idea is that this will be transferred to robotics. Hawking (2015) recently cautioned about the

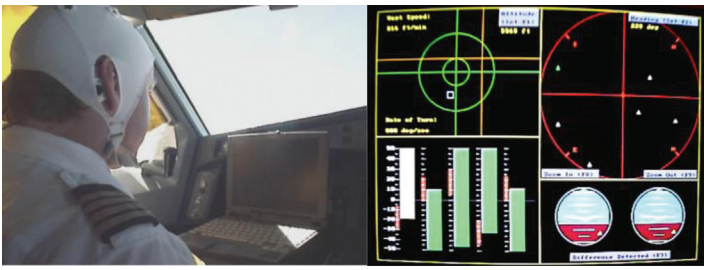

Figure 13: Left panel: Electroencephalography (EEG) and multitasking in the air. Right panel: Multitasking display.

consequences of allowing artificial intelligence and robotics to become the dominant form of control over systems of the human brain.

So there seems to be consequences of an understanding of the diversity of individual minds. One consequence could be the use of that information to structure homogeneity of individuals for control and use, i.e., the future use of an understanding of interacting, distributed systems in the brain could have important unintended consequences.

However, another consequence could be an understanding, encouragement and acceptability of the diversity of complex systems in the brain, i.e., of individuals, and a recognition of the uncertainty principle in the understanding of those systems, i.e., observation of a system may disturb the system enough to make it a different system.

Going back to the old days (1999), these issues were always on the forefront. When we recorded EEG from pilots flying long haul in military planes at the end of the Bosnian conflict and then into Europe, Australia and other places, we were trying to determine the use of brain imaging to establish possible methods for determining individual capabilities for multitasking in the air (I think we were the first to use the term multitasking) (Figure 13). We used gamma activity as an index of distributed networks and this made the pilots unhappy because it identified individuals who should be chosen to fly in circumstances that would require a response to unpredictable events under different levels of fatigue (Weinberg et al., 1999).

If one were to consider the broader implications with respect to the nature of our society as a whole, the question is whether survival of a society depends on acceptability of diversity. The homogenization of ideas has always been necessary for the process of control, and for those who promulgate control this approach would be unacceptable.

The German philosopher Friedrich Nietzsche was, I think, the first to critique what he referred to as the "herd instinct" in any human society. Modern psychological and economic research has identified herd behavior in humans as an explanation of why large numbers of people may act in the same way at the same time. Basically humans seem to mimic behaviors similar to a flock of herding animals, and may not realize that their decisions and actions are largely based upon the requirement to follow what their "herd" is doing, i.e., the group they are following. Each herd includes a leader and the herd follows that leader. The change in this characteristic of brain systems might be implemented in the future by an understanding of how systems of the brain can be modified.

Therefore, recognition and understanding of continuously changing distributed systems of the brain has broad implications for the future of human life on this planet. One consequence could be to increase homogeneity through the control of those systems. However, another consequence may be an understanding, encouragement and acceptability of the diversity of complex systems in the brain, i.e., of individuals and recognition of how that is necessary for survival of the "human" system.

From a broad perspective I think the concept of how we understand the world around us is changing, from a focus on central tendency to an understanding and acceptability of variability. An understanding of the importance and function of variability for survival of any living system is beginning to emerge regardless how molar or molecular is the system. As soon as any system becomes homogenized and variability disappears, the system becomes unable to change – and, conceptually, dies.

What I think will be documented with new technology is that variability of function in the brain is an index of inventive processing, i.e., the analysis of input and the preparation for output, all of which is individual and instrumental for how a species, any species, survives.

Therefore the importance of variability and the understanding of it is universal. An understanding of it is critical, not only for an understanding of underlying principals of brain systems, but also of how humans, of how societies, function. People are different and science should focus on the reasons for those differences rather than on central

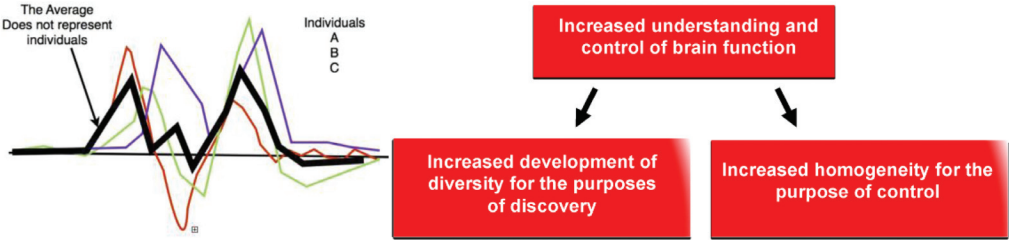

Figure 14: Left panel: the average does not represent individuals. Right panel: the bottom line: will we use increased understanding of brain function to increase diversity or homogeneity?

tendencies. Therefore, recognition and understanding of continuously changing distributed systems of the brain, as a critical characteristic of our physiology, has broad implications for the future of human life on this planet (Figure 14).

Well, I guess what I suggested at the beginning of this is that the pendulum has begun to swing from a focus on localized sources in the brain to an understanding of complex, distributed processing systems.

But what happens when the pendulum begins to swing back again – to an analysis of "molecular" attributes of the "system," e.g., the effect of a small, localized change that could make dynamic changes throughout the brain (the Butterfly Effect)? Well, I guess the answer is that everything evolves – or dies.

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