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COMPORTAMENT**

**COGNITION
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**BRAIN ASYMMETRY IN
DEVELOPMENT, PSYCHOPATHOLOGY
AND EVOLUTION**

Guest Editors:

Joseph B. HELLIGE, Joseph E. BOGEN



**Asociația de Științe Cognitive
din România**

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SPECIAL ISSUE:

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**ASYMMETRIC INFORMATION-PROCESSING IN DEVELOPMENT,
EVOLUTION AND PSYCHOPATHOLOGY**



Joseph E. Bogen
(13 July 1926- 22 April 2005)

ASYMMETRIC INFORMATION-PROCESSING IN DEVELOPMENT, EVOLUTION AND PSYCHOPATHOLOGY

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ABSTRACT

The identification of risk factors that trigger psychosis in later life poses a formidable challenge to medicine. During a field study on lateralized mother-child interaction and based on the hypothesis that brain asymmetry and schizophrenia are functionally related, we discovered a general transformation-law which unifies different aspects of asymmetric visual information processing, hemispheric imprinting, sensory-motor integration, and corollary discharge. Emerging predictions concerning the dimensional conversion of missing information into Kolmogorov entropy were subsequently tested and confirmed in paranoid, schizophrenia by non-linear, dynamical EEG analysis. Compared to matched controls, the schizophrenic subjects showed a significant enhancement of Kolmogorov entropy as well as a stress related reduction in their parasympathetic tone. In the search for candidate genes and the protection of vulnerable individuals, a correlation of these two physiological parameters might present us with a novel diagnostic tool to assess the central dysfunction of schizophrenia before the first psychotic episode strikes.

KEYWORDS: *breast-feeding, entropy, epigenetic, heart rate variability, septal region.*

In the framework of adaptation and natural selection, the propelling force of life is related to survival of the self and the species. In the lowest forms, behaviour is dependent upon direct contact with the environment and is limited to two

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responses – moving towards and withdrawal – in order to preserve homeostasis and metabolism. As organisms progress up the phylogenetic scale, exploration and withdrawal become integrated through higher levels of the neuraxis, and this is accompanied by the development of sensory distance receptors. With the evolution of the cerebral cortex at its climax, behaviour emerges from past learning anticipating the goals for self-preservation and reproduction. One of the most remarkable mental capacities that nature has bestowed upon us human beings is our sense of time in which we exist. We can reflect on our protracted existence that extends from the present back into the past and forward into the distant future, and sometimes we even fathom at novel, previously unlearned things. The ‘representation’ of temporal sequences such as speech is closely related to this kind of awareness and a number of asymmetric brain functions, which have been studied for a long time. The physiological substrate of temporal information processing, though, has remained one of the most mystifying in natural science, despite decades of intensive research by psychologists, anatomists, and clinicians.

Outline of the Article

As space permits simply a broad overview with reference to fuller accounts, in the *first section* a short introduction to information theory is given focussing on its potential in neurophysiology. The application of Kolmogorov entropy (**K**) to brain asymmetry and schizophrenia research, in particular, will be discussed within the framework of the entire article. The *second section* is about a field study on lateralized mother-child interaction and developmental brain asymmetry in the course of which the dimensional transformation-law of visual information processing was discovered. Current concepts concerning brain asymmetry and schizophrenia range between too widely separate extremes: on the one hand, the notion that a relatively recent mutation on a single gene must be responsible (Crow, 2000), and, on the other, the conclusion that a huge array of genes lies at their origin(s). Most controversial, however, is the idea that brain asymmetry might be functional and not directly subjected to genetic influences (Previc, 1991). At the first stage of our investigation, therefore, the conceptual link to altered information processing in schizophrenia (the fundamental nature of which continues to elude laboratory investigators and clinicians alike) was admittedly vague and speculative. Based on the assumption that laterality and prenatal liability to schizophrenia would be related (see for example Gruzelier, 1999; Crow, 2000), we attempted to test Previc’s functional prediction about a possible influence of the utricular organs on the development of foetal brain asymmetry. Yet, in confirming the existence of a symmetrical utriculo-ocular reflex and thus falsifying our initial hypothesis, a more general prediction emerged, and this could be further tested by means of a non-linear electroencephalography (EEG) program. The beginning of the *third section* contains the results showing that the information content **K** of the EEG during a typical left-hemispheric task was actually enhanced over the left brain in

normal subjects, whereas schizophrenic patients showed a slightly reversed pattern. Moreover, the processing of K was significantly increased compared to normal controls, and this pattern appeared to correlate with a particular hypocholinergic stress factor (reduced heart rate variability). Needless to say, no concept so exclusively based on human surface EEG data can be stated in any but very general terms; the value of such studies lies largely in the identification of specific questions that can only be explored by other physiological methods. Upon intracerebral EEG investigations in rats under stress, it has then become clear that enhanced processing of K as well as human brain asymmetry must be viewed as the result of a consistent evolutionary trend that remains to a certain extent fixed. Hence, altered brain-asymmetry during psychosis and other stress related states might constitute a special case of a more fundamental principle of dynamical information processing. The general discussion in the *fourth section* provides a final overview about this conclusion and a focussed description of its related psychopathology in acute schizophrenia, which is best viewed in terms of an asymmetric deficit of the autonomic nervous system.

Information Theory

The central nervous system (CNS) can be regarded, on a functional level, as a complex computational device that transforms incoming sensory information into motor commands so as to act upon the world. The required computations take into account both past experiences and expectations of how the external world would behave. One of the ultimate goals of neuroscience is to identify the principles or single units of information processing performed by the CNS. In their classical works on the *Mathematical Theory of Communication* and *Cybernetics*, Claude Shannon (1949) and Norbert Wiener (1948) laid the foundations for contemporary information coding, and communication. A useful way to think about Shannon's definition of information is that when we observe an event, our uncertainty about the world is reduced. Hence, the amount by which our uncertainty or 'missing information' is reduced correlates inversely with the information content of the event. For example, before a coin is flipped, we are uncertain whether it will come up heads or tails. When we see that it has come up, say, heads, we have been observing an event with probability one-half. Thus the information we have received (the reduction of missing information about the change in outside world) is $I(\frac{1}{2}) = -\log_2(\frac{1}{2}) = \log_2(2) = 1$ bit. If a coin is flipped twenty times or, alternatively, if twenty coins are each flipped together, we receive twenty bits of information. More generally, if an event is almost sure to happen (probability p close to 1), the information we gain from that event is close to zero. If a very unlikely event occurs (probability p very close to zero), we receive much more information. In other words, the bigger the change in knowledge about the event, the more information we have received. Using this basic definition of a single event of probability p , Shannon went on to calculate the average amount of

information carried per symbol in a stream of symbols (e.g., a sequence of words spoken by an individual or a sequence of characters transmitted by a modem over a telephone line). If we have a finite set of symbols $\{a_i\}$, each of which occurs in the stream with probabilities $\{p_i\}$, then the average information in the sequence is given by the weighted average:

$$H = - \sum p_i \cdot \log_2 (1/p_i) \quad (1)$$

This quantity is sometimes called the information entropy, to distinguish it from the physical entropy of thermodynamics, as encountered in physics or chemistry. In fact, however, these two notions of entropy are compatible with each other, and it is not a coincidence that they have the same general form (Shannon & Weaver, 1949; Yockey, 1992; Carter, 2003).

Unfortunately, efforts to quantify information flow in the brain by using the tools of Shannon's theory have not been conspicuously profitable. The reason is what matters in the CNS is not only the uncertainty per se, but also the actual information content of the message in relation to the current state of the organism. Despite the promissory claims in Norbert Wiener's *Cybernetics* (1948), hardly any neuroscientist actually applied information theory to neuropsychiatric problems, 'and by the end of the 1950s even psychologists had lost interest in measuring information rates for sensory-motor performance, mainly because of the difficulty of establishing meaningful probabilities, p_i , for the ensemble of possible responses... What matters about a neural system or subsystem is not merely what it is doing, but the repertoire of alternative modes of action from which what it is doing was selected' (MacKay, 1987, p. 531). The actual problem, however, lies in the information content of the message, and this message 'is a discrete or continuous sequence of measurable events distributed in time – precisely what is called a time series by the statisticians' (Wiener, 1948, p. 8-9). Hence, during his researches on cybernetics, Wiener (1948) recognised that data recorded from physically occurring time series could be mathematically extrapolated. He saw that, if this process could be accomplished with sufficient speed, then the extrapolated values would be obtained faster than the actual physically evolving process that produced the time series, and a prediction of the future would result. The problem of providing predictive output data to forecast the trajectory of aeroplanes and missiles stimulated further research in extrapolation in the wake of World War II, and Wiener composed a purely mathematical treatise, *Extrapolation, Interpolation, and Smoothing of Stationary Time Series*, which was published in 1949, ten years after a note on extrapolation of time series by the Russian mathematician Andrey Kolmogorov had appeared in a French journal. By placing an upper bound on the entropy to a finite string of symbols and by imposing a sequential measure on the phase space of all possible outcomes in a dynamical system, Kolmogorov was thus the first to put probability theory on a rigorous mathematical footing (Zurek, 1989; Li & Vitani, 1997).

It is well known that the information inherent in the flux of signals picked up from the environment by an organism's receptors is highly redundant in the technical sense, and it is just this redundancy which makes perception possible. Perception can thus be defined in information theory as an adaptive sensory-motor response to the challenge of redundancy reduction (MacKay, 1987). In addition, it is desirable to predict the likelihood of such an outcome. In our central nervous system or any other dynamical system of higher dimensions, the flow of information is indeed continuously converging and discarding information H (being essentially defined by Shannon and Wiener as a probability distribution across a representational set of alternatives, from which we may choose in the process of a decision) while generating sequential information in another dimension through 'displaced re-injection' (Zurek, 1989; Rössler, 1979). The resulting information, in turn, can be defined as Kolmogorov entropy by means of shortest possible algorithm able to compress the sequence without loss of information. Physical entropy (S), which according to The Second Law of Thermodynamics cannot decrease within a system, must therefore be viewed as an ensemble of H and K allowing H to decrease while K increases (Zurek, 1989):

$$S = H + K \quad (2)$$

Hence, 'processes which lose information are, as we should expect, closely analogous to the processes which gain entropy' (Wiener, 1948, p. 64). This principle is valid for any information processing system and, despite the different modes of transmission and transformations, applicable to genetics, quantum computation and neuroscience alike (referenced in Fritzsche, 2002a,b).

Mother-Child Interaction and Developmental Brain Asymmetry

There is overwhelming evidence that language processing is localised to specific parts of the cortex, but exactly how such a topological distribution occurs or develops is still under investigation. Listening to filtered speech, for example, which renders most phonemes virtually unrecognizable activates both left and right temporal lobes, while more complex tasks of recognising specific sequences of phonemes involve parts of a larger area including the left inferior parietal lobe and Broca's area (Binder, 2000; Scott et al., 2000). To account for these results it has been suggested, that perceiving phonemes as part of the process of recognizing words in an unconscious, automatic fashion is localised in the superior temporal lobes of both hemispheres, and that parietal and frontal areas, particularly in the left hemisphere, are involved in the conscious use of these sequential representations (Caplan, 2004).

Historically, however, brain asymmetry has been cast in static terms – the left hemisphere being speech related and the right hemisphere visual-spatial. Although this premise has become pre-eminent in clinical neuroscience, conceptual

developments in neuronal information processing and computation are challenging the classic dichotomy. As abnormal brain asymmetry is among the most widely replicated findings in psychopathology, it is important to bring these novel concepts to the attention of psychiatrists and clinical neuroscientists (Podell et al., 1991). Owing to practice and occasional variation with situation, most human beings develop a high degree of sensorimotor asymmetry, the most obvious aspect of which is handedness (Hellige, 1993), and contrary to conventional belief (Broca, 1861; Geschwind & Levitsky, 1968), language functions appear to be essentially unrelated to structural brain asymmetry. Kennedy and colleagues (1999) recently analyzed three individuals with *situs inversus* and found a reversed structural asymmetry, yet, unexpectedly, the usual patterns of left hemispheric language dominance and right-handedness were preserved. Instead, an epigenetic, dynamic factor which influences right hemispheric preference for left-sided cradling and maternal communication appears to be at the core of laterality in humans and apes (Rheingold & Keene, 1965; Weiland & Sperber, 1970; Manning & Chamberlain, 1991; Sieratzki & Woll, 1996). Drawings and *objets d'art* demonstrate that asymmetric child holding preference has been present all over the world for several millennia (Richards & Finger, 1975; Bolton, 1978). To investigate the physiological mechanisms, by which this behavioural pattern primes the development of functional brain asymmetry in the infant, a pilot study was undertaken focussing on mother-child interaction during lateralised cradling and breast feeding (Fritzsche, 2003).

A Primitive-Reflex Stabilizes the Visual Field by Ocular Counter-Torsion

In order to avoid preconditioned or learned breast selection prevalent in western culture, the following field study was conducted in a relatively isolated tribe of the San community in Eastern Namibia. In addition, to ensure minimal disruption of the natural pattern of mother-child interaction, a functional approach by visual estimation was preferred including breast preference, the infant visual perspective of the background optical flow, rotational head tilt and ocular counter-torsion, as well as gender, age, maternal and paternal handedness, sleep-wake patterns, and the emotional behaviour of mother and infant. As most parameters had to be assessed simultaneously and without technical aid, only gaze changes of more than 5 degrees were recorded after initial assessment. The parents were all predominantly right handed as assessed by the preferred skilful use of local tools such as cutting with a knife, sowing seed from a basket, and throwing an arrow at a target.

When not breast-feeding, the infants slept most of the time, but the waking periods usually coincide with breast-feeding. The natural bias for left-sided (71%) versus right sided (29%) breast-feeding among six right-handed San mothers parallels the general human tendency to cradle infants on the left. In addition, trend analysis shows an inverse correlation between the infant's age and left breast preference ($P < 0.05$, $N = 187$, $R = -0.8331$). Hence, the younger the infant and the

more malleable and plastic its central nervous system, the stronger is the tendency to be breast-fed on the left. Only when lactation produced increasing milk pressure in the right breast, did the San mothers start breast-feeding the infant more frequently on the right.

Ocular counter torsion is here for the first time described as a functional primitive reflex. Based upon a fully developed utriculoocular reflex at birth well before the establishment of visual accommodation, it presents a direct insight into the utricular system and its alleged role in the development of functional brain asymmetry (Previc, 1991). In response to sustained head tilt within the gravitational field (Uchino & Isu, 1992), it remains, unlike the vestibuloocular reflex, stable, and counter expectation (Previc, 1991), symmetrical (see Figure 1). The compensatory utricular eye movements, therefore, stabilize the infant's gaze the mother's contour thus splitting the infants' visual field into left and right (Figure 2).

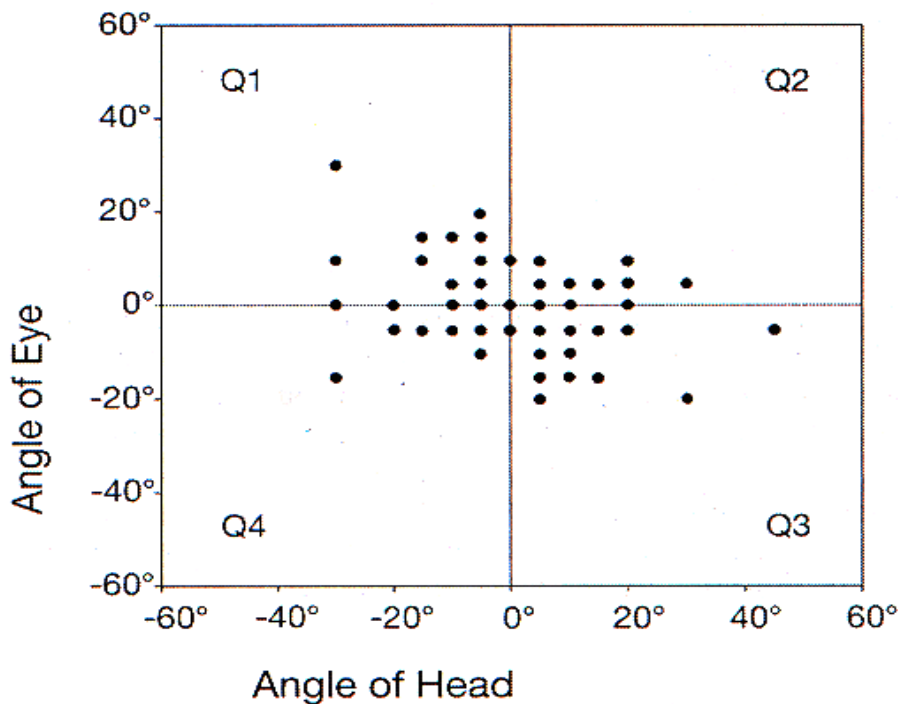


Figure 1 Utriculo-ocular counter-torsion. Sustained utriculo-ocular counter-torsion correlates significantly with the infant rotational head tilt in the gravitational field ($P < 0.000$, $N=187$, $R = -0.3126$). In infants, being preferentially breast-fed on the left, this primitive reflex contributes to the consistent, physiological splitting of the visual field (see figure 2). Reproduced with permission from Fritzsche (2003).

Split Visual Field and Asymmetric Information Processing

During cradling movements and owing to the mother's body screening off the infant's right visual hemi-field, the more salient stimuli of the background optical flow are biased to the infant's left visual hemi-field. Through the chiasmatic crossing, these visual inputs, as well as the mother's moving facial

contour, are then lateralized to the right-hemisphere. Since the visual areas representing optical flow and movement are fully myelinated at birth, the more salient, moving stimuli from the left visual field are consequently lateralised to the infant's right hemisphere – carrying mainly lower spatial frequencies through its immature optical system.

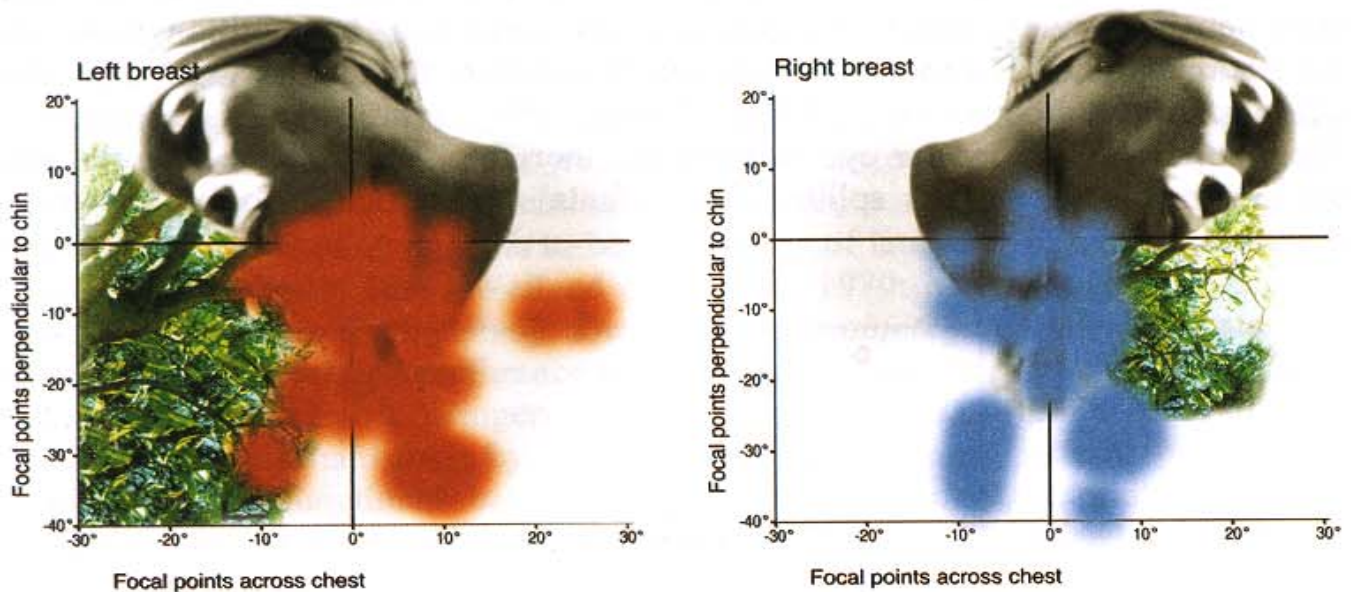


Figure 2 Infants' gaze during breast-feeding. The images are based on a photograph taken from the infant's perspective during typical feeding sessions and depict the sum of 187 superimposed visual fields from the left and right breast divided into degrees and quadrants. Note that the summation of the infants' ocular counter-torsion tends to cluster along the mother's contour along the gravitational midline. In infants, being preferentially breast-fed on the left, this splits the visual field into two representing a right-sided stable foreground and a more salient left-sided background flow (here localised mainly within the lower left quadrant as indicated by the tree). Reproduced with permission from Fritzsche (2003).

To regard the visual 'impulses' that 'flow' along nerve fibres as conveying information is commonplace to date, but how information about the outside world is 'represented' in the brain remains an unresolved question. One of the chief advantages of information theory is that its neurocognitive substrate belongs in a sense to both the psychological and the physiological levels, offering a conceptual bridge by which questions and data at either level can be brought to bear on working hypotheses at the other.

Right Hemispheric Priming for Lower Spatial Frequencies

The question – what can infants see? – has long intrigued laymen and scientists alike. During the early months of life, the refracting power of the infant's eyes including accommodation of the lenses is reduced to relatively low levels of

resolution and, therefore, limited in its transmission of higher spatial frequencies (Held, 1987). Accordingly, the immature optical system preferentially transmitting lower spatial frequencies from the more salient background optical flow in the infant's left visual field compared to the stable foreground in the right visual field (Figure 2) may account for the priming of the right-hemisphere for lower-frequency processing in infants. It is current knowledge that the right-hemispheric preference for lower spatial frequencies and visuospatial function complements the left-hemispheric preference for higher spatial frequencies, speech and other types of sequential information (Bianki, 1983; Hellige, 1995). Not surprisingly, the right hemisphere is functionally more advanced at birth and for some time thereafter (De Schonen & Mathivet, 1989; Chiron et al., 1997; Trevarthen, 2004), while complementary left-hemispheric specialisation for sequential voluntary behaviour appears later in life (Paus et al., 1999).

In Search for a Fundamental Principle

The most satisfying moment in scientific investigation occurs when previously disparate phenomena of unclear origin appear to arise from a common principle. De-emphasising the traditional language/visuospatial dichotomy, Podell and colleagues (2001) propose that task acquisition represents a unidirectional shift from the right to the left hemisphere. While the right hemisphere is critical for the exploratory processing of a novel cognitive situation, the left hemisphere processes established representations and routine strategies such as speech. This developmental theory offers a dynamic, rather than static, view of the functional difference between the two hemispheres. Language acquisition then becomes a special case of a more fundamental principle, which, according to these authors, resolves the emotional ambiguities of missing information. How can we bring this view in line with the characteristic hemispheric preferences for lower versus higher spatial frequencies?

Dimensional Conversion of Information

Hopfield (1997) proposes that the reduction of sensory inputs down to a limited set of receptors or dimensions, as a general principle of information processing, extends to other modalities including audition and language. Thereby a signal can be transmitted with an arbitrarily small error frequency only if enough redundancy is included to correct for errors of noise (Shannon & Weaver, 1994). Yet, the higher the redundancy, the lower the range of available information conveyed in the signal, as shown in Shannon's channel capacity theorem. Since this constraint applies to all information processing, a common computational approach is to consider how a system removes redundant information (Reich et al., 2001) as the signal passes along its pathway. In the visual system there is compelling structural evidence of such a transformation from the retina with over 100 million photoreceptors to the optic nerve with only 1 million optic fibres. In addition, reduction of redundant information occurs, while visual information is

transformed from a higher to a lower dimensional mode of processing (Field, 1995) by removing higher spatial frequencies (Reich et al., 2001). Yet, transforming a set of higher dimensional co-ordinates into another set of lower dimensional left-hemispheric order will not alter the total information. Instead, the redundant information inherent in the frame of reference of higher spatial frequencies must be transformed from a higher into a lower dimensional order of Cartesian power (Field, 1987). Prompting the characteristic lower dimensional left-hemispheric categorical system (see Hellige, 1995), such a dimensional conversion of information simultaneously accounts for the selective reduction of redundant higher frequencies in the left hemisphere.

A simple visualization of this dimensional order is given by the familiar example in geometry of two or more dimensions, in which the Cartesian power of the coordinates is given by a space (x, y, z) or a plane (x, y). The genetic code provides a specific example of dimensional reduction of such a Cartesian power comprising an initial set of four nucleotides (T, A, G, C). Given a source and a receiver, the mapping of the symbols of one alphabet to the other alphabet is called a code. The DNA and mRNA genetic codes, for example, have 64 code words made of triplets in the third Cartesian power from the alphabet of the four letters. Information containing the alphabet of 20 letters of the first Cartesian power, namely the proteinous amino acids each being present or not (= one bit of information), is thus always transferred from mRNA, the source, to protein, the destination, and not vice versa. In other words, by discarding redundant information during dimensional conversion, the flow of genetic information (Kolmogorov entropy) becomes irreversible (Yockey, 1992). This principle also applies to the visual system, in which the dimensional conversion of signals discards information by stepping from the higher to the lower Cartesian power (Field, 1995). If, in a three-dimensional space all the data fall in a plane, it is possible to apply a transform such that all the information in the signal is represented with only two vectors. Due to the loss of redundancy, the description of the signal with these two vectors has consequently less redundant information, and the information within the two-dimensional subspace captures most of the variation with the smallest number of cells. The synaptic changes between the cells in the visual pathway will subsequently result in a representation of what is unique to that input, rather than what is common across all inputs (Field, 1995). Throughout the visual transformation of a higher to a lower dimensional set, the reduction of Shannon entropy necessarily increases the information content of the signal. And according to equation 2, it is here conjectured, this increase contributes significantly to the asymmetric left-hemispheric preference for sequential motor information processing and speech later in life. Left hemispheric mental processes are primarily mediated by established information content, whereas the right hemisphere is critical for the exploratory processing of novel situations, namely missing information, to which none of the representations or strategies pre-existing in the individual's cognitive repertoire readily apply (Podell et al., 1991). The

results not only corroborate the long held hypothesis that brain asymmetry is functionally constrained at the individual level. They are also in line with the assumption that the right hemispheric processing of information precedes, and goes beyond, left hemispheric linguistic function.

Dimensional Conversion of Speech and Meaning and its Psychopathological Reversal

Compared to brains of other mammals the brain of a newborn human infant exhibits two remarkable features. It already has a complex anatomy – all major systems are present in various states of immaturity – and even in its half-developed stage, the human cortex is extremely large. This being in line with the principle that the longer a mammalian species lives and learns from experience the larger is its forebrain. Soon after birth the neuronal networks are being transformed, and some of its tissues and axon pathways develop over decades, responding to exercise and education (Trevorthen, 2004).

According to Lev Vygotsky (1987), mental development constitutes a conversion from the whole to the part, or an integral-to-separable shift by which children categorise their world (Keil, 1987). At the input level, children cannot perceive the different dimensions of adults separately, or do not know which dimensions are more important than others, since they treat all dimensions as a complex clustering across all dimensions. With increasing knowledge and experience, they begin to perceive the dimensions less integrally and learn to select a subset of those dimensions, perhaps only one, for conceptual categorisation (Keil, 1987).

Intriguingly, a reversal of the normal visual acuity of frequency processing has been documented in schizophrenic patients, that is, their visual perceptions were better at detecting lower spatial frequencies, and poorer at detecting higher spatial and temporal frequencies (Schwartz et al., 1987). Leonhard and Brugger (1998) could demonstrate an equivalent dominance failure of left-hemispheric asymmetry facilitating the emergence of delusional ideas in schizophrenic and schizotypic subjects (see also Gruzelier, 1999), and such a psychotic mode of right hemispheric information processing was according to the authors more complex in terms of number and extent of dimensions (Taylor et al., 1999). It is noteworthy that in schizophrenia, the reversal of linguistic expression to this primordial complex pattern of word meaning was first described by Lev Vygotsky more than half a century ago.

Information Processing in Schizophrenia and Normal Controls

Following the characterisation of tertiary neurosyphilis that led Emil Kraepelin (1899) to recognize the distinctive pattern of *dementia praecox* as an organic brain disorder, Eugen Bleuler (1911) coined the term 'schizophrenia', literally meaning 'mind that is torn asunder'. There is now international agreement on its classification, and the clinical criteria based upon characteristic delusions,

hallucinations and lack of insight have high diagnostic reliability. These 'positive' symptoms are often complemented by the 'negative' symptoms of reduced motivation, deterioration of social functioning and affective flattening. The peak age of onset is in early adulthood and the typical schizophrenic course, interspersed with remissions and relapses, requires lifelong medication. Apart from the devastating impact on individuals and their families, this creates a huge economic burden for society.

After a century has elapsed since its first description, schizophrenia still remains a diagnosis of exclusion. One of the first to interpret the origins of psychosis in the light of evolutionary theory was Crichton-Browne, who supposed in 1879 that "the regions of the brain which are latest evolved and which are located on the left side of the brain might suffer first in insanity" (cited by Crow, 2000). Although being inconsistent in terms of methodology and results, the accumulated vast literature supports the view that schizophrenia is characterized by more variable and less complete asymmetry in terms of functional preference (referred to as ambiguous handedness) and brain structure (mainly assessed by autopsy or brain imaging). Yet, there exist no established brain imaging studies, laboratory tests, or neuropsychological test batteries that can confirm this disease to the exclusion of other neuropsychiatric disorders – hence the urgent need for novel diagnostic tests allowing the development of prophylactic and early therapeutic interventions.

Altered Kolmogorov Entropy

One of the most promising findings in schizophrenia research is of abnormal prefrontal activation, particularly in response to tasks that probe executive sequences in working memory (referenced by Goldman-Rakic, 2001). The estimation of dynamical trajectories is impaired (Hooker & Park, 2000) and during acute psychosis, subjective 'internal' time seems to be passing more quickly and physical time (clock time) more slowly than expected, thus merging the passage of time into a 'timeless present' (Melges, 1982). In the build up to such an episode difficulties are typically observed in coordinating simple motor sequences (Chapman, 1966).

Since the information content of any sequence – be it a sequence of DNA, a sequence of numbers, a temporal trajectory, or a sequence of dynamical EEG data – has been defined, and measured at the initiation and conclusion of a each motor activity (Popianov & Dushanova, 1999) as Kolmogorov entropy (K), we tested the hypothesis (Fritzsche, 2002) whether this mathematical parameter could present us with a novel diagnostic method to assess dysfunctional processing of sequential information in schizophrenia directly. The aim of this non-linear electroencephalographic (EEG) pilot study was thus twofold: assessing cortical information processing in schizophrenia compared to normal controls as well as refining the schizophrenic phenotype during numerical backward counting in comparison to the 'passive' background condition.

The clinical and electroencephalographic exploration was performed in a group of 22 patients all suffering from paranoid schizophrenia (according to ICD 10 and DSM IV) with mainly positive symptoms compared to 28 sex- (all male), handedness- (all predominantly right-handed), and age-matched controls (mean-age of schizophrenics: $32.2 \pm \text{SD } 10.41$; mean-age of normal controls $25.5 \pm \text{SD } 7.85$). All sessions were recorded under identical conditions by a conventional 21 channel surface EEG (plus two frontal oculograms for better assessment of eye movement artifacts) recorded over the usual frequency bands from 0.5Hz to 35Hz ($\delta=0.5-4\text{Hz}$; $\theta=4-8\text{Hz}$; $\alpha=8-14\text{Hz}$; $\beta_1=14-20\text{Hz}$, $\beta_2=20-35\text{Hz}$) and the data flow digitized at 400Hz. Given the technical limitations of such digitization and in order to reliably compute the non-linear parameters during a minimum time window of 30 seconds without artefacts, it was in the first stage of this pilot project critical to record stable and thus medicated patients (21 actually being stabilized with classical D2 antagonists, and one by a benzodiazepine). To limit artefacts from eye movements to a minimum, the test persons also had to keep their eyes closed during both background recording and silent numerical backward counting in memory (1000, 999, 998 ...). After 2,5 minutes did the experimenter interrupt the subjects and asked them to say what number they had reached. Throughout the measurement interval, mental operations thus proceeded in a purely internal manner, with no detectable sensory or motor activity. Non non-linear parameters including the maximum second Lyapunov exponent, embedding and correlation dimensions as well as \mathbf{K} were subsequently computed from digitized EEG data by the latest version of NeuroResearcher (R) ' 2005. Owing to limited space, the complex mathematical constraints cannot be described here in any detail; as an introduction, the interested reader may refer to Li and Vitani (1997) or to Elbert et al. (1994). In order to assess the level of psychological stress, the heart rate variability (HRV) was simultaneously recorded by ECG and then computed following established methodology (Ziegler et al., 1992).

As predicted (Fritzsche, 2002b), \mathbf{K} has proved to be a critical marker for schizophrenia. Compared to the matched controls, the schizophrenic patients showed significant increases of \mathbf{K} across all EEG leads, with very high values over the posterior occipital and the anterior prefrontal lobe (see Figure 3). Although there is substantial individual overlap, as shown by the scatter plots, the highest values of \mathbf{K} were exclusively found in patients with schizophrenia. In comparison to the background activity, however, only the normal control cohort scored a significant increase of \mathbf{K} over one left-hemispheric posterior and several prefrontal leads during silent backward counting (compare Figure 3 and Figure 4). The observation that schizophrenia patients exhibited some downward trend, but no significant difference in comparison to the background might be due to a ceiling effect, fixing \mathbf{K} in schizophrenia at abnormally high levels (Figure 4). Yet, this remains a matter of conjecture until further replication in pharmacologically naïve patients.

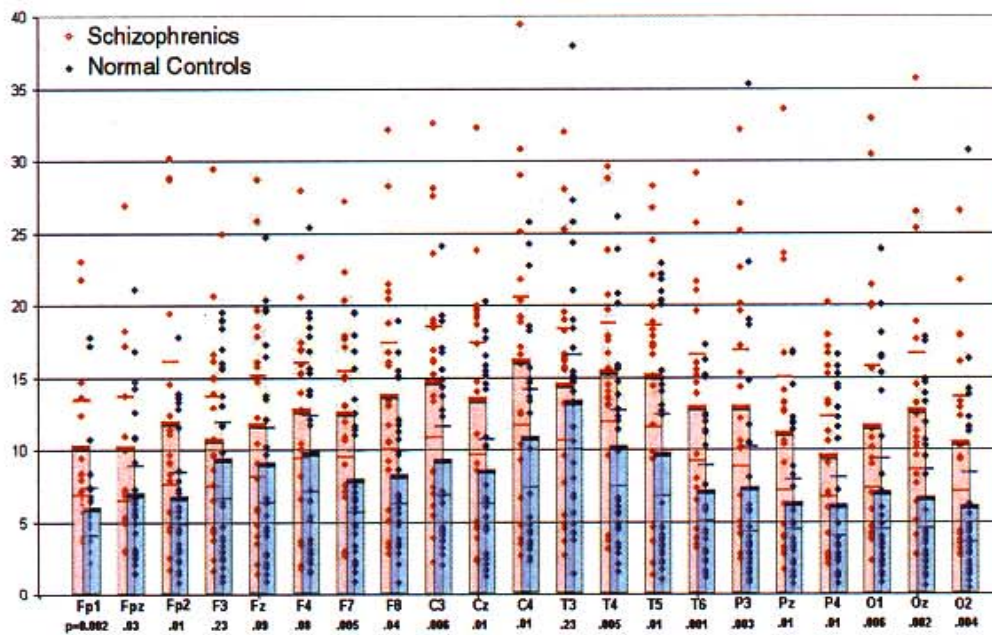


Figure 3 Kolmogorov entropy (K) during background EEG activity. During background activity, the average amount of K shows a significant increase in 22 patients suffering from paranoid schizophrenia over each of the 21 leads, compared to a sex-, age-, and handedness-matched control cohort of 28 normal subjects. The differences are most significant over prefrontal and occipital leads. Although there is substantial overlap with the controls at the individual level, the highest values of Kolmogorov entropy are exclusively found in patients with schizophrenia.

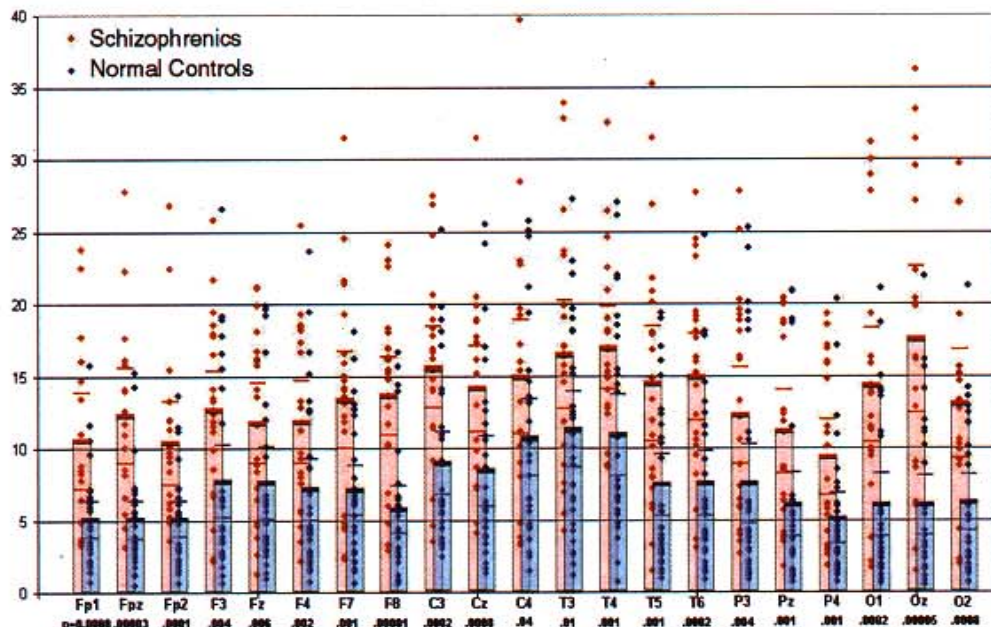


Figure 4 Kolmogorov entropy during silent calculation in memory. While the normal control subjects score a significant increase of Kolmogorov entropy during calculation in memory at the left temporal T5 ($p=0.05$) and prefrontal leads Fpz ($p=0.02$), F4 ($p=0.008$), F8 ($p=0.03$) in comparison to the background activity (see figure 3), the schizophrenic patients exhibit a decreasing trend in the opposite direction. Hence, the average amount of K in the schizophrenic patients shows less significant differences to the control cohort over all leads.

Inverse Correlation of Dynamical Information Processing

During the backward calculation task in normal controls, the average amount of **K** entropy scored a significant increase from 5.03 ± 1.31 to 6.86 ± 1.98 at Fpz ($p=0.02$), from 7.11 ± 2.17 to 9.69 ± 2.62 at F4 ($p=0.008$), from 5.697 ± 1.64 to 8.09 ± 1.82 at F8 ($p=0.03$) and from 7.42 ± 2.13 to 9.61 ± 2.82 T5 ($p=0.05$), while the embedding dimensions decreased significantly from 10.16 ± 0.714 to 9.206 ± 0.72 at Oz ($p=0.03$) (see Figure 5). Taken together, this inverse correlation of -0.33 ($p<0.05$) may illustrate the predicted dimensional conversion of **H** to **K** during the processing of information across a neuronal network (probably involving the paleocortical occipital extension (Pandya et al., 1988)). However, unlike EMG or functional brain-imaging techniques, surface EEGs just 'scratch the surface' and thus rarely capture entire systems. The preliminary result must accordingly be considered 'suspect' until further replication.

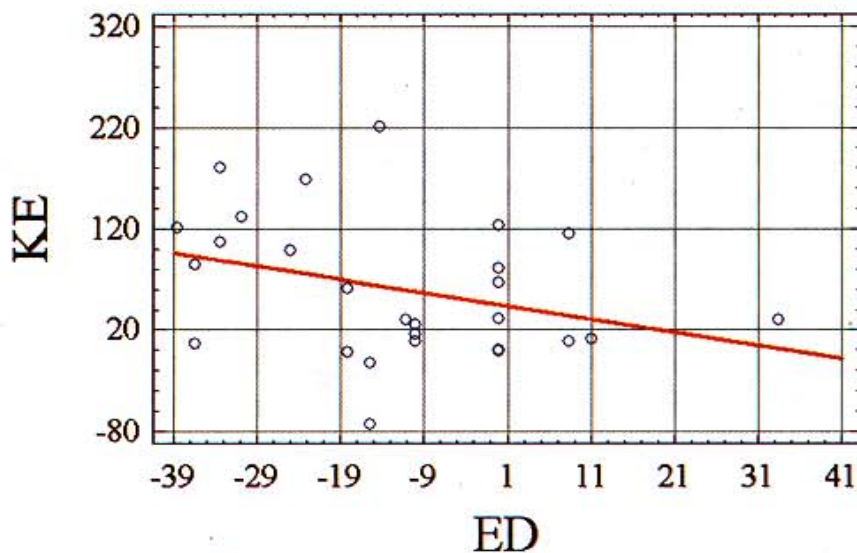


Fig. 5 Inverse correlation of Kolmogorov entropy to embedding dimensions. During backward calculation, the average amount of Kolmogorov entropy (ED) scored a significant increase of Kolmogorov entropy, while the embedding dimensions (ED) decreased significantly over the central occipital lead in normal controls, illustrating the predicted dimensional conversion of information during a sequential working memory task.

Asymmetric Information Processing

Among the non-linear parameter assessed in this study, the Lyapunov exponent, the embedding dimensions and the correlation dimensions showed a consistently symmetric right to left-hemispheric distribution. Only **K** showed significant asymmetries: during background activity, the average amount of **K** scored a left-hemispheric prefrontal distribution of 7.075 ± 1.75 at F7 compared to 5.697 ± 1.64 at F8 ($p=0.005$) in normal controls. In total, 69% ($p<0.01$) of all normal subjects showed such left-hemispheric asymmetry between F7 and F8. This makes sense, as the left prefrontal system appears to be crucial for mental

information processing driven by the contingencies of internal representations (Podell et al., 2001; Laufs et al., 2003). The right prefrontal region, by contrast, is more sensitive than the left to the effects of sensory deprivation. As the degree of sensory deprivation increases (from the eyes open / ears open, to the eyes closed / ears open, to the eyes closed / ears closed condition) a decrease in activity proves more pronounced in the right than the left frontal regions (reviewed by Podell et al., 2001). Hence, during quiet background conditions with eyes closed, **K** tends to be preferentially processed by the left prefrontal region.

During silent backward calculation in memory, the average amount of **K** scored a left temporal distribution of 13.27 ± 3.25 at T3 compared to 10.09 ± 2.61 at T4 ($p=0.007$) as well as 9.61 ± 2.82 at T5 compared to 6.98 ± 1.92 at T6 ($p=0.01$), respectively. This left hemispheric asymmetry in the posterior lobe was also reflected significantly across the individual subjects in 76% ($p<0.01$) between T3 and T4, in 66% ($p<0.01$) between T5 and T6, and in 67% ($p<0.01$) between P3 and P4. This shift into the left posterior lobe appears plausible during backward counting. Left-hemispheric processes have long been noted to be primarily mediated by pre-established routine information, whereas the right hemisphere is critical for the exploratory processing of novel situations to which none of the representations pre-existing in the individual's cognitive repertoire readily apply. These effects have been consistently reported by positron-emission tomography, cerebral blood flow and event related EEG (Podell et al., 2001).

Across all schizophrenic patients, by contrast, no significant hemispheric asymmetry of the total amount of **K** was observed during the background activity, although 66% ($p<0.01$) of the individuals showed a significant left hemispheric asymmetry between P3 and P4. During silent calculation, however, the schizophrenics developed a robust right-hemispheric prefrontal dominance of **K** amounting to 12.70 ± 3.33 at the right dorsolateral prefrontal lead F4 compared to 10.56 ± 3.087 at F3 ($p=0.01$), as well as a left-hemispheric parietal asymmetry of 12.83 ± 4.03 at P3 compared to 9.44 ± 2.78 at P4 ($p=0.03$). This pattern was also significantly reflected across individual data showing a right prefrontal asymmetry at F4 over F3 in 70% ($p<0.01$), as well as a left posterior dominance in 60% ($p<0.05$) at T3 over T4, in 65% ($p<0.01$) at T5 over T6, and in 65% ($p<0.01$) at P3 over P4, respectively. Hence, in addition to the expected left hemispheric advantage of accessing established cognitive tasks in the posterior lobe, in schizophrenia there occurs a right-hemispheric shift of **K** into the prefrontal lobe. Although many of these findings must be regarded as preliminary, they emerge, in sum, as impressively consistent; they are at variance with the normal but consistent with the schizophrenic pattern. For it is currently, but not unanimously, held that prefrontal dysfunction in general and alterations of brain asymmetry in particular (left-hemispheric deficit, left-right shift of cerebral dominance, etc.) are common features in schizophrenia. If this explanation is true, another critical question remains: how can an increase of **K**, particularly over the posterior occipital lobe,

account for the motor deficits in schizophrenia, and how do they relate to psychopathology?

Psychotic, Stress-Related Heart Rate Variability

To underpin our conceptual understanding of autonomic sensory-motor dysfunction and based on the fact that schizophrenic patients exhibit robust reductions of the parasympathetic tone, we proceeded to evaluate the simultaneously recorded ECG from all sessions with respect to HVR. For, currently, influential theoretical models propose a central role for afferent somatic information in the expression of emotional states (Damasio, 1999) by autonomic feedback of arousal, influencing learning and facilitating concurrent and prospective decision-making (Peters, 2000; Critchley, 2005). The additional analysis was furthermore bolstered by the observation that the low HVR in schizophrenia is not caused by typical D2 antipsychotic medication (Malaspina et al., 2002; Bär et al., 2005).

The computational analysis was based upon established methodology (see for example Ziegler et al., 1992) and a computational part of the HRV mode of NeuroResearcher (R) ' 2005. Before evaluation, however, the data used for calculating spectral analysis of the following frequency bands (low frequency of 0.04-0.15 Hz associated with sympathetic/parasympathetic balance and high frequency of 0.15-0.4 Hz reflecting centrally mediated cardiac vagal tone) we visually re-checked and corrected all artefacts within the R-R intervals registered over a time period of 2.5 minutes.

In comparison to the average Kolmogorov entropy between schizophrenics and normal controls (background EEG: $p=0.000003$; calculation in memory: $p=0.002$), the HRV shows substantially less statistical overlap between schizophrenics and normal controls (background: $p=0.0000001$, calculation in memory: $p=0.0000002$) as shown in Figure 6 and 7 on the x and y axis, respectively. The scatter plot in between these two variables yields an even better, albeit not complete, separation between the two groups. We hope that a study under way with pharmacologically naïve schizophrenics and other psychiatric patients would elucidate this option. Yet, far from perfect, it is already a good result because, currently, only pooled averaged data with standard deviations and statistical probabilities of differences from controls are presented for schizophrenia. When individual data are available, however, it is evident that each of the abnormalities reported in the medical literature occurs only in some proportion of individuals. For example, in a sample of schizophrenic brains with third ventricular enlargement, which constitutes the most widely replicated finding and almost twice that of controls ($p < 0.01$), only 12/23 schizophrenic ventricles are larger than the largest control ventricles (Kelsoe et al., 1988).

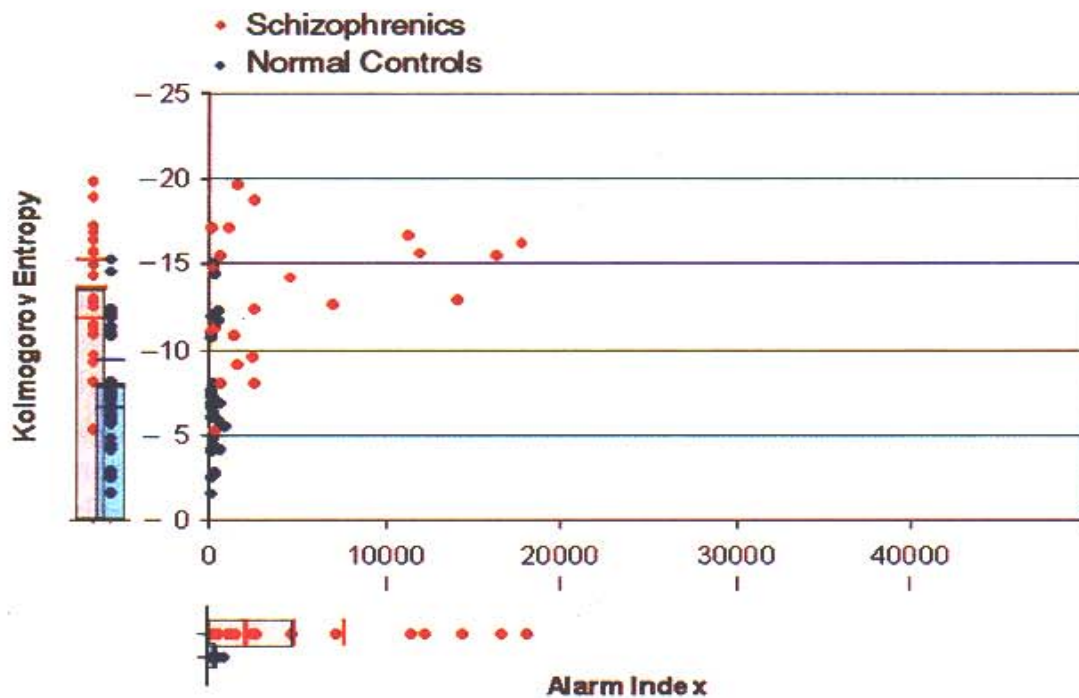


Fig. 6 Correlation of Kolmogorov entropy and alarm indexes during background activity. This scatter plot separates a substantial subset of schizophrenic cohort from the matched controls in between two variables of sensory-motor integration being defined as Kolmogorov Entropy (the data being identical to those on figure 3, yet averaged across all leads) and the extent of the heart rate variability reduction (Alarm Index).

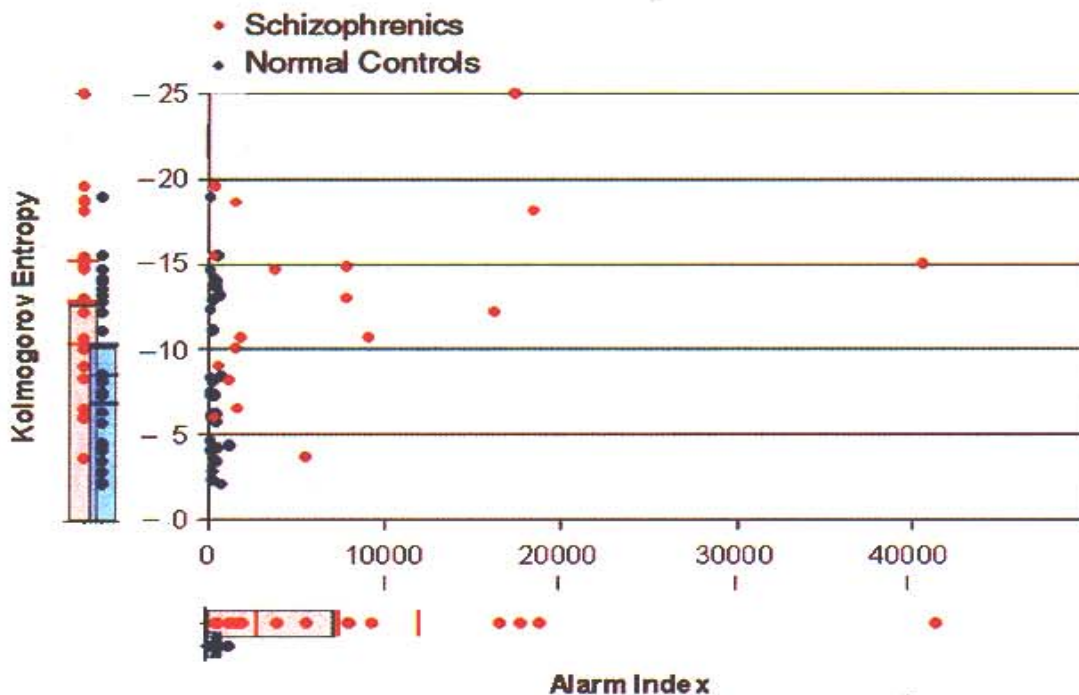


Fig. 7 Correlation of Kolmogorov entropy and alarm indexes during silent calculation. During silent calculation in memory, the scatter plot yields an even better separation between schizophrenics and controls than in the background EEG (figure 6).

The mechanism, which appears to suppress central parasympathetic activity in schizophrenia, is unknown. However, the well established anatomic and physiological lateralisation of the autonomic cardiovascular system at the peripheral level suggests some type of parallel hemispheric lateralisation of autonomic control at the central level, with the right hemisphere predominantly modulating sympathetic tone and the left hemisphere modulating parasympathetic tone. While its cortical organisation has remained elusive for a long time, regional cerebral blood flow during autonomic cardiovascular arousal reportedly increases in the brain stem and the right anterior cingulate and insular cortex (Critchley, 2005). A study with schizophrenics has recently revealed that excessive fear related arousal co-varies with a reduction of medial prefrontal and amygdala activity, this phenomenon being more pronounced in paranoid patients. A functional or pathologic disconnection in these limbic prefrontal midline structures might therefore contribute to abnormal arousal as well as abnormalities in autonomous regulation in schizophrenia (Williams et al., 2004). In particular, while the anterior cingulate cortex is implicated in generating autonomic changes, the medial prefrontal cortex is increasingly recognized to support processes of internal self-reference that predominate in states of rest and disengagement, and in computational models of control, forward efferent-copies and corollary discharge are furthermore proposed to enable prediction and correction of action (for details see General Discussion below).

Rats under Stress

Owing to obvious ethical constraints, intracerebral EEG recordings were out of question in our human patients. We therefore devised an equivalent stress model known to elicit massively reduced heart rate variability, during which nine male Wistar rats were subjected to immobilisation during 5 hours on 5 consecutive days. For EEG recording, electrodes were placed at 14 different intracerebral locations, and for HRV assessment, ECG recordings were done on one fore- and one hind leg. The data were amplified and subsequently evaluated by using the same equipment NeuroResearcher (R) ' 2005. In line with our data recorded from our schizophrenic patients, the processing of Kolmogorov entropy was significantly enhanced in the rats under stress compared to the normal situation prior to immobilisation. In particular, the intracerebral electrodes scored a significant increase in the midbrain reticular formation at the level of the left nucleus parabrachialis lateralis (from 3.7 to 7.3, $p < 0.01$) and in the basolateral nucleus of the left amygdala (from 4.45 to 5.58, $p < 0.05$). Recordings from the right parietal cortex also scored an increase of K from 3.38 to 5.25, $p < 0.05$ (Mayorov & Vyazovskaya, 2006).

In sum, the rats exposed to stress exhibited an enhancement of K within left-sided subcortical structures being intimately related to the representation of stress and both part of the central autonomic and limbic system. Unlike the prefrontal lobes, showing merely an increasing trend, the most significant increase

was localised in the other associative area, the right parietal cortex. The results concerning the rats' right parietal cortex are basically in line with current knowledge about human beings under severe stress (Metzger et al., 2004). The involvement of the prefrontal-limbic systems in stress-related depression has also been extensively studied. Although missing unanimous consensus, most studies point to a cortical inhibitory role (Pape, 2005) over the left-subcortical limbic region, which basically subserve negative affective states. Hence, lesions in the dominant hemisphere are usually associated with a catastrophic reaction – fear, despair, anger – while lesions in the non-dominant hemisphere are accompanied by an indifference reaction – unawareness, lack of concern, euphoria – (referenced in Liotti & Tucker, 1995; Podell et al., 2001). Whether stress reaction are adaptively constrained to anticipate surprise by enhancing right-hemispheric spatial awareness while at the same time resorting to emotionally ingrained, left-hemispheric escape routines remains, at present, an intriguing open question.

General Discussion

Our results support the view that cortical dominance of information processing shifts from the right to the left hemisphere during ontogeny and phylogeny. When right-handed subjects perform a demanding sequential task in working memory, this is reflected by a significant increase of Kolmogorov entropy over the left hemisphere. However, while K increases over all leads, this physiological asymmetry of information processing is reduced or even reversed in schizophrenia. Although highly significant, these changes are neither specific nor pathognomonic for schizophrenia. As shown by the robust decrease of heart-rate variability in schizophrenic patients and immobilised rats, alterations in functional brain asymmetry could rather be interpreted as the consequence of cholinergic deficits under stress.

Stress and Schizophrenia

The development of the CNS through evolution is characterised by increasing powers of anticipatory stress coping so as to avoid danger before disaster strikes. Intelligent anticipation requires knowledge and the ability to draw analogies from past situations, which may be different from an impending threat. Hence, unlike fear, which has reference to a specific aspect of the outside world, anxiety is particularly distressing; anxious individuals are in constant suspense, attempting to reduce uncertainty to clarify the situation. Being watchful and alert they often excessively overreacting to noise or other stimuli, or they feel helpless in the face of danger, which cannot be fully anticipated. It is therefore of interest to note that immobilisation stress in rats correlates with reduced HRV and an increase of Kolmogorov entropy particularly in those brain areas that are known to process alerting, stress related action. No less interesting is the fact that coping with stress is profoundly dysfunctional in schizophrenia.

Since the original descriptions by Kraepelin (1899) and Bleuler (1911), psychological stress and impaired filtering of sensory stimuli have been hypothesized to represent specific risk factors of developing acute psychosis. Schizophrenic patients often attend to apparently extraneous stimuli in their surroundings that normal individuals generally ignore. This stressful defect in the regulation of sensory stimuli suggests that neuronal control mechanisms, particularly prefrontal function, responsible for the filtering or gating of sensory input to higher brain centres are deficient.

The sensory-motor correlation of **K** to HRV is intriguing for another reason. After a cascade-like traversal through unimodal, polymodal and supramodal association areas (Mesulam, 1998), information from the entire cortex converges upon key limbic structures including amygdala and septal region (Swanson & Risold, 2000). Being at the core of the schizophrenic dysfunction, the latter influences the activity of the phylogenetically oldest part of the brain, and controls the limbic output to the autonomic (sympathetic and parasympathetic) centres (Bogerts, 1999), which, in turn, regulate heart rate and its variability. Elementary autonomic drives such as aggression, flight, and sexuality, which can indeed be evoked by direct electrical stimulation in the area of the hypothalamus and septal region (Hess & Brügger, 1943), are mediated by inputs from the amygdala ultimately depending on information from the sensorimotor association cortex and its limbic connections (Nauta, 1971; Nieuwenhuys et al., 1988; Mesulam, 1998; Swanson & Risold, 2000). It is thus entirely plausible that disturbances in the limbic chain of information processing may lead to a dissociation of elementary emotional modes of response from higher cognitive control. Bleuler (1911) regarded this uncoupling of cognition and emotion as the basic functional disturbance in the schizophrenias.

Blank Spells and Autonomic Dysfunction

To complicate matters, Bleuler (1911) observed episodic mental changes in early schizophrenia during which almost everything was recorded that reached the senses, while at other times the opposite condition prevailed. The patients exhibited relatively short periods of 'inattention' during which even the most powerful stimuli were incapable of influencing their brain of thought or of arousing their attention. Albeit limited to sudden pauses in thinking, Bleuler stated that the Kraepelinian concept of 'blocking' was of fundamental significance for the symptomatology and diagnosis of schizophrenia. The subjective experiences during such episodes are often described by patients as 'trances', 'attacks', 'dazes', 'blank spells', or 'stoppages of the mind'. In most cases these paroxysmal episodes range from a few seconds to one or two minutes within the first two years of the illness, but in chronic patients and in patients with additional catatonic symptoms, they usually last for two to three hours. It is also important to note that the patient is to some extent aware of the disrupting process: "You can very easily go into a trance – it goes on as soon as the mind stops and then you realize you are not

actually seeing anything or hearing anything. It's a delight – you don't feel anxious until you come out of it" (Chapman 1966). In the build up of these phenomena, before the block occurs, the schizophrenic patient has particular difficulty in coordinating motor sequences for simple actions.

It is tempting to compare these episodes of paroxysmal dissolution in mental function with the altered states of consciousness in epilepsy. However, only with the advent of depth recording was it possible to obtain specific EEG abnormalities from schizophrenic patients. These insights have provided unique contributions to our knowledge of psychosis, as studies of this nature will not likely ever be repeated owing to ethical constraints. During periods of acutely psychotic behaviour abnormal electrical activity was found predominantly in the septal region and to a lesser extent in the hippocampus and amygdala, with an even greater degree of abnormality in paranoid patients. Patients with temporal lobe epilepsy and acute psychosis exhibited higher amplitude spiking and more slow-wave activity compared with what was typically seen in schizophrenia. Although the anatomical regions, from which the abnormal depth recordings were obtained, were the same for the two groups, the pattern of activity was different, and this was so even during periods when the epileptic was displaying psychotic features indistinguishable from the schizophrenic (Heath, 1954, 1961).

The temporal lobe, with its strongly interconnected limbic brain regions of Broca's famous 'great limbic lobe' (1878), has been of special interest in schizophrenia research ever since the concept of the illness emerged (Arnold, 1997; Bogerts, 1999). The adjacent basal forebrain and the extended amygdala, which have been implicated in schizophrenia (Heimer, 2000), as well as the brain stem and the hypothalamus are supposed to regulate attentional information processing and heart rate fluctuations (Bär et al., 2005; De Rosa & Baxter, 2003). The rostral parts (including the medial septum) are reciprocally connected to these corticolimbic structures, and more caudally the cholinergic nucleus basalis of Meynert as well as the noradrenergic nuclei of the reticular formation project directly to the amygdala (see Nieuwenhuys et al., 1988; De Rosa & Baxter, 2003). It is of interest in this context that our rats under immobilisation stress exhibited a significant increase in Kolmogorov entropy within the amygdala and reticular formation.

MacLean cites clinical and experimental evidence suggesting that the lower part of the limbic lobe, fed by the amygdaloid complex, is primarily concerned with emotion and behaviour that ensures self-preservation. In his wording, the circuits of this lower, caudal part are "so to speak, kept busy with the selfish demands of feeding, fighting and self-protection". The structures linked to the septum in the upper, caudal part of the lobe, on the other hand, are involved in "expressive and feeling states that are conducive to sociability and the procreation and preservation of the species" (MacLean 1970, p. 340; see also Hess & Brügger, 1943). In schizophrenia this situation appears to be pathologically reversed since actual or perceived challenge to survival in the form of severe stress often results in

neural dissolution from the evolutionarily recent systems of positive social behaviour and communication to the more primitive stress- or catatonia-like avoidance systems.

Evolutionary Constraints towards Sociability

In evolved systems there is a sense in which function determines structure, and that is the key to understanding the physiology of the human brain. Accordingly, behaviour in the present is generated by information processing mechanisms that exist because they were under relentless selective pressure in the past, in the ancestral environments in which the human line evolved. As the immune system changed through the process of evolution, so did its interplay with the autonomic nervous system. To survive as a species, individuals must be able to distinguish friend from foe, and evaluate whether the environment is safe enough to enter into social and sexual contact. As the cholinergic, parasympathetic nervous system has passed through three distinct evolutionary stages, each prompting a characteristic behavioural pattern, social engagement has finally become inversely related to stress reactivity (Porges, 2001; see also Sheehan & Numan, 2000; Sparks & LeDoux, 2000). The first stage is characterized by a primitive unmyelinated visceral vagus that fosters digestion and responds to threat by depressing metabolic activity (freezing behaviour). The second stage is associated with a sympathetic nervous system capable of increasing metabolic output and inhibiting the visceral vagus so as to foster mobilization behaviour necessary for 'flight or fight'. The third stage, unique to mammals, is characterised by a myelinated vagus that can rapidly down-regulate cardiac stress response and control facial expression and vocalization (Porges, 2001). In the course of evolution, the mammalian nervous system has thus evolved with special functions to maintain visceral homeostasis and to react rapidly to social challenge. As a consequence and without conscious awareness, the autonomic nervous system evaluates risk in the environment and regulates the expression of social adaptation to communication, reproduction and the formation of pair bonds – a highly evolved human behavioural pattern that is severely disturbed in schizophrenia. Another typical sign of schizophrenia, *anhedonia* – a marked and refractory defect in social capacity, which is mainly interpersonal in schizotypy (Mehl, 1962) – goes into the same vein. At the physiological level such a reduction of parasympathetic vagal tone is best exemplified in our schizophrenic patients by their very low rates of heart rate variability. It is thus tempting to speculate that the reciprocal frontal-limbic connections of the septal region Swanson and Risold, 2000), which includes cholinergic nuclei, could be centrally involved in the phenomenon of behavioural anticipation, and elucidate the typical loss of foresight and social withdrawal in schizophrenic patients.

Delusions of Alien Control and Dysfunctional Information Processing

Hallucinations and loss of self/control, as well as a sudden arrest in the stream of thought, were among the most frequent symptoms experienced by our patients with paranoid schizophrenia, particularly by those suffering from passivity or delusion of alien control. This delusion, which Schneider included among his first rank symptoms, can be best described as actions being created, not by the patient herself, but by some outside forces. "She experienced a 'mystical awareness' in which she felt she could 'see beyond' ordinary reality. But later her sense of 'psychic powers' and revelations dissipated as she entered the 'abyss of timelessness.' Along with this, she had lost her 'grip' on who she was and felt 'pushed and pulled' by 'strange forces and voices' that made her do things against her will" (Melges, 1982). Yet, dysfunctional sensory-motor control in the 'abyss of timelessness' does not only account for psychotic hallucinations involving the self at the interface between subject and object. The enhancement of **K** in schizophrenia, it is here conjectured, may directly correlate with altered time estimation, and this we are currently attempting to validate in pharmacologically naïve patients.

A psychotic patient cited by Melges (1982) knew that the "clocks still marched onward," but she thought to be "in a different realm" where "everything is happening at once". Yet she asserted that "Time has stopped; there is no time . . . The past and future have collapsed into the present, and I can't tell them apart. The world has become timeless." That subjective or 'internal' time seems to be passing more quickly and physical time (clock time) more slowly than expected during a psychotic experience is perhaps best exemplified by the effects of dopaminergic pharmaceuticals on time perception, namely, the ability to accelerate the speed of subjective time in the seconds to minutes range through D2 agonists, and to decrease the speed of the 'internal clock' with the typical antipsychotic dopamine D2 antagonists (Meck, 1996).

Pandya (1971) found reasons to attribute visual and proprioceptive defects associated with frontal lobe lesions to the loss of a mechanism of corollary discharge (efferent/re-afferent copy) that pre-sets sensory processing mechanisms for such input changes as would predictably result from impending motor output. It could be asked if not perhaps a wider aspect of schizophrenic symptomatology could be interpreted in terms of corollary discharge (see also Numan, 2000). More specifically, it would seem possible to envisage a pre-setting not only of exteroceptive processing mechanisms, but also of those mechanisms dealing with interoceptive information to enable prediction and correction of action and, by extension, the interpretation of the behaviour of others (Critchley, 2005). Such a presetting could then establish a temporal sequence of affective reference points serving as 'navigational marker' and providing, by their sequential order, goal directed forms of behaviour (Pandya, 1971). The obvious deficit in schizophrenia to increase **K**, particularly during a working memory task involving the prefrontal cortex, could disrupt this physiological process. For many of our schizophrenic

patients had such problems as evidenced by lack of volition and related cognitive deficits not only to anticipate motor sequences, but also their future perspective (Melges, 1982; Hooker & Park, 2000; Frith et al., 2000; Delevoeye-Turrell et al. 2002).

Information theory currently plays an important role in the analysis of learning systems (Ghahramani, 2003). Bestowing on higher evolved organisms the capacity of conscious awareness in the context of behavioural planning and memory retrieval, no further motor component is required, once the neuronal networks are established (Vakalopoulos 2005). Subsequent reactivation will therefore possess motor properties without any overt movement as shown in our experimental setting by the relatively high baseline levels of **K** both in normal controls and schizophrenics. If abnormally fixed, however, this process is presumed to have an ongoing dynamic in schizophrenia during which dysfunctional motor efferent copies will result in perceptual aberrations. Consequently, the schizophrenic patient not only fails to identify the boundaries between self and non-self and those between present, past and future. At a cognitive level this deficit typically involves a period of inattention and sudden arrest of the stream of thought frequently occurring in the vast majority of schizophrenic patients. In the build up of such episodes difficulties in behaviour are typically observed in coordinating simple motor sequences and these blocking phenomena may, according to Chapman (1966), result in catatonic stupor. A similar, or at least related, dysfunction could be postulated to explain the phenomenon of passivity. Generally speaking, as a direct consequence of the neuronal confluence of perception and action, corollary discharge (also termed efferent copy) is held to collapse sensation and movement into a unique algorithm of sensory-motor integration (Vakalopoulos 2005). Based on this unique yet all too often misunderstood (Jordan, 2004) learning paradigm encapsulating the representation of environmental regularities (Jordan 2004) and resulting in what Vakalopoulos (2005) calls a premotor relation (consisting of motor efference and perceptual re-afferent copies), any planned output in comparison to an actually occurring input is strictly coded by concurrent sensory-motor information (Numan, 2002). Related sensory-motor dysfunctions can be best understood by moving the eyeball by a subtle push with our finger in comparison to a normal gaze. In the first un-physiological instance we erroneously perceive the visual input from outside as moving, while in the second physiological instance the environment remains stable during the upcoming eye movements by corollary discharge (Sommer & Wurtz, 2002). Now just imagine: if we were made unaware of the finger push, we would assume to be 'pushed' by some 'outside' force. Against this conceptual background, the data collected from our paranoid schizophrenics (who exhibit enhanced processing of **K**, particularly over primary sensory areas without any obvious movement) make sense: the passivity phenomena are erroneously understood as being brought about by some outside forces, simply because corollary discharge dysfunction in schizophrenia (Ford et al., 2001) presets the

mental processing for an impending sensory input not through a predictable motor output, but unpredictably.

Sensory-motor integration is a phenomenon best described as equivalent to both the algorithm postulated by Vakalopoulos (2005) and the algorithmic entropy defined by Kolmogorov, with the mere difference that the former description is held constrained to a specific application and the latter mathematically rigorous and general. Moreover, Kolmogorov's discovery of the optimal coding scheme is pivotal in formalising unsupervised learning, be it physiological or pathological. That is, an unsupervised learning paradigm can be realised formally by casting the learning problem as one of discovering a general transformation or coding rule for the system's sensory data which, in an evolutionary adaptive sense, ought to be as efficient as possible to function as a signal without executive control (Ghahramani, 2003). A solution to this problem, we suggest, can be best described by the dimensional transformation rule of sensory-motor integration from \mathbf{H} to \mathbf{K} (see equation 2), actually closing the neuronal confluence of perception and action between the organism and the world in a circle of corollary discharge. In other words, from the simplest and most automatic to the most deliberate, motor action is not only initiated by sensory signals, but also regulated by inputs that action itself induces by its movement through the environment. Exactly this impossibility of a sharp separation between objects and with the observer (Bohr, 1938) corresponds to the pattern of sensory-motor integration which, half a century ago, Viktor von Weizsäcker (1950) called the gestalt cycle – the principle of the indissoluble union of perception and movement, time and space, subject and object.

Conclusion

Our data, as well as accumulating evidence from many other studies, support the view that cortical control shifts from the right to the left hemisphere in the course of development. This right-to-left shift of hemispheric specialisation appears to be universal and independent of stimulus modality. It is not limited to humans but can be meaningfully applied to any species capable of learning, and thus opens the avenue for tracing the evolutionary continuity in the development of cerebral lateralization across species (see for example Bianki, 1983, Podell et al., 1991). In addition to being more consistent with general biological assumptions, our dynamical approach based on information theory emphasises individual differences and argues against a fixed assignment of particular mental tasks to one or the other hemisphere. What is cognitively novel or unpredictable to one individual can be an established fact to another. As such, changes in functional brain asymmetry can neither be specific *per se* nor pathognomonic for schizophrenia. As shown by the robust decrease of HRV in schizophrenia, alterations in brain asymmetry (from a partial reduction in left hemispheric dominance to a complete reversal of hemispheric asymmetry) could rather be interpreted as the consequence of a cholinergic deficit. In being itself asymmetrically distributed to the left (referenced in Previc, 1998), this cholinergic

deficit would in turn prompt some form of asymmetric re-adaptation (Hartmann et al. 1993) of the remaining brain. Left-hemispheric dopaminergic upgrading in schizophrenia (Reynolds, 1983; Previc, 1998) imparting subsequent alterations in the over-all topology of the CNS, though, must for the present remain a matter of conjecture.

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