Septo-Hippocampal Cognitive Defense Strategies, Theta/Gamma Coding Scheme, And Pacemaker-Induced Chronobiological Self-Organization

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Abstract:

This paper reviews previous research on «phase-locked » (especially frequency modulated) neural rhythms, during defensive behaviours and cognitive conflict resolution, while explaining and emphasizing the importance of natural biological pacemakers, in the regulation of adaptive behaviour and in cognitive self-organization.

It is suggested that cognitive self-organization of adaptive defensive behaviours is primarily based on the biofeedback of appropriately modulated and pace-resetted Theta-rhythm and other central biological rhythms. It is also suggested, in the light of recent research on the biobehavioural and neuropsychological bases of defense systems, that the septo-hippocampal system, with its Theta/Gamma coding scheme, is a fundamental system in cognitive defense strategies, in equilibrium between behavioural approach and defensive avoidance (through defensive approach), in conflict resolution, and in chronobiological self-organization .

الملخّــص:

يحاول هذا المقال إبراز أهمية مفهوم الناظمة أو"البيسميكر" (pacemaker) الطبيعي، في تنظيم السلوك ألتكيفي وفي التنظيم الذاتي المعرفي، علي أساس التغذية البيولوجية الراجعة الإيقاعية، المرتبطة بإيقاع" ثيتا"(Θ) على مستوى "الهيبوكمبس" (حصان البحر)، وبإيقاعات بيولوجية آخري؛ وهذا على ضوء البحوث الحديثة في ميدان نيوروسيكولوجيا الأجهزة الدفاعية وآليات التعديل الإيقاعي والتحكم السلوكي الحيوي للجهاز الحاجزي- الحصيني كجهاز أساسي في الاستراتيجيات الدفاعية المعرفية، في الموازنة بين سلوك الاقتراب و التجنب الدفاعي (من خلال الاقتراب الدفاعي)، و في حل النزاعات.

INTRODUCTION:

During the past twenty years of research on the neuropsychology of defense systems and on the role of the septo-hippocampal system in defensive behaviours and conflict resolution, there has been mounting evidence relating to the particular importance of the modulated hippocampal Theta-rhythm in pacemaker-induced biological self-organization and mediation of cognitive defense strategies.

On the other hand, the newly investigated and recently eveloped research fields of psychoneuroendocrinology (PNE) & sychoneuroimmunology (PNI), integrating neurohormonal, neurophysiological & neuropsychological processes into a unified field of cognitive psychoneurobiology, consecrated the inseparability of mind and body and the interdependence between the couples emotion-motivation & perception-action. Indeed, in their new non-cartesian conception of the human psyche, PNE and especially PNI scientists*1 advocated holistic views and forwarded unified interpretations to explain the complex, non-linear, and fluctuating time-dependent neuropsychological and bioenergetic processes, underlying cognitively learned defense strategies and neurohormonally-dependent acquired immunoreactivity. In doing so, they undoubtly paved the way for new theories and stimulated a host of laboratory studies, during the past ten years, on the role of the septo-hippocampal system (and related relevant limbic and prefrontal structures*2) in stress-modulated immune response, anticipatory and

goal directed behaviour, cognitive defensive approach and risk assessment behaviour, temporal coding of information & working memory, and adaptive modulation of biological clockings.

1. Hippocampal Theta, Cognitive Emotional Processing And Learning Strategies:

Hippocampal Theta (Θ) being linked to orienting reaction (OR) and exploratory & search behaviour [rather than to defensive reaction (DR) associated with freezing or stereotyped behaviour] promotes positive emotions and coping rather than negative emotions and discomfort. Moreover, emotional processing at limbic level is often associated with search (or exploratory) behaviour and active self-stimulation, as well as creative behaviour, increased psychobiological resistance and successful coping, leading to normal anxiety and emotional intelligence, while maladaptive primary uncontrolled emotional tension at lower neurological levels is often associated with no-search behaviour and freezing or panic behaviour,as well as stereotyped behaviour,decreased psychobiological resistance and unsuccessful coping, leading to pathological anxiety, emotional neuroticism and psychosomatic disorders (Gray,J. 1982, 1987; Iversen,S.D. 1982; Rotenberg,V.S. 1984; Rotenberg,V.S & Boucsein,W. 1993).

Concerning the role of the type of Theta activity and its relationship to behavioural and cognitive learning strategies, it has been shown that high frequency (7 to12Hz) serotonergic Theta is associated with Type1 behaviour (that is with behavioural activation and voluntary vigorous movements), while low frequency (4 to 6 Hz)

cholinergic Theta is associated with Type 2 behaviour (that is with behavioural inhibition, immobility during stressful events, sensory processing and exploratory behaviour); and both Type1 Theta and Type 2 Theta can be conditioned or modified by anxiolytic drugs (Gray & Ball, 1970; Vanderwolf, 1988; Wyble et al, 2004).

Thus, we can say, that the appropriate conditioning of the hippocampal Theta rhythm, may have very important behavioural and cognitive applications in the fields of learning, memory acquisition, self-organization, and psychotherapy. Nevertheless, the neuropsychological/chronobiological mechanism responsible for the biocybernetics of emotional stability, qualitative information acquisition and adaptive behaviour is a very complex non-linear mechanism. This non-linear mechanism (and probably non-thermodynamic*3 mechanism) is thought to be a fluctuating pacemaker-like chronobiological device, located in the septo-hippocampal system, and functioning as a synchronizing interface between the autonomous nervous system and the somatic nervous system. This synchronizing interface, with its modulated Theta rhythm, seems to be well suited, to respond, in a conditioning and cognitive manner, to internal and external factors or cues, properly programmed in time, in order to, reinforce emotional maturity and search behaviour and stimulate learned adaptive defense strategies.

At this point, and without underestimating the importance of the mesolimbic system*4 and other dopaminergic rewarding systems*5, in defense behaviour [through the behavioural activation stem(BAS)],

in reward sensitivity, and in instrumentally learned behaviour (following continuous reinforcement), we must however say, that the predominantly cholinergic(though also GABAergic)*6 septo-hippocampal system is more appropriate for cognitive processes associated with defensive "behavioural inhibition" as indexed by, selective attention, sensitivity to punishment & frustrative non-reward, risk assessment behaviour, exploratory & preplanned behaviour, and emotional intelligence. Indeed, it is through the septo-hippocampal behavioural inhibition system (BIS) or fear-frustration system*7, that behaviourally and cognitively learned readjustment of biological rhythms, adaptive emotional processing, and qualitative information acquisition can readily take place, owing to, increased selective attention, facilitated conditioning and discrimination learning, and increased resistance to extinction*8.

2. The septo-hippocampal system, the immune system and neurogenegis :

The immune system being one of the major defense systems of the organism, along with neurobehavioural defense systems such as the Behavioural Inhibition System(BIS), the Behavioural Activation System(BAS) and the Fight/Flight/Freezing System(FFFS), it is interesting to know the contribution of each of these three systems to the specific immune response, and the particular relationship of the septo-hippocampal BIS to acquired or adaptive immunity(mediated by lymphocytes B and T).

It is a well established fact that the septo-hippocampal system contributes to the immune system by inhibiting the immunosuppres-

sive effects of glucocorticoids and the HPA axis, through the generation of a Type II Theta rhythm [associated with Type II behaviour (see above)].

A team of scientists, led by Prof Michal Schwartz of the Weizman Institute of Science (USA), showed that immune cells (especially autoimmune T cells*9 in the hippocampus, a «neurogenic» brain region*10) can have the potential ability, if their levels are controlled, to maintain cognitive ability and cell renewal throughout life. Schwartz and his colleagues pointed out that the role of the autoimmune T cells, in neurogenic brain regions, and contrary to what was believed before their discovery*11, is not to induce autoimmune diseases, and therefore affect cognitive function and the level of intelligence, but rather to maintain learning and memory abilities (Ziv et al, 2006). It is thus clear, from this new vision of the role of brain immune cells, that treatment of debilitating degenerative condition, such as Alzheimer's and Parkinson's diseases, becomes possible, through manipulation and boosting of the immune system.

Another team of scientists identified an immune-responsive mesolimbocortical system with a potential role in regulation of emotional behaviour (Lowry et al, 2007).This team found a small subpopulation of serotonergic neurons, referred to as Type II serotonergic neurons, in the caudal interface of the dorsal and medial raphe nuclei, that is selectively responsive to peripheral immune activation, paradoxically not associated with behavioural activity, and apparently distinct from classically known serotonergic neurons

(associated with behavioural arousal and motor activity, and therefore termed Type I serotonergic neurons). To confirm the paradoxical behaviour of these immune-responsive serotonergic neurons, Linthorst et al (1995), in an earlier work, showed that following acute immune activation, behavioural activation dramatically decreases while serotonergic activity increases, particularly in brain regions associated with mood regulation like the limbic system. To sum up, it can be said that immune activation increases the activity of a subpopulation of serotonergic neurons, that is not directly associated with the level of behavioural arousal, and which is different from the subset of serotonergic neurons activated by anxiogenic stimuli or uncontrollable stressors. We suspect responsiveness of Type II serotonergic neurons to peripheral immune activation to be achieved through reciprocal feedback loops, between cholinergic and non-anxiogenic serotonergic nuclei in limbic system.

3. The septo-hippocampal system, defense strategies, and pacemaker-induced chronobiological self-organization :

3.1- The septo-hippocampal system, defensive behaviours and drug action :

It is now a well documented and well corroborated fact that septo-hippocampal "behavioural inhibition" does not mean immobility, passivity or surrender, but means rather a cognitive strategy involving conflict detection, risk assessment behavior (through external scanning), memory search (through internal scanning), exploratory behaviour designed to resolve conflicts, goal-oriented behaviour and increased arousal and attention. And,

as McNaughton & Corr put it « the conflict that activates the BIS is one between goals experienced by the subject rather than inherent in a paradigm; and(…) although termed "the behavioural inhibition system", the BIS is, and has always been, postulated to generate additional output to attention and arousal »(McNaughton & Corr, 2004).

Moreover, being linked to risk assessment and normal anxiety, the septo-hippocampal system is naturally more involved in defensive approach than in defensive avoidance*12. Indeed, conventional anxiety is often seen as being generated by concurrent and equivalent activation of frustration and approach systems, with the BIS functioning to assess risk, and increase risk aversion in conflict situations.

Another important feature of the septo-hippocampal BIS is its relatively marked sensitivity to classical anxiolytics (such as benzodiazepines), as compared to the relative insensitivity of the defensive avoidance system, and the marked insensitivity of the behavioural approach system (BAS), to these drugs (Gray & McNaughton, 2000).This psychopharmacological specificity of the septo-hippocampal system has had, and will undoubtedly continue to have, important scientific implications, and crucial therapeutic applications, for the fields of clinical neuropsychology, social psychiatry, neuropsychopharmacology, and cognitive-behavioural therapy. These scientific implications and therapeutic applications

have also been encouraged by the recently discovered fact of a clear and sharp distinction between fear and anxiety.

Indeed, it has been shown that, fear had the function of moving the animal away from danger, involved fight, flight or freezing, and was insensitive to anxiolytic drugs, whereas anxiety had the function of moving the animal towards danger, involved "behavioural inhibition", increased risk assessment and defensive quiescence, with all these manifestations being sensitive to anxiolytics (Gray & McNaughton, 2000).

We can add, to what has already been said on the sensitivity or insensitivity of the two main neural defense systems (BIS & FFFS) to drug action, the fact that the action of many clinically effective drugs also depends on their interaction with more global neuromodulating systems. Indeed anxiolytic drugs, act directly on a range of neurotransmitter(NT) rich sites (supramammillary nucleus, locus cœrulus, raphe nucleus) to alter indirectly septo-hippocampal function and so behavioural inhibition and defensive approach. And, it is this interaction of anxiolytic drugs with the four main ascending neuromodulating systems (cholinergic, serotonergic, noradrenergic and dopaminergic), and henceforth with the septo-hippocampal system, which is expected to be crucial, not only for mood changes (cyclic and non-cyclic), but also for personality modifications (towards introversion or towards extroversion), gender-dependent reactions to stress &/or pain, and chronobiological changes.

To illustrate the tight interaction between brain structures controlling defensive behaviours, neuromodulatory systems, and

anxiolytic &/or antidepressant drugs, we can say, for example, that while diazepam, alprazolam, and buspirone are all anxiolytic drugs, and imipramine an antidepressant drug, the former affects anxiety but not depression, the second affects anxiety and depression, the third affects all forms of anxiety but not panic, and the fourth affects anxiety, depression, obsessive-compulsive disorder(OCD), and panic. Therefore, anxiety, depression, obsessions and panic must each depend on different parts of the brain (as already mentioned above).

Moreover, it is a known fact that classical anxiolytic drugs, like benzodiazepines, ethanol, meprobamate and barbiturates, have a dampening or blocking effect on Theta activity in the hippocampus. However, the nature and specificity of this dampening effect remain a matter of debate, and sometimes generate conflicting reports; with some authors finding enhanced Theta under benzodiazepines (Kopp et al, 2004), some reporting suppressed Theta under these drugs (Hajos et al, 2004; Ujfallussy et al, 2005), and some still reporting enhancement of the Delta-slow Theta & Beta EEG waves (2.5-4 Hz & 20.5 Hz) concurrently to a suppression of medium frequency and high frequency Theta bands(5.5-7 Hz) in humans under Lorazepam (Fingelkurts et al, 2004). For our part, however, we think that classical anxiolytics, can only have, on the long run, various distorting actions on many septo-hippocampal cognitive functions, owing to their non-selective action and their broad-range side effects. Some of these side effects are well known, vary from the mild forms of insomnia, amnesia and myalgia to serious forms of anterograde amnesia, oniroid

delirium, etc... We also think that, by their agonistic interaction on GABAA receptors, benzodiazepines have, an inhibitory action on hippocampal Theta and exploratory behaviour, a tendency to increase NREM sleep at the expense of REM sleep, hindering effects on learning tasks involving associative, episodic & spatial memories, and most of all inhibition of estrogen-induced neuronal changes in the female hippocampus, and their replacement by progesterone-mimicking inhibitory effects [owing to the fact that progesterone interacts directly, and in an agonistic manner (in the same way as Benzodiazepines), with hippocampal GABAA receptors (Rupprecht & Holsboer, 1999; Murphy & Segal, 2000)].

3.2- The septo-hippocampal Theta rhythm and Theta/Gamma coding scheme:

During exploratory behaviours and rapid-eye movement (REM) sleep, the hippocampus exhibits a prominent coherent Theta rhythm (with a frequency of 4 to 8 Hz in humans and 3 to 12 Hz in rodents). Generation of this rhythm depends on two types of neurons in the Medial Septum (MS)*13: cholinergic neurons, acting via muscarinic receptors as slow modulators of hippocampal excitability, and GABAergic neurons, acting via fast GABAA receptors as inhibitory modulators of cholinergic input. Moreover, it has been shown that Theta and Gamma rhythms often occur together in many brain regions, with Gamma being modulated at Theta frequency, and with the two rhythms being part of a common functional system (Bragin et al, 1995).

Concerning the driving of the Theta rhythm at a particular frequency, it has been hypothesized by Wang (2002) that it is the septal GABAergic neurons that may play the role of pacemaker neurons for this driven Theta rhythmicity, whereas other reports favoured and continue to favour fundamentally cholinergic induction of Theta frequency oscillations (Teitelbaum et al,1975; Chapman & Lacaille,1999). Moreover, it is a well documented fact that, while cholinergic septal projections terminate at both the principal pyramidal neurons and the GABAergic inhibitory interneurons of the hippocampus, GABAergic septal projections terminate predominantly at these GABAergic interneurons. Thus, while septal cholinergic input provides a modulatory inhibition of pyramidal neurons via the activation of inhibitory interneurons, septal GABAergic input has the main function of providing massive disinhibition of pyramidal neurons. It is therefore suggested that both cholinergic-to-GABA and GABA-to-GABA inputs may provide a synchronous orchestration of the entire hippocampal formation via a recurrent feedback loop, of inhibitions and disinhibitions, between the septum and hippocampus.

However, the precise neural mechanism underlying the generation of the Theta rhythm in the hippocampus remains unresolved and very complex (Buzsáki, 2001), probably because the tendency of hippocampal networks to oscillate at Theta frequency, reflects a resonance mechanism (Hutcheon & Yarom, 2000) rather than Theta rhythmogenesis proper. Nevertheless, because the cholinergic excitatory-inhibitory recurrent feedback loop between

pyramidal cells and interneurons is more efficient in the buildup and triggering of inhibition (of pyramidal neurons), than the mutual GABAergic connections between interneurons, it has been suggested that cholinergically induced slow Theta (5 to 6Hz) and cholinergically induced Gamma frequency oscillation (~ 40Hz) occur together and are part of the same phenomena (Bragin et al,1995; Jensen &Lisman1996; Mann et al, 2005). This phenomena is known as the Theta/Gamma clocking system or Theta/Gamma coding scheme and accounts for multi-item storage in working memory, with items being encoded, stored or retrieved via the different Gamma subcycles within each low frequency Theta oscillation (Lisman & Idiart, 1995; Jensen & Lisman, 1996). Moreover, we suspect this Theta/Gamma scheme, which allows for 5 or 6 different items to be stored in working memory, and for 5 or 6 different places, along a well known track, to be recalled from long-term memory, to be one of the most powerful spatio-temporal information computing and information processing schemes, and one the most appropriate and most fundamental clocking systems for natural biological self-oscillation and self-organisation.

3.3- Septo-hippocampal pacemaker-induced chonobiological self-organization:

The notion of biological pacemaker*14 is a fundamental notion in the field of biocybernetics of self-organized systems. It represents a central issue for biological self-oscillations and for chronobiological phenomena associated with homeostasis, circadian rhythms, hormonal cyclicity, rhythmic brain activity, and qualitative information processing.

There are several natural pacemakers in the human organism, from the simplest heart's Keith & Flack sinusal knot, to the most complex autocatalytic proto tRNA Hypercycle. Some of these pacemakers are circadian pacemakers, like the supraoptic or suprachiasmatic nuclei, and some could very well be circatrigintan (or circalunar)*15 pacemakers, like the pineal gland, while others are frequency modulating and phase resetting pacemakers*16, integrating several rhythms, like the MS/DVB complex of the septo-hippocampal system, and others still, are much more than simple rhythm drivers, they are multistationary and dissipative (i.e.non-thermodynamic) autocatalytic self-oscillators, like the Hypercycle of Eigen (see Eigen & Schüster, 1979).

The detailed study of all the natural pacemakers, their chronobiological interdependency, and their relationship to endogenous rhythms &/or external synchronizers, concerns the field of Chronomics, created and developed by the eminent scientist Franz Halberg (b.1919), and is therefore beyond the scope of this paper. However, our main aim, in this section, is to emphasize the particularity and importance of the septo-hippocampal pacemaker, as a chronobiological interface between circadian cycles and circaseptan and circatrigintan cycles, and as a sequential, modulating and integrating paceresetter.

Concerning this septo-hippocampal pacemaker and its regulating influences on hormonal cyclicity, cognitive emotional processing and adaptive behaviour, we have already pointed to its

non-linear, fluctuating and modulating character, and stressed its particular sensitivity to gonadal hormones (such as estrogen)(see Belloum, M. 2010/2011), chronobiotic drugs (such as barbiturates and benzodiazepines), and stress. We have also pointed to the importance of this pacemaker (or rather paceresetter) in multi-item memory tasks, through its Theta/Gamma clocking system, and its wide possibilities to switch from one type to another type of behaviour (for example from Type2 to Type1 behaviour and vice versa), by way of its Theta rhythm phase resetting and phase precession schemes. Now, what must be said about the possible role of the septo-hippocampal system in biological self-oganization, and hence in " psychological individuation", is its well documented increasing involvement, in gene expression*17, during learning tasks and hormonal modulation (Cavallaro et al, 2002; Robles et al, 2003; Birzniece et al, 2001), and its role in genetic programming during REM sleep (Jouvet, M. 1998). With these two last features (gene expression & genetic program-ming*18), and the already mentioned functions of hormonal enteroception, Theta rhythm phase resetting, and Theta/Gamma phase locking, the septo-hippocampal chronobiological oscillator emerges as an interface synchronizer bridging the gap between endogenous synchronizers and external synchronizers, between denary cycles and duodenary cycles, between defensive avoidance (of FFFS) and behavioural approach (of BAS), and between genotype and phenotype. This means that this kind of synchronizer is at the centre of adaptive biological self-organization, and that it is best suited for regenerating rhythms, defensive

quiescence, tension reduction, and genetic reprogramming, provided it remains under natural functioning, being neither submitted to chronic stress and very high levels of glucocorticoids, nor exposed to the distorting and desynchronizing side-effects of contraceptive pills*19 and hypnotic and/or anxiolytic drugs.

CONCLUSION:

Concerning defense strategies leading to adaptive behaviour, we favour reliance on discriminative scrutiny, intelligent risk assessment, and defensive quiescence, rather reactive fear, impulsiveness, and stereotyped defensive avoidance. Therefore, we think that adaptive defensive behaviour should rather originate from a natural and conscious activation of the septo-hippocampo-prefrontal feedback loops*20, than from entire and exclusive reliance on emergency systems such as the sympathetic nervous system and the HPAaxis. Indeed, entire and lengthy reliance on the mainly adrenergicand glucocorticoidic response to persistent stress, will lead, in the end, to impairment of hippocampal plasticity following alteration of hippocampal morphology (Pavlides et al, 2002; Sapolsky, 2003), and also to a number of other known pathologies, such as hypertension, insulin-resistant diabetes, immunosuppression, and reproductive impairements.

We also suggest that an appropriately pace-resetted septo-hippocampal slow Theta rhythm (5 to 6 Hz), through both cholinergically induced Gamma modulated oscillations and immune-responsive Type II serotonergic neuron activation, is the fundamental

pacemaker, and resonance mechanism, responsible for natural biological self-organization and including adaptive behavioural defense, adaptive immune and autoimmune responses and neurogenesis within a unified and integrative chronobiological scheme.

To sum up, we must say that man ought to live in harmony with all types of cyclic temporal factors in nature, keep record of all important life events happening in synchrony with cosmic events, and remain insightful and emotionally intelligent*21 in dealing with every "meaningful coincidence", or "synchronicity" as Jung (1964) preferred to call it, in the thirties*22. This also means that man ought to live as a kind of "cycled man", and as a quintessence of both earthly manifestations (as governed by denary cycles) and cosmic manifestations (as governed by duodenary cycles).

This quintessence, in turn, will lead, through appropriate interactions, reinforced by exercise, meditation or prayer, to a kind of "Octuple Way"of spiritual rebirth and wisdom, that is a human way or path, half way between Absolute Spirit and organic matter, between Pure Energy and physical matter, and between a cold calculating machine and an instinctively driven animal.

Notes:

*1: like Ader et al (1991), Haas & Schauenstein (1997).
*2: mainly involved in " behavioural inhibition" & emotional control and decision , like the Ventromedial Nucleus of the Hypothalamus, Mammillary Bodies, Anterior Thalamic Nuclei, Cingulate Cortex, Prefrontal (Orbitofrontal)Cortex, Medial Septum, Habenula Nucleus & Pineal Gland.
*3: that is dissipative & multistationary information creating (i.e negentropic") mechanism.
*4: extending between the Ventral Tegmental Area and the Nucleus Accumbens.
*5: including Lateral Septum, Lateral Hypothalamus and Medial Forebrain Bundle.
*6: and with ascending monoaminergic neuromodulatory inputs.
*7: as opposed to the "hope-relief"system of BAS (see Gray, 1972).
*8: through partial reinforcement extinction effect (PREE) (see Gray, 1975)
*9: that is immune T cells that recognize the brain's own components.
*10: a « neurogenic » brain region is a region of the adult brain that retain the ability to support and promote cell renewal (neurogenesis) throughout life.
*11: until quite recently, it was generally believed that each individual is born with a fixed number of neurons in the brain, and that these neurons gradually degenerate and die during the person's life time and cannot be replaced.
*12: which depend on another defense system, termed FFFS (or fight/flight/freezing system) by McNaughton & Corr (2004), and essentially centered around the amygdala, medial hypothalamus and periaqueductal gray.
*13: or rather in the Medial Septum/Ventral limb of the Diagonal Band of Broca (MS/VDB) complex.
*14: defined here as a mechanism or basic system that drives cellular activity at a particular rhythm.
*15: &/or circaseptan (i.e lasting 7±2 days); n.b: circaseptan rhythms were also found to periodically determine acute heart problems (Mikulevky & Valachova, 1996; Rawson et al, 2000).
*16: for this reason they are called "pacesetters".
*17: through receptor mRNA expression levels.
*18: as well as reprogramming (see Jouvet, M. 1974).
*19: see Belloum, M.(2010/2011).
*20: for example through learned self control, meditation & respiratory exercices, etc…
*21: rather than superstitious or purely logic, fearful or ignorant.
*22: at that time C.G.Jung was corresponding and working closely with the famous physicist, and prominent co-founder of Quantum Mechanics, Wolfgang Pauli (see Jung, CG.1964, p: 379-386).