Inherited Real Risk of Schizophrenia: Pathogenesis, Bedside Diagnosis and Primary Prevention

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ABSTRACT

The comprehension of the pathogenesis of schizophrenia finds a new impulse in studies on non- linear dynamics of EEG signals and in the growing genetic molecular evidence of the mitochondrial origin of this disease. These data are consistent with the information known by Quantum Biophysical Semeiotics, that clinically investigates microcirculation both on a functional (i.e., by studying its non-linear dynamics), and on a structural viewpoint.

Mitochondrial and microcirculatory dysfunctions reflect those of a genetically altered mit-DNA and of a functional mitochondrial cytopathy known as Congenital Acidosic Enzyme-Metabolic Histangiopathy, originating from this mutation and which is particularly intense both in patients with schizophrenia and in those with Inherited Real Risk of this disorder. Preclinical diagnosis of Inherited Real Risk of schizophrenia presents the opportunity to examine subjects with a predisposition to this disease since birth in order to perform an efficient pre-primary and primary prevention.

Key Words: schizophrenia diagnosis, mitochondrial dysfunction, primary prevention, quantum therapy, deterministic chaos

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Introduction

The complex pathogenesis of schizophrenia has not yet been fully explained in a unique, consistent, and harmonic form according to shared scientific opinion. Recent works agree that schizophrenia is a complex, heterogeneous behavioral and cognitive syndrome that develops as a result of interplay between biological predisposition (genetic factors alteration, i.e., inheriting certain genes) and the kind of environment a person is exposed to. These lines of research are converging: brain development disruption is now known to be the result of genetic predisposition and environmental stressors early in development (during pregnancy or early childhood), leading to subtle alterations in the brain that make a person susceptible to developing schizophrenia (Owen *et al*., 2016).

Advances in genomics, epidemiology, neuroscience and non-linear dynamics analysis have led to great progress in understanding the disorder, and the opportunities for further scientific breakthrough are numerous, i.e., genetic alteration and mitochondria dysfunction are novel researches and insights into the pathogenesis of schizophrenia. Genetic evidence (Hjelm *et al*., 2015) has supported the hypothesis that schizophrenia is a polygenic disorder with an enrichment of mitochondrial targets/mitochondrial dysfunction caused by the disruption in function of several or many genes.

Mitochondrial dysfunction has also been widely implicated in schizophrenia by genome-wide association. Mitochondrial dysfunctions cause cellular dysfunction, also known as mitochondrial cytopathy. Mitochondrial cytopathies (Schmiedel *et al*., 2003) are the basis of mitochondrial diseases,

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which are often caused by mutations, acquired or maternally inherited, in the mitochondrial DNA or nuclear genes that code for respiratory chain complexes in mitochondria.

There is no doubt that those with strong genetic components to schizophrenia have a significantly increased risk for developing schizophrenia over that of the general population. However, large-scale genetic studies show that there are no schizophrenia-predisposing genes with large effect sizes, therefore functional studies of intracellular pathways and understanding the confluence of environmental influences and genetic predisposition, and their combined effects on developmental mechanisms and intracellular cascades, are needed (Vereczkei and Mirnics, 2011).

There are several studies about the role of genetic alteration of mit-DNA and schizophrenia: they highlight that mitochondrial dysfunction affects neurodevelopment and neuronal functions, it leads to oxidative stress and inflammation (Prabakaran *et al*., 2004) and neuro-progressive changes in this disorder could be induced by mitochondria. There are documented alterations in brain energy metabolism, electron transport chain activity (Manatt and Chandra, 2011), and expression of genes involved in mitochondrial function (Scaglia, 2010).

Mitochondrial impairment may affect bioenergetics in the developing brain and alter critical neuronal processes leading to neuro-developmental abnormalities. Oxidative/nitrosative stress responses due to mitochondrial dysfunctions might activate immuno-inflammatory pathways and subsequently lead to neuro-progressive changes in schizophrenia, supporting a role for mitochondrial impairment in the pathogenetic pathways of this disease (Rajasekaran *et al*., 2015).

Decreased mitochondrial respiration, changes in mitochondrial morphology, increases in mitochondrial mit-DNA mutations and polymorphisms are current evidence supporting the role of mitochondrial abnormalities and dysfunctions in the pathogenesis of schizophrenia.

Also, complexity estimators have been broadly utilized in schizophrenia investigation: early studies reported increased complexity in schizophrenia patients, associated with a higher variability or "irregularity" of their brain signals. However, further investigations showed reduced complexities, thus introducing a clear divergence. Nowadays, both increased and reduced complexity values are reported. The explanation of such divergence is a critical issue to understand the role of complexity measures in schizophrenia research. The conflicting results in terms of both increased and reduced complexity values have been reported in different studies depending on the patients' clinical status or symptom severity or medication and age status (Fernández *et al*., 2013).

However, in other medical fields, i.e., in cardio-physiology and neuro-physiology, using different statistical measures, results agree and are consistent each other: i.e., HRV time series analysis (Al-Awee *et al*., 1999; Bär *et al*., 2007, 2008) and EEG signals (Korsakova *et al*., 2011) are deterministic chaotic under normal physiological conditions, while signals tend to linear regularity in pathological cases.

These findings are confirmed by recent research on patients with schizophrenia compared with control groups. The objective of these studies was to investigate the nonlinear brain dynamics of chronic and medicated schizophrenia patients using distinct complexity estimators. The EEG complexity of participants were investigated and compared using different statistical invariants, i.e., approximate entropy (ApEn), Shannon entropy (ShEn), Kolmogorov complexity (KC) and Lempel-Ziv complexity (LZC) (Akar *et al*., 2016; Sabeti *et al*., 2009) or fractal Dimension statistics (Raghavendra *et al*., 2009; Zhao *et al*., 2016). In all these studies lower complexity values were obtained in schizophrenia patients. Same results are given by fractal analysis in Magnetic Resonance Imaging (MRI) (Bullmore *et al*., 1994; Squarcina *et al*., 2015; Sandu *et al*., 2008) and in cerebral cortical surface (Ha *et al*., 2005), therefore widely corroborating that subjects with schizophrenia, tested over different time series non-linear analysis, have lower chaotic rhythms compared with healthy subjects (Benarous and Cohen, 2016). Moreover, schizophrenia is characterized also by disturbed sleep architecture. The analysis on sleep EEG time series show decreased nonlinear complexity of the EEG time series and diminished chaos in schizophrenia (Keshavan *et al*., 2004). Additional evidence connected with the role of complexity in pathophysiology and diagnosis of schizophrenia is given by the different studies on smooth pursuit eye movement (SPEM) dysfunction in schizophrenic patients.

An early investigation applying chaos research methodology to the eye movements of schizophrenic patients was completed by Huberman (Huberman, 1987). Invisible inner rhythms of the human body which could be correlated to chaos theory were found and therefore the human body could be also interpreted as a place of motions and oscillations acting as a complex system: new methods of listening to this variegated drumbeat were developed allowing detection of subtle differences between various states (health, declining health, sickness).

The functional complex dynamics termed as deterministic chaos has to be intended from a structural point of view as hierarchical superior order, and this higher order is physiological, typical of healthy subjects, as mentioned above, while the dynamics pathologies such as schizophrenia are represented by lower complex dynamics (Kleszczewski and Rutkiewicz, 2004).

The evidence about SPEM dysfunction in schizophrenia suggests two major conclusions. One is that there are multiple structural and functional disturbances of the eye in schizophrenia., all of which could be factors in the visual disturbances of patients. The second conclusion is that certain retinal findings can serve as biomarkers of neural pathology, and disease progression, in schizophrenia. These data suggest that a greater understanding of the contribution of retinal and other ocular pathology to the visual and cognitive disturbances of schizophrenia is warranted (Silverstein and Rosen, 2015).

The separation of positive and negative symptoms that contribute to disorganization from those that define reality distortion and psychomotor poverty has revealed significant new associations between SPEM and schizophrenic symptoms. These findings are interpreted in light of the proposal that the disorganization syndrome is the central form of pathology in schizophrenia. The term disorganization has to be intended as lower complexity or loss or order, as well as the heart fibrillation can be understood in a similar perspective (Lee *et al*., 2001).

Mitochondrial dysfunctions and the loss of complexity behaviour in schizophrenia are two core aspects of the clinical investigation of Quantum Biophysical Semeiotics (QBS) and of its bedside diagnosis. QBS framework offers the opportunity to obtain important data for a better comprehension of the pathogenesis of this disorder, its genetic predisposition and its Inherited Real Risk (Stagnaro, 2004a). QBS allows to perform an original pre-primary and primary prevention. In fact, QBS theory offers an approach "as a whole" of the pathophysiology of inherited mitochondrial neurodegenerative diseases (and schizophrenia as well) all of which are characterized by an Inherited Real Risk (IRR) of Brain Disorders (Stagnaro and Caramel, 2011).

The combination of Clinical Microangiology and "Angiobiopathy" theory (Stagnaro, 2009a), allows to consider schizophrenia as a disease resulting from a neurological and microvascular-based dysfunction (i.e., secondary to an impaired endothelial function (Vetter *et al*., 2015) associated with mitochondrial functional impairment (i.e., the congenital alteration of mit-DNA in related neuronal cells). Microvascular functions measured by fractal dimension of micro-vessel oscillations, in accordance with the above quoted papers, show physiological complex behaviour (deterministic chaos), while loss of their complexity is sign of pathology (or predisposition to disease).

QBS is a new discipline in the medical field and an extension of the classical medical semeiotics with the support of quantum and complexity theories. It is a scientific trans-disciplinary approach that is based on the "Congenital Acidosic Enzyme-Metabolic Histangiopathy" (CAEMH) (Stagnaro and Stagnaro-Neri, 1987), a unique mitochondrial cytopathy that is present at birth and subject to medical therapy. The presence of intense CAEMH in a well-defined area (i.e., myocardium) is due to gene mutations in both n-DNA and mit-DNA. This is the basis for one or more QBS constitutions (Stagnaro and Stagnaro-Neri, 2004a) which could bring about their respective IRR (Stagnaro and Caramel, 2012, 2013a,b).

QBS method allows the clinical and pre-clinical diagnosis of IRR of various brain disorders (Stagnaro and Stagnaro-Neri, 2004b; Stagnaro, 2009a; Stagnaro and Caramel, 2011) through the auscultatory percussion of the stomach (Stagnaro, 1985a,b, 1986). Made with the aid of gastric aspecific reflex, this diagnosis is consistent and dually reflects the informative nature and quality of parameters collected by QBS microcirculatory investigations. The pathophysiology of QBS reflexes is based upon local microvascular conditions. In case of genetic alteration of both DNAs, intense CAEMH, and IRR of Brain Disorders, there is a microcirculatory remodeling, especially intense under environmental risk factors,

due to vasomotility and vasomotion impairment (e.g., functional imperfection) and structural obstructions, i.e., pathological Endoarteriolar Blocking Devices (EBDs) and Arteriovenous Anastomosis (AVA) (Stagnaro, 2009c). According to QBS, most of these inherited impairments are already present, in a similar form, in micro-vascular neurobiological systems and clinically observable since birth, through ureteral reflexes diagnosis.

Briefly, in health, from the microcirculatory point of view, during stress tests, both vasomotility (chaotic-deterministic oscillations of arterioles) and vasomotility (chaotic deterministic fluctuations of nutritional capillaries and post-capillary venules) are maximally activated (Stagnaro and Stagnaro-Neri, 2004b; Stagnaro, 2009a; Stagnaro and Caramel, 2011), particularly in frontal, pre-frontal and limbic cerebral regions. On the contrary, in individuals with a family history positive for schizophrenia and, of course, in patients in the first stages of schizophrenia, under identical conditions a dissociated form of microcirculatory activation (type II dissociated) appears, characterized by increased vasomotility, decreased vasomotion and lower chaotic oscillations compared with healthy subjects. The flow- and flux-motion in the cerebral microcirculatory bed appears to be clearly decreased, due to the dangerous phenomenon of the so-called "microcirculatory blood-flow centralization."

It is generally admitted that schizophrenia diagnosis, particularly in initial stages, is usually difficult; however, QBS diagnosis allows to identify IRR of schizophrenia even when the patient is asymptomatic (i.e. in pre-clinical stages, or even from birth).

Inherited Real Risk of Schizophrenia: Bedside Diagnosis

As in all other IRR of pathologies, including the neurodegenerative disorders, the genetic predisposition to schizophrenia is transmitted by the mother, even if apparently healthy. Therefore, a mild Inherited Real Risk (IRR) of schizophrenia (SZ) is present in all mothers (100% of examined cases) of patients suffering for this disorder, or at IRR of SZ in its different stages of evolution (early stages, IRR in strong evolution, etc.).

QBS is able to make IRR of brain disorders diagnosis in particular through the auscultatory percussion of the Stomach as applied to elicit the brain 'Gastric Aspecific Reflex' (GAR) - related with the non-local quantum behaviour of biological systems (Stagnaro and Caramel, 2011).

In health, "intense" digital pressure (800-1200 gr/cm^2) on the vertex or on the scalp projection of the right or left prefrontal lobes does not provoke simultaneously GAR (the reflex appears just after 16 seconds due to physiological tissue acidosis); thus there is not IRR of brain disorders and this is the physiological state (Stagnaro, 2009a). If the stomach moves simultaneously, dilating for at least 1 cm or more, then there is IRR of brain disorders or overt brain disease (if the stomach dilates more than 1.5 cm). Once an IRR of brain disorders has been established, then the diagnosis should be refined in order to identify whether or not a certain patient is exposed to an IRR of Schizophrenia. In case of IRR of Schizophrenia, the specific trigger points (to be stimulated with low-medium digital pressure, 300-600 gr/cm^2), are located on the frontal and prefrontal areas of the scalp (as well as inferior occipital) and the left posterior temporal lobe (Heschl gyrus). When a medium low pressure stimulus is applied on the afore-mentioned trigger points specific to IRR of Schizophrenia, the following parameters have been observed in the patients either with aspecific symptoms or at an early stage (asymptomatic): latency (less than 8 sec), duration (more than 4 sec) and stomach dilatation (1,5 cm – 4 cm).

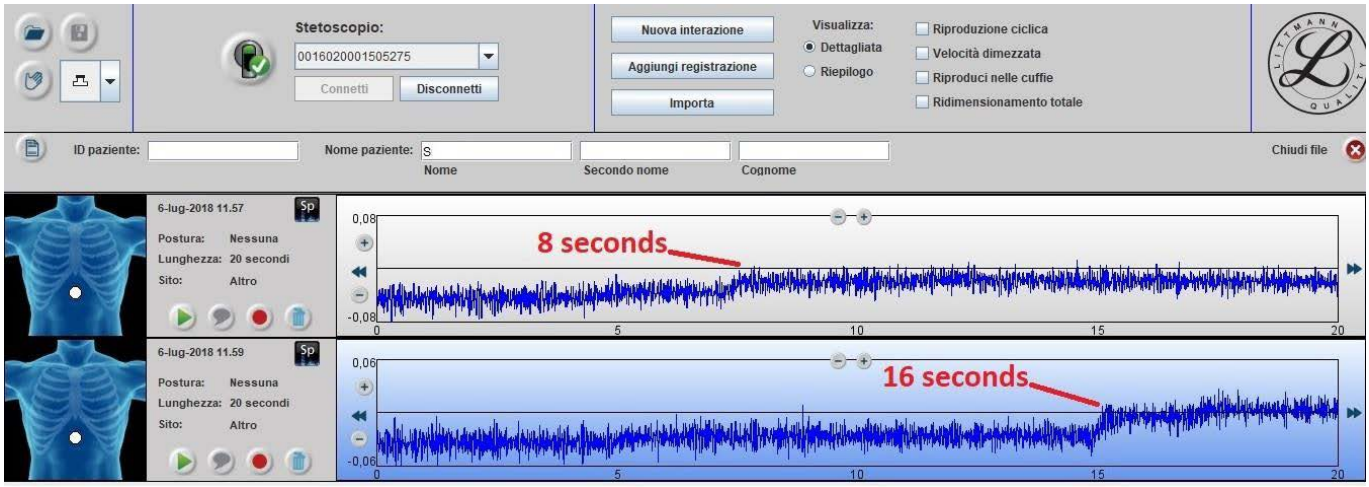
LATENCY time (in seconds) of GAR, following application of an intense pressure stimulus (magnitude 800-1200 gr/square cm) over the vertex of the cranium

Normal	16 seconds
Aspecific Symptoms	0 seconds
Early stage brain disease	0 seconds
Overt brain disease	0 seconds

DILATATION (in cm) of GAR, following application of an intense pressure (magnitude of the stimulus 800-1200 gr/square cm) stimulus over the vertex of the cranium

Normal	0 – 0,5 cm
Aspecific Symptoms	0.5 – 1 cm
Early stage brain disease	1 – 1.5 cm
Overt brain disease	1.5 – 4 cm

CONTRACTION (cm) of GAR, following application of an intense pressure (magnitude of the stimulus 800-1200 gr/square cm) stimulus over the vertex of the cranium



Graph 01. Measurement done by Litmann 3M 3200 placing the bell of the electronic stethoscope on the skin projection area of the stomach. In healthy patients under intense stimulus applied on brain trigger point the Gastric Aspecific Reflex (GAR) appears physiologically after 16 seconds (modification of the sound of the graph), while under stimulus of mean magnitude in schizophrenia trigger points, the GAR appear after exactly 8 seconds (physiologically, negative sign of IRR of SZ).

Normal	0 cm
Aspecific Symptoms	0 cm
Early stage brain disease	0 – 0,5 cm
Overt brain disease	1 – 1.5 cm

IRR of Schizophrenia:

Stimulus: Low-medium pressure (magnitude of the stimulus: 300-600 gr/cm^2*)*

Trigger points: posterior temporal, inferior occipital, frontal and prefrontal, slight posterior anterior pressure (300 gr/sqcm2) on the lateral part of ocular globe

	LATENCY (in seconds)	**DURATION (in seconds)**	**STOMACH DILATATION (in cm)**
Normal	= 8 s	3 < D < 4	0 – 0,5 cm
Aspecific Symptoms	≤ 8 s	D ≥ 4	0.5 – 1 cm
Early stage brain disease	< 8 s	D ≥ 4	1 – 1.5 cm
Overt brain disease	<< 8 s	D >> 4	1.5 – 4 cm

Inherited Real Risk of Schizophrenia: Primary and Pre-Primary Prevention

QBS tools are not only useful for diagnostic purposes, but also for therapeutic monitoring, because they are able to measure the microcirculatory activity before and after each treatment, in order to understand the effectiveness of treatments and interventions applied. At this point, we could wonder whether QBS Constitutions and IRR of degenerative pathologies are reversible.

Through a proper prevention treatment termed "type A" or "green" therapy, i.e., modified Mediterranean diet, CoQ10, conjugated-melatonin, carnitine, a genetic reversibility for future generations is possible (Stagnaro and Caramel, 2013c), but this could not be enough for the current generations, especially under environmental negative conditions. The green therapy stimulates the activity of mitochondria by acting on metabolism, the peptides' net, improving and normalizing mitochondrial and tissue oxygenation, and expression of the normal operation of mitochondrial oxidative phosphorylation. Indeed, the mitochondrial functional cytopathy above mentioned (CAEMH) is the 'conditio sine qua non' of more frequent and severe human disease and not. By this way, tissue oxygenation and mitochondrial activity are improved, mitochondria are running well, but it remains the genetic alteration of mit-DNA: CAEMH, QBS Constitutions and IRR of disorders are still positive (the IRR becomes "residual"). This means that a continuative "type A" therapy averts the risk that the disease can emerge, despite the genetic problem is not yet healed.

QBS method allows an efficient pre-primary prevention with recursive effects able to reverse the genetic alteration of mit-DNA and the mitochondrial cytopathy at the base of neurodegenerative pathologies such as AD. This is possible under a Type B or blue therapy. In particular, we have successfully used a Quantum Therapy (Stagnaro and Caramel, 2013c,d) for the pre-primary prevention of cancer, Type 2 Diabetes Mellitus, osteoporosis, Coronary Artery Disease and Amyotrophic Lateral Sclerosis. "We are not going to regenerate new neurons, but we will stop the decline," McKew hopes. In this respect, Quantum Therapy's central action mechanisms

consist in remodeling neurological centers, when heritably altered.

Conclusions

Overt Schizophrenia is not reversible by currently available medical treatments, and research is concentrated mainly on genetic, histopathology and clinical tests. QBS can provide for schizophrenia a biological preventive evaluation, because biological system functional modification parallels gene mutation and the subject's neurological and social developments. Furthermore, QBS is able to make a diagnosis of schizophrenia not only at the first very initial stages, but even many years before clinical manifestation, therefore allowing an efficacious primary prevention and prompt implementation of those measures and preventive treatments which can favour healing of IRR of schizophrenia or other severe neurodegenerative disorders.

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