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IN QUEST FOR SCIENTIFIC PSYCHIATRY:
Towards bridging the explanatory gap

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ABSTRACT

The contemporary epistemic status of mental health disciplines does not allow the cross validation of mental disorders among various genetic markers, biochemical pathway or mechanisms, and clinical assessments in neuroscience explanations. We attempt to provide a meta-empirical analysis of the contemporary status of the cross-disciplinary issues existing between neuro-biology and psychopathology. Our case studies take as an established medical mode an example cross validation between biological sciences and clinical cardiology in the case of myocardial infarction. This is then contrasted with the incoherence between neuroscience and psychiatry in the case of bipolar disorders. We examine some methodological problems arising from the neuro-imaging studies, specifically the experimental paradigm introduced by the team of Wayne Drevets. Several theoretical objections are raised: temporal discordance, state independence, and queries about the reliability and specificity, and failure of convergent validity of the inter-disciplinary attempt. Both modern neuroscience and clinical psychology taken as separate fields have failed to reveal the explanatory mechanisms underlying mental disorders. The

data acquired inside the mono-disciplinary matrices of neurobiology and psychopathology are deeply insufficient concerning their validity, reliability, and utility. Further, there haven't been developed any effective trans-disciplinary connections between them. It raises the requirement for development of explanatory significant multi-disciplinary "meta-language" in psychiatry (Berrios, 2006, 2008).

We attempt to provide a novel conceptual model for an integrative dialogue between psychiatry and neuroscience that actually includes criteria for cross-validation of the common used psychiatric categories and the different assessment methods. The major goal of our proactive program is the foundation of complementary "bridging" connections of neuroscience and psychopathology which may stabilize the cognitive meta-structure of the mental health knowledge. This entails bringing into synergy the disparate discourses of clinical psychology and neuroscience. One possible model accomplishment of this goal would be the synergistic (or at least compatible) integration of the knowledge under **trans-disciplinary convergent cross-validation of the commonly used methods and notions**.

PART I. Epistemological foundations

INTRODUCTION

Since the very historical definition for psychiatry (JC Reil, 1807) as a medical discipline there existed the explanatory gap originated by the mind-brain debate.

There are two traditions that may be demarcated. First, there is the **medical tradition as found in anatomy and physiology**. Perhaps Thomas Willis (1621-1675) is the best known early modern practitioner of this science. Willis studied the brain most carefully, and in fact compared a normal brain with the abnormalities he found in patients who had congenital mental retardation. His most detailed work on abnormal behaviors is *Pathologiae Cerebri et Nervosi Generis et*

Hypochondriacae (1670). Most often this tradition sees the brain to behavior connection as strictly causal. In one version this tradition is ontologically reductive.

The second tradition relates the **brain (and other bodily workings) to the mind, and then the mind to behavior**. Perhaps the best known early theorist in this research was René Descartes (1596-1650), who in his *Les Passions de l'Ame* (1649) attempted to describe the bodily bases for human passions, and theorizing how unchecked passions lead to abnormal or excessive behaviors. Various types of relations are hypothesized in this tradition as to how the brain (and body) affects the mind, and as to how the mind then affects behavior. In this tradition the mind is often treated as a separate ontological kind, and is taken to have representational properties that are responsible for behaviors. In some versions, the way in which the mind brings about behavior is held to be non-causal.

Of course, there are intermediate positions, and some confusing attempts at combination. One such would be the position of Sigmund Freud (1856-1939), who held that the mind was explanatorily independent from the brain, but not ontologically. He held that one day we would be able to explain mental pathology in terms of brain functions, but until that time one needed independent mental constructs to explain the etiology of such pathologies. So Freud was not reifying the mind as a separate ontological entity, but did hold that it had due to its representational (or ideational) nature, the mind could be (and for therapeutic purposes had to be) discussed in ways independent of the physiology of the body.

In 1807 Johann Cristian Reil coined the term "psychiatry". The very etymology of this term suggests pure curative (*iatreo: to heel* (gr.)) nature of psychiatry, not necessarily associated with scientific causal explanations. To a great degree even current psychiatry remains basically "healing practice" that hasn't developed yet normative disciplinary structure and language. Thus it remains isolated from many other areas of human knowledge. One further step was Wilhelm Griesinger postulate (1845) that mental diseases are in fact brain malfunctions.

Yet at the same time the simplistic physical explanations (school of "somatics" and Jacobi) were opposed to the spiritual explanations of mental disorders, generated by religious traditions. 'Treatment' was by exorcism, though in some forms this spiritual cause may be seen even in XIXth Century ('psychics' and Heinroth in Germany).

In more contemporary times, the waning of psychoanalytic (and other theories of psycho-therapy) influence has been accompanied by increased work on the brain to behavior medical model. The rise of theories of about the roles of serotonin and dopamine typify this new version brain causing behavior theories. But even this has expanded to include more physical causes than just the

brain; one large body of work is searching for genetic causes for abnormal behavior. Neuroscience has reported advance the functional morphology of the nervous system.

But the other tradition has not died away. Many neuroscientists are seeking the causal correlates on consciousness, which is held to have effects on behavior in ways different from bio-chemical causality.

These problems became extremely significant at the end of XXc. when "scientific" psychiatry was proponed by Spitzer & DSM III (1974) and consequently in R. Kendell's (1976) conceptual vision for psychiatry as a kind of "proto-science". Thus special interest is to be paid to descriptive character (or phenomenalism in the common sense) of the international psychiatric classifications (that is, the so called 'evidence') in comparison to the scientific classification (or categorization) in the other fields of the natural knowledge, medicine and biology in particular. One contrast to be outlined is between psychological, psychiatric explanations which use 'mental' terms and the ordinary (traditional) medical diagnoses and explanations that are (almost wholly) put in physical terms.

The transitional area between the genome and the phenotype (behavioral level) is occupied by the endo-phenotype (*Gottesman et Al., 2003*). It includes the whole diapason from the genetic diathesis to the clinical phenotypes, namely the brain metabolism and electrophysiology *ex tempore* (during task performance), chrono-biology, cognitive psychology and so on. Different endo-phenotype concepts were designed for schizophrenia and bipolar disorders (*W.Drevets et Al., 2007*).

The aim of the present study is to examine the influence of neuro-scientific methods on the introduction of significant criteria for scientific diagnosis and explanations in psychology and, specifically, in psychiatry. We intend to emphasize explanations for different mental states, with a concern for the diagnostic issues entailed; namely to study the relations between the explanatory and "diagnostic" (taxonomic) aspects of mental disorders.

Our study is focused on the frame shift of scientific research in neuroscience from "exploring the brain itself" (pure neuroanatomy and neurophysiology) towards "exploring the mind-and-brain as "unified system in health and disease".

For this reason we introduce in the first section an optimal model of refined cooperation between basic disciplines (as biochemistry) and clinical cardiology in the sample case of myocardial infarction. It is compared then to the cognitive situation in psychiatry. There are adopted some preliminary regulatory definitions for the evidence strength in clinical psychology and psychiatry. The underdeveloped scientific status of the field is

demonstrated with a meta-empirical case study from biological neuropsychiatry. The core problem is addressed in a narrower scrutiny of one particular experimental design. It represents one presumably advantageous study of brain activity and clinical patterns. The major epistemic limitations are outlined as: temporal discordance (i), problematic reliability and specificity of the data acquired (ii) and lack of convergent validity (iii) between the constructs of neuro-biology and clinical psychiatry. In the next section we develop another case study in the field of clinical psychology. Having in mind the limitations of both approaches we suggest another complementary model for integrative or conformable dialog between neuroscience and psychopathology. In our perspective this theoretical model may affect in a great extent the current taxonomy, therefore diagnosis and treatment effectiveness.
The quintessence of our claim is:

(i) values and narratives themselves are an important counterpart of the psychiatric assessment but they are exposed to the risk of drowning into the floating sands of "*understanding it makes it normal*" or anti-psychiatry without rigorous scientific evidence basis.

(ii) Current psychiatric evidence is nothing else but fragmented/ extracted from the context patent's narrative. Insofar there is questioned its reliability and validity, especially convergent validity with the data from other branches of mental health knowledge, such as clinical psychology and neuroscience.

(iii) Neuroscience and clinical psychology seem not to care about convergent validity either.

(iii) due to both poor evidence strength and interference of the values psychiatry remains a "proto-science"

(iv) therefore we introduce the notion of "proof" (though in non-conventional sense), to say that we need convergent cross-validity of the facts emerging in the multi-disciplinary

matrix of psychiatry in order to stabilize its meta structure and set a prerequisite for the formulation of adequate meta- language.

I.

Let us start this preliminary theoretical exposition with a sample case, adopted from the clinical bio-medicine. This case is supposed to demonstrate in an appropriate way how the "ideal pattern" of epistemic configuration of the cross-disciplinary communication should look like as it regards the health sciences in general.

Case study on bio-medical correlation in the example of Myocardial Infarction

We assume several interconnected methodological levels of assertion.
The first one entails the **basic biological indicators (markers) associated repeatedly with the disease state.** Dependent on the various medical issues these markers may involve methods and background data from genetics or from the epigenetic protein and metabolic processes. Those of the data concerned with genetics are state-independent and thus are sensitive to the health/disorder distinction but less specific as the clinical analysis demands differential diagnosis potential of the marker. The markers which originate from bio-chemistry (resp. clinical chemistry) are more specific when a certain abnormal state entails from environmental and multifactor influences.
In the particular case of myocardial infarction such markers are:

- Creatin - phosphokinase (CPK) enzymatic MB fraction and
- Elevated concentrations of troponin.

The latter are embraced as more reliable (in the sense of stability) and valid (in the sense of causal inference) markers for ischemic damage of the heart. Troponin protein is a cellular component, interacting with cardio-muscular contraction and its acute release into the peripheral circulation is always consistent with myocardial cellular death. This underpins a strong causal connection and causal inference. The statistical reference also

indicates at the relatively high rate exceeding 90 % of the diagnostic value of this bio-chemical marker for acute phase of the myocardial infarction.

Let's say this must be the prototype of epistemic 'proof'.

The second level of methodological significance, which is presumed to validate the underlying (ongoing) biochemical processes indicators, is in the area of patho - physiological findings. In our case these are X-ray dynamic invasive examination records. It is an established common practice to assess the obstruction of the blood flow via coronary arteriography. This method may visualize the degree of the obstruction as well as to demonstrate other functional morphology in details (e.g. the functional capacity loss of the ventricles). It can also localize the specific region of the infarction.

The third level of cross-disciplinary linkage is the level of the clinical observation and the self-report of the patient. Usually there exists a strict overlap of these three levels (or areas of knowledge) which asserts the clinical causal reasoning by inductive inference.

This means that the clinical severity of the myocardial ischemia corresponds to the patho-physiological findings as well as with the bio-chemical correlates. In this sense the facts from those three domains of exploration are cross-validating each other. They are also stable as it regards the repetition of the results, sensitive to demarcate health from disease and specific enough to differentiate acute infarction for the other forms of ischemic disease.

Therefore the data from all three domains are incorporated in the classification diagnostic and treatment standards.

II

Having in mind this prototype "ideal case" of coordination between biological science and clinical practice, we aim at the development of similar pattern of cooperation between psychiatry and neuroscience. It is very important to stress beforehand on two essential aspects of our perspective.

In first place, considering the high diversity of social and cultural values interfering with the natural evidence as well as the extraordinary complexity of the mental disorder we do

not advocate the establishment of an equipotent to the “myocardial infarction” model. We have no fundamental claim at identity or inter-theoretic reduction necessarily matching the classical ‘bridging law’ concept. Our goal is the achieving of either convergence or a conformable dialog between neuroscience and mental health disciplines. The integration and inter-play of the facts from both fields consists the scientific foundation on which any further diagnostic procedures are grounded. We can not develop for instance a “comprehensive assessment” (or values-based assessment in the terms of Bill Fulford and Juan E Mezzich) having not reliable and relatively stable scientific basis for explanation and understanding of disorder.

Given the example of ischemic disease any further collection of knowledge, predominantly in the area of molecular biology does not discredit the conceptual explanatory model as described but only expands the knowledge towards novel and more advantageous predictive criteria, respectively point out relevant risk factors. This supports the prevention strategy in global public health. The very foundations of the causal explanation of myocardial ischemia remain relatively conservative. The new data emerging just complement the current explanatory constructs. So far the modifications in the classification and nomenclature systems seem not to touch in any way these foundations.

What happens in psychiatry is that there do not exist any similar stable fundamental constructs which may integrate the cross-disciplinary structures (or at least improve the communication between the different branches) in the areas of interconnected concerns. Thus the very concept of the mental disorder and the consequential particular issues are challenged by many “paradigmatic” distortions which vary in the different cultural and national contexts. This reflects on international standards which appear to be only conventional. Therefore every revision in the “Mental and Behavioral Disorders” chapters either in ICD or DSM causes tremendous debate in the academic and professional community.

As a result the everyday practice in psychiatry is governed by a multitude of divergent “rules” and incoherent concepts. It is given bellow the outline of a longitudinal history of a patient, which illustrates this incoherence.

T.P., 42 years old: academic background in the field of philosophy. He was admitted to psychiatric clinic for first time at the age of 22 in 1988. The diagnosis was a "catatonic form" of schizophrenia. It is worth stressing that the syndrome of catatonia has very distinctive clinical features compared to the other constructs in psychopathology. It requires psychomotor phenomena like stupor or excitation, accompanied by dreamy like state with picturesque experiences reported by the patient after the acute phase of the episode. T. has been hospitalized a further four times in the next 20 years in different psychiatric hospitals each time his diagnose being revised. The range of diagnostic hypothesis varied from paranoid schizophrenia, through bipolar affective disorder to schizoaffective disorder. Any of these categories is supposed to have strong demarcation criteria as envisaged in the classification standards ICD and DSM. The revision of the diagnostic status has enormous consequences in the treatment strategy and most importantly in the long-term prognosis of the psychological and social functioning of a patient.

Commentary: Such "frame shift" of the diagnosis is similar to as if there was shift from e.g. "myocardial infarction with ST elevation (elevation of the ST segment in ECG)" to cardiac arrhythmia. Contrastingly to the arrhythmias the ischemic infarction entails many complications and severe prognosis, thus is liable to more aggressive and complex treatment. Although both states have some overlapping clinical presentations (arrhythmia may appear as a symptom of the infarction) they have strict and clear differential diagnostic criteria based on the biochemical and physiological tests mentioned earlier. Notwithstanding the serious medical aspects of the "scientific anarchy" in psychopathology, there are a number of other issues to be considered. Most of the psychiatric diagnoses should include a dimension of normative social function. This function is often represented in legal and economical terms. For instance psychological/psychiatric expert testimony may be considered as crucial expert statement in a criminal court trial Mental health enquiry is also a critical argument in the procedures for personnel selection. In these cases any expertise disagreements may discredit the final judgment. Usually any court sentence or psychological personnel assessment have significant social and economical consequences for the person involved.

This case illustrates probably in somewhat “mechanistic” manner the contrasts in the common practices and procedures among clinical bio-medicine and psychological medicine. In this context it is also an example for the underdeveloped scientific status of psychiatry (RE Kandel, KWM Fulford) or namely its **status of proto-science.**

Our further scrutiny is attempting to construct an explanation for the “proto-scientific” cognitive situation is psychiatry via addressing the issues raised by the methodology and data on different levels of determination of mental disorder. Let me specify in advance that we prefer to avoid terminology like 'level' and 'hierarchy' because:

(i) there is no attempt at solution of the ontological problems of the mind and brain in this program

(ii) We are interested in how the scientific cross-disciplinary constructs (not the ontological kinds /properties) may actually interact in a synergistic manner

(iii) this is why we privilege the notion of "domains" or respectively 'disciplines'

(iv) **For these reasons we prefer to use a “horizontal” structure of inter-disciplinary cooperation rather than strictly “vertical” hierarchic structure.**

In this sense a mono-domain (mono-disciplinary, mono-level) explanations are demonstrated to be poor as opportunities of dialogue. There are many and different operators involved in mental health care problem solving (psychologists, social workers, and doctors). They come from diverse backgrounds and belong to distinct paradigmatic traditions. This is why it is of utmost importance to establish relatively compatible terminology and methodology between the different disciplinary languages in order to fit the general epistemic matrix of mental health care: let's say a "meta-language". An intra-correlative mono- disciplinary validity (as in clinical psychology) itself can not capture the whole picture of the mental disorder in its diverse complexity. Inter-disciplinary cross-validation is capable to enhance the "transcription" of the terminology and methodology and thus to enhance the dialogue between the mental health operators.

III.

Now we shall focus on the theoretical premises for the 'desired model for scientific psychiatry' as proposed.

Following Fulford, we divide mental health knowledge into realm of facts and realm of values. We also share Fulford's view for 'evidence based' assessment as a counterpart (not an alternative to) the 'values based assessment' approach.

Furthermore we assume the provisional **division of the realm of facts** into two interrelated domains which are supposed to differ in the level of satisfaction of the criteria for significance introduced in the above case study: stability, validity, sensitivity and specificity:

- Proofs: facts which satisfy in equal extent the four criteria and
- Evidence: facts which satisfy partially the four criteria, mostly stability and sensitivity.

Of course the two categories we introduce are de-contextualized from their original use when applied to our field of interest. Traditionally epistemology recognizes proof as logically deduced conclusion in contrast to the evidence which is defined as empirical or inductive inference. This binary opposition is exciting in itself for further exploration for logic and philosophy of science. However it is not the subject of this essay.

In order to clarify the working definitions we intend to further use in the following sections, let us illustrate the given meaning of the two notions two examples from fields of science and practice which do not belong to mental health in essence.

- Narrative vs. terrain archaeology. It is an explicit fact from HPS that the narratives used in archaeology are often involved into contradiction with the physical findings (terrain digging). This was the particular case with Troy, when Schliemann's excavations questioned the evidence available from literature sources such as "Iliad" (the archaeological narrative);
- Judicial science and practice: courts tend to distinguish [contestable] evidence (when it refers to testimonial narrative) from proof (when it refers to physical evidence). Legal practice credits more the second type of evidence.

We prefer to address these particular cases because in psychiatry the implicit controversy is quite similar. Contemporary psychopathology is still based on self-reports of the patients and the observation of the clinician, which are much like the narratives of a testimony or "Iliad" by Homer. Anyone has his own personal perspective and assessment of the story and it depends on the rationale of the judge or the jury (in the case with judicial practices) to credit one version or another. In the same way you may have been a delusional person in the modern cultural and ethnical context of Western Europe and regarded as a profit in other times and cultural situations**.** This is one of the key arguments of the anti-psychiatry movement generated in XXc by Foucault and Szatz who understood mental illness as a "socio-cultural phenomenon" (Foucault) or simply as a "Myth" (Szatz).

Our emphasis is put on the radically *embedded* *error of the so called 'scientific' psychiatry (including the theorists of DSM) which actually applies methods for quantitative assessment of the patient's narrative.* This is to say that for several decades experts believe that structured descriptive psychopathology is scientific. It relies upon the post-positivist concepts of C.G. Hempel and methods like self- assessment questionnaires (and personality inventories designed after the same model). These 'clinical assessment tools' are adjusted to easily and in a presumably "objective" mode collect data about subjective experience. But they do nothing else but retell the fragmented narrative of the patient pretending to have scientific structure (parted in scales and items)! The great multitude of such 'clinical tools' produces paradigmatic anarchy. Any method is assumed as valid if standardized with the same kind of method. The so called 'external' validity in psychology is supposed to be for example the correspondence of an IQ score with the evaluation (marks) of the student at school. In fact one inter-subjective method is validated with another subjective method!

In order to be really scientific and produce creative dialogue at the intersection of the humanities and neuroscience, however psychiatry needs to reassess the very notions of validity and evidence because the currently employed ones (as is exemplified in the case studies in the paper) are (i) not scientific at all and represent (ii)"monopolist" streamlines that preclude any constructive cognitive pluralistic account of the mental disorder as complex phenomenon.

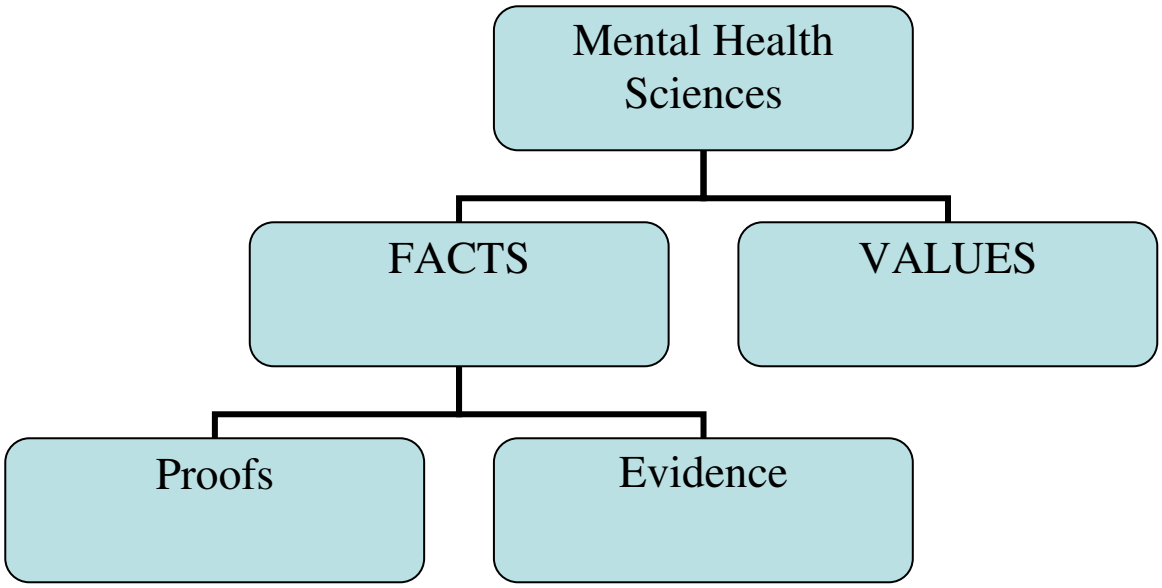
This is why we need a cognitive vehicle to "enable" the "translation" of the natural evidence into clinical practice and *vica versa*. And this cognitive vehicle in my agenda is the cross-disciplinary convergent validation which may delineate scientific "proofs". The proofs can bridge the explanatory gap and serve as prototypes for terms and notions of the "meta-language". The so called 'translational' neuroscience is promoting similar credo in the last few years but unfortunately it remains only a 'slogan' without any comprehensive intrinsic grasp of the problem.

On the other hand judicial practice introduces one more level of significance (credibility): the physical evidence (often named proof). Terrain archaeology applies almost the same approach. We propose this type of distinction for psychiatry: any physical, biological evidence is indicated for clarity as a proof. And the rest of the facts need re-validation against the available proofs.

It is crucial to underline that we do not privilege one method to the other! We introduce a pattern of corresponding validity of the data. In the same way as physical evidence (proof) may confirm the statement of the testimony, but the version of the testimony also sustains in some way the credibility of the physical evidence. The elevated troponin from our first case study is validated through coronary arteriography but coronary arteriography also serves as reverse confirmation of the validity potential and the specificity of the troponin test as bio-marker.

The power of evidence is mainly statistical and is more dependent thus on the research framework. There is enormous and controversial database collected in different paradigmatic ‘windows’. Any frame shift or ‘switch’ from one paradigm to another compromises the extrapolation of the results. At the same time psychiatry desperately needs secure facts (proofs) to improve its normative standards. The latter appear to be very weak and contestable due to permanent lack of grasp and mutual understanding between neuroscientists and mental health service operators.

Our further enquiry focuses on the crossing dialogue between these two main domains of the realm of facts (see figure).



In future proofs may not fill the whole '***explanatory gap***' existing in between the neurosciences and humanities dealing with mental health but hopefully may enhance the conformity of the dialog between the natural (neurobiological) and psychological branches.

IV. STATEMENT OF THE CORE PROBLEM (argument)

Case study from biological neuropsychiatry

The overview of the neuroscience – psychiatry interconnections covers a wide and heterogeneous correlation analyses. Some of hem originate from the context of behavioral genetics and are directed to linkage of specific genetic polymorphisms with the findings of neuro-imaging (A. Hariri et Al.). Other studies claim at registration of neural activity phenomena corresponding with the narrative of the patient - guided or non-guided 'introspection' (Den Boer, Fuchs). These investigations bring to life the

important connection between personal experience (phenomenology) and neuroscience, thus named neuro - phenomenology (Fuchs).

Our modest meta-empirical analysis is though focused on another aspect of the interplay between in vivo neuro-imaging methods and psychiatry – the challenging area of clinical psychological tools. Clinical questionnaires (inventories) are trait and state- assessment methods which are widely applied in the arena of psychiatry. Presumably they carry out precise and thus incorporated in the clinical judgment information about the individual characteristics of mental disorder. There are introduced a large scale of definitions for validity and reliability of the clinical assessment questionnaires. Notwithstanding none of these definitions with the respective criteria included addresses the data of neuroscience (see previous exposition). Neither the clinical neuroscience is interested in establishment of explanatory connections with clinical psychology, except the domain in it, which examines the psychological features of organic brain damage (neuro-psychology).

What happens in the current neurosciences – mental sciences dialog is that any of these two branches of science speaks its own language which seems to be untranslatable to the language of the others. As it was also stressed in one of our preliminary announcements (Machamer, Stoyanov, 2009), psychology and psychiatry puts all its terminology almost wholly in "mental terms" contrastingly to other fields in medicine, where the phenomena are defined in physical terms. The actual issue is related to the well known "***explanatory gap***" which exists in between neuroscience and psychological medicine. There are many theoretical and methodological conceptualizations of how is it possible to connect the two sides of this gap (Bolton & Hill, 2001, 2003, Broome et Al., 2009).

We tend to believe that with the introduction of our model of cross-validation we may further contribute to this debate.

This was our initial reason to select Drevets' 2006 paper as typical example of an explanatorily irrelevant correlation between a clinical depression assessment psychological rating scale and the respective findings from high-resolution fMRI.

This approach is considered as a prime example of one of the current patterns for a 'desirable' collaboration between neuroscience and psychiatry.

The main focus of their work is on finding the binding potential of the serotonin transporter receptor – a protein (neurotrnsamiiter) assumed by some to have substantial explanatory role in the pathogenesis (and treatment) of BAD. This is demonstrated using specific and selective radio- ligand assay in Positron Emission Tomography 3-D mode scanner. In other words the PET method applied is supposedly penetrating into the neural substrate of BAD. This research however is interested predominantly in the data acquisition about biding potentials. In their perspective, the psychological and psychiatric clinical assessment is just a kind of attendant data. The latter is collected with some of the common used evaluation instruments: DSM IV structured interview, Montgomery - Asberg Depression Rating Scale, Hamilton and Beck's Inventories. Psychological rating scales as well as the standardized interview usually consist of separate groups of items (questions, self-assessment statements, clinical observation reports). The authors presuppose the clinical data as consistent and perform the statistical analysis mainly of the imaging results and eventually post hoc correlation analyses of the clinical manifestations and the binding potential for serotonin transporter. It entails from the presumption, that the *clinical assessment data* are simply attending the biological study and thus are not essentially encompassed in the research agenda. This is the reason for conducting of the imaging radio-ligand assay temporally apart from the clinical examination. We will argue that such a neuro-biologically centered design does not take into significant account ***the corresponding validity*** of the clinical and psychological data but takes them as given. Insofar these data present mere statistical correlation and any further valid causal and clinical inference grounded on them may be questioned as non-legitimate. Besides it is worth mentioning also the fact that MADRS is not conventionally accepted for assessment of depression. Its major application is limited in Northern America. Another worldwide standardized tool is the McKinley and Hathaway depression scale from the Minnesota Multiphase Personality Inventory (MMPI).

Now we shall further scrutinize the different essential limitations entailed.

1

Arguments from chrono-biology

The first methodological limitation of such research model is deficit what we call "***temporal gap***" or **time discordance**.

This temporal gap between getting the PET data and administering the clinical depression test may affect the consistency of the correlations at least from chronobiological perspective

It is not specified in the experimental paradigm layout when the clinical examination is supposed to be given. Based on other papers presented in the field (Drevets et Al., 2007) we may guess it was given within the same day. Nevertheless as it has already been mentioned, many studies (Cornelissen, Halberg, Madjirova) demonstrate the instability of circadian rhythm of emotions, motivation, and hence cognitive performance as one of the cardinal features of BAD.

It is challenging even to synchronize the actually presented mood features with any other parameter within the normal fluctuations of the biological rhythm, as illustrated on the next diagram:

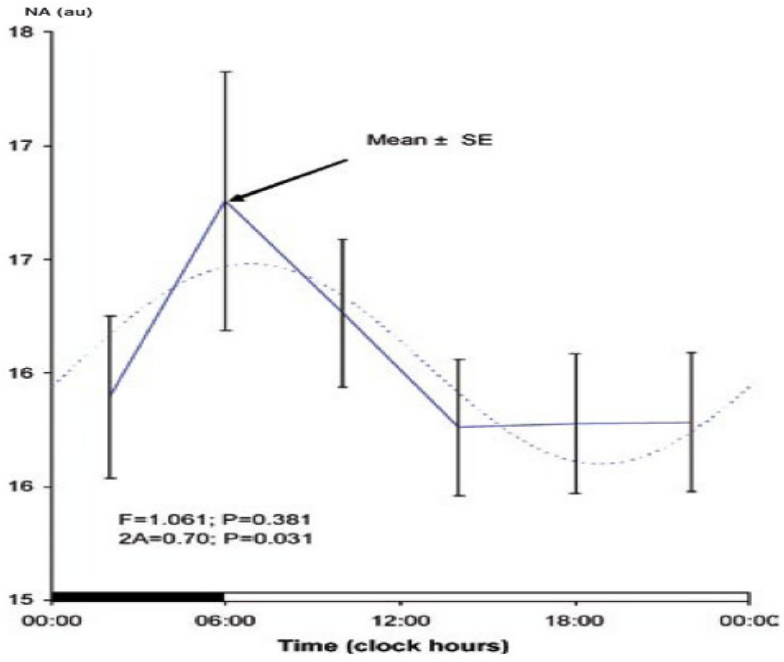


Fig. 2.
Circadian rhythm in negative affect

On this diagram (Cornelissen, Halberg et Al. 2005) it is illustrated the circadian curve of the negative affect (axis). It is evident that even a temporal gap from three and more hours is associated with considerable change in the dynamics of the affect. There are also many healthy individuals whose circadian regulation is defined as "arrhythmic", i.e. instable (up to 45% of the population (Madjirova, 2005)). In other words PET and clinical assessment may actually detect two different emotional states.

Furthermore in mood disorders it as practically impossible to synchronize the mental state with the neuro-biological investigation due to the manifest "desynchronosis" of the rhythms of affects and motivation unless the two measurements are performed simultaneously. Establishment of a simultaneous "**double blind control**" design will help to eliminate this confounding factor (see the end of the section).

2

Bio-marker's specificity and grading potential

So the instability of the rhythm may contaminate or distort the cross validation validity of the clinical and PET data. Such a confounding factor MAY compromise the grounds of any cross-disciplinary statement that *he evidence of the Binding Potential for STR is reliable and valid grading correlate of the clinical severity of certain syndrome.* Although such statement is not explicit the authors however conclude:" *the elevated 5HTT binding in cortex, thalamus, and striatum specifically [binding potential] correlated with the presence of anxiety symptoms [*Beck Inventory Score] *associated with BD…*" Moreover curiously it is stated previously that the severity of depression ratings (MADRS score) "…*did not correlate with the BP in any region*". That difference is of immense importance because according to the clinical psychological protocol Beck's inventory is designed for measurement of the severity of anxiety and MADRS - for evaluation of depression. The disorder in question is Bipolar Disorder - Current Major Depressive Episode. This means that there is no significant connection of the biological finding with the basic symptom of the mental disorder addressed. Insofar the second objection raised is that it was detected just the **presence** (vs. control subjects) not the **grading** of the anxiety. Eventually the authors simply elicit the presence of

accompanying symptom or from some point of view even an artifact! It is not helpful neither for the comprehensive diagnosis of BAD, no for the more precise drug choice and treatment plan.

In the same context if a bio-marker which is not registered ex tempore with the clinical phenomena it may be rather regarded as "surrogate" epiphenomenon than as specific causal correlate of disease. By definition any bio-marker must reflect on fundamental patho-physiological feature of disease. In order to detect the basic pathological process in the brain and in behavior as well a psychiatric biomarker should detect in a most precise way the characteristics of the mental state in real time. As it has already been shown even though Drevets' experimental paradigm detects the brain process, it is not coherent in time and as conceptual content with the psychiatric examination and psychological testing. This is why it is impossible to use such data to assert an **explanatory connection** of neurophysiologic findings and clinical conceptualizations.

Let me go in depth with this facet of the analysis. In the case of myocardial infarction troponin level was correlated to a significant enough extent with the coronary arteriography. This correlation is the prerequisite for the establishment of a valid trans-disciplinary explanatory connection. In particular it concerns the reconstruction of the intrinsic ***mechanism*** underlying the ischemic attack: obstruction of the coronary blood flow – myocardial ischemia – hypoxia – cellular death – leading to the release of cellular troponin into the circulation. This deterministic chain contains assertive reverse explanatory connection. Thus the latter could serve as a secure bio-marker of diagnostic significance, and if needed the specialist could skip the coronary investigation in situations where resources were scarce.. Often, though coronary intervention is indicated, the medical service may not have the necessary capacity in technological equipment and/or trained specialists to perform the invasive confirmation of the diagnosis. But the reliable and valid correlation of the arteriography and the increased level of troponin in the serum means it does not have to be performed (unless as therapeutic intervention), since the level of troponin is a reliable indicator.

If extrapolated by analogy to clinical psychology and psychiatry, we should assume that the neuro-imaging or genomic data are relevantly correlated with the psychiatric diagnosis. However PET or MAUDI-TOFF (genomic scan apparatus) tests are really

expensive and most of the ordinary medical services can not afford them. This argument reflects the practical aspect of the medical knowledge. As it was outlined by Retsner and Gottesman in order to serve as a diagnostic biomarker it should meet a number of criteria in first place specificity and **easy-to-perform non-invasive procedure.** The ordinary medical specialist must have in availability a convenient test which can measure secure correlate of disease with minimum resources invested, including technical equipment, chemicals, time wise. [Economical reasons often motivate the search for reliable but at the same time cheep diagnostic tools. Another typical example in this sense is the Pappanicolau cytological screening for cervical cancer.] Nonetheless we have no valid (i.e. referring to neuro-scientific findings) and reliable correlate of the pathological mechanisms underlying mental disorder. Drevets' results can not be interpreted as such because the correlation established is with **anxiety** inventory (i) and more importantly because the statistical analysis does not indicate any specific values of the two constructs, binding potential and anxiety score (ii). So this conclusion is only a valid indicator for the presence the symptom, **not for its grading!**

Further analysis revels that the post hoc statistical differences relative to control subjects range far from the expected significant *p* values. Therefore it is questioned in ***prima facie the reliability*** of the neuro-imaging data. Furthermore there is no reference to the clinical evaluation of the severity of the symptoms (anxiety and/or depression). It is disregarded the serious practical difference implied from the specific score of the psychological tool for the categorization of any mental disorder or psychopathological phenomenon.

The most plausible reason for this poor statistical record may be presumed from another article of the same group (2007). There are reported PET data about the regional metabolism with 18 FDG (radio labeled glucose, included in the essential metabolism of the neurons) in patients with bipolar depression. It is specified that the ratings were obtained in the same day with the PET scan and give though completely unsatisfactory correlation of the regional cerebral glucose metabolism with the severity of depression. It is evident that the *p* correlation values are again border to significant. Even though the authors state it precisely that "……"***none of these correlations would have remained significant after correction for multiple comparisons***." On the other hand mental disorder is by definition complex, multifactor state; thus multiple and diverse causal

mechanisms involved must be taken into consideration (*D Bolton 2008, RE Kendell 2003, KF Schaffner 2006*)

Again we face double blind experience from a methodological point: the regional metabolic anomalies reported are not helpful in diagnostic and especially therapeutic issues (i) and the correlation as demonstrated is in most general outlines – as positive and negative (ii). Insofar such rough and statistically insignificant results can not help to highlight the explanatory connections between patho-physiological processes and clinical features observed in mental disorders. However there is collected enormous amount of similar contradictory and uncertain results in different branches of neuroscience genetics, biochemistry, physiology etc. Most of them though remain only unproven hypotheses which are worthless for implementation in the current diagnostic and treatment procedures in psychiatry.

One major epistemic error in this cognitive framework is the presumption that clinical data is the problematic property addressed and the neuroscience can deliver the confirmatory instrument capable enough to establish sufficient explanatory models. Actually both disciplines turn to be problematic in respect to their evidence strength. Therefore each of their constructs needs further cross-validation it in real time with the corresponding external independent constructs. Such approach may serve as a model for "proof" as stated before. The proof on its hand is the ultimate prerequisite for introduction of convergent validity among neuro-biology and psychological medicine.

3.
Convergent operations validity

The crucial challenge before the neuroscience-psychiatry dialog is to create a certain model for equalization of the evidence strength among the corresponding databases of psychology and neurosciences. This can help for the formulation of "bridges" between the common used notions, methods and relevant information and hence to enhance the effective transference of data to clinical practice as it happens in the case with myocardial infarction.

Clinical psychological correlate may eventually replace the PET scan if there is satisfactory enough data for the convergent validity of the two constructs and their respective items in the same way as troponin concentration is replacing coronary investigation in many routine cases. For instance McKinley & Hathaway scale for depression assessment may relate to BP of 5HTTR in central brain regions in the same way as troponin is related to the coronary assay. In further perspective psychological test can help the drug treatment monitoring as specific phramaco-psychological dynamic indicator.

The third problem arising in Drevets' study as well as in many other similar scientific designs is that they are not addressing the problem of **convergent operations** validity. Such studies fail in demonstrating the real time correspondence of the psychopathological and neuroscience items. In the terms of cross-disciplinary cooperation the two kinds of methods (in vivo neuroimaging and psychological tests) are two different operations. In order to integrate their results and make them conformable (translatable) it is required not only post hoc established statistical reliability and specificity but mainly cross-validity of the correspondent data.

In our view there exist two kinds of connections of correspondent constructs:

- ***Intra-correlative*** representing the connections inside certain disciplinary matrix (or domain of disciplines). The validation of mono-disciplinary constructs is predominantly statistical per se. One psychological method is validated statistically with another or a neuro-physiological method is validated with neuro-biochemical test. This approach is sufficient per se for the regulation of the an intrinsic nomothetic network (notions, categories).
- ***Inter-correlative*** constructs play the role of explanatory connections between different (diverse) disciplinary systems. It is not satisfactory enough to reveal statistical (quantitative) reliability between such properties. One supplementary demand is the establishment of trans-disciplinary explanatory convergence of the qualitative compounds explored. Therefore this kind of constructs serves as precondition for the integration of the respective nomothetic networks via convergent cross –validation.

Inter-correlative convergence facilitates interplay ability and mutual exchange of the two kinds of methods in situations of economical deficit. For the reason of introduction of inter-play ability it is of utmost importance the accomplishment of simultaneous investigation of the phenomena: in our case the 5HTT BP in the cortex and basal ganglia with MADRS (Montgomery - Asberg Depression rating scale).

The reliability of the correlation (i.e. stability of the intra-correlative data collected) does not tell anything about its validity yet. Both domains of methods (from neurobiology and psycho-pathology) are characterized with limited trans-disciplinary convergence capacity of the cognitive content. The methods of neurobiology acquire specific high-technological research information, put in terms of biochemistry and patho-physiology which is difficult for transformation into practical knowledge. When applied in cognitive neuroscience psychological tests such as Raven IQ matrices are given only in parts and thus are not regarded as convergent operations but just as stimuli. Besides the sophisticated protocol and immense cost of the neurobiological methods, there is no sufficient grasp in the current literature of their possible diagnostic or prognostic validity and utility as well. On contrary the methods of psychology and psychopathology deliver data for the clinical diagnosis which are put almost wholly in mental terms. Convergent validity as presented in contemporary psychological standards requires the validation of the constructs with another presumably independent but also psychological, (i.e. mono-disciplinary intra-correlation) construct. Sometimes the validity construct includes sociological or other methods which however belong to the same domain of humanities. The only concept in psychology validated with external biological data is the theory of HJ Eysenck. Yet there are validated only several of its compounds (dimensions). This makes psychological assessment information irrelevant /inconsistent with the data of neuroscience and underlies the implicit discontinuity of the cognitive content among neuroscience and psychological medicine. On its hand the discontinuity obstructs the conformable dialog and inter-disciplinary cooperation. In terms of epistemology such results are no more *than mono-disciplinary conditions (or law like statements*). **Therefore they are divergent and inappropriate for establishment of any type of explanatory connection.** Most of the contemporary findings in neurobiology are similar

in their cognitive content and therefore they can not be incorporated in any way into the international classification standards.

Another argument refers to the counterbalance of the experiment. The counterbalance is methodological demand given the abovementioned effect of "desynchronosis". There are two time scale factors liable to elimination. One may register certain mind-and-brain pattern presumed as manifest depression on clinical level which correlates with the data of the receptor expression and binding potential in the brain. However it also may be false in cases when desynchronosis affects the adequate coordination/coherence between brain – body activity and the psychic experience. In terms of methodology the interpretation of validity is undermined **by false positive input**. The convergent validity could be established with the agency of two kinds of blind reports:

- One experimental "blind" study of the brain activity compared to the respective results from the psychological evaluation performed thereafter and
- One or two within 4 hours simultaneous control surveys in order to assert that the corresponding data are convergent indeed.

In addition the longitudinal course, structured data from the lifestyle may also serve as external convergent validity operation. The life events in the patient's history might be assigned with ranks /weight/ related back to the instruments of interest.

In conclusion to this case study the strategic limitation of such designs is exactly the admission of the clinical tools (as structured interviews; Montgomery – Asberg; Hamilton and Beck's scales) just for the reason of clinical assessment and thus its fragmentation from the other relevant data. However it is well known that mental states, either normal or pathological are very dynamical as well as are their neuro-physiological correlates. Therefore such design can not contribute in any way for the integration of neuroscience and psychiatry and hence for the improvement and stability of the psychiatric diagnostic and treatment standards.

As it is evident from this overview the more such neuro-biological studies are getting into depth with functional anatomical details the more they give a most superficial and rough account of the clinical psychological ratings. In this way they undermine the chances for integrative dialog with the real clinical practice.

Taking into consideration these limitations we propose another conceptual model for unification of neuroscience and psychological medicine.

V. Case study from clinical psychology

Current and historical theoretical backgrounds of clinical psychology and psychopathology

As it has been stressed in our study many of the psychological tests are designed in a pure generic way. In most general perspective there are two methodologies in the construction of the psychological tools: "*bottom-up*" from items to scales and constructs and "*top – down*" from defining the construct to the scales and the respective items. The first algorithm is inductive and empirical and the second is deductive and intuitive in its essence. There are further refined three possible approaches for scales construction (Burisch, 1984):

- *External or empirical.* Externalists distinguish types (or groups) of human personality and behavior, normal or abnormal without any claim at insight into the dynamics of verbal behavior in relation to the inner core of the personality (Meehl, 1945, Burisch, 1984). According to Meehl's argument the peculiar narrative of the psychological test responses is a "*verbal behavior of its own right*" which is often separate from the subtle personality core experience. Thus it is regarded to be related to non-test properties discovered empirically. In this perspective the scale membership of the items presumed is defined by factors external to the questionnaire itself. The common preliminary to item writing procedure is conduction of open-ended interviews with representative subjects from the target group (*respondent population*, Dawis, 1987). One standard recommendation of the empirical approach is to formulate the items in interviewee's own language, which is supposed to deliver a certain level of authenticity and to contribute further to its validity.

- *Inductive.* Inductivists tend to invent the items or more often to borrow them from previous tests. The ranging of the items and scales then is inferred from post-processing of the data accumulated under the "blind" administration of the test. The initial pool of items is picked on a 'random' principle or according to some theoretical prerequisite from earlier scales. Then the questionnaire is administered in a pilot study to a sample population. The items are grouped (ranged) into different scales with assigning of differential weight using statistical formats such as the Likert method and the factor analysis. The basic procedure performed in Likert's format is to select and group the items according to their ability to discriminate between higher and lower scores (ratings) on total score. Though the factor analysis and semantic differential suggest more sophisticated methodologies for item selection the clue assumption is the same: statistical assessment in arranging of the scales from the items included in the initial test pool.
- *Deductive or intuitive approach*. Here the items are composed and the scales construed according to a common sense formulations. The main idea is that it is suitable to invent the items as hypostasis of the presupposed general constructs. Basically personality traits (i.e. the constructs such as 'neuroticism' or 'depression') are determined beforehand in the terms of the everyday language.

In summary the external approach composes the items from an initial pool collected from opened interview narratives and then groups them into respective scales supposed to discriminate different properties. The inductive approach adopts structural items from previous tests, applies them to the cohort groups and composes the scales and constructs on the basis of data analysis. In deductive approach the choice and definition of the constructs precedes the formulation of the items.

Thus they have very poor or none at all theoretical basis but are construed in concepts adopted from the "folk" psychology unless the more sophisticated deductive approach. Of course there are also few exceptions such as the deductively constructed personality tests of Rorschach or Murray-Morgan (known also as TAT). On the other hand they have less or no practical application in the field of clinical assessment. These methods serve

mainly for the purposes of legal expertise (Rorschach) or social and organizational psychology (the method of T. Leary). At the same time they still suffer from various controversies with the norms (Garb, 2009), what compromises their utility.

However the vast majority of the psychological assessment tools are standardized according to entirely "*atheoretic" empirical procedure*. In other words the items have been selected and keyed on the basis of their ability to distinguish diagnostic groups. The basis for the presumed "independent" assessment is actually the clinical judgment of the psychiatrist. The current diagnostic hypothesis is raised and developed under the dominant psychiatric standard and is then is supplemented with the clinical psychological results. It is assumed that the psychological inventories are validated back to the psychopathological constructs and forward to the psychosocial outcome of the treatment.

Similarly, the external validation of a suicidal questionnaire is supposed to be the incidence of the suicidal behavior and the external validation of a personality traits inventory applied in personnel selection for the army is measured with the ratings of registered antisocial incidents on a mission.

As it has already been emphasized previously, both kinds of dimensions lay INSIDE the domain of *value-in* subjective assessment of human psychology, namely **the narrative**. This is why they can not be credited as truly 'external' and 'independent' validity operations. We assert therefore that only value-free facts (such as neurobiological constructs) can play this role.

This is exemplified in the case with one of the common used personality inventories: MMPI (Reddon, Marceau, Jackson, 1982). Addressing the particular topic of depression MMPI as one example of predominantly empirical scale construction (Hathaway and McKinley, 1938) has no explicit presupposition about the nature of depression. It relies upon the tacit clinical knowledge expressed in common sense formulations which correspond to the clinical reality. The main purpose of MMPI is diagnosis of personality disorders but separate scales of MMPI, as the depression and paranoia scale are also employed as independent measurements for other mental disorders.

Let us enter now into historical reconstruction of the exemplary case with MMPI. This personality inventory was actually the first one to face the problem of validity and though it has been revised numerous times is still regarded as valued instrument in clinical

practice as well as in other kinds of psychological expertise. Addressing the particular topic of depression MMPI as one example of predominantly empirical scale construction (Hathaway and McKinley, 1938) has no explicit presupposition about the nature of depression. It relies upon the tacit clinical knowledge expressed in common sense formulations which correspond to the clinical reality. The crucial methodological claim raised by Starke Hathaway reminds in an exciting way the future claim of DSM III-TR (Spitzer, 1973). His model is free of "theoretical burden" and is referring to the clinical reality as it is. In other words it is "*atheoretical*" in the same sense as DSM III and is conceptualized in the framework of post positivist descriptions of the verbal (in the case with MMPI) and non-verbal behavior. The central method applied by Hathaway was extraction of the actual psychiatric patients' responses to determine the direction for the item composition, scale construction and scoring. The method of contrasted groups was then employed in order to prevent the interference of theoretical rationale or intuitive guidance to contaminate the item selection. In practical terms there were compared the item frequency of endorsement among a group of patients (criterion group) judged high on the trait (say depression) and a reference normal group (or a type of control). Put in his own words, Hathaway aimed at "*sampling of behavior of significance to psychiatrists*". The source for the initial pool was over 1000 items withdrawn from:

- Contemporary textbooks and directions for case taking;
- Guides to mental status examination and the respective protocols attached
- Previously published tests/scales such as Humm-Wadsworth (1935)

The selection of the final 504 items was a process guided in two ways: the personal clinical experience and training of the authors and the linguistic considerations. The former were directed to limit the repeated items to 25 content areas assumed to be of clinical interest and the semantic considerations included:

- First person self-descriptive sentence declarative format of the items;
- Simplified wording based on the contemporary word-frequency tables
- Brevity, clarity and simplicity preferred to the grammatical precision

As far as these constraints governed mainly the cognitive structure and the form of the sentences, we become interested in their cognitive contents as a sort of pre-theoretical

supposition for the item construction. For this reason we did a scrutiny of the 1930-1938 publications in American Journal of Psychiatry. First of all it turned out that there was a guideline for diagnostic assessment: Revised classification of mental disorders (Statistical manual, 1934). This means that there existed standardized procedures and technologies for conducting and recording of a psychopathological interview. They differ of course from the later clinical practices but nevertheless allow the presentation of relatively structured data. We would like now to illustrate the outcome with the following samples from the original articles. The first record is from a paper published at the very time when McKinley and Hathaway started their project at the University of Minnesota. It is a publication on the language use in affective disorders and includes excerpts from an interview with the patient and subsequent language analysis. The following record represents an example for the contemporary attempts in elaboration of a structured interview. It is part from a publication on prognosis of mental disorder published in 1937 by Bond and Braceland The last paper gives us the image of the third-person narrative in case report by Grover.

Recording of March 2, 1937:

EXCERPTS.

(Now, how long have you been in the hospital?) Two days, I think. (And will you tell us a little bit about your illness?) You mean what I just told you? (Some of that, yes.) It's such a jumble of confusion that—How far back do you want me to go on it? (Well, tell me a little bit how you first started not to feel very well.) Well, I really think I started to feel the worst when I thought my father was dead, and we had a terrible, terrible mixup, my husband yelling at him, I'm confused as to just what he said, except that he'd take care of the situation or something to that effect, is in my memory, and that he shouldn't ask me to do as much for him, that I was trying to do the best I could for him. He shouldn't be unreasonable. That's right, I think that's the words, that's what it amounted to. And then my father saying that he had never had anything, worked all his life and tried to save money, and that he hadn't wanted to—wanted him to—around, and

never wanted him to give him a ride downtown with him in the car. Quite a bit of yelling and hollering. As I say, it was all a terrible hubbub in my ear. And then I remember, it seems to me as though I put my arms around my father's neck and kissed him and kissed him, and begged him to live, and that he did. The reason he was so terribly down and out, I thought, was because I'd been starving him, thinking that he couldn't eat food because of the condition he had been in.

Language Analysis.

Articulatory movements: Fairly vigorous, but not markedly so.

Pitch: The range of pitch is wide, with rapid gliding tones punctuating the speech. But the steep glides are used in conjunction with the numerous emphatic accents; they do not form a part of the rising and falling pitch movement that ordinarily belongs to phrase and sentence units. Were it not for emphatically accented words, this patient's speech would have a narrow pitch range. The pitch patterns tend to be stereotyped, for much the same pattern recurs with each emphasis.

Emphatic accent: The emphatic accents are excessively frequent. Most of the sentences contain several: *e. g.*, "When the food *did* go back on him, in *my* mind I thought it *was* sort of a paralysis, and that he *shouldn't* take so much food, that he *couldn't* digest so much food, because in *June* he had a *terrible, terrible* vomiting spell and just *shook, just* as hard as he could from head to foot." The contrastive type of accent predominates, but the rhetorical type is also used.

Tempo: Individual words are pronounced in a choppy, staccato manner. In the stream of utterance, however, the rate of speed is average (about 170 words per minute). Changes in speed are slight and infrequent, but sudden. Short phrases and word-groups, rather than long portions of the speech, are marked by a quick spurt or by a sudden slowing down of speed. Pauses are infrequent; they are primarily of the prosodic type.

Resonance: The resonance is strongly pharyngeal, but there is no glottal activity. Because of the emphatic accents, which have a heavy force of articulation, the speech contains many sudden changes in volume.

Vocabulary and phrasing: The patient speaks in a colloquial style. Words referring to concepts of degree are frequent, and they express notions of an extreme type. There is a good deal of repetition of phrase patterns.

Syntax: The syntactic structure is loose and often incoherent. Several of the sentences are broken, and many contain syntactic fragments that have no structural relationship to the rest of the sentence. The syntactic elaboration is rich, exhibiting a variety of techniques. The statements vary in length; phrases as well as complete predications function as statements.

Response: The responses are initiated rapidly. Some of them are short, consisting of a single statement; but once the patient gets beyond three or four statements, she is apt to continue speaking until interrupted. In her short responses, she tends to avoid or interrogate the question, but she is able to maintain rapport with the question throughout a long response. Although the statements cluster about a single theme, the line of development from

7433. Mr. S. W. R. Admitted 10-24-27. Dementia præcox—improved.

Father had convulsions to age 13, always sickly; a minister.

Paternal aunt had hysteria and "lots of imagining."

Patient is fifth of six children.

As child healthy, normal, "quickest of all the children."

In dentition very sick: strabismus developed which is now corrected by glasses.

At six to school; bright through high school and normal school.

Pleasant, kind, athletic, modest.

From 21 to 25 taught successfully.

At 25 entered a university: attended all social affairs.

Quiet and bashful, hard to get acquainted with.

Always one or two strong friendships with men.

"No time to bother with girls" or religion.

Clean, particular, exacting and methodical.

At 25 begged rides to Chicago: saw a clerk stealing and rode with a bootlegger.

Both he and companion saw bootlegger give signals and gave themselves up to police for protection.

On return he thought papers were stolen from his room and "broadcast": restless, depressed.

At 26 before admission hallucinated: "I am God." "I am I."

At 27 admitted to hospital: "They scoffed the Inferior." "Truly he was the Creator of all Laws": active and noisy.

Ideas of persecution became stronger.

At 28 discharged unimproved.

At 32 at home, "supporting himself, constantly improving as mother lets him alone. At times he is mildly upset." (From family physician.)

CASES 1 AND 2.—E. S. and H. S. Two sisters who present an identical psychosis. Little information has been obtained concerning their early life except that they were always said to have been peculiar. There is a difference of about 10 years in their ages, the older being about 50 years of age. Not much is known concerning their conduct before admission to a state hospital except that the janitress in the house in which they lived said she had known them six years; that they never visited with other tenants in the house and scarcely answered their greetings of the day. They dressed in a very fantastic manner and at times talked about their imaginary ideas. They were admitted to a state hospital in 1923 and were found to have a very bizarre trend of thought to which they have constantly adhered during their hospital residence since that time. They believed they were made by a machine which they referred to sometimes as "it" and sometimes as "he." Each one said that neither she nor her sister were ever born, but that both had lived for thousands of years. They felt very sure that all their activities were controlled by this machine and that they would never die. Their only explanation for admission to the hospital was that they lost contact with the machine for some reason which was unknown to them, but when they re-established contact with it their difficulties would be solved.

During all these years they have both clung very tenaciously to the ideas above expressed. When any attempt was made to obtain any information from them concerning their past life, they invariably reverted to their ideas about the machine as given above. They spent a large part of their time doing art work in the occupational therapy class and when not thus engaged sat together conversing in a very low tone of voice, always making sure that no one around them heard what they said. When interviewed together, the older sister took the lead in the conversation, the younger quickly agreeing to her statements. When interviewed separately, they expressed the same trends.

These patients were separated in the institution at times, but were so much depressed by separation and the one seemed to depend to such a great extent on the other that separation was not continued. During the periods that they were apart, there was no change in either as regards the false beliefs which they held. The older, more dominant, sister died about a year ago. Since that time there has been no change whatsoever in the younger sister. She sticks very tenaciously to the ideas she expressed when they were together. She insists the sister is not dead but that she has gone away.

It is interesting to note that the dominant sister was more masculine in her physical development than the other. Her pelvis was narrower and she had a much lower pitched voice. In fact if one did not see her one could well

It is evident so far that the critical part of the psychiatric statement was formulated exclusively on the basis of the value-loaded third-person descriptive psychopathological protocols, quite similar to the common practice introduced the same time by the German and French psychiatry. In practical terms the way McKinley and Hathaway justified the formulation of the items was deeply imprinted with the contemporary descriptive psychopathology and their own attitude to which particular **excerpt from the narrative** is or is not significant for the psychiatric assessment.

The instrument for the candidate item collection was structured interview: Hathaway himself summarized this as follows:

"…the entire venture began because…we wanted to condense those long psychiatric interviews which were very expensive for the patient"

This means that the goal of this inventory was determined in quite homologous way with the goal of DSM almost 40 years thereafter. Moreover according to Bucchanan (1994) the authors focused on their test's potential to standardize psychiatric diagnosis. It is crucial for our analysis of the cognitive content to refer to another statement of Hathaway:

"…no item was ever eliminated from a scale because its manifest content seemed to have no relation to the syndrome in question" (by Buchanan, 1994).

This was entailed as a consequence from two facts: (i) McKinley and Hathaway relied upon clinical experience and training (their own or of their peer's) in the item composition and (ii) they took it for granted that the contrastingly high clinical scores in the patient's group compared to the reference group were indicative and strong enough to be interpreted as suggesting some form of psychopathology.

Interestingly the same cognitive situation seems to take place in the previously given case from neurobiology: Drevets and his associates were registering phenomena of neural activity without any comprehensible relation to the syndrome in question!!!

Back to contemporary use of MMPI its main purpose is the diagnosis of personality disorders but separate scales are also employed as independent measurements for other mental disorders such as depression. A range of issues are raised by the kind of empirical approach implied in MMPI (Reddon, Marceau, Jackson, 1982):

A range of issues are raised by this kind of approach:

(i) Quite heterogeneous measurements which undermine the expert value of the diagnostic tools in many legal situations;

(ii) Overlap of the measures and bi-variant prediction;

(iii) No cross-validation of the item analysis, *viz.* the so called intra-disciplinary correlation inside the psychological domain;

(iv) No theoretical basis for scale keys and interpretations

(v) Reliability and validity of the criterion measures under suspicion.

Insofar many studies attempt to develop various statistical procedures for "factor analysis" following decomposition algorithms. Actually this type of redefinition of the test implies deletion of repeated or profile contaminating items and to some degree re-formulation of the rest of the items. Moreover the discriminate and convergent validity of the scales is established with the use of statistical techniques of comparison between similar types of methods. In best case it is revealed within the framework of multitrait-multimethod and factor analysis procedures. In this framework McKann (1991) pursued analysis of MMPI, MCMI (Million Clinical Multiaxial Inventory) and the "measurements" conducted via assessment criteria for DSM III (Widiger, Wiliams, Spitzer, 1986). A certain type of cognitive non-sense is introduced: quantitative clinical description of psychopathology is counter-validated with quantitative clinical psychological questionnaire. Technically the DSM assessment interview is driven from a similar if not identical **type of** cognitive content.

Our basic claim is that practically a clinical interview for depression and a clinical psychological rating scale consist of same kind of cognitive content. The provisional difference is instantiated with two comparable complementary cognitive structures. The test is composed of self-evaluation reports (items) formulated as questions or statements. The psychopathological structured interview (e.g. DSM) is formulated in the terms of subjective experience indicated as symptoms (actually these are self reports recorded by the physician) complemented with the so called 'signs' or the presumably 'objective' observations of the overt behavior of the patient. However the cognitive content of the clinical judgment is beyond any doubt the same subjective as the narrative of the patient. Insofar none of the compounds of the structured psychopathological interview is independent to the inter-subjective system created in the situation of clinical assessment. Therefore repeated protocols from various clinicians which serve to sustain the reliability claim of the 'scientific' DSM can not be regarded as independent measurement for the cognitive content and the value of the psychological rating scales or *vica versa*. This means they have

identical or at least similar cognitive content and **thus can play the role of independent validity operation for the other!**

Furthermore, in the context of our project there has not been demonstrated yet the trans-disciplinary convergent validity of MMPI as well as other similar questionnaire tools.

The previous dissection of the epistemic situation in neuroscience is very similar as no convergent validation with independent "external" to neuroscience methods is foreseen in the experimental paradigms conducted by the high technology neuro-imaging[1]. Thus most of the imaging research reports mainly empirical findings and can not capture the actual mechanism which underlies abnormal behaviors. Similarly DLPFC (dorsal lateral prefrontal cortex) is announced in different studies to be hypo-active (decreased metabolic activations in fMRI) both for psychotic and affective disorders (schizophrenia and major depression). One of the reasons for the inability of the conventional techniques to capture the mechanism is that it penetrates into the non-specific oxygen-dependent essential neural metabolic processes. Whilst the most probable candidates for explanatory mechanisms in pathophysiology of the mental disorders lie in the domain of the multimodal regulation neuro-chemical pathways and networks which might be localized in one and the same region according to the principle of multiple realization. As a consequence both psychopathology and neuroscience are governed by the scientific anarchy principle of "*anything goes*" (P. Feyerabend). This concern in a greater extent clinical psychology and psychopathology where hundreds of clinical assessment tools are invented and validated with previous questionnaires under the above-mentioned pattern of inductive construction of the scales.

It has been demonstrated recently in the studies performed by H. Garb (2009, Garb and Cigrang, 2008), most of the validity claims for the psychological tests are problematic because of multiple reasons. They refer also to the few personality exploration tests with highly sophisticated theoretical background as the test of Rorschach (Garb, 2009).

[1] *The one advantage of the information acquired from neuroscience to be considered is however the lower diversity of the methods and higher density of the data within smaller cohort groups*

The disagreement emerging in the arena of clinical psychology is inescapably interwoven with the uncertainty of the procedures and underpinnings of the justification procedures performed in psychiatry.

Insofar the conventional agreement standards in the development of DSM III-V (Aragona 2008, 2009) also seem not to satisfy the claims for 'scientific' concept raised by the authors of DSM. There are several constraints (Stoyanov, Popov, Korf, 2008, Korf, 2008) which undermine the scientific value of DSM. Even if we consider DSM as scientific it is neither falsifiable in the Popperian sense nor verifiable in the classical Aristotelian theory of the convergent truth. To this end there are no arguments strong enough to falsify/ verify the DSM or parts of it because of:

(1) Publication bias;
(2) Markers exhibit not enough power compared to the biomarkers in medicine;
(3) No therapies related in clear causal relation with markers and diagnosis;
(4) Brain not so deterministic to give strong causal relationships.[2]

Therefore we depend on robust methodology in order to obtain markers with significant brain-to-behavior and reverse explanatory connection which can further support the diagnostic reasoning and categorization as well as the therapeutic strategies in psychiatry. In the 2002 research agenda of Kupfer, First and Regier for DSM V there are discussed *inter alia* in one of the chapters the possible contributions of neuroscience. Anyway no satisfactory model for synergistic cooperation of psychopathology and neuroscience is exposed.

As a conclusion to this case study:

(i) We still need some source of external validity able to meet the "moral imperative" for turning psychology (hence psychopathology or at least a part of it) into a "robust science" (*'Nature' editorial, October 2009*). As it has been stressed several times in the essay this

[2] *We address here the traditional localization view for determinism*

imperative comes from the normative functions of psychiatry in many critical areas of expertise, i.e. the demand to establish cross-culturally relevant norms in order to prevent abuse

(ii) psychiatry is not unitary science but an inter-discipline, therefore it can not count sole on qualitative comprehensive values-based assessment though it should be aware and respect the values. The inter-disciplinary structure of psychiatry involves many facets from neuroscience which is regarded as one possible source of external validity. Neuroscience shares same notions and categories with psychopathology. But there are not introduced any relevant rules for "translation" of the data among these inter-connected domains of common interest.

If the case is a relatively homogeneous science (mainly in ontological sense, but also as domain 'location' of the explanatory mechanisms involved), then you might be skeptical about the possible value of the external validity. This is the case with many social sciences as well as many subareas of psychology such as social psychology. Their explanations vary inside the domain of humanities as far as they are concerned in quantitative assessment of human behavior. Note that even within e.g. sociology there exists a debate between experts who prefer to credit quantitative approaches (sociometrical) and those who believe it is impossible to capture in a 'scientific' manner the human relationships and the group interactions as well. The latter refer mainly to ethno-methodology (Garfinkel) and logic of the practice.

The problem with mental health is much more complex because we have more sophisticated disciplinary infrastructure, which is adopting data from divergent and very often incompatible domains of knowledge. So whilst a debate like the one in sociology counts on the intrinsic tensions and shortcomings of the different schools and conceptualizations, in psychiatry (and clinical psychology) it is related to different levels/domains of explanatory connections referring to the same terms and taxonomies. Psychiatry and clinical psychology will always exhibit or imply some inextricable ’understanding’ component. At the same time they are heterogeneous inter-disciplines which share various interconnections with biological sciences (neuroscience) of real practical significance. If you have certain type of destructive harmful behavior (as

violence) it is culturally irrelevant and incontestable as a subject of normative determination. As soon as it is determined abnormal and delusion-motivated it is liable usually to biological intervention based on assumptions adopted from neuroscience.

CONCLUSION to part I

According to our proposal we take the best existing clinical standard in the model of convergent cross-validation with the data of neuroscience and then get back to the clinical evidence in order to improve it.

We may regard this program as a radical "frame shift": then we need not to reconstruct past behavior/brain of other people, but you launch a novel and proactive research framework: an agenda to completely rebuild the taxonomy and therapy in psychiatry.

We have two measures (clinical and biological) considered as valid for different reasons. They are valid however inside their own divergent domains (disciplinary matrix) and thus are not liable for "translation" to the other. The simultaneous cross-validation is supposed to be the cognitive 'vehicle' to address a possible resolution of this problem. Any convergence of clinical assessment and neurobiological data will provide synergistic explanation for the mechanism of production of the disorder and facilitate the inter-domain translation.

There are some reservations applied to this model, namely:
(i) Psychological explanation itself is not "commonsense"; it has the claim at scientific validity
(ii) We examine the 'interface' between scientific psychology, cognitive neuroscience and psychiatry not for the interface with the commonsense (or folk) psychology
(iii) therefore the problem is entirely situated inside the so called "explanatory" domain: I do not expect to 'create' interface with the values and narratives as they represent to a great extent the common sense. The values and the narratives of the common sense are

another and quite important counterpart of the psychiatric assessment and case management. However if one counts on the values only as ultimate epistemic construct for understanding of mental disorder it will lead to nothing else but anti-psychiatry (iv) insofar I address the problem of convergent cross-disciplinary validity as a problem of the cognitive meta-structure of the explanatory disciplines. In my perspective they are supposed to give a relatively stable ground to be superposed with the comprehensive assessment of the narrative. This "scientific basis" has nothing to do with the current categorical taxonomies of DSM and ICD but is mostly complementary with the idea for broad diagnostic prototypes. (Mezzich et. Al 2005). In the terms of Schaffner my program is a quest for a type of "***reductive ethio-pathogenetic validity***", which may bridge the explanatory gap between humanities and neuroscience. It is supposed to be complemented with the "clinical validity", which actually includes the person-centered comprehensive assessment.

The simultaneous in extenso cross-validation is one complementary approach for the establishment of interconnections of the common used notions and categories, in other words a type of bi-conditional rule for translation of the data of neuroscience to psychopathology and vica versa.

On one hand this may eliminate to a greater extent the stochastic factor and the informational “noise” in the system. On the other it may facilitate the **equalization of the evidence strength** of the biological and psychological methods, consequently their inter-playability directed to economy of resources.

It needs to be emphasized that strong evidence (matching the criteria of specificity, sensitivity, validity and reliability) is the necessary foundation for the establishment of bi-conditional law-like constructs. A valid bi-conditional connection is the prerequisite for at least conformable dialog (i) or integration of neuroscience and psychological disciplines as well (ii). It may further expand the fields of exchange and interplay ability of the methods and data, respectively can enhance the unification of the common used scientific terms and criteria for validity. Finally the inter-play ability and unification underlies the possible effect of minimization. Minimization is directed to collection of maximum significant data with minimum recourses capacity invested. Basically in the

case of psychiatry this means revision (re-validation) of the clinical psychological assessment tools according to the evidence from the simultaneous cross-validation with neuro- imaging methods. As an outcome we shall have reliable but inexpensive instrument for exploration of mental disorders. These results can also affect the prevention and the treatment, especially the drug choice and therapeutic monitoring.

The critical point in this proposal is that both psychiatry and clinical psychology claim at evidential 'explanatory' component ***without*** neuroscience.
Here is the contribution of our program in this context:

1). Psychiatry and clinical psychology can not drive their claims for evidence validity from narratives. Narratives represent the values, evidence represents the facts. The facts of psychiatry are derivative from narratives; therefore they should not be regarded as evidence, but as fragmented de-contextualized narratives.

2). Psychiatry and clinical psychology share interconnected concerns with neuroscience and this is why they basically need cross-validation with facts anchored in neurobiology. This can define prototypes of real evidence, where both domains are mutually informed. The evidence strength is granted with my framework of equivalence, where the clinical psychological tools and neurobiological scan are regarded as convergent validity operations and none of them is privileged to the other.

Let us repeat again that this model does not affect the values counterpart of the clinical assessment. Its goal is only to provide stable fundamental explanations and taxonomy as the current ones seem deeply controversial and unstable. Without reliable and valid taxonomical apparatus and underlying explanatory connections to address the subtle mechanism of disorder psychiatry is governed by "*anything goes*" - complete epistemic anarchy (Stoyanov 2009) as well as the value loaded principle "*understanding it makes it normal*" (Gurova, 2010 forthcoming, Meehl,1968). The final outcome from such cognitive situation is anti-psychiatry or socio-political abuse with the instruments of psychological and psychiatric assessment. Taken as sole approach to the mental health

values - based assessment has not enough epistemic potential to fix either of these dangerous outcomes.

Our goal is not some sort of obsessive "hyper order" but a cognitive situation of extended probability and coherence of the nomothetic networks in mental health. If we apply metaphors from political engineering, the current situation should be described as "scientific anarchy" whilst we should aim at a status of "scientific democracy" or cognitive pluralism in philosophical terms. However pluralism should be at **the extent of compatibility** of the different views, not necessarily their unification.

There are three possible routes resulting from such investigation synergy.

- The one of them consists in discovering more similarities than differences between the schizophrenic and the bipolar spectrum. This will bring to a new life the classical views for the "unitary endogenous psychosis" of Zeller-Neumann-Griesinger and Klaus Conrad's concept in modern times.
- The second route is revealing true nosographic borders of the diagnostic ENTITIES in psychiatry which may lead eventually to its medicalization (we prefer the notion of '*scientification'*).
- And the third opportunity comes to be the maintenance of the discursive dialog in the areas of psychological medicine and neuroscience.

PART II: **Cross-disciplinary validation of the common used notions and methods in psychiatry and neuroscience**

(Methodological underpinnings of proactive project proposal)

Major premises:

Both modern neuroscience and clinical psychology taken as separate epistemic entities have failed to reveal the explanatory mechanisms underlying mental disorders. The data acquired inside the mono-disciplinary matrices of neurobiology and psychopathology is deeply insufficient regarding validity, reliability, and utility. There haven't been developed any effective trans-disciplinary connections between them as well.

One possible model for cooperation is a synergistic integration of knowledge using trans-disciplinary convergent cross-validation of the common used methods and notions.

The major goal of our program is the foundation of complementary "bridging" connections of neuroscience and psychopathology which may serve to stabilize the meta-structure of the mental health knowledge.

MOTIVATION:

Review of the contemporary state-of-art

1. Findings in healthy individuals

Our project's rationale rests on the emerging data from cognitive neuroscience *viz. Canli, Zhao, Rubino, Christoff, etc.* There is considerable database collected in the experimental paradigm of the dual-task problem solving including the IQ test of Raven, Tower of London, Tower of Hanoi, Wisconsin Card Sorting Test and other problem solving tasks.

- Besides the cognitive functions, a paradigm of personality influences on brain reactivity to emotional stimuli proposed by Damasio (1997) was used in the work

of T. Canli (2001). In it, responses to pictures from the International Affective Picture System (Lang and Greenvald, 1993) were correlated successfully with the personality scores determined with Neo-Five factor inventory (Neo-FFI[3]). (The FFI was administered after the scan procedure.) For instance, extroversion was found to correlate with the level of activation to positive compared with negative picture series, especially in the anterior cingulum, amygdala and other structures of the meso-limbic system. Neuroticism was linked to the levels of activation in the left temporal and frontal lobes. predominantly to negative pictures

- Another important consideration arises from the results of Fischer et Al. (1997), who compared specific basal ganglia activation to extroversion and neuroticism in the paradigm of HJ Eysenk. In this experimental design though the personality and brain explorations were conducted separately from each from the other, the authors give us a hint of awareness that the temporal gap between tests and imaging matters.[4]. This model is quite promising considering that Eysenck himself has predicted in his theory published in 1967 the brain arousal as neuro-correlate of the dimensions defined in his inventory (EPI).
- A meta-analysis of the subsequent developments in the investigation of amygdala activation during processing of emotional stimuli conducted by Costafreda et al. (2008) indicates significant predictors of distinction between the responses to emotional and neutral stimuli. The magnitude of amygdala reactivity to negative emotional stimuli was found to be greater than to unspecified positive emotions. Another conclusion driven from the same systematic review of 385 PET and fMRI studies are that external stimuli seem to be prioritized over internally (imagining) generated ones.
- In other work, especially of Rubino and associates (2007), there is a positive correlation between the measured medial prefrontal cortex activity and the phobic proneness response in individuals who were exposed to fearful and threatening facial stimuli during the fMRI scan. In addition they found a positive association between the personality style assessed with PMQ (*personality meaning*

[3] The Neo-FFI (Costa and McCrae, 1991) concept is derivative from the paradigm of HJ Eysenck (1969).
[4] This study is considerate about the time interval as it is specified that all the investigations were performed between 11am and 3pm

questionnaire) and the differential modulation of the prefrontal cortex activity during cognitive evaluation of emotional stimuli.

- The most recent report of the Hariri group (2009) further contributes to this mainstream work in "affective" neuroscience. They examined the relationship between individual differences of typical reactions to instructed or spontaneous emotional reappraisal and predictions of the responses in the distributed network of the amygdala and prefrontal cortex. Four blocks of perceptual negative emotional face processing were used as stimuli. The imaging results were then correlated with the scores of the reappraisal scale in ERQ (*emotional regulation questionnaire*), administered before the fMRI scan. According to their data acquired the self-reported reappraisal predicted decrease of the amygdala response activation and higher activity of the prefrontal and parietal cortical regions.

2. Findings in mentally ill individuals

- A number of recent reviews implicate the neural networks of the limbic-cortical-striatal-palidal-thalamic neural circuits which normally regulate the evaluative, expressive and experiential aspects of human behavior as well being the pathophysiological substrate of the affective disorders (Phillips, 2003, Drevets, 2008).
- These findings in groups of healthy individuals are consistent with a recent meta-analysis of the brain activations in depression (Fitzgerald 2008). The major areas of activation are summarized as they are recorded under the following conditions: rest, treatment, induction of positive and negative affect. Despite the complexity of brain – behavior regulation and the diverse imaging methods applied, it was claimed that determined patterns of considerable change in distributed brain regions are involved in the depressive disorder and may be positively identified with the neuro-imaging techniques. Basically these regions belong to the same cortico-limbic circuit as described in healthy individuals: DLPFC, pregenual anterior cingulate, insula, superior temporal gyrus, etc.

- In terms of neuro-chemical correlates, this system is operating mainly with serotonin, acetylcholine and modulated by glutamate and co-existing substances as endorphins. Central serotonin system, specifically postsynaptic 5HT 1A and 5A subtypes receptor deregulation is connected with depressive disorder in population genetic and genomic studies (Hariri, 2009, Stoianov et. Al. 2009), in vivo neuro-imaging (Drevets, 2008, Neumeister 2004), and in post-mortem neuro-pathological findings (Stockmeier 2003).
- Pharmacological citalopram challenge. fMRI results in the paradigm of Anderson (2008) also indicate anomalies of serotonin mediation at pre-synaptic level, namely of the 5HT 3C receptor regulation. This hypothesis is consistent with *ex juvantibus* data from the treatment of depression with selective serotonin reuptake inhibitors (SSRI). Basically this is our argument for the implementation of citalopram challenge in the experimental group of depression.
- There was recently introduced the *Olanzapine* challenge for investigation of the human reward mechanisms (Abler 2007) in healthy individuals as well as for assessment of the cortical function and longitudinal clinical outcome indicator in relation with COMT genotype in patients with schizophrenia (Bertolino 2004). One important methodological emphasis of our project is that most of the generalized "*mono-transmitter*" reductive theories like the Dopamine hypothesis have experienced historical failure (Kendler, Schaffner, in press). This is why we need informative "*connectivity*" model for exploration of the mental disorders. Olanzapine challenge is suitable for the purpose because (i) it is serotonin-dopamine antagonist (SDA), in other words it represents selective bi-modal ligand, affecting simultaneously two neuro-chemical systems; (ii) it is indicated for the treatment of both schizophrenia and bipolar disorder (especially mania syndrome). Another critical consideration entailed is that the neural pathways are not simply 'enhanced' or 'inhibited' as it was stated in many psychopharmacological theories, but deregulated *as complex compounds of the whole neural network.* For this reason we introduce multi-channel alternative instead one-channel working hypothesis,

- These arguments are coherent with the aberrant salience theory (Kapur 2003). According to Kapur [dopamine] is mediating the salience of environmental events and internal mental representations. Although salience theory is supposed to create heuristic framework linking biology, phenomenology and treatment of schizophrenia, it is plausible as a conceptual explanatory model for other mental disorders as well.

In summary the cognitive and clinical neuroscience of emotions and personality is concerned with correlating brain images and cognitive tasks or assessments, but questions about the external validity of such correlations remain. Though sometimes especially in cognitive science, the tasks and stimuli are presented with fMRI (subjects were in the machine at the time the tasks and stimuli were presented) the procedure is exclusively empirical: focused on correlation of the disparate properties of cognitive performance and neuroimaging. Particular experimental designs address narrow problems of cognitive (or emotional) stimuli processing. Insofar psychological cognitive tasks are **not performed *totally*** (i) and the research agenda has **no validation objective** (ii). In other words the psychological tests or emotional pictures in these methodologies **serve only as inert stimuli**. Further, most of the above listed methods are not routine clinical assessment tools in psychiatry (with the exception of the Raven IQ test). Nevertheless these results are quite encouraging because they have positive predictive value as it regards our experimental proposal.

Therefore **our basic hypothesis** is that if visual (facial) stimuli exhibit certain patterns of brain *cortico-limbic brain circuit* activity then the items of MMPI scale regarded as verbal stimuli should also serve to elicit specific areas a brain function that are thought, for theoretical reasons, to be part of the mechanisms by which these disorders are produced. We may complement them with another, more "clear" visual stimulus as well: the color personality test of Luscher.

Review of neuroimaging techniques

1. An examination of the modern neuro-imaging developments indicates that PET is inconvenient to perform when an extended task, e.g. a depression rating scale and or the test of Luscher, is required. Concerns include (i) the patient's exposure to ionizing radiation and (ii) the relatively short time of elimination of the radio-ligands from the brain receptors making this a bad measure for the administration of a lengthy psychological test.
2. fMRI also does not meet the requirements of our proposal. It is not specific or selective enough to illuminate the neurotransmitter dynamics which underlie the metabolic activation thought to be involved in psychiatric disorders. This means it can not register the subtle mechanism thought to be involved and thus cannot provide a sufficient explanatory account in terms of purported mechanism for production for the disorder. Moreover according to the argument of Korf and Gramsbergen (2008) the **BOLD signal actually detects restorative processes, rather than productive processes, i.e., those that preserve the iso-energetic balance of the brain after performance of certain tasks**. The same problem arises with 18FDG PET assays on metabolic utilization of glucose. fMRI results may give an account of an effect, but not of the causal mechanism that brings about the disorder. Thus, their relation to diagnostics and therapy of mental disorders is unclear.

We prefer to privilege Pharmaco - fMRI (Deakin, Anderson, 2002, 2008) as an alternative because:

- It detects a BOLD signal under specific modulator or challenge conditions (when specific drugs are administered) similar to the actual treatment substances agents. In this context pMRI might be used to measure the effects of drug action during certain tasks or in the presence of certain stimuli..
- There are emerging recent results from studies with number of agents: *mCPP* as an agonist of the serotonin auto-regulatory receptors (Anderson 2002), their

antagonist *citalopram* (Anderson 2008); second generation SDA antipsychotic *olanzapine* (Bertolino 2004, Abler 2007) *vs.* Placebo controls.

- Easy to repeat scanning without exposition to ionizing radiation.
- At the same time pMRI includes higher levels of spatial and temporal resolution and therefore time-and-region sensitivity of the drug effects (Ragland 2007).

Theoretical rationale:

Taking into consideration the limitations of the currently employed methodologies and experimental designs we propose another model for unification of neuroscience and psychological medicine; namely simultaneous cross-validation of the neural and mental phenomena. It may facilitate the **enhancement and equivalence of the evidence strength** among the biological and psychological methods. As a consequence their inter-playability will economize resources: revalidated clinical measures could be strong enough as the neurobiological markers. The simultaneous administration of the whole scales – *in extenso* cross-validation is one complementary approach for the establishment of interconnections of the common used notions and categories, in other words a type of bi-conditional rules for translation of the data of neuroscience to psychopathology and *vice versa*.

We expect strong evidence for relevant correspondence (convergence) with brain neuro-imaging and the following psychological battery of clinical significance:

- **McKinley and Hathaway** scale for depression from the MMPI and
- **MMPI scale for paranoia**.
- **Luscher color personality test**. (optional)
- Common used in clinical practice cognitive methods such as "Simple and Complex Analogies" test. (optional)

Justification for the emphasis on the McKinley-Hathaway depression rating scale:

The McKinley and Hathaway scale is actually one of the instruments employed in the overall MMPI. Our further arguments are as follows:

- The MMPI is a multi-axial (multi-phasic) inventory, presumably able to identify differentially the behavioral properties of several major diagnostic entities: depression, paranoid schizophrenia, and more importantly personality disorders. If our goal was the identification of only depression, then of course Hamilton, Zung or Derogatis are more suitable tools. However according to our definition the posed objective is to cross-validate a number of different candidate "prototypes' of diagnostic items with respective neuro-biochemical markers in order to set explanatory inter-domain connections. The two clinical rating scales are commonly used to diagnose two major prototypes of the psychiatric categories: bipolar disorder and schizophrenia as well as depression. In this sense MMPI encompasses broader diagnostic issues than isolated depression rating scale. **We hope to highlight the differences between brain signatures of the different prototypes brain disorders**
- MMPI is widely applied in "sub-areas" of psychiatric and psychological expertise: probably the most crucial is the personnel selection for the army;
- Historically MMPI is one the first empirical clinical inventory and many subsequent "inductive" inventories adopt some items and ground their validity claims on correlation with the MMPI scales;
- MMPI was designed on the basis of structured psychiatric interview, similarly to the DSM structured interview. So on one hand it is broad and relatively sensitive diagnostic tool, on the other it lacks a really "independent" source of external validity.

Justification of the employment of the Luscher color test:

- This method is assumed to be very sensitive in evaluation of emotional reactivity and the functional mental states.
- It has also biological and physiological theoretical background, similarly to Eysenck PI.
- Most importantly it represents single color tables: this may reduce the “noise” in the system via minimization of the cognitive processing of the input information. Particularly

the clarity of the stimulus is entailed from the elimination of the *gestalt* phenomenon (figure/background) and thus may preserve a shortcut to the emotional processing.

Contrastingly to modern neuropsychiatry in our paradigm is aiming at promotion of convergent and integrative assessment of the entire mind-and-brain mechanism underlying mental disorder. This is why **the clinical assessment tools are not regarded only as inert stimuli but also as convergent validity operations**.

Another critical facet of our experimental proposal is the simultaneous survey of the neuro-biological functions and their mental correlates. That is, the instruments of psychiatric assessment should be administered while the patient is being imaged. We underpin this aspect of the protocol with the **temporal gap argument.**

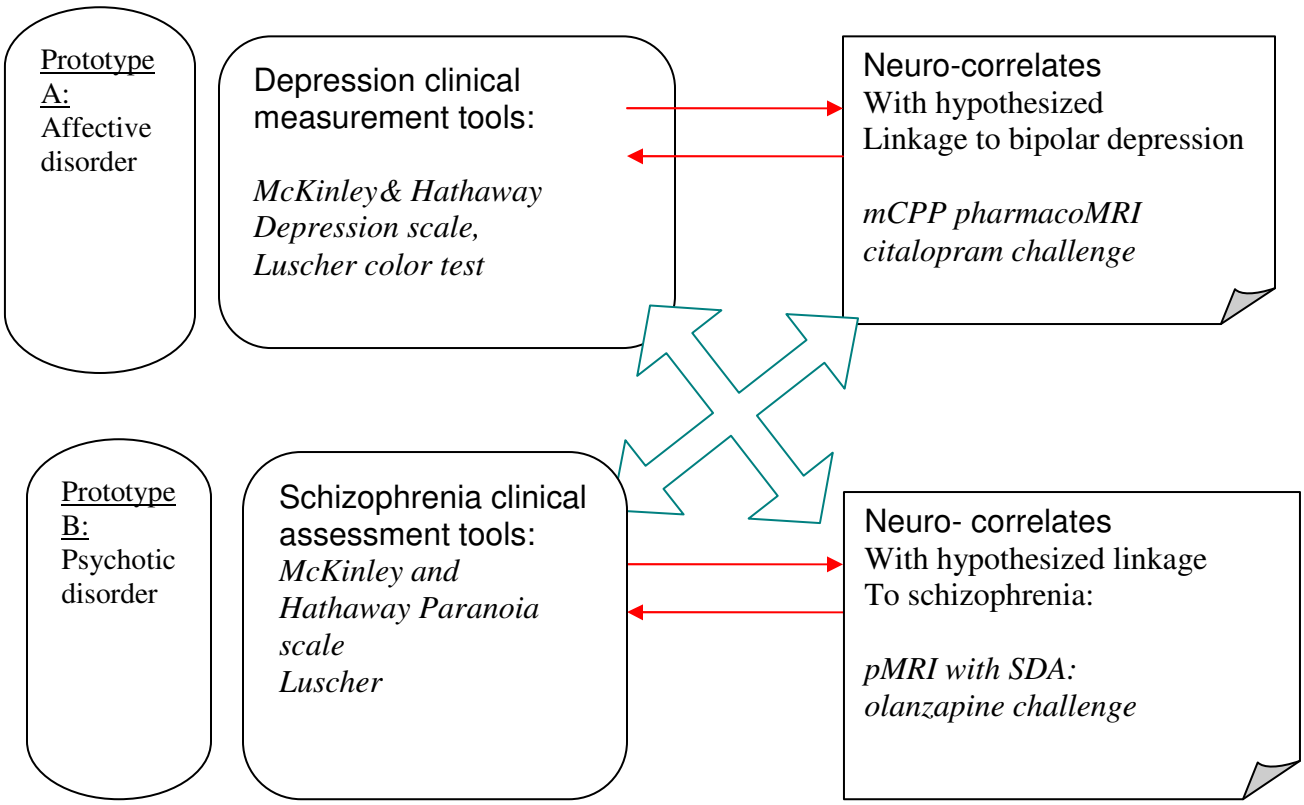
This temporal gap between getting the imaging data and administering the clinical depression test may affect the consistency of the correlations at least from chronobiological perspective. Even a temporal gap from three and more hours is associated with considerable change in the dynamics of the affect (Cornelissen, Halberg, 2001). There are also many healthy individuals whose circadian regulation is defined as "arrhythmic", i.e. instable (up to 45% of the population (Madjirova, 2005)). Furthermore in mood disorders it as practically impossible to synchronize the mental state with the neuro-biological investigation due to the manifest "*desynchronosis*" of the rhythms of affects and motivation. In practical terms **the imaging and the clinical assessment may actually detect two discrepant emotional states.** These phenomena may undermine the cross-validity unless the two measurements are performed simultaneously.

Establishment of an additional simultaneous "**double blind control**" design will help to eliminate this confounding factor (see the end of the section).

For these complex reasons the psychological tools must be executed IN EXTENSO (ii) and simultaneously (ii) with the neuroimaging, the essay repeated within the same day (iii).

<u>Objectives of the project:</u>

The cross-validation pattern model is illustrated in the next figure.



Remarks to abbreviations and legend:

Bmax : receptor density for D1, D2 and 5HT2a

BP: binding potential

Kd (dissociation constant): affinity

In the right section of the figure there are presented two prototypes of disorders in the domain of clinical phenomena assessment with the respective assessment tools used in everyday practice. In the left section there are presented two correspondent sub clusters of data/methods assumed to penetrate into the biological mechanism of the disorder group listed on the other side.

The model of cross-validation consists of two interwoven patterns:

(i) 'Orthodox' correlation between the correspondent clusters of notions aiming at establishment of convergent validity: indicated with red arrows;

(ii) First line open control: deliberate 'paradox' cross-validation of non-correspondent constructs. In other terms this control serves the purpose of discriminate validity test: indicated with intersecting green arrows

(iii) Second line blind control: measurement of the brain activity without any clinical data available

(iv) Second line blind control: counterbalance of the experiment: clinical ratings and brain activity detection performed simultaneously in other segment of the circadian cycle.

Hypotheses:

1. The item groups (scales, series of items) have certain neuro-correlates, which differ among the experimental groups. We are looking at significant correlations of the psychological rating scale score and the pattern of BOLD activity, which is corresponding to the density and occupation of the respective receptor population;
2. These neuro-correlates represent distributed (not localized) functional neural networks. For instance McKinley and Hathaway depression rating scale in depressive patients must correspond to activations of pathways which belong to distributed systems including nucl. accumbens, hippocampus, nucl. Amygdale, medial prefrontal and orbitofrontal cortex. On one hand these systems may exhibit operational properties of serotoninergic neurotransmission, demonstrated in pharmaco MRI with administration of 5HTR agonist such as *mCPP*. It is well known that limbic structures, hippocampus in particular have pluripotent re-transcription properties and may exhibit various neuro-mediator components in respect to the specific functional state of the mind-and-brain system. Therefore similar neural structures but modulated with dopamine or glutamate/GABA may express in a pharmaco MRI experiment when correlated with e.g. McKinley and Hathaway paranoia scale or series of projective personality test (TAT, Rorschach, Lüscher) in patients with presumed diagnosis from the schizophrenia spectrum. This way we may demonstrate the differential role of multiple realizations at the level of the neuro-behavioral regulation and introduce complementary data to

contribute in neuroscience-informed psychiatric taxonomy and treatment strategies.

3. ***The valid constructs in both psychological and neuro-imaging methods must operationally converge under prototype time-and-space correlations.***
4. All other constructs demand revision.

EXPECTED RESULTS and outcome:

On a theoretical level our project may reflect in a meta-empirical scientific program (agenda) for proactive research: fostering of the elaboration and validation of common used terms and notions. These proofs-based quasi axiomatic structures may secure the scientific foundations of psychiatry. On its hand being grounded on more or less uncontestable knowledge psychiatry may further expand the "inter-personal awareness" of the values and comprehensive assessment system. Eventually the concordance of the information from both values based and neuroscience-informed exploration can further endorse the Integrative classification and diagnosis project.

In the field of clinical psychiatry the stabilization *('scientification'*) of knowledge can improve diagnosis, prevention and treatment procedures and contribute to the medical prognosis of disease.

As it was already mentioned Eysenck's dimensional diagnosis project was later supported by neuro-physiological data. However there are some arguments which restrict the normative functions of the dimensional model and its derivative factorial personality models in clinical diagnostic practice. Mainly the factorial methodologies refer to 4 or 5 axial dimensions which is not satisfactory for comprehensive assessment and psychopathological diagnosis. On the other hand currently employed categorical diagnosis standards seem to be also irrelevant given the fallacies of DSM and ICD.

For this reasons we aim at endorsement of the *prototype diagnosis* with neuro-imaging bio-markers. **In this context our project is a long-term perspective, grounded on continuous and tangible convergence of clinical and neuro-biological operations. This entails determination of stable broad prototype taxonomic units demarcated with neuro-biochemical indicators and predictors of the drug treatment response**.

We take also into serious consideration the argument of *Broome and Bortolotti* (2009) that biomarkers can not serve as sole diagnostic criteria. This is why we aim at epistemic *"frame shift*" of the current taxonomies towards "high umbrella" prototypes, **further extended/ superposed with narratives of the person centered comprehensive assessment.** However the strong evidence (matching the criteria of specificity, sensitivity, validity and reliability) **can deliver the necessary, though not sufficient** (!) foundation for the establishment of bi-conditional law-like constructs between neuroscience and clinical psychiatry. A valid bi-conditional connection sets a methodological prerequisite for conformable dialog (i) or problem-oriented integration of neuroscience and psychological disciplines (ii).

It may further expand the fields of exchange and interplay ability of the methods and data, respectively can enhance the unification of the common used scientific terms and criteria for validity. Finally the **interplay ability and unification** underlies the possible effect of minimization. Minimization is directed to collection of maximum significant data with minimum resources capacity invested. Basically in the case of psychiatry this means revision (re-validation) of the clinical psychological assessment tools according to the evidence from the simultaneous cross-validation with neuro- imaging methods. As a result we shall rely upon inexpensive instruments for exploration of mental disorders.

Besides the diagnosis our project can potentially reflect the prevention and treatment, especially the drug choice and therapeutic monitoring.

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Provisional protocol:

Group A: Prototype of presumed affective psychosis

Group B: Prototype of presumed psychotic disorder from the schizophrenia spectrum

Group C: Healthy individuals

Counterpart method 1: battery of clinical assessment tests

Counterpart method 2: pharmaco fMRI: regions of interest include cortico – limbic functional circuit, operating with 5HT, dopamine, and glutamate/GABA.

Administration:

Simultaneous, double-blind, placebo controlled, counterbalanced within the same day, next segment of the individual circadian rhythm

Study design for group A:

- *Experimental condition*: depression + paranoia clinical rating scale and mCPP infusion/citalopram challenge.
- *Control condition*: paranoia scale
- *Alternative condition* (optional): olansapine or ketamine challenge

Study design for group B:

- *Experimental condition*: paranoia scale + depression rating scale and olansapine challenge
- *Control condition*: depression scale
- *Alternative condition* (optional): idem

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