INTRODUCTION: THE DEPRESSED PATIENT IN A NEUROBIOLOGICAL WORLD: HISTORY, NEUROPHILOSOPHY AND EVIDENCE BASED PSYCHIATRY

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Abstract: This essay analyzes possible underlying assumptions and provides bridge laws between various levels of complexity of brain processes. A short historical introduction on the main trends in neuropsychiatry over the last century is given. Then Kendler's philosophical agenda are discussed. The central question is: what kind of relationships between mental and neurobiological levels of complexity is or could become useful in the psychiatric practice? The philosophical analysis based on general systems theory and on Searle's concept, assuming the mind as a biological property of the brain. Consequently the individually unique mind exists in a similarly unique brain, containing all information acquired during life. Clinical investigations show that the occurrence and time course of some psychiatric conditions, such as depression, can best be described in stochastic models. Diagnostic systems and research agenda's should take into account for such uncertainties, that are not due to a lack of scientific knowledge, but might be inherent to the neurobiology of the brain, instead. The probabilistic nature of the brain, together with the possible involvement of multiple genes and other molecules may pose limitations on both the biological understanding of mental disorders and evidence based psychiatric practice.

1. AN HISTORICAL INTRODUCTION

From an historical point of view, mental disorders or any other used denominations to madness and insane persons, have always referred to both mental and materialistic concepts. In Ancient Greece, disease was thought due to an imbalance in the four basic bodily fluids (humors). Melancholia was described as a distinct disease with particular mental and physical symptoms by Hippocrates in his Aphorisms, where he characterized all "fears and despondencies, if they last a long time" as being symptomatic of the ailment. Melancholia was a far broader concept than today's depression; prominence was given to a clustering of the symptoms of sadness, dejection, and despondency, and often fear, anger, delusions and obsessions were included.

In the 19th century there was a movement in Germany, initiated by the internist and later psychiatrist Wilhelm Griesinger, stating that psychiatric illnesses are brain diseases ('Geisteskrankheiten sind Gehirnkrankheiten'). Sigmund Freud's psychoanalytic theory may also been considered as an early attempt to understand mental disorders in terms of bodily functioning. Indeed Freud his ideas were based in part on the notion that psychic processes depend on the functioning of neuronal circuitry: for instance suppression of thoughts or desires was considered the consequence of inhibitory neuronal processes. The 20th century introduced a new psychiatry into the world [1]. Different perspectives of looking at mental disorders began to be introduced. The career of Emil Kraepelin reflects the convergence of different disciplines in psychiatry. Kraepelin initially was very attracted to psychology

and ignored the ideas of anatomical psychiatry. Following his appointment to a professorship of psychiatry and his work in a university psychiatric clinic, Kraepelin's interest in pure psychology began to fade and he introduced a plan for a more comprehensive psychiatry. Kraepelin began to study and promote the idea of disease classification for mental disorders. The initial ideas behind biological psychiatry, stating that the different mental disorders were all biological in nature, evolved into a new concept of "nerves" and psychiatry became a rough approximation of neurology and neuropsychiatry. However, Kraepelin was criticized for considering schizophrenia as a biological illness in the absence of any detectable histological or anatomical abnormalities. While Kraepelin tried to find organic causes of mental illness, he adopted many theses of positivist medicine, but he favored the precision of nosological classification over the indefiniteness of etiological causation as his basic mode of psychiatric explanation

Biological psychiatry reemerged in the second at the turn of the 20th century. During the first halve of the 20th century treatments such as insulin coma treatment, drug- or electro-convulsive treatment and lobotomy have been practiced [1]. A breakthrough was the successful treatment of syphilis, often considered a mental disorder, supporting the idea that indeed mental disorders are primarily diseases of the brain (body). The causative organism, Treponema pallidum, was firstly identified in 1905. It was observed that some patients who develop high fevers could be cured of syphilis. Julius Wagner-Jauregg (Austrian physician, Nobel Laureate) tried in 1917 the inoculation of malaria parasites, which proved to be successful in the case of dementia paralytica caused by neurosyphilis, at that time a terminal disease. Later penicillin was explored and its effectiveness confirmed in 1943. Lobotomy (leucotomy) consists of cutting the connections to and from the prefrontal cortex, the anterior part of the frontal lobes of the brain and has been applied for severe psychosis, manic-depressions and compulsive disorders. Half of the Nobel Prize for Physiology or Medicine of 1949 was awarded to António Egas Moniz (Portuguese) for the "discovery of the therapeutic value of leucotomy in certain psychoses". Such interventions were prescribed for psychiatric conditions until the mid-1950s when modern neuroleptic (antipsychotic) and a little later antidepressive medication (monoamine inhibitors and tricyclic antidepressants, *e.g.*, imipramine) were introduced [1, 2]. The discovery of chlorpromazine's effectiveness in treating schizophrenia in 1952 revolutionized treatment of the disease, as did lithium carbonate's ability to stabilize mood highs and lows in bipolar disorder in 1948. Psychopharmacology became an integral part of psychiatry starting with Otto Loewi's discovery of the first-known neurotransmitter, acetylcholine. Later, particularly in the 1950ties, other neurotransmitters, including noradrenalin (nor-epinephrine; initially also epinephrine or adrenaline), dopamine and serotonin began to play their role in psychiatry, both in searching for the cause of mental disorders and in the development of new (psycho) pharmacological treatment options. Nobel prizes to Julius Axelrod (US American, 1970) and Arvid Carlsson (Swedish, 2000), Paul Greengard and Eric Kandel (both US American, 2000) illustrate the scientific recognition of neurobiology and psychopharmacology in the previous 5 decades. In the last 3 decades the position of the psychopharmacology has become very prominent, too prominent according to some. Indeed, criticasters have concluded that drug companies have invented psychiatric diseases that matches the pharmacological profile of their drugs, rather than the reverse: dugs were developed to cure diseases [2]. Genetics were once again (this following previous American investigations and after Nazi-Germany supported eugenetic practice) thought to play a role in mental illness. Other new approaches were developed, essentially to better understand mental disorders at a biological level, which may eventually assist the diagnostic procedures and imply more effective and rationale therapeutic interventions. For instance the analysis of body fluids, such as cerebrospinal fluid (as a direct derivative of the brain), blood and urine became prominent already in the 1950ties. In the sixties and seventies challenge tests were proposed to assess the receptors functioning or the responsively of the organism or some particular subsystem and associated receptors to stress or specific drugs. The dexamethasone suppression test (DST) and its more recent

modifications are prominent examples [3, 4]. Molecular biology of the 1980ties opened the door to search for specific genes contributing to mental disorders. Psychotherapy in various formats was and is still utilized, in particular as a treatment for psychosocial issues. Standardization of the diagnosis and assessment of the profile and severity of mental disorders was achieved with the introduction of diagnostic systems (such as the DSM, diagnostic and statistical manual, and the ICD, international classification of diseases) and with rating scales (*e.g.*, Hamilton rating scale for depression and anxiety) [1]. *In vivo* neuroimaging of the intact functioning brain was firstly utilized as a tool for psychiatry in the mid 1980s and abnormal patterns of both anatomical and functional features in various psychiatric disorders have been and are still claimed. Current neurocognitive approaches [5], making use of a variety of neuroimaging techniques, have contributed to the understanding of brain processes underlying normal and psychopathological mental activity.

2. THE PATIENT

The clinical management, and in particular the treatment options of most psychiatric disorders have improved during the last decades. And yet, despite the introduction and application of a wide variety of novel scientific approaches, methods and machineries, current knowledge of the basic underlying neuropathology is still poor. In the following sections I discuss some major obstacles hindering progress in biological psychiatry firstly in more general terms, and subsequently to illustrate my point of view on major depressive disorder (MDD) in more detail. Parts of the present exposé were published as abstracts [6, 7, 8]. Psychiatry is a medical discipline where the conceptualization of the mind and the brain determines to a large extent diagnostic and therapeutic approaches. Accordingly, the psychotherapeutic approaches are often considered to be opposed to or may perhaps even exclude neurobiological therapeutic interventions, for instance drug treatment. In addition, current psychiatric research literature witnesses a vast arsenal of efforts to relate biomarkers, such as hormones, neurotransmitters or genes and their variants, directly or indirectly to psychiatric disorders or some of their prominent characteristics or symptoms. In addition the neuroimaging modalities developed in the past decades have stimulated the search for brain processes essential in the manifestation of psychiatric pathology. Relatively simple and rather deterministic relationships or correlations between the (neuro-)biological parameters and psychological phenomena are presumed.

In his proposal for a philosophy of psychiatry Kendler [9] gives 8 basic presumptions to which modern psychiatry should adhere. These include: 1) psychiatry is grounded in mental, first-person experiences; 2) Cartesian dualism is false; 3) epiphenomenalism is false; 4) both brain—mind and mind–brain causality are real; 5) psychiatric disorders are complex; 6) explanatory pluralism is preferable; 7) embrace empirically rigorous and pluralistic explanatory models; 8) accept piecemeal integration of complex etiological pathways to psychiatric illness a little bit at a time. The issues raised provide a pragmatic albeit attractive summation of what psychiatry is, should be or might become. However useful these presumptions may be, I discuss whether or not Kendler's agenda does indeed offer a coherent philosophical and scientific framework.

I will discuss several assumptions underlying Kendler's philosophy [9], based in part on the previous philosophical discussion, and will emphasize the necessity of bridge laws linking the neurobiological and mental levels. Or formulated in practical terms: what kind of relationships between psychiatrically and neurobiologically relevant items is, could or should become useful in the psychiatric practice where a diagnosis has to be made and a therapeutic intervention has to be chosen. Central is the question whether there might exist an emerging property of the brain that is directly associated (or perhaps identical) with the mind. Important is also the notion that we experience ourselves as a single

autonomous person. Our conscious attention is focused on one or a few issues only and, moreover, our brain becomes more personal during life. Hence we experience ourselves as a unity, as a single person. Firstly I discuss these issues from a philosophical perspective. Next I show that fast processes in the brain, necessary to execute higher brain functions, including memory, do not directly depend on brain energy metabolism, and remain therefore invisible with current neuro-imaging technologies. These observations have led to the concept of isoenergicity as an emerging property of the brain [7, 8], that will be summarized here too. The basic concept defended here is that of a physically emergent, subjective, qualitative, unified feature of the brain, or which amounts to the same thing, that the mind is a mental, and therefore biological, and therefore physical, feature of the brain. The implications of this concept for disease, therapeutic interventions and psychiatric research strategies are discussed, with an emphasis on depression.

3. PHILOSOPHICAL PERSPECTIVES

This section considers some philosophical ideas relevant for psychiatry and is particularly focused on the mind-brain relationship. Firstly I approach this question from the point of view of the general systems theory, and subsequently from a monistic, materialistic angle.

3.1. GENERAL SYSTEMS THEORY

Even if one does not adhere to a dualistic brain/mind concept, the psychiatric practice is often dualistic. So the mind (psyche) and the brain (or body) are considered basically as different and non-overlapping entities. In this section systems (*e.g.*, body, brain) are entities that consist of elements (*e.g.*, particles, cells, molecules, neurons) and have a boundary, so it can be recognized from the outside. Systems, as used in the general systems theory [10, 11], might not only be considered as physical entities, but also as ideas or conceptions, so it might help to understand the relation and development of epistemological concepts. Stavenga [10] distinguishes 4 possible relationships between two systems (schematically depicted in figure 1 upper panel). Important is to note that interactions do occur only when the systems belong to the same domain, in the present case the physical or biological domain. Moreover, the current general systems theory does not imply that physical systems belong to only to one kind of system: instead any physical entity or system belongs to many (perhaps an infinitive number) of other systems. In the present analysis I consider the mind and the brain as 2 systems, provided that the mind can be conceptualized as a physical system. The first possible distinction is that the 2 systems are completely separated and have no interaction (the R0 relationship). In the context of system theory this contention is meaningful only if we regard the mind as material otherwise the mind has no causative power. Hence I reject substance dualism, as an impossible option. Having thus concluded, I discuss the other possible relationships. An R1 relationship means that the 2 systems have a common boundary, and this is the only site for possible interactions. For instance Cartesian dualism is an example of an R1 relationship, where the "seat" of the mind is the epiphysis (pineal), the organ that controls the brain. But this idea leaves us with the problem that the mind must anyhow invade the pineal and exert physical energy on the brain. The second possible relationship between mind and brain are the hypotheses that the mind is a product of the brain, like urine of the kidneys, and that all causative power is limited to the brain. These series of ideas (to be discussed in more detail later) might be recognized as R2 relationships. Although the mind may be considered in a R2 relationship as a materialistic system, it has little if any causative power by its own. Neuroscientist have questioned the mind or free will as causing behavior, because decisions (often in laboratory experiments) have already been made before the subjects became aware of their decision or, alternatively, the subjects gave irrelevant arguments for their behavior. This conclusion

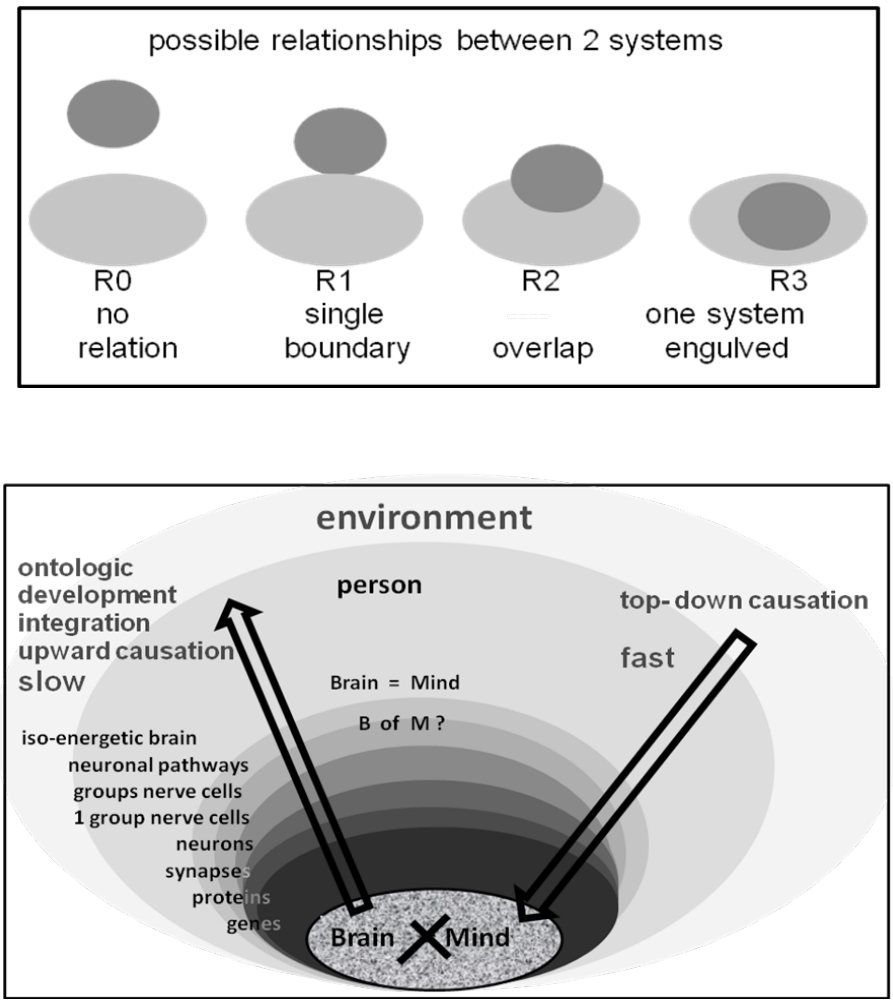

Figure 1: Cartoons of philosophical models on mind-brain relationships. Upper figure shows possible relationships of 2 systems according to systems theories. Accordingly the mind-brain theories may be described as R1-R3 relationship. Lower figure shows the levels of organization (or complexity) of the brain largely based on Searle his concepts. The lowest levels are molecules, whereas the higher levels are formed by aggregates of neurons and neuronal networks. Notice that the next higher level in the lower figure has an R3 relationship with its underlying level, as defined with the systems theory. Whereas the underlying levels has their own dynamics, it is also subject to top-down causation. On the other hand, from an ontological point of view, the higher complexity is an emerging property of the lower level.

may also have implications for psychiatry, as many behavioral therapies and psychotherapies are based on the information of the patient. The 3rd possible relationship between systems is that the 2 systems overlap each other, so that the state of one system is accompanied by a related state of the other. Stavenga [10] illustrated the R3 relationship as the condition of pregnancy: the embryo (system 1) is completely surrounded by the (pregnant) mother (system 2), although both the fetus and the mother have lives of their own. I consider the mind-brain systems as an R3 relationship: the mind is not only part of the brain and depends on that, but also that the mind has its own causative power. In parallel to this reasoning I summarize some philosophical concepts in the following section.

3.2. MIND-BRAIN PHILOSOPHY

The philosophical answer to eliminate dualism is materialism, that assumes that the personal mind (the subjective, qualitative, conscious mind) is reducible to or identical with objective phenomena such as neurobiological, behavioral or functional states, and that, therefore, the conscious mind is, more or less, an illusion (*e.g.,* "The ghost in the machine", the "Cartesian Theatre"). The mind has also been regarded as an epiphenomenon or, alternatively, as an emerging (non-physical) property of the brain ([12] and references therein). Considering the mind as an epiphenomenon tends to deny its importance for functioning and survival of an organism. The question with the emerging mind is: how can a non-materialistic mind (without matter and energy) affect a physical (causally closed) brain [12] [13]? A crucial issue with the "ghost" and the "dualist" concepts is how to imagine that a mind can emerge from a "nutshell filled with proteins, genes and other molecules". Or to put it in more refined terms, how can a splendid mind be the "product" of a neuronal or synaptic network? [14, 15] And how is it possible that even an interactive network of several (perhaps all) brain regions could give a unifying mind with a single focus of attention (the problem of binding? [15, 16]

One solution of such dilemmas is offered by assuming that the mind is an emerging but physical property that is in essence irreducible to all the underlying neurobiological processes. An emergent property is created by the interaction of several elements, but cannot be described as (or reduced to) the additive effects (or properties) of these elements. Formulated as a straightforward question: what is emerging from what? Does it mean that the mind as an apparently non-physical entity could emerge from an apparently physical brain? The issue has been discussed in detail by many philosophers including John Roger Searle [15, 17, 18] and Jeagwon Kim [13]. Kim discussed the concept supervenience "In this is the claim that what happens in our mental life is wholly dependent on, and determined by, what happens with our bodily processes" ([13] p. 14). Searle [15, 17, 18] argued that the supervenience stance leads to over-determination: the mind must be equated with a brain state, but to go to another state of the mind the brain has to change its state. I follow the reasoning of Searle: the only thing that can emerge (or supervene) from a physical (biological) configuration is another physical (biological) configuration. In neurobiological terms, either one has to explain (or reduce) the mind as (to) a property of a collection of any of the constituents of the brain (*e.g.,* proteins, genes, cells, aggregates of cells or neuronal networks), or there is an emerging property that cannot be conceptualized as or reduced to properties of these underlying brain constituents (Fig. 1, lower panel). Then the issue comes down to the question whether there might exist an emerging property of the brain that is directly associated with (or perhaps identical to) the mind. In Searle's terms [18]: there exist emerging properties of the brain that are both physical and mental (opposed to conceptual dualism: it is either physical or mental). The resulting mind-brain concept is indicated as biological naturalism [18] and is characterized "as bottom-up micro macro no time gap, where cause and effect are simultaneously realized and effect (macro) is realized as a macro-feature of the system made out of that microstructure (micro) that in turn explains the existence and causal powers of higher-level or system features" ([18] p. 54). This formulation is nearly identical with the R3 relationship of the general systems theory. Following Searle's analysis a major challenge the neurobiologist is confronted with, is to define a brain configuration that equals the mind. Particularly relevant here is the position of psychiatry in such conceptualization.

4. FAST BRAIN PROCESSING

This section pursues on the idea as formulated as an R3 relationship, as an element of the general systems theory, and as supported by the conceptualization of the mind/brain relationship by Searle,

where "cause and effect are simultaneously realized". I summarize some current ideas to illustrate the speed of processing of -what are conventionally denoted as- higher (psychological) functions. Neuronal transmission of information throughout the brain is based on the generation and propagation of action potentials and on fast neurotransmission between neurons, each lasting 2-5 msec. These neuronal processes are initiated by transitions of protein configurations within nanoseconds (more information in [19, 20]). As compared to the neural processes, how fast proceed higher brain functions, such as memory? This has for instance been assessed with psycho-physiological experiments. In linguistic experiments, done together with EEG recordings, it appeared that visually offered words can be recognized and subsequently vocalized within 50 msec [21]. Non-conscious cerebral processing of auditory and visual stimuli of less than 50 msec duration, are the basis of subliminal perception and masking experiments (and of related advertisements). Such experiments show that unconscious processing of information is very fast and requires only about 10 sequential neural processes (action potentials + neurotransmissions). But the millisecond range does not appear the fastest processing of information. For instance, binaural discrimination of sounds in the human brain is achieved already within 100 microseconds, *i.e.*, more than 10 times faster than glutamate neurotransmission [19, 20]. It should be realized that it takes far more time for (unconscious) information to become conscious; according to Libet's experiments at least 0.4 s [22], *i.e.*, about 10x slower than memory recognition and more than 4000x slower than binaural discrimination.

Interpersonal communication is essential for the expression and assessment of a psychiatric disorder. One criterion is whether or not the disorder can empathically be understood, as defined by Dilthey and Jaspers ("Erklären oder Verstehen"; understanding versus explanation) [23]. Such distinction is strongly supported by the discovery of mirror neurons, which are groups of neurons that become active during watching related motor activity of littermates. In particular mirror neurons in the frontal cortex appear to be involved in empathetic processes; they may be less or inactive in autism. The prefrontal mirror neurons have no direct connection with sensory information, so the question is how they get the input (information) necessary for firing. This can best be understood in terms of unconscious brain activity preceding the activation of the mirror neurons. Considering the speed of (higher) neural processes the brain may "recognizes" empathically relevant environmental clues and subsequently "shapes" the activity into a format to activating prefrontal mirror neurons in a few milliseconds. It takes several hundreds of milliseconds before mirror neurons become active after watching behavior of a littermate. This delay is remarkably similar to that for a sensory stimulus to become conscious [20, 22].

Fast brain processes are essential to achieve a unitary action (also termed binding) of the brain and may eventually evoke conscious perception and activity. fMRI and any other neuro-imaging technique, all based on the detection of differences of local brain energy consumption, do not visualize these initial very fast and most often diffuse information processing of the brain. Being apparently independent on brain energy metabolism led us to the idea [19, 20] that the energy required for fast neural activity depends only on the potential energy (*i.e.*, rest membrane potentials) and such potential energy is distributed more or less evenly over the brain, *i.e.*, the brain can be considered as an isoenergetic configuration. Isoenergicity means that there are no or little energy barriers to distribute information over the brain and that is possible because brain energy metabolism is aimed to maintain or restore isoenergicity after neuronal activity. In the ideal isoenergetic brain there are no energy barriers to propagate and distribute information. Isoenergicity therefore facilitates unitary (binding) activity of the various neuronal subsystems. This is not to say that in addition to isoenergicity many more conditions (and structures) are necessary to form the mind. We mentioned already the easy access to memory, but also the embodiments of somatic functions should be emphasized as well. Of interest may also the notion that the time period necessary to develop a fMRI signal following a sensory

stimulus is close to that required for an unconscious stimulus to becoming conscious, suggesting that consciousness is closely related to focused brain activity (see also our previous comments on mirror neurons).

We explored the philosophical ideas based on systems theory and the philosophical concepts of Searle that cause and effect are simultaneously realized. I describe some experiments that brain processes are indeed faster than neurotransmission processes, often considered as the fastest possible way to distribute information over the brain. Hence modern brain physiology approaches the philosophical propositions, in terms of simultaneousness. These processes are too fast to depend on brain energy metabolism. Hence brain energy metabolism and associated blood flow is a restorative process, and the brain might be considered as isoenergetic, allowing information processing down to the sub-millisecond range.

5. THE PERSONAL BRAIN

In this section I propose the existence of a personal time-space configuration of the brain that is continuously formed during life. This idea conforms to the concept of the mind (and -perhaps counter intuitively- also the person) as a process, rather than as a static entity. Personal memories do not disappear after a night of sleep, or during ECT (electroconvulsive therapy; except recent memories), when the brain is damaged (by stroke or cardiac arrest) or after awakening from a deep coma (although brain damage may impair memory processing). The inefficacy of insulin coma once used to treat schizophrenia and some other psychiatric conditions ([1], p. 208-213) may be seen in this context. So even when the brain is damaged, hence becoming in part dysfunctional and the formation of memory is affected, far most memories do not disappear. We do never regress to a naïve child. Memory problems associated with electroconvulsive interventions or Alzheimer's dementia illustrate that personal memories disappear in a time-dependent manner: the more recent traces disappear before old memories. To summarize, one's perception of the world, one's social network and cultural environment, in other words what makes us a person, is primarily confined to the brain and is virtually independent of the actual electrophysiological state of the brain. Apparently, it is the morphology of the brain -but considered at a micro level- that guarantees continuity of -or perhaps better formulated that creates- the person. Recent memories should be seen as new additions to brain micro-morphology. On the other hand one should not see the cerebral micro-morphology as hardware as opposed to electrophysiological processes being the software [20]. The micro-morphology and electrophysiology together create continuously (or -if preferred in the present context - cause the continuous emergence) a new personal time-space configuration.

The proposed time-space configuration can be generated from an iso-electric brain (when *e.g.,* all electrophysiological activity has disappeared because of ischemia) provided that some (possibly brainstem pacemaker) neurons are still active and that the brain regains its iso-energetic state. Such proposed time-space configuration of the brain changes continuously because of storing new information, so its configuration does never become the same again during life. The alluded time-space configuration is a requisite for consciousness of the person. Such personal brain configuration is unique and can therefore not be reduced to any other entity (or brain) in the universe nor to a scientific (deterministic) model.

In this section I argue that the information that the individual collects during life is -in a way- morphologically - in spatial dimensions- stored. This together with the dimension time, *i.e.*, electrophysiological activity, create a functioning brain. Such proposed time-space configuration is

personal and does never become the same again during life. This conclusion supports Kendler's presumption that psychiatry should be grounded in mental, first-person experiences, and is in line with the current neurobiological analysis.

6. DEPRESSION AND THE BRAIN

Stated briefly, a psychiatric disorder is the collective consequence of external challenges, cultural and social environment, personal experiences and biological disposition. To take depression as an example: external challenges (*e.g.,* severe life events, bereavement) together with personal experiences (*e.g.,* misuse in the youth, previous depressive episodes) and biological dispositions (*e.g.,* gene variants, hypothyroid, hypercortisolaemia, interferon treatments, viral infections) are considered risk factors to develop a depression. Just like in somatic illness an essential characteristic of a psychiatric disorder is the duration of the condition. Short periods of depression are considered as normal and may not deserve psychiatric attention. Many symptoms essential for a psychiatric diagnosis are unspecific, as they are present in the general population as well. In psychiatric patients, however, more symptoms aggregate, they are more severe and last longer. The DSM classification [1, 24] of major depressive disorder is illustrative; 2 essential (sad mood, loss of interest in social interactions) and 4 out of 7 optional symptoms should be present for at least 2 weeks. The structure of a psychiatric condition does not differ from somatic disorders, although the relative contribution of the various symptoms may differ. Unique in psychiatry is that the cultural and social environment and the personal experiences are more prominent, which are -as argued- predominantly if not exclusively linked to the personal time-space configuration of the brain. Life-events considered so important in depression have often been considered to equal stress. This idea has led to vast amount of reports on the physiology of stress in depressive patients (*e.g.,* the DST). But stress and live events should conceptually be distinguished: the impact of a life event depends on its perception and hence on its interpretation of the subject. Such interpretation depends on memory, thus on the constellation of the time-space configuration of that person's brain. Unlike a life event, a stressor affects any subject in a non-specific manner; essentially independent of the person's history. Psychiatric interventions are also focused on the symptoms contributing to the diagnosis: so psychotherapies are aimed to help coping with external challenges and social (sometimes cultural) environment.

Often brain stem neurons containing monoamine neurotransmitters, such as dopamine, serotonin and noradrenalin (norepinephrine) are considered hyper- or hypoactive in various psychiatric conditions. Noradrenergic neurons of the locus coeruleus, projecting to many forebrain regions are presumed to be overactive following stress and in anxiety disorders, and possibly subfunctoning in depression. Similarly brain serotonin neurons have been postulated to be hypoactive in depression [25-28]. Monoamine systems are no autonomous islands in the brain (stem) but are part of a network, instead. So the hypo- or hyperactivity of such systems are not necessarily causally predisposed by a gene variant or defect in the various monoamine neurons, but may be the consequence of the (unconscious) activity of the presumed time-space brain configuration, instead. If indeed the latter is the case, then it is meaningless to search for aberrant genes, but it might be more relevant to investigate the personal history of the patient.

We [29, 30] investigated the time course of recovery from depression. The length of the depressive episodes was determined in each subject of a cohort of 250 depressed subjects of the general population. In this cohort about 20% did not recover during the observation period. In the remainder the distribution of the length of the depressive episodes could be modeled very precisely as an exponential distribution (and not as a mean with Gaussian distribution). The exponential function

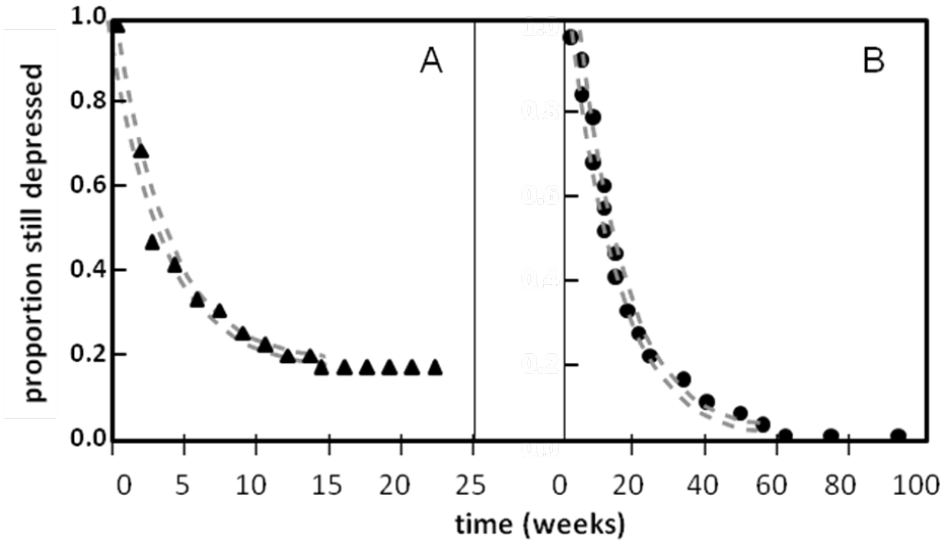

Figure 2: Time course of recovery from depression in MDD diagnosed patients. (A) shows data from a cohort identified in the general population. (B) shows the data from recurrent depression. The grey broken lines are the best fitting exponential decline function. The exponential character of the fits suggest that the mood transitions occur randomly (similar to radioactive decay in labile atomic nuclei). (A) from data of [29]; (B) was composed from data of [30]. Data of cohorts of 250-400 subjects.

signifies that that the recovery is the result of a random (or more precisely stochastic) transition from the depressed to the non-depressed state Fig. **2A**. This stochastic mood model applied to all sub-cohorts: male/female subjects, with or without co-morbid psychiatric or somatic pathologies, severe and non-severe depressed patients. Close inspection of the data indicated that the DSM inclusion criterion for major depressive disorder of 2 weeks was also found, indicating that this criterion is pragmatic and probable not a ”property” of depression. In another study with recurrent depressions [30] we showed, that there was no correlation between the lengths of the depressive episodes, or between the length of the non-depressed periods and the depressive episodes in a single subject (illustrated in Fig. **2B**. These findings together suggest that MDD might primarily be viewed as due to failing mood-transitions. In daily life we may experience fast mood transitions as well, for instance after receiving good or bad news.

Fast depressiogenic and anti-depressive state transitions have also been noticed in patients recovering from depression following one night of sleep deprivation: within a nap of about 5 minutes they may become depressed again [31, 32]. In some (non-depressed) patients electrical stimulation of the subthalamic nucleus, aimed to alleviate tremor in Parkinson’s disease, evokes within 5 seconds depressed mood that has disappeared within 30 seconds after cessation of the stimulation [33, 34]. Electrical stimulation does not imply that the stimulated neuronal pathway become more active: rather it impairs the integration of the stimulated pathway in a functional neuronal network. Hence, electrical stimulation might be seen as a reversible method to block neuronal pathways.

Mood transitions can be fast and might occur stochastically. Depressive mood might be considered as more or less normal state of the brain; the pathology is the inability to evoke anti-depressive transitions. Isoenergicity of the brain facilitates stochastic mood transitions.

7. THERAPEUTIC INTERVENTIONS

In this section I discuss the stochastic transitions in an attempt to understand therapeutic interventions. In somatic medicine at least 4 types of interventions might be distinguished. The type 1 intervention aims to remove the disease-causing agent either by direct challenging its existence in the patient's body or to assist the disease-eliminating activity. Antibiotic therapy is the classical example. Compensation is the type 2 intervention: a component with a similar or identical activity is prescribed or measures are taken to enhance the production of the missing compound. Many anti-diabetic treatments or the L-DOPA therapy and dopamine agonists in Parkinson's disease are examples. The 3rd type intervention aims to remove a pathological agent with non-specific toxins, mechanical devices or irradiation. Cancer may serve as an example. And finally, type 4 treatment is primarily aimed to reduce suffering by, for instance, palliative treatment. Each of these treatments is rational and possibly evidence-based.

To what category do antidepressant interventions belong? In depression the most prevailing treatments are cognitive behavioral therapies and medication. Other regimens include physical exercise, sleep deprivation, light exposure therapy and -in severe cases- electroconvulsive treatment, alone or combined with the routine treatments. Medication has often been thought as type 1 or type 3 interventions, but there is as yet little evidence that deficiencies of brain monoamines cause depression. It appeared that low brain serotonin (due to low plasma tryptophan) is associated with failing impulse-control and aggression rather than with depression [26, 27]. Cognitive therapies have been developed to correct misconceptions associated with the depression (*i.e.*, to reduce the impact of life events). Whether their effects are due to a type 4 rather than a type 1 (or perhaps type 3) effect remains to be proven. Interventions, such as physical exercise, sleep deprivation, light exposure therapy and electroconvulsive treatment are certainly not type 1, 2 or 3 treatments. The latter are perhaps type 4 treatment (alleviating suffering), but that indexation may feel as artificial. In the previous section we described the time-morphology of depression with a stochastic mood model suggesting that major depressive disorders might primarily be viewed as a condition of failing mood-transitions. In view of the transition hypothesis the anti-depressive interventions may seen as to facilitate switching from the depressive to the non-depressed state. Sleep deprivation and electroconvulsive treatments are treatments that could show early antidepressant effects. But their effects are unstable; illustrative are the rapid mood transitions in sleep deprived and responsive patients following short naps [32]. Exercise and light therapy may also improve mood or serve as prophylactic. Their effects could be seen as type 1 therapies, as hypo-activity is often a prominent symptom of depression, whereas exposure to light activates or compensates failing mechanisms in seasonal affective disorders, respectively. Alternatively, these treatments may facilitate mood (and so brain) transitions. Therefore, I suggest to adding another type of treatment. So the type 5 treatment is to facilitate brain transitions. This idea might be seen as an extension of type 1 as that they assist the organism to battle the ailment, but that is a rather artificial formulation for randomly occurring brain states.

There is an ongoing debate on the therapeutic efficacy of antidepressants [35, 36]. In several meta-analyses their effects appear to be modest as compared to placebo. Two comments: 1st the response of depressed subjects to medication varies widely: both fast en clear-cut responses, and no response at all have been reported, and 2nd the placebo response is relatively high and variable. Apparently no meaningful distinction can be made between subjects who need medication and those who recover without medication (or placebo). Is this a matter of lack of knowledge or is this inherent of the current conception of depression? The placebo-drug controversy may serve as another argument supporting the random-mood concept and if so drug treatment is a type 5 intervention.

In short: we argued that -except perhaps cognitive psychotherapy- none of the current anti-depressive interventions treats underlying patho-psychological mechanisms directly. So an anti-depressive

treatment is often not aimed to influence the depressive feelings, but to influence the course and severity of depression. Considering the stochastic-mood concept, thus assuming random brain transitions, a strict causality and possibly a strong prediction between diagnosis and therapeutic response in depression may not always be evident. Therapeutic consequences of mood transitions must also be seen in the context of the micro-morphology of the brain. It can be argued that not only biological therapies but also psychotherapies should change brain micro-morphology to become effective. Or as a research paradigm: how to optimize the effect of a therapy on the change of the brain's micro-morphology.

8. DIAGNOSTIC SYSTEMS

Emil Kraepelin was the founder of the present diagnostic approaches and his ideas were the basis of current classification proposals [1]. It was well realized from the onset onwards that any classification needs a firm scientific basis. The current version of the DSM distinguishes nearly 300 diagnostic entities enabling about 170 different combinations to fulfill the criterion MDD. Such number may be considered as exuberant, but there is as yet no scientific argumentation whether such number is too much, too little or just perfect. The question arises whether or not it is possible to make a rational decision about the treatment of the individual patient and this is in fact challenging the concept of evidence based treatment regimens and -in a broader perspective- strict causality as the usefulness of the medical model for MDD.

The current classification systems (such as the DSM) are formulated to a large extent ex cathedra (by consensus) and are therefore not well amenable to scientific falsification [37]. In other words: a biological or any other parameter or marker will never be sufficiently strong to falsify and reject the DSM. Consider for instance the DST: this test may be found to be abnormal in approximately 70% (at best) of the depressive subjects and in 30% of –perfectly- matched controls [3, 4]. But has the dexamethason test challenged the DSM-classification of MDD? It might -of course- be argued that the dexamethason test is not included in the DSM definition of depression, so it cannot be used as an argument against the DSM. But if that is so, than the question arises what then could be the scientific justification of the DSM? Another example referring to the response to therapies. An intervention may prove to be therapeutically effective in only in 60% of a cohort, as is the case with antidepressants, including SSRI's [35, 36]. Would this partial efficacy (together with a substantial placebo response) ever challenge a clinical classification? The limited therapeutic efficacy is, instead, attributed to such factors as heterogeneity of depression, to patient specific characteristics or to ineffective drugs. But we think there are no criteria to verify or reject classification systems, and as argued in this essay there are no biologically founded parameters to do that, and more generally: such parameters (genes, biomarkers, time-courses of symptoms) will never persuade for changing a classification. Finally another obstacle to challenge the DSM has to be mentioned here: publication bias. It is generally discouraged to publish psychiatric investigations without adherence to some classification system (*i.e.,* the DSM).

A diagnosis identifying MDD should lead to an effective therapy, which is a prerequisite of evidence-based psychiatric practice. We have examined the strengths and weaknesses of causal relationship between diagnosis and therapy of MDD. Three major obstacles for a rational evidence-based praxis were discerned 1st current classification systems are scientifically non-falsifiable, 2nd mood transitions (and so cerebral processes) are -at least to some extent-non-deterministic, *i.e.,* they are random, stochastic and /or chaotic, and 3rd the relatively weak efficacy and specificity of current anti-depressive interventions. These considerations together indicate that a scientific foundation of

the DSM or any other ex cathedra classification is practically unreachable. Our arguments encourage the search for alternative approaches.

9. FINAL REMARKS

The main theme of this chapter is how we conceive the psychiatric patient in a neurobiological context. To appreciate the origins of the current research and conceptualizations, I gave a short overview of the developments of the last 100 years or so. Moreover some philosophical thoughts about neurobiology and psychiatry were discussed. I have argued that the assumption of a unitary mind requires a concomitant configuration of the brain. Such time-space conformation contains all information of the subject has collected during live. We may simplify the concept of a personal brain by saying that: it is not that you have your memories, but you are your memories, instead. The concept of the individual space-time configuration of the brain acknowledges the individual expression of a psychiatric disorder and offers a neurobiological platform of first-person psychiatry.

Psychiatric therapies should be seen as an attempt to reshape the personal time-space configuration. An obstacle might be that new memories and experiences are built in the existing configuration, and not necessarily erasing them. This conclusion might also be seen as a challenge for future research to optimize the efficacy of (psycho)therapeutic interventions. In fact, reshaping the proposed time-space configuration might be the basis of both legal and illegal brainwashing. Possibly the combination of biological and psychotherapeutic treatments might offer new therapeutic avenues. Desensitization exposure therapies as used in phobic disorders might lead to rewiring of the brain, thereby suppressing phobia provoking thoughts.

Another aspect of the here proposed space-time configuration of the brain is its stochastic character, as illustrated with studies on fast mood transitions. Stochastic processes are nearly unpredictable in the individual, and can only be described and understood in a population or cohort. Stochastic processes are a threat for conventional medicine, where the ideal diagnosis guarantees therapeutic success. In depression we questioned whether such an ideal can ever be reached.

In the last decade genetic approaches have changed from relating single genes to psychiatric disorders, usually defined by classification systems, such as the DSM, to the possible involvement of multiple genes. Current investigations suggest that many genes are involved in depression. And even if the underlying multi factorial cause of the disorder is precisely known, for an external observer (clinician, scientist) depression might appear as a stochastic process. A (psychiatric) disorder such as major depression is characterized by features such as duration, recurrence and severity and it might well be that these are better associated with the genetic makeup or with some other biomarkers, than the mood itself. If so, than for instance a gene variant or biomarker may erroneously become linked to MDD, whereas, the gene variant prolongs the diseased state only. Another approach is to recognize endo-phenotypes as subject vulnerable to develop a psychiatric disorder. For instance subjects prone to depression are exposed to stress, concomitant with measuring local brain activity with functional neuroimaging (fMRI). As emphasized, fMRI is unable to show neural processing preceding the development of the imaging signal: so the bias of fMRI is possibly on the execution of tasks or functions, rather than on the initial unconscious psychopathological processes.

The present analysis conforms many items of the agenda of Kendler [9]: that psychiatry is grounded in mental, first-person experiences; Cartesian dualism and epiphenomenalism are false and both brain—mind and mind–brain causality are real, psychiatric disorders are complex and explanatory pluralism

is preferable. The present exposé emphasizes that the various psychiatric approaches force to abandon some brain concepts. By doing so, the present conceptualization reconciles both psychotherapeutic and biological approaches in psychiatry. But it illuminates also the limitations of these approaches: one question is how to influence the brain micro-morphology with current psychiatric interventions. The 7th item of Kendler's agenda is to embrace empirically rigorous and pluralistic explanatory models. I may emphasize here again, that in psychiatry rigorous explanatory models may perhaps be impossible anyway. The last item of Kendler's agenda, accept piecemeal integration of complex etiological pathways to psychiatric illness a little bit at a time, is fully acknowledged.

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