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In quest of specific neurons of mind and mental disorder

JAKOB KORF

University Clinic of Psychiatry, UMC Groningen (the Netherlands)

The essay questions the role of neurons in the concept of mind. The mind is considered as an emerging but physical property of the brain: a mental brain configuration does exist. This configuration is relatively resistant to brain damage, coma, hypoxia and normal (electro)physiological brain states and is envisioned as a relatively stable (nearly anatomical) structure. Consistent with this idea is that, despite the lifetime turnover of their constituents (e.g. proteins and nucleotides) and morphological changes, brain neurons do not divide. Brain neurons are continuously modified, for example by lifetime experiences: genetic and epigenetic support for this thesis is provided. The presumed mental brain configuration guarantees lifetime storage of information, but does not imply that this information and memories remain unmodified during aging. In principle, neurons permanently affected by mental processes can be identified in vitro or in vivo, despite anticipated practical problems. This essay may help to scientifically legitimate complementary neurobiological ad psychotherapeutic approaches in psychiatry.

Keywords: mind, neuron, memory, philosophy, emergent materialism, neuropsychiatry

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INTRODUCTION

In recent reports I have defended the thesis that the mind is an emerging but physical property of the brain: at least one brain configuration exists - but more likely several - that is mental (Korf, 2010; 2012; Korf and Bosker, 2013). According to this view, here denoted as emergent materialism, the mind is shaped through natural evolution and exerts physical power on its constituting elements (e.g. neurons) (Edelman and Tononi, 2000, Stoyanov, 2011; Stoyanov et al., 2011; Korf, 2012). The delineation of a brain configuration with mental properties challenges this point of view. Current knowledge is perhaps insufficient to make reasonable guesses or, better, a scientific hypothesis of the nature of the presumed mental brain complexities. Elsewhere we argued that brain energy metabolism is a restorative process to keep the brain in optimal condition to execute higher brain or mental functions (Korf, 2010, 2012; Stoyanov, 2011; Stoyanov et al., 2011). Part of our arguments is based on psycho-physiological experiments showing that the time course of higher mental functions as memory, sensory information or speaking is much faster than and precedes brain metabolism.

This essay assesses the idea that at least a proportion of the brain neurons are permanently modified through the purported mental configuration and supports this contention with examples. This essay concludes with a discussion on the question how to proceed with our efforts to explore the mental nature of the brain and what could be the relevance for psychiatry.

PERSISTING MEMORY

During life we collect memories from early infancy until old age. Except for experiences shortly preceding physiological transitions (i.e. recent memories), by far most memories are resistant to alterations of conscious states. Indeed after sleep or anaesthesia virtually all experiences are recalled after regaining consciousness. Apparently, authentic or long-term memory is remarkably well preserved in the normally functioning brain, and may also be the case under pathological conditions. I consider three conditions: brain infarctions, coma and Alzheimer's disease. Cerebral vascular incidents (brain infarctions) are due to lasting or transient interruptions of regional blood circulation, thereby depriving the brain from energy substrates. Lasting interruptions of blood circulation cause permanent brain

damage, associated functional impairments and memory loss, whereas short interruptions or transient ischemic attacks have no or mild impacts. Permanent damage by brain infarctions is treated by training (e.g. exercise), thus attempting to compensate the damage through activation of alternative brain regions and functions. Coma is an unconscious state with marginal electrophysiological activity. When brain damage is not too severe, awakening from coma might result in self-consciousness, meaning that the patient experiences himself as a person with body awareness and with personal memories (Azouvi et al., 2009). Alzheimer's disease is a progressive condition that removes personal memories in a retrograde direction: first the more recent memories disappear, whereas fragments of the oldest memories are still present in the most advanced stage of the disease (Stern, 2012). All three conditions show that even after severe disturbances of brain energy metabolism and electrophysiological activity, a substantial proportion of the personal information and memories remains intact

Can memory be restored by new neurons? It is generally accepted that genes play a prominent role in the development of the brain from fertilized ovum onwards to the young adult. Most brain neurons survive during aging, although they may undergo distortions of their morphology, their connections and their biochemical make-up, whereas damaged neuron-supporting glia are replaced. Recent neurobiological research has shown that in the adult brain new neurons are indeed formed. Most of these new neurons are formed in the peripheral zone of the brain ventricles and migrate to the olfactory bulb (Jobe et al., 2012). It is still unclear whether these neurons could indeed become incorporated in a damaged neuronal circuitry, for instance to replace the hippocampus neurons that are affected in the early phase of Alzheimer's disease and are involved in retrieving memory.

These examples together support the conclusion that transient interruptions of brain energy metabolism and electrophysiological activity do not irradiate most of the personal information acquired during life. This robustness suggests that personal information is confined to the brain as anatomically stable configurations.

ON RECEPTORS, GENES AND HORMONES

Conventionally neurons are considered part of a (brain) machine and too simple (and too deterministic) to explain, or perhaps to accommodate for, the mind. Indeed, the neuronal doctrine (Spillane, 1981) offers little if any support to the idea that neurons (and glia) are able to express functions associated with mental activity. Here, I consider the alternative view that neurons are necessary elements in an ensemble to create the mind. The conventional position necessitates proposing an external (non-neuronal) source of the mind, whereas the second thesis assumes neuronal elements that change over time to become mutually interactive to create the mind. The question to be answered is: are at least some cerebral neurons modified during life because of learning or life events?

In his classical essay *The Organization of Behavior*, Donald Hebb (1949) proposed that strengthening the wiring of brain neurons is the basis of learning. This principle is now widely acknowledged and considered as the basic condition for connectionist learning models. These conditions (McLeod et al., 1998) are: 1) neurons integrate information: the input-output is modified following successful learning; 2) the neuronal input-output differences are expressed in terms of electrophysiological changes; 3) the brain is functionally organized according to anatomical and (partially) hierarchical layers; 4) the strength of functional connections between neurons is in their synaptic transmission; 5) learning is achieved through modifying (strengthening or weakening of) the synaptic connection. The discovery of long-term potentiation (LTP), in which neurons reach a supersensitive state resulting in lasting modification of the multi-neuronal attuning, forms electrophysiological support of these principles. LTP is found in many brain areas, particularly in the hippocampus, cerebral cortex and cerebellum. The elucidation of the molecular mechanism of neuroplasticity focuses on the NMDA type glutamate receptor (Rolls, 2012). Other molecular principles of synaptic plasticity have been proposed as, for instance, the phosphorylation of proteins. The plasticity hypothesis alludes to learning mechanisms, but as yet

offers little clues to memory.

Over the last two decades, research has revealed a wealth of data showing that neuronal gene expression is highly susceptible to environmental challenges. The gene c-fos, belonging to the family of the so-called immediate-early genes, is for instance expressed in neurons by sensory activity or stress. In regional brain neurones c-fos and related genes are expressed when a rat is exposed to physical (e.g. immobilization) or psychological (exposure to aggressive littermates) stress or to classical or atypical antipsychotic drugs. Rats treated for two weeks with an atypical antipsychotic drug showed differential tolerance to c-fos expression in mesolimbic brain areas, without cross-tolerance to typical antipsychotic drugs and vice versa (Sebens et al., 1998). Recent epigenetic studies point to possible lifetime consequences of prenatal and early childhood stress for the possible increased vulnerability to psychiatric pathology (Jensen Peña et al., 2012 and references). Such experiments suggest that even psychiatric interventions affect individual neurons. The here referred and many other studies of the last decades have shown that brain neurons become modified as if they "remember" lifetime experiences. But we realize that once taken out of the brain and maintained *in vitro*, neurones may show properties to be differing from those in the complex brain *in vivo* environment, thereby complicating the characterization of their *in vivo* physiology.

PHILOSOPHICAL AFTERTHOUGHTS

The preceding sections have shown that the personal brain can be characterized by two complementary aspects. First, the personal history becomes a hard (nearly anatomical) feature of the brain and involved neurons; second, brain metabolism is conditional and restorative. In this section I elaborate further on the position of the individual brain neuron by restating the mind as being the result of emergent materialism: i.e. a complex system built from less complex entities. Systems biology states that the properties of an emerging complex system cannot be predicted from the properties of its constituting entities (Kauffman, 2008), although these precursor entities pose limitations on the emergent system. In the present context the basic question is: what are the limitations the neuron poses to the mind? To illustrate our inquiry we analyze Hubel and Wiesel's classical experiments (summarized by Reid, 2012) of the 1960s. It appeared that specific neurons are activated by specified visual stimuli: i.e. a square pattern of stripes activates different neurons than a diagonal pattern does. This idea was often formulated as the "grandmother neurons" thesis: there are neurons that are activated when the subject (in Hubel and Wiesel's experiments a cat) recognizes a specific object (nicknamed "grandmother"). In a broader context: some cerebral neurons have a mental function. We already emphasized the fast assessment (in 0.02-0.05 second) of sensory input in a cultural (i.e. lingual) or psychological (i.e. mental) context (Korf, 2012). This implies that "grandmother" is initially perceived (and in some way recognized) by other brain configurations, which sent their information to the "grandmother neurons". Apparently, the activation of the "grandmother neurons" is the outcome of a top-down computation, rather than being the primary result of a bottom-up recognition (and knowledge). The more complex systems (i.e. the cerebral cortex) 'enslave' the underlying elementary systems (Kelso, 1995).

One can also ask the opposite question: what kind of properties should be attributed to the elementary systems to become 'enslaved' by the more complex systems? I will consider the neuronal perspective of lifetime memory. Consider the following two options. First, most (or perhaps all) individual brain neurons remain unaffected or neutral irrespective of the history of the subject; and second, some if not all neurons are modified by life experiences. The first option implies that neurons are just vehicles of information processing (like chips of a computer) and that other physical (or perhaps nonphysical according to the substance dualism, not considered here) configurations direct these brain neurons. Both views imply the existence of (some) neurons that were modified by previous experiences. I favour an intermediate position: the brain contains neurons with and without being affected by past experiences. Hence emergent materialism predicts neural subpopulations (e.g. in the

cerebral cortex or the hippocampus) "memorizing" subject's experiences. But also the opposite might be true: other neurons remain unaffected or neutral regarding incoming information or stored memories. In computer language: the brain "develops programs to enslave" the latter neurons.

Considering the turnover of all neuronal molecules and in spite of the life-time survival of neurons, one may speculate that the memory-neurons are programmed by the connected neuronal network. The network concept assumes that information is carried through neuronal connections between brain regions or between neuronal clusters. However, the brain might also be conceptualized in terms of a cloud with random activities of its constituting elements ("a universe of consciousness", Edelman and Tononi, 2000). Random activities imply that with minimal perturbations concerted activities are possible facilitated by an isoenergetic brain (Korf, 2010), having little or no energy barriers between neurons or sets of neurons.

WHAT ABOUT PSYCHIATRY?

The present analysis argues that at least a part of any psychopathology must be materialized, i.e. confined to the brain. In other words, depression or schizophrenia are not merely "functional" disorders as if these disorders were aberrations of the software of the brain, but should be considered as hardware neuropathology instead. At least some brain neurons have a neuropathology-specific molecular make-up that is amenable to electrophysiological and biochemical characterization. We have predominantly used arguments from non-human neurobiological studies, arguably with indirect psychiatric implications. Indeed, the issue of translation might be raised (Stoyanov, 2011; Stoyanov et al., 2012), thereby emphasizing the need for providing more direct evidence. On the other hand it seems unlikely that far the most of the here reviewed brain mechanisms are specific of the animal brain. The question is whether psychopathology gives sufficiently strong molecular or cell-functional abnormalities to be detectable with modern technologies, such genetic approaches, imaging modalities or peripheral markers. Indeed, the success of more than 6 decades of intensive research is rather modest (Stoyanov, 2011; Korf and Bosker, 2013), but as argued principally reachable. Optimal therapeutic regimens have to focus on both the psychological content of the disorder and how to influence the neuropathology of the disorder. A lot of work still needs to be done to optimize the therapeutic efficacy of concerted biological and psychotherapeutic interventions. This essay may help to scientifically legitimate these complementary approaches in psychiatry.

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Corresponding Author:

Prof. Jakob Korf
Rm 4.14 UCP CG 10 UMCG.
P. O. Box 30.001 9700 RB Groningen,
the Netherlands.

Email j-korf@home.nl or j.korf@umcg.nl

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