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REVIEW

# The dark matter of the brain

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**Abstract**
The bulk of brain energy expenditure is allocated for maintenance of perpetual intrinsic activity of neurons and neural circuits. Long-term electrophysiological and neuroimaging studies in anesthetized and behaving animals show, however, that the great majority of nerve cells in the intact brain do not fire action potentials, i.e., are permanently silent. Herein, I review emerging data suggesting massive redundancy of nerve cells in mammalian nervous system, maintained in inhibited state at high energetic costs. Acquired in the course of evolution, these collections of dormant neurons and circuits evade routine functional undertakings, and hence, keep out of the reach of natural selection. Under penetrating stress and disease, however, they occasionally switch in active state and drive a variety of neuro-psychiatric symptoms and behavioral abnormalities. The increasing evidence for widespread occurrence of silent neurons warrants careful revision of functional models of the brain and entails unforeseen reserves for rehabilitation and plasticity.

**Keywords** Silent neurons · Brain evolution · fMRI · Synchronous activity · Schizophrenia; disinhibition; neuronal plasticity

'Where does a thought go when it is forgotten?' S. Freud

## Introduction

A revolutionary chapter in the history of science was hallmarked by Galilei (1610), looking up at the night sky through a simple telescope of his making. What he discovered then would forever change the field of astronomy and science in general, transforming our views of the Universe, and our place in it. Through the help of a simple but powerful technological leap, Galileo made several revolutionary discoveries, which include the rough landscapes of the Moon, satellites of Jupiter and, most importantly, the vastness of space and countless constellations of stars extending beyond those observable by the naked eye (Galilei 1610). In those remote days, Galileo did not suspect that the vastness of unknown and intangible space, in addition to visible celestial bodies and dust, conceals infinite amounts of invisible matter, dubbed in our days as 'the dark matter' of the Universe. In standard cosmology, the latter refers to the hypothetical constituent of the Cosmos, which does not radiate or interact with electromagnetic radiation, and as such, is not visible. Its presence was postulated by Lord Kelvin based on discrepancies between the velocity of calculated and actual dispersion and rotation of stars around the center of the galaxies, noting that 'many of our stars, perhaps the great majority of them, may be dark bodies' (Kelvin 1904). According to most recent estimates, together with dark energy, dark matter constitutes over ~95% of the total mass-energy content of the Universe, leaving less than ~5% for Galileo and the rest of humanity to observe and contemplate.

Almost four centuries later, advances in genetics and particularly in gene sequencing technologies prompted another scientific breakthrough, but this time in molecular biology. In 2003, the completion of the Human Genome Project, which revealed all ~3 billion base pairs in the human genome, prompted surprising realization that only a small percentage of the DNA accounts for the entire protein-coding

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makeup of humans. The rest of the genomic material was nicknamed by biologists, in resemblance to cosmologists, as 'the dark matter' of the genome, which constitutes as much as ~98% of the entire genetic fabric. Assumed at first to be an evolutionary leftover of DNA lingering throughout natural history in a dormant and fragmented state (Carey 2015), the non-coding genome was subsequently shown to conceal splintered chronicles of life's history along with a wealth of regulatory elements, capable of fine-tuning the activity of certain genes and gene clusters, and influencing a wide range of processes and functions. Parts of obsolescent instructions retained in non-coding DNA sequences can, in fact, occasionally re-emerge in one form or another, and manifests through reactivation of rudimentary ancestral features or relict traits (Parrington 2015). These discoveries suggest that throughout the evolutionary process, large quantities of genetic records that have disappeared from the scene are still kept in a latent state, capable of coming back to influence life affairs.

Similar to cosmology and genomic research, advances in functional brain imaging have been also highly contingent on the arrival of cutting-edge technologies and research tools. The glorious custom of functional brain studies set by Hans Berger, Charles Sherrington, Graham Brown, and others prompted major breakthroughs, which climaxed in arrival of innovative methods enabling non-invasive visualization of intrinsic and task-driven changes in brain activity and metabolism (Roy and Sherrington 1890; Berger 1940; Logothetis 2008). The gold standard here has been relating selected brain structures to specific neural functions, to gain critical information for elucidating normal and diseased brain activity and assisting in diagnostics of neurological and psychiatric disease. Like in cosmology and genomic studies, the explosive advances in neuroscience research and imaging have unveiled major and surprising unknowns at the core of functional models of the brain. In particular, analysis of energy consumption changes related to brain activity showed that baseline expenditure of calories at rest is remarkably stable, with extra energy required for processing environmental inputs comprising only a very small percentage (~1%) of the total energy usage. While the general notion is that bulk of the brain energy is allocated for maintenance of intrinsic activity, the nature and functionality of processes absorbing massive amount of calories remain to be determined. According to Raichle, the metabolic state of the brain circuits could be the cause, rather than the consequence of neural activity, with best part of neural energy expenditure remaining unaccounted (Raichle 2010, 2015). Recent estimates, which are largely based on positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) are especially revealing, and propose that with a fierce appetite for glucose and oxygen, the human brain, which constitutes only ~2% of the body weight, consumes over ~20% of the total body energy. The mechanistic analysis of this intriguing phenomenon is currently hindered by limited sensitivity and resolution of imaging methods, which despite major improvements, remain indirect and crude sensors of neuronal mass action, unable to distinguish even basic neurobiological processes such as excitation and inhibition (Logothetis 2008; Poplawsky et al. 2017). Remarkably, hemodynamic measurements combined with autoradiography studies showed that similar to excitation, inhibition can be associated with increased perfusion of neural tissue and rise in metabolic activity, although these effects can vary depending on the experimental paradigm, partly owning to effects GABA on micro-vessel dynamics (Jueptner and Weiller 1995).

Despite the results of cost-based analysis suggesting greater significance of intrinsic as opposed to evoked brain activity, single-unit electrophysiological recordings and cellular resolution imaging in animal models show that the overwhelming majority of neurons (60–90%) in anesthetized and awake animals are permanently silent (i.e., do not fire action potentials) or show very sparse firing (Berger 1940; Shoham et al. 2006) (Table 1). These findings not only prompt questions concerning the share of inactive neurons in brain energy expenditure, but also their neurochemical identity, phylogenetic origin, and place in functional brain models. In the following, I consider emerging data suggesting that vast numbers of inactive neurons are not a result of experimental intervention but reflect the generic state of brain affairs. I discuss numerous evidence, implying that these neurons could emerge as a result of the trade-off for high conservation of neural evolution, through selection of loss of function, which favored retention of dormant neurons in permanently inhibited state. I review remarkable examples of reactivation of silent neurons and circuits by disinhibition, with their entry into the realm of psyche and behavior, producing an array of maladaptive fits or relict activity. Finally, I propose that neural circuits neutralized by persistent inhibition can afford vast reserves for plasticity and neo-functionalization, with invigorating or disruptive consequence.

## Silent neurons in resting and active brain

The basic premise for functional brain studies is that neuronal activity involves physical and neurochemical changes. Excellent penetration with capability for non-invasive volumetric imaging renders PET and especially fMRI highly suitable for visualization and mapping functional processes in animal and human brain. Nonetheless, both methods produce indirect measure of neural activity and fail in capturing processes in real time and in assignment of readouts to specific neurophysiological mechanisms. The reliance

**Table 1** Summary of reports demonstrating significant numbers of silent neurons in the nervous system using various methods with references

| Model | Brain area | Method | References |
|---|---|---|---|
| Locusts | Mashroom body | Electrophysiology | Perez-Orive et al. (2002), Papadopoulou et al. (2011) |
| Zebrafish | Whole brain | Calcium imaging | Ahrens et al. (2013) |
| Songbirds | High vocal centre | Electrophysiology | Hahnloser et al. (2002) |
| Rat | CA1 hippocampus<br>CA1 hippocampus<br>Barrel Cortex 2/3<br>Auditory cortex<br>Olfactory bulb<br>Cerebellar granule cells | Electrophysiology | Thompson and Best (1989), Henze et al. (2000), Margrie et al. (2002), Brecht et al. (2003), DeWeese et al. (2003), Chadderton et al. (2004) |
| | Auditory cortex<br>Olfactory bulb<br>Gustatory cortex<br>Visual cortex<br>Somatosensory cortex | Calcium imaging | Ohki et al. (2005), Kerr et al. (2007), Greenberg, et al. (2008), Hromadka et al. (2008), Poo and Isaacson (2009), Chen et al. (2011) |
| Mouse | Neocortex | Calcium imaging | Sofroniew et al. (2016) |
| Rabit | Motor cortex<br>Somatosensory cortex | Electrophysiology | Swadlow and Hicks (1996), Beloozerova et al. (2003) |
| Cat | Visual cortex | Electrophysiology | Blanche et al. (2005) |
| Monkey | Neocortex | Electrophysiology | Robinson (1968) |
| Human | Neocortex | Metabolic cost and modeling | Lennie (2003) |

of the fMRI signal on activity-dependent changes in blood perfusion (i.e., blood oxygenation level dependent signal, or BOLD) makes it also subject to major temporal and spatial constraints.

To monitor directly the activity of neural circuits and relate the readouts to brain energy expenditure, it would be appropriate to obtain non-invasive data describing functional dynamics of individual neurons at high spatial and temporal resolution. Cellular resolution $Ca^{2+}$ imaging, for example, provides an excellent means for tracking relative changes in evoked firing activity of neurons and neuronal groups, based on sensing intracellular dynamics of free $Ca^{2+}$. Assuming that experimental procedures and loading of neurons with fluorescence $Ca^{2+}$ indicators do not interfere with physiological processes, cellular $Ca^{2+}$ imaging can also provide a window for measuring spontaneous activity of the brain and its modulation by environmental inputs. Despite that intrinsic activity of neurons is held accountable for the bulk of calories consumed, results of long-term $Ca^{2+}$ imaging with synthetic probes demonstrate that the overwhelming majority of nerve cells are permanently inactive, with only a relatively small fraction firing action potentials in response to sensory inputs (Shoham et al. 2006; Barth and Poulet 2012). In the primary auditory cortex of rat, for example, less than 10% of neurons discharge action potentials in response of acoustic stimuli, with the remaining majority keeping non-responsive (Hromadka et al. 2008). Imaging studies of other cortical areas showed similar results, with bulk of nerve cells in the olfactory bulb (Poo and Isaacson 2009), gustatory cortex (Chen et al. 2011), primary visual fields (Ohki et al. 2005; Greenberg et al. 2008) as well as in the somatosensory cortex (Kerr et al. 2007) keeping silent. These findings are in line with results of $Ca^{2+}$ imaging studies in behaving transgenic mice expressing GCaMP6 $Ca^{2+}$ sensor protein, which show the majority of neurons keeping inactive (Sofroniew et al. 2016), although the overall numbers of active neurons in these experiments was somewhat higher. The latter could be partly due to biases of transgene expression for specific neuron types.

The results of neurophysiological measurements are in agreement with the outcome of $Ca^{2+}$ imaging studies, showing large numbers of non-spiking neurons in the brain of primates, cats, and rodents. The first systematic account of inactive neurons in vivo has been conducted in monkeys using electrophysiological recordings and analysis of the relationship between measured single-unit activity and theoretical calculations of the number of units localized close to active electrodes. Based on these studies, it was concluded that the vast majority of neurons in the monkey brain are electrically inactive, or show extremely sparse spiking (Robinson 1968). In the same vein, vast collections of inactive neurons were identified in different brain parts in anesthetized and behaving rats, suggesting that the presence of inactive nerve cells cannot be attributed to the effects of anesthesia (Thompson and Best 1989; Henze et al. 2000). Thomson and Best, in fact, showed that the apparent silence of the vast majority of neurons in the hippocampal CA1 area under barbiturate anesthesia is not due to drug effects, as barbiturates are known to increase the firing activity of neurons in this brain region. Long-term recordings of the

activity from large populations of neurons in cats showed that the number of inactive units is even higher, with > 90% of sampled cells keeping permanently inactive (Blanche et al. 2005). For comparison, it is noteworthy that similar recordings in murine retina show a much higher percentage of spiking neurons (~ 80%), indicating that the lack of spiking reflects the genuine state of the majority of neurons in the mammalian brain (Segev et al. 2004). While it is not clear if inactive neurons represent a specific class of cells or reflect generic characteristic of multiple neuron types, some data imply that inhibitory interneurons could play a key role in restraining both, the evoked and intrinsic firing activity. Indeed, broader tuning of interneurons and overall higher firing rates with extremely wide connections (Silberberg and Markram 2007; Fino and Yuste 2011) could impose strong inhibitory influences on a large number of target neurons. Another possible explanation for the presence of great numbers of inactive neurons is their narrow tuning to respond only to specific inputs (Olshausen and Field 2004). The computational and energetic advantages of sparse firing for efficient representation of sensory inputs, for example, have been discussed in several studies (Laughlin and Sejnowski 2003; Wolfe et al. 2010), but whether these considerations can explain the perpetual silence of the vast majority of neurons throughout the brain remains to be shown. It is interesting to note that massive collections of inactive neurons have also been reported in songbird (Hahnloser et al. 2002) and zebrafish (Ahrens et al. 2013) brain as well as in insect nervous system (Perez-Orive et al. 2002; Papadopoulou et al. 2011), implying that dormant neurons could be a more general neurobiological phenomenon.

Overall, it emerges that most action potential firing activity in brains of anesthetized and awake animals occurs in less than 10% of the total population of nerve cells, with the rest of neurons keeping in strongly restrained or in a perpetually inactive state. The prevalence of inactive neurons in the brain under rest and active state is highly counterintuitive, given that the primary designation of a neuron is generation of action potentials and information transfer. Without a doubt, inactive neurons and circuits present a major challenge to current functional models of the brain, given the extreme costs of neural tissue. Strong presences of silent neurons in living mammalian nervous system also raise legitimate questions over their possible functional significance and likely impact on brain undertakings. However, what role could massive collections of inactive neurons play? Before bidding for answers to these important questions, I would like to take with the reader a brief evolutionary detour and to look into possible origins and mechanisms that could cultivate silent neurons within the highly demanding environment of the brain, in keeping with Dobzhansky's principle that 'nothing in biology makes sense except in the light of evolution' (Dobzhansky 1977).

## Loss of function selection and dormant neural circuits

The main argument against widespread redundancy of neurons in the brain is based on the false premise of inherent pragmatism of the evolutionary process. It is said that natural selection would not tolerate inefficiency and idleness, and any redundancy would be weeded out. Such reasoning appears especially pertinent to brain affairs and neural evolution, given the extreme energetic tissue costs. The principal shortfall of this argument is that it fails to recognize two important and unique properties of neural circuits. The first is their functional versatility and plasticity. Indeed, for the most part, brain circuits are general purpose computing elements, which do not commit in full to any specific function but work as multipurpose devices (Eagleman 2017). This principle not only empowers neurons and neural assemblies with the capability to become recruited into multiple circuits supporting different processes, but also renders them capable of contributing to multiple functions at the same time (Meyrand et al. 1991; Tierney 1996). Putting it eloquently, for the majority of neurons and neural circuits it is irrelevant what inputs they process, or where the data comes from. Regardless of the source and information type, the multipurpose circuits at work over a certain time period can figure out what to do with the information and how to process it.

A simple and illustrative example supporting this powerful principle has been provided by studies of the somatogastric system of crustacean, where modulatory inputs can tune the same circuit to produce multiple activity patterns, to support a variety of complex behaviors (McClellan 1982; Getting and Dekin 1985). Neurophysiological evidence suggests similar arrangements also in the vertebrate nervous system, with numerous examples of neural circuits supporting multiple behaviors (Fig. 1a, b). In lamprey, for instance, the same spinal cord neural circuits are used to produce different undulatory behaviors such as crawling, burrowing or swimming (Ayers et al. 1983). Likewise, in the locomotor system of anuran amphibians, the same networks of axial-based limb circuitry support from tail-based swimming activity at the pre-metamorphosis stage to limb-based swimming followed by the transition in kicking movement, which empowers also jumping locomotion of adult specimens (Sillar et al. 2008). From these and a multiple similar reports, it emerges that in the course of neural evolution, natural selection promoted formation and consolidation of multipurpose circuits and set of rules, which have been kept generally conserved, with only minor particulars modified, to ensure the most adaptive outcome. Such a simple but highly effective strategy not only afforded an astonishing wealth of neural functions and behaviors, but also warranted great stability of the basic architecture of brain circuits throughout phylogeny.

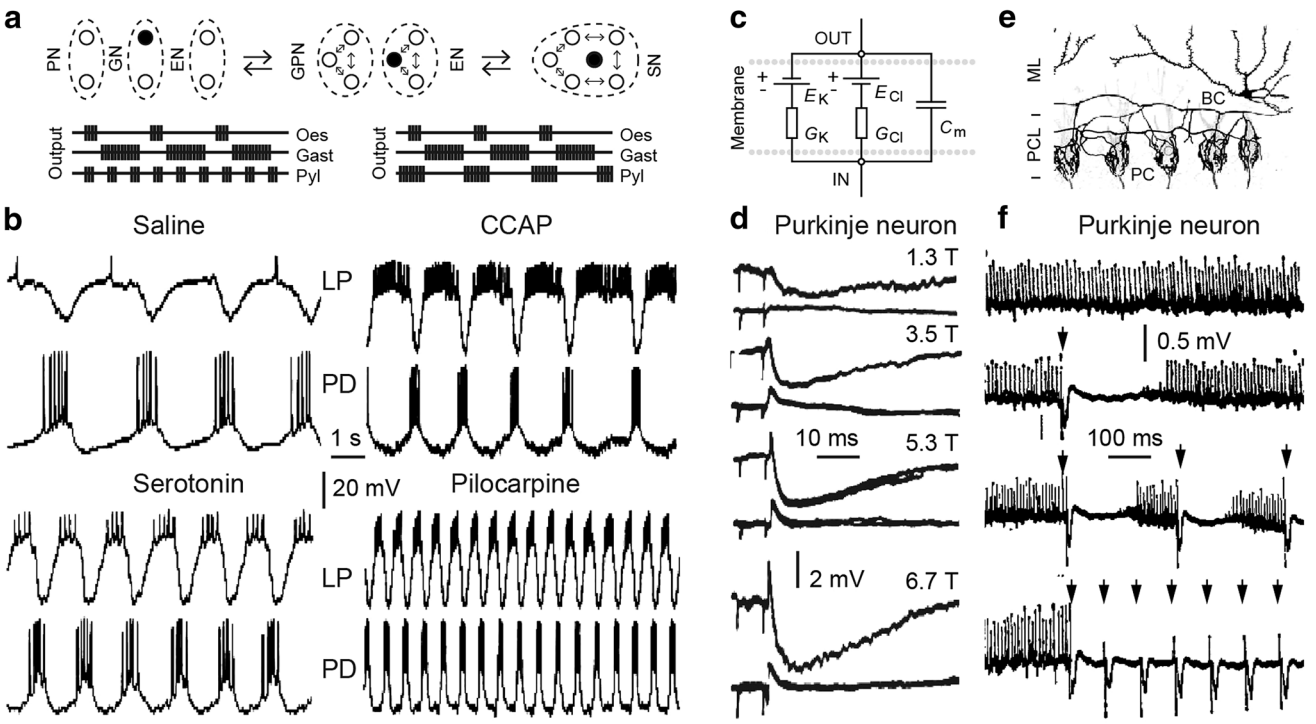


**Fig. 1** Functional versatility and inhibition empower remarkable plasticity of neural circuits. **a** Schematics of three distinct functional networks of the somato-gastric nervous system of the lobster formed by the same population of neurons (top) enabling generation of two distinct rhythmic outputs (bottom), which underlie different functions (swallowing and gastric mill digestion). Switch between different modes is enabled by modulator inputs. *PN* pyloric net, *GN* gastric net, *EN* sophageal net, *SN* swallowing net. **b** Examples of pharmacological switching of somato-gastric neurons between different rhythmic activities enabling various functions. *CCAP* crustacean cardio-active peptide. Adapted with permission from Meyrand et al. (1994), Nusbaum and Beenhakker (2002). **c** Equivalent electrical circuit driving inhibitory synaptic transmission in neurons. Gradient driven ($E_K$ and $E_{Cl}$) fluxes of $K^+$ and $Cl^-$ across the membrane ($G_K$ and $G_{Cl}$) activated by specific ligands causes a build-up of a negative charge inside the neuron, resulting in the membrane hyperpolarization and inhibition of firing activity. **e, f** In cerebellar Purkinje neurons, electrical stimulation of the inhibitory inputs from local interneurons (BC—basket cells) (**e**) causes rapid membrane hyperpolarization (**d**), which readily suppresses their spontaneous firing activity (**f**). Traces illustrate evoked excitatory and inhibitory post-synaptic potentials (positive and negative deflections) at different stimulation intensities (T—threshold). **e** S. R. Cajal drawing of basket cell—Purkinje cell connections. Reproduced from the original conserved at the Institute Cajal (CSIC), Madrid, Spain. **d, f** Adapted with permission from (Andersen et al. 1964)

The second unique characteristic of neural circuits, which is of key relevance to this discussion, is inhibition. In conjunction with excitation, inhibition shapes and coordinates the activity of neurons and neural circuits at all levels of information processing and integration (Buzsaki et al. 2007) (Fig. 1c–f). Importantly, in addition to stabilizing and coordinating neural dynamics, inhibition can also act in a standalone mode, completely shutting down the activity of neurons and bringing to a halt dynamics of neural circuits. As noted by Sir Charles Sherrington, 'inhibition of an excited state is not a prerequisite for the production of inhibition; inhibition can exist apart from excitation no less than, when called forth against an excitation already in progress, it can suppress or moderate it' (Sherrington 1932). From an evolutionary point of view, by silencing neuronal activity, inhibition could play a pivotal role in selection of neurons and circuits, retaining them in inactive (i.e., dormant) state. One of the key consequences of this neurophysiological mechanisms is that in suppressed state, neural circuits are no longer within reach of selective pressure, and, therefore, cannot be weeded out (Kavanau 1990). In phylogenetic terms, this course could, therefore, facilitate build-up of non-functional neurons and circuits, as once selective pressure has departed, collections of inactive neurons are left behind in invisible for the evolutionary process (i.e., dark matter). Overall, functional versatility of neural assemblies on one side and their capability to evade natural selection on the other can significantly attenuate (or under certain circumstances even remove) the eliminating power of evolution, which acts on brain affairs indirectly and predominantly be means of behavior (Mayr 1958; Corning 2014). Through build-up of obsolete neurons and circuits, permanent inhibition could also contribute towards gradual increase in nervous system size in surviving lineages. Kavanau regards the retention of obsolete systems of neural networks and the ever increasing need for inhibitory–modulatory control as a price

paid by brain evolution for the multi-functionality of neural circuits (Kavanau 1990).

The same sets of basic mechanisms possibly also contributed to the fact that brain size does not scale with its functional capacities. Noted already by Charles Darwin, dissociation between the brain size and functional abilities has been systematically studied for the first time by his peer and co-founder of evolutionary psychology Romanes, who observed no intellectual superiority of men against women, despite the significantly larger brain size of the former (Romanes 1887). More recent evidence backing this principle comes from computed tomography (CT) and fMRI scans of human brains, showing numerous cases of major deficiency of neural tissue or underdeveloped brains in individuals with well-maintained social compatibility and academic performance (Lewin 1980; Feuillet et al. 2007; de Oliveira et al. 2011) (Fig. 2). It is important to note that vast collections of dormant neurons and circuits under certain conditions can switch in active state and engage in functional architecture of the brain, bringing to life ancient rudimentary traits or atypical behaviors. Through the same process, neural evolution can afford new combinations of neurons and circuits for functional upgrade, topping up already in use circuits and reshuffling networks by means of existing connections. If favored by selective pressure, the revived networks can be consolidated within the functional matrix of the brain. As discussed in the following, emerging functional and clinical evidence is in agreement with the premise of occasional reactivation of obsolete circuits and rapid rise of non-standard functional traits and inexplicable behaviors.

## Reactivation of dormant circuits

Massive repositories of dormant neurons and networks not only present abundant reserve for neo-functionalization, but also retain the potential for their revival in primeval ancient form, driving non-standard, or frequently, pathological fits. Numerous examples of the reactivation of fossilized circuits enabling relict behaviors have been documented, with some accessible at all times, or nearly all times, from late embryo to adult, while others emerging during a certain phase of life or seasons, or can be triggered by penetrating stress and injury. In latter cases, acute disinhibition of obsolete circuitry enables their rapid reactivation and interference with various physiological and behavioral affairs. One of the best known and widely discussed examples of revival of dormant circuits from clinical neurology is the advent of the palmar

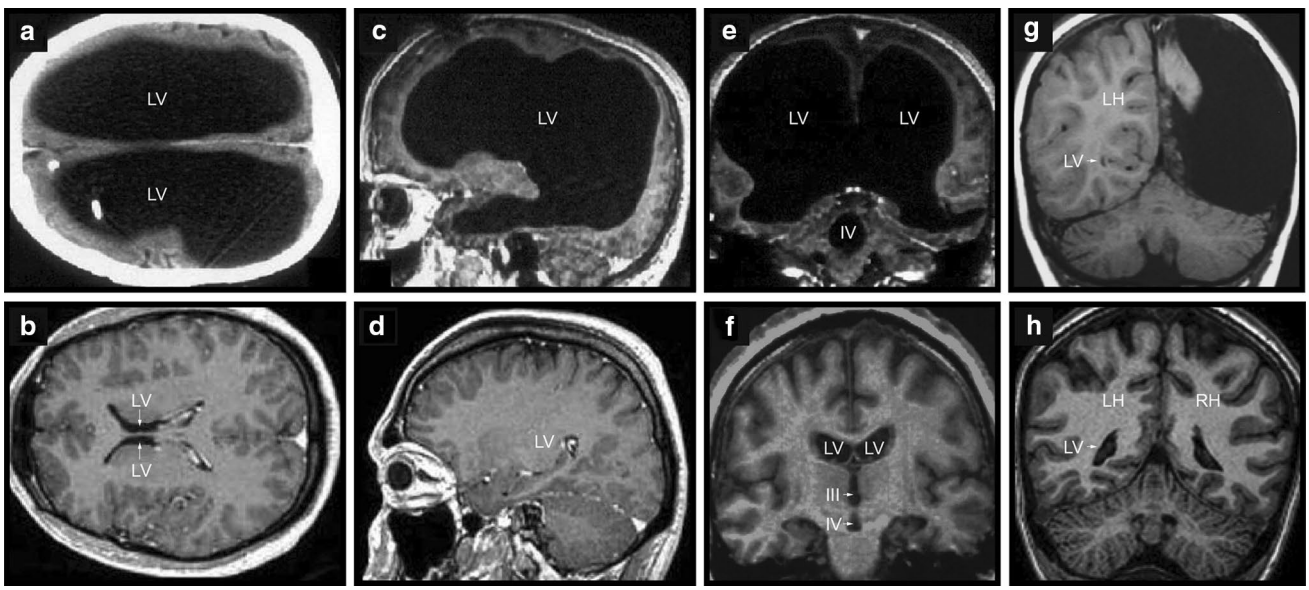


**Fig. 2** Examples of extensively compromised brains in overtly normal young and adult humans. **a** CT and (**c, e**) T1-weighted MRI brain image with gadolinium contrast of a married man and father of two children, who worked at the moment of imaging as a civil servant. On neuropsychological testing, he proved to have an intelligence quotient (IQ) of 75: his verbal IQ was 84, and his performance IQ 70. *LV* lateral ventricle, *IV* ventricle IV. Adapted with permission from Feuillet et al. (2007). **g** An MRI scan of a 7-year-old girl after hemispherectomy at the age of 3 years for Rasmussen syndrome. Though the dominant hemisphere was removed, with its language centers and the motor control for the left side of her body, the child is fully bilingual in Turkish and Dutch, with her hemiplegia partially recovered. With only noticeable by slight spasticity of her left arm and leg, she leads an otherwise normal life. Adapted with permission from Borgstein and Grootendorst (2002). *LH and RH* left and right hemispheres, respectively. **b, d, f, h** MRI scans of anatomically matching planes of the normal human brain. Adapted with permission from Corkin et al. (1997) and Forsdyke (2014) and MRI brain atlas (http://w-radiology.com/atlas_brain_mri.php)

grasp reflex in humans affected by acute brain injury or brain disease. Although the adaptive significance of this reflex for arboreal ancestors of men and for infants clinging firmly to adults is evident, during development this reflex becomes suppressed by the outputs of more slowly maturing higher circuits (Swaiman and Wright 1975). Nonetheless, the motor apparatus and neural circuits supporting this reflector activity remain preserved over many decades of human life and can switch on after frontal lobe lesion, spinal cord disease or losses of parts of the midbrain, causing the removal of stabilizing supra-spinal influences (Matthews 1982).

A series of more sophisticated examples of revival of relict neural functions and behaviors, including highly complex undertakings during courting and reproductive rituals, nesting habits and egg care have been also documented (Buckley 1969; Kavanau 1987), implying a wide-ranging presence of this mechanism throughout the animal kingdom. It is interesting to note that relict traits are more readily activated in natural hybrids (Kavanau 1990), inferring that the dormant circuits are more accessible and released in individuals with mixed genetic background. Shelduck, *Tadorna tadorna*, and Egyptian goose *Alopochen aegyptiacus* hybrids, for instance, reverts to Anatid pre-mating ceremonies, which are phylogenetically much older and simpler than the complex mating ceremonies of their parents (Lorenz 1970). Likewise, a hybrid female lovebird (male *Agapornis roseicollis* × female *A. personata fischeri*) covers four successive single-egg clutches with fresh nesting material instead of incubating them, an example of the reactivation of millions of years old ancestral habits from cold-blooded pre-incubatory times in reptiles (Kavanau 1987). These and many other examples of the revival of ancestral behaviors in various phylogenic branches substantiate the notion of retention of obsolete behavioral traits and their neural correlates in a latent state over millions of years, with the possibility of sudden revival.

The reactivation of ancient neural networks with the emergence of inexplicable neutral or maladaptive traits has also been considered in the context of human neuropsychiatric disease, including the Tourette's syndrome (TS), autism spectrum disorders, schizophrenia, and some neurodegenerative diseases. Although these discussions are still at a premature stage, important clues have nevertheless emerged. In his deliberations on multiple TS cases, Oliver Sacks observes that some of compulsive tics could result from release of primordial acts and behaviors of our ancestral primates, due to unrestrained episodes of hyperactivity of old centers in the brain, like those activated due to excitatory lesions of encephalitis lethargy (Sacks 1995). Neurophysiological studies have shown that both remitted and active TS reveal enhanced intra-cortical excitability resultant from disinhibition, which leads to ectopic activity of selected groups of cortical neurons, contributing towards the overt or subliminal perception of premonitory urges and generation of tics (Llinas et al. 2005; Leckman et al. 2010). Results of fMRI studies are in general agreement with the role of abnormal connectivity and deficient inhibition in unwanted and unrestrained behaviors (Leckman et al. 2010).

A breakdown of cortical connectivity, largely attributed to disinhibition of local networks, has been also implicated in schizophrenia, leading to disruptions of intra-cortical communication and appearance of positive symptoms (Fornito et al. 2012; Lisman 2012). Although at this stage the interpretation of functional brain imaging data remains problematic, emerging evidence infers a significant role of displaced de novo activity in disruption of cortical connectivity. Bullmore and colleagues, for instance, propose that disintegration of local connectivity due to disinhibition could play a major role in incongruities of fMRI signals in schizophrenia as well as in diminishing network synchrony (Zalesky et al. 2012) (Fig. 2a). Analysis of circuit dynamics with fMRI showed also a considerable decline of intra-cortical synchrony with a deficit in information processing, while results of modularity analysis show a rise of displaced activity with dissociation of functional nodes and connectivity (Alexander-Bloch et al. 2010) (Fig. 3a). In agreement with the results of brain imaging studies, EEG data show desynchronization of neural dynamics with local disinhibition, which is manifested largely in reduction of beta and gamma oscillations (Uhlhaas and Singer 2010) (Fig. 3b). With an overall increase in cortical circuit dynamics in schizophrenia, the most parsimonious interpretation of the loss of temporal coherence is rise of activity not bound to perennial circuits. Mechanistically, disinhibition and collapse of synchrony in schizophrenia have been suggested to be partly linked with a deficit in GABAergic drive, due to a reduction in the 67-kDa synaptic enzyme (known as GAD67) (Lisman 2012). The deficit of top–down inhibition with release of latent circuits is also in line with attenuation of inhibitory drive in carriers of risk-for-schizophrenia alleles of the RAC-alpha Akt1 gene and the D2 receptor gene (Tan et al. 2011), as well as with the ameliorative effects of antipsychotic GABA enhancers (Nejad et al. 2012).

In the same context, reports from studies of autistic savants displaying a wide range of extraordinary abilities and outwardly inexplicable behaviors are of special interest. While the neural basis of the sudden emergence of peculiar fits of savants remains poorly defined, careful analysis of their substrate suggests a deficit in top–down inhibition. In true Jacksonian style, Snyder and colleagues recently proposed that the extraordinary abilities of subjects with contracted savant syndrome emerge once brain circuits, held normally in check by inhibition, become untethered and activated (Snyder et al. 2003). The most compelling argument advocating the role of dormant circuits in generation of savant skill is that the extraordinary signs can emerge suddenly after stress or injury,

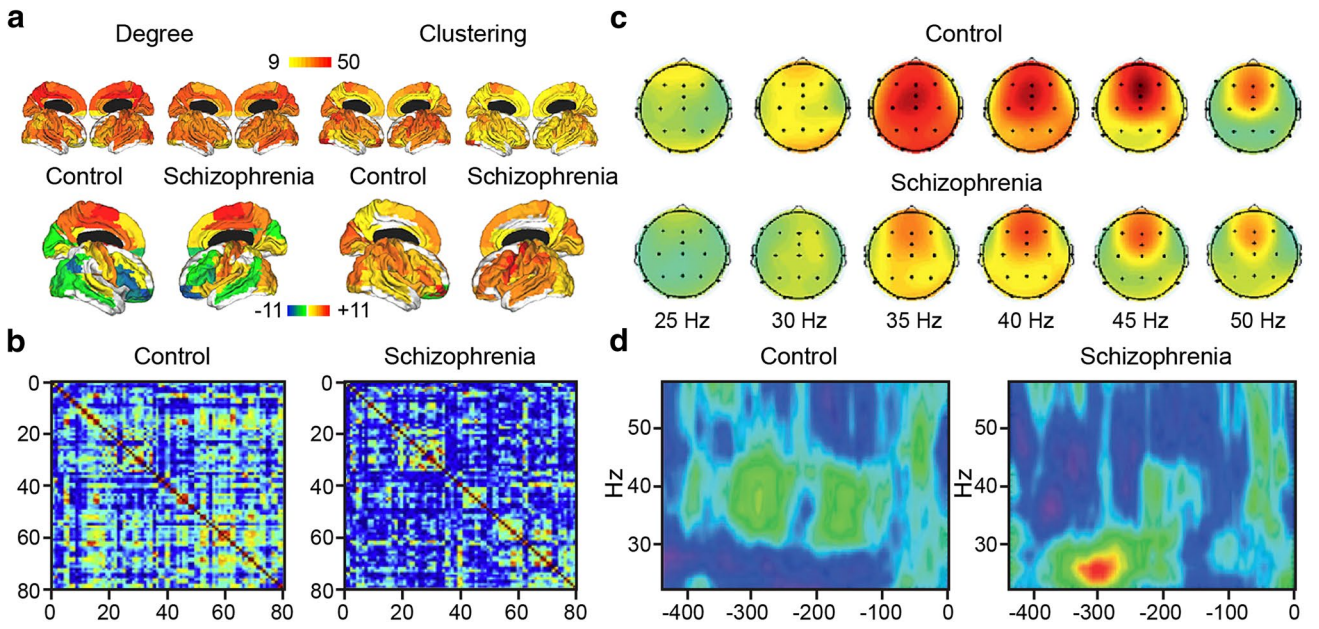


**Fig. 3** Disruption of the short-range connectivity with local synchrony deficit in the brain of schizophrenia patients, suggestive of the disinhibition of cortical networks. **a** Comparison of topographical properties of functional networks between healthy and schizophrenia (representative and mean, top and bottom, respectively) show a deficit in synchrony and breakdown of the connectivity. Cortical surface rendering of the degree and clustering, which reflect the extent of synchrony show reduced connectivity and desynchronization of cortical networks in schizophrenia patients. Accordingly, a functional connectivity matrix taken from a typical normal subject and schizophrenic patient (left and right panels) comparing 78 anatomical nodes interconnected by 3003 edges show weaker connectivity and loss of synchrony. Adapted with permission from (Lynall et al. 2010; Fornito et al. 2012). **c** Widespread steady-state evoked potential (SSEP) response is seen to 35–45 Hz stimulus trains (γ-oscillations), which is considerably larger in healthy controls compared to patients with schizophrenia. Adapted with permission from Krishnan et al. (2009). **d** Example of a lower 40 Hz oscillations induced in schizophrenia patients during a visual gestalt task, as compared to healthy controls. Adapted with permission from Spencer et al. (2008)

without any prehistory (Treffert 2006; Sacks 2007), and occasionally diminish rapidly upon recovery from illness (Sacks 2007). Of note, disinhibition of dormant cortical circuits has been also implicated in numerous accounts of experimentally induced savant-like activities in healthy volunteers. Using a low-frequency transcranial magnetic stimulation (rTMS) of selected brain areas, the activation of compulsive analytic and artistic capabilities have been documented by selective modulation of cortical inhibition, without altering normal brain functions (Snyder et al. 2003; Young et al. 2004). It is important to note that, while in general savants excel in a narrow spectrum of abilities, numerous cases with alterations concerning a wider range of physical and cognitive facilities have been also shown (Kehrer 1992; Treffert 2014), reflecting perhaps broader capabilities of brain networks to support atypical skills and behaviors. Accordingly, results of brain imaging studies in savants, similar to TS and schizophrenia, show specific functional changes suggestive of the emergence of de novo activity with a general increase in dynamics of cortical circuits (Treffert 2014). The release of latent cortical circuits due to deficits in top–down inhibition has been also implicated in sudden emergence of an obsessive interest and performance in calculus, music, and art in elderly affected by the neurodegenerative disease. The results of a meta-analysis of a large cohort of subjects with frontotemporal dementia, degeneration in specific regions of the frontal and anterior temporal lobes of the left hemisphere have been shown to activate compulsive savant-like skills and artistic interests (Miller et al. 1998). Based on accumulating clinical evidence, Miller et al. argued that unusual creative tendencies in these subjects are due to the ravage of higher up circuits, which have kept under persistent inhibition neural networks driving these extraordinary abilities, maintained otherwise over a lifetime in a dormant state (Miller et al. 1998).

From the above discussion it emerges that while normally kept in a dormant state, under piercing stress or disease, the inactive neurons and neural circuits can switch on and enter into the realm of psyche and behaviors. Multiple emerging examples of the revival of latent neural networks and dormant facilities in animals and humans call for further research and suggest that the revival of obsolete networks can influence a wide spectrum functions, ranging from simple reflexes to highly sophisticated fits and behavioral undertakings.

## The past and the future of brain's dark matter

In his remarks on evolution and dissolution of the central nervous system, John Hughlings Jackson speculates that disinhibition of lower brain centers after removal of the influence from structures above may play a key role in the emergence of a range of neurological symptoms (Jackson 1887). Founding his theory on the principle of hierarchical organization of nervous centers, Jackson notes that each reflex, in addition to undertaking its specific function, also inhibits the activity of subordinate circuits. Because Jackson's concept of neural hierarchy assumes a modular organization of the nervous system, dissolution implies downgrading brain mechanisms to more primitive evolutionary levels, reviving phylogenetically older circuits. The functional model of the brain proposed by Jackson makes two important predictions relevant to our present discussion: first, it assumes the existence of dormant circuits maintained in a suppressed state, and second, it infers the possibility of their revival and re-entry into the realm of mind and behavior. Jackson's evolutionary views had a major influence on the concept of minds 'dark energy' and hidden brainpower postulated by William James, who envisaged the multilevel and complex nature of mental operations, contingent on different intensity of metabolic activity (James 1907). While in his interpretations W. James remains strictly within the frame of theoretical psychology, his theory of latent mental rule and different levels of mind power played a decisive role in the emergence of 'a ten percent brain myth', a popular belief claiming that we use only a small fraction of our brain and mental capabilities (Jarrett 2015).

Although Jackson made the first attempt to set the premise of dormant brain circuits on experimental grounds, it was the neurosurgical genius of Wilder Penfield, who demonstrated the composite and intertwined co-existence of eloquent and inert (non-responsive) cortical fields using brain mapping with electrical micro-stimulation (Penfield 1977). With gradual recognition that non-responsive cortical areas of Penfield's patients, after all, present higher order associative networks processing a specific type of neural information, frustration and puzzlement also grew upon the arrival of striking CT and structural MRI scans demonstrating severely defective and downsized brains in individuals with normal social compatibility and above average IQ. In the most dramatic cases, adequate social coherence and normal intellectual performance were documented in subjects missing > 90% of their cerebral mass (Lewin 1980), verifying the incredible plasticity of neural tissue. Together with outstanding questions concerning the energy expenditure and global network dynamics under rest and activation (Attwell and Laughlin 2001; Raichle 2015), the perplexing discoveries reviewed above call into question established functional models of the brain, and above all the way it acquires, stores and processes information, and warrant their careful revision.

Clearly, no theory of brain function can be considered complete unless it seamlessly integrates vast collections of dormant neurons and inactive circuits, and explains sudden rise of relict behaviors from animal studies, as well as outbursts of extraordinary creativity and intellectual capacities in humans affected by penetrating stress, trauma or disease. Unlike dubious spare mass of neural tissue envisaged in 'ten percent brain myth' laying around and waiting to be given a job to do, discussed herein brain's dark matter epitomizes the tangible and highly composite byproduct of the natural evolution, trapped in inactive and invisible state by inhibition. Rooted deep in the phylogenic past, vast collections of fossilized neurons and networks once had been the integral part of functional circuits and played their adaptive role in life affairs. While silent at present, they remain fit and ready to reengage in neural processes, to influence functions of the body and mind. As discussed above, in addition to breeding sorrow and misery, the reviving circuits can occasionally also enhance facilities of the brain, in way which otherwise never could been perceived or imagined. Careful analysis of the functional impact of dormant networks should not only elucidate the fundamental rules and mechanisms of neural processes but may also yield valuable clues towards their employment for healthcare benefit.

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## Compliance with ethical standards

**Conflict of interest** This manuscript describes original research and is not under consideration in any other journal. The author reports no potential conflict of interest.

**Ethical approval** This is a review paper and does not involve human or animal tissue. The original sources of presented and discussed material are fully acknowledged in compliance with journal's policies.

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