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Optogenetic neuronal control in schizophrenia

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ABSTRACT

Schizophrenia is a serious mental disorder characterized by a heterogonous spectrum of clinical manifestations. Schizophrenia is basically incurable. The discovery of antipsychotic medications in the late 1940s has helped control some of the symptoms but has not reversed the course of the disorder and has had limited effect on the debilitating symptoms of the illness.

In recent years brain stimulation technologies have emerged in the bio-scientific scenery. Deep brain stimulation now plays an important role in the treatment of many neurological disorders, and seems promising in treating depression.

Optogenetics is a new technology that offers control over neuronal activity by turning on and off distinct neuronal populations. It has a great advantage over previous brain stimulation technologies in that it is accurate and specific to the neurons intended for activation and control.

There is no evidence that brain stimulation has been investigated in schizophrenia patients. This possibility was discussed in a single commentary that proposed the hippocampus and nucleus accumbence as targets for DBS in schizophrenia, however it was emphasized that the neurophysiology and neuroanatomy of schizophrenia have not been elucidated to the extent that brain stimulation can be planned.

In light of new optogenetic technology time is ripe to seriously consider optional targets of intervention in the brain of schizophrenia patients. Any such target should involve neuronal circuits (1) known to be relevant for schizophrenia, (2) involved in cognitive and brain functions that are disturbed in schizophrenia, and (3) relevant to alleged neuronal network mechanisms that are presumably damaged or malfunctioning in schizophrenia.

This paper reviews the relevant literature and proposes that optogenetic interventions in schizophrenia should begin in the prefrontal cortex and the Globus-Pallidus Subthalamic nuclei systems.

In the protocol for the prefrontal cortex, wide-arbore and chandelier inhibitory interneurons should be targets for optogenetic intervention and in the Globus-Pallidus Subthalamic nuclei the fast spiking neurons should be targets for optogenetic intervention.

These subsystems are critical modulators of neural complexity which is directly relevant to connectivity organization in the brain. Schizophrenia is described as a disturbance of connectivity organization in the brain treatable by the relevant optogenetic interventions promoted in this paper.

Introduction

Optogenetics is a new technology that offers control over neuronal activity by turning on and off distinct neuronal populations using cell-type specific, optically sensitive, molecular neuronal activity "switches." These "switches" are microbial, light-sensitive ion conductance-regulating proteins, e.g., channelrhodopsin-2 (ChR2) and halorhodopsin (NpHR). They are genetically engineered to become part of the cellular machinery and introduced individually to target neurons relevant for activating or inhibiting pre-chosen neuronal circuits [1].

Schizophrenia is a serious mental disorder characterized by a heterogonous spectrum of clinical manifestations [2]. Liddle has classified this heterogeneity into three overlapping types of clinical descriptions, (1) disorganized, (2) reality-distortion, and (3) poverty schizophrenia [3]. Schizophrenia typically evolves as a non-reversible gradually deteriorating disease progressing toward poverty schizophrenia with grave deficits of mental and social functioning. Disorganized schizophrenia is characterized by marked disintegration of conscious experience where the experience of reality is fragmented. In reality-distortion schizophrenia, delusions prevail generated from false reconciliation of experiences and from the collapse of logical inference. In poverty schizophrenia the patient becomes incapacitated due to destruction of higher mental functions such as volition and emotions, and constriction of experience and thought (poverty and perseverations of thought).

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Schizophrenia is basically incurable; the discovery of antipsychotic medications in the late 1940s has helped control some of the disorganization and reality-distorting symptoms but has not reversed the course of the disorder and had little, if any, effects on the debilitating symptoms of the illness.

In recent years brain stimulation technologies have emerged in the bio-scientific scenery. Deep brain stimulation (DBS) now plays an important role in the treatment of Parkinson's disease, tremor, and dystonia. DBS may also have a role in the treatment of other disorders such as obsessive–compulsive disorder, Tourette's syndrome, and depression [4]. The effects of DBS on cognition and clinical psychiatric symptoms are just beginning to be researched. Page et al. [5] examined the effects of deep brain stimulation of the subthalamic nucleus on tests of set-shifting and dual task performance in patients with Parkinson disease. All patients revealed a clinical benefit from DBS of the subthalamic nucleus (STN).

There is no evidence that DBS has been investigated in schizophrenia patients. Bakay [6] discuses this possibility in a commentary and proposes hippocampus and nucleus accumbence as targets for DBS in schizophrenia, however he emphasizes that the neurophysiology and neuroanatomy of schizophrenia have not been elucidated to the extent that DBS can be planned.

In light of the new optogenetic technology able to target individual neurons in the brain and the time is ripe to seriously consider optional targets of intervention in the brains of schizophrenia patients. Any such target should involve neuronal circuits (1) known to be relevant for schizophrenia, (2) involved in cognitive and brain functions that are disturbed in schizophrenia, and (3) relevant to alleged neuronal network mechanisms that are presumably damaged or malfunctioning in schizophrenia. While targets of intervention can be selected solely based on neuro-anatomical structures involved in schizophrenia, a more specific mode of intervention, i.e., addressing which specific action-inhibition algorithms to apply, – require a more elaborated assumption about regarding the specifics of the disorder.

This paper first addresses the neuro-anatomical structures involved in schizophrenia and its relevant cognitive disturbances, and then goes to generate the presumed neuropathology algorithm relevant for designing a set of optogenetic interventions that may provide an initial set of protocols for optogenetic treatments in schizophrenia.

Neuro-anatomical structures involved in schizophrenia

The most renowned brain structure in schizophrenia is the prefrontal cortex. It has been repeatedly found to be involved in schizophrenia especially with imaging studies. Deficient cognitive function in schizophrenia has been related to prefrontal cortical functions. This has been recently reviewed in relation to neuronal circuits [7] neural plasticity [8] and schizophrenia genetics [9].

Fig. 1 shows the relevant cytoarchitecture of the prefrontal cortex with its dopaminergic afferents, dopaminergic activity, which is both tonic and phasic, has both excitatory (direct) and inhibitory (via interneurons) effects on the pyramidal neurons which make up the neural network of the prefrontal cortex and its afferent and efferent connections with the rest of the cortex.

While responding to the embedded sequence within the serial reaction time task, schizophrenia patients did not activate frontal or parietal areas, but had greater activation in the right anterior cingulate, left globus pallidus and the right superior temporal gyrus [10]. Paucity of activity in bilateral frontal cortex, left parietal cortex and bilateral caudate nucleus was found in patients and may represent cerebral dysfunction associated with schizophrenia, whereas the hyperactivation of the right superior temporal gyrus, the right anterior cingulate cortex and the left globus pallidus

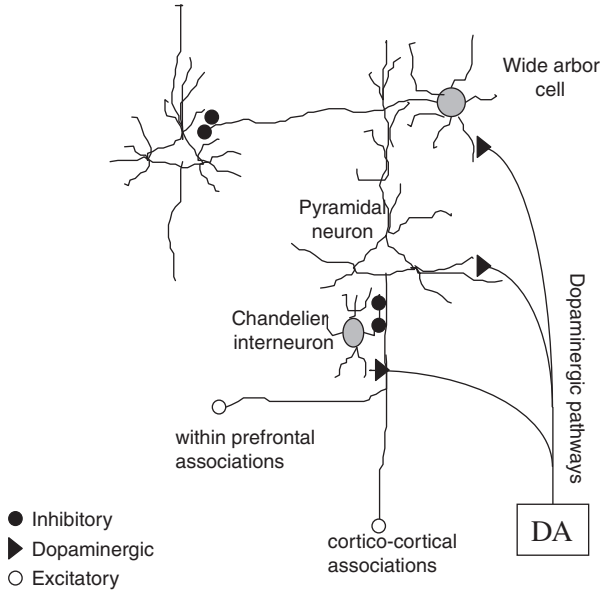

Fig. 1. Dopaminergic circuit of the preforntal cortex.

may represent a compensatory cerebral action capable of facilitating near-normal task performance [10]. This description supports the idea of dynamic regulatory control from the basal ganglia that attempts to compensate reorganizing cortical efforts to compute the task.

Comparison of globus pallidus volume between neuroleptic-naive patients with schizophrenia and healthy controls using structural MRI found that the volume of the external segment of the globus pallidus was positively correlated with the severity of global symptoms, as measured by the scale for the assessment of negative and positive symptoms [11]. Using SPM (statistical parametric mapping) of brain positron emission tomography (PET) scans obtained in resting conditions from severely affected schizophrenia patients, increased activity in: globus pallidus, insular cortex, cuneus, claustrum, post-central gyrus and pre-central gyrus; decreased activity in fusiform gyrus and superior temporal gyri, were demonstrated [12]. These results permit correlation of negative symptomatology with abnormalities in the cortico-striato-pallido-thalamic neural circuit. According to Galeno and colleagues [12], severity of negative symptoms is clearly correlated to abnormal left external pallidal activation, evidencing the relevance of this nucleus for cognitive, planning and social capabilities.

Basal ganglia volumes in drug-naive first-episode schizophrenic patients before and after treatment were measured using high-resolution magnetic resonance imaging (MRI) scans. Compared with controls, absolute volumes of interest of caudate nucleus, nucleus accumbens, and putamen volumes were smaller in patients at baseline and increased after treatment. Additionally altered asymmetry in caudate volume in patients suggests intrinsic basal ganglia pathology in schizophrenia [13]. The total volume and shape of several basal ganglia structures were compared in subjects with and without schizophrenia [14]. Left and right volumes of the caudate, putamen and right globus pallidus volume were significantly increased in subjects with schizophrenia as compared to comparison subjects after total brain volume was included as a covariate. Significant differences in shape accompanied these volume changes. There were few significant correlations between volume or shape measures and either cognitive function or clinical symptoms. For example a positive correlation between an attention-vigilance cognitive dimension and the volume of the caudate and putamen, and a negative correlation between nucleus accumbens

volume and delusions was found. Mamah and colleagues [14] conclude that basal ganglia volumes relative to total brain volume were larger in schizophrenia subjects than in healthy comparison subjects.

As early as the beginning of the eighties Creutzfeld [15] realized that in the neocortex various aspects of the world and of the physical and social relationships of the individual to the world are represented through thalamocortical projection systems. There is no unified representation of the world in any single cortical area. All neocortical outputs feed into action systems of the brain. The synthesis of the distributed cortical representations of the world is thus realized through the action elicited by their combination. The action systems of the midbrain-cerebellum and the basal ganglia feed back into neocortical areas (internal loops). The role of the basal ganglia is thus relevant to a unified conscious experience of the world. Exactly the experience that vanishes in schizophrenia patients replaced by disorganized delusional experience.

During various states of vigilance, brain oscillations are grouped together through reciprocal connections between the neocortex and thalamus [16]. During behavioral states associated with brain disconnection from the external world, the large-scale synchronization of low-frequency oscillations is accompanied by the inhibition of synaptic transmission through thalamocortical neurons. Sustained fast oscillations that characterize alert states are synchronized over restricted territories and are associated with discrete and differentiated patterns of conscious events. This description relates to an increase of neural complexity were subsets have increasing statistical dependence [17]. Recent studies have revealed that the brain as a whole is not affected to the same degree by anesthetics, but that specific brain regions (and particularly cognitive processes mediated by these regions) are more sensitive to anesthesia and sedation than others. Inhibition of activity in multimodal association cortices (such as parietal and prefrontal association cortices) by sedative concentrations of anesthetics produces amnesia and attention deficits, whereas activity in unimodal cortices and in the thalamus remains largely unaffected by low doses of anesthetics [18]. This shows the relevance of cortical–cortical connectivity for attention and memory. Activity in the midbrain reticular formation, thalamus, and unimodal cortices appears to be suppressed only by anesthetic concentrations causing unconsciousness. Besides those regional suppressive effects, anesthetics impair functional connections between neurons in distributed cortical and thalamocortical networks, indicating their relevance for emergence of consciousness.

During behavioral quiescence, the neocortex generates spontaneous slow oscillations that consist of Up and Down states. Up states are short epochs of persistent activity that resemble the activated neocortex during arousal and cognition. Using thalamocortical slices, Rigas and colleagues [19] found that persistent cortical activity during spontaneous Up states effectively drives thalamocortical relay cells through corticothalamic connections. However, thalamic activity can also precede the onset of cortical Up states, which suggested a role of thalamic activity in triggering cortical Up states through thalamocortical connections. In support of this hypothesis, they found that cutting the connections between the thalamus and the cortex reduced the incidence of spontaneous Up states in the cortex. There is resemblance between the description of Up states and task-related networks not correlated with the default network (see above), thus providing support for involvement of thalamocortical involvement in brain organizations transiting from non-task to task related networks.

According to Huguenard and McCormick [20] feed-forward and feedback connections between cortex and thalamus reinforce the thalamic oscillatory activity into larger thalamocortical networks to generate sleep spindles and spike-wave discharge of generalized absence epilepsy. The degree of synchrony within the thalamic network seems to be crucial in determining whether normal (spindle) or pathological (spike-wave) oscillations occur. Ferrarelli and colleagues [21] found deficit in sleep spindles in schizophrenia subjects and have related them to dysfunction in thalamic-reticular and thalamocortical mechanisms in these patients. They propose that these findings could represent a biological marker of illness.

The above partial mini-review indicates that targets for possible optogenetic intervention in schizophrenia involve the prefrontal cortex (PFC), globus pallidus (GP), subthalamic nucleus (STN), substantia nigra reticulata (SNr) and compacta (SNc) and striatum. These are listed in order of their preferential importance with the assumption that the PFC is listed highest as a candidate neural formation for intervention.

Presumed neuropathology algorithm relevant for designing optogenetic interventions in schizophrenia

What do we know about the underlying disturbances of neuronal circuitry in schizophrenia? There is sufficient literature to support a ‘disconnection syndrome’ for schizophrenia [22], recently more evidence has been added to sustain this hypothesis. Whitford et al. [23] found that first-episode schizophrenia patients exhibited volumetric deficits in the white matter of the frontal and temporal lobes at baseline, as well as volumetric increases in the white matter of the frontoparietal junction bilaterally. Furthermore, these first-episode schizophrenia patients lost considerably more white matter over the follow-up interval relative to comparison subjects in the middle and inferior temporal cortex bilaterally. Buchsbaum et al. [24] found that compared with normal volunteers, schizophrenia patients showed higher relative metabolic rates in the frontal white matter, corpus callosum, superior longitudinal fasciculus, and white matter core of the temporal lobe. Elevated activity in white matter was most pronounced in the center of large white matter tracts, especially the frontal parts of the brain and the internal capsule. In another work Whitford et al. [23] found that although grey matter volume decreased longitudinally in schizophrenia patients, particularly fronto-parietally, electroencephalographic power increased in the slow-wave and beta-frequency bands, suggesting abnormally elevated levels of neural synchrony. Andreone et al. [25] found cortical white-matter microstructure disruption in frontal and temporo-occipital lobes in a large sample of 68 patients with schizophrenia and 64 healthy controls. Brambilla and Tansella [26] conclude that diffusion weighted imaging (DWI) studies in schizophrenia strongly suggest that white matter communication is disrupted. This supports the hypothesis that there is a cortico-cortical and transcallosal altered connectivity in schizophrenia, which may be relevant to the pathophysiology and the cognitive disturbances of the disorder.

While these findings can support the idea of reduced dependence among brain systems, is there also evidence for disturbed integration? Recent descriptions of a ‘default network’ organization in the brain may provide such evidence. Recent blood oxygenation level dependent functional MRI (BOLD fMRI) studies of the human brain have shown that in the absence of external stimuli, activity persists in the form of distinct patterns of temporally correlated signal fluctuations [27,28]. These spontaneous low-frequency fluctuations (<0.1 Hz) in the blood oxygen level-dependent (BOLD) functional magnetic resonance imaging (MRI) signal have been shown to reflect neural synchrony between brain regions. This phenomenon of synchrony between brain regions is also called the ‘‘default network’’. The default network of spontaneous low-frequency fluctuations has been described in healthy volunteers during stimulus-independent thought and was found to be negatively correlated with regions activated during atten-

tion-demanding tasks [29]. This condition was also formulated as two anti-correlated networks task-related and stimulus-independent; the stimulus-independent network was proposed to have a role in self monitoring while the task related network had the role of cognitive performance [30].

Buckner and Carroll [31] speculate that the default network is relevant to a set of processes by which past experiences are used adaptively to imagine perspectives and events beyond those that emerge from the immediate environment. Within this default mode network that is engaged during rest and disengaged during cognitive tasks Hampson et al. [32] investigated the posterior cingulate cortex and a medial frontal region incorporating portions of the medial frontal gyrus and ventral anterior cingulate cortex during a working memory task. They found that the two regions were functionally connected in both conditions. In addition, performance on the working memory task was positively correlated with the strength of this functional connection not only during the working memory task, but also at rest. Thus, it appears these regions are components of a network that may facilitate or monitor cognitive performance, rather than become disengaged during cognitive tasks. In addition, these data raise the possibility that the individual differences in coupling strength between these two regions at rest predict differences in cognitive abilities important for this working memory task [32].

The largest study to date of the default network in schizophrenia was performed by Garrity and colleagues [33] on 22 patients and 21 controls. Healthy comparison subjects and patients had significant spatial differences in the default mode network, most notably in the frontal, anterior cingulate, and parahippocampal gyri. In addition, activity in patients in the medial frontal, temporal, and cingulate gyri correlated with severity of positive symptoms. The patients also showed significantly higher frequency fluctuations in the temporal evolution of the default mode. They conclude that schizophrenia is associated with altered temporal frequency and spatial location of the default mode network. They hypothesize that this network may be under- or overmodulated by key regions, including the anterior and posterior cingulate cortex. In addition, the altered temporal fluctuations in patients may result from a change in the connectivity of these regions with other brain networks [33]. A similar study by Bluhm et al. [29] with a slightly smaller sample (17 patients and controls) found that healthy volunteers demonstrated correlation between spontaneous low-frequency fluctuations of the BOLD signal in the posterior cingulate and fluctuations in the lateral parietal, medial prefrontal, and cerebellar regions, similar to previous reports. Schizophrenic patients had significantly less correlation between spontaneous slow activity in the posterior cingulate and that in the lateral parietal, medial prefrontal, and cerebellar regions. Connectivity of the posterior cingulate was found to vary with both positive and negative symptoms in schizophrenic patients. They indicate that these data suggest significant abnormalities in resting-state neural networks in schizophrenia [29]. Using a similar number of controls and patients Zhou et al. [34] found that the bilateral DLPFC showed reduced functional connectivities to the parietal lobe, posterior cingulate cortex, thalamus and striatum in FES patients. They also found enhanced functional connectivity between the left DLPFC and the left mid-posterior temporal lobe and the paralimbic regions in first-episode schizophrenia patients. They suggest that functional disconnectivity associated with the DLPFC exists in schizophrenia during rest.

As evident from the above, schizophrenia is related to a widespread cortical whole-brain disturbance. Years of brain research find schizophrenia patients impaired on a multitude of brain structures and functions. Accordingly, in order to pinpoint the psychopathology of schizophrenia a generalized system-based approach should be adopted, one that takes into account the normal workings of the brain when conscious mental experience is coherent, stable, malleably meaningful and logical. The psychopathology of schizophrenia probably involves some general characteristic of brain organization.

Nervous systems facing complex environments have to balance two seemingly opposing requirements. The need to quickly and reliably extract important features from sensory inputs and the need to generate coherent perceptual and cognitive states allowing an organism to respond to objects and events, which present conjunctions of numerous individual features. The need to quickly and reliably extract important sensory features is accomplished by functionally segregated (specialized) sets of neurons (e.g., those found in different cortical regions), the need to generate coherent perceptual and cognitive states is accomplished by functional integration of the activity of specialized neurons through their dynamic interactions [35].

The mathematical concept of "neural complexity" (C_N) [36] captures the important interplay between integration (i.e., functional connectivity) and segregation (i.e., functional specialization of distinct neural subsystems). C_N is low for systems whose components are characterized either by total independence or by total dependence. C_N is high for systems whose components show simultaneous evidence of independence in small subsets, and increasing dependence in subsets of increasing size. Different neural groups are functionally segregated if their activities tend to be statistically independent. Conversely, groups are functionally integrated if they show a high degree of statistical dependence. The inversed U-shaped graph at the bottom of Fig. 2 demonstrates C_N as a value of connectivity balance (disconnection overconnection) where optimal balance is achieved at the highest C_N values.

It can be useful to describe schizophrenia as a disorder of C_N where a segregated brain organization (i.e., total independence among cortical systems) causes fragmentation of experience leading to disorganized schizophrenia and reality distortion [22,37], and where total dependence (overly connected systems) leads to poverty schizophrenia constrained experiential processing, freezing brain-dynamics, limiting it to a few repetitive computations (i.e., poverty of thought and perseverations).

In order to pinpoint the neuro-pathological origin of schizophrenia it is mandatory to discover what regulates neural complexity (i.e., connectivity balance) in the brain. A regulatory structure for neural complexity must have massive, distributed and parallel connectivity with most, if not all, brain formations. Since the brain cortex performs the higher mental functions then neural-complexity regulators would require massive connectivity spread to the cortex. Since neural complexity regulation will require response monitoring, then massive cortical afferents (inputs) would be required to feedback to the C_N regulatory systems. Based on these intuitions, it seems that the basal ganglia with their striatum and thalamocortical connections are most suitable to regulate cortical neural complexity.

As noted, the main structures of interest are the 'Prefrontal cortex', 'striatum', the 'globus pallidus' (external segment GPe and internal segment GPi), the 'subthalamic nucleus' (STN), the 'substantia nigra' (divided into pars reticulata SNr and pars compacta SNc) and the thalamus itself.

The whole system starts as a major output of the cortex, almost every part of the cortex, except for the primary olfactory, visual and auditory cortices, sends axons to the striatum. The origin of the connection is in the pyramidal neurons of layer *V* of the cortex. The corticostriatal connection is glutamatergic and excitatory. The corticostriate connection is the first in a chain of strong reduction in numbers between emitter and receiver neurons [38], i.e., a numerical convergence exists. The effect of this is that if each striatocortical neuron has its own message, it will be mixed or compressed, in the input map. In primates, the striatum has 96%

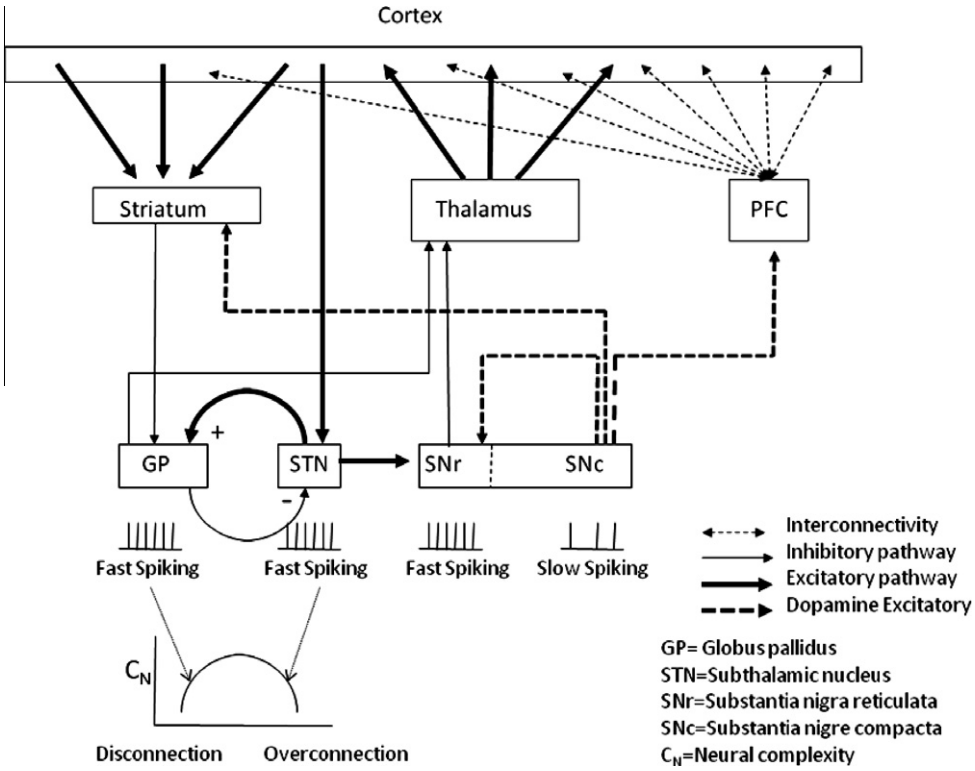

Fig. 2. Cortical sub-cortical circuits relevant to brain organization.

spiny neurons indicating its late evolutionary development, thus relevance to higher mental functions.

Striatal neurons are activated by cortical stimulation. At rest, spiny neurons are left in a state of low excitability by two types of potassium conductance that hyperpolarize the cell. Striatal neurons need strong synchronized input from their excitatory cortical afferences in order to activate downstream formations. These are the striato-pallidonigral bundle: the two nuclei of the pallidum and the substantia nigra. Inhibitory neurons in the striatum send long axons to their targets in the pallidum and the substantia nigra. The pallidonigral set comprises the direct targets of the striatal axons: the two nuclei of the pallidum and the pars lateralis and pars reticulata of the "substantia nigra". One characteristic of this ensemble the very dense striato-pallidonigral bundle.

In addition to the striato-pallidal afference, the lateral pallidum receives a major connection from the subthalamic nucleus. It also receives dopaminegic afferences from the nigra compacta. Contrary to two other elements of the basal ganglia core, the lateral pallidum is not a source of output to the thalamus as it sends its axons essentially to other basal ganglia elements (intra systemic connections).

The medial pallidum, though absolutely similar to the lateral, is phylogenetically younger, as it appears only in primates. The medial pallidum is a "fast-spiking pacemaker" with spontaneous discharges in awake monkeys at about 90 Hz [39], 70–80 for Filion and Tremblay [40]. In opposition to that of the lateral pallidum, the activity is continuous [41] devoid of long intervals of silence [41]. In addition to the massive striatopallidal connection, the medial pallidum receives a dopaminergic innervation from the nigra compacta. Contrary to the lateral pallidum, it is a major source of basal ganglia outputs.

As mentioned above the substantia nigra is divided to pars compacta and pars reticulata The pars reticulata differs from the compacta by that it sends axons to the superior colliculus [42,43]. The border between the two basins is not clear cut but their difference in the participation of distinct subsystems provides sufficient reason for considering the two apart. The neurons that send axons to the superior colliculus have high discharge rates (80–100 Hz) (hence also a fast spiking pacemaker) and "the signal conveyed by the cells is a decrease in discharge rate" [44]. These neurons are involved in occular saccades.

The pars reticulata is most often considered as a single entity. It is another "fast-spiking pacemaker" [45] and shows responses that may be related to memory, attention or movement preparation [46]. In addition to the massive striatopallidal connection, the nigra reticulata receives a dopamine innervation from the nigra compacta and glutamatergic axons from the pars parafascicularis of the central complex.

One of the most important recent discoveries is that the basal ganglia machinery is not simply set in motion from the outside (from afferent inputs). It has indeed several "autonomous pacemakers", defined as sets of "neurons capable of periodic spiking in the absence of synaptic input" [45] i.e., able of producing its own activity. Among autonomous pacemakers, the pallidonigral ensemble belongs to the "fast-spiking pacemakers" "capable of discharge rates in excess of 200 Hz for sustained periods" [45]. The regularity and frequency of the pacemaker is linked to cyclic nucleotide-gated channels (HCN2 and HCN1) present on the dendrites of pallidal neurons. Pacemakers are oscillatory systems they are indeed chaotic oscillators. In a recent paper about humans, Rasouli et al. [47] wrote that "robust fractal dynamics (could be) observed in single neurons... the neuronal dynamics of the internal segment of the globus pallidus are essentially a nonlinear and nonequilibrium process". Such systems were found relevant to a double need: regularity and adaptability functions.

The pallidonigral pacemaker is modulated by striato-pallidonigral inputs. As mentioned above, after the huge reduction in number of neurons between the cortex and the striatum the striatopallido-nigral connection show further reduction in the number of transmitting compared to receiving neurons. This repre-

sents a huge reduction in neuronal connections. The consecutive compression of maps cannot preserve finely distributed maps as in the case, for instance, of sensory systems. The very particular and contrasted geometry of the connection between striatal axons and pallidonigral dendrites offers particular conditions (the possibility for a very large number of combinations through local additions of simultaneous inputs to one tree or to several distant foci. Pallidum is precisely one cerebral place where there is a dramatic change between one afferent geometry and a completely different efferent one. The inmap, and outmap are totally different. This is an indication of the fundamental role of the pallidonigral set: the spatial reorganisation of information for a particular "function", which is predictably a particular reorganisation within the thalamus preparing a distribution to the cortex.

It is predicted that this convergence of stirato-pallido-nigral transmission may serve as an 'assessment' of relationships among large spread cortical connectivity states, and via a particular reorganisation within the thalamus, prepares a neural-complexity-inducing efferent distribution to the cortex.

Contrary to the neurons of the pars reticulata-lateralis, dopaminergic neurons are "low-spiking pacemakers" [45], spiking at low frequency (0.2–10 Hz). Their activity is linked to reward and prediction of reward. Due to its widespread distribution, the dopaminergic system may regulate the basal ganglia system in many places.

As indicated by its name, the subthalamic nucleus is located below the thalamus; dorsally to the substantia nigra and medial to the internal capsule. The subthalamic nucleus is lenticular in form and of homogeneous aspect. The subthalamic neurons are "fast-spiking pacemakers" [45] spiking at 80–90 Hz. The subthalamic nucleus receives its main afference from the lateral pallidum. Another afference comes from the cerebral cortex (glutamatergic), particularly from the motor cortex, subthalamic axons leave the nucleus dorsally, most are afferent neurons with multi-targets to the other elements of the core of the basal ganglia [48].

The subthalamic nucleus and lateral pallidum are both fast-firing pacemakers [45]. Together they constitute the "central pacemaker of the basal ganglia" [49] with synchronous bursts. The pallido-subthalamic connection is inhibitory; the subthalamo-pallidal is excitatory. They are coupled regulators or in other words, coupled autonomous oscillators. The lateral pallidum receives a lot of striatal axons, the subthalamic nucleus not. The subthalamic nucleus receives cortical axons, the pallidum not. The subsystem they make with their inputs and outputs corresponds to a classical systemic feedback circuit. It will be proposed below (Fig. 2) that having converging striatal inputs, the globus pallidus monitors cortical integration while the subthalamic nucleus with its direct cortical afferents, monitors cortical segregation, coupled together they are in a position to balance cortical segregation-integration equilibrium, thus optimizing cortical neural-complexity.

Efferents from pallidum, subthalamic nucleus and substantia nigra (only the SNr) reach the thalamus and from there ascend distributing to the cortex via excitatory glutamatergic pathways. This completes the cortical-striatal-pallidal-subthalamic-nigral-thalamic-cortical feedback and interconnected circuitry.

If we summarize the relevant findings of the above mini-review, we find that schizophrenia, with its heterogeneous manifestations, can be attributed to a disorder of neural complexity in the brain. Potentially, neural complexity could be regulated by basal ganglia via a feedback network involving cortex-basal-thalamic-cortical pathways.

It is proposed that the GP STN coupled dynamics is a 'neural complexity engine' in the sense that it is in a position to monitor (input) and regulate (output) cortical neural complexity. The fact that the GP receive a two stage convergence input from the cortex puts it in a favorable stance to detect cortical integration (overconnectivity). Conversely the direct cortical pathway reaching the STN puts it in a favorable stance to detect cortical segregation. Coupled contradictory (excitability wise) oscillators governed by opposing cortical dynamics generate (via efferents to the SNr) an optimal cortical complexity-related SNr oscillator which via efferent ascending nigral-thalamic-cortical pathways is in a position to dynamically and responsively, balance cortical neural complexity (right section of Fig. 2). The slow spiking generator of the SNc can regulate this 'neural complexity pacemaker' via the dopaminergic pathway hitting key targets of the system, namely the SNr, the striatum and the prefrontal and frontal cortex.

The bottom part of Fig. 2 shows the neural complexity (C_N) graph where over-integration via the GP represent reduction of neural complexity, similarly disconnections and segregation monitored by STN represent reduction of neural complexity but their balanced optimization outputted to the nigral thalamic cortical pathway, increases levels of neural complexity.

According to this model schizophrenia starts as a disturbance (reduction) of neural complexity in the first psychotic episode. Typically disconnection dynamics ensues first, collapsing levels of neural complexity, fragmenting cortical integration and correlated conscious experience (resulting in disorganized and realty distortion schizophrenia; see above). This may occur due to developmental delays that leave the cortical organization insufficiently developed to cope with the increasing demands of adult life challenges [37]. As a result a critical developmental phase-transition where cortical maturation reaches the threshold that enables coping with (i.e., brain computing) adult-life demands is not reached, explaining why schizophrenia starts at this typical age of early adulthood.

It is assumed that the initial 'collapse' of neural complexity just described, is immediately counterbalanced via the neural complexity pacemaker, described above, creating integration dynamics in the cortex. Evidently the integration dynamics go too far and become overconnected dynamics resulting in deficient poverty schizophrenia.

The cortical organization and plasticity does not remain 'indifferent' to these grave oscillations of connectivity balance that destroy optimal neural complexity. Both the disintegration occurring in the segregation shift as well as the over-integration characteristic of the integration shift, have implications on the natural plasticity dynamics of millions of synapses spread in the cortex. A fixation process may occur and it is probably relevant to assume that with every perturbation to the connectivity balance, resuming optimal connectivity balance and recovering neural complexity, becomes more difficult and less likely. Despite this connectivity disturbance the neural complexity pacemaker continues its regulatory action plunging the cortex into consecutive shifts of segregation and integration as it 'tries' to rebalance cortical neural connectivity and recover optimal neural complexity levels. This can explain the deteriorating protracted progression of schizophrenia.

According to this model schizophrenia is essentially a disorder of un-reached neural complexity levels in adolescence, followed by ineffective neural complexity pacemaker activity that plunges the cortex into gradual progressive deterioration of neural complexity via oscillating dynamics of integration-segregation shifts attributing to schizophrenia its typical clinical heterogeneity and prognosis of cyclic deterioration.

The model also explains the many findings of involvement of the dopaminergic pathways in the disorder. According to this model altered dopaminergic activity could reflect compensatory regulatory efforts of the SNc on the neural complexity pacemaker. As to antipsychotic medications typically working on the dopaminergic system, they seem to be effective in pushing the system from segregation to integration but not in rebalancing the system and restituting its neural complexity levels.

As explained above, substantia nigral neurons that send axons to the superior colliculus are involved in occular saccades explaining the findings about altered saccade eye movement in schizophrenia [50] probably reflecting basal ganglia pacemaker alterations.

Proposed optogenetic interventions

The prefrontal cortex is most frequently indicated in the psychopathology of schizophrenia. It has massive efferent afferent interconnectivity (Fig. 2) with most of the cortical systems and thus is probably best suited to be involved in the connectivity balance spread in the brain. Due to the massive efferent afferent interconnectivity of the prefrontal circuitry it can (at least in part) act as a relay to whole brain connectivity organization, in other words input–output activity of the prefrontal pyramidal neurons can associate, or dissociate signals arriving by efferents from vast cortical regions with efferent signal from the prefrontal cortex to vast spread-out cortical areas. Based on this assumption the input–output transmission relationships of the pyramidal neurons of the prefrontal cortex become connectivity organizers in vast cortical brain regions if not for the entire brain. If the input–output transmission is inhibited a disconnectivity dynamics will ensue in the brain. If inversely, the input–output transmission is enhanced, efferents will readily excite afferents overly connecting vast spread-out brain circuits, and overconnectivity dynamics will develop.

Fig. 1 shows how the pyramidal neurons that receive and forward signals from the PFC make connections with inhibitory neurons, the "Wide-arbor" and "Chandelier" cells. These have inhibitory effects both on the dendrites (Wide-arbor) as well as the axons (Chandelier) of the pyramidal neurons and are in an ideal position to control input–output relationships of the pyramidal neurons. Wide-arbor inhibitory activity on dendrites will reduce effects of incoming afferent signals to the pyramidal neuron, and Chandelier inhibitory activity on the axons will inhibit pyramidal outputs reducing efferents signals from the pyramidal neurons. In other words, control over the input–output threshold of pyramidal neuronal activity is directly regulated by the activity of these interneurons. Based on this hypothesis, optogenetic control over the activity of the wide-arbor and chandelier interneurons readily controls the connectivity-organizing effects of the prefrontal cortex on the brain.

Fig. 1 shows that dopaminergic activity in the prefrontal cortex has both excitatory (directly via excitation of pyramidal dendrite) and inhibitory (via the interneurons) activity over the pyramidal neuronal network. Even though this puts the dopaminergic activity in a modulator role for the prefrontal cortex, probably by fine-tuning the activity just mentioned, it is less relevant as a target of direct optogenetic intervention as the intervention on the interneurons themselves will probably have a corrective effect in patients where it seems that dopaminergic manipulation alone does not effectively alter the course of the disease (see above).

The inter-neurons with their inhibitory effect fine-tune the prefrontal system allowing the activity of maintaining connectivity balance. By intervening in these interneurons with optogenetics it may be possible to control the input–output relationships of pyramidal neuronal activity thus directly controlling the connectivity balance in the brain. Let us assume that in schizophrenia patients with negative signs schizophrenia over connectivity dominates brain organization, then by activating inhibitory chandelier cells, the inhibition of these cells on the axons of the pyramidal neurons will increase the threshold of their output and thus disconnect the input signal from output signals. Based on the assumption of relay connectivity with the rest of the cortex, the disconnection of input–output relationships would cause a vast disconnectivity dynamics spread in the brain. Inhibition of this same inter-neuronal activity would increase input output relationships of the pyramidal neurons (by reducing their thresholds) thus creating readily input–output connections of efferent–afferent activity ensuing as an over-connectivity dynamics in the brain.

The subthalamic nucleus and lateral pallidum are both fast-firing pacemakers [45]. The pallido-subthalamic connection is inhibitory; the subthalamo-pallidal is excitatory. The lateral pallidum receives mainly converging striatal axons, while the subthalamic nucleus receives mainly cortical axons. As previously mentioned, it is assumed that having converging striatal inputs, the globus pallidus monitors cortical integration while the subthalamic nucleus, with its direct cortical afferents, monitors cortical segregation. Together they are coupled autonomous oscillators presumably acting as coupled regulators sensitive to the cortical connectivity changes and in a position to output a "corrective signal" whenever the connectivity balance is disrupted or extensively shifted. This would serve as a corrective signal if forwarded to the substantia nigra reticulate (SNr) via excitatory connections in the form of fast spiking activity. Convergence into slow spiking activity occurs in the substantia nigra compacta (SNc) efferent of the dopaminergic activity. In total it seems there is a feedback system inputting from the cortex via the straium GP and STN, and outputting through the SNr and SNc, signals relevant to the ongoing conditions of brain organization. It is presumed that this system is involved in ensuring connectivity balance and optimal neural complexity (C_N) in the brain. The coupled GP–STN oscillators acting as a nonlinear optimization engine have a critical role in this C_N feedback-regulating system, thus putting them in a critical position for optogenetic intervention.

Before concluding it must be acknowledged that potentially every structure of the subcortical systems described in Fig. 2 can be a target for optogenetic intervention. An explorative protocol for optogenetic intervention may include all. However if the assumption forwarded in this work, both for the etiopathology of schizophrenia in general and the roles of the relevant neuronal subsystems, (i.e., the prefrontal and GP–STN) – then it is proposed to begin with protocols designed to intervene in the prefrontal and GP-STN activity.

Conflict of interest statement

There are no conflict of interest to report..

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