THE NEW CHEMISTRY OF MIND: A HYPOTHESIS

STEPHEN SZÁRA

A GONDOLKODÁS KÉMIÁJA: ÚJ HIPOTÉZIS

A pszichofarmakológia ötvenegynéhány évvel ezelőtt született mint egy új, szűkkörű klinikai tudományág, főleg az LSD-25, a klórpromazin és néhány más szer hatásának az ösztönzésére. Ahogyan az évek teltek, és az idegkémiai meg idegélettani kutatások kimutatták, hogy az idegsejtek a szinapsisokon keresztül, kémiai anyagokkal közvetítik az aktivitásaikat, a pszichofarmakológusok belátták, hogy további tudományos fejlődést csak úgy lehet biztosítani, ha együttműködnek a biokémikusokkal, élettanászokkal és farmakológusokkal. Így jött létre egy nagyobb tudományág, a neuropszichofarmakológia.

Az utóbbi években az is kiderült, hogy a pszichiátriának a társadalmi kapcsolatok számbavételére is szüksége van a betegek kezelése folyamán és hogy ezeknek a kapcsolatoknak is van biológiai alapjuk. Így született meg egy még szélesebb körű kutatási stratégia: határterületi kutatás (translation research).

Ennek az új határterületnek a kidolgozásához egy új kutatási hipotézist javaslok, amit pszicho-nukleotidának (PN) neveztem el. Két típust különböztetek meg: egyszerű PN (SPN) és összetett (CPN). Az elképzelés az, hogy ezek a PN-ek közvetitik a szavak értelmét két különböző nyelv vagy szaknyelv között. Ugyanakkor résztvesznek egy transzformációban is, ami a nyelv és annak idegrendszeri reprezentációja között folyik le mint be- és kikódolás. Végső fokon a PN-ek elősegitik az egész agy integrált működésének megértését, sokkal természetesebben, mintha csak a kognitív kortexra figyelnénk, mivel a PN-ek egybefogják a gondolkozást az emócióval és a társadalmi viszonyokkal is, ezzel elősegítve az egész agy működését és a teljes személyiség beilleszkedését a társadalomba

KULCSSZAVAK: pszichofarmakológia, pszichonukleotida, határterületi kutatás, biológiai alapok

SUMMARY

Psychopharmacology was born some 50 years ago as a relatively narrow clinical discipline with LSD-25 and chlorpromazine, among a few others, being the early prototypes. In the course of its development, psychopharmacology grew into a wider scientific discipline as psychoactive drugs were assumed to interact with biochemical processes at the synapses to influence transmission of activities among neurons in producing their effects. Thus biochemistry and neuropharmacology have been adopted as collaborative disciplines and this larger field was named neuropsychopharmacology.

More recently it has been recognized that, at the clinical level, neuropsychopharmacology has also extensive contact with social issues so that there is an increasing emphasis on translational research in recent announcements from the National Institute of Mental Health in the USA to facilitate and encourage collaboration among clinicians, basic science and social science researchers.

To help the process of translational research in mental health, a new organizing principle is proposed based on a novel concept of Psychonucleotides (PNs). There are two types of PNs: Simple PNs (SPN) and Complex ones (CPN) and they are seen as temporary modules mediating meaning between the linguistic and neuronal levels in the brain. As the proposed mediating takes the integrative processes of the whole brain into consideration the development of large scale neuronal theories for translational research should became easier and more comprehensive by going beyond the focus on the cognitive cortex and taking also emotional and social processes into consideration.

KEYWORDS: psychopharmacology, psychonucleotides, translational research, biological bases

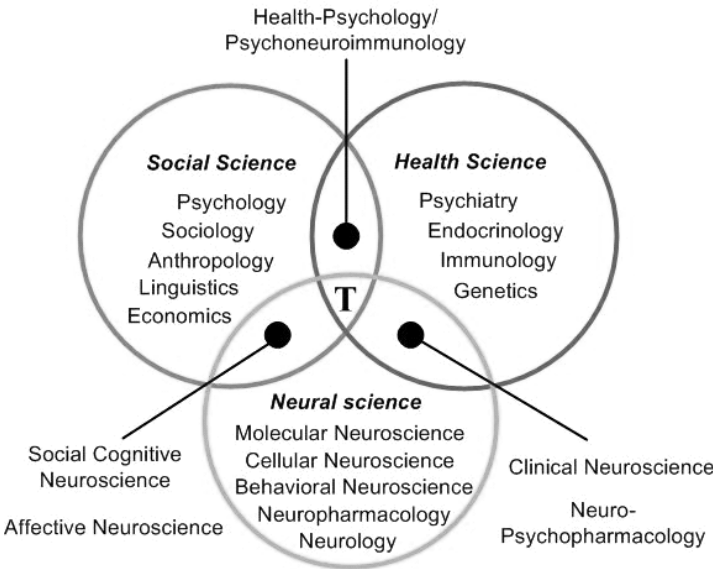
INTRODUCTION

Psychopharmacology is a relatively new discipline that has emerged during the past 50 years from some serendipitous observations. The first was the accidental discovery in 1943 of the hallucinogenic action of LSD-25 by Albert Hofmann in Basel, Switzerland. The second was the discovery in 1952 of the tranquillizing effects of chlorpromazine by French psychiatrists Jean Delay and Pierre Deniker in Paris. These two observations are generally acknowledged to be the inspiration for the subsequent growth of the research and practice of psychopharmacology, as documented in several volumes of historical records by Tom Ban and his colleagues (Ban et al 2000).

THE WIDER CONTEXT

It is not widely known, or appreciated, that those very same discoveries have also spawned the development of a much larger and wider discipline some 20 years later known as Neuroscience a discipline that is aimed at studying the brain and its various cellular components through increasingly sophisticated analytical methodologies. Neuroscience also explores the chemical components (neurotransmitters, modulators, receptors etc.), some of which controlling ion channels, others transmitting their activities to second messengers and entering a complex network of enzymes, promoters, kinases, and transcription factors, that in turn feed back to ion channels and receptors affecting the signaling of the neuron they are part of (Greengard, 2001, Kandel 2001). Overlapping with neuroscience is a narrower discipline that focuses on the effects of drugs on neuronal activities and it is called Neuropharmacology (Cooper, Bloom and Roth 2003) and if we include the study of psychological effects of drugs and the use of drugs for psychiatric therapy the discipline is usually enlarged to Neuro-Psychopharmacology.

Figure 1 shows the relationships between neuroscience and its potential neighbors. The three large circles, arranged in the style of Venn diagrams, represent three large, traditional scientific research fields in the social sciences, health sciences, and neural sciences. Each of them may be considered relevant to the brain sciences either directly or indirectly. The intersections of the boundaries of these fields define some of the collaborative, borderline, disciplines that are usually younger than the major, traditional fields. Most of these disciplines have been defined and described by Ochsner (2007) with special emphasis on social cognitive neuroscience from an information processing perspective. The Neural Science categories were revised from a more biological perspective which placed neuro-psychopharmacology into the borderline area where neuroscience and psychiatry overlap. The capital "T" at the center triangle of triple overlap represents an even younger discipline called translational research. The US National Institute of Mental Health (NIMH) has recently announced interest in supporting research in "…the neurobiological bases of social behavior, including its developmental, cognitive and affective components. NIMH is interested in these research topics at both the basic and translational level of analysis" (NIMH 2006). One of the Areas of High Priority (AHP) for the Division of Adult Translational Research an Treatment Development (DATR) at NIMH is to "Delineate specific neural circuits contributing to one or more major mental disorders or subtypes of mental disorders" (DATR 2008).



THE PROBLEMS OF TRANSLATION

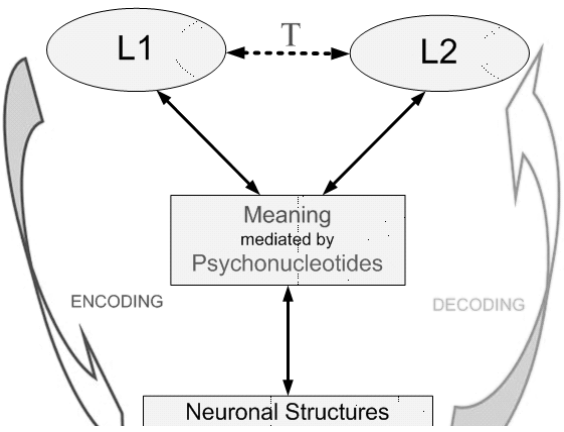
Before we could achieve such a translational goal and find specific neural circuits in mental disorders we would have to face another problem that involves the neurobiological bases of normal health and behavior. Only if we know how normal, healthy people's brain operates, can we ascertain deviations to the pathological directions. We are still far from a comprehensive understanding of the full spectrum of operations controlled by the brain, such as human language.

There is still yet another problem that lurks behind the translation process itself which relates to the neurobiological bases of language. We know that the human brain evolved in such special way that learning a language is almost automatic in children even those from impoverished social environments (Chomsky 1986). Cognitive scientists and linguists have accumulated volumes of discussions about the possible biological evolutionary origins of human language (Deacon 1997, Jackendoff 2002; Lieberman 2000 Harnad 2005) but neuroscientists were slow to go beyond the traditional focus on the Broca and Wernicke areas of the cortex in speech and understanding language, and acknowledging the role of basal ganglia and cerebellum in speech processing (Lieberman 2000; Geiser et al 2008; Teichman et al (2006); Wallentin et al 2006). There is still a huge (some even call it abysmal [Cooper, Bloom & Roth 2003]) gap in our knowledge about the mechanisms of how the myriads of interacting receptors, ion-channels, synapses, and other components of the brain eventually add up to, or transform neural activity into cognition, language and behavior in healthy individuals (Horgan 1999).

Translation, whether it involves different languages, dialects, or professional jargons, requires additional learning and the ability to keep the representations of the two domains in the brain functionally separated but accessible when needed. It is quite likely that the common denominator between them is meaning as it applies to the corresponding concepts that have been recognized more than 100 years ago by the American semiologist Charles Sanders Peirce (Peirce 1931/1958) when he defined meaning as "the translation of a sign into another system of signs".

Figure 2 shows a simplified depiction of the relations between translation and meaning processing in the brain of a bilingual person. The lexicon of these two languages are represented in the brain as two distinct domains (L1, L2) that can be selectively addressed through a single, common conceptual store as it was demonstrated by cross-language selective priming studies (French & Jacquet 2004). Figure 2 also shows that this conceptual store representing meaning is connected to a biological substrate of neuronal structures and dynamics (Klein et al 2006; Gandour et al 2007; Illes et al. 1999).

Translational research that involves a dialog between clinical and laboratory scientists may involve a process in their brain similar to the one depicted in Figure 2. This is not just a simple translation between two languages, but a more complex creative mesh between two distinct conceptual systems to work out new solutions that require new interpretations or even new concepts.



MEANING AND SEMANTICS

The notion of meaning is itself a nebulous concept that has occupied philosophers from Plato and Aristotle to Wittgenstein and Quine (Crystal 1987; Noth 1990). Psychologists and neurobiologists also study meaning, which they call semantics (Tulving 1972) and have developed many ingenious ways to approach this problem. From the voluminous literature here are some representative studies.

Early researchers, studying the visual processing pathways in monkeys with a crossed-lesion

design, have found that semantic meaning is perceived only if the reciprocal connections between the amygdala-hippocampal complex and the inferotemporal cortex (area TE) remained intact (Mishkin 1982).

Others, by recording brain activity from electrodes implanted in the brain of behaving rats found that theta-oscillation in the hippocampal-entorhinal system is a major organizer of the navigation behavior and controls the traffic between episodic and semantic memory in the brain (Buzsaki 2005).

Investigations with brain imaging technologies were conducted to learn how the human brain stores, represents, and retrieves semantic knowledge. Although some cortical areas (such as the left inferior frontal gyrus and the ventral temporal cortex) were generally reported to be primarily associated with the storage and retrieval of semantic knowledge, other areas were also shown to be variably involved (Thompson-Schill 2003: Rodd et al 2005). The results suggested that a large, distributed network of semantic representations may be organized by attribute, and perhaps additionally by category (Thompson-Schill 2003).

The standard theories of cognitive science assume that knowledge resides in a semantic memory system separate from the brain's modal systems for perception, action, and introspection. Since the experimental results with brain imaging could not support such separation, there is a growing movement that proposes "grounding" of cognition in multiple ways, including modal simulation of bodily states, situated action and social interaction. (Martin et al 2000; Barsalou et al 2003; Barsalou 2008a, 2008b; Caramazza & Mahon 2005).

In spite of these promising findings and continuing accumulation of data at both ends of the spectrum, neurotransmitters, modulators, receptors, and ion-channels on the neuroscience level, and the deluge of reports on activated brain areas detected by brain imaging during various psychological manipulations at the cognitive level, we still do not understand how these levels are interacting in producing the higher level phenomena. I am in complete agreement with Eric Kandel who proposed that for this kind of understanding we need to move to the systems level of neural circuits, and discerning how neural networks are organized and interact with each other, to form coherent representations and how attention and awareness shape and reconfigure neural activity in those networks (Kandel, 2006).

In the rest of this paper I am going to propose some specific neural modules that may mediate the grounding process between the neuronal level of the brain and the cognitive level of the mind and hopefully become a useful tool for translational research.

PSYCHO-NUCLEOTIDES: NEW CHEMISTRY

I am postulating the existence of temporary modules which I will call Psycho-Nucleotides, or PNs, for a simple reason: they connect the psychological level (widely assumed to be cortically-based) with brain-stem and mid-brain nuclei in a reciprocal fashion (hence a new meaning for "Nucleotides"). Their proposed structures are described below. At this point I would like to suggest considering PNs as "quasi-atoms" from which the 'quasi-molecules" of Meaning arises in an emergent fashion with brand new properties just as it happens with traditional atoms and molecules. This is what the "New chemistry" in the title of this paper refers to. These meta-molecules, in turn, could be seen as the major players in processing information, namely, comparing perceptual information with memories of the past or with current needs of the organism, making decisions, and guiding the actions to fill those needs and ensuring survival.

I postulate two types (or classes) of these Psycho-Nucleotides: Simple PNs (SPNs) and Complex PNs (CPNs). These PNs are considered to be emergent and self-organizing dynamic structures that are active only for limited time periods (milliseconds to minutes). They operate at the subsymbolic or subconceptual level and cooperatively interact with each other to produce psychologically and behaviorally meaningful functions. Experimental and clinical data will be identified to support the plausibility of their existence and provide some arguments for their usefulness and significance.

Simple Psychonucleotides (SPNs)

The proposed structure of SPNs is based on the recognition of the recurrent structure that exists between the cortex and the brainstem nuclei (such as the Locus Coeruleus (LC) and Nucleus Raphe Dorsalis (NRD) and probably others) (Figure 3).

The highly divergent arborization of the noradrenergic (NE) projections from LC and of the serotonergic (5HT) projections from NRD to nearly all cortical neurons (Cooper, Bloom, Roth, 2003) could be seen as the hallmark of a scale-free architecture (Barabási and Albert, 1999; Eguiluz et al., 2004; Freeman, 2005) generating emergent properties, such as:

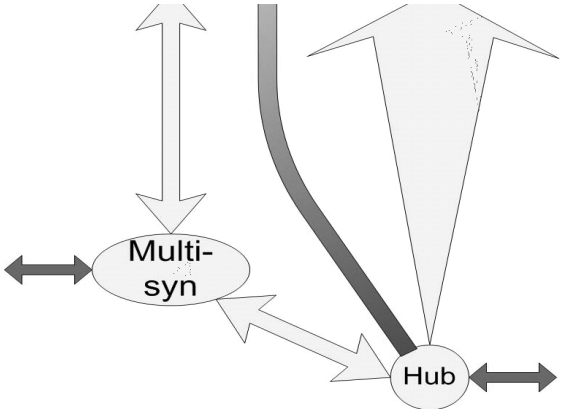
— Stability and robustness of operation (Aldana & Cluzel 2003);
— Resistance to random failures (Albert, Jeong & Barabási 2000);
— Sensitivity to targeted attacks on the hubs (Albert, Jeong & Barabási 2000);
— Facilitating the formation of synchronized cortical fields (Barahona & Pecora 2002; Buzsaki 2006);
— Promoting the evolution of dynamic order (Zhou & Lipowsky 2005).

It is interesting to note, that property C (sensitivity to targeted attacks on the hubs) may have been the source of success of psychopharmacology when serendipitously applied drugs that selectively targeted the biological processes involving NE, DA or 5HT, which originate from anatomical hubs.

It is now well established that nearly all of the aminergic neurons, that play a crucially important role in the operation of the mammalian brain, have two operating modes: tonic and phasic. Each mode has its special role in coordinating the complex interaction that regulates the sleep/wake cycle (NE and 5HT) (Aston-Jones and Bloom 1981; Hobson 1975), mood and vigilance (Aston-Jones et al 2001) or action patterns during daytime (involving dopamine) (Cohen, Braver, Brown, 2002). They do not operate alone but almost always in interaction with each other, using the long range direct and indirect connections between various areas of the brain. Each activity, once triggered is also modulated by the locally expressed receptor types for the particular neuromodulator involved (Cooper, Bloom, & Roth, 2003). In many areas of the brain the released modulator may even diffuse to significant distances before reaching their receptors (volume transmission) (Agnati et al 2000; Freeman 2005).

I will propose some properties of such SPNs that are either based on existing experimental data, or specified to such an extent that they may be experimentally verified.

SPNs are dynamic modules with three major components (Cortex, Multi-syn, Hub) interconnected in the way shown on Figure 3. As can be seen, it is a closed circuit in the sense that activities can circulate among the three major components: The Cortex, one or more midbrain nuclei [Multi-synaptic pathway] and what I prefer to call a "Hub". These Hubs are easily identified functionally with one of the several small, mostly brainstem nuclei (LC, Raphe, VTA, Meynert etc.) from which large, divergent, one-way projections to the whole, or parts of the cortex closes the circle. There are also monosynaptic projections from cortex to the Hub, shown in rainbow colors. This projection may be involved in the phasic operation of the module (Aston-Jones et al, 2001).



The diagram pictures a general prototype of SPNs and many different variants are likely to exist. Each SPN may be using only one type of cortex, and identified by its Brodman number (Brodman, 1909/1994). The two double headed, light-blue arrows suggest that two-way communication is possible, but not mandatory. The dark-blue double headed arrows simply indicate potentially active two-way connections with other anatomical structures (unspecified in this prototype diagram but likely to be other PNs.

Most of the SPNs have limited active life-spans (in the millisecond range) but may be reactivated repeatedly by interactions with other PNs as they

are viewed as being organizationally closed but informationally open.

Some of the SPNs may be active for longer periods of time (seconds or minutes), especially those that are more closely involved in interacting with the environment either as receiving information (Perceptual SPNs) or contributing to acting (Motor SPNs).

It is quite likely that some SPNs are permanently active, especially those that are involved in controlling autonomic bodily functions (cardiovascular, pulmonary, temperature regulation, or interfacing with the hormonal and immune systems of the body). Most of these autonomic SPNs may not have substantial neocortical components; instead one of the subcortical or brainstem nuclei can serve the [Cortex] part in the dynamics of the circuitry.

SPNs, by themselves (i.e. isolated from their surrounding structures) would likely to have very limited behavioral repertoire but when embedded and in communication with others, in a holistic fashion, they may perform complex perceptual, cognitive, and motor functions.

SPNs are seen as emergent neuronal systems, having been evolved and developed in the brain of organisms from their early embryonic stages (around six weeks in humans) when their two telencephalic vesicles start an intense growth period by a massive proliferation and migration of neurons and glia cells. The growth of axons is under the guidance of genetically programmed release of diffusible chemical attractants and repellants (Dent et al 2004; Marin et al 2002; Braisted et al 1999).

SPNs are also shaped by local growth and learning processes and, later in life, by learning processes that may include pruning, or "weeding out" of unused or unnecessary connections (Rakic et al, 1994).

In the diagram, the dark blue double-headed arrows indicate, that at various points of the triangular loop of the SPN is communicating with other cortical and subcortical areas in the brain. These communicating links maybe quite substantial anatomically but are assumed by the current hypothesis that they are active only periodically, while the tonic projections from the hub are largely continuous, and providing continuous existence for the SPNs during the waking state of the organism (Aston-Jones et al. 2001).

The current proposal for SPNs makes it possible that several other prominent anatomical structures (such as the hippocampus, cerebellum and other parts of the brain) may be incorporated into the SPN triangle as extensions of the "Multi-synaptic" member of the circuitry.

Complex Psychonucleotides (CPNs)

The Complex Psychonucleotides (CPNs) are considered to be functional supermodules, and based on the architecture of the basal ganglia and operating on the principle of disinhibition (Chevalier & Deniau 1990) and internal dopamine modulation (Gerfen 2000; Haber 2003; Wise, Murray & Gerfen 1996).

The unique properties of CPNs are assumed to be the followings:

Figure 4 is a simplified version of basal ganglia circuits. Several components (such as the subthalamic nucleus, globus pallidus exterior and the nucleus accumbens that is part of the ventral striatum) have been omitted to emphasize two recurrent, parallel pathways (between cortex and the thalamus, and also between striatum and SNc/VTA) that were suggested to play a pivotal role (very much like the Hubs in SPNs) in integrating cognitive, emotional and motor processes in the mammalian brain (Haber, 2003; Turner & Ander-

son, 2005; Joel & Weiner, 2000; Floresco & Grace, 2003).

The presence of two consecutive inhibitory links in a strongly convergent part of the loop that gives rise to the disinhibitory type of positive feedback to the thalamus and controls initiation of intentional motor functions (Chevalier & Deniau, 1990; Hikosaka et al., 2000; Gruber et al., 2006).

The Reticular Nucleus of the Thalamus (RTN) that partially surrounds the nuclei of the thalamus complex (not shown explicitly on Figure 4) is a largely inhibitory network that provides a strict gating projections to the sensory, motor, and limbic relays inside of the thalamus (Nolte, 2002; Guillery, Feig & Lozsádi, 1998; Steriade, 2000);

It is reasonably well established that the basal ganglia are connected with the prefrontal cortex in a series of recurrent loops forming at least five functional modules that may be seen as members of the family of CNPs (Alexander et al., 1986; Middleton & Strick, 2000). As research continues in the spirit of the current paradigm, it is quite likely that more members of the CPN family will be identified.

Inside the CPN diagram the striatum and SNc/VTA are shown to be connected to each other with reciprocal links, the striatum sending GABAergic inhibitory signals, while the SNc/VTA responding with dual types of dopamine signals: tonic and phasic (Gillies and Arbuthnott 2000).

Figure 4 also shows dark blue, double headed arrows, indicating potential connecting links to other structures, making the CPNs part of the integrated operation of the brain. Because of the built in disinhibitory links (mentioned above), CPNs are intrinsically intermittent (rather than continuous) in operation.

METHODOLOGICAL CAVEATS

It is expected, that the frontline methodology for identifying the postulated modules will be the rapidly evolving functional imaging techniques, such as Positron Emission Tomography (PET) and functional Magnetic Resonance imaging (fMRI). These methods provide steadily improving spatial resolutions (1-2 mm) but relatively low, several seconds, of time resolution (Momjian et al. 2003; Sharma & Sharma 2004). There are, however, a number of methodological problems that will need to be sorted out. PET and fMRI images are known to be only indirectly related to the location and timing of changes in the underlying neuronal activities (Lauritzen & Gold 2003). Furthermore, the Brodman cytoarchitectonic fields have been defined by in vitro histological procedures on a few human specimens and, since there are significant individual variations in the area boundaries, the in vivo detected images will need to be treated with considerable caution (Uylings et al., 2005). There is also a large volume of literature on the problems of statistical treatment of imaging data (Peterson, 2003; Sun et al, 2005) including the estimation of brain connectivities from spatial, temporal , and other features of the imaging data (Horwitz et al, 2005; Quigley et al., 2002; Daglish et al. 2005).

FUTURE DIRECTIONS

First of all, there is a need to identify the dominant anatomical and physiological components for all the 47 SNPs that can be identified on the cytoarchitectonics as defined by Brodman (1909/1994). Although Brodman originally defined 47 areas on each hemisphere, a number of new areas have been identified that are now designated as Brodman 48 to 52 (Brodman Areas online). Since imaging studies have shown that the same area in the two hemispheres may be selectively activated in only one side of the brain it may be necessary to identify and describe over 100 SPNs for a complete description of the brain. Most of the frontal cortex areas and perhaps a few others are known to be also parts of the complex modules (CPNs). It is quite likely that the number of CPNs will grow from the currently accepted five cortico-striato-thalamo-cortical loops of Alexander et al (1986).

While these PNs are identified and studied, it is quite likely that new questions will arise regarding their modular structures, physiological operations and about their molecular and genetic biology thereby allowing translational research programs to expand their vista and contribute more fruitfully to their cooperative endeavors.

It is quite likely, that computer simulation studies will help to see how the PNs can interact with each other to perform various types of high level comparator functions that are involved in social interaction processes (Hurley 2008, Gallese 2004; Frith 2007; Szára in preparation).

Once the PNs are better understood, the neuropsychology and brain-imaging studies may experience a boost from this new conceptualization of SPN and CPN modules that could simplify their interpreting work, seeing high level psychological

and emotional functions as processes of interaction among certain well defined PN modules. One promising start in this direction has been reported by Jeffries and his colleagues from the NIMH (Jeffries et al., 2002). In a PET-study of 18 Tourette patients and 16 normal controls, using [18 F]-Fluoro-2-deoxy-D-glucose they have found a dramatic reversal in correlation between two cortico-striato-thalamo-cortical circuits in all Tourette patients when compared to matched controls. It is also hoped that applying similar methodologies for clarifying these interactions to other clinical problems may lead to the identification or refinement of pathological processes underlying various disease manifestations such as schizophrenia, depression, post-traumatic stress disorder, obsessive-compulsive behavioral disorders (addiction, gambling, etc.). These new insights into the pathology of mental disease could open new avenues for novel therapeutic drugs and for other new, non-pharmacological, interventions.

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