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A Weird Concept with Unusual Fate: Nootropic Drug

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L'Homme ne va pas passivement attendre des millions d'années pour que l'évolution lui offre un meilleur cerveau.

Corneliu Giurgea, 1972

Un concept singulier avec un devenir inhabituel : médicament nootrope.

Résumé

Cet article présente l'émergence d'un concept neuropharmacologique atypique par le fait qu'il est à peine mentionné dans les traités de référence, mais, en même temps, fait l'objet d'un nombre de publications scientifiques qui augmente depuis plusieurs décennies et a pénétré largement dans les médias. Les causes plausibles d'une telle disparité sont analysées, en essayant de distinguer la spécificité philosophique du concept discuté. Une molécule synthétisée dans les années 1960 en tant que dérivé cyclique du principal neuromédiateur inhibiteur du cerveau, le GABA, conçue en vue d'en faire un médicament tranquillisant et inducteur de sommeil, s'est avérée n'interférer

nullement avec le GABA et n'avoir aucune activité hypnotique. Cette substance, le piracetam, pratiquement dépourvu de toute toxicité aiguë sur les animaux d'expérience, a montré dans plusieurs tests animaux des activités suggérant un effet anti-amnésique et pro-cognitif. La pharmacologie insolite du piracetam a amené le chercheur en charge de la neuropharmacologie dans la firme pharmaceutique où le produit a été créé à introduire en 1972 le concept de médicament qui agirait 'directement' sur les mécanismes intégratifs du cerveau. Appelé *nootrope*, un tel médicament stimulerait l'activité mentale en étant efficace dans les troubles de l'activité intégrative. Les critères définissant un médicament nootrope sont seulement fonctionnels, sans référence à des mécanismes moléculaires par lesquels il pourrait agir. De ce fait, le concept rentre difficilement dans le cadre de la pharmacologie, qui est basée sur le caractère primordial de l'interaction Drogue – Récepteur. Plus profondément, le concept nootrope est de nature *holistique*, dérivant d'une *approche synthétique* de l'activité du cerveau, distincte de l'approche analytique cartésienne. D'autre part, la persistance et l'ampleur de l'intérêt pour ce concept pourrait refléter l'aspiration humaine d'acquérir des capacités mentales plus étendues.

Introduction

The history of every branch of science provides some examples showing that the development of scientific concepts not always proceeds linearly, from a rational hypothesis to a duly validated theory. The case of a neuropharmacological concept that remains atypical and odd, while enjoying a maintained attention, is presented and analyzed here.

Nearly forty years ago, a neurophysiologist involved in drug discovery in Belgium has put forward the concept of drugs able to promote, enhance and protect the cognitive function, termed by him *nootropic* drugs. As cognition is the typically human higher activity of the brain, nootropic concept looked quite appealing for scores of people dreaming to enjoy better and longer-lasting mental activity and for drug makers keen to produce such enviable products. However, it hardly found any place in the corpus of current neuropharmacology, to which it is extraneous as being a holistic type of concept, in sharp contrast with the prevailing propensity towards ever more detailed molecular comprehension. Nevertheless, the nootropic idea shows an amazing

persistence in the scientific endeavor and it was largely incorporated in the common culture. Therefore, the origins, the fate and the characteristics of the atypical concept 'nootropic drug' undoubtedly deserve reflection, mainly since an objective evaluation of its status might hopefully reveal some points of more general significance.

Working hypothesis infirmed, outcome rewarding!

The demonstration in the years 1960s that the gamma-amino-butyric acid (GABA) acts as a major inhibitory neurotransmitter in the brain stirred a high scientific interest and put GABA-related pharmacology into the focus of pharmaceutical industry. In the wake of that interest, the chemists in the pharmaceutical division of the Belgian company UCB synthesized in 1964 a cyclic derivative of GABA, the 2-oxo-1-pyrrolidine acetamide alias piracetam, intended to be a calming type of drug, particularly a sleep-inducer. But, in spite of its chemical kinship with GABA, piracetam did not show any type of interference with that prominent neurotransmitter and no sleep-inducing activity. However, the professional skill of those days' researchers at UCB and especially the insightful inventiveness of Corneliu Giurgea[1], at that time the chief neuropharmacologist there, turned an apparent failure into an outstanding success for their company. Marketed in 1971, piracetam brought about an impressive commercial success that, within a few years upon its launch, largely contributed to raise UCB to a truly European stature.

What chiefly matters for the current subject is the fact that the peculiar effects of piracetam led Giurgea to introduce in 1972 the novel concept of "*nootropic drugs*". He defined these as drugs having the essential characteristics of piracetam, namely: *i)* to directly activate the *integrative* activities of the

1. Corneliu E. Giurgea (1923 – 1995), a Professor of neurophysiology in the Faculty of Medicine in Bucharest (Romania), holding an M.D. from that university and a Ph.D. from the Pavlovian Laboratory in St. Petersburg (at that time "Leningrad"), was brought to Belgium in 1963 by UCB company that appointed him Head of the Department of Neuropharmacology. In 1965, he was also appointed Associate Professor of psychopharmacology in the Catholic University of Louvain (UCL), where he taught a lively course. The professorial appointment in a catholic university of him, who declared being a Jewish-born atheist, lastingly impressed and motivated Giurgea (as he told in 1990 to this author).

brain, having a direct positive action on mind, *ii)* the activation being selective for the telencephalon and not manifested on lower brain levels, so that *iii)* to exert a restoring effect in troubles of the higher brain activity (Giurgea, 1972). The term *nootropic* was coined by Giurgea in lexical analogy to "psychotropic", upon joining the Greek words for "mind" (νοοσ) and "towards" (τροπειν).

In subsequent review publications aimed to popularize the nootropic concept, Giurgea (1980, 1986) detailed the definition, saying that a nootropic drug should: 1) enhance learning and memory, 2) increase the resistance of learned behaviors/memories to conditions that tend to disrupt them (such as electroconvulsive shock and hypoxia), 3) protect the brain against various physical or chemical injuries (e.g. barbiturates, scopolamine), 4) increase the efficacy of the tonic control mechanisms of the cortex on the subcortical levels of the brain, and 5) lack the usual pharmacology of other psychotropic drugs (e.g. sedation, motor stimulation) and possess very few side effects and extremely low toxicity. This is the definition of 'nootropic' currently included in Wikipedia (http://en.wikipedia.org/wiki/Nootropic).

Nootropic – an atypical pharmacological concept

Any pharmacologically-educated reader is stricken by the obvious functional and phenomenological character of the above definition that does not make any mechanistic reference. The core concept of the whole pharmacology is that of *receptor*[2], a molecule, usually protein, with which the drug interacts chemically, thus inducing an effect in the cells where the receptor is expressed. One should notice, however, that none of the above mentioned defining characteristics of a nootropic drug suggests a Drug–Receptor interaction. In fact, the doses at which piracetam exerts its pharmacological effects are so high[3] that one could hardly imagine any specific interaction with some receptor structures. On the same line, the very requirement that a nootropic drug should possess extremely low toxicity implies very weak affinity of that drug for the molecular components in the cells of the receiving organism. As mentioned, the defining criteria for nootropic drugs have been tailored on the

2. An authoritative historical perspective on this basic concept was given by Rang (2006).
3. The therapeutic doses of piracetam are of the order of several grams (!) per day (Winblad, 2005).

characteristics of piracetam, which was indeed very well tolerated in all animal species tested in preclinical studies, as well as in several thousands of patients included in controlled clinical studies (Winblad, 2005). The acute toxicity of piracetam is so low that no LD_{50} (the median lethal dose required to kill half of tested animals) could be determined for that compound.

A basic principle of neuropharmacology asserts that every molecule that influences the behavior or exerts a therapeutic effect on patients suffering of neuro- and psycho-pathologies acts upon modulating (increasing or reducing) the effects of various combinations of neurotransmitters by which brain neurons communicate synaptically. Nootropic drugs, being supposed to lack the usual pharmacology of other psychotropic drugs are thus at odds with this principle too. As for piracetam, it has been reported to influence cholinergic, serotoninergic, noradrenergic, and glutamatergic systems (Winblad, 2005), thus exerting some effects on neurotransmission. However, these effects do not result from any direct receptor agonism or antagonism, piracetam showing no noticeable affinity for the receptors of those neurotransmitters, in contrast to the currently used psychotropic drugs.

The unusual fate of the nootropic concept

Since nootropic drugs do not fit the paradigmatic frame of contemporary pharmacology, it is of little surprise that they hardly found any place in the major treatises of pharmacology. However, this comprehensible neglect is rather strangely contrasted by a vast amount of clinical studies that reported a therapeutic benefit of piracetam in a diverse range of indications. Those studies have been reviewed in short by Shorvon (2001) and in somehow more detail by Winblad (2005). This article being a meta-analysis of the 'nootropic' concept, not a pharmacological review, the points evoked below are aimed only to substantiate the epistemological commentary, without taking any overt position about supposed merits or failures of nootropic drugs.

The prototypal utilization of piracetam is in cognitive disorders, including age-related memory impairment (Israel et al, 1994) and mild-to-moderate dementia (Hermann & Stephan, 1992). The report that a two-week regimen of piracetam enhanced verbal memory in healthy college students (Dimond & Brouwers, 1976) fuelled the popular perception of that drug as *cognitive*

enhancer in healthy people, too. Another pathology in which controlled studies revealed efficacy of piracetam is vertigo, a type of dizziness that specifically refers to the illusion of rotatory movement of him or the environment (Rosenhall et al., 1996). In fact, the initial utilization of piracetam in the first years of its "career", while still considered as GABA-related (Giurgea et al, 1967), was as an anti-motion sickness drug. A severely debilitating, though hopefully rare pathology for which double-blind studies (Brown et al., 1993; Koskiniemi et al., 1998) documented efficacy of piracetam is cortical myoclonus, uncontrollable muscle movements, sometimes accompanied by generalized seizures, that result from abnormal electrical activity in the sensorimotor cortex. Piracetam alone or in combination with anticonvulsant drugs was reported to produce sometimes marked improvements. Numerous medical papers reported also effects of piracetam in various other pathological conditions, either brain activity-related as alcoholism, dyslexia[4], dyspraxia and dysgraphia[5], or clotting, coagulation, vasospastic disorders and stroke, or even sickle-cell anemia[6].

Faced with such a plethora of putative activities claimed for piracetam by medical practitioners in need of pharmacological tools, one can realize why skeptical critics depicted piracetam as "a drug in search of a disease". The skepticism is understandable and no stance is to be taken beyond what the facts may speak for themselves. At the same time, one has to notice the distinctiveness of a drug whose almost complete absence of toxicity made it a good candidate to assess in various pathologies lacking suitable medication[7].

Not only the purported activities, but also the reported cellular effects of piracetam and other nootropic racetams are astonishingly diverse (Shorvon, 2001; Winblad, 2005; Malykh & Sadaie, 2010). Following a putative modulation of neuronal nicotinic acetylcholine receptors in cortical neurons (Zhao

4. *Dyslexia* is a specific difficulty in interpreting written language, often accompanied by problems with writing or spelling.
5. *Dyspraxia* is a motor learning difficulty that can affect planning of movements and co-ordination. *Dysgraphia* (or *agraphia*) is a deficiency in the ability to write, regardless of the ability to read, not due to intellectual impairment.
6. *Sickle-cell anemia* or drepanocytosis, is a genetic blood disorder characterized by red blood cells with abnormal, rigid, sickle shape that results in a risk of various complications.
7. An extended list of medical uses of piracetam and related medical publications can be accessed on the site http://www.piracetam.com/.

et al., 2001), the effect currently enjoying most attention is a positive allosteric modulation of the AMPA receptors, a major type of receptors for glutamate (Ahmed & Oswald, 2010). This allosteric modulation might conceivably arise from increasing the number of available postsynaptic receptors and/or restoring their function upon increasing the fluidity of membrane lipids. In fact, piracetam-induced changes to physical properties of cellular membranes have been repeatedly reported in the last fifteen years (Peuvot et al., 1995; Eckert et al., 1999; Mingeot-Leclercq et al., 2003). A restoration by piracetam of age- or pathology-altered fluidity of cell membranes, via a *non-specific interaction* with cell membrane phospholipids could render conceivable effects in such various disorders ranging from dementia and vertigo to myoclonus and stroke. Incidentally, one can observe that the non-specificity of piracetam's interactions and its putative fluidizing effect are reminiscent of the case of general anesthetics, for which a membrane lipid-fluidizing effect was long accepted as basic mechanism, but was amended in the last years (Franks, 2006).

Returning from the prototypal nootropic drug back to the nootropic concept, we have to mention two points that illustrate a surprisingly enduring appeal of that concept on both specialists and general public. Thus, in what concerns the specialists, thirty years after the 'birth' of piracetam, a comprehensive review (Gouliaev & Senning, 1994) identified in chemical and biomedical publications more than 1650 piracetam-like compounds synthesized in view of development as nootropics, many of them containing the same 2-oxo-1-pyrrolidine acetic acid (racetam) substructure. Indeed, in the last decades of the 20th century, on the traces of UCB, numerous pharmaceutical companies including several major ones (e.g. Hoffman-La Roche, Ciba-Geigy, Parke-Davis) have embarked upon developing nootropic drugs. As for the current level of scientific attention towards 'nootropic', it is documented below in the section "**Long-lasting interest**".

An easy (though obviously crude) measure of the penetration into all media of the subject 'nootropic' can be quickly obtained via a Google search of this term. Such a search retrieved on August 12, 2010 about 169,000 items. In the mass media, the nootropics are emphatically nicknamed '*smart drugs*', while professionals use the more sober term '*cognitive enhancers*'[8] (see Figure

8. Google searches indicate over 6,500,000 items for 'smart drugs' while only 95,000 items for 'memory enhancers'.

1). These terms designate a very large spectrum of products, not only medicinal drugs, but also dietary supplements, nutraceuticals[9] and functional foods[10] supposed to improve mental functions. Piracetam itself, because of its uncommon lack of toxicity is occasionally considered a dietary supplement. While this designation might be simply pejorative, the same lack of toxicity entails the off-label use of piracetam for a wealth of therapeutic applications.

The terms 'nootropic' and 'cognitive enhancer' are loosely considered as equivalent, while this is not true. Any nootropic according to the above-mentioned criteria set by Giurgea (1972) would be a cognitive enhancer, but the opposite is not true: only a cognitive enhancer that has neuroprotective effect and is devoid of toxicity would justify the label nootropic. Hence, it is abusive to call 'nootropic' various brain stimulants, like e.g. the amphetamines, that do exert cognitive enhancement, while having toxic effects.

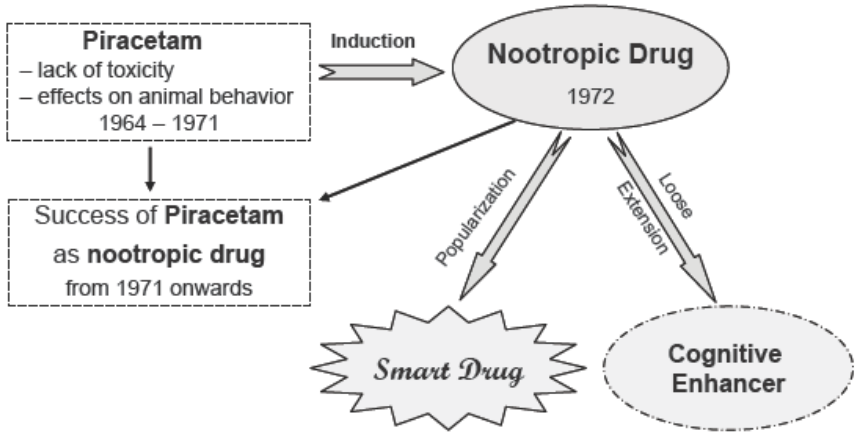

Figure 1. Schematic view of the unfolding of 'nootropic drug' concept. The substance of nootropic concept evolved upon an induction operation (in the sense of logic) from the characteristics of piracetam and, in turn, promoted the success of that compound as prototypal nootropic drug. The term 'smart drug' is currently used in mass media as being an obvious catchword. The pharmacological notion 'cognitive enhancer' derives from 'nootropic' but is not equivalent to this (see text).

9. A term combining "nutrition" and "pharmaceutical"; is a food or food product that provides medical benefits.
10. Foods claimed to have health-promoting or disease-preventing properties, due to medicinal additives or/and particular processing.

Non-conventional Belgian progeny of piracetam

Understandably, the success of UCB's piracetam as first nootropic drug stimulated not only other drug companies to develop competitor nootropics, but also people at UCB to search for a better successor that would surpass the forerunner. The ensuing medicinal chemistry activity resulted in numerous racetam derivatives, subsequently assessed in a succession of filtering animal tests aimed to select the most promising candidates for further development. In the late 1970s and early 1980s, the α-ethyl analog of piracetam, synthesized in 1974 and termed *etiracetam*, emerged as a seemingly promising second generation nootropic, since it has shown activity in animal tests of induced memory deficits (Sara, 1980). Later on, it appeared that of the two stereoisomers of etiracetam, only the (S)-enantiomer – at that time termed only ucb L059, subsequently receiving the generic name *levetiracetam* – actually had anti-amnesic activity (Verloes et al., 1988), attributed to its stereospecific effect of facilitating cholinergic function both *in vivo* and *in vitro* (Wülfert et al., 1989). But, in spite of the initial promises, the nootropic activity of levetiracetam was too meager to substantiate its development as a nootropic drug.

Remarkably, more than two decades after piracetam, other people working in that company turned once again a looming failure into a success, showing that levetiracetam has anticonvulsant activity (Gower et al., 1992) far above piracetam. Though that activity of levetiracetam initially did not cope with the then usual criteria for the selection of anticonvulsant drug candidates, the costly development as an antiepileptic drug was daringly assumed. Rewarding the risk-taking, levetiracetam was worldwide approved as antiepileptic and within a few years it became the most prescribed new-generation antiepileptic drug. This 'progeny of piracetam' is an efficient treatment of several types of epilepsy (De Smedt et al., 2007), quite original in its properties and mode of action (Margineanu & Klitgaard, 2002). Its anticonvulsant effect appeared correlated with a specific binding on a protein present in the brain (Noyer et al, 1995), initially mysterious but later on identified to be a synaptic vesicle protein, the SV2A (Lynch et al., 2004). The development of levetiracetam is in itself an interesting saga narrated several times, including by some of its main actors (Klitgaard & Verdru, 2007), but it is out of our focus here.

The tight correlation between the anticonvulsant potencies in a suitable animal screening test and the affinity towards the levetiracetam-binding site of the different racetams represented a powerful tool allowing a target-oriented drug-discovery that resulted in the selection of a potential successor of levetiracetam, its 4-*n*-propyl analogue (Kenda et al., 2004) *brivaracetam*. This has about 10-fold greater anticonvulsant potency than levetiracetam in animal tests (Matagne et al., 2008), and recently published clinical results (French et al., 2010) seem encouraging. Therefore, one can conclude that the nootropic piracetam provided the chemical template for the creation "at home" of notable newer drugs that – while no longer nootropics – treat a severe neurological pathology with unmet medical needs.

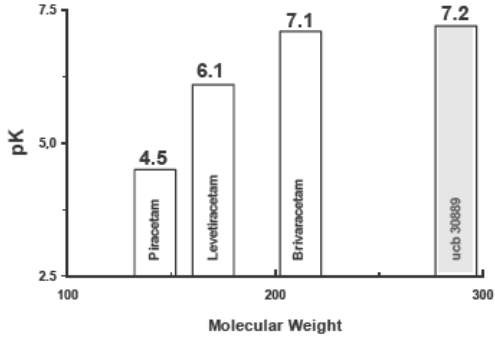

Figure 2. Affinity for the levetiracetam-binding site (SV2A protein) vs. the molecular weight of piracetam, its two antiepileptic derivatives (levetiracetam and brivaracetam) and a derivative (ucb 30889) of levetiracetam that serves as experimental marker (Gillard et al., 2003). The affinity is indicated by the value of pK (the negative logarithm of the dissociation constant) given above each bar. The crude data were taken from the publications by Noyer et al. (1995), Gillard et al. (2003) and von Rosenstiel (2007).

While not pursuing the discussion of the non-nootropic offspring of piracetam, it is interesting to note that piracetam almost completely lacks affinity for the binding protein of levetiracetam and brivaracetam (SV2A). The plot of the affinity vs. the molecular weight (Figure 2), drawn on the basis of published data, illustrates in a relevant case the general non-specificity of piracetam. This is a small molecule (MW = 142.2) whose nearly negligible interaction with all chemical components of the organism might probably explain its innocuousness, but certainly obscures the molecular underpinning of its therapeutic effects, in particular of the purported nootropic activity.

Incidentally, one should notice that some other small molecules exert a multitude of effects on organisms, in particular on brain functions, without having necessarily a Ligand–Receptor type of interaction that would account all the effects. A particularly striking example is the alcohol (ethanol; MW = 46.1), but it is not the only one.

Long-lasting interest

A reliable scientometric assessment of the interest towards the nootropic concept can be obtained upon searching the number of references to that term in the vast database of biomedical publications from over the world of the US National Library of Medicine (PubMed; http://www.ncbi.nlm.nih.gov/sites/entrez?db=PubMed). A search of 'nootropic', done on 17 August 2010, indicated a list of 3128 references, starting with the paper of Giurgea from 1972. More informative than the total number of references is the distribution in time of the number of scientific publications devoted to or referring to 'nootropic', shown in Figure 3 that indicates an exponential type of increase over the years.

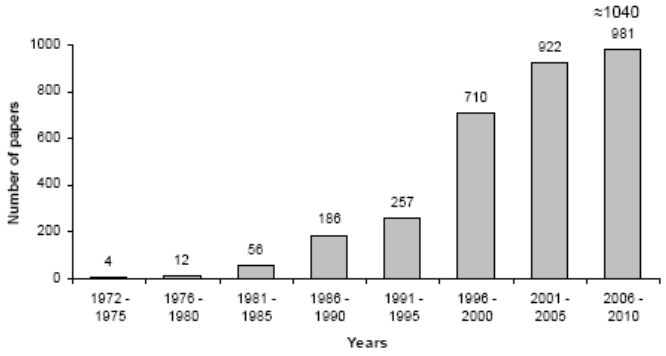

Figure 3. The evolution in time of the number of scientific papers referring to 'nootropic' listed in the PubMed database, accessed in August 2010. Above each column is indicated the number of items from the corresponding five-year interval. On top of the last column is also indicated the approximate number estimated to correspond to the completion of the year 2010 (see text).

The actual number of items appearing in the complete interval 2006 – 2010 will be higher than the value included in the graph, which runs only up

to the day of the search[11]. Consequently, one sees that the scientific "visibility" of the concept nootropic increased continuously in the four decades since its introduction, no fading being noticeable to date.

Since the concept 'nootropic' owes its very appearance to the peculiar effects of piracetam (Fig. 1), it is relevant to assess the scientific interest towards piracetam, too. A search in the PubMed database of the term 'piracetam', done on 12 August 2010, indicated a total number of 2314 references, starting in the year 1972. The distribution in time of those references, shown in Figure 4, indicates a bimodal type of evolution, obviously different from that in Fig. 3. One observes a continuous increase in the number of papers referring to piracetam during nearly two decades, followed after 1990 by the start of a decline. Such an evolution seems normal for any compound, whose interest as novelty lessens after some time. The data in Figure 4 show, however, that the incipient decline in the interest towards piracetam was promptly reversed by a new and more pronounced increase in the number of publications referring to it. The second wave of mounting interest that lasts to date is to be attributed to the advent of levetiracetam as a fairly "hot" scientific subject and to its wide recognition as a safe, broad-spectrum antiepileptic drug (De Smedt et al, 2007) with beneficial pharmacokinetic properties (Patsalos, 2000). The new impetus given by levetiracetam to the interest towards piracetam does not imply, however, that the references to this latter one would be just historical, since the specific interest towards nootropic drugs is as high as illustrated in Figure 3, and piracetam itself continues to be the focus of many studies and review articles (e.g. Winblad, 2005; Winnicka et al., 2005; Malykh & Sadaie, 2010).

11. There are about 90 references from the first seven months of 2010, so that one can infer that more than 60 new references would add in the remaining of the year 2010, rising the five-year value for the complete interval 2005 – 2010 to about 1040.

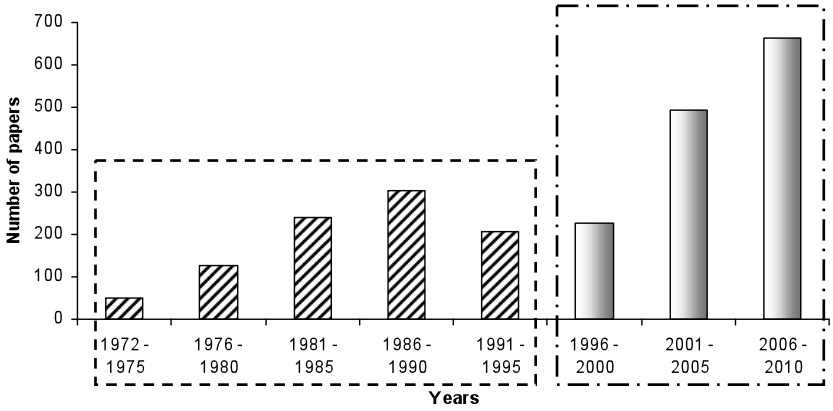

Figure 4. The evolution in time of the number of scientific papers referring to 'piracetam' listed in the PubMed database, accessed in August 2010. The bars corresponding to the period after 1995 are drawn differently from those corresponding to the preceding 25 years and the two frames are added to highlight the bimodal appearance of the ensemble of values.

Theoretical underpinning and implications of 'nootropic' concept

Having seen in what 'nootropic' concept is atypical within the context of contemporary neuropharmacology, a logical further step is the enquiry about the theoretical background from which it emerged and the philosophical ideas that ensured its endurance, if such ideas can be actually pinpointed.

The article by Giurgea (1972) reveals the general ideas that led his author to formulate as defining criteria for a putative novel class of drugs characteristics that are practically those of a given substance (piracetam). The main line of the title[12] plainly indicates the focus on *integrative activity* of the brain. Subsequently, the whole Introduction and most of the next section (on neurophysiological and neuropharmacological premises) are devoted to presenting and clarifying that notion. When doing this, the *synthetic* type of approach of brain functions, that uses mainly behavioral methods to study the brain is highlighted, paying tribute to Sherrington and to the school of Pavlov (to which Giurgea considered himself to belong). Likewise, that author stressed

12. «Vers une pharmacologie de l'activité intégrative du cerveau».

that the functional characteristics of human cortical activity cannot be found at cellular level, since the cerebral cortex is made of neurons essentially similar to those at lower levels, the specificity of the cortex being the extreme complexity of inter-neuronal organization. The observation of the famous neurosurgeon Wilder Penfield that human brain is distinct among all mammal brains by the fact that most of the cortex is neither sensorial nor motor, but *associative*, is quoted by Giurgea as highly relevant for the primordial role of integrative activity.

All these clearly show that 'nootropic' emerged as a *holistic* type of concept, opposed to the analytical attitude in pharmacology that posits that each pharmacological effect derives from a given molecular interaction between the drug and some receiving component (known or not *yet* known) present in given parts of the organism. Indeed, nootropic drugs are not aimed at a given type of neurons, from a given region of the brain, but they are meant to activate the *integrative* activities of the brain and to have a direct positive action on mind[13].

The general idea of the holism that the properties of a system cannot be determined or explained by its component parts alone – epitomized in Aristotle's phrase "The whole is more than the sum of its parts" – led in the latter half of the 20th century to *systems thinking* that contrasts the scientific reductionism of Cartesian origin. The systemic approach got an authoritative expression in Ludvig von Bertallanfy's *General System Theory* (New York, 1968). Systemic approach applies to every branch of science that deals with complex entities, but it is obviously unavoidable in life sciences, since life is a phenomenon that occurs *only* in very complex systems (for an informative and easily readable presentation: Capra, 1996). The system undisputedly on the very top of the complexity is the human brain, an intricate web of some 2×10^{10} neurons and more than 10^{11} glial cells, each neuron acting as a full-fledged computer, connected with some 10^4 other neurons. That nerve cells, instead of working individually, act together was stressed more than a century ago by Golgi and it was emphasized by Sherrington, who hypothesized that inter-

13. Without naming Descartes for the mind-body dichotomy, Giurgea referred to that dualism that he appeared to reject and to adhere to the opposite notion (formulated by the neurophysiologist Vernon Mountcastle) of *neuro-psychic identity*. This asserts that the highest integrated aspects of human brain activity, including the introspection, are but complex aspects of a neuronal activity easier to grasp at elementary level.

neuronal communication involves some sort of a *population code* that might contain *emergent properties*[14], not available in the responses of single neurons (Jermakowicz & Casagrande, 2007).

Among the most basic emergent properties manifested in animal brains is neuronal *synchronization*, a collective coherent regime of firing in ensembles of coupled neurons, the functioning of animal brains as exquisite data processors ultimately relying on the interplay of the cellular property of neurons to be excitable and of their supra-cellular level feature to respond *synchronized*, as integrated elements of neuronal networks. In spite of being at present largely recognized and studied, not even this relatively simple emergent property is specifically addressed by the current drugs (Margineanu, 2010), though the idea that emergent properties of neuronal networks can represent targets for pharmacology was formulated in the recent years (Faingold, 2004). This being the case, it is not so surprising that the holistic type of concept 'nootropic drug' – assumed to have a "direct positive action on mind", i.e. aimed at the most intricate emergent property – remained extraneous to the Cartesian oriented nowadays pharmacology.

On the other hand, the endurance of the nootropic idea and its *de facto* integration in the common culture appear to have been due to at least two leading causes. Firstly, it seems quite understandable that an increasing aged population, as is the case in all developed countries, is preoccupied to keep as long as possible a normal mental activity, being sensitive to all the means to achieve this. But also, one should not neglect that the promise of nootropic (i.e. *smart* !) drugs to promote better and more performing mental activity even in young and healthy people matches a typically human desire to acquire new capacities and to expand the boundaries of the existence, both physically and mentally.

Transcendentalist aspirations are as ancient as our species itself, but in the last decades of the previous century became visible, particularly in USA, an intellectual and cultural movement supporting the use of science and technology to improve human mental and physical characteristics and capacities – the *transhumanism* (Bostrom, 2005). The phrase from Giurgea's article of

14. An informative philosophical discussion of the concept 'emergent properties' is in the *Stanford Encyclopedia of Philosophy*, freely accessible: http://plato.stanford.edu/entries/properties-emergent/.

1972 that I have chosen as epigraph to this paper clearly shows that he had a transhumanist position, expressing a belief that the humans may eventually be able to transform themselves into beings with expanded mental abilities. Whether or not the originator of the nootropic concept was explicitly influenced by some transhumanist writings is neither evident nor important, but the fact that transhumanist aspirations largely fuel the quest of *smart* drugs is obvious.

Concluding remarks

The above discussion being in no way aimed to defend or promote the nootropic concept, it is to be concluded by attempting some generalizations. The fate of nootropic concept might be instructive for the multiplicity of the trails on which science advances and for the intricacy of the interaction between scientific knowledge and lay culture. The discrepancy between the quasi absence of the nootropic concept from standard treatises of pharmacology and the fairly large diffusion of the nootropic idea in the contemporary public culture reminds – keeping all due proportions – the comparatively different perceptions of Freudian psychoanalysis in the medical establishment vs. the artistic media and public culture. The fact that the nootropic concept akin to the psychoanalytic theory deal with human *mind* – the most complex function emerging from a biological background – suggests that it might not be purely coincidental that these ideas do not match the science solidly rooted on Cartesian thinking. The two examples are illustrative for the difficulty to cope in analytical terms with the bewildering complexity of brain and mind.

An all-purpose remark substantiated by the history of the first nootropic drug and that of its anticonvulsant derivative is that experimental and observational results that infirm a starting hypothesis do not necessarily preclude a positive outcome, when the working scientist or team are able to understand the unexpected results and suitably open-minded to duly rectify the objective pursued. This might sound trivial, but, in applied research fields, the capacity of behaving that way can make the difference between a costly failure and a serendipitous discovery, occasionally major. Also, the case of 'nootropic' illustrates the possibility that a concept can emerge not exclusively by regular generalization of common features of a representative number of similar facts, as customarily, but also by discerning conversion of some unusual elements

into the prototype of a potential novel category. Such epistemological alchemy is quite unexpected in a profit-oriented environment supposed stern, but that might occasionally get a better reward from nurturing intellectual audacity.

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