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Review

# Cajal and brain plasticity: Insights relevant to emerging concepts of mind

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ABSTRACT

The main legacies of Cajal are his drawings of brain structure and their connections, and his ideas of brain plasticity, not only in the mature brain but also during development and after brain injury. As the 21st century begins, many scientists are asking an old question: "how does the brain express the mind?" Although most models of mind incorporate the brain connections produced by Cajal, his ideas of plasticity are largely ignored. The purpose of this chapter is to review how some of Cajal's ideas can be useful in understanding the expression of the mind. I have also introduced several concepts and facts not available during Cajal's life. I cover the concept of homeostasis, the global projections of the monoamine neurons, and the actions of "mind-expanding" drugs. The global projecting neurons, because their monoamine transmitters have such a long history, are considered 1st order systems. The point-to-point connections are considered 2nd order systems. Their importance in theories of functional localization studies is briefly reviewed. Finally, a new model is presented called "Plastic Homeostasis," which incorporates the plastic interactions between 1st and 2nd order neurons. It is hoped that this review will encourage others to study the ideas presented by Cajal when considering functions of the brain. The emerging models of the mind would be well served by a review of the theoretical writing of Cajal.



## Contents



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> Mind: Mental or psychic faculty. The seat of awareness, thought, volition, feeling, and memory; cognitive and emotional phenomena and powers considered as constituting a presiding influence; the mental faculty of a human being (especially as regarded as being separate from the physical); (occas.) this whole system as constituting a person's character or individuality. (Oxford English Dictionary, 2006)

## 1. Introduction to Cajal

Santiago Ramon y Cajal worked on the details of the brain for 50 years, and he better than most understood the working of the mind. Cajal, at the age of 37, speculates on how intelligence is manifested by the plasticity of neurons in the brain (1894). Some neurons expand their processes to receive new inputs while others reduce them to maintain an overall equilibrium. During the process of learning, Cajal envisioned plasticity of the cortical neurons. In later writing Cajal developed a more cautious and limited view of brain neuroplasticity and stated that "nerve paths are something fixed, ended, immutable. Everything may die, nothing may be regenerated" (Cajal, 1913–14). These descriptions of a static mature nervous system influenced neuroscience thinking for over 50 years, and encourage the notion of fixed circuits linking disparate brain regions. In order to present the background and data to propose a new direction for "Models of the Mind", I will present some of the concepts of neuroplasticity as enunciated by Ramon y Cajal (1894, 1933). Unfortunately, the existence of chemical transmission, the details of the globally projecting brainstem neurons and the concept of homeostasis were discovered after Cajal's research was completed. These ideas will be reviewed in this chapter as they complement and expand Cajal's contributions to our knowledge of the brain. His work on brain anatomy which elucidated many of the point-to-point connections underlying sensory and motor circuits is very well known. However, his more theoretical writings dealing with higher order brain functioning have not received equal appreciation (Cajal, 1899; Azmitia, 2002).

## 2. Neuroplasticity

### 2.1. *Neuronal doctrine*

A century ago there was a debate between the reticular and the cellular views of the brain. Prof. Golgi, using the silver staining technique, could not reconcile the flexibility of the brain with the notion of individual "watertight compartments" and concluded the neurons were part of a syncytium (Mazzarello, 2000). In contrast, Prof. Cajal argued neurons were separate units of life and interacted with each other over a distance. The difference in interpretation of similar material arose because Golgi (1898) assumed the neurons were static; while Cajal – based on his studies on development, evolution and brain trauma – concluded that the neurons were dynamic (Cajal, 1899, 1933).

Cajal appreciated the plastic and vital properties of the neurons, and their contribution to brain functions such as memory and learning, sleep and mental disorders. He proposed diffusible chemical factors influenced the shape of neurons and modified their participation in neural circuits (Cajal, 1899). Cajal viewed the entire neuron and its connections as a fluid entity. He wrote; "morphology of the nerve cell does not obey an immanent and fatal tendency, maintained by hereditary, as certain authors have defended, but it depends entirely on the physical and chemical circumstances present in the environment" (Cajal, 1933, p. 55). As will be discussed below, he considered neuronal retraction as integral to neuronal plasticity as neuronal expansion. This concept assumes that retraction should be as normal and active a process as expansion. This idea was confirmed and extended by work showing that blocking actin recycling in growth cone produced a rapid neurite retraction (Gallo et al., 2002). This provides a molecular explanation of the bidirectional movement of normal healthy neurons during intellectual activity as envisioned by Cajal.

Cajal believed that sleep served the purpose of giving neurons a "rest" by encouraging neuronal retraction, and loss of neuronal contacts (Cajal, 1899). He wrote; "according to this scholar (Duval, 1895) nerve cell processes have amoeboid movement and contacts between terminal axonal branches and the soma and dendrites could loosen by protoplasmic retraction. In this way, dissociation would take place with the consequent functional rest of the cells. Thus during sleep, dendrites of pyramidal cells would shrink and cease excitation arriving from the sense organs" (p. 189, Cajal, 1899). He studied lizards exposed to several hours in a cold environment or while hibernating. He noticed the size of neuronal cell body became smaller, the length of the dendrites retracted, and the number of spines were reduced. He also showed that these neurons received fewer connections on the surface of the neuron (Fig. 1A). Contemporary studies confirm that neuronal retraction occurs throughout the brain in ground squirrels during hibernation and exposure to cold (Fig. 1A) (von der Ohe et al., 2006). To

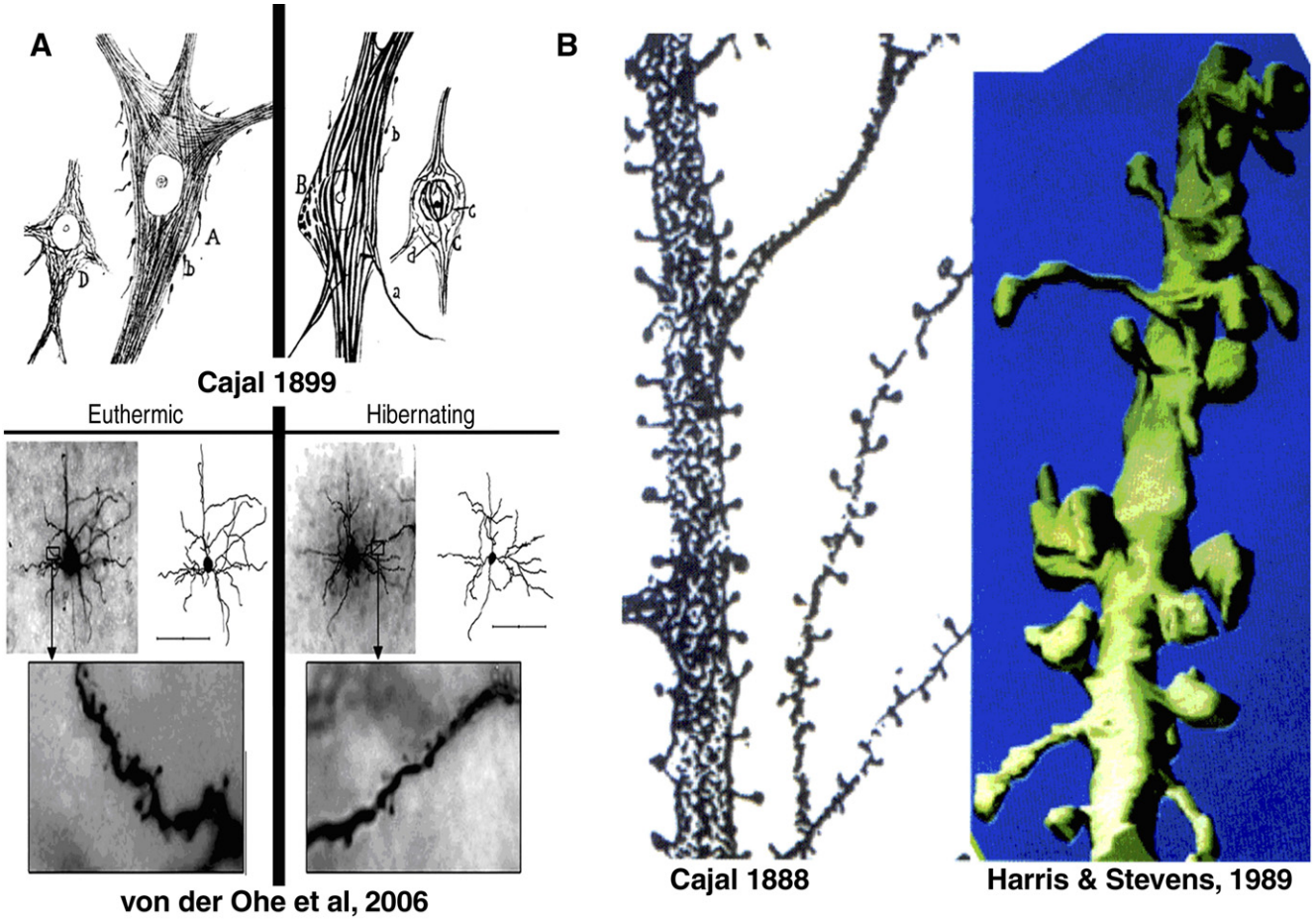


**Fig. 1 – Comparisons of neuroplasticity. (A) Cajal's observations of neuronal retraction in hibernating animals are compared to the drawings of von der Ohe et al. (2006) who studied hibernating squirrels. (B) Cajal shows dendritic spines are evenly distributed along the dendritic shaft of a neuron (figure shows an area of Cajal's original drawing (1888)). EM reconstruction of spines and dendrites modified from Harris and Stevens, 1989 (modified from Fig. 2 of Segal, 2002).**

Cajal these observations made sense because the mind needs to rest, and this requires that the neurons "rest". These experiments led Cajal to conclude neurons were individual living cells, thriving in a fixed enclosure, sensitive to external factors and capable of either growing or shrinking as the environment changes.

### 2.2. *Dendritic spines*

Cajal discovered dendritic spines on Purkinje, pyramidal and other large neurons (Cajal, 1888, see also 1921). He not only discovered spines on neuronal dendrites, he postulated that they were transient and crucial to normal brain functioning (Fig. 1B). Cajal wrote that mental disorders such as hysteria and rabies infection resulted in loss of spines. The transient nature of spines was confirmed by the method of two-photo imaging. Individual spines appeared and disappeared over days in the cortex of living animals (Trachtenberg et al., 2002). In addition, loss of spines in mental disorders was observed at both the light (Marin-Padilla, 1975) and electron microscope levels (Purpura, 1979). Thus, these important properties of spines were observed first by Cajal, and then verified by more sophisticated methods decades later.

### 2.3. *Growth cones*

Cajal is attributed with the beginning of the field of neuroembryology (Hamburger, 1980). He studied the developmental stages in chicks and humans and described axonal growth cones as a moving "battering ram". This observation was confirmed by Prof. Ross Harrison, who developed the technique of tissue culture (Harrison, 1907). This discovery provided the "proof" that neurons are distinct cells, not part of a syncytium. The visualization of the "synapse" in brain tissue was made 50 years later (Palay, 1956).

### 2.4. *Growth factors*

Cajal proposed his theory of chemoaffinity in 1892, and modified his neurotropic theory over the next 40 years (see Azmitia, 2002). His final growth factor theory had five characteristics: (1) the "tropic" agent is enriched in Schwann cells, (2) it does not function as an attraction factor, (3) it does not have the ability to serve as a survival factor, (4) it increases longitudinal growth of neurites by promoting assimilation of protoplasmic material and (5) it is not saturable but acts as a catalytic agent. These criteria are consistent with chemicals

acting as neurite extension factors (NEF). S100B, an abundant soluble protein, is concentrated in Schwann cell, not an attraction factor, and not a survival factor. S100B increases longitudinal growth of neurites by promoting tubulin polymerization (Deinum et al., 1983). S100B acts by inhibiting the PKC phosphorylation of microtubule-associated proteins (MAPs) so the NEF can be considered catalytic (Baudier and Cole, 1988; Sheu et al., 1994). S100B regulates intracellular kinases by entering through the neuronal membrane via RAGE (receptor for activated glycosylated end-products) and not by binding to a saturable membrane receptor (Hsieh et al., 2004). Cajal also stressed that the NEF is very sensitive to the surrounding conditions of the sprouts, influenced by temperature, sleep, starvation, injury and mental illness. These attributes could reflect serotonin regulation of S100B release from astrocytes, since this globally projecting neurotransmitter system responds to all of these factors (Fig. 2A). Thus, we can assume that Cajal's chemoaffinity factor is not only similar to the glial protein S100B, but may also include its release by 5-HT1A receptor agonist (Whitaker-Azmitia et al., 1990).

Cajal correctly assumed that the integrity of the cytoskeleton was the structural basis on neuroplasticity, a concept which we (Azmitia and Liao, 1994) termed "neuronal instability" (Fig. 2B) based on the instability of microtubules (Mitchison and Kirschner, 1984). Cajal incorrectly assumed the dynamic fibrils inside the neurites are capable of life, and he called them neurobiones (see Azmitia, 2002). He thought these neurobiones responded to their environment living inside the neuron!

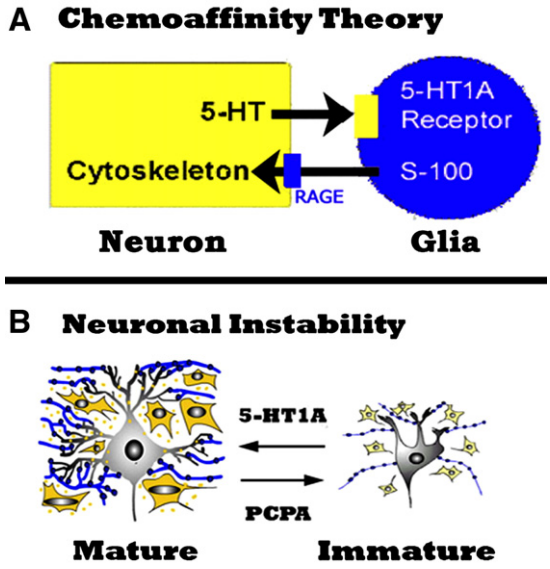


**Fig. 2 – Extension of Cajal's theories. (A) Cajal first proposed a theory of chemoaffinity in 1899, and modified it over the next 40 years (1933). In this illustration, we show the release of S100B from glial cells by the action of the 5-HT1A receptor agonist. S100B enters the neuron through the RAGE and acts as a neurite extension factor by stabilizing the cytoskeleton. (B) Cajal, in his theory of intelligence, postulated that neurons can both expand and contract in size. In this illustration, we have proposed a similar change in size dependent on the instability of the cytoskeleton. The neurons assume a more mature phenotype in the presence of a 5-HT1A receptor agonist and an immature phenotype when 5-HT levels are reduced by the action of para-chlorophenyalanine (PCPA), an inhibitor of the rate limiting enzyme for serotonin synthesis, tryptophan hydroxylase.**

### 2.5. *Neuronal intelligence*

Cajal postulated that cortical neurons in the adult brain could both expand and contract during learning and memory. Cajal presented his views of an individual, plastic neurons changing during intellectual activity in his Croonian Lecture read on March 8th, 1894 to the Royal Society of Science in England.

> "… one can admit as very likely that mental activity provokes a greater development of the protoplasmic apparatus and of the nerve collaterals in the part of the brain most utilized. In this way, preexisting connections between groups of cells could be notably reinforced by multiplication of the terminal branches of protoplasmic appendices and nerve collaterals; and, in addition, novel intercellular connections could be established thanks to the new formation of collaterals and protoplasmic expansions. One objection immediately presents itself: how can the volume of brain remain constant if there is a multiplication and even new formation of terminal branches of protoplasmic appendices and nerve collaterals? In response to this objection, we cannot dismiss the possibility of either a corresponding diminution (retraction) of cell bodies or a proportional compression of the regions of the brain whose functions do not correspond directly to intelligent activity" (pp. 466–467, Cajal, 1894; Azmitia, 2002)."

Intelligent activity is within the definition of the mind, and Cajal felt this could be produced by a group of cells showing an expansion of existing connection and the formation of new connections, all dependent on the ability of the neuron to sprout. Thus, the mind is reduced to the plastic properties of the neuron; its response to activity, its environment, and the growth factors necessary to support new collaterals. This is "Reductionism" taken to the level of the most basic viable component of the brain, the single neuron.

### 2.6. *Neurogenesis and de-differentiation*

However, Cajal was not always right about the plastic potential of the neuron. He wrote; "but the functional specialization of the brain imposed on the neurons two great lacunae: proliferation inability and irreversibility of intraprotoplasmic differentiation." Modern neurobiology has shown neurogenesis in the adult hippocampus (Aimone et al., 2006) and olfactory bulb (Lledo et al., 2006). However, these two regions are considered to be exceptions to the general rule in the central nervous system under normal conditions (Rakic, 2002). Likewise, neurons can lose their adult phenotype when deprived of trophic factors (Hagg et al., 1989) or 5-HT (Huang et al., 1997), and assume their mature differentiated state when these factors are restored (Fig. 2B). Neurogenesis and reversible differentiation in the adult brain are no longer questioned; but

rather than negating the ideas of Cajal, these studies expand the plastic potential of neurons.

## 3. Localization of brain function

### 3.1. *Early history*

In ancient Greece around the 5th centuries BC, Alcmaeon of Croton and Anaxagoras of Athens are considered the first to suggest thought was located in the brain (Finger, 1994). In the 4th BC, Hippocrates proposed that intelligence was manifestation as a humoral spirit inside the brain, and Galen (130 AD) more specifically localized these spirits to the ventricles of the brain. A neural mechanism for explaining the function of the mind (soul) in the brain was proposed over 1000 years ago by an Islamic physician/philosopher working in Persia (Fig. 3) (Wisnovsky, 2003). Avicenna, the Latinized name of Abu Ali ibn Sina, wrote that all human awareness (consciousness, intelligence) begins with knowledge of the self, which is acquired by several interacting brain centers without the aid of external sensory input. He called this active power the "agent intellect". 600 years later, Rene Descartes in 1641 proposed the theory of a Mind–Brain Dichotomy. He concluded that the basic, essential self that represents the mind, is a nonphysical, spiritual core which is not identical to the

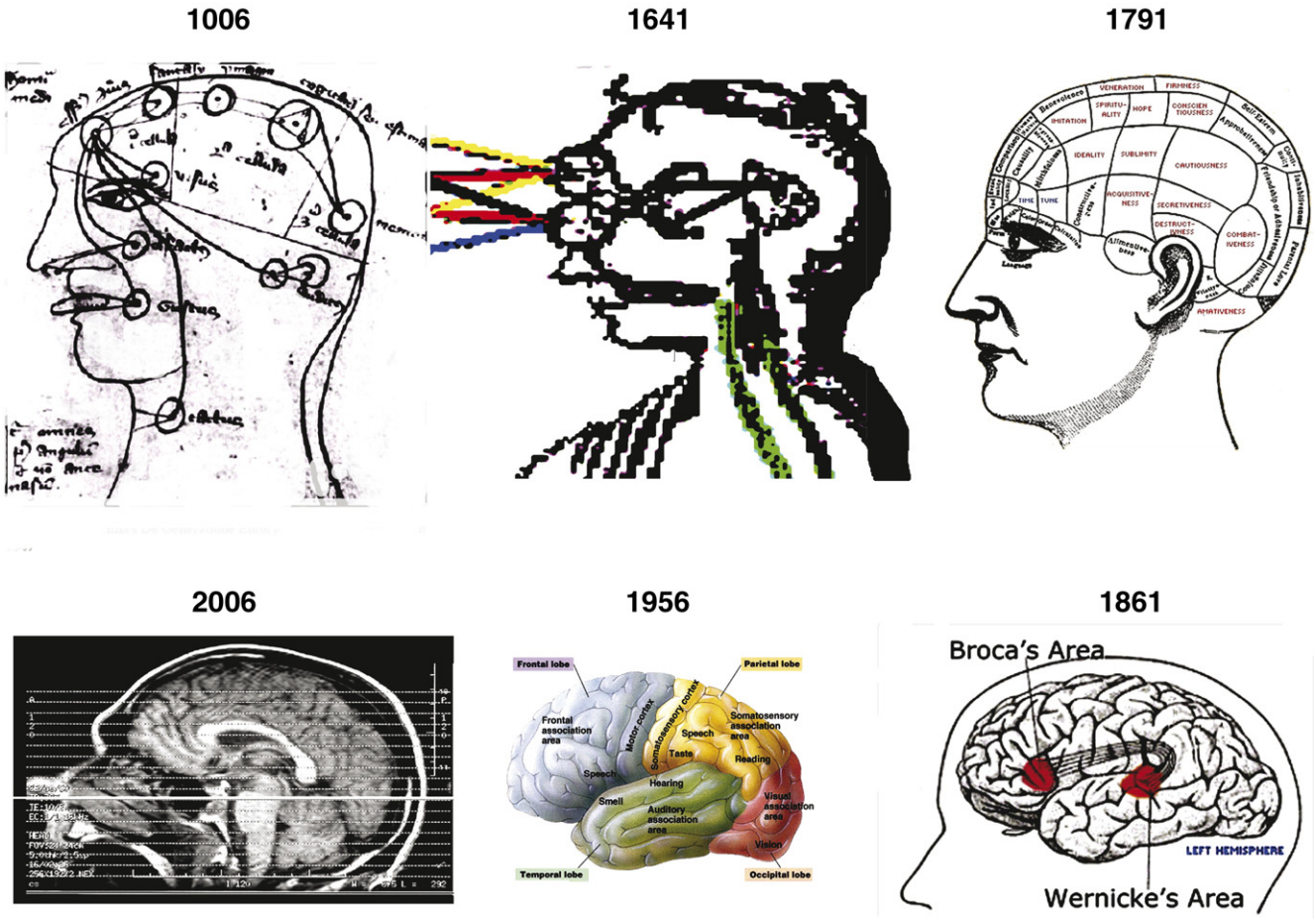


**Fig. 3 – The emerging models of the mind. The search for the seat of the soul, or the expression of the mind, has evolved over the last 1000 years. In 1006, Aricenna, an Islamic physician/philosopher, recognized the expression of the mind was within the connections of the brain, and distinct and separate from direct sensory inputs. Descartes (1641), over 600 years later, proposed the brain and mind were separate. The body functioned as a machine in response to external stimuli, while the mind (soul) metaphysical yet resided in the pineal gland. Gall (1791), was a first rate neuroanatomist who wrote that many of the characteristics of the mind (e.g., inspiration, intelligence and ideality) were located to the surface of the neocortex and were reflected as a change in skull morphology. This marked the beginning of the "science" of phrenology. Modern localization of higher functions began with the announcement by Broca (1861) that expressive aphasia was confined to an area in the ventrofrontal lobe of the left hemisphere. Wernicke (1886) found an area in the superior temporal lobe where a lesion disrupted receptive aphasia. The work and writing of Wilder Penfield (1959) on localization of higher functions, including memories and out-of-body experiences were localized to the entorhinal cortex. Many functions are now localized to specific brain regions. Damasio (2000) is using functional MRI to explore the cortical and subcortical connections sub-serving higher order functioning. These images provide sufficient resolution to pinpoint selected brain regions in the awake subjects who perform complex task associated with the concepts of mind.**

brain (in direct contrast to Avicenna). But a little over a century later, phrenology gained wide and popular acceptance. The German neuroanatomist Franz Joseph Gall (1758–1828) was renowned for his accurate drawings of the cortical surface. He began to notice that not only was the surface unique from person to person, but so was the overlying skull. He proposed many of the properties of the mind were localized to the cortical surface, and then reflected in bumps on the skull surface.

Most modern theories of brain function reject this separation and conclude that an understanding of brain functioning is essential to understanding the mind. Studies of functional localization by Paul Broca (1861) and Karl Wernicke (1886) found loss of a specific functions related to aphasia are due to a lesions of a restricted area on the left side of the neocortex. A more direct approach to functional localization was provided by Wilder Penfield (1959), whose stimulation studies of the human cortex revealed a functional information about the cerebral cortex in general, and more specifically about the entorhinal cortex. Probably his most striking report dealt with the expression of a person's relationship with his body after studies performed in the entorhinal cortex. "The stimulating current was shut off and a generalized slow wave rhythm set up as an after-discharge. While this was continuing the patient exclaimed: "Oh God! I am leaving my body." He looked terrified and made gestures as though he sought help" (Penfield, 1955, p. 458). The idea that the mind had a location deep within the brain was, in general, similar to Avicenna's idea.

### 3.2. *The 21st century*

There are many models and theories on how brain structures and functions can be fused into a representation of mind. A common strategy is to construct a mechanistic network based on known functions of specific brains regions and their connections. These point-to-point connections are referred as 2nd order systems (see Fig. 4). These models use electrical or magnetic equipment to explore higher order association cortex and its subcortical projections. The current theories of mind largely retain the idea of localization of function as their basis, but use much more sophisticated tools to localize "thinking." Damascio, writes that ": …the self process requires a composite representation of the ongoing state of the organism as reflected in subcortical and cortical somatic maps within the central nervous system" (p. 463, Damasio, 2000). He proposed a scheme for the mind by made up of two layers of mental functioning. The first layer is a presentation of a representation of current events, and the second layer is a viewer who represents the mind. Although this dual-layered model is intriguing, it is built on a static foundation. "Neurons are commanded by biological design to be about other cells and other actions…" and the "brain is seen as a complex device concerned with regulating and, of necessity, representing body states…" p. 464, 2000. Damasio's first and second layers of mental functioning are probably based on the connections we consider 2nd order systems.

Knowledge of brain connections (point-to-point) was certainly a major benefit of the work by Cajal, and formed the basis of many theories of mind. Neural networking focuses on the connections between areas and neurons within those areas. At the extreme, these networks are considered to function as a computer, fast, complex and rigid. "Hawkins brings incredible focus and an entrepreneur's sense of urgency to his endeavors… He wants a computer program that works like the cortex, and he wants it now… He wants the brain in silicon" (Miller, 2006). The rigid connections between the cortical maps are emphasized in other models of the mind; "… a brain whose wiring enables it to distinguish between inner-world representations and outer-world representations and to build a metarepresentational model of the relation between outer and inner entities is a brain enjoying some degree of consciousness" Churchland, 2003.

One current model proposes that cortical connections can be opened or closed by the action of dopamine postsynaptic receptors. O'Reilly (2006) discusses the intricacies of the dopamine D1/D2 balances in the gating of working memory states in prefrontal cortex. The information transfer in and out of the prefrontal cortex is regulated by the receptor balance at the synapses, rather than a change in the configuration of the connections themselves. Receptor functional plasticity is viewed to occur on a static wiring diagram. Although the global dopaminergic neurons appear to be a critical component, and the notion of balance is proposed, this author unfortunately focuses on a single brain area and does not consider the principles of neuroplasticity in the expression of the mind.

## 4. Globally projecting neurons

### 4.1. *Neuroanatomy*

Before there was a brain, there were neurotransmitters. The monoamines were synthesized and stored in unicellular organisms as soon as oxygen became available on earth (Azmitia, 2001). In these primitive cells, the monoamines functioned as antioxidant scavengers and were able to regulate much of the cell differentiation (mitosis, migration and maturation). In plants, there is more serotonin in a leaf, than in the hippocampus due to the large quantities of available tryptophan, the immediate precursor for serotonin. The monoamines are present in all animal brains, and in the mammals form part of what has become to be known as the "Globally Projecting Systems." We can consider these neurons, because of their early history as 1st order neurons (Fig. 4A).

The monoamine neurons, largely composed of highly branched fine processes, were below the detection of the Golgi technique. Cajal identified the large multipolar soma and highly branched dendrites with spines of these brainstem neuronal clusters (e.g., the Central Median Nucleus) and wondered "how extensive were the axons?" (Azmitia, 1978). Largely through the use of histochemical fluorescence (Hokfelt and Fuxe, 1969) and immunocytochemistry (Steinbusch, 1981), we can answer Cajal question. The global neurons of the brainstem send axons to every region of the brain, and are near every cell in the cerebral cortex (Foote and Morrison, 1984; Lidov and Molliver, 1982) (Fig. 4A).

During development, these fine unmyelinated fibers densely innervate the local and inter-regional point-to-point connections. The neurons do not convey a specific message but rather function by mass action (Wiklund et al., 1981). Thus

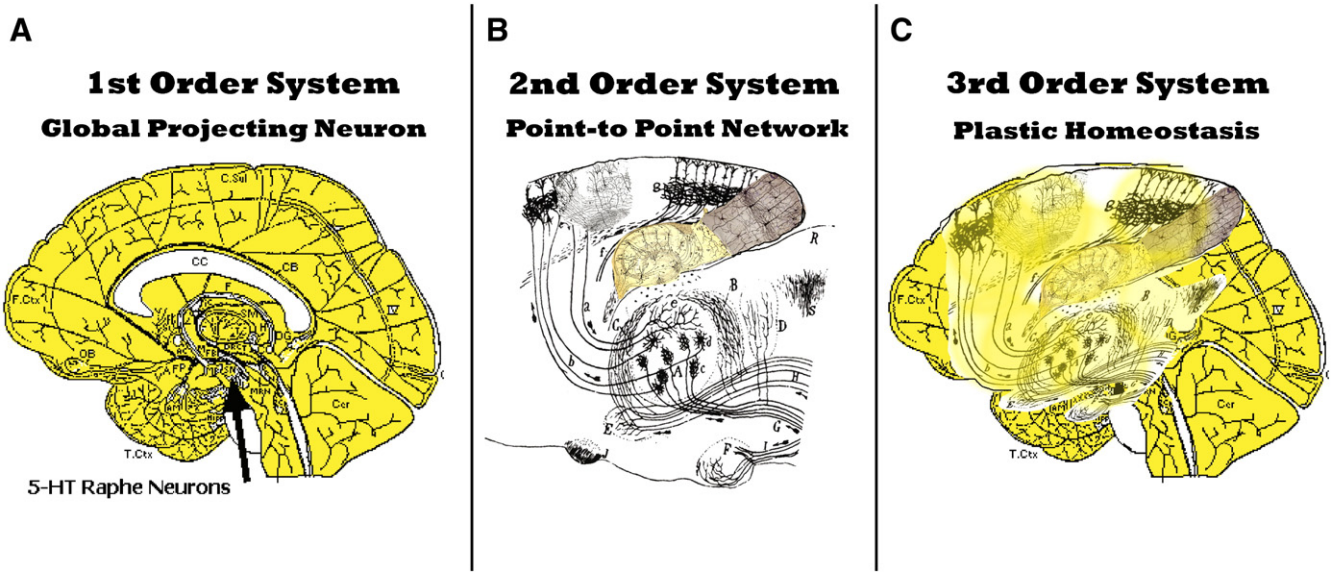


**Fig. 4 – A model of the mind based on neuroplasticity. Cajal understood neuroplasticity and gave us many of the point-to-point networks in the brain currently used in most modelers' theory of the mind. In this chapter, commemorating the centennial celebration of the Nobel Prize of 1906 to Cajal, we propose that the expression of mind should be expanded to include the principles of neuroplasticity, and incorporate the more recent findings of globally projecting neurons and homeostasis. (A) The globally projecting neurons are principally the monoamines (i.e., serotonin, norepinephrine and dopamine). These are all ancient molecules which served basic anti-oxidant and differentiating functions in unicellular organism. In the human brain these chemicals function as neurotransmitters (largely working by "mass action" rather than acting exclusively through a specific synapse). In addition, these chemicals regulate cell differentiation (mitosis, migration and maturation) and are especially important in stimulating neuroplasticity of their target cells. These neurons have fine, highly branched axons that innervate the entire brain. The importance of this system to the mind is illustrated by the actions of "mind-expanding drugs that target these monoamines. These neurons can be considered first order. (B) Point-to-point networks were described by Cajal in his studies of neuroanatomy. The networks propagate through specific synapses and convey precise and rapid information. The point-to-point connections have increased in complexity as the brain has evolved, and the principle neurons (pyramidal and Purkinje) are large, multipolar cells with long, myelinated axons. These neurons can be considered the second order system. (C) Homeostasis keeps two or more systems in balance. In the neuroplasticity mind model, the process is in constant flux, and dependent on the inherent plasticity of the neuron. The two systems in balance are the globally projecting neurons and the point-to-point neurons. Both sets of neurons change their morphology in response to the actions of the other set. We can envision their interactions in three graduating steps. (1) The globally projecting neurons principally provide the unity, harmony and essence of mind expression, a 1st order system. (2) The point-to point neurons underlie the quality, depth and speed of mind expression, a 2nd order system. (3) Both systems working together create a unique, complex and personable 3rd order system. Here lies the full expression of the mind based on a plastic neuron, which provides for the fluidity and changing states of consciousness.**

a few global neurons (1st order neurons) can communicate with numerous point-to-point neurons (2nd order neurons). This blanket network could provide, either directly or indirectly, the simultaneous monitoring and regulation of large areas of interacting brain systems.

Extending Cajal's idea of neuroplasticity, monoamine neurons are not only morphologically modifiable (see Fig. 2B), but also exert a modifying influence on their target neurons (Azmitia and Whitaker-Azmitia, 1991). During development (Lauder, 1983) and in the adult brain (Brezun and Daszuta, 1999) 5-HT can stimulate neurogenesis. 5-HT is also able to stimulate neuronal survival of both glutamate (Dooley et al., 1997) and cholinergic neurons (Riad et al., 1994). Finally, 5-HT can also be considered a differentiating factor during development (Vitalis and Parnavelas, 2003; Akbari et al., 1994) and in the mature brain (Azmitia et al., 1995). The 5-HT global neurons (1st order) have a regular slow firing rate which delivers a constant stream of transmitter when the brain is awake and active. This may have trophic consequences on 2nd order neurons throughout the brain during this time period.

This notion of a global 1st order system is to be contrasted with the hypothesis that proposes many modular cerebral networks (second order systems) acting in parallel to achieve a state of unconscious awareness (Dehaene and Naccache, 2001). This parallel mechanism assumes that the target areas in the prefrontal and anterior cingulate cortices are the initiation sites for downstream coherent activity, rather than the recipient sites of a globally projecting system. These attempts to pinpoint a specific area recall Cajal quote: "Following Hitzig, Ferrier and other physiologists, Flechsig localized the higher mental activities in the frontal lobe, i.e. in the *anterior association sphere of the human cerebral cortex*. … it appears to us truly difficult to admit that processes so complex as memory or personality and volun-

tary acts could be localized in a given point of the cortex." Cajal, p.544, 1904.

### 4.2. *Mind-expanding drugs*

The sense of self does no have to be confined to a physical location; it could be the neurotransmitter itself acting throughout the brain. As we said above, the global projecting monoamine neurons had important cellular actions before there was a brain. If these 1st order systems have an action in the expression of the mind, then drugs which activate this system should have an action on the mind itself. Researchers have proposed that out-of-body experiences can be elicited by a variety of "mind-expanding drugs", most of which are alkaloids. These drugs can be classified as (1) Indoleamine; (2) Phenylethylamine; and (3) Ergot. (1) Indoleamines act through the serotonergic system and produce an altered sense of self as a religious, visually rich, mind-expanding experience. These drugs include Psilocybin (Magic Mushroom), Cohoba epena, Bufotenine and dimethytryptamine. (2) Phenylethylamines act through the catecholamine system and produce a racing, visually and auditory-rich, and deep introspection and insights that expand awareness. The main drug in this class is peyote (mescaline). (3) Ergots act through the serotonin and catecholamine systems and produce deliriums, hallucinations and delusions involving all sensory systems with periods of depersonalization, psychic breakdown and intense creative insights. The ergot fungus that grows on rye bread and LSD are the principle drugs in this class. All these monoamine-related drugs are termed "mind expanding" because they provide the user with an abnormal (outside the normal) cognitive experience. These "mind-expanding drugs" may mimic mental disorders such as schizophrenia and severe anxiety disorders (Bron et al., 1976; Gouzoulis-Mayfrank et al., 2006). These mental disorders involve the monoamine neurons since they can be treated with specific monoamine targeted drugs such as neuroleptics (dopamine) or SSRIs (serotonin-specific reuptake inhibitors). Dementia, a disorder where the patient's mind is either reduced or lost, is associated not only with loss of point-to point neurons, but also with lost of global monoamine system (Gottfries, 1986). In summary, the monoamine global systems may be a component of the mind.

## 5. Homeostasis

In order to discuss the importance of neuroplasticity to whole brain activity, a discussion of homeostasis may be necessary. "By an apparent contradiction, it maintains its stability only if it is excitable and capable of modifying itself according to external stimuli, and adjusting its response to the stimulation. In a sense it is stable because it is modifiable—the slight instability is the necessary condition for the true stability of the organism" (Cannon, 1929). Walter Cannon in his discussion of homeostasis said a "slight instability" is required for "true stability of the organism." At the level of the brain, we can say neuroplasticity is required for a balanced brain, a framework for a stable mind. The ability to change morphology, stimulate neurogenesis and differentiation, and promote cell survival is regulated by global systems. Damasio, suggests that evolutionary old, midline brainstem systems comprise the "core consciousness and the generation of the sense of self…" (Damasio, 2000, p. 465). This is an accurate description of the serotonergic neurons in the midbrain raphe nuclei (Azmitia and Segal, 1978; Steinbusch, 1981; Jacobs and Azmitia, 1992). The central action of these ancient 5-HT producing cells in homeostasis has been previously proposed (Azmitia, 1978, 1999).

5-HT neurons are highly plastic (Azmitia and Whitaker-Azmitia, 1991) and can sprout in response to a wide variety of signals (e.g., $O_2$, $CO_2$, glucose, BDNF, S100B, pH, temperature, hormones) (Azmitia, 2001). When 5-HT is secreted at its terminals, it interacts with at least 14 separate receptors, each having a different affinity for 5-HT, a specific location, a unique molecular structure and an individual transduction pathway. One of these receptors (5-HT1A) at one location (astroglial membrane) is able to release S100B (Cajal's chemoaffinity molecule) (Whitaker-Azmitia et al., 1990) (Fig. 2A).

The actions of this S100B have already been discussed. But what happens when 5-HT is loss? Short-term decreases in 5-HT occur every night during sleep (Trulson and Jacobs, 1979). This is consistent with Cajal's notion that neuronal connections are unstable and labile during sleep (see Azmitia, 2002). Further, serotonin levels fluctuate over the year (Singh, 1964; Wirz-Justice et al., 1977) and brain homeostasis should show a similar trend. It was shown that as 5-HT levels decrease, the incidence of suicides increases (Dreyer, 1959; Bjorksten et al., 2005). Suicides can be viewed as the loss of brain homeostasis, and the ultimate rejection of the self.

## 6. Cajal's contribution to mind

How could a man who worked, mainly alone in a country outside the mainstream of scientific culture, be pertinent to our discussion of the mind in the 21st century? Most neuroscientists have not read much of Cajal's writings, and many only skim his articles to copy the drawings illustrating point-to-point connections. Nearly all the mind modelers mention Descartes, Gall, Broca, Wernicke and Penfield, but most fail to write about Cajal's ideas. Is functional localization a more relevant principle for models of the mind than neuroplasticity? This is ironic, since most of the networks considered as a basis for models of he mind, use the neuronal connections first illustrated by Cajal (Fig. 4B).

In writing this review for the Cajal Club, I sought to keep the works and thoughts of Cajal relevant. The explanations for the longevity of Cajal's views probably reflect his half-century relation with the brain, and its higher functioning. Cajal probably spent more time drawing neurons than any person who has lived before or after his work. His relationship was personal, he anthropomorphizing the struggles and successes of neurons. Cajal's insights into the brain came from his understanding of the neuron. Since all models of the mind are based on the working of the brain, the neuron needs to be understood before making a model of the mind. "A good theoretical model of a complex system… should downplay the inessential details… (but) one does not really know which are the inessential details until one has understood the phenomena under study" (p. 83, Herz et al., 2006).

Most attempts to understanding the basis of the mind have focused on neuronal activity along established circuits (point-to-point connections), or the molecular actions of neurotransmitters divorced from their cellular homes. Cajal, who described the circuits emphasized that the parent neurons were vigorous and viable. He knew their intricate morphology and personalized the smallest actions of the neurons. Furthermore, he stressed their ability to change their shape in response to experience, not only by growing but also by contracting.

After Cajal's work was finished, it took decades to again show injury-induced plasticity of neurons (Liu and Chambers, 1958). The renaissance in brain neuroplasticity occurred in the 1970 with studies of reactive synaptogenesis (Lynch et al., 1972; Raisman and Field, 1973) and of monoamine sprouting (Stenevi and Bjorklund, 1973; Azmitia et al., 1978). The ability of undamaged monoamine neurons to expand their normal territory had enormous implications for understanding the expansion of the mind produced by learning. Brain mapping studies confirmed this expansionist viewpoint and sensory cortical representation is now accepted to be fluid (Clark et al., 1988). Kandel (2001) writes "this malleability of cortical architecture has profound implications for medicine and for psychoanalytically oriented psychiatry. What can be formed by experience can presumably be undone by experience" (p. 282). This concept of the plasticity of the mental faculty of a human being is only just being realized, yet it was integral to the ideas of Cajal as early as 1894.

Some may claim that the neuron is too small to be important when devising a scheme to explain the mind. There are $10^{12}$–$10^{14}$ neurons, so how can any one be important? A similar question can be raised about global economics; how can any one individual be important? Yet, the Nobel Prize in Economics has repeated gone to microeconomics, a branch of economics that studies how individuals, households, and firms make decisions to allocate limited resources. But how do the plastic properties of individual neurons explain the mind?

## 7. Conclusion: neuroplasticity based mind

A few of the theories of Cajal have been reviewed here, and were the subject of a previous symposium sponsored by the Cajal Club and the Cajal institute: Changing views of Cajal's neurons (Azmitia et al., 2002). In this paper, I have tried not only to discuss what Cajal thought, but how his ideas may be relevant to understanding the mind. The power of neuroplasticity impinges not only on the intellectual faculties of the human mind, but also on its expansion and demise. This synthesis can be considered a 3rd order system (Fig. 4C). It integrates the characteristics of the globally projecting neurons (1st order) with the more precise actions of the point-to point connections (2nd order).

Ten points need be considered in proposing a new plastic view of the mind.

(1) The mind is based on the plastic properties of the neuron.
(2) The mind, like the neuron, can expand and contract.
(3) The mind should reflect ongoing and previous internal and external stimuli.
(4) The mind should have as it core the integration of the higher association areas of prefrontal, entorhinal and anterior cingulate cortices, as well as primary somatosensory regions.
(5) The mind incorporates ancient neurons with strong connections to the thalamus, hypothalamus and amygdala.
(6) The mind may be expressed through midline brainstem structures.
(7) The mind appears to be a second level system that monitors and reflects first order experience information.
(8) The mind should incorporate the principles of a homeostatic system.
(9) The mind is influenced by "mind-expanding" drugs.
(10) The mind is lost in dementia.

Cajal did not know about homeostatic systems, globally projecting neurons or mind-expanding drugs. He did not consider neurogenesis or differentiation as processes occurring in the mature brain. Yet all these discoveries directly branch off Cajal main ideas of neuronal plasticity and intelligence. We, provided with the neuroscience studies performed in the 100 years since Cajal's Nobel Prize, can propose that globally projecting brainstem neurons, such as the serotonin, dopamine and norepinephrine neurons, may be part of the biological substrate of the mind. The mass action of the global network coupled with the precise control of the point to point network provides a morphological framework for fresh insights into how the mind might function at a higher unified-level than any of its component parts can achieve alone. An important condition of this neuroplastic view of the mind, is that it is in constant flux which can imprint a record of its activity to influence future actions. The mind can be expanded by ingestion of a serious hallucinating drug, or it can be diminished by a wasting dementia such as Alzheimer's disease. The mind of a child is different from the mind of an adult, and sense of self is a reflection of the morphology of our neurons, as first described by Cajal.

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