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REVIEW

Neuronal plasticity: historical roots and evolution of meaning

G. Berlucchi · H. A. Buchtel

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Abstract In this paper, we outline some important milestones in the history of the term "plasticity" in reference to the nervous system. Credit is given to William James for first adopting the term to denote changes in nervous paths associated with the establishment of habits; to Eugenio Tanzi for first identifying the articulations between neurons, not yet called synapses, as possible sites of neural plasticity; to Ernesto Lugaro for first linking neural plasticity with synaptic plasticity; and to Cajal for complementing Tanzi's hypothesis with his own hypothesis of plasticity as the result of the formation of new connections between cortical neurons. Cajal's early use of the word plasticity is demonstrated, and his subsequent avoidance of the term is tentatively accounted for by the fact that other authors extended it to mean neuronal reactions partly pathological and no doubt quite different from those putatively associated with normal learning. Evidence is furnished that in the first two decades of the twentieth century the theory was generally accepted that learning is based on a reduced resistance at exercized synapses, and that neural processes become associated by coactivation. Subsequently the theory fell in disgrace when Lashley's ideas about mass action and functional equipotentiality of the cortex tended to outmode models of the brain based on orthodox neural circuitry. The synaptic plasticity theory of learning was rehabilitated in the late 1940s when Konorski and particularly Hebb argued successfully that there was no better alternative way to think about the modifiability of the brain by experience and practice. Hebb's influential hypothesis about the mechanism of adult learning contained elements strikingly similar to the early speculations of James, Tanzi and Cajal, but Hebb did not acknowledge specifically these roots of his thinking about the brain, though he was fully aware that he had resurrected old ideas wrongly neglected for a long time. Lately the concept of neural plasticity has been complicated by attributing considerably different meanings to it. A scholarly paper by Paillard is used to show how an analysis in depth can clarify some confusion engendered by an unrestricted use of the concept and term of neural plasticity.

Keywords Neuronal plasticity · Behaviour · Learning · Synaptic modifiability · Neural path resistance

The term plasticity has been in use in brain science for well over a century to refer to the suspected changes in neural organization which may account for various forms of behavioral modifiability, either short-lasting or enduring, including maturation, adaptation to a mutable environment, specific and unspecific kinds of learning, and compensatory adjustments in response to functional losses from aging or brain damage. Several authors have tried to rein in the unfocused use of the term (e.g., Konorski 1948; Vital-Durand and Jeannerod 1975; Paillard 1976; Buchtel 1978), but researchers have tended to apply the concept to virtually any change in the nervous system. An idea of the multiplicity and variety of meanings which have been attributed to the term neural plasticity can be gathered by a perusal of the many reviews and books that continue to appear in the specialized literature (e.g. Zilles 1992; Yuste

G. Berlucchi (✉)
Department of Neural and Visual Sciences,
University of Verona, Strada Le Grazie 8, 37134 Verona, Italy
e-mail: giovanni.berlucchi@univr.it

G. Berlucchi
National Institute of Neuroscience, Verona, Italy

H. A. Buchtel
VA Ann Arbor Healthcare System
and the University of Michigan, Ann Arbor, USA

and Bonhoeffer 2001; Johansson 2004; Pascual-Leone et al. 2005; Cooke and Bliss 2006; Møller 2006; Ansermet and Magistretti 2007; Mercado 2008). Nowadays the modifiability of synaptic transmission between neurons is usually regarded as a fundamental, if not the sole, mechanism of behavioral modifiability. In this paper we focus on the birth and initial developments of ideas that led to the theory that learning occurs because of changes in the efficacy of synaptic transmission along specific brain pathways.

The origins. In their brief history of synapses and synaptic transmission, Cowan and Kandel (2001) give priority to Cajal for speculating in 1894 that learning requires the formation of new connections between neurons, and credit to Konorski (1948) and Hebb (1949) for proposing that the strength or effectiveness of specific synapses may change as a result of activity. In reality modern ideas about the cellular basis of learning, and particularly about synaptic plasticity, predate Cajal by a few years and Hebb and Konorski by several decades. In dealing with the historical evolution of ideas in this field it seems opportune to distinguish between plastic changes consisting in the formation of new neural pathways from those based on the modification of existing pathways. Although some early authors, including Freud (Centonze et al. 2004), may have used the term plasticity in reference to the nervous system and learning before William James, it was the latter who first addressed the problem of brain plasticity from a strikingly modern perspective in his *Principles of Psychology* (1890). He linked the property of plasticity with behavioral habits and with the habilitation of specific brain paths by repeated use. In his words:

> *Plasticity,* then, in the wide sense of the word means the possession of a structure weak enough to yield to an influence, but strong enough not to yield all at once….. Organic matter, especially nervous tissue, seems endowed with a very ordinary degree of plasticity of this sort: so that we may without hesitation lay down as our first proposition the following, that *the phenomena of habit in living beings are due to the plasticity of the organic materials of which their bodies are composed.* (James 1890, vol. I, p. 105; italics in the original)

> If habits are due to the plasticity of materials to outward agents, we can immediately see to what outward influences, if to any, the brain-matter is plastic. Not to mechanical pressures, not to thermal changes, not to any of the forces to which all other organs of our body are exposed; for nature has carefully shut up our brain and spinal cord in bony boxes, where no influences of this sort can get at them. She has floated them in fluid so that only the severest shocks can give them a concussion, and blanketed and wrapped them about in an altogether exceptional way. The only impressions that can be made upon them are through the blood, on the one hand, and through the sensory nerve-roots on the other; and it is to the infinitely attenuated currents that pour in through these latter channels that the hemispherical cortex shows itself to be so peculiarly susceptible. The currents, once in, must find a way out. In getting out they leave their traces in the paths which they take. The only thing they *can* do, in short, is to deepen old paths or to make new ones; and the whole plasticity of the brain sums itself up in two words when we call it an organ in which currents pouring in from the sense-organs make with extreme facility paths which do not easily disappear… (James 1890, vol. I, p. 107; italics in the original)
> For the entire nervous system *is* nothing but a system of paths between a sensory *terminus a quo* and a muscular, glandular, or other *terminus ad quem*. A path once traversed by a nerve-current might be expected to follow the law of most of the paths we know, and to be scooped out and made more permeable than before; and this ought to be repeated with each new passage of the current. (James 1890, vol. I, p. 108; italics in the original)

In addition to suggesting potential mechanisms for reinforcing existing neural connections, James also advanced the notion that brain components happening to be active at the same time could drain into each other, thus forming new association paths:

> *When two elementary brain-processes have been active together or in immediate succession, one of them, on reoccurring, tends to propagate its excitement into the other.* (James 1890, vol. I, p. 566; italics in the original)

> Potentialities of new paths are furnished by the fibres which connect the sensory cells among themselves; but these fibres are not originally pervious, and have to be made so by a process which I proceed hypothetically to state as follows: *Each discharge of a sensory cell in the forward direction (that is, the direction towards the motor cells) tends to drain the cells lying behind the discharging one of whatever tension they may possess. The drainage from the rearward cell is what for the first time makes the fibres pervious. The result is a new-formed 'path', running from the cells that were 'rearward' to the cell that was 'forward' on that occasion; which path, if on future occasions the rearward cells are independently excited, will tend to carry off their activity in the same direction so as to excite the forward cell, and will deepen itself more and more every time it is used.* (James 1890, vol. I, p. 584-585; italics in the original)

…..the deepest paths are formed from the most drainable to the most draining cells; … the most drainable cells are those which have just been discharging and…. *the most draining cells are those which are now discharging or in which the tension is rising towards the point of discharge.* (James1890, vol. II, p. 585; italics in the original)

James synthesized his neural association and drainage theory as follows:

The amount of activity at any given point in the brain-cortex is the sum of the tendencies of all other points to discharge into it, such tendencies being proportionate (1) to the number of times the excitement of each other point may have accompanied that of the point in question; (2) to the intensity of such excitements; and (3) to the absence of any rival point functionally disconnected with the first point, into which the discharges may be diverted. (James, 1890, vol. II, p. 567; italics in the original)

Although James had no concept of the synapse, as shown by reference to the continuity between projecting fibers and receiving neuronal cell bodies in his sketches of putative neuronal circuits, his speculations have an amazing modern flavor insofar as they clearly posit the possibility that, (1) neuronal paths are either formed or opened up by use, (2) functional association is promoted between neurons which happen to be simultaneously active, and (3) akin to hydraulic models, "drainage" is a process by which an activated neural path captures all available energy from surrounding parts by virtue of its lowered resistance to conduction during functional activity.

Students of the brain in James' times frequently cited his theory of emotion (the so-called James–Lange theory) and his law of forward conduction, which anticipated the law of dynamic polarization (Berlucchi 1999), but there are only infrequent references to his speculations on brain plasticity and its possible neuronal mechanisms, although implicit traces of such speculations are apparent in the thinking about the relations between neurons and learning by neuroanatomists, neurophysiologists and neurologists at the transition between the nineteenth and twentieth centuries. Nevertheless, the term plasticity was incorporated into the neurological lexicon, generally without an overt acknowledgment of James' coinage of it.

Enter the synapse. Sherrington was responsible for naming the synapse and for identifying it as the device that ensures the unidirectionality of transmission along neural pathways (Sherrington 1897, 1900, 1906). Although he attributed the property of being molded by experience even to simple nervous reactions (Buchtel 1978), he did not elaborate on the possible relations between learning and synaptic plasticity, and indeed he mostly restricted his use of the term plasticity to refer to the tendency of muscles of decerebrate animals to retain the posture imposed upon them (Sherrington 1909). The very first hypothesis that associative memories and practice-dependent motor skills may depend on a localized facilitation of synaptic transmission was put forward by the Italian neuropsychiatrist Eugenio Tanzi in 1893, 4 years before the coming into existence of the term synapse. At a time when Golgi and his diffuse nerve net theory held sway over brain science in Italy, Tanzi and his disciple Ernesto Lugaro were not afraid to manifest their fervent admiration for Cajal and their staunch support for the neuron theory. Convinced of the correctness of Cajal's view of the nervous system as an aggregate of neurons separated by tiny distances, Tanzi had proposed that the waves of nervous excitation must normally encounter some difficulties in crossing such distances that we now call synaptic fissures:

Le minime interruzioni fra neuroni vicini e funzionalmente solidali spiegherebbero in modo abbastanza soddisfacente anche la ragione del fatto notorio, messo in luce da Helmholtz, per cui i processi nervosi, attraversando la sostanza grigia, soffrono una diminuzione di velocità. La causa dell'indugio risiederebbe nella difficoltà di superare l'intervallo libero. (Tanzi 1893, p. 439)
The minimal interruptions between adjacent and functionally related neurons could also provide a rather satisfactory explanation of the well known fact, demonstrated by Helmholtz, that nervous processes undergo a reduction of speed when crossing the grey matter. The reason for this slowing would lie in the difficulty to surpass the free interval.

Tanzi then proposed that the repetitious activity of a neuronal path during a specific learning or practice could cause a hypertrophy of associated neurons along that path, thus reducing the interneuronal distance and making the crossing easier.

Noi possiamo ritenere…..che la corrente nervosa, come ogni altro atto funzionale, provochi ogni volta che passa un maggior risveglio dei processi nutritivi; e che i neuroni attraversati dal movimento si ipernutriscano, non diversamente dal muscolo che ha lavorato. Ora, se la nutrizione si accompagnerà, come nel muscolo, coll'ipertrofia; e se l'aumento di volume avverrà….nel senso della lunghezza, l'esercizio della funzione diminuirà la distanza fra i neuroni solidali e contigui…..Se ora noi pensiamo che le distanze interposte fra l'arborizzazione terminale di un neurone e la cellula del neurone successivo costituiscano una resistenza o…una specie di mal passo che l'onda

> nervosa dovrà sorpassare non senza stento, è evidente che la conducibilità del sistema nervoso deve essere in ragione inversa degli intervalli interneuronici. L'esercizio, in quanto tende ad abbreviare le distanze, aumenta dunque la conducibilità dei neuroni, ossia la loro capacità funzionale. (Tanzi 1893, p. 469)
> We may assume… that like every other functional act, each passage of the nervous current increases the nutritional processes, and that the neurons traversed by the current over-nourish themselves not unlike a muscle that has worked. Now, if nutrition, as in the muscle, will be accompanied by hypertrophy, and if the increase in volume will occur in the sense of length, functional exercise will decrease the distance between adjoining and contiguous neurons….If now we think that the distances between the terminal arborisation of one neuron and the body of the next neuron constitute a resistance or… a kind of difficult passage that the nervous wave must overcome not without difficulty, it is evident that the conductivity of the nervous system will stand in an inverse relation with the spaces between neurons. To the extent that exercise tends to shorten distances, it increases the conductivity of neurons that is their functional capacity.

Lugaro (1898a, 1905, 1909) expanded on Tanzi's hypothesis by applying the term plasticity to the practice-related synaptic changes envisioned by his teacher, with the addition of a visionary intuition of the chemical nature of synaptic transmission in the central nervous system. Lugaro was strongly influenced by Cajal's thinking about the neural bases of mind (see below), and already in 1898 he presented a clear view of how mental associations may depend on newly formed associations between neurons, based on a coincidence of activity. Bold characters are inserted in the following citations to stress Lugaro's early use of the term plasticity with reference to the modifiability of brain paths under the influence of the environment:

> Ė ben certo che nel corso dell'evoluzione gli elementi nervosi hanno acquistato al pari dei muscolari la capacità di accrescersi sotto l'impulso funzionale; un certo stato di attività è anche necessario affinché non si atrofizzino. L'ipertrofia funzionale si esplica appunto con l'allungamento e la moltiplicazione dei rami terminali. Pare inoltre che gli elementi del tessuto nervoso abbiano acquistato come proprietà generica la capacità di influenzarsi a vicenda, in modo che quelli che simultaneamente funzionano tendono a mettersi in reciproca connessione; e così si rende possibile e facile il trasmettersi dell'attività funzionale dall'uno all'altro e quindi il ripetersi e la solidarietà abituale dei processi funzionali. Questa proprietà è certo poco chiaramente spiegabile nelle condizioni attuali della scienza, ma essa ci è resa manifesta tutti i giorni dal fatto del continuo stabilirsi di legami associativi fra le impressioni simultanee, in modo che il ripresentarsi isolato dell'una provoca il ripresentarsi dell'altra. Si tratta probabilmente di oscuri fenomeni di chemotropismo, analoghi a quelli che, secondo Cajal, nello sviluppo embriologico dei centri nervosi guidano a destinazione le estremità in accrescimento delle ramificazioni neuroniche. In base a queste proprietà elementari, la cui origine rimonta alle prime fasi dell'evoluzione e si deve probabilmente ad una continua selezione di variazioni accidentali, il sistema nervoso subisce continui perfezionamenti nell'evoluzione individuale sotto lo stimolo delle funzioni in atto; i rapporti di solidarietà funzionale tra i vari elementi si fanno sempre più stretti, si stabiliscono rapporti nuovi sempre crescenti di numero……L'organizzazione dei rapporti più delicati tra gli elementi anatomici della corteccia avviene sotto l'azione degli stimoli esterni durante il corso della vita individuale, ed è pressoché continuo; però le connessioni già bene organizzate tendono spontaneamente a ripetersi nello sviluppo embriologico dei discendenti in ragione della loro semplicità e della loro costanza. Perciò la struttura corticale del neonato, ancor vergine di impressioni esterne, è già un simbolo generico della costituzione del mondo esterno, della struttura della specie, dei suoi bisogni e della sua condotta di fronte alle più svariate eventualità della vita….La **plasticità degli elementi nervosi cerebrali**, che permette ai rapporti interni di plasmarsi a seconda degli stimoli esterni, diminuisce con il progredire degli anni; questa proprietà, che rappresenta una continuazione nell'adulto dell'impulso formativo dell'embrione, si attenua man mano, e in un tempo variabile da un individuo all'altro finisce coll'esaurirsi quasi del tutto. (Lugaro, 1898a, p. 38)
> It is assured that in the course of evolution the nervous elements, like the muscular ones, have acquired the capacity to grow under the functional impulse; indeed a certain degree of activity is necessary to prevent their atrophy. Functional hypertrophy manifests itself through the elongation and multiplication of the terminal branches. It further appears that the elements of the nervous tissue have acquired as a generic property the capacity to influence each other mutually, such that those that work simultaneously tend to establish a reciprocal connection; and this enables and facilitates the transmission of functional activity from one to the other and therefore the repetition and habitual solidarity of the functional processes. To be sure, this property cannot be clearly explained in the present state of science, but it is revealed to us every day

> by the fact of the continuous establishment of associative links between simultaneous impressions, such that the representation of one of them alone causes the representation of the other. Obscure phenomena of chemotropism are likely to be at play, akin to those that according to Cajal guide to their destination the growth extremities of the neuronal ramifications during the embryological development of the nerve centres. Based on these elementary properties, whose origin goes back to the first phases of evolution and is probably due to a continuous selection of accidental variations, the nervous system undergoes continuous refinements under the stimulus of the functions in operation; the relations of functional solidarity among the various elements become closer and closer, and ever more numerous relations establish themselves anew…The organization of the most delicate relations between the anatomical elements of the cortex occurs under the action of external stimuli in the course of an individual life and is virtually continuous; however the connections already well organized tend spontaneously to recur in the embryological development in proportion to their simplicity and consistence. Therefore the cortical structure of the newborn, still virgin to external impressions, is already a generic symbol of the constitution of the outer world, of the structure of the species, of its needs and its conduct against the most varied events of life… The **plasticity of the nervous elements**, which allows the internal relations to be molded according to the external stimuli, decreases as the years go by; this property, which represents a continuation in the adult of the formative drive of the embryo, declines progressively and reaches an almost complete annulment in a variable time from one individual to the other.

Lugaro explicitly connected the concept of plasticity and the term plastic activity with Tanzi's hypothesis of the functional modifiability of synapses and with Cajal concept of neurotropism in a Treatise of Psychiatry, which was published in Italian in 1906 and in English in 1909:

> Alla fisiologia ed alla psicologia il neurotropismo fornisce ulteriori schiarimenti. Esso non esclude la possibilità che in certi organismi, che hanno raggiunto, a mezzo di riflessi coordinati, adattamenti di alta perfezione, ma non ulteriormente perfettibili, le connessioni fra i vari neuroni si stabiliscano in modo permanente: è probabile che così avvenga negli invertebrati. Ma dove la struttura dei centri nervosi, pur essendo già elevata, è perfettibile, cioè specialmente nella corteccia cerebrale, è chiaro che le attività chemotropiche possano ancora determinare lo stabilirsi dei nuovi rapporti anatomici. Con un meccanismo di progressivo accrescimento che tende ad avvicinare e collegare sempre più intimamente gli elementi posti in connessione, aveva già Tanzi interpretato la consolidazione dei ricordi e degli automatismi che divengono abituali; con lo stesso meccanismo Cajal interpreta la formazione di ogni nuova associazione, il perfezionamento del meccanismo anatomico cerebrale, l'incremento progressivo della visibilità anatomica che costituisce il substrato dell'ideazione, dell'immaginazione, della previsione. Quest'**attività plastica dei neuroni**, che è una continuazione di quella ben altrimenti accentuata del periodo embrionale, è naturale che sia più vivace nell'età infantile e giovanile anziché nell'adulta (Lugaro 1906, pp. 113–114).
>
> Neurotropism throws a considerable light on physiological and psychological problems. It does not exclude the possibility that in certain organisms the connections between the various neurones are immutable. Such would be the case in those organisms which have acquired—by means of coordinated reflexes—adaptations of a high degree of perfection, but incapable of further improvement. Probably this holds in the case of invertebrates. But where the structure of the nerve centres, although already highly organised, is still capable of further perfection—especially in the cerebral cortex—it is clear that chemotropic activities can still be the factor in bringing about new anatomical relationships. Tanzi formerly explained the consolidation of memories and automatic actions which become habitual, by means of an ever expanding mechanism which tends to approximate and unite in a progressively more intimate manner elements connected with each other; with the same mechanism Cajal explains the formation of every new association, the process by which the cerebral anatomical mechanism is perfected, and the progressive increase in anatomical pathways which constitutes the substratum of ideation, imagination and foresight. This **plastic activity** of neurones, which is just a continuation of what is more accentuated in the embryo, although in quite a different manner, is naturally more active in infancy and youth than in adult life (Lugaro 1909, pp. 96–97).

Lugaro cannot be credited for introducing the term plasticity into the neurosciences, as instead one of us has argued previously (Berlucchi 2002), eliciting the protestation of Jones (2004). It nevertheless remains true that in linking plasticity with Tanzi's learning hypothesis, Lugaro was the first to give the name plasticity to synaptic modifiability, a denotation that persists to this day.

Cajal, the concept of plasticity and the term plasticity. Cajal was one of the pioneers in the foundation of the concept of neural plasticity, having proposed cortical changes possibly associated with learning already in 1982 (see DeFelipe 2006). His great intellectual and empirical contributions to the field do not appear to have been influenced by the ideas and terminology of William James. Indeed Cajal used the term plasticity very sparingly and possibly did not even particularly like it. Jones (2000) and Stahnisch and Nitsch (2002) have claimed that Cajal borrowed the term plasticity from a thesis of Minea, a pupil of the Romanian neurologist Marinesco. The thesis was published in 1909; it was about changes in neurons of sensory ganglia following compression and transplantation, and the plasticity it alluded to was therefore something entirely different from the plasticity associated with habit and learning by James, Tanzi, Cajal and Lugaro. The evidence taken to support the attribution to Minea of priority in the use of the term plasticity consists in the following brief sentence in Cajal's book on degeneration and regeneration in the nerve centres:

> The studies of Marinesco (on sensory ganglia transplantation) have been confirmed by his pupil Minea who, in his doctor's thesis, gave a good representation of the metamorphic phenomena of the sensory neurone, which he called *plasticity*, provoked by the compression and transplantation of ganglia into various organs. (Ramón y Cajal in DeFelipe and Jones 1991, p. 430)

Yet in itself this sentence may as well be taken to imply that Marinesco and Minea had applied to just one of many possible forms of neuronal modifiability a term already in use with other meanings in other contexts. A first reason for this interpretation is that in the two-volume book on the nerve cell that Marinesco published in 1909 with a preface by Cajal, there is a chapter entitled "theorie de l'amiboidisme nerveux et plasticité des neurones" (theory of nervous amoeboidism and plasticity of neurons) in which plasticity is discussed as a class of morphological reactions of neurons to pathological influences including osmotic challenges, and by no means as a basis or correlate of learning (Marinesco 1909). The book includes the description of several experiments by Marinesco and Minea on neuronal reactions to traumatic, toxic and viral agents and to inanition and thermal stresses, without any mention of possible neuronal plastic effects from learning and experience. A second and more important reason for denying that Cajal appropriated the term plasticity from Minea and Marinesco is that Cajal himself had used the terms "plasticity" and "plastic" in a Jamesian sense already in 1894. Around 1893 Cajal had begun to speculate on the brain bases of mentation, and such speculations were published in his 1894 Croonian Lecture (Ramón y Cajal 1984a) and in a number of Spanish papers, some excerpts of which have recently been translated into English with commentary by DeFelipe (2006). Being a shrewd promoter of his own work, Cajal himself had ensured a broad exposure of his findings and ideas to the contemporary scientific community by publishing German translations of his Spanish papers in the widely circulated *Archiv für Anatomie und Physiologie* edited by Wilhelm His. Between 1893 and 1895 three extensive papers by Cajal appeared in this journal (Ramón y Cajal 1893, 1894b, 1895). The first massive paper was a review of Cajal's findings on the neurohistology of the spinal cord and various brain centres; the second paper was especially relevant for the concept of plasticity and indeed for the term plasticity itself; and the third paper was an exposition of a possible function of the cells of the glia. The latter paper was reviewed in the *American Journal of Psychology* by Allin, a psychologist of the University of Colorado at Boulder, who started his review with the following words:

> The Spaniard of Barcelona, of such world-wide reputation, has with perfect right ventured over the line of strict anatomy into the provinces of psychology. The invasion is a welcome one. Such scientific incursions are like that of the spies into Canaan—they bring back rich and exceedingly good fruits" (Allin 1896, p. 428)

The foray of Cajal into the provinces of psychology was motivated by his dissatisfaction with both "the arid determinism of Claude Bernard and the bitter, despairing ignorabimus of du Bois Reymond" (Ramón y Cajal 1894b). The good fruits that he brought back from that foray were ingenious speculations on the possible relations between the plasticity of neurons and mental activities, leading to the proposal that mental characteristics such as hereditary and acquired intelligence, professional skills, artistic aptitudes as well as the effects of education, either good or bad, depended upon different patterns of cortical organization and adaptation. More specifically, Cajal assumed that the "cerebral gymnastic" associated with mental exercise was apt to modify the patterns of connections of cortical pyramidal cells, which he designated as psychic cells, through an enhanced development of their dendrites and axonic collaterals. Inspired by the experimental findings of Mosso on an increase of blood flow through the grey matter of human cortical areas activated by mental processes (Mosso 1880), Cajal argued that such hyperemia is apt to increase the mass of nervous protoplasm through an enhanced assimilation, thus promoting the growth and elongation of the neuronal dendrites and axons or even the expression of new processes.

In the paper published in the *Archiv* in 1894 (Ramón y Cajal 1894b) there are at least three instances of the use of the words plasticity and plastic changes, as attested by the following quotations with the relevant words in bold characters:

> Diese **Plasticität der Zellfortsätze** (plasticidad de las expansions celulares in Spanish: see DeFelipe 2006) variirt wahrscheinlich in verschieden Lebensaltern: bedeutend beim Jüngling, vermidert sie sich beim Erwachsenen und verschwindet fast ganz in Alter. (Ramón y Cajal, 1894b, p. 195)

> This **plasticity of the cell processes** is likely to vary in different life periods: conspicuous in youngsters, it decreases in adults and disappears almost completely in old age.

> Angenommen, dass… hinsichtlich der morphologishen und histologischen Differencirung, zwei Nervenapparate existiren, der sensorich-sensible, der der Entwickelung night fähig ist, und der cerebrale, der Vervollkommung fähige; angenommen, dass nur die Hirnrinde ihre **Wachstumplasticität** (plasticidad de crecimiento in Spanish: see DeFelipe 2006) bewahrt hat, ihr inneres Differencirungvermögen, um sich den wachsenden, von Tag to Tag sich mehr complicirend Nothwendigkeiten des Kampfes ums Dasein anzupassen, so ist e seine Culturaufgabe der Gesellschaft die Zeit abzukürzen, welche die Hirnzellen auf them Wege zur Vollkommenheit brauchen… (Ramón y Cajal 1894b, p. 197)

> Supposing that … with regard to morphological and histological differentiation there exist two nervous apparatus, the sensory-sensible one, which is incapable of development, and the cerebral one, which can be perfected; supposing that only the cerebral cortex has maintained its **plasticity for growth**, its inner power for differentiation, in order to meet the needs of the fight for existence which increase in number and complexity day after day; so it is a cultural task of the society to shorten the time required by the brain cells to reach their perfection.

> Was nütz es, dass das für die Pyramidenzellen des Gehirn aufbewahrte **plastische Entwickwelungvermögen** in so hohem Maasse den Apparat der psychischen Vorgänge vervollkommen? (Ramón y Cajal 1894b, p. 200)
> What is the purpose of the maintenance in such a high degree of **plastic powers of development** by cerebral pyramidal cells in the perfection of the apparatus for psychical processes?

Stahnisch and Nitsch (2002) claim that later on Cajal used the expression "plasticity" to refer to regenerative capacity of both peripheral and central nervous system, and that his concept of neuronal plasticity was ambiguous as to the possible existence of central neurogenesis and regeneration. To our knowledge it is very difficult, if not impossible, to find the word plasticity and its derivatives in Cajal's publications after 1894. In discussing various hypotheses and theories of brain plasticity, Cajal acknowledged the originality and priority of Tanzi's hypothesis in the 1904 *Textura del sistema nervioso del hombre y de los vertebrados* (see DeFelipe and Jones 1988) as well as in the second volume of the *Histologie du Système Nerveux de l'Homme et des Vertébrés* (Ramón y Cajal 1911). Cajal rated Tanzi's hypothesis favorably by observing that it was based on real facts of nervous connectivity, it was in accordance with the well known acquisition of an easy, automatic character by frequent habitual acts, and it was compatible with some kind of physico-chemical resistance to the nervous activities underlying effortful voluntary acts. However, he also stated that Tanzi's hypothesis was insufficient by itself to account for the achievement of complex intellectual and motor abilities with specific long-lasting practices, and maintained that in addition to the reinforcement of preexisting nervous pathways by exercise, as postulated by Tanzi, the acquisition of refined talents must involve the creation of new pathways through an ever expanding growth of dendritic arborizations and axons. Although the word "plasticité" (like, for that matter, the word synapse) is conspicuously absent in the analytical index of the *Histologie*, it appears nevertheless at the end of Cajal's discussion of the putative changes of neuronal connections associated with the acquisition or loss of mental abilities:

> Si la faculté de croissance des neurons chez l'adulte et leur pouvoir de créer de nouvelles associations nous expliquent la capacité d'adaptation de l'homme et son aptitude a changer ses systèmes idéologiques, ….on conçoit egalement que l'amnésie, l'indigence des associations d'idées, la torpeur intellectuelle, l'imbécillité et la demence puissant se produir, lorsque pour de causes plus ou moins morbide l'articulation entre neurones devient lâche, c'est-à-dire lorsque l'expansions s'atrophient et cessent d'etre en contact….Notre hypothèse rende même compte de la conservation plus grande des souvenirs anciens…….par cela meme qu'elles ont été formée à l'epoque où la **plasticité des neurones** atteignait son plus haut degree. (Ramón y Cajal, 1911, p. 890, bold added)
> If the faculty for growth of the neurons in the adult and their power to create new associations explain to us the adaptation capacity of man and his attitude to change his ideological systems… one can as well conceive of amnesia, lack of association of ideas, intellectual torpor, imbecility and dementia as arising from more or less pathological causes, when the articulation between neurons becomes lax, that is when

> the expansions undergo atrophy and cease to be in contact….Our hypothesis also explains the greater conservations of old memories….because they have been formed at a time when the **plasticity of neurons** attains its highest degree.

Among the theories discussed by Cajal (Ramón y Cajal 1911) there are also some referring to the so-called neuronal amoeboidism, such as those of Duval (1895) and Demoor (1896). Like the pathological reactions of neurons described by Marinesco under the title "plasticité" in his book (Marinesco 1909), the phenomena of neuronal amoeboidism hypothesized or observed by Duval and Demoor should be clearly distinguished from the functional modifiability of normal neuronal circuits envisaged by Tanzi and Cajal. Duval (1895) had been inspired by Tanzi's hypothesis on the gradual approximation of neurons as well as by previous observations of amoeboid movements of neurons in transparent invertebrates to propose a theory of sleep whereby the terminal elongations of neurons, compared to the pseudopodes of an amoeba, were supposed to retract in order to interrupt interneuronal communication. By contrast, the activation of mental associations, memory and imagination by stimulating beverages such as tea and coffee was attributed to amoeboid movements that established closer contacts and interactions between neurons. A similar theory of sleep was entertained by Demoor (1896), who examined the morphology of cortical pyramidal neurons in dogs injected with morphine, chloral hydrate and chloroform and observed a moniliform (beaded) appearance of the dendrites. The experiments by Demoor, like previous attempts in the same direction by Lugaro (1898b), were poorly controlled and were rightly criticized by Bawden (1900), Schiefferdecker (1906) and Cajal himself (Ramón y Cajal 1911). The only reason for citing them in the present context is that Demoor was one of the first after James to use the term plasticity in the phrase "plasticitè morphologique des neurones". He equated neuronal plasticity with neuronal amoeboidism (Demoor 1905), but it seems obvious that abrupt amoeboid movements of the neurons can hardly account for the practice-related changes in existing synapses postulated by Tanzi, or for the formation of new neuronal associations postulated by Cajal. Cajal thought that the property of amoeboidism could be attributed to glial cells but not to neurons and developed a theory of glial function in modulating neuronal interactions (Ramón y Cajal 1895) which he later abandoned completely (Ramón y Cajal 1911).

Ups and downs of plasticity and the synaptic theory of learning. After Sherrington named the synapse in 1897 and described its properties shortly thereafter (Sherrington 1897, 1900, 1906), James' proposal that habit depends on the habilitation of specific nervous pathways by a reduction of their resistance, Tanzi's hypothesis that learning and memory depend on physical and functional changes in the articulation between neurons, and Cajal's influential view of mentation as a product of the kind and degree of interneuronal associations in the cortex, became quickly entrenched in neurological and psychological thinking. The following examples taken from two elementary textbooks of psychology published in the first years of the twentieth century show that synaptic modifiability had come to be regarded as the crucial mechanism in the accepted neural theory of learning.

> …the process of transmission of energy across the synapse leaves its resistance to the passage of the impulse in that direction permanently lowered in some degree, so that the more frequently the discharge of energy has taken place the more readily will it take place in the future. This permanent lowering of resistance, or increase in permeability of synapses seems to be the essential condition of the formation of neural habits, and is therefore an effect of the highest importance. (McDougall 1905, p. 32)
>
> Each sensory path makes connections with several motor and associating paths or neurones and any impulse will take the path that offers least resistance. The point of departure for the various alternative paths is a synapse, and the ease with which the synapses open determines the resistance of the paths….The course of an impulse through the cortex is largely controlled by synapses that owe their degree of resistance to the frequency with which they have been used….All agree that whenever two neurones are active at the same time some change is induced in the synapse that makes it act more readily later. (Pillsbury 1911, pp. 49–50)

But after the initial enthusiasm the synaptic theory of learning came promptly under attack and some of the proposed connections between mental factors and neuronal activities were harshly criticized, as in the following citation from Meyer (1912):

> The neuron theory held its sway over neurology, and, as a part of this theory, appeared the doctrine of the synapse. The ear, say, is stimulated. A nervous process runs along a neuron, but only to find itself blocked at a point which is both an end point of the path thus far taken and a division point from which many directions may be taken. The tension becomes greater and greater. The protoplasm stretches out its arms like an amoeba and touches the protoplasm of another neuron. The nervous process then crosses this bridge. Thus far this seems plausible, and the doctrine of the synapse has always seemed plausible to the

> neurologist who asked no further question. But the psychologist asks a further and absolutely essential question: Why does the protoplasm stretch towards one neighboring neuron when the organism happens to be in one situation, towards another neuron when the organism is in another situation? General silence on the part of the neurologists. But some psychologists had an answer ready. They brought in their *deus ex machina.* The ghost does it. Consciousness, feeling, will, or whatever you call it, turns the bridge in the proper direction as the switchman turns the switch in the railway yard. Thus the doctrine of the synapse is largely responsible for the reawakening of the ghost theory of animal behavior. […] It was among European psychologists chiefly that the physiological doctrine of the synapse reintroduced the ghost into the explanation of animal behavior. In America the ghost became popular through the great influence of one man, James, whose followers assign to one kind of mental states which does not seem to have any proper business, to the feelings, the job of stamping in and stamping out complete paths of nervous conduction. But they never state any definite law explaining how the proper feeling itself, with its stamping power turned in the proper *direction,* comes into existence at the proper time. […] When a nervous process is forced to stream over a path other than that of least resistance, it is forced most probably by another nervous process. (Meyer, pp. 368–370; italics in the original)

Although Meyer blamed the psychologists for assuming an influence of psychological forces on the formation of synapses, similar assumptions were explicitly made by no less a neuroscientist than Cajal. Indeed he explicitly granted a causal power to the will in directing the growth of the neuronal processes and thus in controlling the patterns of new interneuronal associations:

> Die neugebilten Fortsätze dürften in der gleichen Richtung wie die dominierended Nervenströme verlaufen oder in derjenigen Richtung, in welcher die noch unvollkommene Zellenassoziation der Gegenstand wiederholter Erregungen von seiten des Willens ist. (Ramón y Cajal, 1894b, p. 194)
> The newly built cell processes should course in the same direction as the dominant nervous streams, or in the direction in which the as yet incomplete cell association is the object of repeated stimulations from the part of the will.

This statement provoked a critical reaction from the German anatomist Schiefferdecker (1906), the author of a very erudite book on neurons and neuronal paths. The book features a long section on the "Plastizität der Neurone" where contemporary views on the so called neuronal ameboidism as well as Tanzi's and Cajal's (but not James') theories are carefully and critically reported. There Schiefferdecker wrote that in principle he understood how the dominant nervous streams could impart a direction to the growth of neuronal processes, whereas he could not understand the proposed action of the will, unless the will was regarded as nothing else than the activity of certain nerve cells. Also Tanzi's hypothesis was not spared the criticism of Schiefferdecker, who argued that if the distance between neurons in a potential path is initially too great to allow interactions, no exercise could reduce it because the path is not functional to begin with. On other hand, if the distance allows neuronal interactions in a path from the beginning, it must be already so small that the margins of the putative improvement generated by the exercise must be negligible.

Opposition to the synaptic plasticity theory also came from students of the development of invertebrate nervous systems. Coghill (1926), for example, wrote:

> That nerve cells grow after they have acquired their definitive function and that such growth is a factor in the development of behaviour was proposed as early as 1893 by Tanzi and in 1895 by S.R. Cajal. Both of these investigators, however, regarded such growth as activated by nervous function or exercise. But we find no evidence that the growth of nerve cells in *Amblystoma* is stimulated by nervous function… Contrary to Tanzi and Cajal, we believe that nerve cells grow by their own intrinsic potentiality, and that nervous mechanisms while growing acquire their specificity in behavior through the primary correlation of their growth processes with receptor and effector functions. "Plasticity" becomes a function of growth. (Coghill 1926, p. 55)

Lashley (1924) was another eminent opponent of theory that learning involves a diminished synaptic resistance along a repeatedly exercised neural path, and that neural paths allied to the trained one can benefit from the training through a process of drainage or induction. His attack on the theory was based on two kinds of evidence: (1) a learned response could be performed by means of neural paths that had never been used during the learning process and were completely separated from the trained path; (2) in higher animals and especially in humans there are many instances of temporary associations or one-trial learning, which by definition do not require any repetition of stimuli and responses. With regard to point 1, Lashley (1924) argued that the interocular transfer of a brightness discrimination in the rat, an animal with a virtually complete crossing of the optic pathways, could not be accounted for by the eventual convergence of inputs from the two eyes onto neurons in the visual cortex, because the training-dependent wearing down of resistance in one afferent path could not affect the other. Since interocular transfer was successful even after bilateral removal of the visual cortex, Lashley tested the possibility of a convergence on common synapses on the output side by pathways differently affected by training in another experiment on a monkey. He found good intermanual transfer of a motor habit to a hand that was not utilized in the learning process because it was temporarily paralyzed by a lesion of the contralateral primary motor cortex. When the paralysis improved and the hand used for learning was in turn paralyzed by damaging the other motor cortex, the untrained hand took over and performed the task successfully. Lashley felt that the drainage theory, according to which the excitation of one neuron through some of its synapses exerts some kind of a suction upon all synapses of that neuron, was ruled out by the lack of anastomoses between neural fibers. Thus, convinced of having obtained evidence that both afferent and efferent paths not utilized during training could sustain a trained habit, he arrived at the following conclusion:

> ……we have evidence of the utilization of neural paths in the performance of a learned reaction which were not activated during the course of learning. In this case the drainage theory is definitely ruled out. (Lashley 1924, p. 373)

Herrick (1926) has appropriately remarked that the cases cited by Lashley in refutation of the theory of the relation of learning to variable synaptic resistance and drainage do not exclude the existence of association neurons that can integrate information over different synapses. That Lashley's interocular transfer argument was indeed flawed has been shown throughout the years by a multitude of "split-brain" experiments proving that interocular transfer of visual discrimination requires the convergence of information from the two eyes onto shared neural centers, either directly or indirectly through the corpus callosum or other interhemispheric connections (Sperry 1961; Berlucchi 1990; Glickstein and Berlucchi 2008). As to his point 2, Lashley was of course right in calling attention to the existence of learning that does not require repetitions, but wrong in implying that such learning does not involve changes in synaptic transmission. New associations and response patterns can be established instantaneously not from the formation of any new path, but rather thanks to a transient brain set, based on expectation or instruction, which facilitates the mental or behavioural outputs required at the moment and inhibits competing responses (Sperry 1953).

Nevertheless Lashley was such a powerful influence in physiological psychology and neuropsychology that between the 1920s and the 1940s his notions of mass action and functional equipotentiality of the cortex tended to outmode orthodox connectionistic models of the central nervous system based on the histology of Cajal and the physiology of Sherrington and Adrian.

This may explain why in those years neural and synaptic plasticity was not a fashionable study subject, with the exception of analyses of functional recovery after brain damage, which however as a rule did not extend to the neuronal level (Bethe 1925, 1931; Bethe and Fischer 1931; Goldstein 1931). This trend was inverted in the late 1940s when Konorski (1948) attributed two fundamental properties to the central nervous system, reactivity and plasticity, and redefined a morphological concept of plasticity according to which :

> Plastic changes would be related to the formation and multiplication of new synaptic junctions between the axon terminals of one nerve cell and the soma (i.e. the body and the dendrites) of the other. (Konorski 1948, p. 89)

The similarity between this statement and those made by McDougall and Pillsbury several decades earlier (see above) is impressive.

A year later Hebb published *The Organization of Behavior* (Hebb 1949), and the history of plasticity, if not of the entire neuroscience, took on a new course. Hebb's work returned to the topic of plasticity frequently during his long career, and contemporary researchers often refer to modifiable neuronal circuits as "Hebbian" in honor of the theoretical contributions he made to the field. Synapses that change as a consequence of simultaneous firing are often referred to as "Hebbian Synapses" (see Cooper, 2005). However, Hebb himself acknowledged that he did not deserve credit for the concept of changes at the synaptic level as the fundamental basis for learning and memory. The letter reproduced in Fig. 1 to one of the authors (H.B.) shows that he was sensitive to being given false credit for initiating the concept (he was interested and happy to hear of Tanzi's previous theoretical explorations into this realm). One of Hebb's recurrent themes in his writings (e.g., Hebb 1958) was that psychologists need to be aware of the most up-to-date neurophysiological research and, likewise, neuroscientists theorizing about the physical basis of plasticity underlying learning and memory need to keep abreast of contemporary psychological and the latest neuropsychological findings. As we continue into the twenty-first century and the level of analysis continues to sharpen, we would do well to remind ourselves of this sage advice.

Turning to more recent efforts to refine our use of the term "neural plasticity", one of the more influential modern-day scientists who have tried to provide a rational framework for the use of the term is Jacques Paillard. In the middle of a very productive scientific career working on the neurophysiology of sensorimotor integration and the

Donald Olding Hebb
RR 1 Chester Basin
Nova Scotia B0J 1K0

August 25 1977

Dear Gus:

You're quite right, I had never heard of Tanzi. Your information is quite interesting in view of the fact that in my view, in 1946 or so when I was drafting O of B, I wasn't proposing anything new. All I considered I was doing was making a more operational statement of a widely held idea that "synaptic resistance" was reduced whenever an impulse "crossed the synapse." Thanks to you, I can credit Tanzi with the idea (you say his hypothesis quickly disappeared from the literature, but it seems possible at least that the idea remained, degraded in the "synaptic resistance" form, and its origin was forgotten so that Tanzi stopped getting any credit for it). I have been amused and irritated both (irritated at the authors' ignorance of the literature of the 20's, 30's and 40's--but mostly the 20's, I suppose) when every now and then someone refers to "Hebb's postulate" or in some other way credits me with something I take no credit for. The bottom two paragraphs of page 60 (O of B) specifically make the point that it was an old idea, repeatedly rejected by critics of learning theory, but now revived in a new physiological context (i.e., the idea was not new).

But that's not too important. What is important is to give Tanzi the credit due to him. Good for you! I hope things go well with you. I'm retired (with one day a week fraternizing at Dalhousie) and thoroughly enjoying it.

Yours,

Don

Fig. 1 In 1977 one of the authors of the present article (HAB), who had graduated in Psychology at McGill University and knew Donald O. Hebb well, wrote to him asking if he knew about Tanzi's old hypothesis of a reduced resistance at exercized synapses. Hebb's reply is reproduced here to show that he was unaware of previous work on the subject of synaptic plasticity, but was nevertheless sure that the view of the brain presented in his book on the organization of behavior did not propose anything particularly new. In Hebb's book *The Organization of Behavior* (1949), a second-hand reference to Cajal on page 230 attributes to Cajal the idea that the change at the synapse in learning is an ameboid outgrowth of the cell, although, as we have seen, Cajal had quickly dismissed the possibility of a neuronal ameboidism. In resurrecting the synaptic hypothesis of learning, Hebb took as his starting neurophysiological point the concept of "optional synaptic transmission" as envisioned by Lorente de Nó (1939). Like Tanzi, Hebb favored the hypothesis of an increase in the efficacy of existing synapses, as opposed to the formation of new synapses

adaptation of the sensory and motor systems to internal and external events, he published in French a reasoned argument that both structure and function need to be carefully considered in deciding whether the term plasticity is applicable to an observed phenomenon (Paillard 1976). His paper has recently been translated into English and deserves the attention that would be expected of a theoretical paper by a researcher of Paillard's stature (Will et al. 2008). In this paper, Paillard pointed out that not every change in the nervous system should be called plastic; in his view, only those that are both structural and functional deserve this term. As Will et al. (2008) point out, Paillard would not have been aware of the possibility of neurogenesis and so all his speculations on structural modifications encompassed changes in neurons that already existed, that is, changes in the size of cell parts and their relationships to other neurons in terms of synaptic numbers and propinquity. Paillard organized his essay by indexing a number of "traps" into which a researcher might fall when considering whether to use the term plasticity. The first trap was semantic.

Plasticity refers to a change in structure in response to an external force and the maintenance of that shape after removal of the force (as opposed to “elasticity”, where the shape returns to its original form after removal of the force). An organism grows and maintains a new shape through maturation, but Paillard points out that this should not be considered an example of plasticity despite its conformity with the basic meaning of the term. The second trap was related to levels of organization. Cells are parts of a larger organization, and that organization may be part of an even larger organization. As Paillard wrote, “Obviously, living organisms [organizations] are composed of a series of hierarchically interlocked substructures, organized in ‘systemic units’. “These systemic units are defined by their “interface structure” with the next higher level and by its “relation structure”, the latter being equivalent to a connectivity network in current terminology. The systemic units are open and are specified by their structure, operating principles and function. When studying the entire organization, as is done when looking at changes in behavior of an animal in a novel environment, the researcher needs to be aware that observed changes can reflect modifications of the structure, the operating principles, or the functions. Assigning the term plasticity to the change without knowing where the modification has occurred leads to problems, according to Paillard. The third problem concerns stability. In order to see change, there must be some degree of stability upon which the change is imposed. Furthermore, the concept of plasticity assumes that a change must itself be stable (and not temporary). This raises the problem of level of analysis: Even in a stable system, there are changes at the molecular level that are ignored. The essence of Paillard’s argument is that the term plasticity is appropriate only when the system achieves a novel function by transforming its internal connectivity network or by changing the elements of which it is made. This seems a reasonable criterion and, if followed, would assure that the term “neuronal plasticity” would be used with less of the “gay abandon” that one of us (Buchtel 1978) bemoaned thirty years ago.

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