The ladder of progress in neuroscience

We have read with great interest the recent article in TINS by Charles G. Gross
1 on the famous debate that opposed Richard Owen and Thomas H. Huxley over the problem of knowing whether or not the human brain can be distinguished from that of other primates on the basis of anatomical criteria. This article gives an excellent description of the strikingly complex and divergent way of thinking of these two major figures of the history of biology, as well as a fairly good idea of the hot and humid Victorian atmosphere within which major battles over the issue of phylogenetic evolution were being fought. We were particularly amused to see that there has been very little evolution in the way scientific papers, grants and issues concerning academic positions are being dealt with since the 19th century, except perhaps for the recent advent of electronic survey methods (for example, citation index), whose abuse might well lead to the progressive extinction of original scientific thought. We regret, however, the use of expressions such as ‘phylogenetic scale’ and ‘infra-human primates’ in Gross’s article. These terms give the unfortunate impression that the author sees vertebrate evolution as representing one linear series of ever increasing complexity, with man at its acme, much like the Scala naturae concept proposed by the French naturalist Buffon in the late 18th century. This simplistic, unilinear concept of phylogeny is responsible for some of the most profound misconceptions surrounding the evolution of the brain. For example, the 19th century, Scala naturae concept of phylogeny led distinguished comparative neurologists, such as James W. Papez, and Cornelius U. Ariëns Kappers, G. Carl Huber and Elisabeth C. Crosby to propose that the telencephalon evolved according to a progressive and unilinear increase in complexity, with the telencephalon of living vertebrates representing the various stages of this hypothetical process. Revised concepts of vertebrate phylogeny, and recent anatomical, chemical and physiological data have forced us to reject such a unilinear view of telencephalic evolution. Yet, this simplistic vision of telencephalic evolution still pervades most modern neurobiology textbooks. Contemporary evolutionary biologists believe that, instead of forming well-ordered scales or ladders, living vertebrates are the results of various distinct branches or radiations (clades) that have evolved largely independently and at different rates for more than 400 million years. Each vertebrate genus is most often viewed as a bush of several related species, not a step on a ladder of progress. Thus, the term ‘bush’, with its inherent luxuriance connotation, appears a much more accurate metaphor for phylogenetic evolution than ‘scale’ or ‘ladder’. Likewise, the term ‘infra-human primates’ can easily be replaced by the expression ‘non-human primates’, which is devoid of evolutionary biases. This terminology would be more in keeping with one of Charles Darwin’s favorite precepts: ‘Never say higher nor lower’.

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Reply
I am deeply appreciative of the generous praise by André Parent and Lili-Naz Hazrati in my recent article in TINS. However, I am rather chagrined that they mistakenly thought that I had made the, indeed serious, error of seeing vertebrate evolution as a linear series of ever increasing complexity with man at its acme because I used the terms ‘phylogenetic scale’ and ‘infra-human primates’. I used these terms as both the protagonists in my article, Owen and Huxley, believed in a phylogenetic scale and in ‘higher’ and ‘lower’ animals, as did virtually all of their contemporaries with the exception of Darwin. It would have been a major ‘Whiggish’ error for me to have recast the debate in sophisticated, modern terminology. Incidentally, Gould, in the very work that Parent and Hazrati cite in support of their position, commonly uses ‘lower’ and ‘higher’ as adjectival modifiers for primates, vertebrates, animals and taxa, and he is certainly a bush, not a ladder, man.

As Parent and Hazrati point out, Darwin was careful not to take a linear, progressive view of evolution; this was another one of the ways in which he was not merely in advance of his contemporaries but was also ahead of many neuroscientists today.
Consistent with Darwin's extreme caution, his most explicit statement of this view, 'It is absurd to talk of one animal being higher than another', remained buried in his unpublished transmutation notebook 'B' of 1837 (Ref. 4). In practice, Darwin, like Gould and myself, often wrote of 'higher' and 'lower' animals, for example in the first four chapter headings of and throughout The Descent of Man, so perhaps he did not find the adjectives quite as 'unfortunate' as Parent and Hazrati do. Or perhaps he was not as concerned about his language being 'P.C.' (phylogenetically correct)

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**Modulatory functions of neurotransmitters in the striatum: ACh/dopamine/NMDA interactions**

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The striatum is viewed as a structure performing fast neurotransmitter-mediated operations through somatotopically organized projections to medium-size spiny neurons. This view is contrasted with another view that depicts the striatum as a site of diverse modulatory influences mediated by cholinergic interneurons and by dopamine and N-methyl-d-aspartate receptors. These two operational and organizational modes both contribute, through their mutual interaction, to the function of basal ganglia. Detailed knowledge of the neural mechanisms by which such interactions take place and are expressed in behaviour, can provide new insight into the pathophysiology and new clues for therapy of disorders of basal ganglia.

The basal ganglia are a conspicuous complex of nuclei thought to work in strict synergy with the cerebral cortex, and subserve motor as well as motivational functions. The core, and the primary site, of functional interactions in the basal ganglia is the caudate–putamen (CPu) and its main cell type, the medium-size spiny neuron. These neurons receive massive input from the cerebral cortex, thalamus (intranlaminar nuclei) and mesencephalon (substantia nigra pars compacta and ventral tegmental area) and provide direct projections onto major basal ganglia output areas such as the globus pallidus and the substantia nigra pars reticulata. Medium-size spiny neurons, by way of intrastriatal collaterals, also provide a major proportion of intrinsic striatal input, and can thus be regarded as the fundamental cell module of the CPus.

The operations performed by corticostriatal projections and medium-size spiny neurons are regarded to be of a fast-neurotransmitter-like nature. Thus, cortically elicited fast EPSPs recorded from medium-size spiny neurons are mediated by glutamatergic receptors of the AMPA (d,L-α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) subtype; in turn, these neurons use GABA as their fast inhibitory transmitter. However, other striatal neurons, such as the cholinergic interneurons, the dopaminergic projecions and the excitatory afferents to N-methyl-d-aspartate (NMDA) receptors are the basis for operations that we will refer to as 'modulatory' to distinguish them from 'fast' neurotransmitter-like actions.

Modulatory influences act indirectly by setting the excitability of the neuron to incoming phasic input mediated by fast neurotransmitter actions. Modulatory influences have relatively long kinetics of activation/desensitization, being related to modulation of voltage-operated ion channels as in the case of muscarinic and dopamine (DA) receptors or to operation of voltage-gated ion channels as in the case of NMDA receptors. Modulatory influences on neuronal excitability might not even be labelled as facilitatory (+) or inhibitory (−), their actual sign depending on the membrane potential. Modulatory actions can have long-lasting transcriptional effects that might be the basis for adaptive and plastic changes.

The CPus are one of the areas of the brain rich in such modulatory receptors as muscarinic, DA, NMDA, substance P, somatostatin and neuropeptide receptors. Medium-size spiny neurons use, in addition to GABA, typical neuromodulators such as opioid peptides and substance P as cotransmitters.

Organization and function of striatal modulatory influences

A central role in the modulatory operations taking place in the striatum is played by acetylcholine (ACh) neurons. Acetylcholine neurons, often indicated as large aspyne neurons, account for 1–2% of the striatal neuronal population. In all species examined, they are among the largest neurons of the striatum both for the size of the perikaryon (about 30 μm in its longest dimension) and the area of distribution of the dendritic tree (up to 0.5 mm²). Striatal ACh neurons are interneurons, although a subpopulation of them also projects to neocortex.

Striatal ACh neurons receive three major synaptic inputs: (1) from intrinsic medium-size spiny neurons