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TINS special issue: The Neural Substrates of Cognition
The neural substrates of cognition

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Introduction

The reviews in this issue of *TINS* represent a particularly interesting subset of formal presentations at a meeting held last year in Madrid, Spain. This meeting was sponsored by the Juan March Foundation, was organized by myself, Adam Sillito and Javier Cudeiro, and was entitled 'The Neural Substrates of Cognition'. Further details of the meeting, including a list of speakers, can be found at http://www.udc.es/dep/medicina/neurocom_arch/juanmarch.htm. Sadly, The Juan March Foundation, long a sponsor of such meetings, announced that this would be their last meeting on a topic of neuroscience.

The rationale for the meeting was based on dramatic, recent advances in our understanding of neuronal substrates, mostly at the cortical level, for various cognitive processes, including plasticity and attention. The meeting was characterized by excellent and provocative presentations and lively discussions, which are hard to reproduce in a journal format. Nonetheless, the papers presented here cover a subset of the topics presented and discussed, and do a good job of representing the flavor of the meeting.

Feedback projections

Many accounts of the functional organization of the brain view this as a simple stream of information flowing in one direction. This starts with sensory transduction at the periphery, proceeds to sensory processing stages, then to sensorimotor integration, and finally to motor areas for a final output to various muscle groups and other effectors. This unidirectional, feedforward model, which is all that most textbook accounts of the CNS consider, ignores functional pathways going in the other direction: feedback pathways. This is despite the fact that feedback pathways often and perhaps typically are larger than their feedforward counterparts. For instance (as noted by Cudeiro and Sillito in this issue [1]) the feedback from the visual cortex to the lateral geniculate nucleus (LGN) is at least an order of magnitude larger in terms of axon number than is the feedforward, geniculocortical projection. Feedback pathways involving the cortex have long been known about, but their functions have remained enigmatic. Two papers in this issue explore this topic: that by Cudeiro and Sillito [1], and another by Sillito et al. [2].

Cudeiro and Sillito [1] concentrate on feedback from cortical layer 6 to the LGN, a feedback that runs with the geniculocortical pathway in the other direction. They summarize the many past attempts to make sense of this pathway, which has led to a large but somewhat mystifying smorgasbord of suggestions. They also describe their own experiments that help to shed more light on the problem; these experiments show how this feedback, operating via metabotropic glutamate receptors, influences certain spatiotemporal aspects of geniculate neuronal receptive fields. They also review studies of other modulatory effects on geniculate cells, effects involving the release of nitric oxide from axon terminals of brainstem origin. A main point they make is that the corticogeniculate feedback pathway is modulatory and serves to influence retinogeniculate transmission rather than to drive relay cells strongly and directly. They state that '…it needs to be emphasized that the facilitatory influences under physiological conditions are expressed in LGN cells as a modulation of their response to retinal input and that the feedback does not inject extra spikes into the LGN cell response.' [1].

Sillito et al. [2] take a somewhat more expansive view of feedback in the visual system, reviewing pathways that include both the aforementioned corticogeniculate feedback and a pathway from the higher-order extrastriate area known as MT or V5 back to V1. They point out the strategic position of a group of layer 6 cells in this feedback circuitry. These not only give rise to the corticogeniculate projection, but also have collaterals that project to layer 4 and thus can influence the geniculocortical input. In fact, the authors refer to these layer 6 cells as 'gatekeeper' neurons. Finally, they point out that the feedback from MT to V1 targets these very same layer 6 cells. This means that MT can indirectly influence a peripheral site of visual processing, namely the LGN, and Sillito et al. offer evidence that this indeed occurs.

There has been one major problem in deciphering the function of these feedback pathways, a problem summarized in Figure 1. This is clearly mentioned by Cudeiro and Sillito [1] and is emphasized here because it is often overlooked and is perhaps a general feature of feedback pathways. This relates to the facts that these pathways are often highly topographic in organization and involve both inhibitory and excitatory elements. An important point is that corticogeniculate axons from layer 6 (and indeed all such corticothalamic axons from layer 6) target not only relay cells but also local (GABAergic) inhibitory cells, which include cells of the thalamic reticular nucleus and local interneurons. Figure 1(a) shows the usual depiction of this circuit, which is organized as a classic feedforward inhibitory pathway. Here, activation of a corticogeniculate axon leads to both monosynaptic excitation and disynaptic inhibition of the relay cell. Figure 1(b) represents a very different picture, because of details in the organization. Here, activation of a corticogeniculate axon leads to monosynaptic excitation of some

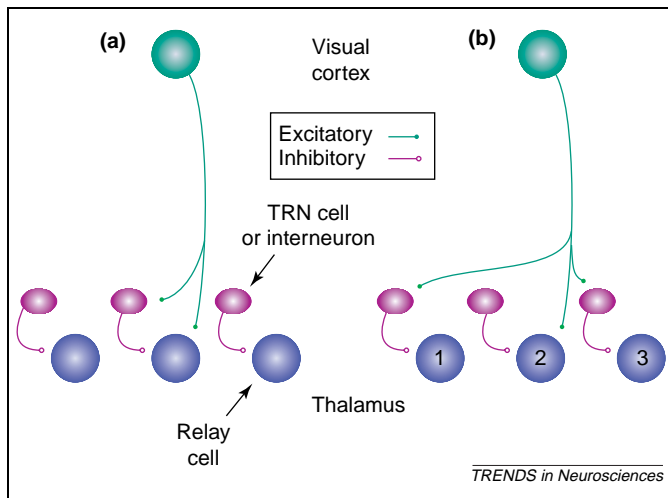*Corresponding author:* Sherman, S.M. (msherman@bsd.uchicago.edu).

Figure 1. Two possible patterns for corticothalamic projection from layer 6 to local GABAergic inhibitory cells (interneurons and cells of the thalamic reticular nucleus, TRN) and relay cells. **(a)** Simple excitation and feedforward inhibition of a single relay cell. **(b)** A more complicated pattern, in which activation of a cortical axon can excite some relay cells directly and inhibit others through activation of reticular cells. For further details, see text.

relay cells (represented by cell number 2) and disynaptic inhibition of others (cells 1 and 3). These circuits depicted by Figure 1 are very different functionally, and evidence for both exists, perhaps reflecting considerable heterogeneity in the circuit (reviewed in Ref. [3]).

The difference should be emphasized to underscore the importance of topography. Attempts to understand feedback pathways often involve large-scale removal or inactivation of the source, and inspection of Figure 1 should reveal that such large-scale interruptions of the cortical source would have the same overall effect on both of the illustrated circuits; furthermore, such interruption would remove both excitation and inhibition onto relay cells, leading to a net effect of very little change to membrane potential. In other words, productive investigation of this feedback pathway might require topographic precision of the type rarely employed, and this might be a general feature for feedback pathways in the CNS.

Attentional mechanisms

Attentional processes are of obvious importance in our ability to perceive and recognize our surroundings. Maunsell and Treue [4] review recent findings regarding the neuronal substrates of attention in areas of visual cortex. A metaphor for attention is a spotlight, as if somehow one manages to direct and focus a spotlight on a particular feature of the environment. Maunsell and Treue point out that there are two kinds of attention: space-based and feature-based. Space-based attention refers to the ability to spotlight a particular, limited region of visual space and attend to objects therein, whereas feature-based attention refers to the ability to pick out an array of objects distributed widely in the visual field, based on a unifying parameter such as color or shape.

Maunsell and Treue note that studies of space-based attention have a longer history than those of feature-based attention and that the neuronal correlates are better documented [4]. In particular, in many regions of visual cortex, one can record cells that show an elevated response

to a visual target, as if that target had increased contrast, whenever that target falls within the attended region of visual space. One question addressed by Maunsell and Treue is the nature of neuronal correlates of feature-based attention, and the answer seems to be a similar process: neurons respond better to a stimulus that involves an attended feature, as if that feature had elevated physical contrast. They go on to argue that combining these two types of attentional mechanism enables visual areas to set up a 'saliency' map that incorporates attended parameters, both space-based and feature-based. Questions still unresolved include how these increased neuronal responses are established, where in the visual system attentional mechanisms are initiated, and how far peripherally in the system are they discernable.

Plasticity

Two of the papers in this issue, by Majewska and Sur [5] and by Delgado-García and Gruart [6], deal with issues of plasticity in neuronal structures. Majewska and Sur concentrate on the sort of plasticity seen during development and in response to changes in cellular activity levels, and Delgado-García and Gruart focus on a widely studied model of motor learning.

Majewska and Sur start by reviewing the literature on the development of cortical structures [5]. They note that such development ultimately reflects the nature–nurture issue, meaning that the formation and maturation of pathways is governed by a mixture of intrinsic properties, which depend largely on molecular cues, and environmental properties, which determine activity levels evoked in afferents. Of particular interest is new evidence regarding the environmental properties: exciting, 'gee-whiz' technology has enabled the visualization of single dendritic spines on cortical cells, and of the reshaping and/or turnover of these spines as a function of changes in activity of their inputs. These experiments not only provide new insights into the ongoing cortical substrates of plasticity that underlie such phenomena as development, learning and memory, but also enable the investigator to watch plasticity happening in real time.

In addition, Majewska and Sur describe experiments in which the inputs to auditory thalamus are switched neonatally, from the normal inferior collicular input that carries auditory signals to retinal input that carries, of course, visual input, meaning that any information relayed to auditory cortex is from visual sources. The surprising result is that the auditory cortex contains many neurons that have receptive fields normally associated with visual cortex, including visual responsiveness with the property of orientation selectivity. The authors are also quick to point out that 'Rewired auditory cortex takes on many properties of visual cortex but also retains some of its original network properties.' [5] One fascinating conclusion supported by these studies relates to the possibility that thalamic input can be so powerful in determining cortical properties: if true for auditory cortex, might this be extrapolated for all cortical areas? This would imply that one should look to the nature of thalamic inputs rather than corticocortical inputs to understand

the functional organization of cortical hierarchies, an issue Ray Guillery and I have discussed elsewhere [3].

Delgado-García and Gruart review work concerning a different example of plasticity, involving eye-blink conditioning [6]. This model has a long history, and there has been much debate and controversy regarding the neuronal site for the plasticity underlying this form of learning. Much of this has focused on the cerebellum, and the idea has been forwarded that the hippocampus also has a role. However, Delgado-García and Gruart make a compelling case that this is an oversimplification, raising the plausible objection that the cerebellum is not much involved in either the actual acquisition or the retention of the learned behavior, and that the hippocampus is involved in the acquisition but not in the retention. Instead, the authors propose that a much more complex circuit is involved, including a number of other forebrain structures. The somewhat sobering conclusion is that the search for the engram, at least for this well-studied model of learning and memory, will be more arduous than once thought.

Genetic classification of neurons

Nelson et al. provide the final paper in this issue, describing ongoing studies aiming to bring modern molecular techniques to study of the cortex [7]. They argue that two huge problems are ripe for solving by these approaches. One is a proper classification of cortical neurons, and the other is the opportunity to manipulate these cells by molecular techniques as an approach for studying their functional properties.

The problem for classification is huge. When one initiates a study of an unexplored brain region, one of the first questions to resolve is the number of distinct neuronal types involved. In this regard, the cortex remains a mystery. Although anatomists have described a number of morphological types, such as stellate and pyramidal cells, and physiologists have likewise done so, examples being simple and complex cells in visual cortex, the cortex still lacks a complete neuronal classification. How many distinct types of pyramidal, simple or whatever cell are there, and what other distinct classes exist? Nelson et al. describe the exciting possibility that new techniques will permit the classification of neurons based on molecular markers related to distinctive patterns of gene expression. This essentially involves determining the unique genetic fingerprints of each distinctive neuronal type.

Why bother? As Nelson et al. point out, 'The importance lies less in the biological insights implicit in the classification than in the enabling of multiple investigators to refer unambiguously to the same neurons.' [7] The ability of different workers to refer to the same neurons is of obvious importance, and this not only applies to workers interested in a particular area, such as monkey V1, but also can be extended to identifying homologous cell types in other cortical areas and in other species. This is particularly important because much cellular and circuit work is done in one set of species (mostly rodents), whereas work more related to more integrative issues and behavioral correlates is done in other species (often monkeys), leaving a huge gap in a comprehensive understanding of brain function. For example, being able to specify that a neuronal type recorded in cortical area MT of a behaving monkey is the same cell studied *in vitro* in a rat cortical area would be of obvious value.

Nelson et al. seem to play down the importance of '…the biological insights implicit in the classification…' [7], but I believe this is arguable. Such a classification not only provides insights into development and functional organization of any cortical area but also, by enabling the same class of neuron to be identified in different cortical areas and species, provides important clues regarding the evolution of new areas and the conformity of cortical areas to one or a few plans. In other words, has the whole cortex in all mammals evolved from only one or very few circuits, or is the number very large? A first answer to this question will involve determining the distributions of the various neuronal classes among cortical areas and species.

The final point made by Nelson et al. is self-evident and thus only briefly outlined here. Identifying neuronal classes using unique patterns of gene expression should mean that modern genetic techniques can be used to target genes and their phenotypes for manipulation, thereby altering neuronal function in controlled ways. Obviously, observing how complex circuits function as a consequence of subtly manipulating their neuronal elements offers the potential for great insight into understanding how these neurons and circuits function.

Concluding remarks

The obvious conclusion from a consideration of the papers in this issue, and others delivered and discussed at the Juan March meeting in Madrid last year, is that we are at a very exciting time in neuroscience. Powerful new techniques have been developed, and these offer the prospect of a revolutionary new understanding of the functioning of complex neuronal circuits, perhaps best exemplified by the cortex. In particular, there have been dramatic advances involving the nature and significance of ubiquitous feedback pathways throughout the CNS, of mechanisms underlying attention, of the nature of plasticity involved in development and learning, and of new prospects for neuronal classification and manipulation. These are indeed exciting times to be interested in the brain.

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