Clinical–ethical implications and applications

Benedetti Fabrizio

in Placebo Effects: 2nd Edition: Understanding the mechanisms in health and disease

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The recent neurobiological advances in placebo research can stimulate the development of new clinical trial designs for the validation of new treatments, and lead to an uncertainty principle, whereby it is not possible to fully understand the action of a therapeutic agent. One of the main implications of the recent advances of placebo research is the possibility to induce drug-like effects without drugs, thus opening up the possibility to reduce drug intake. As social stimuli may activate the same biochemical and receptorial pathways onto which drugs act, several cognitive and affective factors can eventually modulate the action of drugs.

Emotion, motivation, reward value, pleasure, and their mechanisms

Edmund T. Rolls

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Emotions can be defined as states elicited by instrumental reinforcers (rewards and punishers), which are the goals for action. Motivational states can be defined as states in which an instrumental reinforcer is the goal for action. The principle of operation is that genes can specify goals for actions that are in the selfish interests of the genes. By specifying the rewards (e.g. a sweet taste) and punishers (e.g.
painful touch), the specification is simpler than trying to specify detailed
behavioural responses to stimuli, and allows much greater flexibility
of the actions, which can be learned instead of pre-specified by the
genesis. The principle of operation of the cortical systems in primates is
that there is a first tier of processing that computes what the stimulus
is independently of its reward value. This is adaptive, for it enables
objects to be seen, tasted, etc and their locations remembered even
when they are not rewarding, for example when hunger is not present.
The ventral cortical systems perform this what computation for taste
(the insular taste cortex), olfaction (the pyriform cortex), vision (the
inferior temporal cortex), and hearing. A second tier of processing,
involving the amygdala and orbitofrontal cortex, then computes the
reward value of the stimuli, and this is used as an input to other
systems, including the anterior cingulate cortex which is important
in instrumental learning by enabling the outcome of the action (the
reward obtained or not) to be associated with the action; the stratum
(for habits, that is well-learned behavioural responses to a stimulus
that has been rewarded previously but which now are performed as a
stimulus-response association that is no longer under the direct control
of the goal or reward value); and autonomic outputs including via the
visceral insula and hypothalamus. The separation or ‘what’ from reward
systems is much less clear in rodents, with changes in reward value
influencing sensory processing in early stages of processing. In rodents
there is much less dominance of cortical processing to compute ‘what’
representations before and separate from reward evaluation, in that
for example in rodents there is a pre-cortical pontine taste area that
distributes taste information independently of cortical processing to brain
systems such as the amygdala and hypothalamus. The orbitofrontal
cortex, which develops considerably in primates, enables, with its well-
developed recurrent collateral connections that are the hallmark of the
cortex, to show very rapid rule-based changes in responses to reinforcers
to enable behaviour to change very rapidly when the reinforcers being
received change. This is very important is many types of behaviour,
including social behaviour, where great sensitivity to reinforcers including
punishers can be adaptive. The amygdala has been present from
much earlier in evolution, and without the highly developed recurrent
collateral system of cortex, is less able to compute rule-based changes of
behaviour when reinforcement contingencies change. The orbitofrontal
cortex implements multimodal convergence of visual, olfactory, taste,
 somatosensory, and auditory inputs from the ‘what’ cortical systems, to
produce a value representation of a stimulus, which can then be used as
the input to ‘neuroeconomic’ decision systems between different ‘value’
stimuli in a third cortical tier of processing in more anterior regions such
as the ventromedial prefrontal cortex and medial prefrontal cortex area
10. The evidence is that decisions are made in this third tier of cortical
processing for emotion and motivation by cortical attractor decision-making networks. In addition to this system for emotion, humans and perhaps some other animals have a reasoning system that can evaluate outcomes that may be in the long-term interests of the individual, such as not to eat very rewarding and pleasant foods that might be unhealthy. This reasoning, explicit system, may take decisions that are sometimes in conflict with the gene-goal-specified emotional system, as described in Chapter 22, and this makes the whole operation of the system complex, with its two emotional systems, and the noise-influenced decision-making within and between them described in Chapter 5.

Inferring Consciousness Out There
Marcello Massimini and Giulio Tononi

This chapter describes a preliminary exploration in search of criteria for consciousness in the biological and physical world beyond the human skull, including dolphins, octopuses, parrots, bees, and computers. It argues that assessing the complexity of behavior and measuring the size of the brain may not provide a reliable estimate in animals. Likewise, it explains why some artificial systems, such as feed-forward deep learning networks, that are composed by many elements and that perform incredible feats, may not be conscious. Finally, it suggests that in the future precise empirical measurements of information integration may offer a valid tool to infer on the capacity of consciousness in non-human entities.

A general model of cortical function: concluding considerations
O.D. Creutzfeldt

The function of the cerebral cortex within the framework of a general brain model cannot be reduced to a simple formula. Any general
consideration of cortical function necessarily depends on the concept of brain function itself. From a behavioural-ethological point of view the brain may be understood as being a control system that transforms into adequate behaviour, signals from the outside world as received through the sense organs, and data about the state of one's own body as monitored by enteroreceptors and chemosensors. ‘Adequate’ in this model means that the needs of the organism are satisfied by taking into account the environmental and social conditions, so that the organism can survive in a given environment. The central nervous system could thus be considered as being an information processing control system and its individual elements and subsystems, including those of the cerebral cortex, are dealing with particular performances of the whole brain in the interest of survival of the individual and the species. In technical terms this control system could be considered as being a distributed system, where the various functions are represented and performed (or completed) by separate subsystems in parallel.

Hierarchical organization

Edmund T. Rolls

in Cerebral Cortex: Principles of Operation

Hierarchical cortical organization is found in all sensory systems, in the reward system, and in the memory systems. Adjacent cortical areas in the hierarchy are connected by strong forward connections, and weaker backprojections which have synapses in cortical layer 1. There is convergence from cortical area to cortical area, in that neurons in a cortical area receive inputs from a limited region topologically of the preceding cortical area. This enables neurons to operate with the number of synapses from the preceding cortical area received by a neuron limited to in the order of 10,000 synapses. This is a major cortical principle of operation, for if each processing system consisted of only an input and an output cortical area, any neuron in the output area would need to receive the biologically implausible number of tens of millions of synapses to cover the whole space of the input cortical area. The convergence from cortical area to cortical area is such that after approximately at most four areas or stages of cortical processing, the convergence is sufficient to enable a single neuron at the top of the hierarchy to receive input from anywhere in the first cortical area, as illustrated in Fig. 2.1. A consequence of this connectivity is that within a neocortical area, the computation is local. Consistent with this, the
recurrent collaterals of pyramidal cells spread mainly with a region of 1–3 mm, and the inhibitory neurons operate within a similar extent of neocortex. One reason for the number of areas in a hierarchy being limited to approximately a maximum of four is that this keeps the computation time within reasonable limits, of approximately 20 ms per cortical area for the computation and information transmission, which is sufficient for a cortical area to be influenced by its recurrent collaterals and to fall towards a basin of attraction that reflects the previously learned constraints implemented in the strengths of the local recurrent collaterals. (Sections B.2.6 and B.3.3.5). Topography is often present associated with this connectivity, though in higher cortical areas the maps can become highly fragmented and local (as described in Section B.4.6), because the dimensionality of what is being represented is high (that is, there are many types of item, e.g. object, being represented). The cortico-cortical backprojections are not sufficiently strong to make neurons at earlier stages in the hierarchy have the same responses as at higher stages. Face selective neurons with receptive fields that can be up to 70º are not found in the primary visual cortex, where the neurons respond to features such as bars and edges and have receptive fields in the order of 1º (Chapter 25). Instead, the cortical backprojections are used for gentle influences on earlier cortical stages, such as top-down attention, and memory recall if there is not a strong bottom-up input. Each cortical hierarchy thus operates computationally with a feedforward style of computation, in which new representations are built at each succeeding stage, in a divide and conquer approach to computation. An advantage of this hierarchical organisation is that the same or a similar architecture and process can be repeated a number of times, which simplifies the evolution of the neocortex, which can proceed by adding another stage on to the top of an existing hierarchy. Another advantage is that this simplifies the genetic specification of the cortex, in that once a useful and stable cortical network in one area has evolved, it is safest and quickest in evolution to add something with a similar specification as the next stage (Chapter 19). Another advantage is that by dividing a computation into successive stages, each stage can perform a much simpler computation. Another advantage is that within any one stage of the hierarchy performing a particular computation, the information that needs to be exchanged between the nearby neurons is of the same type (e.g. about the presence or not of a nearby edge in vision). That facilitates cortical design, in that generic connectivity between nearby neurons can be specified with self-organization of neuronal selectivity during development. This obviates the need for a neuron with a particular type of response to the input to have connections with another neuron with another particular type of response, which would be impossible for genetic specification, given that we have only in the order of 25,000 genes. Issues of what the genes may specify to implement
the design of any one cortical area are described in Chapter 19. The localization of function that is present can be viewed partly in this way, and has the effect of minimizing the average length of the connections between neurons, which is very important in keeping brain size down (see further Chapter 3 and Sections B.4.6 and D.4). Another advantage and property of hierarchical cortical organization is that there are major connections between adjacent areas in the hierarchy, which again simplifies the genetic specification of cortical design, in that a neuron does not need to have its connectivity specified to one of a myriad of cortical areas. In primates (including humans), the identity of stimuli is computed first (‘what representations’), independently of reward value, and then at a later stage reward value is computed, and then at a later stages decisions between stimuli of different value are made. This independence of perceptual from ‘value’ processing is advantageous, for then information is available to other brain systems, including memory and language systems, even if a stimulus is not currently rewarding. This independence of perceptual from reward processing appears to be much less in rodents.

CRF
Jay Schulkin

in The CRF Signal: Uncovering an Information Molecule

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Chapter 5 explains how excessive fear is tied to anxiety disorders, and vulnerability to the breakdown of mental and physical health. CRF in the brain is tied to these events. CRF, for instance, may be constrained by the neurotransmitter GABA in key regions of the forebrain and is mobilized by brainstem catecholaminergic neurons that are critical in coping with and adapting to everyday life; and of course, one is less able to do so when these information molecules are compromised by genetic predispositions and social duress. One hypothesis about CRF and the brain is that at least two forebrain sites are differentially involved in regulating both adaptive fear and deleterious chronic anxiety. There are great varieties of events that can cause fear in individuals: anything from downsizing at work to acts of terrorism and crime.
Introduction
Edmund T. Rolls

in Cerebral Cortex: Principles of Operation

Introductory, background, information about the following aspects of cortical function are provided as follows: Neurons, synapses, and the synaptic modification used in learning (which is extended in Chapter 9). The types of coding of information by neuronal responses, including local (grandmother-cell), distributed, and sparse distributed, which is extended in Chapter 8 and Appendix C. An introduction to pattern association networks, autoassociation networks with attractor properties, and competitive networks. A description of some major processing pathways in the cerebral cortex, which is developed for two key systems, the episodic memory system in Chapter 4 and the visual object recognition system in Chapter 25. These two Chapters illustrate how many of the principles are combined to produce what are essentially theories of how the episodic memory and visual object recognition cortical systems operate. A description of some of the properties of cortical neuronal architecture, which is extended in Section 18.2.

The traditional concept of placebo
Benedetti Fabrizio

in Placebo Effects: 2nd Edition: Understanding the mechanisms in health and disease

The history of medicine is basically the history of placebos, as most medical interventions were nothing but placebos, i.e., inert. Over the centuries, doctors started using sham treatments to see whether the clinical improvements were attributable to patients’ imagination and/or spontaneous remissions. Today placebos are widely used in clinical research to validate the efficacy of a therapy as well as in clinical practice to please and to placate anxious patients. The placebo effect represents a good example of how a mental activity may affect several physiological functions, thus it is an excellent model to study the mind–body interaction. The nocebo effect, which is opposite to the placebo
effect, is also a good model to understand the interaction between mind and body.

**Studying neuronal function using the Drosophila genetic system**

J. Douglas Armstrong and Stephen F. Goodwin

in *Molecular Biology of the Neuron*

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This chapter discusses the use of Drosophila as a system for studying neuroscience across multiple levels. The simple organism has some distinct advantages over many others yet at the molecular and genetic level, the nervous system shows a high degree of evolutionary conservation. There are a few technical limitations, largely in neurophysiological techniques but these are rapidly being addressed and recent transgenic developments have the potential to more than address the balance.

**Amnesia: Learning about Memory from Memory Loss**

Howard Eichenbaum

in *The Cognitive Neuroscience of Memory: An Introduction*

Published in print: 2011  Published Online: May 2012


This chapter reviews evidence from studies of amnesia in humans. It provides a detailed overview of the case of H. M., to provide a closer perspective on the nature of his amnesia. H. M. was an epileptic for several years when, in an effort to alleviate his disorder, his medial temporal lobe area was removed. The surgery did indeed reduce the frequency of his seizures considerably — however, he had become severely amnesic. The chapter then explores the distinction between declarative and procedural memory, using several examples from the experimental literature on amnesia.
Linking dendritic processing to computation and behavior in invertebrates
Richard B. Dewell and Fabrizio Gabbiani

in Dendrites

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This chapter summarizes results obtained in invertebrate preparations on the dendritic processing of neural information. Connecting the cellular characteristics of neurons to the information processed by neural networks can be extremely difficult, but ultimately must be accomplished to build a mechanistic understanding of the nervous system. In invertebrates there has been less investigation specifically into dendritic function, but this research is generally well grounded in the ecological and behavioral context of the neural processing. Thus, invertebrate model systems have proven favorable to connect the function of dendrites to neuronal networks and to behavioral input-output relations, in part because of the compactness of their nervous systems. A series of vignettes illustrate recent research on invertebrate dendrites and their roles in neural function. While the ecology of the animals and the neural morphology might differ from those of vertebrates, the dendritic mechanisms and neural challenges are identical to those of other animals. Invertebrate models have much to teach us about how the nervous system functions, including in vertebrates.