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Predictive Coding in the Brain: It's Not Just About Afferents and Efferents — The Brain Is at Work

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ABSTRACT: There are multiple brain functions, including sensory, motor, cognitive, perceptual, memory-related, chemosensory, behavioral, and salutogenic processes. However, beyond establishing afferent and efferent functional pathways, the brain actively compares predictions. This requires specialized neuronal populations involved in both motor and sensory domains to process information prospectively, functioning as a neurobiological processor that generates inferences. The aim of the present work is to offer a perspective on brain function based on its predictive capacity.

KEY WORDS: brain, predictive coding, neuroanatomy.

INTRODUCTION

"If our brain were so simple that we could understand it, we would be so simple that we couldn't". Emerson M. Pugh

During the mid-20th century, many non-invasive tools were used to localize human brain functions through brain mapping (Savoy, 2002), including those related to sensorimotor aspects (Quairiaux *et al*., 2011), cognitive functions, which are well developed in the human brain (Rubia, 2000), perceptual function, action programming, memory tracking (Lopes da Silva, 2002), chemosensation, a fundamental aspect for identifying potential food sources, threats such as predators, and mediating social and sexual interactions (Rubenstein & Rakic, 2013), behavior, and salutogenic function (Smith, 2002). It has also been proposed that the properties of neurons composing our brain form the basis for motor synchronization in motor coordination (Llinás, 2008), among other brain functions (Raichle, 2010). We focus here on predictive function, which allows animals (Feldman Barrett, 2021) with developed nervous systems, including humans, to significantly increase their chances of obtaining food and surviving various threats posed by their environment, whether wild or urban. This predictive ability clearly has evolutionary utility, as it allows for anticipation of an outcome and the initiation of a motor response before missing the opportunity to feed or suffering unnecessary and avoidable bodily injury (Llinás, 2008) in the pursuit of food or in defensive actions against competitors or predators. As it processes information, the brain shapes its entire operation, specifying neuronal connectivity states that generate sensory and motor operations not as separate elements but as integrated ones, as well as more complex emergent properties such as cognition (Llinás, 2008; Brydevall *et al*., 2018).

The mechanism underlying predictive coding in the human brain, at least (Fig. 1), is the prediction error, which allows comparing predicted outcomes with those that occur in the external world. Interestingly, similar mechanisms operate through dopaminergic neuroglial circuits to optimize learning and memory. Although prediction was initially considered fundamental to motor activity, increasing evidence indicates that it is also essential in the processing of sensory information (Llinás, 2008; Koster-Hale *et al*., 2013).

The central element for understanding how the brain performs predictive coding of sensory information is the prediction error, during which neural signals processed by the brain transmit not only information about the perceived stimulus, but also about the difference between the observed and anticipated stimulus, which is the product of neural networks dedicated to sensory prediction (Koster-Hale *et al*.,

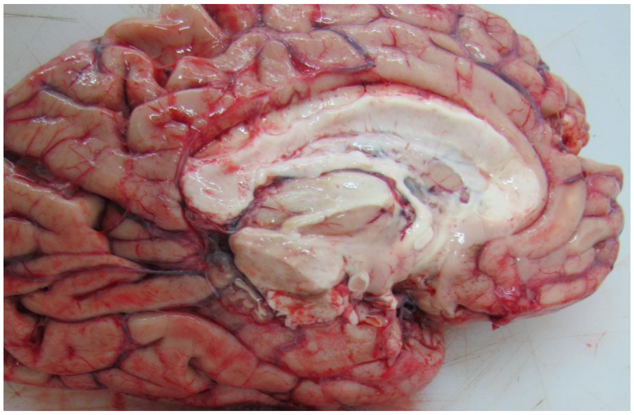

Fig. 1. Left hemisphere of a human being seen at the level of the corpus callosum; the section includes diencephalic structures and part of the midbrain.

2013; Brydevall *et al*., 2018). This predictive coding of information has been observed in occipital cortical neurons involved in visual information processing (Rao & Ballard, 1999; Clark, 2013), in which connections from a higher-order visual cortical area, understood as an association area, generate predictions about the activity of neurons at a lower level, such as the primary visual area. This is achieved through cortico-cortical association synapses, whereby feedback connections from neurons processing sensory information allow the system to determine the difference between what was predicted and what actually occurs in real time, which corresponds to the external stimulus (Rao & Ballard, 1999).

Unlike the dopaminergic reward prediction error system, which involves a single neuronal population, in purely sensory areas such as the occipital cortex, not only are sensory neurons needed to detect the stimulus and respond to the prediction error, but also a separate neuronal group is required to generate the prediction, which is generally located in a different cortical area (Rao & Ballard, 1999; DiCarlo *et al*., 2012) of a given brain gyrus or lobe. This involves short and/or long arc-like neuro-neuronal chains along with their respective glial cells. Evidence has shown that a sensory system for predictive neuronal coding requires at least three types of neurons: a group of prediction neurons, also referred to as representation neurons, a second group that responds to external stimuli, and a third group that calculates the deviation in predictions, in other words, the prediction error-detecting neurons (Rao & Ballard, 1999; Summerfield *et al*., 2008; Barrett & Simmons, 2015).

This processing operates via an inhibitory mechanism in sensory neurons, leading to repetition suppression in response to expected stimuli, while unexpected stimuli result in disinhibition of these error neurons, causing neuronal activation. Therefore, prediction error is greater when the stimulus is unexpected and elicits a strong response in the "error" neurons, those that initially process the external stimulus. This type of cortical neural circuit engages in multiple feedback connections and compares the prediction to the actual stimulus, serving as an essential process for efficient perception (Rao & Ballard, 1999; Summerfield *et al*., 2008; Barrett & Simmons, 2015).

Consistent with the diverse neuro-neuronal interconnectivity in predictive processing, a hierarchy has been demonstrated among the visual information processing areas (Rao & Ballard, 1999), which governs both prediction generation and the determination of prediction error by the neurons exposed to external stimuli. The ability to detect this difference has been linked to abstraction capacity and object recognition in the parietal and inferior temporal cortices (DiCarlo *et al*., 2012). Furthermore, the capacity of error neurons to increase their response to unexpected stimuli has been associated with the ability to recognize objects and novel stimuli appearing in the visual field (DiCarlo *et al*., 2012; Barrett & Simmons, 2015), which reflects predictive capability.

This processing requires excitatory neuronal groups using glutamate (Traynelis *et al*., 2010) or inhibitory neurons using GABA (Roth & Draguhn, 2012), specifically granular neurons that receive thalamic afferents with varying degrees of intensity (Summerfield *et al*., 2008). In the first case, thalamo-cortical transmission is primarily directed toward layer IV, where these neurons, receiving the real stimulus, are located with respect to the prediction (Rao & Ballard, 1999; Barrett & Simmons, 2015). When the received information does not match the prediction, previously considered unlikely, GABAergic neurons are inactivated, and granular cells in layer IV are activated in a specific pattern that emulates the external world. This mismatch negativity occurring in the visual cortex is evidence that the brain operates with a predictive coding system for perception (DiCarlo *et al*., 2012; Summerfield *et al*., 2008; Barrett & Simmons, 2015).

Thus, the difference between the observed and predicted signal is processed through an inhibitory neural architecture. However, glutamate also plays a key role by acting on NMDA receptors, allowing transmission of the sensory stimulus from the thalamus to layer IV of the cortex and facilitating connections with memory systems for learning. This enables predictive coding to be adjusted based on stimuli from the external world. In this way, predictions in the brain evolve or adapt according to individual experience, and in this regard, the circuit is not exclusively inhibitory (Wacongne *et al*., 2012). It could be said that neurons in the visual cortex behave as residual error detectors, establishing the difference between a statistical prediction based on an internal model and the sensory perception of the real world (Barrett & Simmons, 2015; Wacongne *et al*., 2012).

DISCUSSION

The reviewed evidence compiles neuroanatomical, histological, and physiological substrates to support the idea that the brain is not a machine at rest, passively waiting to receive stimuli and respond to them. Instead, it behaves as an active generator of inferences, relying on prior experience to estimate the probability of the causes behind the stimuli it receives, using a Bayesian approach to calculate the likelihood of incoming stimuli (Llinás, 2008; Barrett & Simmons, 2015). In this way, the brain generates representations of the external world it knows and makes predictions based on past experiences, suggesting that it anticipates sensory stimuli rather than passively awaiting them (Summerfield *et al*., 2008). Essentially, the brain creates hypotheses about the world, which are tested against sensory experience to confirm or reject them, making perception a process as active as motor control.

Furthermore, mechanisms have been described that demonstrate the brain operates with a tendency to minimize prediction error through an active process of inference that evolves over time (Llinás, 2008; Barrett & Simmons, 2015). Therefore, the organization of the cerebral cortex provides the neurobiological substrate for this computational-like arrangement. In this structure, the primary visual cortex, with well-defined layers, rich in granular cells, and a more prominent and differentiated layer IV, processes external sensory information. In contrast, the association cortex, located anteriorly in the parietal lobe, is agranular, with less differentiated layers and a lower population of layer IV granular cells, and is where predictions are generated (Rao & Ballard, 1999; Llinás, 2008; Barrett & Simmons, 2015).

Additionally, prediction neurons are located in the agranular cortex (parietal lobe), sending their prediction signals to the layer IV granular cells of the occipital cortex, also referred to as "error" neurons. Prediction error neurons, located in the supragranular layers (II and III) of the primary visual cortex, compute the difference between the predicted signal and the one received from the external world. They then send recurrent signals carrying the prediction error back to the deep layers of the prediction cortex in the parietal lobe, forming a recurrent neural network (Barrett & Simmons, 2015).

Moreover, an additional neuronal population has been identified: precision interneurons, which adjust future predictions by modifying the weight of these connections and tuning the functioning of the prediction system. Thus, the brain not only reconstructs the external world, it predicts stimuli and adjusts its predictions according to the sensory inputs it receives (Llinás, 2008; Barrett & Simmons, 2015).

These prediction signals travel from neurons located in layers V and VI of the agranular cortex in the parietal lobe to layers I through III of the granular (primary visual) cortex in the occipital lobe. The feedback connections carrying the prediction error signal go from layers I through III of the granular cortex to layers V and VI of the agranular cortex in a reciprocal loop. This reciprocal architecture ultimately enables the integration of prediction to create more efficient perception (Summerfield *et al*., 2008), showing that predictive mechanisms of sensory information are not restricted to visual processing but are also involved in auditory and somatosensory information processing (Llinás, 2008; Brydevall *et al*., 2018; Koster-Hale & Saxe, 2013; Summerfield *et al*., 2008; Clark, 2013; Barrett & Simmons, 2015).

Although, traditionally, studies of brain function have focused on responses evoked by specific tasks, by their very nature such experiments tacitly promote a reflexive view of brain function, while overlooking the alternative possibility that brain functions are primarily intrinsic and involve information processing to interpret, respond to, and predict environmental demands (Raichle, 2010). This aligns with the fact that the modern human brain is approximately three times larger in volume than that of early hominins, greatly exceeding the predicted brain size for a primate species with equivalent body size (Rilling, 2014). In fact, the human brain allocates relatively more cortical area to association regions than to primary motor and sensory areas (Bruner *et al*., 2017).

Furthermore, it is worth noting that most other non-human animals are also capable of detecting associations to predict behaviors. These capacities, regardless of their origin, can be co-opted for social communication, for example, sounds that signal the likelihood of an attack, where animals develop behaviors to alert others, functioning as predictive social signals (Adolphs & Anderson, 2018).

Humans possess a capacity to elaborate plans for the future, which likely emerged when early humans began to prepare for future states. This capacity necessarily required more memory to represent both past and future events, enabling planning to address upcoming states of hunger, cold, or thirst, rather than merely reacting to immediate desires. This may have marked the beginning of rapid cultural development in humans (Smart, 2013).

On the other hand, some argue that self-predictability, as a function, is inherently incomplete, even in the Newtonian mechanistic universe in which our brain operates at the macroscopic level. The strongest argument against complete predictability lies in quantum factors. According to the basic principles of quantum theory, nature is inherently unpredictable; Heisenberg's uncertainty principle ensures that there is always an irreducible indeterminacy in the behavior of subatomic systems. While quantum effects are likely too small to exert significant influence over brain function, the hazy superposition of potential realities converging into a single concrete reality (Davies, 1986) suggests a limitation to deterministic frameworks. Therefore, addressing the brain-body-mind problem requires more than the prerequisites of modern physics and quantum dynamics. For a complete brain-body-mind construct, we must incorporate uncertain causalities, and consequently, multiple uncertain causalities (Bas¸ar & Güntekin, 2007) generated by the brain's predictive function.

CONCLUSION

The brain not only receives afferent input and sends efferent projections to and from the extracorporeal world, but it also compares internally generated predictions based on prior information and formulates expectations from past experiences. This process demands efficient memory systems and dedicated neuronal populations responsible for generating hypotheses about future motor and sensory events during information processing. Thus, the brain is a neurobiological processor that engages in inference-making for prediction. It is capable of anticipating future outcomes and preparing efficient responses when confronted with those stimuli.

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