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Visual Plasticity: Blindsight Bridges Anatomy and Function in the Visual System

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Some people who are blind due to damage to their primary visual cortex, V1, can discriminate stimuli presented within their blind visual field. This residual function has been recently linked to a pathway that bypasses V1, and connects the thalamic lateral geniculate nucleus directly with the extrastriate cortical area MT.

The primary visual cortex (V1) in the occipital lobe is the major cortical destination of the input from the eye, after an intermediate relay station in the lateral geniculate nucleus of the thalamus (LGN). Both structures contain a map of the contralateral visual scene and damage along this pathway destroys part of the map, leading the patient to clinical blindness in the corresponding part of the visual field. There are, however, parallel neuronal pathways from the eye that bypass V1 and reach other subcortical and cortical targets in the brain (Figure 1). The intricacy of these alternative pathways has made it difficult to link structure (anatomy) to function (behavior). This is nevertheless a fundamental goal for understanding how the brain enables vision, as ''anatomy is to physiology as geography is to history; it describes the theatre of events'' [1].

That such V1-independent pathways are not simply vestigial was first noted a century ago by the British neurologist George Riddoch [2], who reported that patients with occipital lesions could detect moving targets within their otherwise blind field. It was not until the 1970s, however, that the study of residual visual functions in the absence of V1 and subjective awareness became systematic, leading Weiskrantz [3] to coin the suggestive oxymoron 'blindsight' to describe such apparently counterintuitive phenomena. These earlier discoveries set the stage for a recent study by Ajina *et al.* [4], who report evidence that human blindsight is mediated by an

intact pathway between LGN and the middle-temporal visual area MT (also known as V5).

Ajina *et al.* [4] subdivided a large group of patients with V1 damage into those with or without blindsight, according to a psychophysical test with moving visual stimuli. Diffusion-weighted magnetic resonance imaging (dw-MRI) and tractography were used to reconstruct non-invasively white matter tracts that bypass V1. All patients with blindsight showed intact connections between LGN and extrastriate area MT, a cortical area best known for its role in motion vision. The converse was also true, as LGN–MT tracts were significantly impaired, or not detectable, in patients without blindsight. Alternative pathways that bypass V1 and reach MT from the ipsilateral superior colliculus and/or the pulvinar were also considered, but could not be consistently associated with the presence of blindsight.

Although a few previous studies have also attempted to combine anatomy with function, they were based on single cases and targeted only one pathway of interest [5,6]. Ajina *et al.* [4] compared different tracts and parametrically related anatomical properties to behavioral data. Moreover, the presence of LGN–MT connections in patients with blindsight, and its absence in those without it, provides simultaneous positive as well as negative evidence about the occurrence of blindsight. Admittedly, there are inevitable limitations intrinsic to the methodology used by Ajina *et al.* [4]. Tractography does not directly detect axons, but rather reconstructs large fiber bundles from diffusion data, and changes in the thresholds may impact substantially on reconstruction of fascicles. It also cannot provide information about the directionality of the pathway, although the assumption is that LGN drives activity in MT through feedforward processes. Other potential V1-independent pathways to MT, originating from the pulvinar and the superior colliculus, are difficult to dissect because these structures are so close together relative to the spatial resolution of tractography. These caveats aside, however, the study by Ajina *et al.* [4] is bound to rekindle old

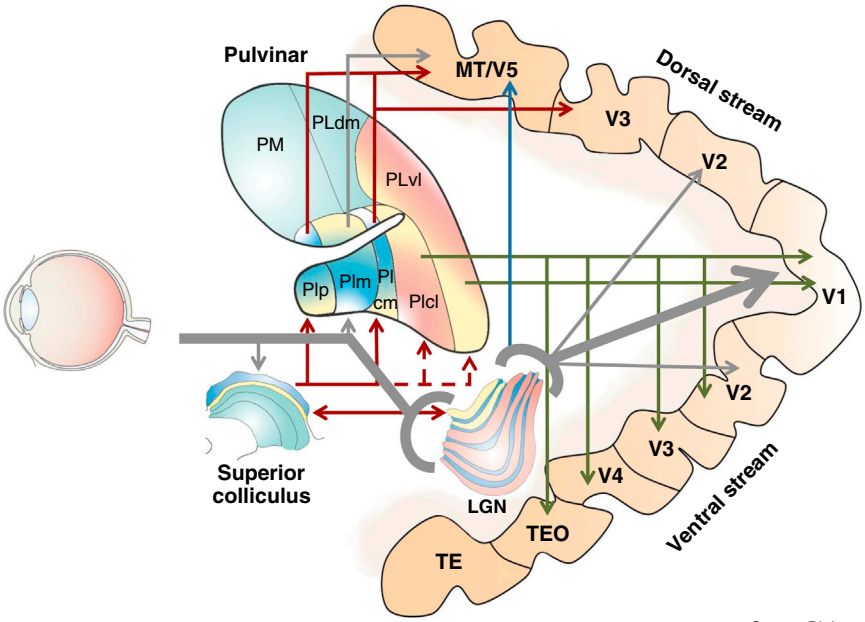

Figure 1. Connections from the eye to the visual cortex involving intermediate relays in LGN, superior colliculus and pulvinar.
Gray arrows indicate direct projections for the eye, with thicker lines showing the major geniculo-striate pathway involving LGN and targeting V1. Red arrows indicate projections originating from the superior colliculus and reaching the dorsal stream cortical areas via the pulvinar, with dashed lines showing disputed input to subdivisions of the pulvinar. Green arrows indicate projections from pulvinar subnuclei to areas along the cortical ventral stream. The blue arrow indicates projections from the Koniocellular layers of LGN to area MT. In LGN and superior colliculus, yellow layers indicate Magnocellular, blue Koniocellular, and pink Parvocellular channels. In the pulvinar these pathways are not clearly segregated and shaded blue-yellow; pink-yellow colors indicate the conjoint presence of the respective channels in given subdivisions. Light green denotes areas of the superior colliculus and pulvinar not interesting for the present purposes. Abbreviations: Plcl, pulvinar inferior centro-lateral; Plcm, pulvinar inferior centro-medial; Plm, pulvinar inferior medial; Plp, pulvinar inferior posterior; PLdm, pulvinar lateral dorso-medial; PLvl, pulvinar lateral ventro-lateral; PM, pulvinar medial; TE, temporal inferior rostral; TEO, temporal inferior posterior.

issues and, at the same time, recasts longstanding debates into a new perspective more apt for empirical testing.

Recent studies, especially those on early cortical development and maturation [7,8], have lent support to the uniqueness of area MT. Anatomically, while higher-order cortical areas are supposed to rely mainly on the inputs from lower-level cortices for their specialized functions, MT receives three V1-independent projections: two thalamic projections from LGN [9] and from the medial subdivision of the inferior pulvinar [8], and a tectal projection from the superior colliculus via the pulvinar [10] (Figure 1). Functionally, motion selectivity of MT matures at least as early as V1 [7], probably because pulvinar projections to MT are stronger than LGN input during the early postnatal period [8]. Interestingly, early-life lesions to V1 in monkeys lead to greater connectivity between pulvinar and MT than lesions in adulthood [11], and similarly the likelihood of developing blindsight in humans is greater the earlier the damage to V1 [12]. These results indicate the complexity and dynamic plasticity of signal relays from subcortical inputs to the same cortical target. Most notably, they highlight the predominance and inter-individual variability of different V1-independent pathways as a function of time that may help to understand susceptibility to develop blindsight in adulthood.

But how do the important results of Ajina *et al.* [4] on LGN–MT connections generalize to other aspects of blindsight besides motion perception? A broad spectrum of visual abilities

persisting after V1 lesion have been documented, including shape, wavelength, facial or bodily expression discrimination. If the neuronal pathway sustaining blindsight remains elusive and partly under dispute, it is because the question is somewhat ill-posed. It seems that a better way of conceiving blindsight is as a constellation of multiple nonconscious visual abilities that likely reflect the variety of existing V1-independent pathways. For example, the superior colliculus has been shown to determine visually guided eye movements [13] or manual responses [14]. Also, an entirely subcortical route involving the superior colliculus, the inferior pulvinar and the amygdala seems necessary for processing emotional salience (affective blindsight) in humans [6] and monkeys [15].

A longstanding principle in parcelling the visual cortex into functionally meaningful areas involved dividing the dorsal from the ventral stream, both starting in V1. The dorsal 'where' stream is specialized for visually guiding behavior and motion perception, whereas the ventral 'what' stream is largely devoted to object recognition and stimulus invariance. This distinction barely considers subcortical structures such as LGN, superior colliculus and pulvinar, and how they can promote or participate to this division of labors in the visual cortex. Blindsight can thus become a unique experimental model for integrating the role of subcortical structures within the functional architecture of vision originally charted on the cortex. In fact, a bias in blindsight towards properties processed by the dorsal stream has been traditionally reported and interpreted as resulting from direct connections between the superior colliculus or LGN with cortical areas in the dorsal stream. Nevertheless, spared abilities to distinguish familiar faces [16] or object categories [17] have been reported more recently. They clearly pertain to ventral stream functions and can be hardly accommodated with the notion of dorsal stream primacy in blindsight. This suggests that other V1-independent pathways may play a role akin to the one reported for MT in motion perception, but for different visual properties.

These pathways may involve the pulvinar, which, in both monkeys and humans, is segregated into subdivisions mirroring the cortical dorsal/ventral distinction [8,18]. A subset of nuclei in the inferior pulvinar connect and function predominantly as a subcortical component of the dorsal stream, whereas more lateral nuclei send projections and contribute to functions in the ventral stream. It is also possible that the cortex does not need to be involved at all, at least in some forms of blindsight. For example, blindsight has been shown in patients with hemispherectomy, where the entire cortical mantel of one hemisphere has been removed [5]. Accordingly, several neurons in the monkey superior colliculus respond very poorly to simple visual stimuli, but participate instead in early stages of figure–ground segmentation or are activated by real objects [19]. Likewise, neurons in the monkey superior colliculus and pulvinar can selectively encode faces or facial expressions [20]. These results induce reconsideration on the role that subcortical structures may play in normal vision. Therefore, sensitivity to different stimulus attributes shown in blindsight can be the testing ground for the functional efficacy of V1-independent pathways reported in monkeys. On the other hand, animal histology and physiology offer viable support to interpret blindsight phenomena, while also fostering investigation of new anatomically-plausible functions in human blindsight.

What remains of the utmost importance for future studies is to profit from the approach Ajina *et al.* [4] took in making associations between the specific blindsight function studied, both in terms of stimulus properties and task requirements, and its anatomical substrate. More than ever, investigation of blindsight keeps promoting and updating our understanding of the visual brain, drawing function and anatomy together.

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Balancing Selection: Walking a Tightrope

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Combining modern transgenic techniques with fitness measurements and enzyme activity assays, a new study demonstrates a habitat-dependent tradeoff between two alleles of a key detoxification enzyme in fruit flies. The elegant findings provide concrete, elusive evidence supporting a foundational and controversial theory about the maintenance of genetic variation.

Genetic variation is a ubiquitous property of natural populations, and its maintenance in the face of random and deterministic forces is at the heart of one of the great debates in evolutionary biology. This variation arises from new mutations, changes in DNA sequences spanning single-nucleotide polymorphisms to whole genome duplication events, and is the substrate for evolutionary change. Such mutations can be advantageous, neutral or deleterious — a range prefigured by Charles Darwin who pondered the fate of "favourable", "injurious" and "neither useful nor injurious" variations as he outlined the process of evolution by natural selection [1]. Population genomics has now revealed that genomes of a randomly chosen pair of individuals from the same species generally differ by 0.1% (for example, in humans) to 10% of their sequence [2]. Such findings have helped energize the debate over the importance of various mechanisms that could facilitate the maintenance of such tremendous genetic variation within species. In an elegant new chapter to this debate, Chakraborty and Fry in this issue of *Current Biology* [3] demonstrate that natural selection likely acts to maintain a single amino acid polymorphism in a key enzyme used by flies to detoxify dietary ethanol byproducts. Leveraging modern genetic tools, including insertion of alternative alleles of this enzyme into the genomes of isogenic flies, coupled with enzymology and laboratory fitness studies, their study sets a new bar in the field.

To place Chakraborty and Fry's study in context, a history of the field is helpful (Figure 1). In the mid-1900s, as methods emerged to observe genetic variation directly, interest in explaining patterns of genetic variation within natural populations surged. Decades before DNA sequencing, Dobzhansky and colleagues peered through microscopes at dye-stained chromosomes, cataloguing variation in the orientation of large stretches of DNA in fruit flies (*Drosophila* species) [4]. They proposed that this variation persisted through the action of balancing selection, a collective term for evolutionary processes that adaptively maintain variation in populations. Specifically, they hypothesized that fruit from different plant species provided spatially distinct habitats exerting different selection pressures on flies, and genetic variation persisted because no one chromosomal variant was superior across all habitats. Levene confirmed mathematically that Dobzhansky's intuition could occur [5]. Dempster then showed that selection pressures varying in time, rather than space, could also maintain genetic variation [6]. Over the ensuing decades, as dozens of expansions of these models were constructed [7] — including models for traits controlled by many genes [8], in contrast to Levene's single locus model — empirical evidence for balancing selection also began to mount (e.g., [9]).

In the 1960s, Hubby and Lewontin captivated evolutionary biologists when they uncovered surprisingly high levels of genetic variation in *Drosophila* allozymes [10]. Balancing selection, and spatially varying selection in particular, became a popular explanation for the maintenance of this variation. By 1974, merging theory with natural observations, Gillespie and Langley proposed that spatially varying selection might be the primary evolutionary process responsible [11].

Alternative explanations, however, tempered the enthusiasm for widespread balancing selection in nature. Kimura's neutral theory of molecular evolution, now

