V1-bypassing thalamo-cortical visual circuits in blindsight and developmental dyslexia

Samy Rima[1] and Michael Christoph Schmid[1,2]

Vision rests on computations that primarily rely on the parvocellular and magnocellular geniculate relay of retinal signals to V1. Secondary pathways involving superior colliculus, koniocellular lateral geniculate nucleus and pulvinar and their V1-bypassing projections to higher order cortex are known to exist. While they may form an evolutionary old visual system, their contribution to perception and visually guided behaviour remain largely obscure. Recent developments in tract tracing and circuit manipulation technologies provide new insights. Here we discuss how secondary visual pathways mediate residual vision (blindsight) after V1 injury by relaying signals directly into higher order cortical areas. We contrast these findings on blindsight with new studies on dyslexia suggesting that dysfunction of secondary visual pathways might contribute to dyslexic's perceptual difficulties. Emerging from these considerations, secondary visual pathways involving koniocellular LGN may be critical for detection of visual change, whereas pulvinar function appears more linked to visuomotor planning.

Addresses
[1] Université de Fribourg, Switzerland

[2] Newcastle University, United Kingdom

Corresponding authors: Rima, Samy (samy.rima@unifr.ch),
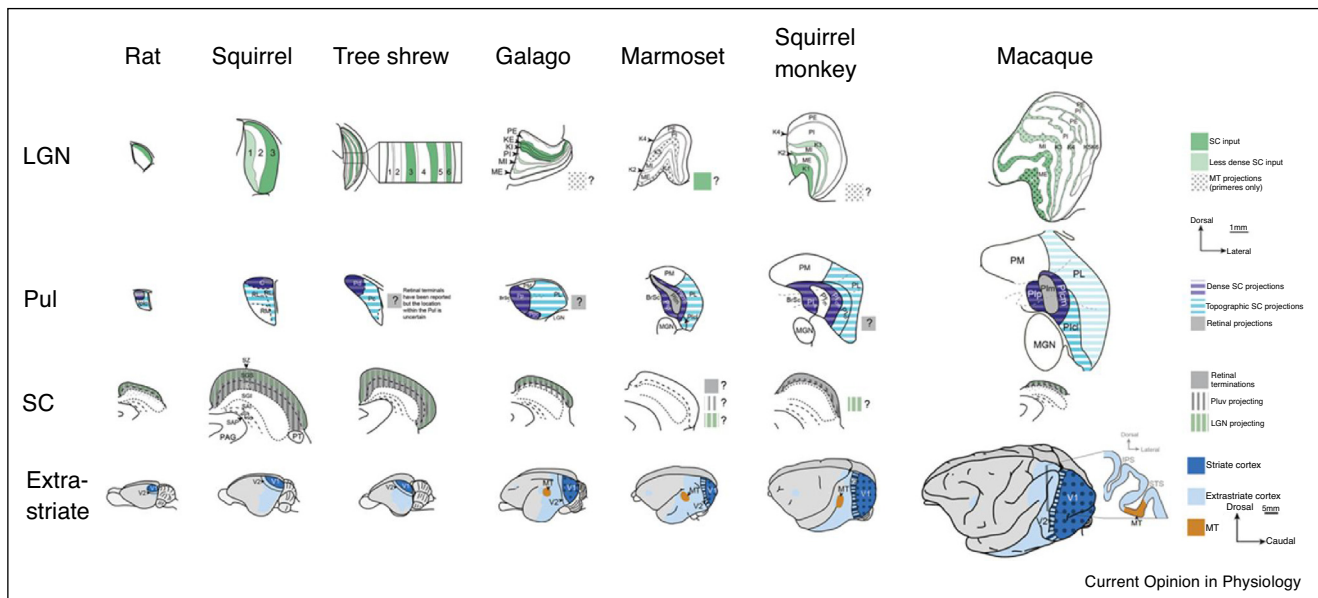Christoph Schmid, Michael (michael.schmid@unifr.ch)

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In vision, secondary pathways bypass primary visual cortex (V1) and feed retinal information directly into higher visual cortical areas. The relative strength and contribution of each of these subroutes to perception and visually guided behaviour vary within the mammals of the Euarchontoglires clade [1] (Figure 1), to which modern primates belong. This variation seems to stem from specie specific retinal ganglion cell (RGC) organization and distribution that emerged from different ecological pressures which, in time, moulded the visual system of each specie. This has led some species of the clade to favour diurnal versus nocturnal lifestyles, with different degrees of front-facing eyes (binocular vision) versus side-facing eyes and more or less visually guided grasping [2].

While the origin of V1-bypassing routes undisputedly lies in the retina, the precise transfer points in the midbrain and thalamus remain an area of intense study, as multiple subroutes exist. In macaques, a dedicated set of ganglion cells projects from the retina to reach the superficial layers of the superior colliculus (SC) in the midbrain [3]. From there two main parallel projections emerge that bypass V1 [4,5]: one is to the ventral koniocellular/intercalated layers of the lateral geniculate nucleus (LGN) and from there to multiple areas of visual association, most prominently area MT [6–9]; a second projection reaches the inferior and lateral parts of the visual pulvinar and similarly projects to multiple areas of visual association cortex [10–12]. In addition to these SC mediated routes, certain ganglion cells also project directly, without the SC detour, to LGN konio layers [8,13,14] and inferior pulvinar and from there on to visual association areas [15], in both macaques and marmosets. There is anatomical evidence that the strength of the pulvinar route might be particularly prone to developmental shaping in marmosets [16–19]. An important set of electrophysiological recordings in LGN and pulvinar has influenced our current understanding of visual function in these regions: LGN recordings in marmosets established that most dorsal konio neurons are sensitive to short-wavelength visual stimuli [20,21], whereas ventral konio neurons tend to be more sensitive to achromatic stimuli with low spatial and high temporal frequencies [13,14]. Recordings from the pulvinar in macaques established a wide set of visual functions, including responses to faces, snakes [22,23] and saccade related activity depending on recording location [24–26]. A direct functional confirmation of the SC-MT route via pulvinar has been established by Berman and Wurtz [11,12] in a seminal study using electrophysiological collision tests in macaques. In addition to these insights on a healthy, undisturbed visual system, a major part of our understanding about the contributions of these subcortical structures to visual function arises from studies in which the primary geniculo-V1 pathway has been damaged or inactivated permitting the analysis of V1-bypassing route contributions to residual visual

Figure 1

Organization of subcortical structures and their subdivision involved in V1 bypassing circuits. Adapted from Baldwin and States [1]. The visual system in humans follows closely the overall primate organisation [2], but detailed circuit information is still lacking.

function. In this review, we will first describe recent advances from these studies, before contrasting them with new insights on developmental dyslexia in which a V1-bypassing projection has been found to be compromised.
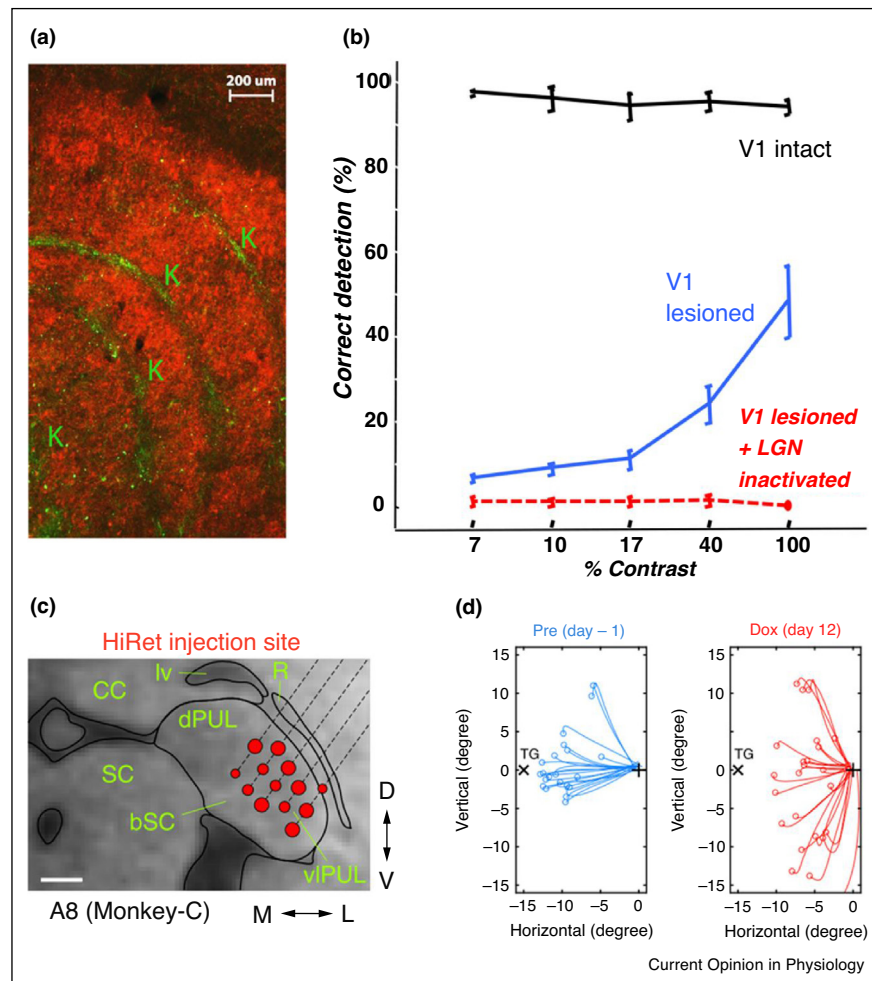
Blindsight

While conscious vision in humans is deeply disrupted following a lesion of V1, significant residual visual function remains, [27–31] including the capacity to execute saccades toward visual stimuli presented within the scotoma [27,28] and to detect visual motion [29]. This 'blindsight' phenomenon has instigated a lively debate about which circuits that bypass V1 are responsible for the residual vision of these patients. Several nonhuman primate investigations have demonstrated significant residual neuronal activity in motion sensitive area MT despite a lesion of V1, consistent with preserved motion detection capacities in blindsight [32–35]. Another extrastriate area, V4, which was initially shown to be silenced by V1 cooling [36], appears to regain some residual activity in chronic V1 lesions [37] and become more sensitive towards the detection of visual motion [38] in macaques. While it is largely accepted that the SC has a critical function in mediating blindsight by relaying visual signals to cortex [32,39], the thalamic relays via LGN versus pulvinar remain a topic of rich debate [40–42].

For a long time, the LGN route appeared an unlikely candidate due to strong degeneration caused by V1 injury. But evidence in macaques shows that a significant amount

of cells projecting directly towards visual association cortex survive this degeneration [9,43]. Pharmacological inactivation of LGN neurons eliminated functional activation of visual association cortex and visual detection capacities in a monkey model of blindsight [44] (Figure 2b). Similar inactivations in pulvinar had no effect on basic vision but induced neglect-like visuomotor symptoms [45] shifting the focus for blindsight-related circuits further to LGN. Indeed, electrophysiological recordings from LGN neurons surviving V1 lesions confirmed intact visual processing of these neurons [46]. Modern optogenetic methods now enable the CamK-II specific targeting of koniocellular neurons in an intact visual system of macaques, however so far with no clear delineation of visual response characteristics [47,48] (Figure 2a). Evidence for the involvement of a geniculo-extrastriate pathway in blindsight exists also for humans. In 2015, Ajina et al. [49] used psychophysics and connectivity measures to show that patients with V1 lesions that could discriminate motion (blindsight positive) had an intact LGN-hMT+ tract, while those that couldn't discriminate motion (Blindsight negative) had a severely impaired or no measurable tracts. The other pathways tested, which included a connection between hMT+ and the superior colliculus (SC), and with hMT+ in the opposite hemisphere, did not show this pattern. In a subsequent study, Ajina et al. [50] used fMRI to demonstrate that blindsight positive patients had intact functional connectivity between the LGN and hMT+ which was not the case for blindsight negative patients. Furthermore, their results suggest that this was specific to the

Figure 2

Involvement of K-MT and SC-PUL-MT pathways in blindsight. **(a)** eYFP fluorescence of K layers that express CAMKII and calbindin. Adapted from Klein *et al.* [47]. **(b)** Effect of LGN inactivation on the correct detection of rotating checkerboards with a scotoma induced by a V1 lesion. Adapted from Schmid *et al.* [44]. **(c)** Injection site of lentiviral vector (HiRet), which carried eTeNT under the tetracycline responsive element. **(d)** Saccade trajectories and saccade endpoints before administration (Pre) and during Dox administration (Dox). (c) and (d) are adapted from Kinoshita *et al.* [51].

LGN, as both patient groups had preserved connectivity between hMT+, the pulvinar and contralateral hMT+. Observations in humans thus confirmed the experimental discoveries in V1 lesioned macaques in which residual visual function was abolished if the LGN was silenced which further strengthens the involvement of a geniculo-extrastriate pathway in blindsight. Although konio neurons can receive inputs from SC as well as directly from the retina [2], it remains to be determined which of these inputs is essential for LGN-dependent blindsight.

Recent advances in chemogenetic and optogenetic technologies have however also brought new groundbreaking evidence to the Pulvinar contribution. Kinoshita *et al.* [51] in an important new study directly tested the role of superior colliculus to ventrolateral pulvinar (vlPul)

pathway in blindsight monkeys using pharmacogenetics (Figure 2c). They first confirmed the ability of monkeys to make visually guided saccades to high contrast stimuli in the contralesional visual field. Then, they mapped the ventral pulvinar by electric microstimulation of the SC. Following the identification of the vPul, they inactivated it through the injection of muscimol. The precision of the injection location was later confirmed through Gadolinium-based magnetic resonance imaging. This inactivation severely impaired visually guided saccades to the contralesional visual field. The authors then used pharmaco-genetics to investigate the role of the SC-vPul pathway in the generation of visually guided saccades to the contralesional visual field. They injected 2 retrograde viral vectors, one in the SC and the other in the vPul. The goal of these injections was to selectively

inhibit neurons of the SC-vPul pathway using doxycycline. During the oral administration of Doxicycline, the accuracy of vision guided saccades to the contralesional visual field declined and reaction times increased. The confirmation of this finding with similar results in mice [52] highlights the importance of this pulvinar route for re-foveation to high contrast peripheral targets during blindsight across species.
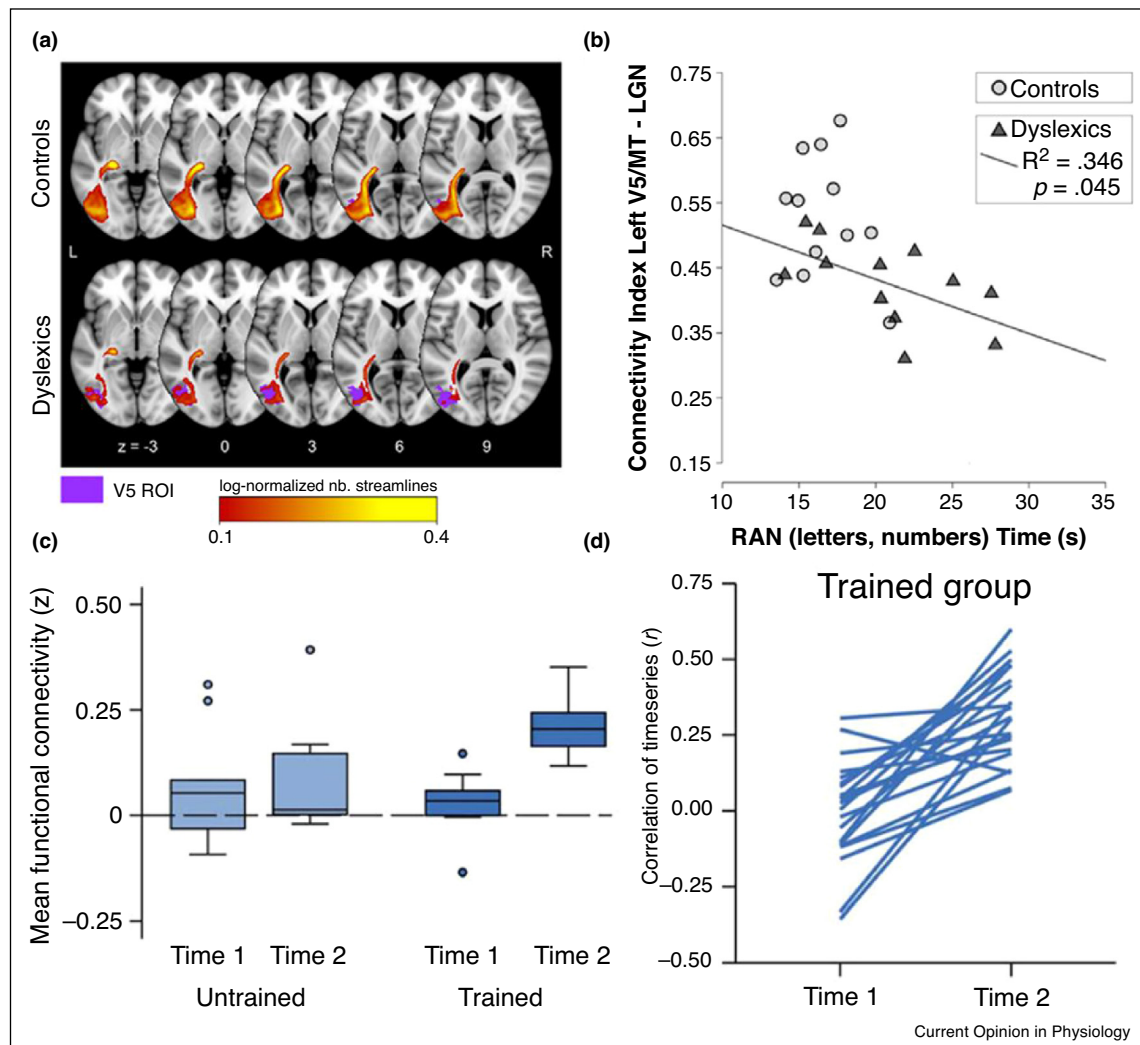
Thus, there is good evidence for V1 bypassing projections in blindsight that implicate both the LGN and Pulvinar. In the absence of double dissociation experiments in the same primate species, there is no clear-cut answer as to which of these subcortical pathways is ultimately critical for blindsight. With positive evidence for either route, the possibility remains that both pathways contribute in parallel with the LGN route possibly more concerned

with basic visual detection and the pulvinar pathway more directly linked with visuo-motor behavior.

Developmental dyslexia

While there is strong evidence that the residual visual and visuomotor capacities of blindsight rely on visual circuits that bypass V1 into extrastriate cortex, the function of such a circuitry in other clinical contexts – or even everyday vision – remains largely unknown. A recent investigation of subcortical circuits in subjects with developmental dyslexia, however, points to at least one secondary visual pathway bypassing V1 in dyslexia. It is known that dyslexics of different age groups and language backgrounds show deficits in visual motion processing [53]. A current prominent theory ascribes these deficiencies to a disrupted LGN magnocellular pathway [54].

Figure 3

Involvement of V1 bypassing circuits in reading acquisition and reading deficits. **(a)** Dyslexics present decreased connectivity bet ween left LGN and left area MT, which **(b)** negatively correlates with reading skills. Adapted from Müller-axt et al. [56]. **(c)** and **(d)** Learning to read increases cortico-subcortical functional connectivity. Adapted from Skeide et al. [66].

Empirical data for the magnocellular theory of dyslexia saw light in 1991 when Livingstone *et al*. [55] showed that dyslexic subjects had diminished visually evoked potentials to rapid and low contrast stimuli, but normal responses to slow and high contrast stimuli. Investigation of the post-mortem dyslexic LGN by Livingston revealed histological abnormalities in the ventral magnocellular layers, but not the dorsal parvocellular layers. Direct evidence for a deficient visual pathway bypassing V1 in dyslexics was recently provided by Müller-Axt, Anwander, and von Kriegstein, [56]. The authors used ultra-high-resolution fMRI and tractography to show reduced structural connectivity from the left LGN to left motion area MT with seemingly intact LGN V1 connections (Figure 3a). The strength of the left LGN MT connectivity was negatively correlated with the rapid naming abilities of dyslexics (Figure 3b). This lateralization corroborates recent anatomical evidence that shows that the size of the left LGN is smaller in dyslexics as compared to left LGN of controls [57], and aligns with with reports of abnormalities in the areas activated during reading in dyslexics [58,59] which are mostly confined in the left hemisphere. fMRI has shown that moving stimuli do not invoke the same activity in area MT in dyslexics as it does in control subjects [60] with strong correlations between cortical activity, speed discrimination thresholds, and reading speed [61]. We have recently partially confirmed this finding: the higher sensitivity to detect visual motion in the right hemifield seen in skilled readers was absent in individuals with developmental dyslexia [62]. Furthermore, transcranial direct current stimulation of left area V5/MT in dyslexics seems to lead to improved reading speed and fluency [63], while transcranial magnetic stimulation showed that stimulating left area MT lead to impairments in word recognition [64]. There are therefore good reasons to link the observed motion deficits in developmental dyslexia to an altered left-hemispheric motion processing system in the brain of these subjects. However, there is at the moment somewhat of a conundrum about the LGN involvement which will need to be resolved in future research to determine whether the original magnocellular theory should be extended towards koniocellular function, and to what extent the LGN-MT pathway [8] might consist of a mixture of koniocellular and magnocellular inputs.

Compared to the evidence for a deficient left hemisphere LGN-MT system in dyslexia, very little is known about the involvement of the other secondary pathway structures. Deheane's neuronal recycling hypothesis proposes that reading makes use of brain areas initially devoted to more primitive visual functions, and that the practice of reading would carve out a reading network in the visual system through plasticity [65]. Evidence for plasticity of subcortical sensory circuits after reading acquisition comes from a recent resting-state fMRI study [66]. The authors showed (Figure 3c and d) that, after learning to read for six months, functional connectivity (SC-Pul, subcortical-cortical, left hemisphere) increased for previously illiterate adults. This increased connectivity also correlated with letter identification and word reading skills on the individual level. While the contributions of the SC and the visual pulvinar to developmental Dyslexia remain largely unknown, there is preliminary evidence for pulvinar disruption [67] in addition to the known LGN deficit [55].

The commonalities in the V1-bypassing circuits between blindsight and developmental dyslexia are intriguing. Further investigations using cell-specific double dissociation experiments in primates should help to clarify the roles of the pulvinar versus LGN routes. Drawing upon our considerations from blindsight and dyslexia, we speculate that anticipatory visual processing in normal vision, such as during reading, might invoke the detection properties of the LGN-MT circuit and saccadic planning function of the SC-Pulvinar route in concert as to visually locate upcoming objects such as words, and further guide the fovea for analysis at highest acuity.

Conflict of interest statement

Nothing declared.

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