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Conclusive Evidence for Human Transneuronal Retrograde Degeneration in the Visual System

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Abstract

For several decades there was controversy concerning the existence of transneuronal retrograde degeneration in the human visual system in spite of a substantial body of data indicating this degeneration in certain species of non-human primate. Over the past few years, however, compelling evidence both from human magnetic resonance imaging and optical coherence tomography has shown conclusively transneuronal retrograde degeneration in both the white matter of the optic tract and in the ganglion cells of the retina. In this review the evidence for primate degeneration and degeneration in non-visual human neural systems are discussed before the presentation of the recent human data.

Damage to axonal fibers in both central and peripheral nervous system leads to degeneration. The degeneration can be anterograde (Wallerian) in which injury to the cell body or proximal regions of the axon leads to degeneration in the axon distal to the damage. Retrograde degeneration is death of the cell body following axonal injury and can be seen throughout the Central Nervous System (CNS) in sensory systems including visual [1], auditory [2], olfactory [3], somatosensory [4] and pain [5] as well as motor systems [6].

Transneuronal (or trans-synaptic) Retrograde Degeneration (TRD) is degeneration that occurs in neurons that are undamaged by the primary insult, but lose their projection target. Neurons in the Lateral Geniculate Nucleus (LGN) show retrograde degeneration following posterior cortical damage [1,7]. TRD would therefore refer to degeneration of the retinal ganglion cells and their axons. While the evidence for both anterograde and retrograde degeneration is uncontroversial, there has been considerable debate over whether or not TRD exists in the human nervous system. This review will consider the evidence for TRD in the human visual system, comparing to both the non-human primate visual system and non-visual systems.

TRD Has Been Shown to Occur in Motor and Medial Temporal Systems

An early report of TRD by Smith [8] described the case of a patient who had a hemicerebellectomy 14 years prior to post-mortem histological examination. This patient showed degeneration of both fiber tracts and projection nuclei having direct connections with the cerebellum. Furthermore, there was evidence of transneuronal degeneration in the corticopontine and central tegmental tracts. This detailed report provides strong evidence of TRD in the motor pathway.

A seminal study by Cowan & Powell [9] showed TRD in the mammillary bodies following damage to the anterior thalamic nuclei. This study in the rabbit provided some of the first evidence for this process in the CNS, and furthermore indicated that both the age at which the trauma occurred, and the time elapsed since damage affect the severity of the TRD.

TRD in the Primate Visual System Has Been Well-Characterized

The first modern report of TRD in the visual system was presented by van Buren [10] who performed an occipital lobectomy in a juvenile macaque monkey followed by histological analysis four years later. The LGN showed extensive degeneration such that it was no longer possible to distinguish the 6 layers in stained sections in the lesioned hemisphere. Furthermore, the volume of the right optic tract was reduced to 44% of the left side. These losses were reflected in a reduction in the number of ganglion cells in the right hemiretinae of the two eyes. This comprehensive investigation provided strong evidence for the existence of TRD in the macaque monkey.

Since the early work of van Buren, multiple studies have confirmed the existence of TRD in the macaque monkey, and have attempted to characterize the factors contributing to TRD. Weller & Kaas [11] investigated the loss of ganglion cells in the retinae of primates with varying durations of striate cortex lesions. Interestingly, although TRD was found in all macaque monkeys, both the rate of cell loss and the absolute loss were greater in infants compared to adolescent and adult animals. This is consistent with the finding in the mammillary bodies described by Cowan & Powell.

The P-type ganglion cells, which make up 90% of the total ganglion cell population, have small receptive fields and are sensitive to wavelength, appear to be selectively destroyed in all cases investigated by Weller & Kaas [11], a pattern also found by Cowey et al. [12] in two macaque monkeys with long standing lesions. In contrast to the macaque monkeys, neither owl nor squirrel monkeys lesioned as adults showed any signs of TRD. This is consistent with the anatomy of prosimian primates in which there is no measurable TRD [13].

In addition to the primate species, age at insult and lesion duration, the size of the lesion also affects the amount of TRD that can be measured in the retinal ganglion cells. The results of Cowey et al. [12] confirm the finding of Weller & Kaas [11] that survival time following lesioning of striate cortex correlates with retinal ganglion cell loss. Additionally, they showed that in animals matched for survival time, the larger lesion size led to greater ganglion cell loss, particularly where the lesion extended beyond V1.

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The majority of early studies on primate species concentrated on loss of ganglion cells measured in the retina, with some measurements of degeneration of the LGN [12]. More recently, Cowey et al. [14] performed an elegant histological examination of the degeneration in both the optic tract and retinal ganglion cells in the retina. Degeneration in the optic tract was quantified using the ratio of the ipsi- and contra-lesional sides. Ganglion cell loss was measured using the ratio of ganglion cells in the nasal (degenerated) and temporal (intact) hemiretinae in the eye contralateral to the lesion. The rate of decline in these ratios was steep and significantly correlated over the first three years.

Electroretinogram in Human Homonymous Hemianopia

The pattern evoked electroretinogram (pERGs) uses a bioelectrical signal to monitor the retinal activity resulting from a patterned stimulus. A signal can be recorded using a stimulus located within a hemifield. The signal is believed to reflect spiking activity in the ganglion cell fibers [15]. The spatio-temporal characteristics of the stimulus can be modulated to preferentially activate subsets of ganglion cells (such as the P-type described above). The first report of abnormal PERGs in a hemianopic patient was provided by Stoerig & Zrenner [16] who found differences both between the two hemiretinae of the patient and in comparison to a sighted control subject. This finding was strengthened by a larger study by Porrello & Falsini [17] of eight hemianopic patients (6 right hemisphere damages). They not only found a significant difference between affected and unaffected hemiretinae in the patients, but also that the loss in signal correlated with the time since the lesion. The signal loss was also greatest for the low temporal, high spatial frequency stimulus indicating preferential loss of P ganglion cells.

Retinal Examination: Fundus Photography and Optical Coherence Tomography (OCT)

The presence of damage to the RNFL following optic tract damage can be visualised by inspection of the fundus, and results in band atrophy in the eye with temporal hemianopia (loss of crossing fibres) [18,19]. This example of direct retrograde degeneration is uncontroversial, and this pattern of retinal degeneration has also been seen in cases of congenital occipital cortex damage [20]. In contrast the presence of such a pattern resulting from acquired visual cortical damage has been controversial [21].

The introduction of optical coherence tomography, OCT [22] to ophthalmic practice has allowed a quantification of the human Retinal Nerve Fiber Layer (RNFL) thickness. This technique is now being extensively employed to determine ganglion cell damage in a variety of ophthalmological conditions such as glaucoma [23], as well as neurological conditions such as multiple sclerosis, reviewed by Jindahra et al. [24].

Recently, in the first study to conclusively show decreased RNFL thickness in human acquired hemianopia, Jindahra et al. [25] compared both congenital and acquired cases to control subjects. The authors found a decrease in the mean RNFL thickness in patients with both congenital and acquired hemianopia. Furthermore, the authors divided the peripapillary RNFL into 12 sectors in order to compare the differences in the crossed and uncrossed projections. Consistent with the known projection pattern, they found that in the eye contralateral to the lesion, loss was greatest in the nasal and temporal sectors (band atrophy), while in the ipsilateral eye, these sectors were spared. A follow-up study to monitor RNFL thinning over time showed that in the majority of patients with homonymous hemianopia, degeneration was detectable within100 days of the lesion [26]. A cross sectional study of 38 patients examined at different time intervals post-stroke revealed that the greater part of the degeneration occurred in the first 1 – 2 years slowing down to approach the attrition rate with age at 10 – 20 years.

These OCT studies using time domain methodology have measured the RNFL thickness rather than the thickness of the ganglion cell layer which has been possible in the primate studies. It is not proven that such thinning reflects ganglion cell loss rather than thinning of surviving axons. Spectral domain OCT has the potential to measure the ganglion cell layer thickness directly but it will not be possible to measure ganglion cell density.

Structural Magnetic Resonance Imaging of The Optic Tract

Only within the last year have examples of human optic tract degeneration in the case of acquired homonymous hemianopia due to cortical damage been published. The distinct nature of the optic chiasm means that it is possible to identify at least the anterior portion of the optic tract in the vast majority of human subjects, even when it is severely atrophic [27].

There are several methods for measuring volume in T1-weighted MR images. In these images, each voxel is assigned an intensity value based on the proportion of white and gray matter within that $1mm^3$ volume. At the outside edge of the optic tract, therefore, there will be voxels that contain both white matter and Cerebrospinal Fluid (CSF) which will affect the appearance of the voxels. More problematic for investigating degeneration is the issue that within the optic tract, a crude measure of volume will not distinguish between degenerating and intact white matter.

In the first paper to use Magnetic Resonance Imaging (MRI) to examine TRG of the human optic tract, Bridge et al. [28] used the relative intensity values of the optic tract white matter on the damaged and undamaged sides to quantify degeneration. In all three of the subjects with V1 lesions, there was evidence of degeneration in the ipsilesional tract, with the greatest difference in the long-standing lesions. The sensitivity of this method was such that degeneration of fibers could be detected at least as early as 18 months post-lesion (the earliest measured); degeneration that could not be detected by simply determining the outline of the tract in coronal section. Using a simpler cross-sectional measurement, Cowey et al. [14] also found degeneration in their three subjects with long standing lesions one of which was common with Bridge et al. [28]. They did not, however, find any difference in a fourth subject who was scanned at around 8.5 months post-lesion. It remains to be seen whether an examination of the intensity values within that patient's tract would have revealed early changes.

The use of MRI to quantify optic tract degeneration provides a different measure from OCT. In the latter case, it is the unmyelinated fibers in the RNFL that are measured. The MRI, however, is based predominantly on the myelin volume of the tract. Inspection of the primate data suggests that primary degeneration is of the optic tract, followed by the ganglion cell layer [14]. Parallel longitudinal imaging of the optic tract and OCT of the RNFL is necessary to determine the relative time courses of degeneration.

Further considerations that would be useful to determine include

the relationship between the size of the cortical damage and the severity of the TRG, as shown in the primate data. Additionally, it would be useful to consider whether the age at which any damage is sustained affects the amount of TRG. Thinning of the RNFL appears to be greater in cases of congenital hemianopia (that is to say pre- or peri-natal occipital damage) compared to acquired hemianopes [25]. However, as reviewed by Jindahra et al. there is a paradox here in that although the damage is evident on clinical examination only in congenital and not in acquired hemianopia the difference in RNFL thickness between the two groups measured by OCT was a trend that did not reach statistical significance. It may be that, as with primates, early visual cortical damage results in greater TRD. Characterization of the factors contributing to the severity of TRD, such as the specific location and extent of cortical damage would be useful for the understanding of both the human visual system and in other neural systems in which the TRD is more difficult to measure and quantify.

What Conditions Modulate Transneuronal Retrograde Degeneration and are There Implications for Rehabilitation?

In the presence of conclusive evidence in humans of TRG measurable in both the optic tract and the retina it is necessary to consider the pattern of this degeneration; whether degeneration can be prevented by stimulating activity in alternative visual pathways that are unaffected by the damage to the visual pathway; and whether there would be any clinical benefit of such a measure.

A major consideration is the time-scale over which the degeneration occurs. For reasons described earlier, the measurements taken from human subjects are not as sensitive as those measured histologically in the primate. Therefore, it is not clear when the TRD starts to occur. While the data from OCT suggest TRD can be detected as early as 100 days, longitudinal studies combining OCT and MRI are required to give sufficient insight into the time course of degeneration. Although the data from Bridge et al. [28] suggest TRD can be detected at 18 months post-lesion, this was the earliest time point that was measured and therefore additional data are required. This time point appears to contrast with the primate data suggesting that the degeneration begins significantly earlier than this, detectable around 100 days post-lesion in the optic tract. One technique that may increase sensitivity to initial stages of TRG is diffusion-weighted imaging. Subtle changes in the axon membrane and/or myelin sheath of the ganglion cells may be reflected in increased longitudinal diffusivity in the white matter of the optic tract and nerve, as shown in sight-recovered subject MM [29]. Considerable attention has been focussed recently on designing Diffusion Tensor Imaging (DTI) sequences specifically to target the optic nerve, which is located in an area of the brain showing high distortion [30]. An early study using DTI derived measures suggests that it may be possible to determine subtle changes in the optic nerve [31].

An understanding of the mechanisms and time course of TRG may permit intervention to prevent the death of ganglion cells that may still be able to provide visual information to spared regions of cortex. In particular, where neurorehabilitative procedures are being applied, whether behaviourally or interventionally such as Transcranial Magnetic Stimulation (TMS) or Transcranial Direct-current Stimulation (tDCS) it may be that stimulating neuronal activity in the visual cortex can reduce TRG.

Conclusion

Investigations over past few years have shown conclusively that transneuronal retrograde degeneration is present in the human visual system. It is now important to improve our understanding of the mechanisms of loss such that we can use this knowledge to minimize loss of neural tissue look towards rehabilitation where possible.

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