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Saccadic palsy following cardiac surgery: a review and new hypothesis

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Abstract

The ocular motor system provides several advantages for studying the brain, including well-defined populations of neurons that contribute to specific eye movements. Generation of rapid eye movements (saccades) depends on excitatory burst neurons (EBNs) and omnipause neurons (OPNs) within the brain stem; both types of cell are highly active. Experimental lesions of EBNs and OPNs cause slowing or complete loss of saccades. We report a patient who developed a permanent, selective saccadic palsy following cardiac surgery. When she died several years later, surprisingly, autopsy showed preservation of EBNs and OPNs. We therefore considered other mechanisms that could explain her saccadic palsy. Recent work has shown that both EBNs and OPNs are ensheathed by perineuronal nets (PNs), which are specialized extracellular matrix structures that may help stabilize synaptic contacts, promote local ion homeostasis, or play a protective role in certain highly active neurons. Here, we review the possibility that damage to PNs, rather than to the neurons they support, could lead to neuronal dysfunction—such as saccadic palsy. We also suggest how future studies could test this hypothesis, which may provide insights into the vulnerability of other active neurons in the nervous system that depend on PNs.

Keywords

supranuclear gaze palsy; omnipause neurons; burst neurons; PPRF; RIMLF; eye movements

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Conflicts of interest

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Introduction

Eye movements have become a popular tool to study brain function,^{1,2} owing partly to their ease of measurement and substantial knowledge about distinct populations of neurons that contribute to different types of movement. One of the best-understood forms of eye movements is saccades, which are rapid, brief, conjugate eye movements that shift the line of sight to bring target images onto the fovea. Saccades are critical for exploring a visual scene, reading, and resetting the eyes during optokinetic or vestibular nystagmus. The brain stem populations of neurons that generate saccades are well known. Two critical components are premotor burst neurons (PBNs) and omnipause neurons (OPNs). PBNs compose a network of excitatory burst neurons (EBNs) and inhibitory burst neurons (IBNs) that fire in push-pull at rates of up to 1000 spikes/s in the macaque during saccades;³ at other times they are silent. Horizontal saccades are generated by PBNs in the paramedian pontine reticular formation (PPRF) and vertical saccades by the rostral interstitial nucleus of the medial longitudinal fasciculus (RIMLF) in the midbrain. In contrast, pontine OPNs inhibit both populations of PBNs by firing at all times except during saccades, when they are silent. Thus, both PBNs and OPNs are highly active neurons. The pathways for pursuit, vestibular, and vergence eye movements are distinct from the saccadic system in that they do not depend upon PBNs and OPNs.

A number of clinical disorders are known to cause failure of the brain stem network that generates saccades. For example, discrete infarction of the paramedian brain stem and metabolic or degenerative disorders⁴⁻⁶ that target PBNs or OPNs cause saccades to become slow or absent. Based on these studies, well-developed models have been tested for the generation of saccades by the brain stem.⁷ Although the brain stem control of saccades is well understood, one disorder stands apart in remaining a mystery: the syndrome of saccadic palsy following cardiac or aortic surgery. This syndrome is the focus of our review, and to illustrate the challenge, we describe two well-studied patients for whom autopsy data are available.^{8,9}

Cases

In 1986, Hanson *et al.*⁹ described a 31-year-old man undergoing surgery to repair an aortic aneurysm and valve that was complicated by bleeding and hypotension who awoke with an “inability to move my eyes.” Saccades were initiated with difficulty (usually with a head thrust and blink), and were slow both horizontally and vertically. Nystagmus quick phases were absent. The visual system and pursuit, vergence, and vestibulo-ocular reflex eye movements were normal. Two months after the operation, he developed sepsis and died of septicemia. Neuropathological examination revealed focal neuronal necrosis with axonal loss and astrocytosis in the median and paramedian pons in the region of the PPRF. The ocular motor nuclei, medial longitudinal fasciculus, midbrain, and frontal eye fields appeared normal.

A second patient, reported by Eggers *et al.*,⁸ was a healthy 50-year-old woman who underwent otherwise uncomplicated aortic valve replacement for an incidentally discovered ascending aortic aneurysm. Upon awakening from anesthesia, she was unable to redirect her

gaze and began using head movements to facilitate gaze shifts. She was discharged and had no problems except for her visual complaints for 3 months, when she developed complex partial seizures. Ten months postoperative, general neurological examination was notable only for diffuse hyporeflexia. Visual acuity, pupils, visual fields, and fundoscopic examination were normal. Straight-ahead fixation was steady, and no saccadic intrusions or nystagmus were seen with ophthalmoscopy. She made no reflexive saccades, and volitional saccades consisted of extremely slow eye movements that eventually reached the target, except for slightly faster downward saccades. Extraocular range, pursuit, vergence, and vestibular slow-phase eye movements were normal. Vestibular and optokinetic nystagmus quick phases were absent. To make rapid head-free gaze shifts, she used exaggerated head turns associated with blinks to generate contraversive vestibular slow-phase eye movements that placed the eyes in the corner of the orbits until the head was maximally rotated, at which point the eyes would continue to slowly drift toward the target. Her saccadic palsy persisted for the rest of her life. Eight years after her cardiac surgery, while anticoagulated for her mechanical valve, she died of a massive bleeding peptic ulcer.

Postmortem gross and histologic examination of the pons in the region of the abducens and omnipause neurons found no lesion (Fig. 1). A normal-appearing blood vessel was present in this region, suggesting that a prominent perivascular space, which could have collapsed during the embedding and sectioning process of the tissue, might explain the area of signal abnormality on *in vivo* and *ex vivo* 7-Tesla magnetic resonance imaging (MRI). Staining the OPN area with LFB-PAS, GFAP, and CR3/43 showed no evidence of demyelination, reactive gliosis, or abnormal microglia activation (Fig. 2). Staining of the abducens nuclei, PBNs in the PPRF and the RIMLF, and cerebellar fastigial nucleus neurons also revealed no abnormalities.

A number of similar saccadic palsy cases have been reported without pathologic evaluation,^{10–19} most commonly in the setting of aortic valve or root surgery requiring cardiopulmonary bypass and hypothermic circulatory arrest. MRIs have failed to show evidence of brain stem infarcts. Thus, the process that could selectively impair brain stem saccade-generating reticular nuclei while sparing all other eye movements remains unknown. An ischemic cause seems likely given the immediacy after surgery. Embolic, hypotensive, hypoxic, or hypothermic mechanisms have been proposed.

Discussion

The syndrome of saccadic palsy following cardiac or aortic surgery is now well recognized,^{10–19} but its pathogenesis is poorly understood. The initial case of Hanson and colleagues demonstrated evidence of damage in the paramedian pontine region that houses both PBNs and OPNs. However, in this case, it is difficult to conceptualize a process—either ischemic or hypoxic—that would selectively involve these brain stem neurons, leaving adjacent areas intact. Even more puzzling is the case described by Eggers and colleagues, who, despite a profound and persistent saccadic palsy, had normal-appearing PBNs and OPNs at autopsy. Here, we first review the evidence that these patients' saccadic palsy was indeed due to a disorder of the brain stem saccade-generating network of neurons. Second, we examine possibilities to account for the apparently normal structure, but

abnormal function, of PBNs and OPNs in the second patient. Specifically, we develop the hypothesis that damage to perineuronal nets (PNs), which surround and support saccade-related neurons, could have led to the saccadic palsy. Finally, we discuss what predictions our hypothesis about ischemic-induced damage to PNs makes about findings in saccadic palsy, and how it might generalize to account for malfunction of other highly active neurons throughout the brain.

Evidence for damage to the brain stem saccadic network

Separate but overlapping pathways govern the pursuit, vestibular, vergence, and saccadic eye-movement systems. Both of our patients had a selective palsy limited to voluntary and reflexive saccades. The brain stem neurons that are essential for generating saccades receive inputs from the eye fields of the cerebral hemispheres via the basal ganglia, the superior colliculus, and the cerebellum.^{2,20} Thus, the question arises: could disruption of inputs to PBNs and OPNs cause the saccadic palsy observed following cardiac surgery? The cortical eye fields lie within the watershed of the cerebral arteries and are, therefore, vulnerable to any failure of cerebral perfusion. Clinical reports of such patients, in which there is documented evidence of bihemispheric ischemia, describe disruption of all voluntary eye movements—saccades, pursuit, and vergence—but sparing of reflexive eye movements such as the quick phases of vestibular and optokinetic nystagmus.^{21–24} This picture of ocular motor apraxia is consistent with injury to the cortical eye fields rather than the brain stem, quite unlike the selective saccadic palsy following cardiac surgery. Furthermore, the supranuclear ophthalmoplegia and chorea described in children following hypothermic cardiopulmonary bypass surgery also implicates cortical and basal ganglia rather than brain stem injury in some cases.²⁵ Other cases of saccadic palsy, generally with preservation of pursuit and vestibular eye movements in addition to dysarthria or other progressive supranuclear palsy (PSP)-like features, suggest brain stem injury despite normal neuroimaging.^{11,14,15} Indeed, many well-studied patients^{8,9,16} show such a selective saccadic palsy in which all forms of saccades—voluntary and reflex—are impaired, but other eye movements are preserved.

Additional evidence that the cause of the saccadic palsy following cardiac surgery is disruption of the brain stem saccade-generating neurons comes from basic studies in macaques. The saccade-generating network consists of segregated PBNs in the PPRF for generating horizontal saccades and in the midbrain RIMLF for vertical and torsional saccades.²⁰ Thus, selective lesions in the pons or midbrain can separately impair horizontal or vertical saccades. However, the mediocaudal region of the PPRF corresponds to the nucleus raphe interpositus (RIP), which contains glycinergic OPNs that project to both horizontal and vertical PBNs.²⁶ Experimental damage to monkey OPNs in the RIP with kainic acid,²⁷ ibotenic acid,²⁸ or muscimol²⁹ leads to slowing of saccades in all directions. Such saccadic slowing is predicted by simulation models of OPN lesions incorporating membrane channels. Miura and Optican proposed that loss of glycine from OPN lesions leads to lower-than-normal EBN activity because of reduced T-type calcium channel current and NMDA current, resulting in slow saccades.⁷ Burst and omnipause neurons may be at special risk from hypotension or hypoxemia because of their high firing rate and metabolic demands.

Thus, the weight of clinical and basic evidence and autopsy findings in the case of Hanson and colleagues all point to selective disruption of the brain stem machinery for saccade generation—specifically PBNs and OPNs. However, we are still left with the puzzles of why such neurons are selectively vulnerable to ischemia and, in the case of Eggers *et al.*, why PBNs and OPNs appeared to be preserved. Since it appears that PBNs and OPNs continue to receive inputs from the cortical eye fields and the cerebellum, what other mechanism could impede their normal function?

Possible role of perineuronal nets

PNs are specialized condensed extracellular matrix structures of aggregated macromolecules ensheathing neurons that have high firing activity, such as the PBNs and OPNs of the brain stem saccadic network.³⁰ PNs consist of a backbone of hyaluronic acid attached to glycoproteins and chondroitin sulfate proteoglycans (CSPG) as aggrecan (ACAN) by a linking protein (HPLN1).³¹ The functions of PNs remain largely unclear. They may form a specialized microenvironment to help stabilize synaptic contacts, play a role in neuroplasticity and neuroprotection, or serve as rapid ion exchangers for potassium ions.³² PNs frequently enwrap highly active fast-firing GABAergic neurons expressing the calcium-binding protein parvalbumin.²⁶ Saccadic burst and omnipause neurons stand out from the surrounding reticular formation by being uniquely ensheathed by PNs.³⁰

PNs may be particularly vulnerable to hypoxia, as a focal cerebral ischemia rat model found that ischemia damages PNs more than the ensheathed neurons in the peri-infarct zone.³³ Thus, we are interested in whether damage to brain stem saccadic network PNs could account for selective saccadic palsy following cardiopulmonary bypass for aortic aneurysm repair and valve replacement. Several functions have been suggested for PNs that could underlie potential mechanisms for malfunction of OPNs and EBNs.³¹ For example, PNs may be important for maintaining membrane-channel properties necessary for normal functioning in these highly active neurons by serving as rapid local buffers of excess cation changes in the extracellular space around somatic membranes of fast-spiking neurons.³²

Damage to PNs might also help explain other neurological phenomena reported following cardiac surgery. PNs surround GABAergic projection neurons in specific portions of the globus pallidus and substantia nigra and in subpopulations of striatal and thalamic inhibitory neurons.³⁴ Hypoxic injury to these PNs could provide an explanation for the reported childhood cases of choreoathetosis and dyskinesia with or without supranuclear ophthalmoplegia following hypothermic circulatory arrest with normal neuroimaging.^{25,35,36} Delayed-onset epilepsy developed in our patient and some others.^{14,18} Seizures are common late sequelae of ischemia, and hippocampal neurons are particularly vulnerable to ischemia. The hippocampus contains a network of PN-ensheathed fast-spiking GABAergic interneurons that are thought to form a large electrically coupled syncytium to rhythmically synchronize cortical neurons.³⁷ Studies in a postischemic rat model demonstrated *in vivo* and *in vitro* spontaneous epileptiform discharges from the CA3 area months after global ischemia, combined with a loss of GABAergic interneurons, a finding that has been associated with aberrant sprouting of glutamatergic fibers leading to enhanced synaptic excitation and reduced synaptic inhibition in temporal lobe epilepsy models.³⁸ Whether

selective vulnerability of hippocampal PN-bearing interneurons could contribute to postischemic temporal lobe epilepsy requires further study.

Implications of the perineuronal net hypothesis

The hypothesis that hypoxic–ischemic damage to PNs might contribute to the saccadic palsy that follows cardiac and aortic surgery makes specific predictions. First, it should be possible to examine the structural integrity of PNs using immunolabeling techniques, and such studies are planned in the case reported by Eggers *et al.* Although this hypothesis is based on only one case who died 8 years after symptom onset with an otherwise normal-appearing brain stem, demonstrating abnormal PNs in this case would certainly justify further investigation. Second, it should be possible to selectively lesion PNs in macaque and measure the effects on specific types of eye movements; the brain stem control of saccades would seem a good place to start, given the well-established neural substrate for these eye movements. Such an approach has already been shown to be feasible through injecting the enzyme chondroitinase ABC to digest chondroitin sulfate chains of PNs in the monkey fastigial nucleus neurons and performing saccade-adaptation experiments.³⁹ If an attempt to lesion PNs surrounding PBNs and OPNs caused a saccadic palsy, then this might serve as a reductionist model to study the effects of lesioning PNs in other areas of the brain and an accessible means to investigate the potential and mechanisms of action of putative therapies.⁴⁰ Pharmacologic manipulation of PNs and other extracellular matrix structures to affect neuronal plasticity, stability, or recovery has been discussed for conditions like stroke and Alzheimer disease as well.^{31,41} In a similar fashion, if damage to brain stem saccade-related PNs was responsible for some cases of saccadic palsy after cardiac surgery, targeting those regions with therapies to promote repair of PNs may offer a way to restore function in patients if the neurons are still intact.

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Figure 1.

(A) Brain stem sagittal view demonstrating cutting planes. The blocks containing the rostral interstitial nucleus of the medial longitudinal fascicle (RIMLF), the oculomotor nucleus (nIII), the paramedian pontine reticular formation (PPRF) including the excitatory (EBNs) and inhibitory burst neurons (IBNs), the nucleus raphe interpositus (RIP) containing omnipause neurons (OPNs), and the abducens nucleus (nVI) were cut in a series of 10 μm - and 5 μm - thick sections. Rostral view of corresponding plane through the pons at the level of the RIP containing OPNs by *ex vivo* 7-Tesla MRI (B) and gross section (C). No pathologic lesions were visible. Blood vessels are indicated by arrows. To accomplish postmortem imaging before brain sectioning, the brain was suspended in Fomblin (Solvay Solexis, West Deptford, NJ) to reduce image artifacts and underwent three-dimensional 7-Tesla MRI on an actively shielded scanner (Siemens, Erlangen, Germany) in a custom-designed chamber using a volume transmit coil and 32 channel receive coil, as previously described.⁴² T_2^* - and T_1 -weighted images from the whole brain were respectively acquired at 420- and 310- μm isotropic resolution using multi-echo and inversion-prepared gradient echo sequences with multiple inversion times, respectively. Scale bar (B, C) = 1 cm. INC, interstitial nucleus of Cajal; IO, inferior olive; MB, mammillary body; MT,

mammillothalamic tract; nIV, trochlear nucleus; NVI, abducens nerve; RN, red nucleus; TR, tractus retroflexus; PC, posterior commissure; SC, superior colliculus.

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Figure 2.

Omnipause neurons (OPNs) in the nucleus raphe interpositus (RIP) appear histologically normal (arrows). (A) Drawing of a transverse section of the pons at the level of the RIP. The box indicates the area for detailed views of RIP in (B–D). (B) LFBPAS staining showed no evidence of demyelination. (C) CR 3/43 staining showed no abnormal microglial activation. (D) GFAP staining showed no reactive gliosis. The arrows point to putative OPNs; the dotted lines indicate the midline. ICP, inferior cerebellar peduncle; MCP, medial cerebellar peduncle; ML, medial lemniscus; MLF, medial longitudinal fasciculus; MVN, medial vestibular nucleus; NV, trigeminal nerve; nVI, abducens nucleus; NVI, abducens nerve; nVII, facial nucleus; NVII, facial nerve; PT, pyramidal tract; RIP, nucleus raphe interpositus; SO, superior olive; SVN, superior vestibular nucleus; LFB-PAS, Luxol fast blue periodic acid–Schiff; GFAP, glial fibrillary acidic protein. Scale bar (A) = 5 mm; (B–D) = 200 μ m.