REVIEW

Current landscape in motoneuron regeneration and reconstruction for motor cranial nerve injuries

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Abstract

The intricate anatomy and physiology of cranial nerves have inspired clinicians and scientists to study their roles in the nervous system. Damage to motor cranial nerves may result from a variety of organic or iatrogenic insults and causes devastating functional impairment and disfigurement. Surgical innovations directed towards restoring function to injured motor cranial nerves and their associated organs have evolved to include nerve repair, grafting, substitution, and muscle transposition. In parallel with this progress, research on tissue-engineered constructs, development of bioelectrical interfaces, and modulation of the regenerative milieu through cellular, immunomodulatory, or neurotrophic mechanisms has proliferated to enhance the available repertoire of clinically applicable reconstructive options. Despite these advances, patients continue to suffer from functional limitations relating to inadequate cranial nerve regeneration, aberrant reinnervation, or incomplete recovery of neuromuscular function. These shortfalls have profound quality of life ramifications and provide an impetus to further elucidate mechanisms underlying cranial nerve denervation and to improve repair. In this review, we summarize the literature on reconstruction and regeneration of motor cranial nerves following various injury patterns. We focus on seven cranial nerves with predominantly efferent functions and highlight shared patterns of injuries and clinical manifestations. We also present an overview of the existing reconstructive approaches, from facial reanimation, laryngeal reinnervation, to variations of interposition nerve grafts for reconstruction. We discuss ongoing endeavors to promote nerve regeneration and to suppress aberrant reinnervation and the development of synkinesis. Insights from these studies will shed light on recent progress and new horizons in understanding the biomechanics of peripheral nerve neurobiology, with emphasis on promising strategies for optimizing neural regeneration and identifying future directions in the field of motor cranial neuron research.

Key Words: *axon degeneration; cranial neuropathy; facial nerve; facial paralysis; motoneuron; nerve regeneration; peripheral nerve; recurrent laryngeal nerve; synkinesis; vocal fold paralysis*

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Introduction

Motor cranial nerves arise from the brainstem and innervate an intricate network of musculature in the head and neck. The complex anatomy and physiology of cranial nerves make repair and development of regenerative therapies a formidable challenge. Nerve injuries were first classified by Seddon as neuropraxia, axonotmesis, or neurotmesis (Seddon, 1942). Sunderland (1951) modified this classification into a five-tier scheme based on histopathology (**Table 1**). Once injury occurs, there is potential for axonal regeneration, but it is dependent upon injury severity and the biochemical and microphysical milieu. Release of neurotrophic growth factors, inflammatory cytokines, and angiogenic factors are critical modulators in nerve recovery and are targeted in regenerative therapies. Aberrant regeneration and synkinesis can occur if regenerating axons are misdirected; thus, voluntary movements lead to simultaneous activation of intended and unintended muscles. Preservation of the epineurium and surgical interventions including connective tissue scaffolds and conduits encourage proper regeneration and can lower synkinesis occurrence (Geuna et al., 2009). Further, maintaining motoneuron connectivity at the neuromuscular junction (NMJ) and harnessing reinnervation capacity may be important in lessening the impact of sarcopenia (Arnold and Clark, 2019).

The head and neck accounts for only 12% of body surface area but is densely innervated with cranial nerves that perform diverse biological functions. Afferent cranial nerves play important roles in assimilating sensory information, while efferent nerves execute motor functions whose injury leads to paralysis. This review focuses on clinical manifestation of motor cranial nerve dysfunction, reconstructive options, and related nerve regeneration. We focus on seven cranial nerves with predominantly efferent functions—facial (VII), recurrent laryngeal (branch of X), hypoglossal (XII), spinal accessory (XI), oculomotor (III), trochlear (IV), and abducens (VI) nerves—and highlight shared patterns of injuries. For each nerve, we discuss available methods of repair/reconstruction, experimental techniques, and future directions of regeneration research.

In conducting this review, we searched the following databases from their inception for published, unpublished, and ongoing trials: Cochrane Library, Ovid Medline, Google Scholar, PubMed, and Web of Science. We imposed no limits

Table 1 Classification of nerve injuries by Seddon and Sunderland

Sunderland	Seddon	Description	Examples
I	Neuropraxia	Localized damage to myelin	Relatively mild injury often involving compression of the nerve at a bony interface or indolent growth of a tumor
II	Axonotmesis	Loss of axon continuity with damage to myelin	Motor vehicle accidents, falls, and physical assault are all common inciting events for grade II–IV injury
III		Injury to myelin, axon, and endoneurium	
IV		Injury to myelin, axon, endoneurium, and perineurium	
V	Neurotmesis	Complete transection of all components including epineurium	Laceration from sharp objects including knives, glass, surgical instruments, or animal bites

to the coverage dates and included articles from 1942 (Seddon's classification) through September 2019, with emphasis on recent publications. For each nerve, search terms included the anatomic name and keywords applicable to nerve injury, including "neuropathy", "nerve injury", "paresis", or "paralysis", "reconstruction", and "nerve regeneration." Two authors performed the initial search to identify studies that met criteria of this review. The review was restricted to the English literature and included original clinical and translational literature as well as reviews. The authors appraised the full-text articles and selected applicable studies for inclusion.

Facial Nerve

The facial nerve (FN) is a complex cranial nerve whose diverse functions include motor innervation to the ipsilateral muscles of facial expression, taste to anterior 2/3 of the tongue, sensory touch, temperature, and pain. Denervation of facial musculature is associated with decrease in quality of life (QoL) and psychological distress (Nellis et al., 2017). Efforts at rehabilitating FN injury focus on restoring motor functions and counteracting the untoward effects of facial paralysis. This section summarizes functional problems associated with facial paralysis and provides an overview of surgical management, as well as ongoing research in FN reconstruction and regeneration.

Epidemiology and clinical manifestation of facial nerve injury

Facial paralysis occurs at an incidence of 20 to 32 per 100,000 (Lorch and Teach, 2010). Congenital facial palsy is associated with Moebius syndrome, Goldenhar-Gorlin syndrome, and hemifacial microsomia (Jenke et al., 2011). In older children, facial paralysis is often acquired in Lyme disease, Bell's palsy, or complications from otitis media (Sharma et al., 2015). In adults, etiologies for FN disorders are more numerous, including infections (Ramsey-Hunt syndrome, Epstein-Barr virus, human immunodeficiency virus), trauma, iatrogenic, and neoplastic processes (Jenke et al., 2011). Inadvertent FN injuries are of particular concern in head and neck surgery which places the extratemporal branches of the nerve at risk, as well as otologic operations where the nerve may be at risk amid its course within the temporal bone. In a retrospective review of 1810 patients, oral and maxillofacial procedures accounted for 40% of iatrogenic FN injuries, resection of head and neck malignancies for 25%, and otologic procedures for 17% (Hohman et al., 2014). Primary FN tumors are rare and comprise only 0.8% of intra-petrous lesions (Rosenblum et al., 1987).

The functional consequences of facial paralysis can manifest in each division of the FN. Peri-ocular manifestations include a loss of blink reflex and inadequate eye closure, leading to exposure keratitis and vision loss (Homer and Fay, 2018). The resultant loss of facial tone in the mid- and lower face causes oral incompetence, speech/articulation difficulty, and nasal valve collapse. Moreover, facial synkinesis can occur following Wallerian degeneration and is associated with depression, diminished self-esteem, and poor QoL (Nellis et al., 2017). Facial paralysis not only creates psychologic disturbances for patients but also stigma and social burden. Studies by Ishii et al. (2016) using infrared eye-tracking technology demonstrated altered perception of patients with a paralyzed face compared to those with symmetric faces. Furthermore, Li et al. (2016) demonstrated that observers perceived patients with facial paralysis as less trustworthy, unintelligent, and more distressing compared to controls.

Facial reanimation

Approaches to facial paralysis are multifaceted, involving a combination of nerve repair, grafting, substitution, and tissue rearrangements, including local muscle transfers, soft tissue reconstruction, and microvascular anastomosis to deliver new functional muscle and nerve. In this section, we present reconstruction techniques by anatomic region of the face and highlight unique considerations for each.

In treating paralysis of the upper face, reconstruction is directed towards managing ptosis and impaired eye closure. Brow ptosis is improved via various brow lifts, including direct, forehead, pretrichial, and coronal brow lifts (Meltzer and Byrne, 2008). Eyelid weight placement, tarsorrhaphy, and tarsal strip procedures have been widely practiced to establish eye closure (Mehta et al., 2013). In the mid- and lower face, reconstructive options are categorized as static or dynamic. In static reanimation, facial asymmetry is improved by repositioning paretic tissues of the face to counteract the effect of gravity, such as by tensor fascia lata sling (Ibrahim et al., 2013). A static sling improves oral incompetence and facial asymmetry at rest, but its inability to produce active movements is a drawback.

In contrast, dynamic reanimation allows for facial movements created through patient-initiated efforts (Kim, 2016).

If primary neurorrhaphy is possible, an epineurial repair is performed at the time of injury. If the defect is too large for tension-free anastomosis, cable grafting of autogenous nerves can be used (Kim, 2016). A cable nerve graft provides an ideal conduit for regeneration by acting as a scaffold containing Schwann cell basal laminae, which provide native neurotropic growth factors (Millesi, 2007).

In instances where FN is severely damaged or unavailable for grafting, nerve transfers may be indicated. Nerve transfers involve substituting an alternative nerve as the source of neural input to achieve muscle movement. Examples of these include the hypoglossal-facial (Conley and Baker, 1979) and the masseteric-facial (Spira, 1978) transfers. Contemporary approaches favor a partial transection of the hypoglossal nerve to minimize impairing tongue movement and tone, often with a jump graft bridging the hypoglossal hemi-transection to FN. Patients who undergo nerve transfers learn to produce facial movements by activating tongue (in the case of hypoglossal transfer) or mastication muscles (in the case of masseter transfer). Disadvantages of nerve transfers are requirement for patient-initiated effort and potential donor site morbidity. To improve upon this, the cross facial nerve graft was developed to attain spontaneous, rather than volitional, movements. In this procedure, the surgeon connects the contralateral FN to the damaged FN and deliver motor axons via a long interposition nerve graft across the face (Lee et al., 2008; Peng and Azizzadeh, 2015). These approaches can be combined with vascularized free tissue transfers to optimize facial symmetry and functions. An example is the gracillis free flap, which has achieved satisfactory outcomes in facial reconstruction (Boahene, 2008; Hadlock et al., 2011). In counseling patients who desire to undergo facial reanimation, clinicians often consider the limitations of reanimation procedures, including donor site morbidity, graft failure, need for repeat operations, and variable outcomes.

Research in facial nerve regeneration

To date, FN research focused on enhancing regeneration by modulating growth factors and inflammatory cytokines. After Wallerian degeneration, a complex immune cascade is activated, leading to neurotrophic growth factor release that serve as therapeutic targets (Jessen et al., 2015). The glial cell-derived neurotrophic factor (GDNF) is a notable example of a category of growth factors that stimulate dopaminergic neuron differentiation, which delays FN regrowth (Barras et al., 2009). Others have also evaluated the effect of reducing oxidative stress at the time of injury. In a study by Wang et al. (2009), inhibiting nitric oxide synthase led to an earlier onset of axonal regeneration than primary FN repair. Another important finding in the peripheral nerve literature relates to macrophage-induced blood vessel regrowth (**Figure 1**). Macrophages detect hypoxia within a nerve bridge and release vascular endothelial growth factor A that guides Schwann cell migration across the defect to facilitate regeneration (Cattin et al., 2015).

Cellular replacement therapies have been investigated for potential salutary effects on nerve repair and regeneration (**Figure 2**). The underlying mechanism putatively involves anti-inflammatory and neurotrophic modulation. Small animal studies have shown successful regeneration of a buccal nerve gap using undifferentiated adipose-derived stem cells (ADSCs) and bone marrow-derived stem cells (Eren et al., 2016; Watanabe et al., 2017). Transdifferentiated ADSCs, which functioned as Schwann-like cells, augmented regeneration in a rat model with transected buccal nerves (Sun et al., 2011). In this experiment, decellularized allogenic arterial conduits containing transdifferentiated ADSCs demonstrated similar regeneration as SC-seeded conduits and superior regeneration compared to unseeded and ADSC-seeded conduits. Additionally, Toma et al. (2015) demonstrated functional NMJ in neurons derived from induced pluripotent stem cells. These results provide a rationale for using induced pluripotent stem cells-derived motoneurons for cell replacement and open the door to studying stem cell-derived motor neurons in FN injuries. There are ongoing studies for assessing the therapeutic benefit of induced pluripotent stem cells-derived motoneurons in mouse sciatic nerve models as a proxy of FN injuries.

In addition to optimizing regeneration, others evaluated agents for inhibiting aberrant regeneration. Yian et al. (2001) showed that vincristine injection prevented reinnervation of a selected muscle. A recent study examined an endogenous inhibitor of nerve regeneration, myelin-associated glycoprotein, in a transection *Thy*1- green fluorescent protein rat model. The study demonstrated that intraneural myelin-associated glycoprotein application effectively inhibited FN regeneration; its effect was comparable to vincristine-induced neuro-inhibition (Ali et al., 2019a). These studies have therapeutic implications for targeting nonselective regeneration and synkinesis.

Another interesting question is whether FN regeneration and synkinesis development differ based on motor versus sensory nerve grafting. One of the first studies to address this was performed in 36 rats with tibial nerve transection and isogeneic motor, sensory, and mixed nerve grafting. This work demonstrated robust regeneration through motor and mixed nerve grafts, but reduced regeneration through sensory nerve grafts (Nichols et al., 2004). In a subsequent study, Brenner et al. (2006) corroborated these findings, demonstrating higher nerve density, percent nerve, and total fiber counts in nerves after motor versus sensory nerve grafts. However, more recent studies in this topic yielded contradictory results. Ali et al. (2019b) found no difference in histological or functional outcomes for motor versus sensory grafting in a 5-mm nerve gap rat model. The authors noted that their findings support the current practice of using sensory nerve grafts in humans but also acknowledged the inherent limitations of a small nerve gap model, rather than distinct FN physiology.

Emerging bioengineering solutions to the challenges of facial paralysis involve optimizing the bio-electrical interfaces in FN injuries (**Figure 2**). Examples include an electroactive polymer artificial muscle device (Ledgerwood et al., 2012) and a similar implantable system for restoring eye blinks

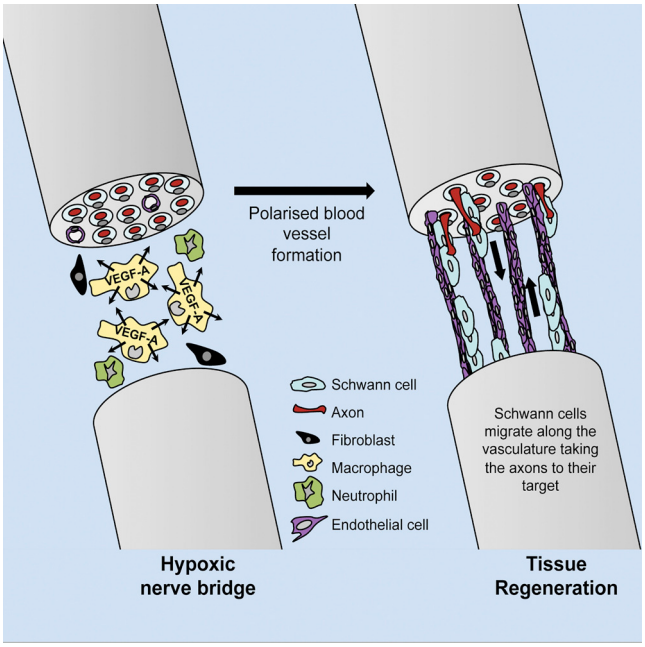

Figure 1 Choreography of regeneration across the injured nerve. Macrophages secrete VEGF-A in response to hypoxia, which polarizes vasculature to relieve hypoxia. Schwann cells then use these blood vessels to cross the defect and guide axons. VEGF-A: Vascular endothelial growth factor A. With the permission from Cattin et al., 2015.

after facial paralysis. In a recent study, Jowett et al. (2019) presented a novel implantable neuroprosthetic device for electrical animation of a hemiparetic face. This innovative approach demonstrated the ability to produce electrically stimulated, independent facial movements through a biocompatible implant and broadened the horizons for technologies to treat facial paralysis.

Recurrent Laryngeal Nerve (Branch of X)

The recurrent laryngeal nerve (RLN) constitutes a large branch of the vagus nerve and carries efferent, afferent, and parasympathetic fibers. Central nuclei of RLN lie within the nucleus ambiguus of the medulla. Situated at the crossroads of the respiratory and digestive tracts, the larynx performs three physiologic functions sometimes called the 3 P's: airway protection (prevents aspiration), airway provision (constitutes part of the airway), and phonation (voice). RLN-innervated intrinsic laryngeal muscles include the paired right and left thyroarytenoid, lateral cricoarytenoid, and posterior cricoarytenoid muscles. The interarytenoid muscle with recognized transverse and oblique components is unpaired in a central anatomic location. The paired right and left cricoarytenoid muscles are innervated by the superior laryngeal branch of the vagus. These muscles work in concert to accomplish the elegant and highly coordinated movements

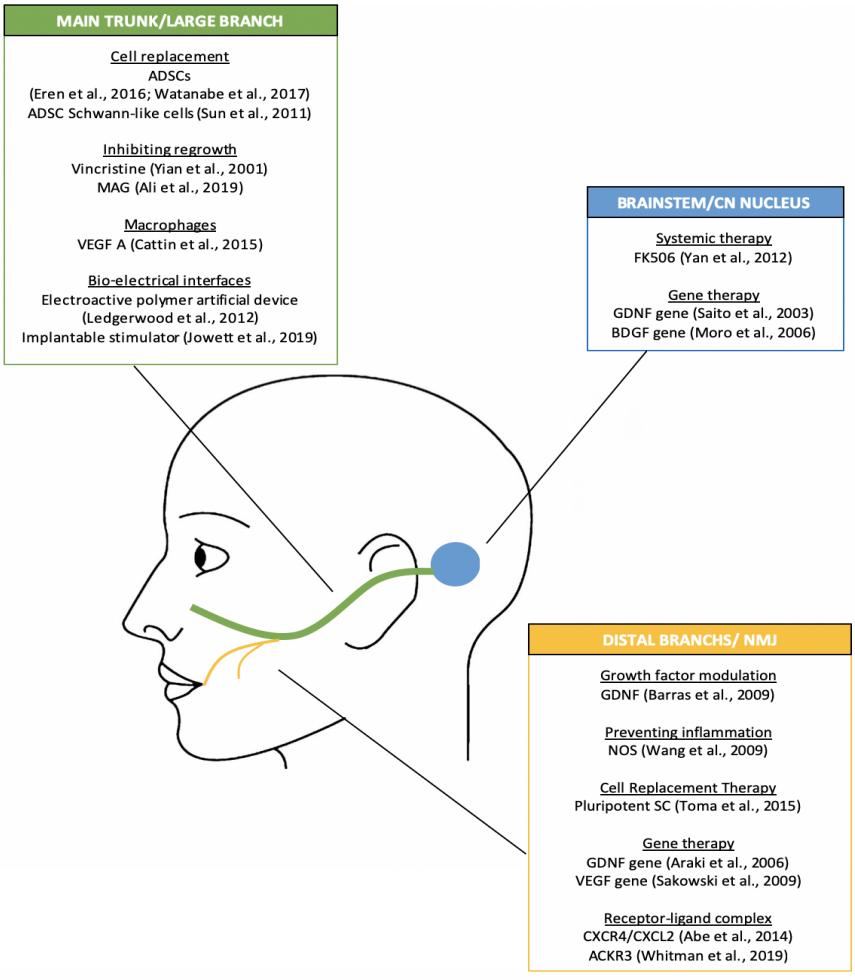

Figure 2 Examples of targeted regenerative therapy and research by anatomic sites. Applications may overlap and are not comprehensive. Therapies for brainstem/cranial nerve nucleus target neuronal cell bodies; main trunk therapies target injury to neuronal projections and axonal-Schwann cell interactions; nerve branch therapies may address axonal repair, sprouting, reinnervation, and muscle endplates at the NMJ. ACKR3: Atypical chemokine receptor 3; ADSCs: adipose-derived stem cells; BDNF: brain-derived neurotrophic factor; CN: cranial nerve; CXCL12: chemokine C-X-C motif ligand 12; CXCR4: C-X-C motif chemokine receptor 4; GDNF: glial cell-derived neurotrophic factor; MAG: myelin-associated glycoprotein; NMJ: neuromuscular junction; NOS: nitric oxide synthase; VEGF-A: vascular endothelial growth factor A.

necessary for normal laryngeal function.

Epidemiology and clinical manifestation of recurrent laryngeal nerve injury

The incidence of RLN palsy varies by the mechanism of injury, as detailed in this section. In a clinical observation study of 600 cases of RLN paralysis, the authors developed the following classification schema: surgical reasons comprise the subcategories of neck surgery, chest surgery, post-intubation effects, whereas non-surgical reasons include disorders of the neck, chest, and idiopathic (Hirose, 1978). An additional potential division would be that of intracranial versus extracranial site, with intracranial etiologies involving disease processes that include RLN paralysis in addition to other cranial nerve or neurologic deficits. Patients with unilateral RLN injury may develop a breathy voice, lose vocal projection, and exhibit phonatory instability. Additional morbidity may result from aspiration risk and the need for feeding tube placement to enable safe intake of food. Bilateral loss of RLN function is less common, and typically airway symptoms predominate due to the loss of vocal fold abduction and narrowed glottic airway. Bilateral paralysis may also result in significant vocal dysfunction and/or dysphagia.

In reference to unilateral paralysis, post-operative injury is the most common inciting event (Dralle et al., 2004; Randolph et al., 2011). The factors that relate to this phenomenon are complex and nuanced and must include a discussion on hospital or surgeon volume, technique, nature and extent of disease process, and possible use of intraoperative nerve monitoring. An updated estimate of the prevalence of RLN injury following thyroidectomy varies from 1% to 2% from high-volume studies (Dralle et al., 2004). To reduce incidence of iatrogenic injury, many institutions now employ a perioperative nerve assessment protocol with intraoperative nerve monitoring (Randolph et al., 2011). While thyroid neoplasms are the most common disease process of the neck that puts the RLN at risk, any tumor that involves the paratracheal region can contribute to the incidence of RLN paralysis, either through direct compression or in subsequent extirpative operations.

Given its origin from the "wandering" vagus nerve, RLN is at risk from not only disease processes in the neck, but those in the chest as well. Unlike in the neck where injury is primarily related to the process of removing a neoplasm, mediastinal RLN injury commonly occurs due to operations involving the great vessels or the heart (Salem et al., 1971). In addition to this difference, the afflicted age range is variable, with mediastinal injury occurring more frequently in pediatric patients due to operations for congenital cardiovascular anomalies. Although the incidence of RLN paralysis following mediastinal surgery is not as well characterized as for thyroid surgery, one study estimated the incidence between 5–10% depending on the operation (Salem et al., 1971). Intrinsic diseases of the chest, such as cardiac chamber enlargement and aneurysms, may exert a compressive effect on the RLN. Neoplastic processes involving the esophagus, lungs, or mediastinum may also affect the RLN, typically via tumor infiltration or through the process of their removal (Hirose, 1978).

Idiopathic vocal fold paralysis is a well-established phenomenon that is thought to be related to idiopathic dysfunction of the RLN, possibly due to a virus. Clinicians arrive at this diagnosis in the absence of other explanatory symptoms, neurologic deficits, or imaging findings (Havas et al., 1999). Depending on a variety of clinical factors, many of these patients will recover some degree of vocal fold mobility or vocal function over time (Sulica, 2008). Other rare causes of RLN injury in pediatric patients include intracranial anomalies such as Chiari malformations, intraventricular hemorrhage, or obstructive hydrocephalus (Arora et al., 2016). Additional uncommon causes in adults can include vascular accidents, demyelinating diseases, motor neuron diseases, and tumors or abscesses that involve the cranial nerves proximal to their exit from the skull.

Treating recurrent laryngeal nerve injuries

Recovery after RLN injury is variable and depends on the injury mechanism, severity, and timing. In patients within a year of paralysis onset and whose RLN nerve may not be definitively injured, observation may be indicated if the level of functional impairment is limited. With unilateral paralysis, this typically means the patient has an acceptable voice-related QoL and no significant dysphagia (Hogikyan and Sethuraman, 1999). With bilateral paralysis, it implies an adequate airway.

The goals of treating RLN injury are to improve impaired laryngeal functions, which may include voice, airway protection, and/or breathing. Depending on the injury etiology and timing, temporary and permanent treatments are available. Treatment options include conservative approaches, utilizing voice therapy with trained speech and language therapists to maximize compensatory maneuvers. Temporary procedural solutions primarily involve vocal fold injection (VFI). Permanent corrective procedures include laryngeal framework surgery and nerve reinnervation. VFI is the least invasive approach and one of the most commonly practiced treatments, owing to its tolerability, efficacy, and safety. It is a particularly attractive option when neurogenic RLN recovery remains possible because several injection materials dissolve over time, imparting temporary benefit and continued assessment for recovery. In VFI, biocompatible materials are injected into the paraglottic space or glottic larynx to increase bulk and vocal fold medialization. Main considerations in selecting the appropriate materials are differences in longevity, bio-durability, risk of immune reactivity, and cost (Lynch and Parameswaran, 2017). Laryngeal framework surgery is a potentially permanent treatment for glottic insufficiency, relying on the same architectural principles as VFI. These phono-surgical procedures include medialization thyroplasty or laryngoplasty, arytenoid adduction, and cricothyroid subluxation (Hess and Fleischer, 2016). In medialization laryngoplasty, a biocompatible implant is placed through a surgical incision in the thyroid ala into the paraglottic space to provide medialization of an immobile vocal fold. Surgeons

may utilize additional corrective procedures to ensure appropriate symmetry and height of the afflicted vocal fold during phonation, including arytenoid adduction or cricothyroid subluxation. The aforementioned procedures are primarily utilized for unilateral vocal fold paralysis.

The options for bilateral vocal fold paralysis differ due to the nature of the disease process and resultant anatomic insufficiencies. Options for patients with symptomatic airway obstruction include emergent airway interventions, such as endotracheal intubation or placement of a tracheostomy tube. Glottic enhancing procedures can be used on patients with bilateral vocal fold paralysis to potentially avoid the need for permanent tracheostomy. These can include arytenoidectomy (total or medial), transverse cordotomy, and vocal fold lateralization (Bosley et al., 2005). The decision to pursue one of these surgical options is complex and must include a discussion on voice-related QoL, resultant aspiration risk, and subsequent vocal quality.

The above options—geometric alteration of glottic insufficiency via VFI, medialization laryngoplasty, or primary neurorrhaphy—typically fail to restore tensing capability of the vocal fold and thus result in suboptimal pitch control (Tucker and Rusnov, 1981). With its history dating back to the early 1900s, laryngeal reinnervation is another option for managing RLN injures with an overall goal of restoring the connection of motoneurons with denervated laryngeal muscle. The surgeon's decision to offer a patient a reinnervation operation depends on the injury mechanism, timing, patient anatomy, and health. These procedures can involve primary neurorrhaphy of the RLN, autologous cable grafting for nerve gap defect injuries (where tension-free anastomosis cannot be achieved with end-to-end repair), neuromuscular pedicle utilization, and nerve transfer options, including hypoglossal or ansa cervicalis transfer (Wang et al., 2011). While the specifics of each of these options is beyond the scope of this review, such reinnervation procedures have proven effective in restoring vocal fold tone in various studies. A landmark study by Wang et al. (2011) demonstrated better glottic closure, phonation, and electromyographic reinnervation of laryngeal muscles in 237 patients undergoing ansa cervicalis-to-RLN anastomosis, compared to age- and gender-matched controls. Similarly, Paniello et al. (2011) performed a randomized controlled trial, which assessed the efficacy of vocal fold medialization laryngoplasty versus reinnervation and concluded superior outcomes in reinnervation for patients under age 52. Thus, for carefully selected patients, laryngeal reinnervation remains a viable option for restoring vocal fold capabilities. Finally, a discussion on managing RLN injuries must involve voice and swallowing therapy, which are invaluable adjuncts that focus on correctly compensating for impaired vocal fold function while avoiding counterproductive compensatory behaviors.

Research in recurrent laryngeal nerve regeneration

The penultimate goal of research in RLN injuries is restoring normal physiologic function, which requires that the correct nerves coordinate to the correct muscles. However, since RLN injuries are prone to spontaneous reinnervation, resultant synkinesis is a frequent problem (Shindo et al., 1992; Crumley, 2000; Johns et al., 2001). The capacity for spontaneous RLN regeneration was described in detail by Rosko et al. (2018), who showed that following resection of a 5-mm RLN segment in rats, nerve fibers spontaneously regenerated across the nerve gap to form intact NMJs and reinnervation to the thyroarytenoid muscle. Retrograde neuronal labeling after RLN injury demonstrated that reinnervation to laryngeal muscles originated from RLN cell bodies and neurons that normally did not project to the larynx through the RLN (Nomoto et al., 1991; Hydman and Mattsson, 2008). Even if native RLN neurons regenerate, normal innervation patterns to specific muscles are not preserved. This quest to interface correct nerves to the correct muscles remains a key unrealized goal.

Transgenic expression of various neurogenic growth factors to limit neural degeneration or enhance recovery following RLN injury has been explored by multiple authors, and gene therapy has been presented as a therapeutic strategy with great potential in the larynx (Heavner et al., 2007). Possible benefits from this type of therapy include enhanced health and innervation status of laryngeal muscles and improved laryngeal function and survival of associated brainstem neuronal cell bodies. Shiotani et al. (1998) first demonstrated increased muscle fiber caliber in the thyroarytenoid muscle in a paralyzed larynx rat model after transduction with the human insulin-like growth factor-1 gene. Brainstem transduction in rats was successfully demonstrated by Rubin et al. using an empty adenoviral vector and an adeno-associated viral vector containing a GFP reporter gene after peripheral injection into the RLN (Rubin et al., 2001, 2003). To assess the potential benefit of gene transfers into the brainstem, Saito et al. (2003) employed an adenoviral vector encoding GDNF in rat models with lesioned nucleus ambiguus. This experiment revealed neuroprotective effects of GDNF gene therapy to the motoneurons of the nucleus ambiguus, ameliorated choline acetyltransferase immunoactivity, and decreased the activity of nitric oxide synthase. In a similar study, Moro et al. (2006) found a synergistic effect of GDNF- and brain-derived neurotrophic factor-adenoviral gene transfer for preventing motoneuron loss at the nucleus ambiguus.

Another more functional approach is to evaluate vocal fold motion recovery or nerve to motor endplate contact in laryngeal muscles as outcome measures. Araki et al. (2006) showed histologic and functional recovery of the RLN after adenovirus-mediated GDNF gene transfer in a rat RLN crush model. Sakowski et al. (2009) used an engineered zinc finger protein transcription factor to induce vascular endothelial growth factor and similarly observed better nerve-endplate contact in the thyroarytenoid muscle and accelerated recovery of vocal fold mobility post injury. An adeno-associated vector carrying the transgene for an insulin-like growth factor-1 transcription factor similarly achieved improved nerve-endplate contact and vocal fold mobility recovery versus controls when injected peripherally

into the crushed RLN (Rubin et al., 2012).

Another important discovery is differential expression of neurotrophic growth factors post RLN injury in various laryngeal muscles with respect to absolute levels and the temporal sequence of expression. Hernandez-Morato et al. (2014) explored expression of GDNF, netrin I, and more recently laminin III in non-pooled rat posterior cricoarytenoid, medial thyroarytenoid, and lateral thyroarytenoid muscles after RLN injury. Their studies elucidated the complex interplay and temporal changes in various factors and receptors, which the authors postulated could potentially be manipulated to enhance the desired selective reinnervation while reducing synkinesis (Halum et al., 2012; Hernandez-Morato et al., 2014; Montalbano et al., 2019). Several authors also explored selective delivery of neurotoxins to specific laryngeal muscle groups to limit aberrant synkinetic reinnervation following RLN injury (McRae et al., 2009; Paniello and Park, 2015). A future therapeutic strategy could couple this with selective neurotrophic enhancement of desired neural ingrowth to optimize physiologic function. Thus, the theme of seeking correct nerve to correct muscle flows through contemporary research in laryngeal reinnervation but as yet remains an unrealized goal.

Hypoglossal Nerve (XII)

The hypoglossal nerve carries signals from the medulla to the tongue muscles. In humans, lateral branches of the hypoglossal nerve supply the retrusor tongue muscles, whereas medial branches innervate protrusor tongue muscles (Bassiri Gharb et al., 2015). Injuries to the hypoglossal nerve can arise from meningitis, stroke, central nervous system malignancy, and compression at the bony skull base outlet (Atalay et al., 2019). Iatrogenic causes of hypoglossal nerve damage include laryngeal operations, head and neck surgeries, or morbidity associated with partial transection of the hypoglossal nerve during facial reanimation (Okui et al., 2019; Tham et al., 2019). Literature on primary repair of hypoglossal nerve injury is limited. Most studies focused on tongue weakness secondary to hypoglossal nerve transfer for facial reanimation or laryngeal reinnervation and are beyond the scope of this discussion.

Spinal Accessory Nerve (XI)

The spinal accessory nerve (SAN) has a long and superficial course in the posterior triangle of the neck that renders this nerve vulnerable to injuries (AlShareef and Newton, 2019). Iatrogenic SAN injuries comprise the most common etiology of this cranial neuropathy, and mostly from lymph node biopsies, tumor resection, or neck dissections. Spontaneous idiopathic SAN palsies have been reported but are rare (Sergides et al., 2010). The incidence of SAN paralysis has not been well described. Injuries to this nerve result in weakness of the sternocleidomastoid and trapezius muscles, leading to disabling instability of the affected shoulder girdle. Consequently, patients compensate by overusing the other shoulder and back muscles, such as the levator scapulae and rhomboid, and can experience chronic intractable pain, contracture, and muscle spasms.

Surgical reconstruction of SAN paralysis has been described. In addition to direct repair, distal nerve transfer techniques are used, including the transfer of medial and lateral pectoral nerves (Novak and Mackinnon, 2004; Maldonado and Spinner, 2017). Challenges to these procedures are resultant weakness in donor muscles, which require extensive muscular re-training, i.e., using arm adduction or rotation to mobilize the trapezius. Elhassan et al. (2015) reported effective stabilization of the scapulothoracic joint using a triple-tendon transfer technique (i.e., transfer of the levator scapulae to the lateral aspect of the spine of scapula, rhomboid minor to the spine of the scapula, and rhomboid major to the medial spine of the scapula). Recently, Mayer et al. (2019) published a method of selective fascicular nerve transfers from the upper trunk of the brachial plexus and proclaimed shorter distance of nerve transfer, which improved cognitive synergy to the target function of shoulder movement. In studying the long-term outcomes following surgical reconstruction of SAN injuries, Goransson et al. (2016) reported improved shoulder movements in 43% of neurolysis patients, 71% of direct repair, and 22% of nerve-grafted patients. To date, basic science or translational studies in SAN regeneration have not been explored.

Ocular Motor Nerves

Functional vision is the result of several discrete systems working in concert; the optic nerve carries sensory input for vision, which synchronizes with eye movements to maintain a focused fovea. Visual sensory information and pursuit are in turn maintained by the efferent ocular nerves (Karatas, 2009). Specifically, the oculomotor nerve (III) innervates the inferior oblique, medial/inferior/superior rectus muscles, and the levator palpebrae superioris. The trochlear (IV) and abducens nerves (VI) innervate the superior oblique and lateral rectus, respectively. Damage anywhere along the ocular nerve pathways, from cerebral cortex to the NMJ, can affect eye movements.

Etiology of ocular motor problems

Disorders that affect eye movements include trauma, ischemia, tumors, and inflammatory eye disease. One the most common reasons for emergency orbital surgery are orbital blowout fractures (Lee et al., 2015), which can lead to entrapment of extraocular muscles or impingement of the optic nerve. If untreated, patients develop diplopia, strabismus (eye misalignment), permanent blindness, and disfigurement (Alinasab et al., 2018). Secondary cranial nerve palsy may also be due to underlying neurological, malignant, or ischemic damage (Park et al., 2018). Classic examples of supranuclear lesions include stroke and mass effect from central nervous system tumors. On the other hand, retro-orbital accumulation of glycosaminoglycans in thyroid eye disease can affect ocular mechanics, visual acuity, and patient's psychosocial functions. In patients with multiple sclerosis, internuclear ophthalmoplegia results from autoimmune-mediated

disruption of the medial longitudinal fasciculus. Patients with this condition lose the ability to adduct one or both eyes. Less commonly, congenital misalignment affects 1% of children under the age of ten (Govindan et al., 2005). Extraocular fibrosis, myasthenia gravis, and childhood thyroid disease are also etiological factors of strabismus in children.

Treating ocular motor disorders

Intramuscular botulinum toxin injections have been used to treat eye movement disorders for patients who do not undergo surgical repair. Thyroid eye disease treatment has also seen advances in non-surgical management through thyroid stimulating hormone receptor antibodies. which ameliorate disease severity and reduce the need for orbital decompression (Roos and Murthy, 2019). A large randomized controlled trial showed that insulin-like growth factor-1 receptor antibodies are effective for decreasing proptosis in thyroid eye disease against placebo (Douglas, 2019).

On the other hand, surgical management of strabismus includes tendon corrections, muscular tightening corrections, and restoring damaged nerves. The cornerstone of strabismus surgery is to balance opposing forces in extraocular muscles to attain proper alignment (Tiedemann et al., 2014). Another important consideration is aberrant ocular motor nerve regeneration and consequent ocular synkinesis.

Research in ocular motor synkinesis

Chemokine receptor C-X-C motif chemokine receptor 4 (CXCR4) and its ligand chemokine C-X-C motif ligand 12 (CXCL12) are important regulators of neuron migration (Miller et al., 2008). Atypical chemokine receptor 3 (ACKR3, also known as CXCR7) is an atypical chemokine receptor that functions as a scavenger receptor by ligand endocytosis and regulates CXCL12 availability (Thelen and Thelen, 2008; Abe et al., 2014). In a study by Whitman et al. (2018), *ex vivo* slices of mouse oculomotor nerve were treated with a CXCR4 inhibitor gradient, resulting in non-chemotactic growth. Furthermore, *in vivo* loss of either CXCL12 or CXCR4 caused synkinetic innervation of the orbit by the trigeminal nerve (**Figure 3**). A subsequent study by this group investigated the effect of ACKR3 on CXCR4/CXCL12 signaling. Mice with loss of ACKR3 showed excessive CXCR4 stimulation and aberrant innervation of oculomotor and abducens nerves (Whitman et al., 2019). The study also analyzed a consanguineous family with congenital ptosis and eyelid synkinesis and identified a homozygous missense ACKR3 variant. These studies demonstrated the importance of chemokines and their receptors in ocular motor development and synkinesis.

Utilization of Biomaterials for Cranial Nerve Regeneration

Tissue engineering and biomaterial design have an increasingly important role in neural regeneration. Whereas early biomaterials were limited by immuno-rejection or lack of bioactivity, newer biomaterials overcome these barriers and have great promise for successful clinical applications. The biophysical characteristics of available biomaterials and approaches to tailoring them for nerve tissue engineering were recently reviewed (Amani et al., 2019). Modern biomaterials offer favorable biocompatibility, low immunogenicity, and predictable mechanisms of degradation arising from their stable rate of hydrolysis.

Biosynthetic nerve constructs that support axon regeneration across nerve gaps include hollow conduits, multichannel bridges, hydrogels, and scaffolds of other geometries. These nerve constructs are valuable for large nerve gap injuries, where a tension-free anastomosis is not possible with primary nerve repair. Such biomaterials obviate the need for autologous nerve grafts and the attendant donor site morbidity. Biologic, bio-printed polymers, and stem cell-derived conduits are all areas of active investigation, with each class offering distinct profiles of biocompatibility, durability, mechanical integrity, degradability, and cost (Battiston et al., 2005). Such approaches can also be integrated with neurotrophic growth factors or cellular therapeutics.

While the use of such biomaterials has been investigated extensively in peripheral nerves (Belanger et al., 2016; Dalamagkas et al., 2016; Amani et al., 2019), experience is more limited in cranial motoneuron injury. In FN regeneration,

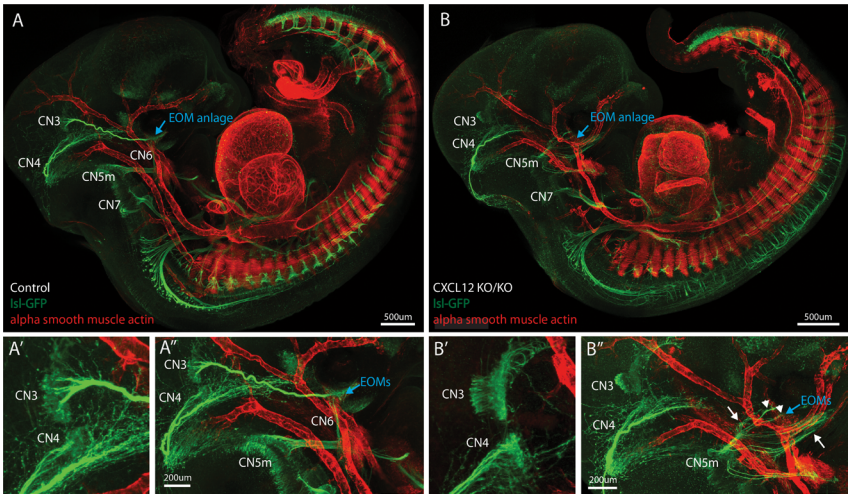

Figure 3 Whitman et al. demonstrated that *in vivo* loss of either CXCL12 or CXCR4 caused synkinetic innervation of the orbit by the trigeminal nerve (V).

(A) Wild-type embryo exhibited the normal trajectory for cranial nerve (CN) III , IV, V, VI, and VII. (B) In the Cxcl12KO/KO embryos, CN III projects into the midbrain and stalls. CN V motors axons project aberrantly along the V1 and V2 sensory pathways toward the developing orbit. Scale bars: 500 μm (A, B); 200 μm (A″, B″). CN: Cranial nerve; CXCL12: chemokine C-X-C motif ligand 12; CXCR4: C-X-C motif chemokine receptor 4. KO: knockout. With the permission from Whitman et al., 2018.

conducting polymers, cross-linked collagen fibers, nerve growth factor-hydrogels, and cultured Schwann cells have shown promise for facilitating regeneration across nerve gap defects (Langhals et al., 2014). Addition of growth factors and stem cells to nerve conduits further enhances FN axon regeneration (Zhang et al., 2017). When seeding polyglycolic acid-collagen conduits with ADSCs and de-differentiated fat cells, Shimizu et al. (2018) and Fujimaki et al. (2019) independently observed improved regeneration following rat FN injury. Polyethylene glycol conduits did not promote motoneuron survival or improve neuromuscular outcomes, however (Brown et al., 2019).

There is also preliminary experience with the use of synthetic nerve constructs for RLN injuries. Similar to the FN, several nerve guidance conduits have been shown to support RLN regeneration across nerve defects, including collagen scaffolds, silicone tubes, asymmetrically porous polycaprolactone, and polyglycolic acid (Kumai et al., 2013; Choi et al., 2014; Suzuki et al., 2016; Wang et al., 2016; Chitose et al., 2017). In some instances, the constructs yielded RLN regeneration that was equivalent or superior to autologous nerve grafts (Kanemaru et al., 2003). Additionally, synchronous co-culturing of nerve conduits with tissue growth factors (e.g., brain-derived neurotrophic factor, GDNF) or cultured Schwann cells produced robust RLN regeneration (Wang et al., 2016; Chitose et al., 2017). It is particularly important, however, to evaluate functional outcomes in addition to histological evidence of regeneration. For example, some studies demonstrated successful nerve regeneration on histological examination that did not correlate with vocal fold function or electrophysiologic parameters (Kumai et al., 2013; Sand et al., 2016; Suzuki et al., 2016). Such findings may reflect either misrouting of axonal fibers (synkinesis) or unsuccessful innervation of the muscle end organ.

In summary, biomaterials possess unique biophysical properties that are conducive to engineering neural constructs that promote nerve regeneration and functional recovery. Future directions involve integrating scaffold topography and biocompatibility with cellular approaches or controlled release strategies to enhance the biological milieu. These advances in biomaterials, which are seeing growing application in the peripheral nervous system, will play an increasingly important role in advancing the burgeoning field of cranial motoneuron regeneration.

Conclusion

The head and neck are densely innervated with motor cranial nerves that account for diverse and elegant biological functions. Morbidity from a loss of motor craniofacial function is disproportionately profound, as has been illustrated throughout our discussion. In this review we discussed clinical manifestation and surgical reinnervation for palsies of the FN, RLN, SAN, hypoglossal, and oculomotor nerves. In parallel, we summarized the current landscape in research endeavors on motor cranial nerve regeneration and remaining challenges for each of these seven efferent cranial nerves. We concluded with a summary on the emerging role of tissue engineering and biomaterial designs in cranial nerve regeneration. Insights from these discussions will shed light on recent progress. New horizons will broaden our understanding of peripheral nerve biomechanics and neurobiology, with emphasis on promising strategies to optimize neural regeneration and identify knowledge gaps and future directions in the field of cranial motor neuron research.

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