



REVIEW ARTICLE

The role of the peripheral and central nervous systems in rotator cuff disease



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Rotator cuff (RC) disease is an extremely common condition associated with shoulder pain, reduced functional capacities, and impaired quality of life. It primarily involves alterations in tendon health and mechanical properties that can ultimately lead to tendon failure. RC tendon tears induce progressive muscle changes that have a negative impact on surgical reparability of the RC tendons and clinical outcomes. At the same time, a significant base of clinical data suggests a relatively weak relationship between RC integrity and clinical presentation, emphasizing the multifactorial aspects of RC disease. This review aims to summarize the potential contribution of peripheral, spinal, and supraspinal neural factors that may (1) exacerbate structural and functional muscle changes induced by tendon tear, (2) compromise the reversal of these changes during surgery and rehabilitation, (3) contribute to pain generation and persistence of pain, (4) impair shoulder function through reduced proprioception, kinematics, and muscle recruitment, and (5) help explain interindividual differences and response to treatment. Given the current clinical and scientific interest in peripheral nerve injury in the context of RC disease and surgery, we carefully reviewed this body of literature with a particular emphasis on suprascapular neuropathy that has generated a large number of studies in the past decade. Within this process, we highlight the gaps in current knowledge and suggest research avenues for scientists and clinicians.

Level of evidence: Narrative Review.

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The human shoulder complex exhibits a unique anatomic design to allow a wide range of motion at various speed and force levels. The shoulder joint complex has an

unstable bone configuration secured by connective tissues and dynamic stabilizers (rotator cuff [RC] muscles) controlled by a sophisticated neuromuscular system.^{157,161} As a consequence, shoulder structures, particularly RC tendons, are prone to various injuries and degenerative disorders.^{19,121} RC tendon tears are common in the general population^{104,123} and can lead to shoulder pain, impaired functional capacities, and reduced quality of life.^{88,164}

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RC tendon tears are not necessarily associated with pain or patient-reported loss of shoulder function^{91,164,165}; however, asymptomatic patients may develop symptoms in a relatively short time.¹⁰⁷ Symptomatic patients usually undergo surgery when nonoperative and pharmacologic options have been exhausted.^{112,130} Surgical management decisions are mainly driven by patients' pain, disability, and functional requirements rather than by the severity of local tissue damage.¹⁵ In the short term, nonoperative treatment may be effective in a fraction of patients,^{35,50,76} but tissue damage and symptoms may progress over time,^{91,107,164} further limiting surgery and rehabilitation.^{79,92,96,98} RC tendon repair is not universally successful; ~25% of repairs fail to re-establish the integrity of the RC⁹⁸ (up to 70% in massively retracted tears³⁶), and patient-reported improvements are limited.^{79,98} Preoperative factors, such as age, chronicity, and severity of muscle-tendon unit impairments, have been repeatedly associated with higher re-tear rates and poorer clinical outcomes.^{79,98} Paradoxically, 2 recent meta-analyses^{98,130} suggested that patients with intact repairs might not have significant differences in symptom improvement compared with patients with recurrent tears. Another major concern is that muscle impairments do not seem to be reversed, even when repair is intact and function is improved at follow-up.²⁶

During the past decades, RC disease has been extensively investigated within the framework of tendon pathophysiology, tendon to bone healing, and muscle changes after tendon tear.^{30,72} A smaller set of studies have investigated how peripheral, spinal, and central neural factors are likely to contribute to muscle-tendon unit changes, impaired shoulder function, and responses to treatment. Expanding our knowledge, or at least considering the potential involvement of both peripheral and central nervous systems, is critical to improve our understanding of RC disease and our ability to appropriately intervene along the continuum of RC injury processes. Therefore, this review aims to scrutinize and highlight the gaps in current knowledge about the nervous system that may be altered in patients with RC disease from the peripheral receptors to the brain and from the brain to the neuromuscular junction. We summarized how these factors may (1) exacerbate structural and functional muscle changes induced by tendon tear, (2) compromise the reversal of these changes during surgery and rehabilitation, (3) contribute to pain generation and persistence, (4) impair shoulder function by impairing shoulder proprioception, kinematics, and muscle recruitment, and (5) contribute to explain interindividual differences in symptoms and response to treatment. Given the current and lively interest in peripheral nerve injuries in the context of RC disease and surgery, we carefully reviewed this body of literature with a particular emphasis on suprascapular nerve (SSN) injury that has generated a large number of studies in the past decade. Within this process, we highlighted the gaps in

current knowledge and suggested research avenues for scientists and clinicians.

Proprioceptors and related spinal reflexes

Shoulder movements and positional changes induce a deformation of tissues surrounding joints, including skin, muscles, tendons, fascia, joint capsules, and ligaments.^{24,27,47,122,144,156} All these tissues are innervated by mechanically sensitive receptors termed proprioceptors that relay information to the central nervous system about movement, position, and forces exerted on shoulder structures (e.g., muscle spindles, Golgi tendon organs, Ruffini endings, Pacinian and Meissner corpuscles). The distribution and the function of proprioceptors in shoulder joints and soft tissue have been investigated in both animal and human studies.^{40,51,139,141,144,147,156} Glenohumeral joint and ligament receptors probably play a minor role in shoulder proprioception,¹²² as illustrated by the small proprioceptive deficit observed after shoulder arthroplasty.²¹ However, they may act as limit detectors, triggering protective and synergistic reflex muscle activity during movement.^{27,46,64,141,149,158} In RC muscles and tendons, a large concentration of muscle spindles and Golgi tendon organs have been demonstrated in rabbits and rats,^{3,22,105,166} but no human data exist. Current theory suggests that muscle spindles are the most important proprioceptors, especially during movement.¹²² They also play a critical role in regulating muscle contraction through spinal reflexes that are essential for joint stability and accurate motor control.¹⁰¹ Golgi tendon organs are equally important proprioceptors, signaling information about force and mass, and are also involved in the regulation of muscle contraction.¹²²

The effect of tendon disruption on muscle spindles and Golgi tendon organs has been studied in a limited number of animal experiments concerning hindlimb muscles only. After tenotomy, muscle shortening and changes in the surrounding extrafusal tissue modify the morphology of muscle spindles that become slack and distorted.¹⁶⁹ In the chronically tenotomized muscle, atrophy of intrafusal fibers, degeneration of supplying axons, and fibrotic thickening of the capsule have been reported.^{67,95} Functionally, acute tenotomy decreases muscle spindle discharge,^{56,160,169} but interestingly, responsiveness of muscle spindles from the chronically tenotomized muscle has been shown to increase.^{56,57,169} Shortening of intrafusal fibers, increased preliminary stretch caused by kinking of intrafusal fibers, change in passive mechanical properties, and increased sensitivity of spindles have been subsequently proposed as potential explanations for this phenomenon. These increases in muscle-tendon afferent outflow have also been suggested to result from non-proprioceptive discharge.^{57,78} Increase in the amplitude of the monosynaptic reflex has also been repeatedly observed

in the chronically tenotomized muscle,^{10,61,75,160} suggesting adaptive changes in motoneuron excitability consistent with the decrease in muscle mechanical loading.⁹⁹ In the Golgi tendon organs, tenotomy also induces morphologic changes, but the physiologic consequences remain to be investigated.⁶⁷ To the best of our knowledge, only 1 study related to proprioceptor function in RC tendon tear has been conducted and reported that experimentally induced inflammation within rabbit RC sensitizes and increases the firing of mechanical receptors.¹⁶⁶

Based on the findings of these studies, it is reasonable to speculate that RC tendon tear is associated with structural and functional alterations of proprioceptors. Either reduced or inconsistent proprioceptive information from the injured muscle-tendon unit and altered muscle reflex activity may impair shoulder proprioception and contribute to impaired kinematics and muscle recruitment (see also the section on shoulder muscle activity and kinematics). Finally, the effects of tendon repair on the structure and the function of proprioceptors remain entirely unknown. Further experiments are therefore required to assess the relative contribution of these mechanisms to anatomic and clinical impairments associated with RC disease.

Central processing of proprioceptive information

Proprioceptive information from the shoulder and more broadly from the upper limb is conveyed through the spinothalamic tracts and relayed to the somatosensory cortex, where it is referred to a central body map allowing the conscious awareness of arm position and movement in space. Unconscious proprioceptive tracts (i.e., spinocerebellar tracts, projecting in the ipsilateral cerebellum) and the cervical propriospinal system are also involved in the coordination movements involving multiple joints of the arm.^{122,125}

Measurement of errors in the perceived position, movement detection latency, or ability to reproduce a determined force level can be used to globally assess shoulder proprioception.^{6,86,108,126,132} A large fraction of studies involving shoulder proprioception assessment have been conducted in patients with shoulder instability.^{6,108,126} In the overhead athlete with isolated infraspinatus atrophy caused by SSN compression, impaired sense of movement associated with different brain activation patterns has been reported, suggesting an important contribution of RC muscle to shoulder proprioception.¹³² Decreased sense of movement^{4,89,131} and a tendency to overestimate the target during force reproduction tests⁹⁰ have been reported in patients with RC tendinopathy, but no data exist in patients with RC tendon tears. In conditions such as knee disorders, functional brain magnetic resonance imaging demonstrated reduced activation of sensorimotor cortical areas and increased activation in proprioception-related brain regions; however, no data exist

in patients with RC disease.⁷⁰ In healthy subjects, transcranial magnetic stimulation (TMS) combined with peripheral nerve stimulation has been used to assess the modulation of the propriospinal system¹²⁵ of the upper limb, which is an important determinant for synergies between forearm, hand, and shoulder muscles. This system remains to be investigated in patients with RC disease.

Proprioception has been insufficiently assessed in patients with RC disease despite its recognized importance in other musculoskeletal conditions.¹²² Therefore, further studies are required to assess proprioception in patients with RC disease and patients who have undergone RC reconstruction.

Nociceptors and peripheral and central pain processing

Nociceptors are high-threshold receptors that detect signals from damaged tissue or tissue on the verge of damage. They can be found in the shoulder, skin, muscles, joints, soft tissue, and bone.^{32,40,41,51,144,149,150} RC disease is associated with local tissue damage and inflammation within the RC and surrounding structures, which release a variety of substances that sensitize nociceptors by decreasing their activation threshold (peripheral sensitization), resulting in hyperalgesia at the site of injury.^{23,34,41} Prolonged release of neuropeptides by nociceptive afferent fibers at the dorsal horn may sensitize nociceptors and cause long-term changes in pain processing at the spinal level and higher centers that result in pain hypersensitivity within but also outside the original zone of injury.¹⁶³ As previously observed in other musculoskeletal conditions,⁵³ sensory abnormalities have been observed on the injured but also on the noninjured side of patients with RC disease, illustrating the involvement of central mechanisms.^{39,48,55} Interestingly, patients with a RC tendon tear and signs of central sensitization have been shown to have worse clinical outcomes after surgery.⁴⁸ Pain may have profound effects on motor behavior mediated at various levels of the nervous system and have an impact on numerous motor parameters, such as reflex amplitude, muscle activity, kinematics, movement planning, and brain activation⁵ (see section on shoulder muscle activity and kinematics).

Pain remains poorly characterized in patients with RC disease, but the use of existing pain assessment tools and the development of biologic markers have the potential for enhancement of our understanding of pain in RC disease.²⁴ Interindividual differences in the magnitude of these changes and their persistence after local tissue damage has healed may explain differences in clinical presentation and response to therapies.²⁴

Motor nerves and neuromuscular junction

The motor innervation of the RC muscles is achieved by nerves emerging from the posterior and the superior

trunks of the brachial plexus, all originating from the C5-C6 cervical roots and C4 nerve root in some individuals.^{2,81,137,167} The architecture and the high mobility of the shoulder complex predispose nerves to various dynamic or static compressive and traction injuries.¹⁴⁸ Cervical radiculopathy, brachial plexopathy, and peripheral nerve trunk injuries are potential comorbidities of RC tendon tear.^{52,136} Motoneuron damage immediately reduces muscle activation and induces progressive muscle changes proportional to the severity of nerve injury.¹⁴⁶ Over time, the muscle tissue can virtually disappear while connective tissue and fat accumulate,⁸⁵ as recently illustrated in the human supraspinatus.^{14,80,102} A particular interest has been placed on the SSN because it innervates the most affected muscles in RC disease (i.e., supraspinatus and infraspinatus) and because it is particularly prone to entrapment.^{106,136} SSN injury can cause shoulder weakness and pain that overlap with the signs of RC disease.¹⁰⁶

SSN injury associated with RC tendon tear: anatomic studies

SSN injury is possible, given the surgical manipulation of previously retracted muscles during RC repair procedures.¹³⁴ In vivo studies have shown that lateral advancement during supraspinatus repair initiates a stretch of the SSN.^{44,162} The main trunk of the SSN may be prone to damage, but also its smaller branches may be injured.⁴⁴ Following a similar principle, medial retraction of the supraspinatus and infraspinatus muscles caused by tendon tear has been suggested to place excessive traction on the SSN and to promote compressive injuries at the suprascapular or spinoglenoid notch. In cadavers, supraspinatus tenotomy changes the course of the SSN.^{1,94} Various anatomic variations have also been suggested to promote suprascapular entrapment (e.g., deep and narrow suprascapular notch,^{60,109,119,124,151} shape or ossification of the superior transverse scapular ligament,^{118,120,151} arrangements of blood vessels,^{120,168} configuration of the fascia securing the SSN to the supraspinatus fossa,²⁸ close relationship of the subscapularis muscle⁷). However, the incidence of these anatomic predispositions in patients with an RC tendon tear and concomitant neuropathy has never been studied. In addition, the potential occurrence of dynamic stretch or compressive strain of the SSN promoted by biomechanical and kinematic impairments in patients with RC disease should not be neglected.^{20,117}

These anatomic studies must be acknowledged as the original incentive for investigating SSN function in RC tendon tears.¹⁰⁶ However, they have not addressed the question of whether these changes are physiologically relevant and whether smaller nerve branches are also likely to be insulted clinically.

Prevalence of SSN injury in patients with RC tendon tear

In patients, diagnosis of SSN injury is confirmed by electrodiagnosis that combines needle electromyography (EMG) and nerve conduction studies (NCS). Various clinical reports, retrospective studies, and prospective studies of the prevalence and the impact of peripheral nerve injuries before or after surgery have been published (see [Table I](#) for supporting material).

After tendon repair, a low risk of iatrogenic nerve injury has been reported,^{25,49,59,170} but comparisons of presurgery and postsurgery EMG/NCS data have not been systematically performed.^{18,42,93,170} Goutallier et al⁴² achieved such comparisons in the largest sample of patients, and findings confirmed the low incidence of SSN dysfunction after RC repair previously reported. In these studies, the long delay between surgery and electrodiagnosis may have allowed nerve recovery. Some case reports also suggested that supraspinatus repair may restore the normal course of the SSN, therefore reducing nerve strain and allowing its recovery, but larger studies are required to prove this concept.^{18,93} The large undocumented occurrence of traumatic events that could have caused direct nerve injury often limits interpretation of the data ([Table I](#)).

Studies suggesting a greater prevalence of SSN motor neuropathy in patients with RC tendon tears involve important recruitment bias. In the studies of Boykin et al¹² and Shi et al,¹³⁵ patients were sent for electrophysiologic examination for persistent pain or severe muscle changes; similarly, Costouros et al¹⁸ and Mallon et al⁹³ selected patients with severe muscle atrophy and fatty infiltration. Whereas some studies are consistent with a higher risk of SSN injury in severely vs. slightly retracted tears,^{13,93} the study of Shi et al¹³⁵ involving a larger spectrum of RC tear severity does not support this hypothesis. These data thus call into question the concept of SSN injury as a direct consequence of muscle retraction. Prospective and carefully conducted studies indicate a rare occurrence of isolated motor SSN injury in patients with RC tendon tears, even in massive or traumatic RC tendon tear.^{16,154} Within the largest series of patients in this topic area,¹⁶ peripheral neuropathy was found in 12% of patients, and only 1 patient exhibited positive signs of SSN injury.

Heterogeneous and incompletely documented EMG/NCS methods are also major limitations in comparing results between these studies.^{13,93,135,154} Some categorize EMG findings on the basis of the isolated or combined occurrence of positive EMG signs,¹³⁵ whereas others use graded scoring based on semiquantitative assessments of EMG abnormalities.^{16,18,135} Regarding NCS, some compared latencies with previously published values^{13,16} or the contralateral side,^{16,18,154} whereas others compared latencies of patients with positive and negative EMG findings.¹³ Severe retraction, ultrastructural muscle

Table I Prevalence of suprascapular neuropathy in patients with rotator cuff tears before or after surgical repair

Studies	N	Tear etiology		Tear severity		Time of electrodiagnosis				Prevalence of suprascapular neuropathy	
		Trauma	Chronic	Mild/ partial	Massive/ full	Before surgery	After surgery	Before and after surgery	Time from surgery or trauma (months)	Before surgery	After surgery
Ha'eri and Wiley, ⁴⁹ 1981	5	/	/	/	/	0	5	0	/	/	0% (0/5)
Kaplan and Kernahan, ⁶⁹ 1984	6	6	0	5	1	5	1	1	/	100% (5/5)	100% (1/1)
Zanotti et al, ¹⁷⁰ 1997	10	0	10	0	10	1	10	1	(24-36)	/	10% (1/10)
Goutallier et al, ⁴² 1996	24	/	/	/	/	19	24	19	8.5	/	~21% (4/19)
Hoellrich et al, ⁵⁹ 2005	9	0	9	/	/		9		17 (6-28)	/	0% (0/9)
Vad et al, ¹⁵⁴ 2003	25	8	17	17	8	25	0	0	/	8% overall (2/25)	/
Mallon et al, ⁹³ 2006	8	0	8	0	9	8	4	4	6	100% (8/8)	0% (0/6)
Costouros et al, ¹⁸ 2007	26	19	7	0	26	26	6	6	8 (3-12) (trauma) 6 (surgery)	27% (7/26, all trauma)	0% (0/6)
Boykin et al, ¹³ 2011	44	/	/	6	38	44	0	0	/	0% (partial tear) 60% (massive tear)	/
Shi et al, ¹³⁵ 2014	60	/	/	SS (14) IS (15)	SS (46) IS (30)	60	0	0	/	29% overall (26/87) 50% (partial SS tear) 54% (full SS tear/minor retraction) 17% (full SS tear/>5 cm retraction) 20% (partial IS tear) 71% (full IS tear/minor retraction) 23% (full SS tear/>5 cm retraction)	/
Collin et al, ¹⁶ 2014	49	24	25	0	49	49	0	0	/	2%	

SS, supraspinatus; IS, infraspinatus; /, undocumented or unavailable information.

changes, or nonuniform denervation may also complicate EMG/NCS in RC muscles.⁸ Ultrasound imaging¹¹⁴ and multisite EMG assessments may help overcome some of these limitations. Standardization of procedure and quantification methods¹⁷⁰ must be pursued to enhance the sensitivity of EMG. Recent progress in nerve imaging techniques^{82,116,145} may also allow enhancement of our ability to study peripheral nerve injuries in vivo.

Relative contribution of denervation to muscle changes associated with RC tendon tears: clinical data and animal models

In humans, imaging techniques cannot discriminate muscle impairments related to tendon tear or denervation when they happen simultaneously.⁸ EMG/NCS is limited, and an objective test such as nerve biopsy cannot be reasonably performed in patients. Consequently, various animal models of RC disease or nerve injury have been developed to understand cellular and molecular mechanism underlying muscle changes.³⁰

In rabbits and rodents, tenotomy associated with full nerve transection has been shown to produce severe atrophy and fatty infiltration, and these data are frequently used to support the role of SSN injury in human RC muscle changes.^{65,66,73,83,127} However, if nerve injury occurs in humans, denervation is more likely to be incomplete, with higher capacity for recovery. In rabbits, fatty infiltration has been repeatedly observed after isolated supraspinatus tenotomy,^{127,129,153} even in the absence of retraction¹⁵² and independent from denervation,³⁸ further clouding the cause-effect relationship between nerve injury and fatty infiltration. There are many transcriptional pathways that control various aspects of the adipogenic, fibrogenic, and myogenic programs.⁶⁸ However, distinct pathways may be triggered by RC tenotomy or denervation as recently reported in rodents.^{65,83} Although small animal models have a limited ability to replicate human RC disease, previously developed transgenic mice associated with tendon or nerve injury have great potential to further understanding of RC pathophysiologic processes.^{73,84} Increased availability in human tissue may also allow further investigations of muscle impairments and comparison of data obtained in animal models.

Direct consequences of RC tendon tears on nerves and neuromuscular junction

Studies that investigated the consequences of tendon tear on motor nerve and neuromuscular junction provide equivocal results.⁶¹ These effects have been investigated in animal models of RC tendon tears in rabbit only. Signs of degenerative histologic changes in the subscapular nerve after tenotomy of the subscapularis muscle have been reported,¹²⁷ but characteristics of these nerve abnormalities

remain unclear. Gayton et al³⁸ reported that motor end plates were not significantly affected after tenotomy in rabbits; confirmation is required, given the small sample size of this work (N = 4). A critical point that has not been addressed is whether neuromuscular junctions are altered in patients with isolated RC tendon tears.

Sensory nerves

Sensory nerve injuries have received less interest than the motor neuropathies discussed before. However, the RC and surrounding structures receive sensory innervation from numerous sensory nerve branches^{29,159} that are equally susceptible to injury. Injury within a peripheral nerve trunk induces a local inflammatory response that causes changes in afferent fibers and in the central nervous system and may lead to neurogenic pain (see section on nociceptors and peripheral and central pain processing and reference 31 for more details). Damage to afferent fibers may also contribute to the impairment of the transduction of proprioceptive information. SSN block has demonstrated effectiveness in the management of postoperative pain,⁶³ and pulsed radiofrequency modulation has been reported to provide promising long-lasting pain relief in experimental models¹⁵⁵ and in patients with shoulder pain.⁶² These data highlight the important contribution of shoulder nerves in the transmission of nociceptive information in patients with RC disease, making them important targets for shoulder pain management.^{63,155}

Shoulder muscle activity and kinematics

Alterations in shoulder muscle activity and kinematics of the glenohumeral and scapulothoracic joints have been widely reported in patients with RC disease.^{87,97,128} One potential contributing factor may be that patients with symptomatic tears display different motor control patterns during movement compared with asymptomatic patients.¹²⁸

Kelly et al⁷¹ observed that symptomatic patients retain supraspinatus and infraspinatus activity despite tendon tears but are unable to activate intact deep muscles (i.e., subscapularis) as efficient co-contractors and that they may preferentially rely on periscapular muscles during elevation. These results have been partially reproduced by Cordasco et al¹⁷ and suggest that symptomatic patients fail to develop alternative muscle activation strategies to compensate for weakened RC muscles and the resulting altered shoulder biomechanics. Importantly, they suggest that RC muscles may continue to be activated despite tendon damage. Shinozaki et al¹³⁸ recently used positron emission tomography with fluorodeoxyglucose^{77,113} to assess shoulder muscle activity differences between asymptomatic and symptomatic patients. They observed increased trapezius activity and lower deltoid activity in the

symptomatic group but no differences in RC muscle activity compared with asymptomatic patients. This technique appears promising, but further developments are required, particularly regarding quantification.

An important issue is whether different muscle activity patterns observed in symptomatic patients are the cause or the result of pain or both. Experimentally induced pain has been shown to increase activity in the antagonist muscle during abduction (i.e., latissimus), probably in an attempt to limit the compression of painful subacromial structures. Similar adaptations have been observed in patients with massive RC tendon tears.^{17,143} Masking pain may reduce these protective mechanisms and further promote local tissue damage. Stackhouse et al¹⁴² reported that pain reduced shoulder strength in external rotation in association with a decrease in voluntary activation when using the twitch interpolation technique.¹⁰³ Sole et al¹⁴⁰ also pointed out that motor adaptation to acute pain may be individual and task specific.⁵⁸ Given the acute nature of experimentally induced pain,⁵ precautions should be taken in trying to generalize these results in patients with chronic RC disease.

In patients with RC disease, pain reduction has been shown to improve glenohumeral motion and to reduce scapular contribution during arm elevation.¹³³ Dramatic increases of peak torque and power have also been reported.⁹ Surprisingly, when it is assessed with isometric contractions, pain reduction has been shown to have no relevant effect on shoulder strength,^{33,115} suggesting that pain-related motor impairments may be particularly visible during movement.

These experiments observed muscle activity pattern changes under pathophysiologic and simulated conditions; however, the relative contribution of muscle-tendon unit impairments, biomechanical abnormalities, pain, impaired proprioception, and deterioration of motor control in shoulder dyskinesia and weakness remains unclear. Poor coping strategies in muscle activation patterns in response to biomechanical changes and pain may contribute to worsen local tissue damage and pain. Interestingly, motor adaptations may also differ between individuals, in particular between symptomatic and asymptomatic patients.

Motor cortical changes

As in various other conditions, RC disease may induce structural and functional changes in the motor cortex that could partly explain changes in motor control and affect muscle activation. Little is known about the cortical organization of motoneurons related to proximal muscles of the arm and even less regarding RC muscles.¹⁰⁰ Functional magnetic resonance imaging has been previously used but is not discriminant for motor cortical mapping of individual RC muscles.⁷⁴ The output of the primary motor cortex (M1) can be objectively measured by motor evoked potentials (MEPs) elicited by TMS, providing direct insight

into the cortical representation and the function of the corticospinal tracts.⁴⁵ Mapping of the infraspinatus muscle has been recently described in healthy subjects,¹¹¹ and the same group observed positive correlation between pain chronicity and reduced M1 excitability in patients with RC disease,¹¹⁰ supporting an indirect inhibitory effect of pain on corticospinal excitability in line with current concepts.⁵ However, the effects of limb disuse and other spinal and supraspinal neural factors cannot be excluded. Similarly,

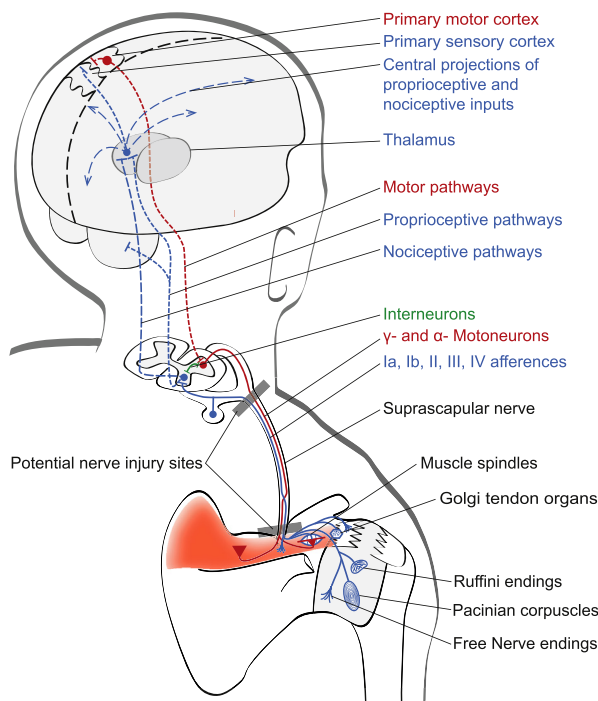


Figure 1 Potential sites for sensory and motor impairments associated with supraspinatus tendon tear. Tendon tear, soft tissue or joint damage, and local inflammatory environment sensitize peripheral nociceptors (mechanical or chemical high-threshold peripheral nociceptors, e.g., free endings) that cause pain and increase the sensitivity of central pain centers (peripheral and central sensitization, respectively). They may also induce impairments in proprioceptive outputs (muscle spindles; Golgi tendon organ, Ruffini endings; Pacinian corpuscles) and in the central processing of proprioceptive information (proprioceptive pathways; primary sensory cortex). Motoneurons innervating both extrafusal and intrafusal muscle fibers (α - and γ -motoneurons, respectively) may equally undergo remodeling and impairments. The neuromuscular junction may also be altered as a result of reduced neural activity, muscle impairments, and central alterations within the motor nervous system. At the nerve level, stretch or compression caused by muscle retraction, mass compression, and manipulation of the previously retracted muscle or direct nerve manipulation during surgery can result in injury of both sensory and motor axons. The suprascapular nerve may be damaged at any point of its path, but the suprascapular notch and the cervical roots are identified as the most common sites for injury. Nerve damage can further increase pain, limit the afferent transduction of proprioceptive information, and aggravate muscle changes.

Table II Suggested deleterious nervous consequences of rotator cuff (RC) disease in studies cited in the current review

Structures/mechanisms	Consequences	Human RC studies	Animal RC studies	Human or animal non-RC studies
Proprioceptors, afferences and related spinal reflexes	Structural/functional impairments of proprioceptors		166	3,22,56,57,78,95,105,160,166,169
Central processing of proprioceptive afferences	↑ Motoneuron excitability	131,132		10,61,75,160
	↓ Sense of position	89		70
	↓ Sense of movement	4,90		
Nociceptors and peripheral and central pain processing	Modified brain activity			
	Peripheral sensitization	40,41,150	149	
Motor nerves	Central sensitization	39,48,55		
	± Injury	1,8,13,16,44,49,59,69,	65,66,73,83,84,127,	
	Iatrogenic	93,94,154,162,170	129,152,153	
Neuromuscular junction	Direct consequence of RC disease			
	↓ = Acetylcholine receptors		38,127	61
Sensory nerves	↓ Cholinergic/noncholinergic muscle stimulation			56,95,160,169
	± Injury			
Shoulder muscle activity and kinematics	Modifications of muscle recruitment and kinematics	17,71,87,97,128,133,138,		
	↓ Voluntary activation	140,142,143		
	↑ = Strength with pain reduction	9,33,115		
Cortical changes	↓ Corticospinal excitability	11,110		

↓, decreased; ↑, increased; =, unchanged.

Numbers refer to references; review articles are excluded.

bilateral alterations of corticospinal excitability in the deltoid and the first interosseous muscles have been reported in patients with RC tendon tears.¹¹ However, spinal motoneuron excitability must be properly assessed to verify that the change in size of MEPs is not mediated at the spinal level.³⁷ C3-C4 propriospinal neurons may also influence the excitability of premotoneuronal sites and therefore the amplitude of MEPs.^{43,125} Peripheral nerve stimulation associated with TMS has been used recently in healthy subjects to assess the modulation of afferent signals on M1 output,⁵⁴ thus opening the possibility for its application in patients with RC disease. Further TMS studies are required to confirm the effects of RC disease on the motor cortex and to understand how these alterations may impair muscle activation, motor control, and shoulder function.

Conclusion and perspective

In this review, we identified a large number of neural structures and mechanisms that may contribute to pain and shoulder dysfunction in patients with RC disease. These structures and mechanisms are summarized in [Figure 1](#). However, numerous questions remain unanswered ([Table II](#)). Current data suggest that inflammation and muscle-tendon unit impairment disrupt proprioceptive function and reflex muscle activity.

Alterations of proprioceptive afferents may impair proprioception and motor control, therefore contributing to poor muscle activation and impaired shoulder kinematics. However, motor control and proprioception impairments in patients with RC diseases have been insufficiently assessed and require further investigations. Current advances in the understanding of pain pathophysiology encourage the enhancement of pain assessment and sensory abnormalities that remain poorly characterized in the clinical setting in patients with RC disease. Recent experiments suggest that the occurrence of motor nerve injury appears to be less frequent than first assumed, yet peripheral nerve dysfunction remains a non-negligible aggravating factor. Thus, this problem must be considered (perhaps with improved diagnostic tools) in clinical practice and further explored through both anatomic and physiologic studies. Some data also highlight that tendon disruption, disuse, and inflammation may have a direct impact on neuromuscular junction and motoneurons, but further studies are needed for confirmation. Increased availability of human tissue obtained during surgeries and animal models of RC disease will also improve our understanding of RC physiopathology and will help define markers able to improve the detection of muscle denervation processes. Damage inflicted to sensory nerves should not be neglected because it may contribute to the generation of

pain and disrupt the afferent transduction of proprioceptive information. Evidence that RC disease induces significant motor adaptations and the important role of pain in these changes have been clearly demonstrated. However, the contribution of proprioception deficits, motor cortical changes, and modified brain activity in patients with RC disease remains to be explored. The problem of motor nervous system dysfunction is particularly relevant as the field begins to explore the mechanisms of reduced muscle force generation after reconstruction. If these problems are induced or aggravated by poor muscle activation, the nervous system impairments may need to be addressed first, perhaps in a way that is consistent with neurorehabilitation instead of standard musculoskeletal physical therapy. In the clinical setting, all these factors may contribute to explain why clinical presentations and responses to treatments can vary considerably between individuals despite similar peripheral tissue damage. Therefore, our final proposal is that different profiles involving different degrees of biomechanical, motor control, proprioceptive, and nociceptive impairments exist among patients with RC disease. The development of standardized tests achievable in the clinical setting to assess each of these aspects is necessary to provide comprehensive assessment and to refine the management of these patients.

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