Nociception Affects Motor Output

A Review on Sensory-motor Interaction With Focus on Clinical Implications

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Objectives: Research has provided us with an increased understanding of nociception-motor interaction. Nociception-motor interaction is most often processed without conscious thoughts. Hence, in many cases neither patients nor clinicians are aware of the interaction. It is aimed at reviewing the scientific literature on nociception-motor interaction, with emphasis on clinical implications.

Methods: Narrative review.

Results: Chronic nociceptive stimuli result in cortical relay of the motor output in humans, and a reduced activity of the painful muscle. Nociception-induced motor inhibition might prevent effective motor retraining. In addition, the sympathetic nervous system responds to chronic nociception with enhanced sympathetic activation. Not only motor and sympathetic output pathways are affected by nociceptive input, afferent pathways (proprioception, somatosensory processing) are influenced by tonic muscle nociception as well.

Discussion: The clinical consequence of the shift in thinking is to stop trying to restore normal motor control in case of chronic nociception. Activation of central nociceptive inhibitory mechanisms, by decreasing nociceptive input, might address nociception-motor interactions.

Key Words: nociception, pain, musculoskeletal disorders, central sensitization, motor control, movement

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Imagine walking with bare feet in your living room. Suddenly, you step on a tack with your left foot, and immediately change your walking movement by pulling away one leg (ie, you flex the left foot, knee, and hip joint). This is an example of an involuntary innate response to the integration of sensory information at the subconscious level. Nociceptors in the foot send signals to the spinal cord, where the signals diverge, activating multiple excitatory interneurons, which in turn excite α and γ motor neurons and subsequent contraction of the flexor muscles of the stimulated limb.[1] Simultaneously, other interneurons excite inhibitory interneurons that relax the extensor muscles, and the crossed extensor reflex helps maintaining balance when 1 foot is lifted from the ground.[1,2]

The flexor reflex is a simple example of nociception-motor interaction: nociception triggers a motor response characterized by stimulation of certain muscles and inhibition of others. However, the interaction between nociception and motor output is far more complex. Especially in cases of chronic nociception (defined as chronic activation of non-adapting polymodal nociceptors), central nervous system adaptations arise and motor output is affected in many ways. Clinicians observe daily the large effect of chronic nociception on motor function. Patients with subacute and chronic benign pain in musculoskeletal disorders present changes in movement performance and motor control strategies.[3,4]

Neurophysiological research has provided us with an increased understanding of nociception-motor interaction. Nociception-motor interaction is most often processed unconsciously. Hence, in many cases neither patients nor clinicians are aware of the interaction. Yet, nociception-motor interaction may prevent normal movement coordination in the presence of chronic nociception.

This study aimed at reviewing our current understanding of nociception-motor interaction, and at explaining to clinicians the potential clinical implications of these complex processes. First, the target populations are defined. Next, the neurophysiology of nociception-motor interaction is explained, including the way ongoing nociception affects motor and proprioceptive pathways. The role of the sympathetic nervous system in mediating nociception-motor interaction is explained. These mechanisms are translated to clinical practice by explaining how they may affect the outcome of motor retraining programs. Finally, priorities for further research in this area are highlighted.

TARGET POPULATIONS

Nociception-motor interaction is of relevance to clinicians working with a variety of patients with subacute and chronic musculoskeletal pain. These include patients with low back pain,[3] (chronic) whiplash-associated disorders,[4,5] insidious onset neck pain, osteoarthritis, complex regional pain syndrome,[6] chronic widespread pain,[7] fibromyalgia,[8]

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knee pain,[9] shoulder pain due to anterior instability, impingement syndrome or rotator cuff tearing, among others. In general, clinicians facing with a patient experiencing any type of chronic nociception should consider nociception-motor interaction.

One of the best studied examples is nonspecific low back pain. In the presence of chronic nociception, the strategies used by the central nervous system to control trunk muscles (ie, motor control) may be altered.[10] More specifically, a delayed contraction of M. transversus abdominis[11] and inhibition of M. multifidus have been observed in patients with low back pain using electromyography. These dysfunctional changes are accompanied by reorganization of trunk muscle representation at the motor cortex.[12] Together, these dysfunctions result in motor control deficits and impaired spinal stability. These motor control deficits have long been regarded as etiologic to low back pain, but the current understanding of nociception-motor interaction suggests that they can be the cause and the consequence (ie, nociception-triggering spinal motor control deficits).[13] Similar mechanisms of discoordination are believed to occur in those with other musculoskeletal pain disorders. The neurophysiology behind the interaction is explained in detail below.

NOCICEPTION IMPAIRS EFFERENT (MOTOR OUTPUT) PATHWAYS

There is a body of literature showing that motor output is altered in response to chronic nociception (ie, tonic activation of nociceptors). The net result is a reduced activity of the corresponding muscle.[14–17] Experimental muscle nociception (ie, experimentally induced nociception in muscle tissue) does not impair muscle fiber membrane properties or neuromuscular transmission,[15] refuting peripheral causes of altered motor output in response to nociception. Nociception impairs motor output through central mechanisms. Various tonic nociceptive stimuli (ie, heat, chemical, and mechanical) result in cortical relay of the motor output in humans. Activated neurons in the somatosensory (SII) cortex produce a pain-dependent inhibitory input to the primary motor cortex (both ipsilateral and contralateral).[18,19] Indeed, tonic nociceptive stimuli applied to human muscle tissue result in long-lasting inhibition of the motor system (ie, the primary motor cortex), mediated through both cortical and spinal motor circuits.[20]

Motor cortex inhibition occurs immediately in response to nociception, but it fades once levels of perceived pain become stable for a given amount of time and no further increase in pain perception is expected by the patient.[18] This implies that motor cortex inhibition reflects "variations" in pain perception and is no longer necessary when pain severity is stable over time.[18] Translating these findings to clinical practice, treatment strategies (eg, pacing pain management[21]) should aim at decreasing variations in pain perception rather than focusing on pain severity.

Chronic nociceptive input by muscle fibers is more effective than nociceptive cutaneous input (ie, nociception arising from the skin) in inducing prolonged changes in neuronal excitability of the motor cortex: muscle nociception-induced inhibition of the motor cortex excitability lasts for many hours after the recovery from nociception in humans.[20] In addition, the decreased excitability of the motor cortex induced by skin nociception is preferentially located in the muscles adjacent to the painful area.[18] This was evidenced in a study of healthy individuals, where experimentally induced M. vastus medialis nociception triggered significant decreases in knee joint dynamics and electromyographic recordings of the hamstring muscles and M. quadriceps femoris during a forward lunge.[9] This brings us to the issue of altered (compensatory) motor strategy in response to nociception, which is discussed in the next paragraph.

Innocuous stimuli to the joint, like mid-range joint movement, trigger reflex discharges in γ-motoneurons, which are important for regulating joint stability during normal movement.[22] In contrast (potentially), noxious movements have marked effects on α-motoneurons, whereas under normal conditions joint afferents only exert weak effects on these neurons.[22] Nociception reduces activity of the painful muscle,[14,15,17,23] yet muscle force is maintained.[24] How do muscles maintain force during nociception? Synergist muscles show a reduced activity in response to experimental muscle nociception.[24] Hence, changes in synergist muscles cannot explain the maintenance of muscle force during nociception.[24] Deep-tissue nociception (eg, nociception in deeply located muscles) decreases discharge rates of low-threshold motor units, but at the same time recruits new units to ensure force maintenance despite reduced motor unit discharge rate.[25,26] In other words, the nervous system uses a different motor unit recruitment strategy to maintain force during nociception, which includes the inhibition of one population of motor units and the concurrent recruitment of a new population of motor units.[25] These observations account for deep muscle nociception ands for nociception induced in nonmuscular tissue such as the infrapatellar pat fad.[26] In addition, the compensatory motor strategy in response to nociception depends on the biomechanical constrains on the musculoskeletal system dictated by the task performed.[27]

Another important piece of evidence addressing nociception-motor interaction comes from the study of repetitive transcranial magnetic stimulation of the motor cortex, which exerts short-term analgesic effects in various chronic pain populations (reviewed in Refs. 28–31). Repetitive transcranial magnetic stimulation of the motor cortex directly targets the various structures of the central nervous system involved in nociceptive processing.[28,29] Focal somatotopical stimulation of the motor cortex addresses the sensory-discriminative aspects of pain,[29] and repetitive transcranial magnetic stimulation reverses the inhibited intracortical motor circuitry, which might restore descending nociceptive inhibition.[29,32]

NOCICEPTION IMPAIRS AFFERENT (PROPRIOCEPTIVE) PATHWAYS

Not only efferent motor pathways are affected by nociceptive input but afferent pathways (ie, somatosensory processing including proprioception) are also influenced by tonic muscle nociception (Table 1). We learned from animal data that muscle nociception produces significant changes in the prioprioceptive abilities of movement-related neurons.[33] Muscle nociceptive input is accompanied by severe reduction of position sense of the hand and by loss of stimulus perception.[34] These data point toward a nociception-induced depression of tonic presynaptic or postsynaptic inhibition of premotor interneurons intercalated in spinal proprioceptive pathways. Nociceptive inputs may modulate (decrease or increase) the impulse activity of the

TABLE 1. Overview of the Anatomical Locations of Nociception-motor Interaction and Their Responses to Chronic Nociceptive Input

Anatomical Location	Response to Chronic Polymodal Nociceptive Input
1. Motor cortex	Inhibition of motor cortex neurons
	Decreased excitability of motor cortex
	Reduced motor output
2. Motor units in muscles	Decreased discharge rates of low-threshold motor units
	Recruitment of new units to ensure force maintenance
	Reduced motor unit discharge rate
	Compensatory motor strategy in response to nociception
3. Muscle spindle	Modulation of the impulse activity
4. Golgi tendon organs	Modulation of the impulse activity
5. Somatosensory processing	Presynaptic or postsynaptic inhibition of premotor interneurons intercalated in spinal proprioceptive pathways
	Reorganization of somatosensory cortex
6. Sympathetic nervous system	Excitatory reflexes of the sympathetic units of joint, skin, muscle, and blood vessel nerves
	Amplification of tonic sympathetic vasoconstrictor neuron activity in skeletal muscles, joints, skin, etc.
	Sympathetic-induced modulation of skeletal muscle contractility
	Sympathetic-induced depression of the sensitivity of prorpioceptors like muscle spindles
	Sympathetic-induced shortening of switch-duration in slow-contracting muscle fibers

muscle spindle afferents, or Golgi tendon organs can impair the ability of the central nervous system to use proprioceptive information.[23]

In addition to altered somatosensory input, nociception also changes somatosensory processing. Cortical reorganization has been identified in patients without a demonstrable or local nociceptive etiology but with chronic pain or nonpainful pathological sensations.[35–39] In some studies, the extent of cortical reorganization was correlated with the intensity of pain in the affected limb.[37,39,40] Cortical changes may be caused by chronic nociception.[41,42] Birbaumer et al's[42] study established that local anesthesia leads to a reduction in phantom limb pain and in an elimination of cortical reorganization in individuals with unilateral upper limb amputation. Similarly, therapies intended to improve the sensorimotor integration in the motor control system, reduce the cortical reorganizations and improve pain.[43,44]

THE SYMPATHETIC NERVOUS SYSTEM MEDIATES NOCICEPTION-MOTOR INTERACTION

Nociception is a frequent and important stressor activating the stress response system, including amplification of tonic activity in the sympathetic nervous system. Noxious mechanical stimuli induced by knee movements, and intra-articular injections of prostaglandins (resembling joint inflammation), evoke excitatory reflexes of the sympathetic units of joint nerves, whereas innocuous stimuli do not.[22] Amplification of tonic activity in the sympathetic nervous system exerts a variety of actions that can explain at least part of the findings on nociception-motor interaction. Indeed, chronic amplification of tonic sympathetic activity induces vasoconstriction in skeletal muscles, modulates skeletal muscle contractility, and modulates discharge of various proprioceptors (eg, muscle spindles).[45] Nociception-induced and sympathetic-maintained vasoconstriction leads to insufficient blood flow for working muscles, producing muscle hypoxia and consequently increased oxidative stress, which in turn can trigger muscle nociception.[46] In addition, chronic amplification of tonic sympathetic activity shortens switch-duration in slow-contracting muscle fibers, requiring antigravity muscles to use a different activation pattern.[45] Finally, amplification of tonic sympathetic activity depresses the sensitivity of proprioceptors such as muscle spindles, which in turn worsens the quality of proprioceptive information to the central nervous system.[47] The latter might explain the findings of impaired proprioception in case of chronic nociception [explained above; see "Nociception impairs afferent (proprioceptive) pathways"]. It is concluded that chronic nociception-induced amplification of tonic sympathetic activity may be a crucial factor of deterioration of motor output.

DOES NOCICEPTION-MOTOR INTERACTION MODULATE THE TRANSITION FROM ACUTE TO CHRONIC PAIN?

Nociception-motor interaction may modulate the transition from acute to chronic pain. This notion is supported by the observation that the effect of acute nociception on motor variability differs from chronic pain states.[48] In fact, acute nociception is characterized by a high motor variability, resulting in a protective adaptation[14] with decreased muscle activity during functional tasks.[48] In chronic pain states, the magnitude of motor variability decreases and the muscle activity increases.[48,49] For example, the neural drive to the M. sternocleidomastoideus in chronic neck pain is less selectively tuned with the direction of force production.[49] This results in increased activation of the M. sternocleidomastoideus when acting as an antagonist.[49] Thus, acute (experimental) neck pain reduces M. sternocleidomastoideus activity,[50] whereas chronic neck pain is characterized by augmented activity and a slowed muscle relaxation pattern of the M. sternocleidomastoideus after contraction.[49]

DISRUPTION OF BODY IMAGE IN PATIENTS WITH CHRONIC PAIN

It has long been established that multireceptive neurones (or wide-dynamic-range neurones) in the dorsal horn of the spinal cord not only have the capacity to activate in response to a variety of nociceptive stimuli and weak mechanical stimulation, but they also hold the capacity to capture all the information coming from the interfaces with the external environment (sensors in the skin)

and the internal milieu (sensors in the viscera and musculoskeletal system).[51] This results in "basic somesthetic activity" informing the brain of information relevant to the integrity of the body, hence contributing in the building of our "body schema"[51] or "body image."

Nociception alters the functioning of multireceptive neurones. Secondary hyperalgesia refers to increased responsiveness of multireceptive neurones localized in the spinal segments of the primary source of nociception.[52] In many cases of chronic pain, a state of "central sensitization" occurs. Although peripheral sensitization is a local phenomenon, central sensitization is a central process of the central nervous system. Central sensitization is defined as an augmentation of responsiveness of central neurons to input from polymodal nociceptors.[53] Central sensitization encompasses altered sensory processing in the brain,[54] malfunctioning of descending antinociceptive mechanisms,[55] increased activity of nociceptive facilitatory pathways, temporal summation of second pain or wind-up,[54,56] and long-term potentiation of neuronal synapses in the anterior cingulate cortex.[57] In addition, the pain neuromatrix is overactive in case of central sensitization and chronic pain. Increased activity is present in brain areas known to be involved in acute pain sensations such as the insula, the anterior cingulate cortex, and the prefrontal cortex, but not in the primary or secondary somatosensory cortex.[58] An overactive pain neuromatrix also entails brain activity in regions not involved in acute pain sensations: various brain stem nuclei, the dorsolateral frontal cortex, and the parietal associated cortex.[58] The net result with respect to multireceptive neurones is a marked augmented responsiveness and expanded, overlapping receptive fields, which in turn disrupts the basic somesthetic activity coming from these multireceptive neurons. Hence, the body image becomes disrupted in those with chronic pain due to central sensitization. Even in absence of nociception, pain is frequently experienced in case of central sensitization. Hence, chronic nociception often results in central sensitization, but is no longer required for the experience of pain once central sensitization has been established.

Disruption of the body image can be recognized clinically by a variety of movement anomalies (summarized in Table 2).[51,59–63] There is evidence showing that acute (experimental) nociception is insufficient to alter the body image,[62] supporting our notion that disruption of the body image becomes relevant solely in those with subacute (6 to 12 wk) to chronic pain (> 12 wk). Note that not all anomalies listed in Table 2 should be present in those presenting with a disrupted body image. We believe that the presence of 2 or more anomalies in combination with chronic pain and evidence of central sensitization suffice. Guidelines for the recognition of central sensitization are presented elsewhere.[64]

TABLE 2. Clinical Signs of Disrupted Body Image in Patients With Chronic Pain

Feeling of swollen limb in absence of visual evidence of edema or swelling (= phantom swelling sensation) (eg, complex regional pain syndrome, rheumatoid arthritis, fibromyalgia)[61]
Phantom swelling sensations enhance when the patients close their eyes[61]
Phantom swelling sensations decrease or disappear when they view the affected limb[61]
Perceiving the affected body part smaller than it should be (eg, chronic low back pain)[63]
Reduced ability to perform mental rotation of the affected body part(s)[60]
Delayed recognition of body part laterality[60,62]
Slower imagined movements when the actual movement is anticipated to be painful[59]
Feeling of joint stiffness in absence of objective signs of decreased mobility[61]
Decreased tactile acuity of (the skin above) the affected region; increased 2-point discrimination threshold[63]
Feeling of being clumsy or less aware of where their limbs are in space[61]
Inability to feel part of the affected body region without visual or tactile input[63]

CHRONIC NOCICEPTION-INDUCED MOTOR INHIBITION MIGHT PREVENT EFFECTIVE MOTOR RETRAINING

Remarkably, the motor control adjustments in response to nociception persist despite the relief of nociception, which has potential implications for pain recurrence.[27] Impaired motor control patterns as typically seen during episodes of various kinds of musculoskeletal pain persist even when the patient recovers. This has been evidenced in various musculoskeletal disorders with high recurrence rates, including neck pain,[65] low back pain,[66] and whiplash associated disorders.[5]

Despite these observations, rehabilitation strategies around the globe continue using motor control (re)training strategies for those with chronic nociception. On the one hand, this seems a reasonable approach given the disrupted body schema in many of these patients. On the other, this strategy contradicts our current understanding of nociception-motor interaction. As explained above, chronic nociception inhibits motor output. Thus, motor retraining during chronic nociception might be fruitless. A possible solution to this problem is discussed below. In this respect, "motor retraining" is defined as the use of exercise strategies aiming at restoring motor control (eg, core stability retraining). Table 3 provides an overview of the clinical implications of nociception-motor interactions.

TABLE 3. Nociception-motor Interaction: Overview of Clinical Implications

Clinicians facing with a patient experiencing any type of chronic nociception should consider nociception-motor interaction
Clinicians are advocated to take nociception-motor interaction into account when treating patients with (sub)acute pain in order to prevent chronic pain
In case of chronic pain due to central sensitization, nociception-motor interactions can be observed by searching for signs of disrupted body image (Table 2)
Treatment strategies like pacing pain management should aim at decreasing variations in pain perception rather than focussing on pain severity
Motor retraining during chronic nociception might be fruitless
Combining drugs that activate descending nociceptive inhibitory pathways (eg, acetaminophen, selective and balanced serotonin and norepinephrine reuptake inhibitor drugs) with motor control retraining appears warranted
Manual joint mobilization, virtual reality or conventional TENS, immediately followed by, or combined with motor control retraining might enable effective motor control retraining

TENS indicates transcutaneous electric nerve stimulation.

DISCUSSION

Activation of Descending Nociceptive Inhibitory Pathways to Enable Motor Retraining?

Cortical influences on nociception-motor interaction are likely to be in part mediated by cortical *N*-methyl-D-aspartate receptors, which have been shown to play an important role not only in mediating nociception and producing analgesia but also in ensuring motor coordination.[67] Disruption of cortex-specific *N*-methyl-D-aspartate function results in motor coordination deficits.[67] These animal observations point toward the close interaction between nociceptive analgesia and motor coordination, and hence may guide us toward using nociceptive inhibition to overcome the delirious effects of nociception on motor performance.

Despite the increasing amount of research in this area, an in-depth understanding of the bidirectional nociception-motor interaction is still far from being achieved.[68] Many questions remain, especially addressing the treatment of nociception-motor interaction. Hence, further research is warranted. More specifically, although studies examining the delirious effects of chronic nociception on motor performance in humans are fairly large in number, studies examining the effect of nociceptive inhibition on motor performance are currently unavailable. Studying the damaging effects of nociception (on the motor response) is one thing, searching for a solution is another. Activating nociceptive inhibitory pathways to overcome the delirious effects of chronic nociception on motor output might be such a solution.

The clinical consequence of the shift in thinking is to stop trying to restore normal motor control in case of chronic nociception in patients with musculoskeletal disorders. For example, restoring muscle trunk control in patients with low back pain is unlikely to be successful unless the delirious effects of nociception-motor interaction are addressed. It is hypothesized that activation of central nociceptive inhibitory mechanisms, by decreasing nociceptive input, may address nociception-motor interactions. For example, activation of the periaqueductal gray matter activates descending seretonergic and noradrenergic neurones that activate the rostral ventromedial medulla and the dorsolateral pons respectively.[69] These brain stem centers provide powerful inhibitory action on nociceptive input at the spinal segmental level. Activation of descending nociceptive inhibition reduces nociceptive input to the central nervous system. Hence, motor output may be (partly) restored under conditions of nociceptive inhibition. This hypothesis is supported by the finding that peak exercise performance improves when using acetaminophen.[70] Acetaminophen primarily acts centrally: it reinforces descending inhibitory pathways,[71] namely the serotonergic descending nociceptive pathways. This strategy may permit motor control-retraining strategies to be undertaken effectively.

In line with this reasoning is the use of serotonin reuptake inhibitor drugs in conjunction with motor control retraining. Serotonin reuptake inhibitor drugs activate serotonergic descending pathways that recruit, in part, opioid peptide-containing interneurons in the dorsal horn.[72] Similarly, centrally acting analgesics such as Duloxetine, a selective and balanced serototin (5-HT) and norepinephrine reuptake inhibitor (SNRI), have proven its efficacy in a variety of chronic pain conditions characterized by central sensitization (eg, diabetic peripheral neuropathic pain,[73] fibromyalgia,[74] and osteoarthritis[75]). It remains unclear whether these clinical effects can be reinforced by combining drug use with motor control retraining.

To explore the clinical consequences of nociception-motor interactions further, the use of virtual reality or conventional transcutaneous electric nerve stimulation (TENS) in conjunction with motor retraining might provide opportunities. Virtual reality has been suggested as a desensitization therapy,[76] and evidence in support of its analgesic effects in patients with chronic pain has been provided.[77,78] Virtual reality provides a realistic, computer-generated environment enabling motor retraining and at the same time distracting the user's conscious attention away from simultaneous nociceptive input. Conventional TENS activates large-diameter afferent fibers, which in turn activate descending nociceptive inhibitory mechanisms by activating the ventrolateral periaqueductal gray and the rostral ventromedial medulla.[79,80] Given its short-term effects, application of conventional TENS before or during motor retraining might provide a solution to overcome the delirious consequences of nociception-motor interactions. Similarly, manual mobilization of joints segmentally related to the primary source of nociception exerts temporally (30 to 45 min) activation of descending antinociceptive pathways.[69,81–84] Hence, manual joint mobilization immediately followed by motor control retraining might also be a solution.

CONCLUSIONS

Research has provided us with an increased understanding of nociception-motor interaction. Chronic nociceptive stimuli result in cortical relay of the motor output in humans and a reduced activity of the corresponding muscle. In addition, the autonomic nervous system responds to chronic nociception with amplification of tonic sympathetic activity. Not only motor and sympathetic output pathways are affected by chronic nociceptive input but afferent pathways (proprioception, somatosensory processing) are also influenced by nociception. Evidence supporting an important role for nociception-motor interaction in the transition from acute to chronic pain is accumulating. The body image becomes disrupted in those with chronic nociception and chronic pain due to central sensitization. Disruption of the body image can be recognized clinically by a variety of movement anomalies.

Giving the likelihood that nociception-induced motor inhibition prevents effective motor retraining, it seems reasonable to search for treatment strategies that reverse the delirious effects of chronic nociception on motor performance. Clinical studies are required to examine whether activating nociceptive inhibitory pathways is capable of doing so.

Key Messages

- Chronic nociception alters autonomic and motor output, making proper central movement control impossible.
- The shift in thinking is to stop trying to restore normal motor control in case of chronic nociception in patients with musculoskeletal disorders.
- Activation of central nociceptive inhibitory mechanisms, by decreasing nociceptive input, might address nociception-motor interactions. This can be accomplished by using virtual reality, centrally acting drugs, or conventional TENS in conjunction with motor control retraining.

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