PROVA ESTRATTA

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CONCORSO PUBBLICO, PER TITOLI ED ESAMI, PER N. 1 POSTO DI COLLABORATORE PROFESSIONALE SANITARIO – TECNICO DI NEUROFISIOPATOLOGIA - CAT. D DA ASSEGNARE ALLA UOC NEUROLOGIA 6 - NEUROFISIOPATOLOGIA

PROVA ORALE A

Valutazione pre-operatoria e monitoraggio intraoperatorio in corso di chirurgia per lesione espansiva al passaggio bulbo-cervicale

a. Esami preoperatori indicati per la tipologia di intervento
b. Indicazioni al monitoraggio, tecniche di monitoraggio e mappaggio applicabili (pess, pem, onda d…)
c. Criteri di warning e considerazioni di base sul regime anestesiologico
d. Pitfalls relativi a posizionamento, eventuali manovre correttive in corso di IOM (ottimizzazione dipolo cefalico, ripresa baseline, build-up…)

INFORMATICA:

Descrivi come utilizzare la funzione "conta se" in una selezione su foglio di lavoro excel.

INGLESE:

Lettura e traduzione di uno stralcio di articolo allegato

ALLEGATO DOMANDA A

INVITED REVIEW

Electrophysiology of Cranial Nerve Testing: Trigeminal and Facial Nerves

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Summary: The clinical examination of the trigeminal and facial nerves provides significant diagnostic value, especially in the localization of lesions in disorders affecting the central and/or peripheral nervous system. The electrodiagnostic evaluation of these nerves and their pathways adds further accuracy and reliability to the diagnostic investigation and the localization process, especially when different testing methods are combined based on the clinical presentation and the electrophysiological findings. The diagnostic uniqueness of the trigeminal and facial nerves is their connectivity and their coparticipation in reflexes commonly used in clinical practice, namely the blink and corneal reflexes. The other reflexes used in the diagnostic process and lesion localization are very nerve specific and add more diagnostic yield to the workup of certain disorders of the nervous system. This article provides a review of commonly used electrodiagnostic studies and techniques in the evaluation and lesion localization of cranial nerves V and VII.

Key Words: Trigeminal nerve, Facial nerve, Corneal reflex, Blink reflex, Jaw-jerk reflex, Masseter reflex, Masseter inhibitory reflex, Trigeminal somatosensory-evoked potentials, Laser-evoked potentials, Contact heat-evoked potentials.

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The electrophysiological studies of the reflex activity mediated by the trigeminal and facial nerves allow the evaluation of their integrity and their central pathways. Their clinical applications include the evaluation of cranial neuropathies, polyradiculoneuropathies, peripheral neuropathies, brainstem lesions, and facial movement disorders. This review discusses the different established reflexes and techniques used to study these two nerves and their connections.

THE TRIGEMINAL NERVE

Corneal Reflex

Neuroanatomy

The corneal reflex is designed to protect the eye and is believed to be purely nociceptive. The reflex afferents are A-delta fibers[1,2] passing through long ciliary nerves and the ophthalmic division of the trigeminal sensory root to reach the pons. The central circuit is similar to that of R2 responses of the blink reflex (Fig. 1B), but it differs from R2 because it is purely nociceptive and thus is relayed through fewer and different interneurons that are more resistant to suprasegmental influences.[1,3] The efferent limb comprises motor fibers of the bilateral facial motor nuclei in the facial nerve that terminate in the orbicularis oculi (OO) muscles.

Technique of Testing and Application

The corneal reflex consists of bilateral involuntary eyelid closure (contraction of the OO) in response to stimulation of either cornea between spontaneous blinks. The stimulation can be mechanical or electrical. Responses are recorded simultaneously from bilateral inferior portions of the OO muscles with surface or needle electrodes placed in the same location as for the blink reflex.

Mechanical stimulation is evoked by application of a small 2-millimeter (mm) metal sphere to the cornea.[1,4] When the sphere touches the cornea, contact is made between the cornea and the electrical trigger circuit that delivers the pulse.

Electrical stimulation of the cornea is done with a thin saline soaked cotton thread connected to the cathode of a constant current stimulator. The anode is placed on the earlobe or forearm. This stimulation produces controlled and reproducible responses with square pulses of 1 millisecond (ms) in duration and 0.1 to 3 milliamps (mA) in intensity yielding controlled and reproducible stimuli.

The reflex threshold in normal subjects rarely exceeds 0.5 mA. Mechanical and electrical stimuli elicit reflexes with similar latencies. Absolute latency values range from 36 to 64 ms with mechanical stimulation and 35 to 50 ms with electrical stimulation. The wide range of latencies narrows within age groups.

When measuring the latency, three pairs of latency times are assessed from stimulus artifact to onset of electromyographic (EMG) response (Fig. 1A).

In contrast to the blink reflex, the corneal reflex does not evoke an early R1 response (Fig. 1A). When the cornea is stimulated (mechanically or electrically), there is direct (ipsilateral) and consensual (contralateral) response. With mechanical stimulation, the direct response latency should not exceed the consensual latency by more than 8 ms. The latencies of the direct responses evoked by stimulation of both corneas separately should never differ by more than 10 ms.[1,4] With electrical stimulus, the difference between the direct and consensual responses should not exceed 5 ms, and the difference between direct responses should never exceed 8 ms (Table 1).

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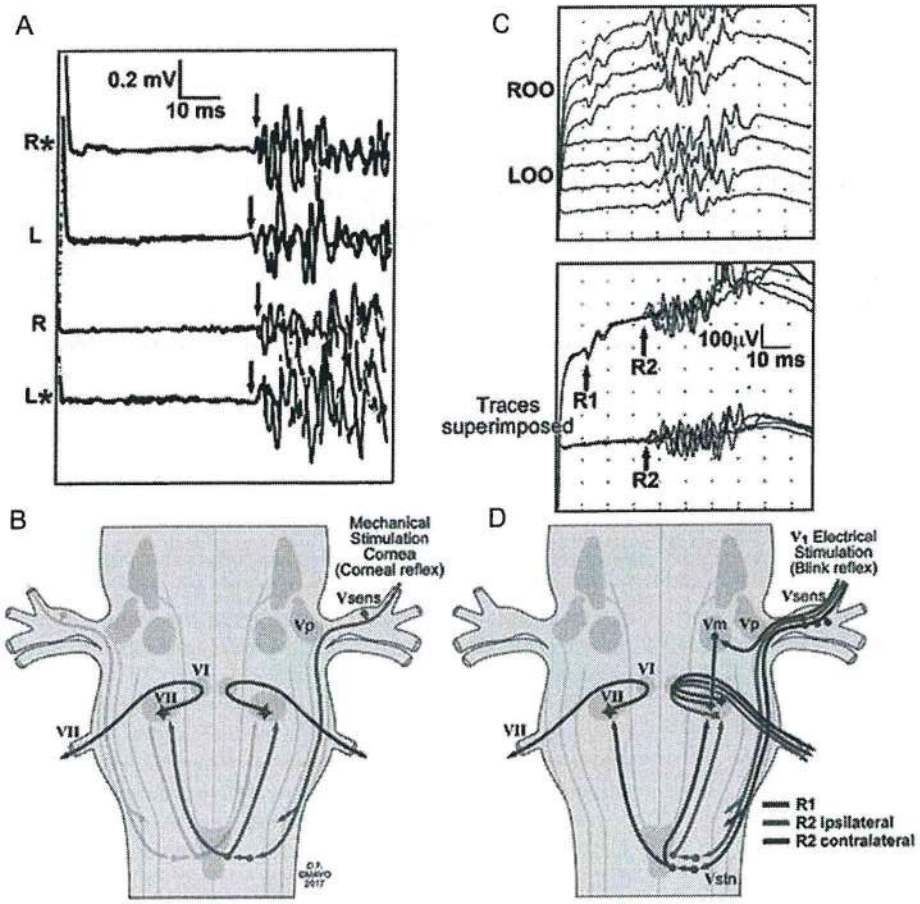

FIG. 1. Normal corneal and blink reflex. **A**, Responses from the right (R) and left (L) orbicularis oculi (OO) muscles after mechanical stimulation of the right (R*) and (L*) cornea. **B**, Presumed central pathways subserving the corneal reflex. **C**, Blink reflex stimulating right side, recording both OO muscles. On ipsilateral side early R1 present at 11 ms and late R2 potential at 34 ms. On the contralateral side only a late R2 potential is seen at 35 ms. **D**, Central pathway subserving the blink reflex. The afferent loop is mediated through V1 that synapses with both the main sensory nucleus in the midpons (Vm) and the nucleus of the spinal tract (Vstn) in medulla. The early response R1 is mediated through Vm and ipsilateral facial motor nucleus (VII). The late R2 response is mediated between Vstn and both ipsilateral and contralateral facial nuclei.

Lesions of the trigeminal nerve abolish ipsilateral responses to stimulation, whereas lesions of the facial nerve abolish the corneal reflex with bilateral eye stimulation.

Blink Reflex

The blink reflex detects lesions involving the (ophthalmic) first division of the trigeminal nerve (V1), the facial nerve or their central pathways in the pons and medulla. Overend in 1896 observed that the reflex was the product of facial stimulation, for it was present in the blind. Kugelberg, in 1952 studied electromyographically the blink reflex evoked by electrical stimulation of the supraorbital nerve. The blink reflex is a surface EMG recording from the OO muscle of the reflex evoked by mechanical or electrical stimulation of the supraorbital nerve. Mechanically evoked blink reflexes show larger latency variation due to less well synchronized afferent volley.[5]

TABLE 1. Corneal Reflex Normative Values

Absolute latency (mech/elect stim)*	36–64/35–50 ms
Direct-consensual Δlatency (mech/elect stim)*	<8/<5 ms
Side–side Δlatency† (mech/elect stim)*	<10/<8 ms

*Mech/elect stim = values with mechanical or electrical stimulation.
†Δlatency = latency difference.

Neuroanatomy

The afferent limb is mediated by the supraorbital branch of V1, and the efferent limb travels in the facial nerve. R1 is an oligosynaptic circuit response and is conducted via large myelinated fibers through the pons, to the principal sensory nucleus of the trigeminal nerve, the whole circuit lying within the pons, before reaching the ipsilateral facial nucleus (Fig. 1D). R2 is polysynaptic with afferent impulses being relayed to facial motor neurons through the dorsolateral pons and medulla before reaching the most caudal area of the spinal trigeminal nucleus.[6] From there, impulses are conveyed through polysynaptic medullary pathways both ipsilaterally and contralaterally to the stimulated side of the face, before connecting to the facial nuclei. The crossing takes place in the caudal medulla.

Technique of Testing

When an electrical stimulus is applied to the supraorbital nerve, surface electrodes deliver single stimuli of an intensity of 2 to 3 times the perception threshold. Surface recording electrodes are placed over bilateral inferior OO. The electrical stimulation of the supraorbital nerve elicits two responses: a first or early response (R1) that is relatively constant, well

synchronized, unilateral, ipsilateral to the side of stimulation and accompanied by a short EMG response in the OO with latency of approximately 10 to 13 ms not visible clinically (considered a proprioceptive reflex). The second or late response (R2) is believed to be nociceptive, more variable and prolonged, bilateral and poorly synchronized with latency of approximately 30 ms[6] (Fig. 1C). The amplitude measurements are usually not helpful in localization as differences as great as 40% can occur in normal subjects.[7]

R1 is a relatively stable response and is used for evaluation of the afferents from the supraorbital and pons regions, not influenced by supratentorial dysfunction (unless during the acute phase of an insult) and disorders of consciousness and cognition.[8,page62] Absolute or side-to-side R1 latency prolongations are considered abnormal (Table 2).[9]

The R2 response correlates with closure of the eyelids and has the same latency as the corneal reflex. It is polysynaptic, more variable than R1, influenced by supratentorial processes, but is crucial in diagnosing medullary lesions. The R2 responses are attenuated during sleep and by sedating medications. With repeated stimulation, the R2 responses tend to habituate. The simultaneous recording of bilateral R2 responses is useful in differentiating an afferent (trigeminal) and efferent (facial) pattern of lesion.[9]

The blink reflex can also be elicited with stimulation of nontrigeminal inputs of peripheral nerves (somatosensory, acoustic, or photic).[1] These reflexes involve central mechanisms, and responses have greater variability of latency, show more dispersion in time, vary with lengthy repetition of stimuli, and show other distinctive differences.[10]

Applications

In lesions of the trigeminal nerve, ipsilateral R1 and bilateral R2 responses can be delayed or be absent depending on the severity of the lesion, but both R1 and bilateral R2 responses will be normal with stimulation of the unaffected side.[11–13] This pattern is typically seen with proximal or distal trigeminal sensory neuropathy. Abnormalities in R1 only or both R1 and R2 may be seen in isolated trigeminal neuropathy. In postherpetic neuralgia, there are frequently significant abnormalities of the R1 blink reflex responses on the affected side compared with the normal side. However, in most patients with idiopathic trigeminal neuralgia, all blink reflexes are normal; an abnormality would suggest a structural lesion.[11,13]

In facial nerve lesions stimulation of the involved side can produce prolonged or absent R1 and ipsilateral R2 depending on the severity of the lesion, with normal contralateral R2 responses. Stimulation of the uninvolved side will produce normal R1 and ipsilateral R2 with prolonged or absent contralateral R2 responses. This pattern is typically observed in idiopathic or secondary facial neuropathies.

TABLE 2. Blink Reflex Normative Values

R1 latency	8–13 ms (<1.3)*
R2 ipsilateral latency	29–41 ms (<8)*
R2 contralateral latency	≤ 44 ms (<8)*

*Indicates side-to-side latency difference values.

The R1 component of the blink reflex is mediated at the level of the lateral midpons and facial nucleus. This probably courses ventrolaterally to the medial longitudinal fasciculus, approaching the intrapontine segments of the abducens, facial, and vestibular nerves.[14,15] Provided that trigeminal nerve functions are intact (i.e., there is a normal corneal reflex, normal trigeminal sensory function, and no masseter paresis), masseter reflex abnormalities (see below) indicate ipsilateral brainstem lesions between the level of the trigeminal motor and oculomotor nuclei, whereas blink reflex R1 abnormalities indicate lesions between the lateral midpons and medial caudal pons.[15,16]

Because of the differences in the circuitry of the R1 and R2 responses, an interesting possibility emerges from the study of the onset latency of the responses: the latency of the R1 depends more on the trigeminal and facial conduction times than on the intraaxial synaptic connectivity, with only one or two interneurons in the circuit.[1] The reverse occurs with regard to the R2, for which the latency is more dependent on interneuronal synapsis than on peripheral nerve conduction time. Therefore, delays are observed predominantly in the R1 response in lesions involving the peripheral nerve and in the R2 response in lesions involving the trigeminal complex in the brainstem, predominantly medullary (Kimura, 1975, Kimura, 1982, Kimura and Lyon, 1972, and Kimura et al., 1970). However, delays in the R1 response can also be detected in clinical manifest or silent pontine lesions in multiple sclerosis (Kimura, 1975).

Blink reflex findings involving both R1 and R2 can be helpful in detecting subclinical sensory ganglionopathy of various etiologies and may be useful in providing evidence of patchy sensory involvement.[13] While subclinical trigeminal abnormalities can be seen in patients with sensory ganglionopathy, sometimes involving R1 and/or R2 responses, overall the most frequent finding is an abnormal R2 response.[17] Taimour et al. reported abnormal blink reflex responses in paraneoplastic sensory ganglionopathy cases. This was believed to possibly reflect the patchy nature of the disease.[17]

In patients with chronic inflammatory demyelinating polyneuropathy, there is no apparent correlation between clinical disability or disease duration and the R1 response. The blink reflex is useful for functional evaluation of trigeminal and facial nerves in chronic inflammatory demyelinating polyneuropathy because of this lack of correlation between clinical features and electrophysiological findings.[18] Delayed responses to supraorbital nerve stimulation are found in hereditary motor and sensory neuropathy type 1 (Kimura 1971). Delay is most significant in the distal segment of the facial nerve, although no facial weakness may be present. By contrast, delayed latencies in acute inflammatory demyelinating polyradiculoneuropathy are often associated with facial weakness. Axonal length-dependent peripheral neuropathies rarely affect the blink reflex.

The blink reflex can also be obtained by stimulation of infraorbital and mental nerves. The responses can be of help for the assessment of the site of the lesion in the trigeminal spinal nuclei in brainstem vascular lesions (Valls-Solé et al., 1996), and in patients with suspected lesions of the maxillary or mandibular divisions of the trigeminal nerve.

Jaw Jerk (Masseter Reflex)

Clinically, this reflex is usually confined to distinguishing between normal and brisk reactions because during clinical examination alone, it is difficult to detect unilateral interruption of the reflex. In addition, even in healthy subjects, reflex movement of the mandible is often impossible to separate from the slight excursion of the jaw with mechanical percussion.[1]

Neuroanatomy

The jaw Jerk (Mandibular or Masseter reflex) evaluates the third division of the trigeminal nerve (V3). It is a monosynaptic tendon reflex that is one of the first reflexes to develop *in utero* and can be recorded in preterm infants.[1] Tapping the chin causes contraction of the masseters—jaw-closing muscles. Afferent neurons are located centrally unlike all other stretch reflexes (in the dorsal root ganglia), in the mesencephalic nucleus in the midbrain (Fig. 2B). The efferent motor neurons are located in the pontine trigeminal motor nucleus and activate only the ipsilateral masseter muscle. Afferent impulses from masseter muscle spindles travel through the motor root of V3 to the mesencephalic nucleus and activate the motor nucleus monosynaptically. The efferent limb of the reflex arc causes the ipsilateral masseter muscle to contract. Whether the afferent fibers travel in the trigeminal motor root[36,47] or the trigeminal sensory root[11,19,20] remains controversial. In addition, the masseter reflex also differs from the extremity deep tendon reflexes because it is potentiated rather than inhibited by vibration.[12]

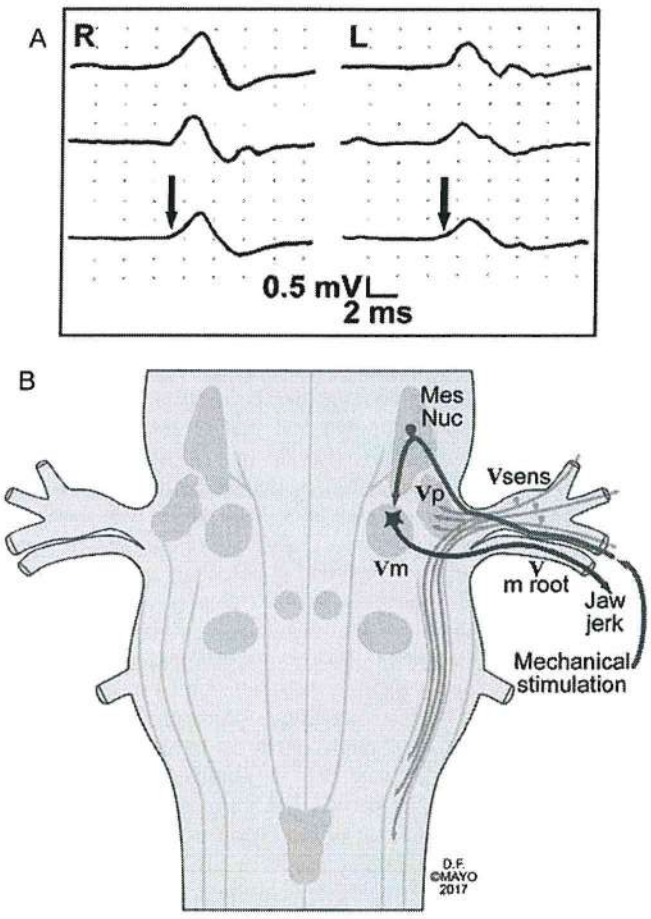

FIG. 2. **A**, Normal jaw-jerk responses from the right (R) and left (L) masseter muscles. **B**, Presumed central pathways subserving the jaw-jerk responses.

Technique of Testing

When the jaw-jerk reflex is assessed electrophysiologically, the reflex hammer is equipped with a microswitch that triggers the sweep of the oscilloscope when striking the examiner's finger resting over the subject's chin ([15,21] Stevens JC, Smith BE, 1996, Daube, Clinical Neurophysiology, p.321–325). Electromyographic responses are recorded simultaneously and bilaterally with either surface electrodes placed on each masseter muscle belly two-third the distance between the zygoma and the lower edge of the mandible, or small diameter concentric needle electrodes inserted into each masseter (in elderly or obese individuals). The reference electrode is placed just below the mandibular angle or over the zygoma.

It is often absent in elderly people and therefore has no definite clinical significance if absent bilaterally, a situation which may occur in healthy subjects. The normal range of latencies is 5 to 10 ms (Table 3).[22] The amplitude is widely variable, and measurement is not considered clinically useful (Kimura, 2001). Since reflex latencies may vary with successive trials, comparison of simultaneously recorded contralateral latencies responses is more meaningful than analyzing absolute values.[14] A difference of more than 0.8 ms or a consistent unilateral absence of the reflex is taken to be abnormal (Fig. 1A).

The masseter reflex is not technically as precise as the blink reflex. Technical problems can include standardizing the mechanical tap and changes in the tone of the masseter muscle (both inter- and intra-individual variability); therefore, four consecutive responses are used to show consistency. If the jaw is not sufficiently relaxed, background muscle activity may obscure the response. This reflex is strongly influenced by dental occlusion and can be asymmetrical or even absent in some patients with temporomandibular disorders.[13,23]

Applications

This reflex assesses function of the mandibular division of the trigeminal nerve (V3). The most common abnormality is the absence of the reflex rather than prolongation of the latency. A unilateral delay or absent response suggests a lesion either in the trigeminal nerve or the brainstem. Using the jaw reflex in conjunction with needle examination of the masseter muscle may document a peripheral lesion if there is evidence of denervation.[11,24,25] Because the afferent nerve cell body is at the mesencephalic nucleus, patients with primarily sensory symptoms and hyporeflexia who have a normal masseter response would more likely be diagnosed with a ganglionopathy

TABLE 3. Masseter Reflex Normative Value

Masseter reflex latency	≤10.5 ms

rather than a sensory neuropathy.[26] This is also why the response is typically normal in patients with Friedrich ataxia.[27]

The observation of an absent reflex response in the face of a normal masseter EMG study is observed in ipsilateral midbrain lesions. However, with pontine lesions, both EMG and jaw jerk may be abnormal, due to efferent cell bodies' involvement.[11,24,25] Polysynaptic brainstem reflexes such as the blink reflex R2 response show increased latencies and decreased amplitudes with supratentorial lesions, particularly those of the lower postcentral area.[28] The masseter reflex is monosynaptic and therefore is not similarly influenced, making it a reliable measure of direct involvement of the reflex arch.[28] Masseter reflex latency and amplitude are not observed to be shifted beyond the normal range by suprasegmental and cerebellar influences.[28]

Using both the masseter and blink reflexes in patients with internuclear ophthalmoplegia due to multiple sclerosis or lacunar brainstem infarctions, lesions can be localized either to the midbrain or pons. If the abnormality is limited to the masseter reflex, this suggests a midbrain lesion, but an abnormal blink reflex R1 latency indicates involvement of the rostral pons.

Masseter Inhibitory Reflex (MIR)

Stimulation of the masseter muscle stretch receptors induces not only the jaw jerk but also inhibitory effects that can be easily observed as a silent period when the stretch is applied during masseter contraction. The silent period in response to chin taps begins at approximately 10 to 12 ms and lasts for 20 to 40 ms.[29] This was believed to be due to unloading of spindles or activation of Golgi tendon organs[28] while electrical stimuli evoke a double phase of silence.

Electrical stimulation anywhere within the mouth or on the skin innervated by the maxillary and mandibular trigeminal divisions may evoke a reflex inhibition in the jaw-closing muscles. This phenomenon can be produced by electrical or mechanical stimulation of the infraorbital or mentalis nerves during voluntary contraction of the masseter muscle, which evokes a reflex inhibition and an EMG silent period of the jaw-closing muscles (masseter, temporalis) and transitory relative or absolute decrease in EMG activity evoked in the midst of an otherwise sustained contraction.[30] This reflex is believed to have a primary role of protecting against powerful jaw closure during biting and chewing.

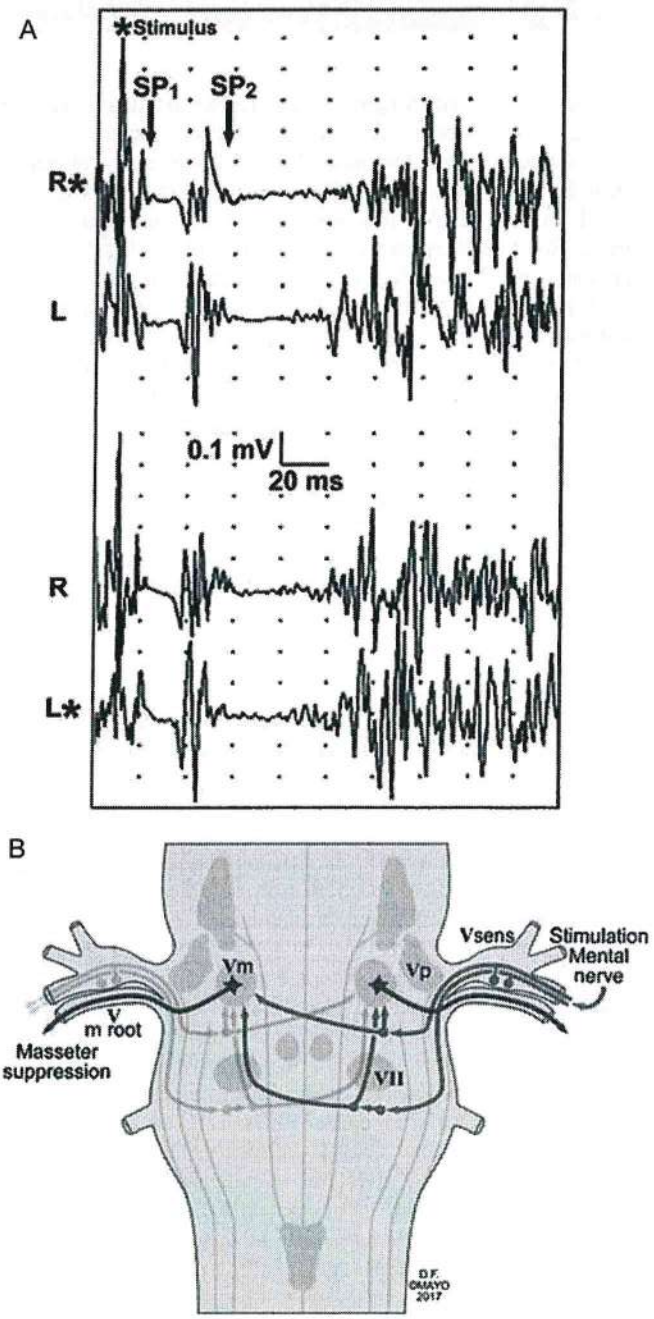

FIG. 3. A, Normal early (SP1) and late (SP2) phase of the MIR. The responses are shown from the right (upper trace) and left (lower trace) masseter muscles after stimulation of the right (R*) mental nerve. B, Presumed location of the bulbar interneurons subserving the SP1 and SP2 of the MIR.

Neuroanatomy

After stimulation of the mental or infraorbital nerve, impulses reach the pons through the sensory mandibular or maxillary root of the trigeminal nerve, respectively[15] (Fig. 3B). The SP1 response is probably mediated by inhibitory interneuron located close to the ipsilateral trigeminal motor nucleus. The inhibitory interneuron projects onto jaw-closing motor neurons bilaterally. The whole circuit lies in the midpons.[31] The afferents for SP2 descend in the spinal trigeminal tract and connect through a polysynaptic chain of excitatory interneurons, probably located in the lateral reticular formation, at the level of the pontomedullary junction.

Technique of Testing

The recording electrode is placed on the masseter muscle bilaterally (same location as for the jaw jerk). Subjects are instructed to clench the teeth as hard as possible for approximately 2 to 3 seconds. The reflex can be measured properly only if the patient is able to clench the teeth and produce a full EMG

interference pattern. Single electric shocks are delivered to the mental or infraorbital nerves through surface electrodes placed over the appropriate foramina. A stimulus intensity of approximately 2 to 3 times the reflex threshold (usually 20–50 mA) yields the best results. It is always necessary to perform several trials. Some authors measure the latency at the last EMG peak crossing of the isoelectric line, whereas others record the beginning of the electrical silence. Each of these methods is clinically satisfactory, provided the normal value determination is maintained and intraindividual measurement differences (between right and left sided stimuli) are avoided.[1]

With an electrical stimulus, two electrical silent periods occur interrupting the voluntary EMG activity in the ipsilateral and contralateral masseter muscles[15,30–32] (Fig. 3A). The first (SP1) corresponds to the SP after a mechanical tap and the second one (SP2) begins 30 to 60 ms after the stimulus (Smith BE, 2009, Daube, Clinical Neurophysiology, p.538–539). Prolongation of either absolute latencies, ipsilateral-contralateral latency difference, or side-to-side latency difference when recorded from one muscle, is considered abnormal (Table 4). Perhaps because electrical stimuli yield mixed nociceptive and nonnociceptive inputs, whether the SP1, SP2, or both components are nociceptive reflexes remains controversial.

Applications

The silent period may be absent in patients with trigeminal sensory neuropathies that result in significant impairment of reflex mechanism involved in chewing.[33] It is also sometimes absent in tetanus and may be unilaterally absent in patients with hemimasticatory spasm.[34] The latency of SP1 is often delayed in patients with demyelinating neuropathies.[35] MIR is especially useful to confirm conduction delay secondary to demyelination in severe neuropathies with absent sensory and muscle action potentials as well as blink reflex, as it can still be measured. MIR remains normal in axonopathies.

An afferent abnormality (absent or delayed direct and crossed responses to unilateral stimulation) indicates a lesion along the afferent path (intra- or extra-axial before the site of crossing of the impulse volley).[31] SP1 is more susceptible than SP2 to extra-axial lesions, such as trigeminal neuropathy.[2]

Brainstem lesions may show an afferent delay or block to unilateral stimulation and abnormal crossed responses to contralateral stimulation, or abnormal crossed responses to stimulation of either side. The lesion involves the dorsal pontine tegmentum at the level of the midpons if both SP1 and SP2 are affected, and the lower pons or the pontomedullary junction if SP2 alone is affected.[31] A unilateral efferent abnormality (absent or delayed responses confined to the muscle on one side, irrespective of the side of stimulation) is extremely rare except in cases of unilateral masticatory spasm.[36]

TABLE 4. Masseter Inhibitory Reflex Normative Values

Early silent period SP1 latency	10–15 ms
Late silent period SP2 latency	40–50 ms
Ipsi-contralateral latency difference SP1	≤2 ms
Ipsi-contralateral latency difference SP2	≤6 ms
Side-to-side latency difference–one muscle record	≤8 ms

Trigeminal Somatosensory-Evoked Potentials

Different approaches have been used to study the trigeminal system by the evoked potential techniques. As these techniques are not frequently used, clinically their practical application and utility remain poorly defined.

The main problems associated with somatosensory-evoked potentials (SEPs) from the trigeminal territory are stimulus artifact (with electrical stimulation), unwanted stimulus spread to facial muscles innervated by the facial nerve, and direct or reflex muscle activities (with mechanical stimulation), which contaminate scalp recordings.[37–39] In addition to the limitations related to puff stimulation that appeared to activate receptors with differing thresholds.[40] The suggested solution was the use of invasive techniques[37,39,41] such as the use of electrical pulses to the tooth pulp or gums and needle electrode stimulation at the mental foramen. Despite the last method reliability, its invasiveness limited its use.[34]

Another consideration was the use of short versus long latency potentials.[42] Very short latency-evoked potentials were recorded by Leandri et al. who described an invasive technique to stimulate the mental nerve without simultaneous activation of the surrounding muscles, with a technique similar to that used to stimulate the infraorbital and supraorbital nerves.

Inferior alveolar nerve (IAN) SEPs have been used to evaluate the sensory function of the mandibular branch through the mental nerve, and a separate technique was reported with stimulation of the mental nerve at the mandibular foramen, with recording early evoked potentials over the scalp.[38] With IAN SEPs, it became possible to evaluate nerve function and its central connections noninvasively. The use of near nerve electrode over the mentalis nerve causes localized stimulation without triggering movement of the jaw and muscle artifact. Hand stimulation of the IAN endings with surface electrodes has been successfully demonstrated[42–45] and normative data have been published.[38,40,46–48] Arcuri et al.[38] 2006 described a reliable technique of a regular pattern of peak events that were stable and not contaminated by muscle artifact.

In a study by Rossini at el. 2016, IAN SEPs were recorded in a noninvasive technique and represented a noninvasive objective method to evaluate sensory nerve function in the maxillofacial region with very similar results. Latencies obtained by this method were more stable then amplitudes, and mean latency values were similar to those reported by Arcuri et al. 2006.

Laser-Evoked Potentials and Contact Heat-Evoked Potentials

Owing to the growing interest in the evaluation of neuropathic pain and somatosensory pain pathways, assessment of nociceptive cerebral–evoked potentials using laser-evoked potentials (LEPs) has been extensively studied and proven to be a very reliable method. It is considered the gold standard objective test that is highly specific for small fiber/spinothalamic tract function evaluation. Because of the short conduction distance

and high receptor density, the trigeminal LEPs are of higher amplitude and recorded easier than with limb stimulation.[2,49,50]

Due to the radiant heat delivered through laser beams and the risk of eye damage and skin burns, another method of stimulating the skin with contact heat conveyed through thermofoil thermodes with brain electrical source analysis was developed and became of practical application in the recent years. Both methods LEPs and contact heat-evoked potentials (CHEPs) stimulate the same type of nociceptors in cutaneous A-delta and C fibers. The main difference in stimulation for LEPs versus CHEPs during the thermode skin application of stimulus is a slope of the temperature rise which is 70 C/s (centigrade/second) for CHEPs that is considerably less than that for LEPs, which is about 1,000 C/s.[51–53]

A large multicenter international study by Granowsky et al.[54] provided previously lacking data set of normative values that facilitated the clinical use of CHEPs. The data are valid only for the equipment, set up, and stimulation parameters used in the study. Normative values at different body parts (face, upper and lower limbs, cervical and lumbar spine) were analyzed for both males and females, compared between both sides of the body, and correlated their amplitudes and latencies with age and sex. Contact heat-evoked potentials latencies and amplitudes were similar on both sides of the body, hence were both reliable and sufficient for normative data with unilateral assessment. Prolonged latencies and reduced amplitudes were associated with aging and correlated with age-related changes in thermal pain perception. Females responded with higher amplitudes and shorter latencies compared with males, but both genders reported similar pain scores.

THE FACIAL NERVE

Blink Reflex

As blink reflex is helpful in the localization of focal demyelinating peripheral facial nerve palsies. For example, if on direct stimulation of the facial nerve, the latency of the response is normal, whereas with supraorbital nerve stimulation the latency is prolonged, this finding indicates that the lesion is proximally located somewhere between the facial nerve nucleus and the stylomastoid foramen, whereas if direct stimulation is abnormal, it would be more distal. An abnormality in the blink reflex response may therefore be seen in patients with Bell palsy, traumatic lesions of the facial nerve, and acoustic neuromas. Abnormality of the blink reflex in these scenarios can be useful in prognosis.[55,56] When the blink reflex is absent on the involved side, the prognosis is poor in a majority of the cases. When the reflex is normal or only R1 is delayed, the prognosis is excellent.[55] Delayed responses or the reappearance of the previously absent responses suggest a conduction defect without substantial axonal loss, from which the patient will likely recover completely or nearly completely.[1]

Lateral Spread and Facial Synkinesis

With simultaneous recordings from the OO (orbicularis oris) or mentalis muscles, facial synkinesis can be measured objectively (Fig. 4A). In normal individuals, after supraorbital nerve stimulation at the supraorbital notch, only the OO muscle contracts, and an abnormal synkinetic response is not obtained from other facial muscles. A manifestation of hemifacial spasm or of aberrant regeneration after a facial nerve lesion, synkinetic R1 and R2 responses may be obtained from other facial muscles (orbicularis oris, mentalis) (Fig. 4B). However, in hemifacial spasm, synkinesis (when present) may be related to ephaptic transmission at the site of injury because of focal demyelination and is believed to be a peripheral process, not occurring at the level of the nucleus.[57,58] Vascular compression of the nerve has been demonstrated in 65% of patients with hemifacial spasm.[34] The phenomenon has also been described in intraaxial brainstem lesions, tumors of the posterior fossa, basilar meningitis, and arteriovenous malformations. With hemifacial spasm, routine blink reflexes are usually normal, although there may be an increase in R1 amplitude and a late activity, suggesting hyperexcitability of the reflex. In addition, there may be lateral spread (due to ephaptic transmission) that can be demonstrated with stimulation of either mandibular or zygomatic branches of

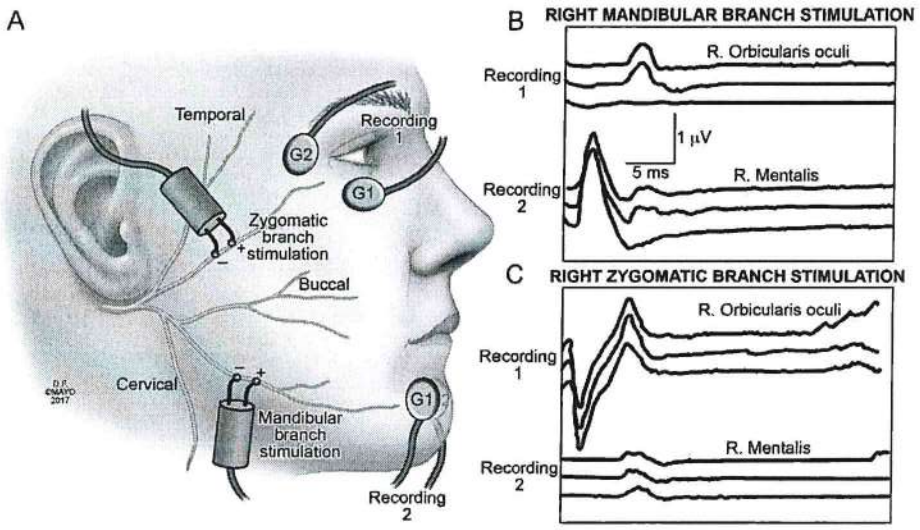

FIG. 4. **A**, G1, recording and G2, reference electrodes placement and stimulation sites to assess the lateral spread response in a right hemifacial spasm case. **B**, Stimulation of the right mandibular branch results in two ipsilateral responses: a normal immediate response at the mentalis and a delayed synkinetic response at the orbicularis oculi. **C**, Similar responses are obtained with right zygomatic branch stimulation.

the facial nerve while recording from the OOs or mentalis muscle, respectively. Microvascular decompression of the facial nerve generally results in loss lateral spread and relief of hemifacial spasm.[34,57,58]

However, synkinesis involving R1 and R2 blink reflex responses does not occur in other facial movement disorders such as essential blepharospasm, facial myokymia, habit spasm, orofacial dystonia, and focal cortical seizures. Therefore, in atypical facial movement disorders, the presence of facial synkinesis would substantiate the diagnosis of hemifacial spasm.

SUMMARY

The described electophysiological studies of the trigeminal and facial nerves and their application in the right clinical contexts, provide useful diagnostic tools to localize the lesion to the peripheral or central nervous systems and sometimes assist in prognostication. Moreover, the addition of these tests to the routine diagnostic armamentarium (nerve conduction studies, EMG, SEP, MRI, etc.) in combination with the neurological examination and disease phenotype, increases the yield of identifying and/or classifying the peripheral nerve process, and ultimately guiding further disease-targeted evaluation and therapy.

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PROVA NON ESTRATTA

RAMONA TOGNI

24/02/2021

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CONCORSO PUBBLICO, PER TITOLI ED ESAMI, PER N. 1 POSTO DI COLLABORATORE PROFESSIONALE SANITARIO – TECNICO DI NEUROFISIOPATOLOGIA - CAT. D DA ASSEGNARE ALLA UOC NEUROLOGIA 6 - NEUROFISIOPATOLOGIA

PROVA ORALE B

Valutazione pre-operatoria e monitoraggio intraoperatorio in corso di chirurgia per voluminosa lesione espansiva mesencefalica con coinvolgimento del chiasma ottico

a. Esami preoperatori indicati per la tipologia di intervento
b. Indicazioni al monitoraggio, tecniche di monitoraggio e mappaggio applicabili (pess, pem, ...)
c. Criteri di warning e considerazioni di base sul regime anestesiologico
d. Pitfalls relativi a posizionamento, eventuali manovre correttive in corso di IOM (ottimizzazione dipolo cefalico, ripresa baseline, build-up,..)

INFORMATICA:

Descrivi come creare un menù a tendina per inserimento dati da utilizzare in una determinata selezione su foglio di lavoro excel.

INGLESE:

Lettura e traduzione di uno stralcio di articolo allegato

ALLEGATO DOMANDA B

thebmj

STATE OF THE ART REVIEW

Diagnosis and management of sensory polyneuropathy

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Series explanation: State of the Art Reviews are commissioned on the basis of their relevance to academics and specialists in the US and internationally. For this reason they are written predominantly by US authors.

ABSTRACT

Sensory polyneuropathies, which are caused by dysfunction of peripheral sensory nerve fibers, are a heterogeneous group of disorders that range from the common diabetic neuropathy to the rare sensory neuronopathies. The presenting symptoms, acuity, time course, severity, and subsequent morbidity vary and depend on the type of fiber that is affected and the underlying cause. Damage to small thinly myelinated and unmyelinated nerve fibers results in neuropathic pain, whereas damage to large myelinated sensory afferents results in proprioceptive deficits and ataxia. The causes of these disorders are diverse and include metabolic, toxic, infectious, inflammatory, autoimmune, and genetic conditions. Idiopathic sensory polyneuropathies are common although they should be considered a diagnosis of exclusion. The diagnostic evaluation involves electrophysiologic testing including nerve conduction studies, histopathologic analysis of nerve tissue, serum studies, and sometimes autonomic testing and cerebrospinal fluid analysis. The treatment of these diseases depends on the underlying cause and may include immunotherapy, mitigation of risk factors, symptomatic treatment, and gene therapy, such as the recently developed RNA interference and antisense oligonucleotide therapies for transthyretin familial amyloid polyneuropathy. Many of these disorders have no directed treatment, in which case management remains symptomatic and supportive. More research is needed into the underlying pathophysiology of nerve damage in these polyneuropathies to guide advances in treatment.

Introduction

Peripheral sensory nerves vary in size and function, ranging from the smallest unmyelinated C fibers and thinly myelinated Aδ fibers that conduct noxious and thermal information[1 2] to the larger Aβ fibers that transmit proprioceptive and vibratory information.[3] As a result, disorders of sensory nerve function are diverse and depend on the type of nerve fiber that is affected; patients present with a wide range of symptoms, from pain predominant (small fiber) to ataxia predominant (large fiber) problems. This article will not attempt to review all peripheral sensory neuropathies that manifest the classic length dependent or "stocking glove" pattern, but will focus on those that have a clearly pain predominant or ataxia predominant presentation. It will also include other disorders that present with sensory ataxia but affect the dorsal root ganglia (DRG), sensory fibers of the nerve roots, and dorsal columns. We will also cover the differential diagnosis of sensory polyneuropathies, the diagnostic approach to patients with sensory problems, and disease specific and symptomatic treatments.

Sources and selection criteria

We searched PubMed for English language articles published from 1 January 2000 to 1 October 2018 using the terms "small fiber neuropathy", "sensory ataxia", "sensory neuronopathy", "dorsal root ganglionopathy", "dorsal root ganglion", "skin biopsy", "quantitative sensory testing", "corneal confocal microscopy", "quantitative sudomotor axon reflex testing", "thermoregulatory sweat testing", "electrochemical skin conductance", "sarcoidosis", "Sjögren's syndrome", "fibromyalgia", "sodium channelopathies", "transthyretin", "sensory Guillain-Barré syndrome", "ataxic Guillain-Barré syndrome", "acute sensory ataxic neuropathy", "Miller Fisher syndrome", "disialosyl antibodies", "ganglioside antibodies", "CANOMAD", "CANDA", "sensory chronic inflammatory demyelinating polyneuropathy", "distal acquired demyelinating symmetric neuropathy", "anti-MAG", "anti-Hu", and "tabes dorsalis". We included a few articles of historical importance that were published in the 1980s and 1990s. These sentinel articles set the conceptual framework for these disorders and their inclusion was necessary. We searched reference lists of articles selected through title, abstract, and full text review. We selected randomized controlled trials, observational, and basic science studies, systematic reviews, and meta-analyses from these sources. Articles were prioritized by study quality and topic. Given that many of the sensory neuropathies discussed are extremely rare, case studies and case series were also reviewed and included if deemed important.

LIST OF ACRONYMS

AAN: American Academy of Neurology
ANA: Antinuclear antibodies
ASAN: Acute sensory ataxic neuropathy
BPI-MSF: Brief Pain Inventory Modified Short Form
CANDA: Chronic ataxic neuropathy with disialosyl antibodies
CANOMAD: Chronic ataxic neuropathy, ophthalmoplegia, IgM paraprotein, cold agglutinins, and disialosyl antibodies
CIDP: Chronic inflammatory demyelinating polyneuropathy
CISP: Chronic immune sensory polyradiculopathy
DADS: Distal acquired demyelinating symmetric neuropathy
DRG: Dorsal root ganglia
EFNS: European Federation of Neurological Societies
EMLA: Eutectic mixture of local anesthetic
ESR: Erythrocyte sedimentation rate
GBS: Guillain-Barré syndrome
IENFD: Intraepidermal nerve fiber density
IFG: Impaired fasting glucose
IGT: Impaired glucose tolerance
LEP: Laser evoked potential
MAG: Myelin associated glycoprotein
MFS: Miller-Fisher syndrome
MRI: Magnetic resonance imaging
mNIS+7: Modified Neuropathy Impairment Score +7
Norfolk QOL-DN: Norfolk Quality of Life-Diabetic Neuropathy
NPS: Neuropathic Pain Scale
QSART: Quantitative sudomotor axon reflex test
SFN: Small fiber neuropathy
SGPG: Sulphated glucuronyl paragloboside
SNAP: Sensory nerve action potential
SNRI: Serotonin-norepinephrine reuptake inhibitor
SSEP: Somatosensory evoked potential
TCA: Tricyclic antidepressant
TTR-FAP: Transthyretin familial amyloidosis with polyneuropathy

Incidence and prevalence

The sensory polyneuropathy category includes extremely common conditions such as diabetic neuropathies (the most common cause of neuropathy worldwide) and very rare conditions, such as specific acute ataxic neuropathies (described only in case series). Table 1 lists the incidence and prevalence of these specific polyneuropathies and their underlying causes, if known.

Clinical presentation

The clinical presentation and findings on physical examination depend on the type of affected nerve fiber and the distribution of nerve damage. Patients may report a combination of positive (paresthesia, burning pain) and negative (loss of sensation) sensory disturbances, as well as gait imbalance. Important considerations regarding the clinical presentation include acuity of onset, time course of progression, and the distribution and quality of sensory symptoms.

Small fiber neuropathies

In small fiber neuropathies (SFNs) the thinly myelinated (Aδ) and unmyelinated (C) fibers responsible for the transmission of thermal and noxious sensory input are affected.[1 2] Clinically, this nerve damage translates to symptoms of sharp, painful, or burning paresthesia; sensory loss or numbness; and the inability to discriminate between hot and cold sensations. Symptoms may be vague, described as a tight feeling or abnormal sensation in the soles of the feet, intolerance of tactile stimuli (inability to wear socks or touch bedsheets), or a sensation of restless legs. The distribution of symptoms may have a length dependent or non-length dependent pattern that affects the limbs, trunk, face, or it may have a combination of patterns.[1 2 40-42] Depending on the underlying cause, the onset of symptoms may be gradual, with slowly progressive worsening, or subacute with more rapid progression. Pain may be prominent and disabling, and a recent large Italian cohort study of patients with painful diabetic neuropathy suggests that pain may be more common in women.[43]

Dysautonomia is often a feature of SFN owing to impairment of the sympathetic and parasympathetic function of Aδ fibers and the postganglionic autonomic function of C fibers. It is essential to ask patients about potential autonomic involvement including orthostasis; palpitations; abnormal sweating; dry mouth, eyes, or skin; gastrointestinal symptoms including cramping, diarrhea, or constipation; flushing or other changes of skin color; and erectile dysfunction.[2]

A patient with SFN may have decreased temperature and pinprick sensation on examination, and potentially allodynia, dysesthesia, or hyperesthesia on sensory testing. Motor strength, proprioception, and muscle stretch reflexes should be preserved in patients with pure SFN. Skin may have a dry, atrophic, or discolored appearance.[1 2 40]

Sensory ataxia

Disorders affecting the large myelinated Aβ fibers, 1a fibers, sensory nerve roots, or DRG will result in impaired vibratory sensation and proprioception. Clinically this results in a combination of symptoms of sensory loss, paresthesia, and gait imbalance. The ataxic sensory polyneuropathies will present acutely or have an insidious onset and gradually progressive course as a result of dysfunction of the peripheral sensory nerves. Physical examination may show absent or reduced vibratory sensations, abnormal proprioception, depressed or absent reflexes, and sensory ataxia.

In sensory neuronopathies (dorsal root ganglionopathies), sensory neurons of the dorsal root and trigeminal ganglia are affected. The clinical presentation is characterized by pronounced ataxia and sensory loss, which may have a non-length dependent or multifocal pattern. In addition, pain and positive sensory symptoms often occur because of the involvement of small and medium sized nerve fibers.[44] The face and trunk may also be affected.[44-46] The results of a physical examination will resemble that seen in patients with ataxic sensory polyneuropathies, although the sensory deficits are more often patchy, non-length dependent, or generalized. The

Table 1 | Incidence and prevalence of sensory neuropathies highlighted in this review*

Diagnosis	Incidence of underlying cause	Prevalence of underlying cause	Incidence and prevalence of the neuropathy (if known)
Small fiber neuropathies			
Diabetic neuropathy (including small and large fiber neuropathy)	In the US 1.5 million people are diagnosed as having diabetes every year (6.7/1000)[4]	In 2015, 9.4% of the US population were estimated to have diabetes[4]	Lifetime incidence of neuropathy is 37-45% in type 2 diabetes and 54-59% in type 1 diabetes[5] Prevalence of diabetic neuropathy is 5-54% depending on the criteria and methods used to define neuropathy and age of included patients[6-9]
Prediabetic small fiber neuropathy		In 2015, 33.9% of the US population over the age of 18 years had prediabetes[4]	Prevalence IGT and neuropathic pain: 8.7-14.8% IFG and neuropathic pain: 4.2-5.7%[9 10 11]
Metabolic syndrome		In 2007-2012, 34.2% of the US population had metabolic syndrome[12]	
Sarcoidosis	Globally, 1.0-35.5/100 000[13] This figure is probably higher in black people (40-70/100 000; US data)[14 15]	Globally, 4.7-64/100 000[13]	Pain and signs of SFN present in up to 28-60% of patients depending on the criteria and methods used to define neuropathy[16-20]
Sjogren's syndrome associated sensory neuropathies	Globally, 6.92/100 000[21]	Globally, 60.82/100 000[21]	Prevalence of "pure sensory neuropathy": 9.2% Prevalence of neuronopathy 0.6% (in a French population)[22]
Fibromyalgia	Annual incidence in UK: 33.3/100 000[23]	Globally, 1.78%[24]	Small fiber pathology is seen in about half of patients with fibromyalgia[25 26]
Transthyretin familial amyloidosis with polyneuropathy	In Portugal: 0.87/100 000[27]	In Portugal: 22.93/100 000[27] Worldwide: 50 000 cases[28]	
Sodium channelopathies (SCN9A, SCN10A, SCN11A)			In a large series of patients with SFN, 9.6% had genetic variants in SCN9A, 4.5% in SCN10A, and 3.4% in SCN11A[29] In a smaller series, 28.6% of patients with idiopathic SFN had the Nav1.7 mutation[30]
Sensory ataxic neuropathies			
Sensory GBS	Overall incidence (included studies from North America and Europe) of GBS: 0.8-1.9/100 000[31] Sensory GBS unknown	Lifetime risk of developing GBS is less than 1/1000[32]	
Miller Fisher syndrome	0.1/100 000 in UK; 15-20% of all GBS in Asia and 1-7% in the West[33]		
Acute sensory ataxic neuropathy	Unknown (case reports/case series)	Unknown (case reports/case series)	
Ataxic GBS	Unknown (case reports/case series)	Unknown (case reports/case series)	
Chronic ataxic neuropathies associated with anti-disialosyl antibodies	Unknown (case reports/case series)	Unknown (case reports/case series)	
Sensory CIDP	Overall incidence of 0.7-1.6/100 000[34 35] Sensory CIDP unknown	Overall prevalence of CIDP: 4.8-8.9/100 000[34 35] Prevalence of sensory CIDP: 24-35% of all patients with CIDP[34 36 37]	
DADS	Unknown; IgM MGUS is associated with a polyneuropathy in 50% of patients[38]		
Paraneoplastic sensory neuronopathy	>500 cases reported[39]		

*CIDP=chronic inflammatory demyelinating polyradiculoneuropathy; DADS=distal acquired demyelinating symmetric neuropathy; GBS=Guillain-Barré syndrome; IFG=impaired fasting glucose; IGT=impaired glucose tolerance; MGUS=monoclonal gammopathy of undetermined significance; SFN=small fiber neuropathy; US=United States.

finding of pseudoathetosis, as a result of impaired afferent proprioceptive input, is a hallmark of DRG dysfunction.[44 46 47] Although motor strength is preserved in pure sensory neuronopathies, it may seem to be impaired on examination owing to the lack of proprioceptive input during confrontational strength testing. The clinical course may be gradual and insidious in idiopathic forms of the disease, but it will typically have a subacute course in patients with paraneoplastic, immune mediated, and toxic causes.[44]

Patients with dorsal column dysfunction may also present with sensory ataxia. Often these patients also have evidence of upper motor neuron signs on examination, which suggests corticospinal tract involvement and will guide the examiner away from localization in the peripheral nervous system. When the dorsal columns and corticospinal tracts are affected, patients will have spasticity, weakness, and reduced vibratory and proprioceptive sensations: the so called posterolateral column syndrome.[48]

Differential diagnosis of small fiber neuropathies

The causes of SFN fall into six broad categories: metabolic, inflammatory, genetic, toxic, infectious, and idiopathic (cryptogenic) (table 2). Many of the known common causes will not be discussed in detail but are included in table 2. Fibromyalgia, which has been associated with pathologic evidence of SFN, does not easily fall into one of the six categories. Alternatively, classification based on clinical phenotype has also been proposed.[49] Despite extensive evaluation, 20-50% of cases of SFN are ultimately classified as idiopathic.[50-53] The most common causes include diabetes, immunologic conditions, sodium channel mutations, and vitamin B12 deficiency.[29] Although immunologic conditions were found in 19% of a cohort of 921 patients with SFN, which exceeds the prevalence in the general population, the exact pathogenic role of isolated autoantibodies remains unclear.[29 54] In one series, the highest yield blood tests in SFN that appeared to be "initially idiopathic" were erythrocyte sedimentation rate (ESR), antinuclear antibodies (ANA), C3 complement values, and autoantibodies that are associated with Sjögren's syndrome and celiac disease.[55] It has been recommended that patients are screened for glucose intolerance, vitamin B12 deficiency, and sodium channel mutations even if there is a known underlying cause.[29 54]

Table 2 | Causes of small fiber neuropathy and ancillary investigations*

Causes	Ancillary investigations
Immune mediated	
Sarcoidosis	ACE, chest radiography, histopathology
Sjögren's syndrome	Anti-SSA/anti-SSB antibodies, Schirmer test, Rose Bengal test, lip and salivary gland biopsy
Systemic lupus erythematosus	ANA, antiphospholipid antibodies, complement levels, ESR, CRP, anti-dsDNA and anti-Smith antibodies
Celiac disease	Antigliadin antibodies (serum IgA endomysial and tissue transglutaminase antibody), IgG deamidated gliadin peptide, small bowel biopsy
Inflammatory bowel disease (Crohn's disease and ulcerative colitis)	Inflammatory markers, endoscopy, barium studies
Paraneoplastic (ganglionic acetylcholine receptor antibody mediated)	Voltage gated potassium channel antibodies, CASPR-2, and anti-Hu antibodies, ganglionic acetylcholine receptor antibodies
"Apparently autoimmune" small fiber neuropathy†	Presence of systemic autoimmune disease, abnormal blood markers of autoimmunity (ANA, ESR, SSA/SSB antibodies, or low complement levels)
Metabolic	
Impaired glucose tolerance and impaired fasting glucose	Two hour glucose tolerance test, fasting blood sugar, glycosylated hemoglobin
Diabetes	Glycosylated hemoglobin, two hour glucose tolerance test, fasting blood sugar
Treatment induced neuropathy in diabetes (insulin neuritis)	Clinical diagnosis in the setting of rapid correction of hyperglycemia
Hyperlipidemia (mostly hypertriglyceridemia)	Lipid profile including fasting triglyceride level
Hypothyroidism	TSH, free T4 and T3
Infectious	
HIV	HIV viral load, and CD4 cell count
Hepatitis C virus	Hepatitis C virus antibody, hepatitis C PCR
Cryoglobulinemia (often associated with hepatitis C)	Cryoglobulins
Leprosy	Serum antibodies to phenolic glycolipid-I, skin or nerve biopsy for acid fast bacilli
Toxic	
Numerous implicated drugs (anti-retrovirals, metronidazole, nitrofurantoin, linezolid, flecainide, statins)	History of drug exposure
Alcohol	History of excessive alcohol use for a long duration
Hereditary	
Sodium channel mutations	SCN9A, SCN10A, and SCN11A mutations
Fabry disease	Alpha-galactosidase enzyme assay, GAL DNA sequencing (especially in women, in whom the enzyme assay may be normal)
Familial amyloidosis	Genetic testing for transthyretin (TTR), apolipoprotein A1 (APOA1), and gelsolin (GSN) mutations
Hemochromatosis	High serum ferritin
Ehlers-Danlos syndrome	Clinical diagnosis
Other	
Sporadic amyloidosis	Serum protein electrophoresis, immunofixation, serum free light chains, abdominal fat pad biopsy, rectal mucosa biopsy
Fibromyalgia	American College of Rheumatology diagnostic criteria (2010)
Idiopathic (cryptogenic)	Diagnosis of exclusion

*Abbreviations: ACE=angiotensin converting enzyme; ANA= antinuclear antibodie ;CRP=C reactive protein; dsDNA=double stranded DNA; ESR=erythrocyte sedimentation rate; HIV, human immunodeficiency virus; PCR=polymerase chain reaction; SSA=Sjogren's syndrome A; SSB=Sjogren's syndrome B; T3=triiodothyronine; T4=thyroxine; TSH=thyroid stimulating hormone.
†This category of small fiber neuropathies has been recently described and its classification is evolving and not widely accepted at present.

Metabolic causes: diabetes and prediabetes

Diabetes is the most common cause of polyneuropathy worldwide and the most common cause of SFN specifically.[56] The association between prediabetes (impaired glucose tolerance (IGT) and impaired fasting glucose (IFG)) and polyneuropathy is still being delineated. IGT is defined by a raised two hour glucose level on an oral glucose tolerance test of 7.8-11.1 mmol/L (140-199 mg/dL). IFG is defined by a fasting glucose of 5.6-6.9 mmol/L (100-125 mg/dL). It is likely that the risk of neuropathy is higher for IGT than for IFG.[57] When considering the diagnostic investigations in these patients, it is important to note that glycosylated hemoglobin may be normal in patients with IGT.[58]

Some studies support an association between IGT and polyneuropathies,[10 59-62] whereas others have failed to show such a correlation.[63-65] It is thought that IGT associated neuropathy mainly affects the small nerve fibers, perhaps explaining why some researchers have found no correlation between IGT and large fiber polyneuropathy[60 66 68] and others have questioned the association between IGT and SFN.[64 69] Such incongruent findings across studies are probably the result of differences in definitions of polyneuropathy (including the use of symptoms or intraepidermal nerve fiber density (IENFD)), degrees of surveillance, and polyneuropathy endpoints.[69] Nonetheless, the identification of prediabetes is of utmost importance because 50% of patients with prediabetes ultimately develop type 2 diabetes,[70] and reducing the risk of conversion to diabetes decreases the risk of developing polyneuropathy.

The Impaired Glucose Tolerance Neuropathy study investigated 32 patients with IGT and neuropathy. It found that 65% of patients had low amplitude or absent sural responses, 83% had decreased IENFD, and 61% had abnormal quantitative sudomotor autonomic reflex test results.[71] Skin biopsy was found to be the most sen-

sitive measure of the severity of IGT related neuropathy, and partial cutaneous reinnervation was seen after the introduction of a suitable diet and exercise. Other features of the metabolic syndrome, including hypertriglyceridemia and central obesity, are also independent risk factors for SFN.[72]

Autoimmune causes

The known autoimmune causes of SFN are diverse and include sarcoidosis and Sjögren's syndrome in addition to systemic lupus erythematosus, celiac disease, and others.

Sarcoidosis

SFN is the most common peripheral nervous system manifestation in sarcoidosis, and its pathophysiology is probably related to a systemic release of inflammatory mediators rather than granulomatous involvement of the small nerve fibers.[16 17 73 74] Unlike pulmonary sarcoidosis, which preferentially affects African-Americans, SFN seems to affects mainly white people.[75] Most patients will have a non-length dependent pattern of numbness, pain, and paresthesia. Half will develop dysautonomia, with orthostasis being the most common manifestation.[75]

Sjögren's syndrome

SFN is probably the most common neuropathic manifestation of Sjögren's syndrome.[76 77] The onset of symptoms is subacute to chronic (weeks to months) although hyperacute presentations have been reported.[77 78] Serologic testing is often unhelpful—the estimated sensitivities of anti-SSA (anti-Ro) and anti-SSB (anti-La) antibodies are 39% of 17%, respectively.[79]

Other autoimmune small fiber neuropathies

Some experts have proposed an additional category of "apparently autoimmune" SFN that could account for some forms of otherwise idiopathic SFN.[80] Patients in this category, who have evidence of systemic autoimmune disorders and blood markers of autoimmunity, have been described as having an atypical, painful SFN that responds to corticosteroids and intravenous immunoglobulins.[55 81-83] This classification is not universally accepted and these findings need to be reproduced in large prospective clinical trials. Acute onset of painful SFN, which might fall into the Guillain-Barré syndrome (GBS) spectrum, has also recently been described.[84]

Genetic causes

Two familial causes of SFN—sodium channel mutations and transthyretin familial amyloidosis with polyneuropathy (TTR-FAP)—stand out given recent developments in the understanding of their underlying pathophysiology and the emergence of new treatment modalities.

Sodium channelopathies

The SCN9A, SCN10A, and SCN11A genes encode the Nav1.7, Nav1.8, and Nav1.9 sodium channels, respectively. Mutations in these genes have been described in painful, predominantly SFNs.[85-87] These mutations produce a gain of function change that results in hyperactive pain signaling in the DRG neurons.[88]

Transthyretin familial amyloidosis polyneuropathy (TTR-FAP)

TTR-FAP is endemic in Japan, Sweden, Portugal, and Brazil. In Europe and Latin America, the ATTR-Val30Met mutation predominates, whereas the ATTR-Val122Ile mutation is most common in the United States.[89] More than 120 TTR gene mutations have been reported to cause amyloidosis.[90] These mutations induce transthyretin misfolding and systemic deposition of amyloid, resulting in autosomal dominantly inherited transthyretin amyloidosis. As amyloid progressively accumulates, it leads to multiorgan dysfunction and ultimately death. The first stage of TTR-FAP is a length dependent, small fiber predominant sensory polyneuropathy with autonomic dysfunction. Patients develop progressive difficulty with walking and ultimately cardiomyopathy. The diagnosis is confirmed by DNA testing and the demonstration of amyloid deposits on biopsy.[91] In addition, diagnostic tools such as magnetic resonance neurography and radionucleotide cardiac scintigraphy are emerging.[89]

Other small fiber neuropathies

Fibromyalgia

The association between fibromyalgia syndrome—characterized by chronic widespread pain, fatigue, exercise intolerance, and cognitive problems—and small fiber pathology was first described in 2013.[25 26 92] Nearly half of patients with fibromyalgia have evidence of reduced IENFD on skin biopsy, and emerging evidence indicates that nearly a third of patients have a distal large fiber neuropathy as indicated by low medial plantar responses.[93] It is unclear whether patients who have fibromyalgia with and without small fiber pathology are clinically distinguishable,[94] although some researchers report that paresthesia and autonomic involvement may predict the presence of small fiber dysfunction.[95] One prospective study compared 30 patients with fibromyalgia with 34 age and sex matched healthy controls in terms of clinical examination, quantitative sensory testing, skin biopsy, blood and cutaneous miRNA isolation. It found that 51 miRNAs were aberrantly expressed in the white blood cells and miR-let-7d correlated with reduced IEFND in the patients with fibromyalgia. In addition, in one group of patients with fibromyalgia, aberrantly expressed miR-let-7d microRNA in white blood cells correlated with reduced IENFD. In the skin of these patients, miR-let-7d and the downstream target of the insulin-like growth factor-1 receptor were also aberrantly expressed in those with small fiber dysfunction.[96]

Although the association between small fiber disease and fibromyalgia sheds light on the underlying pathomechanisms of fibromyalgia, most patients with fibromyalgia do not have the typical symptoms of SFN.[25] That said, the identification of the presence of small fiber dysfunction in fibromyalgia enables screening for other causes of SFN, such as diabetes.[21 95 97]

Differential diagnosis of sensory ataxia

The ataxic sensory disorders can be classified on the basis of localization (nerve, nerve root, DRG, dorsal column) and further differentiated by time course (acute, subacute, chronic) (table 3). Although dorsal column disorders are not a peripheral nervous system process, they can mimic ataxic neuropathies and will be briefly discussed. The sensory

Table 3 | Causes of sensory ataxia and ancillary investigations*

Cause	Onset	Cause	Ancillary investigations
Peripheral nerve			
Immune mediated	Acute	Sensory Guillain-Barré syndrome	CSF, NCS (demyelinating neuropathy)
		Ataxic Guillain-Barré syndrome	Ganglioside antibodies (often anti-GQ1b), CSF, NCS (axonal neuropathy)
		Acute sensory ataxic neuropathy	Ganglioside antibodies (often GD1b), CSF, NCS (axonal neuropathy)
		Miller-Fisher syndrome	Anti-GQ1b antibodies, CSF, NCS (axonal neuropathy)
	Chronic	Sensory CIDP	CSF, NCS (demyelinating neuropathy)
		Chronic ataxic neuropathy with ophthalmoplegia, M protein, agglutination with disialosyl antibodies (CANOMAD) and CANDA	Serum protein electrophoresis, anti-disialosyl antibodies (often GD1b and GQ1b), ESR, CSF, NCS (may be axonal or demyelinating)
		DADS or anti-MAG neuropathy	Serum protein electrophoresis (IgM monoclonal gammopathy), anti-MAG antibodies, NCS (prolonged distal motor latencies, no conduction block)
		Gait ataxia, late onset polyneuropathy	Serum protein electrophoresis (IgM monoclonal gammopathy), anti-CMA antibodies
		Sarcoid	ACE, chest radiography, histopathology, CSF, NCS
Infectious	Chronic	Lyme	Lyme serology
Dorsal root ganglion			
Immune mediated	Subacute/chronic	Systemic lupus erythematosus‡	ANA, antiphospholipid antibodies, complement levels, ESR, CRP, anti-dsDNA and anti-smith antibodies
		Sjögren's syndrome‡	Anti-SSA/anti-SSB antibodies, Schirmer test, Rose Bengal test, lip/salivary gland biopsy
		Celiac disease‡	Antigliadin antibodies (serum IgA endomysial and tissue transglutaminase antibody), IgG deamidated gliadin peptide, small bowel biopsy
		Autoimmune hepatitis	ANA, anti-smooth muscle antibodies, ALKM-1 and ALC-1 antibodies
		FGFR3 antibody associated	FGFR3 antibodies
		Paraneoplastic	Anti-Hu and anti-CV2/CRMP-5 antibodies, malignancy evaluation
Toxic	Subacute/chronic	B6 (pyridoxine)	Vitamin B6 levels
		Chemotherapy: platinum based‡ or taxol‡	Use of platinum based or taxol drugs
Hereditary	Chronic	Friedreich ataxia	Frataxin mutation and expansion of GAA repeats
		Sensory ataxic neuropathy, dysarthria, and ophthalmoparesis	POLG mutations
		Abetalipoproteinemia, vitamin E transporter deficiency	Vitamin E, low circulating β-lipoproteins, VLDL, LDL, chylomicrons, microsomal triglyceride transfer protein mutations
		Neuropathy, ataxia, retinitis pigmentosa	MT-ATP6 mutation
Infectious	Chronic	Leprosy	Serum antibodies to phenolic glycolipid-I, skin or nerve biopsy for acid fast bacilli
		Viruses including HIV, HTLV-1, EBV, and VZV	HIV viral load and CD4 cell count; HTLV-I, EBV, and VZV antibodies
Other	Chronic	Cerebellar ataxia, neuropathy, vestibular areflexia syndrome	Brain MRI (cerebellar atrophy), abnormal vestibulo-ocular reflex, abnormal autonomic testing
		Idiopathic	Diagnosis of exclusion
Nerve root			
Immune mediated	Chronic	Chronic inflammatory sensory polyradiculopathy	CSF, NCS (normal), SSEPs (abnormal), MRI with enlarged nerve roots
Dorsal column			
Nutritional deficiency	Chronic	Vitamin B12‡	Vitamin B12, MMA, homocysteine
		Copper‡	Copper, CBC with differential
		Folic acid‡	Red blood cell folate, homocysteine
		Thiamine (B1)‡†	Thiamine
		Vitamin E†‡	Vitamin E
Infectious	Chronic	Syphilis (tabes dorsalis)	MHA-TP or FTA-ABS
		HTLV-I/HTLV-II	HTLV-I/II, MRI of the spinal cord
Toxic	Chronic	Nitrous oxide‡	Clinical history of nitrous oxide misuse, NCS (axonal neuropathy), MRI spinal cord, CBC (megaloblastic anemia)

*Abbreviations: ACE=angiotensin converting enzyme; ALC-1=anti-liver cytosol antigen; ALKM-1=anti-liver/kidney microsome antibody; ANA=antinuclear antibody; CANOMAD=chronic ataxic neuropathy, ophthalmoplegia, IgM paraprotein, cold agglutinins, and disialosyl antibodies; CANDA=chronic ataxic neuropathy with disialosyl antibodies; CBC=complete blood count; CIDP=chronic inflammatory demyelinating neuropathy; CMA=central myelin antigen; CRMP-5=collapsing response mediator protein-5; CRP=C reactive protein; CSF=cerebrospinal fluid; CV2/CRMP-5=collapsin response mediator protein-5; DADS=distal acquired demyelinating symmetric neuropathy; dsDNA=double stranded DNA; EBV=Epstein-Barr virus; ESR=erythrocyte sedimentation rate; FTA-ABS=fluorescent treponemal antibody absorption; FGFR3=fibroblast growth factor receptor 3; HTLV=human T lymphotropic virus; LDL=low density lipoprotein; MAG=myelin associated glycoprotein; MHA-TP=microhemagglutination assay for *Treponema pallidum* antibodies; MMA=methylmalonic acid; MRI=magnetic resonance imaging; NCS=nerve conduction studies; POLG=polymerase DNA gamma; SSA=Sjögren's syndrome A; SSB=Sjögren's syndrome B; SSEP=somatosensory evoked potential; VLDL=very low density lipoprotein; VZV=varicella zoster virus.
†Will also affect the cerebellar pathways.
‡Will also affect the peripheral sensory nerves.

ataxic disorders will be organized on the basis of localization, cause, and time course.

Acute inflammatory sensory neuropathies

Sensory Guillain-Barré syndrome

The acute sensory polyneuropathies consist of overlapping clinical phenotypes, and the lines are often blurred between sensory GBS, ataxic GBS, acute sensory ataxic neuropathy (ASAN), and Miller-Fisher syndrome (MFS). In 1981, Asbury proposed diagnostic criteria for sensory GBS that included a monophasic episode of acute onset, diffuse, symmetric sensory symptoms; demyelinating electrodiagnostic features (often apparent on motor studies); and albuminocytologic dissociation.[98] Given the scarcity of such reports in the literature, the existence of sensory GBS has been called into question.[99]

A case series in 2001 reported eight additional patients who met the clinical criteria for sensory GBS.[100] Serum autoantibodies (MAG (myelin associated glycoprotein)), GM1, GQ1b, GD1b, anti-Hu, and sulphated glucuronyl paragloboside (SGPG) were normal in the four patients tested. Sensory GBS, owing to its demyelinating features and the absence of ganglioside antibodies, remains separate from the following disorders which share many clinical, electrophysiologic, and laboratory features. These diseases, also classified as GBS variants, are best subdivided into complete MFS and incomplete MFS, which includes the acute ataxic neuropathies (ASAN and ataxic GBS).

Miller-Fisher syndrome

MFS is characterized by a classic clinical triad of ophthalmoplegia, ataxia, and areflexia.[101 102] Less common clinical features include other cranial neuropathies, blepharoptosis, limb dysesthesia, and micturition problems. The ataxia of MFS is thought to be caused by both impaired proprioception (reversible conduction failure in 1a afferents) and cerebellar dysfunction.[103 104] As in other forms of GBS, neurologic symptoms often follow an antecedent illness such as infection with *Campylobacter jejuni* or *Haemophilus influenzae*.[105] The distinctive anti-GQ1b ganglioside antibodies crossreact with surface epitopes of *C jejuni*, supporting the theory of molecular mimicry between nerve and bacteria.[106 107] These antibodies also crossreact heavily with ganglioside GT1a.[108] Electrodiagnostic studies, in contrast to sensory GBS, show a sensory predominant axonopathy.[109] Recovery is gradual but often complete.

Acute ataxic neuropathies

The remaining acute ataxic neuropathies, including both ASAN and ataxic GBS, have recently been classified as incomplete forms of MFS by some experts.[110 111] In the past, ASAN was not considered to be a GBS variant because affected patients do not meet the diagnostic criteria for sensory GBS and lack demyelinating features on electrodiagnostic studies. Both ASAN and ataxic GBS, however, share many features with MFS including acute ataxia, areflexia, antecedent infection, and antiganglioside antibodies but lack the typical ophthalmoplegia.[110 112] The presence of a Romberg sign helps differentiate ASAN from ataxic GBS. Patients with ASAN may harbor anti-disialosyl antibodies to GD1b alone or in combination with antibodies to CD3, GQ1b, or GT1a. Autoantibodies against gangliosides without disialosyl epitopes (GD1a and GM3) may also be present.[112] Given that patients with ASAN typically have an antecedent infection, monophasic course, and excellent recovery, they should be considered under the rubric of GBS, in the subcategory of acute ataxic neuropathy.[112] Ataxic GBS is distinguished by cerebellar-like ataxia and absence of a Romberg sign.[113] Similar to MFS, these patients also harbor anti-GQ1b IgG antibodies.[114] A retrospective chart review identified 54 patients with acute ataxic neuropathy without ophthalmoplegia. The Romberg sign was absent in 37 patients, who were considered to have ataxic GBS. In the other 17 patients, the Romberg sign was present, consistent with a diagnosis of ASAN. In the 37 patients with ataxic GBS, 24 were GQ1b positive compared with three of the 17 patients with ASAN (P=0.0034). IgG antibodies against GD1b but not GQ1b were more common in patients with ASAN (6/17) than in those with ataxic GBS (5/37), but this did not meet statistical significance (P=0.72).[115] However, the opposite was true a minority of the time, suggesting that these diseases lie on a spectrum.

Chronic inflammatory sensory neuropathies

Chronic ataxic neuropathy with disialosyl antibodies (CANDA)

These very rare, acute, and chronic ataxic neuropathies with anti-disialosyl antibodies probably share a common pathogenic mechanism, which is disruption at the node of Ranvier on sensory fibers. Like the acute ataxic neuropathies and MFS, the chronic ataxic neuropathies are also associated with anti-disialosyl antibodies (such as GD1b and GQ1b.) These disialosyl antibody mediated neuropathies can be separately categorized as nodoparanodopathies.[107 111 116] When the full spectrum of clinical features is present in these disialosyl antibody mediated chronic ataxic neuropathies, the disorder goes by the acronym CANOMAD (chronic ataxic neuropathy, ophthalmoplegia, IgM paraprotein, cold agglutinins, and disialosyl antibodies). CANDA (chronic ataxic neuropathy with disialosyl antibodies) is a more general term and allows for the inclusion of patients without ophthalmoplegia and those in whom the cold agglutinins are IgM antibodies.[111] CANDA can relapse, remit, and have cranial neuropathies that result in bulbar dysfunction.[117] The disease process in CANDA may be the result of antibody mediated attack of the nerve root, DRG, and nerves.[111] In electrophysiologic studies, patients with CANDA have absent or reduced sensory responses and diminished motor responses, including demyelinating features.[118 119]

Sensory chronic inflammatory demyelinating polyneuropathy (CIDP)

Patients with sensory CIDP present with a pure sensory neuropathy with intact strength despite often having evidence of acquired demyelination on motor nerve conduction studies.[120-123] A minority of patients with sensory CIDP probably have electrophysiologic abnormalities in the sensory nerves only.[124] Features that differentiate patients with sensory CIDP from those with chronic idiopathic axonal polyneuropathies include early gait ataxia, cranial neuropathy, diffuse hyporeflexia, onset before 55 years of age, and early involvement of the upper extremities.[121]

A small subset of patients with sensory CIDP have chronic immune sensory polyradiculopathy (CISP) in which the disease is localized to the nerve roots. These patients will have normal routine nerve conduction studies, abnormal somatosensory evoked potentials, raised concentrations of cerebral spinal fluid protein, and enlarged nerve roots on magnetic resonance imaging (MRI), which demonstrate inflammation on biopsy.[125]

Distal acquired demyelinating symmetric neuropathy (DADS)

Distal acquired demyelinating symmetric neuropathy (DADS), a variant of CIDP, is characterized by distal,

Table 4 | Myelopathies that present with sensory ataxia*

Etiology	Causes	Associated features	Useful tests	Treatment
Folic acid deficiency	GI disease, folate antagonists, alcoholism	Peripheral neuropathy, optic atrophy, cognitive problems	Serum folate, red blood cell folate, plasma total homocysteine	Folate 1 mg orally twice a day for several days then 1 mg/day
Vitamin E deficiency	Cholestasis, pancreatic insufficiency, hypobetalipoproteinemia, abetalipoproteinemia, chylomicron retention disease	Spinocerebellar syndrome, peripheral neuropathy, pigmented retinopathy, myopathy, movement disorders, gaze palsies	Serum vitamin E	Vitamin E 200-1000 IU/day
Copper deficiency	Gastric surgery, malabsorption, zinc toxicity	Peripheral neuropathy, megaloblastic anemia, pancytopenia	Serum and urinary copper, serum ceruloplasmin, zinc levels	Copper 8 mg/day orally for 1 week, then 6 mg/day orally for 1 week, then 2 mg/day
HIV		Urinary urgency, erectile dysfunction	HIV viral load, CD4 cell count	Antiretroviral drugs
Syphilis "tabes dorsalis"	Tertiary neurosyphilisLatent period 15-30 years	Argyll Robertson pupil, erectile dysfunction, urinary incontinence, optic atrophy, cranial neuropathy	Rapid plasma regain, CSF with lymphocytic pleocytosis, raised protein, and VDRL	Parenteral penicillin G for 10-14 days
HTLV-1/2			HTLV- 1/2 in blood	Possibly steroids

*Abbreviations: CSF=cerebrospinal fluid; GI=gastrointestinal; HIV=human immunodeficiency virus; HTLV=human T lymphotropic virus; IU=international units; VDRL=venereal disease research laboratory.

symmetric, sensory, or sensorimotor polyneuropathy occurring in the presence of an IgM monoclonal gammopathy and myelin associated glycoprotein (MAG) antibodies.[126] Patients who have an identical clinical and electrophysiologic phenotype but lack MAG antibodies can be classified as having DADS-CIDP[76 127]; such patients may carry a better prognosis and respond more favorably to intravenous immunoglobulins, corticosteroids, and plasma exchange.[127] The clinical hallmark of DADS neuropathy is the gradual onset of sensory ataxia resulting from impaired proprioception.[128] Weakness is less prominent and, when present, affects the distal lower extremities.[129] Action tremor can be a prominent feature.[130 131] The electrophysiologic features include extremely prolonged distal motor and sensory latencies representing distal demyelination.[132 133] Pathologically, there is segmental demyelination with IgM and complement deposits in the myelin sheaths and widened outer myelin lamellae.[134] More than half of patients with DADS have IgM paraproteins that recognize MAG or SGPG (which is present in most patients with anti-MAG antibodies). Three quarters of patients with non-anti-MAG DADS have anti-ganglioside antibodies (GD1b, GQ1b, GT1b, and others).[128]

Sensory neuronopathies

The sensory neuronopathies, or dorsal root ganglionopathies, are a small subset of sensory polyneuropathies that result from damage to the trigeminal ganglion sensory neurons and DRG. These uncommon disorders can be broadly classified as inherited, autoimmune, or acquired. Because a comprehensive discussion of these disorders is beyond the scope of this article, emphasis will be placed on two of the more common, potentially treatable, autoimmune causes of sensory neuronopathy: Sjögren's syndrome and anti-Hu paraneoplastic syndrome. Table 3 shows additional causes of sensory neuronopathy.

Paraneoplastic disorders probably affect less than 1% of all patients with cancer making them extremely rare.[135] Although other antibodies and other cancers have been reported with paraneoplastic sensory neuronopathy, anti-Hu antibodies and their high association with small cell lung cancer are the quintessential clinical scenario.[136-144] In addition to sensory ataxia, patients may develop concomitant autonomic dysfunction, cerebellar and brainstem involvement, motor neuropathy, and limbic encephalitis.[145 146] The anti-Hu antibodies, which attack Hu-expressing tumor cells, are thought to trigger a CD8 cytotoxic T cell response.[147-149]

The sensory neuronopathy sometimes seen in Sjögren's syndrome is also associated with autonomic dysfunction and at times brainstem dysfunction.[78 150 151] The underlying pathophysiology of Sjögren's associated sensory neuronopathy is unknown, although T cell mediated infiltration in the DRG has been demonstrated.[152]

Posterolateral syndrome

Not all sensory ataxic presentations localize to the peripheral nervous system, and disorders affecting the dorsal columns of the spinal cord must also be considered. In contrast to the disorders discussed above, which are mainly autoimmune, the myelopathic disorders that present with sensory ataxia (in addition to spasticity and weakness) often have nutritional or infectious causes (see table 4). Tabes dorsalis, a presentation of parenchymatous neurosyphilis, may selectively affect the dorsal columns and spare the corticospinal tracts.[153]

Diagnostic approach

In addition to the clinical examination, the diagnostic evaluation of the sensory polyneuropathies may include a combination of electrodiagnostic studies, testing of autonomic function, laboratory testing, and histopathologic analysis of nerve tissue. Figures 1-3 provide algorithms to guide the diagnostic evaluation of sensory polyneuropathies.

Electrodiagnostic studies

Nerve conduction studies

Nerve conduction studies are a sensitive and specific method of assessing disease in the large myelinated nerve fibers and can provide useful diagnostic information regarding the underlying pathophysiology of the neuropathy (fig 4).[42 154] Most neuromuscular experts advocate for the use of electrodiagnostic studies in distal symmetric polyneuropathy if the diagnosis is known or unknown.[155] Several studies have shown that electrodiagnostic studies in this population can often change the diagnosis and management.[156-158] Others, however, advocate for its use only in patients with atypical presentations.[159] Regardless of this, many clinicians will forgo electrodiagnostic testing in patients who have straightforward distal symmetric polyneuropathy if the underlying cause is known (such as diabetes).

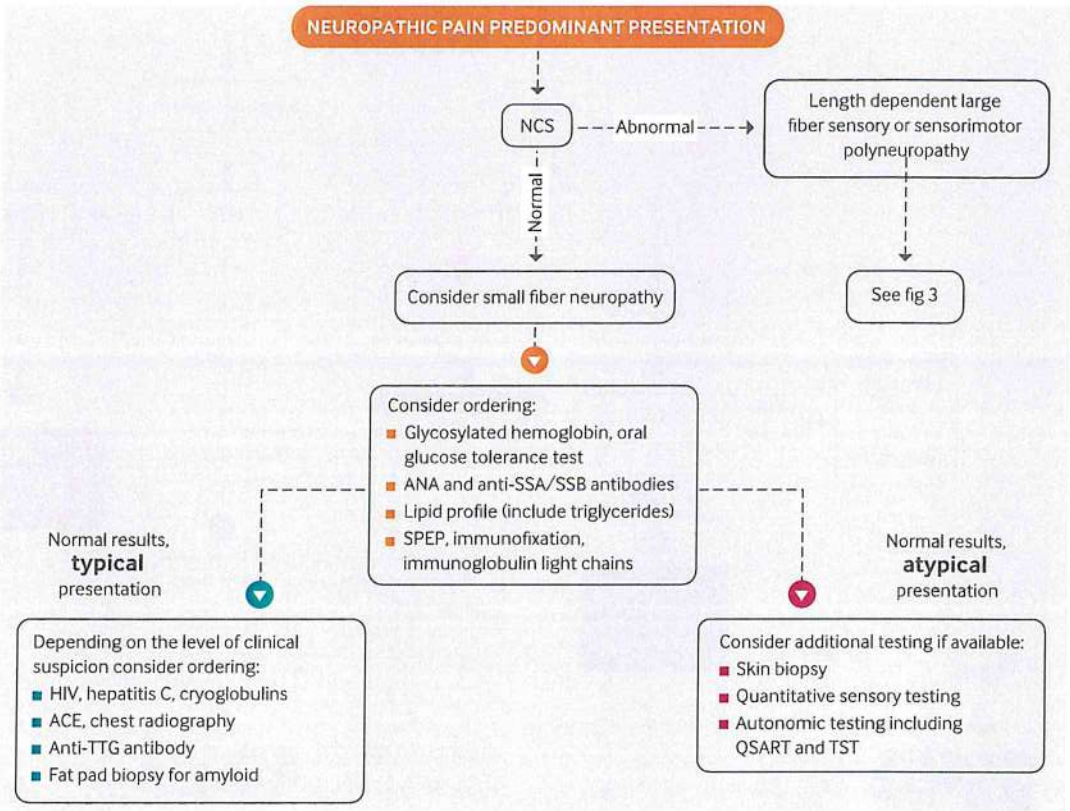

Fig 1 | Diagnostic algorithm for neuropathic pain predominant presentations. Abbreviations: ACE=angiotensin converting enzyme; ANA=antinuclear antibody; NCS=nerve conduction studies; QSART=quantitative sudomotor axon reflex test; SPEP=serum protein electrophoresis; SSA=Sjögren's syndrome A; SSB=Sjögren's syndrome B; TST=thermoregulatory sweat testing; TTG=tissue transglutaminase.

Because electrodiagnostic studies will be normal in disorders that mainly affect small unmyelinated fibers, a normal nerve conduction study does not exclude the presence of small fiber dysfunction. In addition, many disorders with a SFN phenotype may subclinically have involvement of the large myelinated fibers and display abnormalities on electrodiagnostic testing; thus, the presence of large fiber involvement does not exclude small fiber dysfunction.[1]

In sensory neuronopathies, sensory nerve action potentials (SNAPs) may be absent or display reduced amplitudes with relative preservation of conduction velocities. Abnormalities often do not follow a length dependent pattern and may be widespread. In contrast to most polyneuropathies, the upper extremities may be more prominently affected. Motor studies will classically be normal but subtle abnormalities are often encountered.[44 45 160]

The diagnostic criteria for sensory neuronopathies (fig 5), which are based on a large retrospective analysis published in 2009, include at least one absent SNAP or three SNAPs less than 30% of the lower limit of normal in the upper extremities and less than two abnormal motor nerve responses in the lower extremities.[46] These criteria were further validated after another large multicenter study was published in 2014.[161] A recent case-control study suggests that greater than a 50% difference in amplitude in a side-to-side comparison of two or more pairs of sensory nerves could be used as a rapid screening tool, with sensitivity and specificity greater than 90%.[162] Small case series show that blink reflexes may be abnormal in sensory neuronopathies secondary to Sjögren's syndrome, paraneoplastic disease, and idiopathic sensory neuronopathy, suggesting involvement of the trigeminal ganglion.[163 164]

Evoked potentials

Somatosensory evoked potentials—Somatosensory evoked potentials (SSEPs) evaluate the sensory pathways in both the peripheral and central nervous systems. They are particularly valuable when the proximal portions of the peripheral nerves, which are not studied with routine nerve conduction studies, are affected.[165] Bipolar transcutaneous electrical stimulation applied to the skin overlying a selected nerve (often median or tibial) evokes the SSEPs, which are then recorded with standard electroencephalograph scalp disk electrodes. They have an important diagnostic role in CISP, which preferentially affects the nerve roots and proximal nerves and spares the distal sensory nerves.[166] Evidence of proximal demyelination is also often apparent in sensory CIDP.[123]

Laser evoked potentials—Laser evoked potentials (LEPs), which assess the nociceptive pathways both peripherally (Aδ and C fibers) and at the spinothalamic tract centrally, have been called the "most widely agreed upon tool for investigating small fiber damage."[167] A carbon dioxide laser stimulus is applied to the foot and calf.

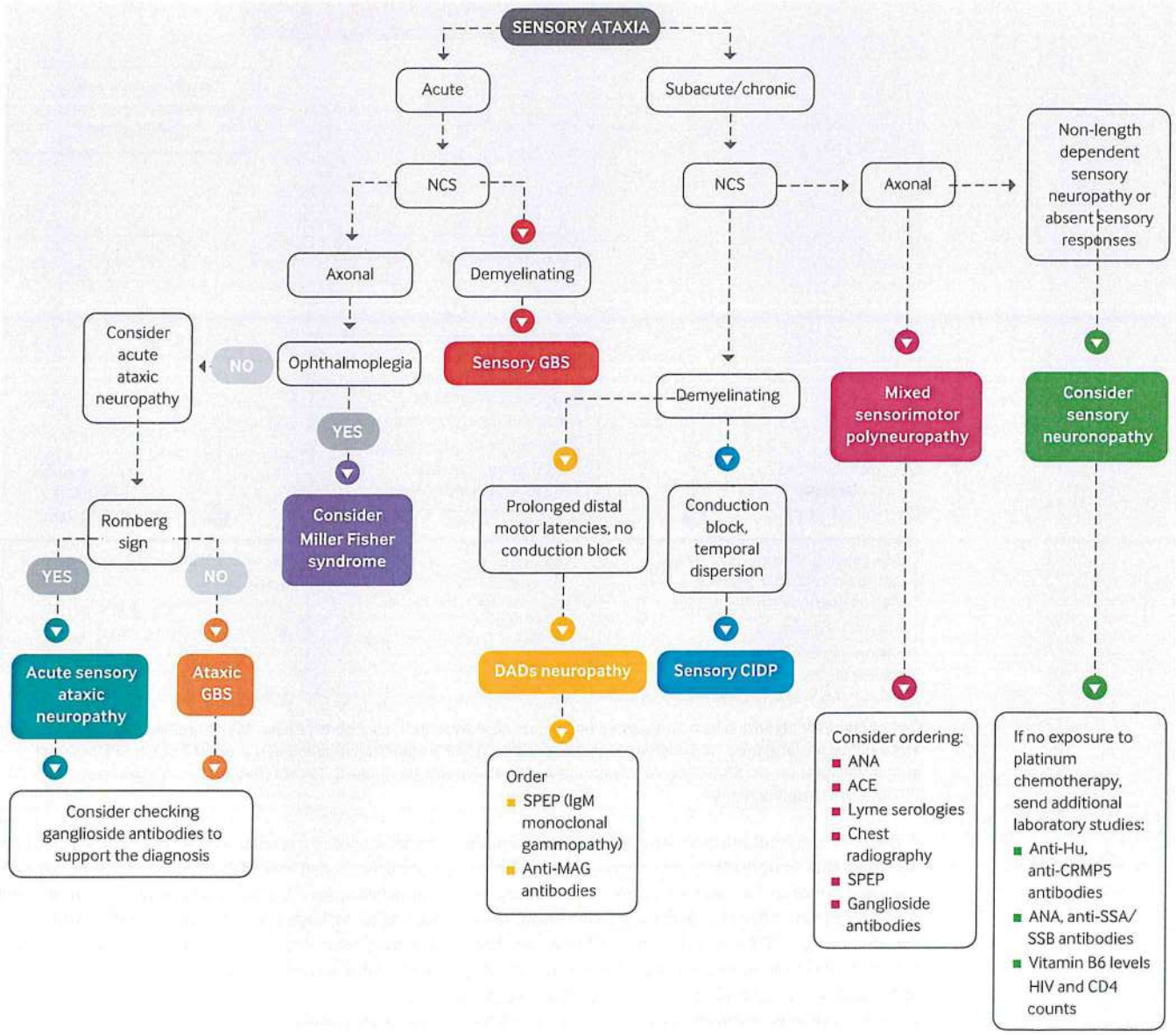

Fig 2| Diagnostic algorithm for sensory ataxic presentations. Abbreviations: ACE=angiotensin converting enzyme; ANA=antinuclear antibody; CRMP-5=collapsing response mediator protein-5; DADS=distal acquired demyelinating symmetric neuropathy; GBS=Guillain-Barré syndrome; MAG=myelin associated glycoprotein; NCS=nerve conduction studies; SSA=Sjögren's syndrome A; SSB=Sjögren's syndrome B; SPEP=serum protein electrophoresis.

The latency and amplitude of LEPs are measured with scalp electrodes. The pain is perceived as first a prickling sensation (Aδ activation) followed by a dull, burning sensation (C fiber activation). Although LEPs have a high sensitivity (in the 70-80% range) for SFN,[167 168] there are few laser testing facilities worldwide.[168] Given their ease of use, LEPs have been proposed as an alternative to skin biopsy in diabetes associated SFN.[167]

Quantitative sensory testing

Quantitative sensory testing (QST) can provide evidence of small nerve fiber damage on the basis of the measurement of abnormal sensory thresholds, and because abnormal QST results correlate with abnormalities of IENFD.[169 170] QST has several limitations, such as its inability to discriminate between central nervous system and peripheral nervous system disease, the need for participant cooperation and attention, and the fact that it may be easily influenced by other factors. Therefore, it should not be used in isolation and needs to be interpreted in the clinical context and in conjunction with other studies.[54 171-174]

Corneal confocal microscopy

Corneal confocal microscopy is an additional diagnostic tool that enables visualization of the peripheral nerves of the cornea and correlates with IENFD (fig 2). This non-invasive technique uses a combination of corneal nerve fiber length, nerve branch density, and nerve fiber density to evaluate the corneal nerve plexus.[175 176] It has been

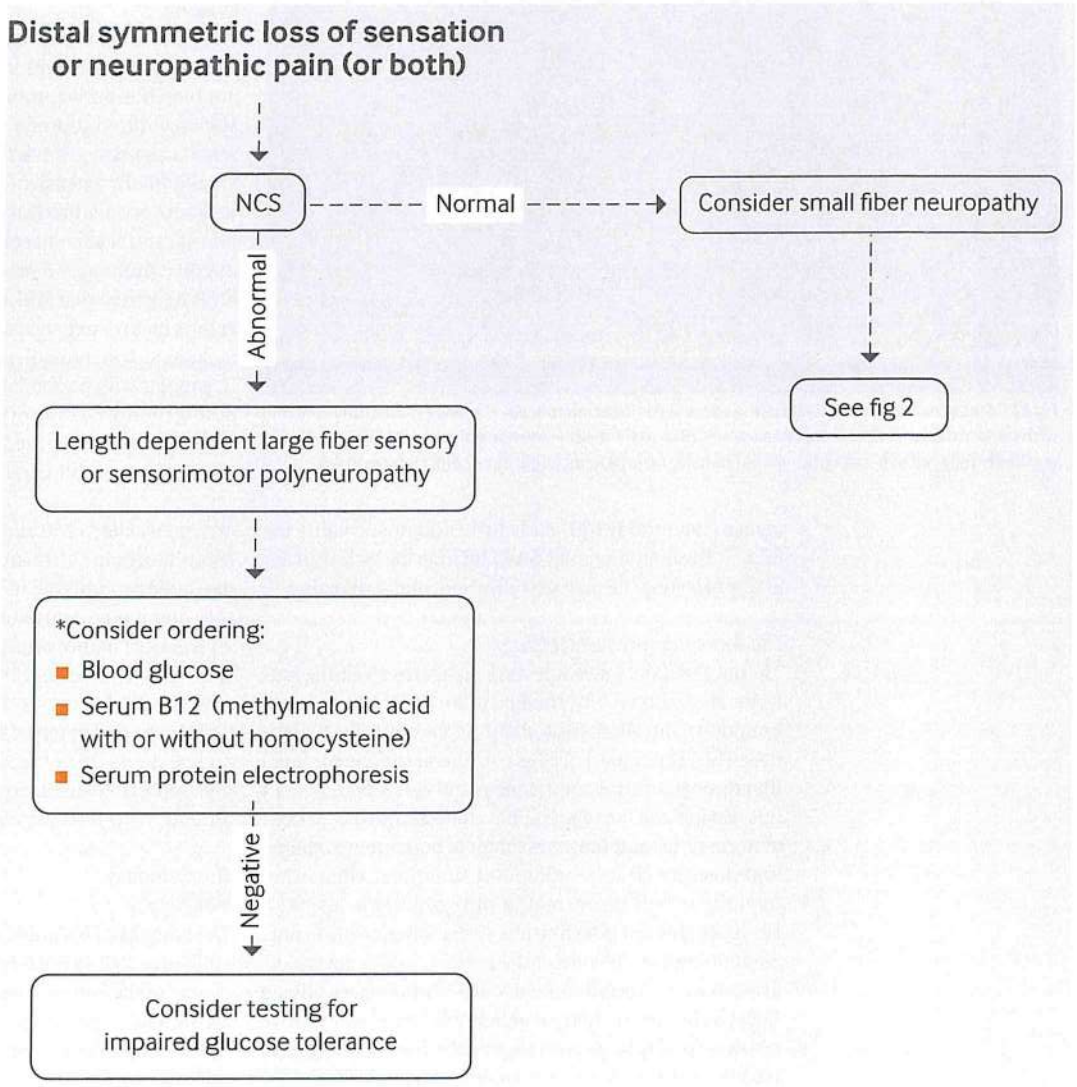

Fig 3| Diagnostic algorithm for distal symmetric loss of sensation or neuropathic pain (or both). Abbreviations: NCS=nerve conduction studies. *Based on American Academy of Neurology guidelines.[154]

shown to detect early small nerve fiber damage in many disorders.[175 177-182] This technique has advantages over skin biopsy as it is rapid and non-invasive, but it is not yet widely available. There is only a modest correlation with disease stage in any patient and the correlation is of limited utility in clinical practice.[183-185] A recent study of nearly 1000 patients with type 1 and type 2 diabetes demonstrated the diagnostic validity of corneal confocal microscopy using a 12.5 mm/mm^2 optimal threshold for automated corneal nerve fiber length in type 1 diabetes (73% sensitivity, 69% specificity) and a 12.3 mm/mm^2 optimal threshold in type 2 diabetes (69% sensitivity, 63% specificity).[176] When considering the entire cohort, a lower threshold for automated corneal nerve fiber length of 8.6 mm/mm^2 could rule in diabetic polyneuropathy and an upper threshold of 15.3 mm/mm^2 could rule it out (88% specificity, 88% sensitivity). How these studies will be incorporated into clinical practice and their role as a clinical trial outcome measure remain to be determined.[176]

Autonomic testing

Autonomic testing can help in the diagnosis of SFN, especially when dysautonomia is present.[186] Sudomotor function testing as a measure of autonomic function may be assessed through thermoregulatory sweat testing, quantitative sudomotor axon reflex test (QSART), or newer techniques such as electrochemical skin conductance.[187] Studies suggest that these autonomic testing modalities provide limited additional diagnostic information when a skin biopsy is abnormal.[188]

Quantitative sudomotor axon reflex testing

Quantitative sudomotor axon reflex testing is a method of assessing postganglionic sudomotor function through the measurement of local sweat production in predetermined sites (forearm, distal and proximal leg, and foot) in response to iontophoresis of 10% acetylcholine. Abnormal QSART test results have been shown to correlate with decreased IENFD.[189] However, a recent moderately sized prospective study found that the addition of QSART to the

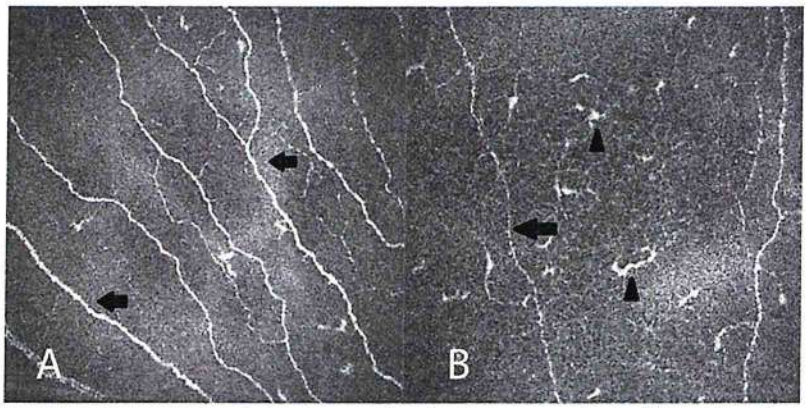

Fig 4| Corneal nerve fiber analysis using corneal confocal microscopy showing (A) healthy control with normal nerve fiber density (arrows) and (B) a patient with diabetic polyneuropathy who has markedly reduced sub-basal nerve fiber density (arrow) and Langerhans cells (arrowheads).

measurement of IENFD adds little diagnostic value for SFN.[188] The limitations of QSART include the technical difficulty of testing, the cost of equipment, and availability.[187]

Thermoregulatory sweat testing

Thermoregulatory sweat testing measures sweating patterns of the body with the use of an indicator dye in a humidity controlled, heated setting for typically 70 minutes. This technique activates peripheral sudomotor function through central autonomic pathways. Advantages of this test include the topographic analysis of sweat pattern abnormalities and the assessment of both pre-ganglionic and post-ganglionic sudomotor function (when other modalities will be normal in pre-ganglionic lesions). However, this test is technically demanding, requires time commitment on the part of the patient, and is not widely available.[187] A recent retrospective study suggests that a novel technique of thermal imaging of forced evaporative cooling corresponds with the results from the standard technique using indicator powder and is more efficient.[190]

Electrochemical skin conductance

Electrochemical skin conductance has been reported in several small studies as a non-invasive, reliable marker of sweat function and SFN.[191-193] Electrical stimulation with low direct voltage current is applied to sudomotor fibers of the palms and soles, which in turn activates sweat glands. However, a recent large systematic review determined that evidence on the use of this technique is limited and of overall poor quality; in addition, it is potentially confounded by technical factors, inconsistent normative values, and funding bias.[194]

Stimulated skin wrinkling

Stimulated skin wrinkling is the reversible undulation of surface skin that is mediated by post-ganglionic sympathetic fibers. It is tested by immersing glabrous skin (smooth skin without hair, as on the palms or soles of the feet) in water or exposing it to EMLA (eutectic mixture of local anesthetic).[195 196] It has been shown to correlate with IENFD in patients with sensory polyneuropathy,[196 197] and it has shown comparable sensitivity to other testing methods for diabetic neuropathy.[196]

Imaging

Magnetic resonance imaging

Most patients who present with sensory neuropathy will not benefit from neuroimaging, but in select situations MRI may provide some additional diagnostic benefit. Small case series have demonstrated non-enhancing, longitudinally extensive dorsal column lesions in patients with sensory neuronopathies, indicative of the degeneration of central afferent connections between the DRG and dorsal columns.[198] A small case series of patients with CISP suggested that MRI abnormalities such as nerve root enlargement or enhancement may be useful diagnostically in patients with normal nerve conduction study results.[125] In patients with posterolateral cord syndrome and sensory dysfunction as a result of dorsal column dysfunction, MRI will often show increased T2 and FLAIR (fluid attenuated inversion recovery) signals at the dorsal columns.

Neuromuscular ultrasound

Neuromuscular ultrasound is an emerging tool that is particularly valuable in immune mediated mixed sensory and motor demyelinating polyneuropathies and in entrapment neuropathies, in which focal nerve enlargement can be detected. In a population of patients with SFN, the sural nerve was found to have a greater cross sectional area compared with healthy controls.[199] Currently, most experts do not recommend using neuromuscular ultrasound in patients with pure sensory polyneuropathy, although this field remains ripe for future study.[200]

Tissue biopsy

Skin biopsy

The European Federation of Neurological Societies/Peripheral Nerve Society Guideline and numerous studies support the use of skin biopsy to assess IEFND and as the gold standard for pathologic diagnosis of SFN (fig 6).[201] It is a reproducible and reliable technique with a specificity greater than 90%, sensitivity approaching 80%, and favorable positive and negative predictive values.[1 2 202-204] Multiple large cohort studies have been conducted to establish normative values for IENFD at the distal leg because age, ethnicity, and sex are known to produce variations.[202 203 205] A recent longitudinal case-control study showed that rates of IENFD decrease are similar at proximal and distal biopsy sites, regardless of cause, supporting a non-length dependent process.[41] Diagnostic criteria for SFN have been proposed to enable patients to be included in clinical trials. Box 1 provides a comparison of the 2008 Devigili criteria and the 2017 Blackmore and Siddiqui criteria (which do not require a skin biopsy).[206 207] In straightforward cases of SFN, supported by a typical history and examination findings, a skin biopsy is often unnecessary, and further research is needed to elucidate the precise role of skin biopsy in clinical practice.

Nerve biopsy

In general, nerve biopsy is not needed to diagnose patients as having a sensory polyneuropathy, although many of the disorders discussed in this review will have characteristic histopathologic features. In sensory CIDP, nerve biopsy may detect demyelinating features, including hypomyelinated fibers on light microscopy and onion bulb

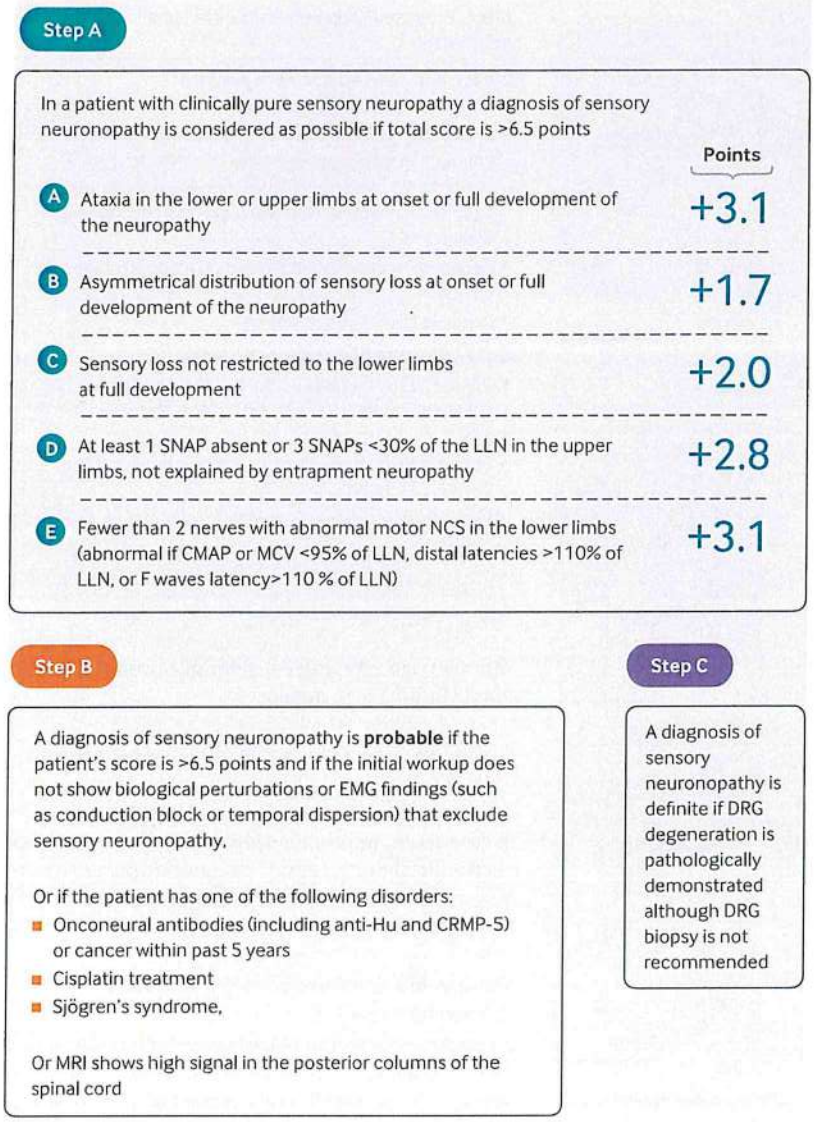

Fig 5| Diagnostic criteria for sensory neuropathy. CMAP=compound motor action potential; DRG=dorsal root ganglion; EMG=electromyography; LLN=lower limit of normal; MCV=motor nerve conduction velocity; MRI=magnetic resonance imaging; NCS=nerve conduction studies; SNAP=sensory nerve action potential. Adapted, with permission, from Camdessanché and colleagues.[46]

formation, as well as mononuclear cell infiltrates in the interstitial tissue.[121] Patients with anti-MAG neuropathies show evidence of demyelination and monoclonal IgM and C3d deposits on myelin sheaths.[208] Ultrastructural studies show widening of the myelin lamella due to M-protein and activated complement proteins, which colocalize with MAG in these areas.[208-212] Although a diagnosis of sensory neuronopathy is considered "definite" only if there is pathologic evidence of DRG degeneration, DRG biopsy is discouraged because of the associated morbidity.[45 161]

Current disease specific treatments

Apart from SFN associated with diabetes and prediabetes, the sensory polyneuropathies discussed are relatively rare, and no universally accepted disease specific treatments exist. Many of the disease specific treatments discussed below are based on expert opinion, retrospective studies, and small prospective studies, rather than large randomized placebo controlled trials. Some treatments discussed are emerging and in various stages of study.

Small fiber neuropathies

Sarcoidosis

Evidence to support the optimal treatment regimen for SFN associated with sarcoidosis is limited. In a retrospective review of 115 patients, the SFN treatment response rates were 76%, 67%, and 71% for treatment with intravenous immunoglobulins, anti-TNF-α, and combination therapy with both, respectively.[75] By contrast, in the same trial patients treated with methotrexate or corticosteroids showed no improvement or even worsening of symptoms.

Transthyretin familial amyloidosis polyneuropathy

The US Food and Drug Administration and the European Commission have recently approved patisiran and inotersen as treatments for TTR-FAP. Several other drugs, such as diflunisal and tafadimis, have shown promising results in large randomized placebo controlled clinical trials. Liver transplantation has traditionally been the standard treatment despite continued deposition of wild-type transthyretin.[213] Patisiran is an RNA interference therapeutic agent that inhibits hepatic synthesis of transthyretin.[214] In a double blind placebo controlled phase III trial, 225 patients were randomized to either intravenous patisiran (0.3 mg/kg/body weight) or placebo every three weeks. Patients receiving patisiran had a significant improvement in the Modified Neuropathy Impairment Score +7 (mNIS+7) (P<0.001), on the Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QOL-DN) questionnaire (P<0.001), and gait speed (P<0.001). In addition, a large phase III randomized double blind placebo controlled trial of inotersen, an antisense oligonucleotide that inhibits the hepatic production of transthyretin, has recently been published.[215] One hundred and seventy two patients(112 in the inotersen group and 60 in the placebo group) were given weekly subcutaneous injections for 66 weeks. As in the patisiran trial, the treatment arm also significantly improved on the mNIS+7 and the Norfolk QOL-DN scores (both P<0.001). However, inotersen was associated with thrombocytopenia and glomerulonephritis in some patients.

The transthyretin tetramer stabilizers include diflunisal and tafadimis. Diflunisal, a non-steroidal anti-inflammatory drug, strongly inhibits TTR amyloid fibril formation. A large international double blind placebo controlled trial of 130 patients found that diflunisal slowed the progression of patients with and without the TTR-Val30Met and non-Val30Met mutations.[216] This orphan drug is widely available and inexpensive. Another randomized double blind placebo controlled trial studied tafamidis in patients with early stage TTR.[217] Although the coprimary endpoints of slowed progression on the Neuropathy Impairment Score-Lower Limbs (NIS-LL) (as determined by NIS-LL response, "responders" had an increase in NIS-LL at 18 months of <2 points) and Norfolk QOL-DN scores were not reached, a statistically significant 52% reduction in the worsening of neurologic function (as

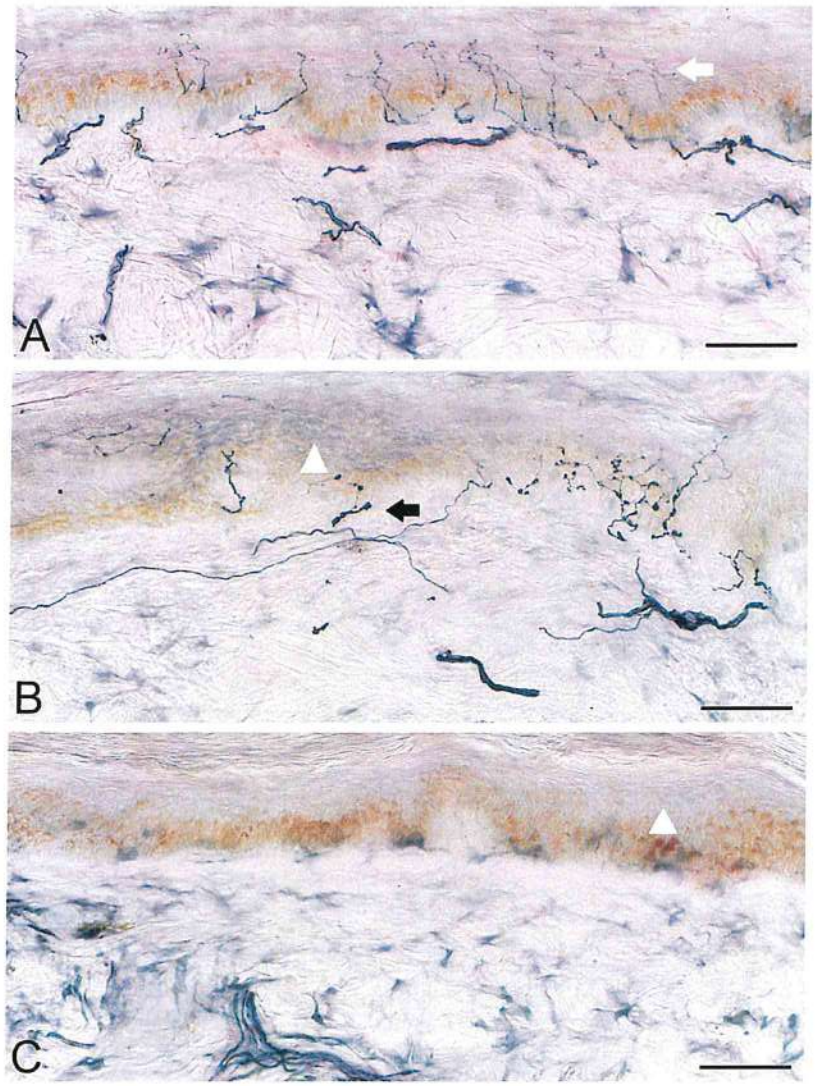

Fig 6| Skin biopsy (scale bars equate to 50 µM). (A) Healthy control with normal intraepidermal nerve fiber density (white arrow). (B) Patient with diabetic polyneuropathy who has reduced intraepidermal nerve fiber density (white arrowhead) and axonal swellings (black arrow), a common finding in such patients. (C) Patient with diabetic polyneuropathy and severely reduced intraepidermal nerve fiber density (white arrowhead).

Box 1 | Proposed diagnostic criteria for small fiber neuropathy

2008 criteria by Devigili and colleagues[206]

The diagnosis of SFN requires at least two of the following:

- Clinical signs of small fiber impairment (pinprick and thermal sensory loss, hyperalgesia, or allodynia, or a combination thereof) with a distribution consistent with peripheral neuropathy (length dependent or non-length dependent)
- Abnormal warm or cooling threshold (or both) at the foot on QST
- Reduced IENFD at the distal leg

2017 Criteria by Blackmore and Siddiqi[207]

- Definite SFN: abnormal neurologic examination (impaired pain or thermal sensation) and any two of QSART, QST, or HRV
- Probable SFN: abnormal neurologic examination and either QSART, QST, or HRV
- Possible SFN: abnormal neurologic examination or QSART or QST

Abbreviations: HRV=heart rate variability testing; IENFD=intraepidermal nerve fiber density; SFN=small fiber neuropathy; QSART=quantitative sudomotor axon reflex test; QST=quantitative sensory testing.

determined by change in NIS-LL from baseline to 18 months) was seen in this intention to treat population (P=0.027). This drug is approved in Europe, South America, and Japan, but not in the US.[89]

Sensory ataxic neuropathies

Miller-Fisher syndrome

A retrospective study and expert opinion indicate that intravenous immunoglobulin probably reduces the time to recovery and prevents the progression of symptoms.[218 219] However, the use of such an expensive treatment in a condition with a favorable prognosis is controversial.[33 218] An evidence based guideline report of the therapeutics and technology assessment subcommittee of the American Academy of Neurology stated that there was insufficient evidence to support or refute the use of intravenous immunoglobulin in this condition,[220] although patients with considerable overlap with GBS should be offered treatment.

Chronic ataxic neuropathy with disialosyl antibodies (CANDA)

Data to guide treatment in these patients are limited.[221-224] In case series, intravenous immunoglobulins have been used with some success,[119] whereas rituximab was the most effective treatment in one small cohort of patients, halting disease in eight of nine patients.[117]

Sensory chronic inflammatory demyelinating polyneuropathy (CIDP)

It is extremely important to recognize this disease because 90% of patients responded to immunotherapy in one series.[123] No prospective randomized placebo controlled trials have studied immunosuppressant or immunomodulatory therapy in the sensory variant of CIDP specifically. In one retrospective series of 15 patients with CISP, all patients responded to intravenous immunoglobulins or intravenous methylprednisolone.[125]

Distal acquired demyelinating sensory neuropathy (DADS)

Many treatments have been tried and abandoned in MAG neuropathies including corticosteroids, intravenous immunoglobulins, and plasma exchange.[212] Although cytotoxic agents such as fludarabine, cyclophosphamide, and chlorambucil may be beneficial, their toxicities limit longterm use.[212] Rituximab, a monoclonal antibody that targets CD20 (a B cell surface antigen) and depletes circulating B cells, has been used with success in 30-50% of patients in uncontrolled trials.[128 225] The primary endpoints in two placebo controlled randomized trials of rituximab failed to reach statistical significance, although secondary endpoints such as time-to-walk scales significantly improved.[225-227] Patients with motor deficits and subacute progression may respond more favorably

to rituximab if the drug is started soon after the onset of symptoms.[228 229] In 2010, the European Federation of Neurological Societies and Peripheral Nerve Society published a guideline on the management of paraproteinemic demyelinating neuropathies. This guideline highlighted the lack of proven efficacy for any therapy in anti-MAG neuropathy but emphasized that some patients may respond to treatment.[230] Two patients have been treated with obinutuzumab, a first generation glycoengineered type-I, anti-CD20 mediated, B cell depleting monoclonal antibody.[231] No improvement or worsening in the patients' neuropathic symptoms was seen after 12 months of treatment.

Sensory neuronopathies

Given the rarity of these diseases, little is known about the best approach to treatment, although a treatment window probably exists. A case series of serial nerve conduction studies in patients with sensory neuronopathy suggests that sensory abnormalities plateau after 7-10 months from symptom onset. On the basis of the rate of decline of sensory response amplitudes, treatment should be started within the first eight months if possible.[232] Beyond this window, the inflammatory reaction probably dampens and treatment becomes unsuccessful. For the patients with paraneoplastic disease, detection and treatment of the underlying cancer is obligatory. For both paraneoplastic and Sjögren's associated sensory neuronopathies, immunosuppressant and immunomodulatory treatment should be provided. Intravenous immunoglobulin, plasma exchange, corticosteroids, rituximab, cyclophosphamide, infliximab, and azathioprine have all been used in uncontrolled studies of Sjögren's associated sensory neuronopathy.[233-238] Corticosteroids,[239 240] intravenous immunoglobulins,[241 242] plasma exchange,[243] rituximab,[244] and sirolimus[245] have been used in patients with paraneoplastic sensory neuronopathy.

Emerging disease specific treatments

Small fiber neuropathies

Diabetes and prediabetes

In early clinical trials, physical exercise has shown promise as a treatment of SFN associated with glucose dysregulation. In prospective randomized trials, exercise results in increased IENFD in patients with diabetes but no neuropathy.[246 247] A small prospective pilot study in diabetic neuropathy also found that pain responded to exercise.[248] A large prospective randomized study of patients with type 2 diabetes associated peripheral neuropathy (the Activity for Diabetic Polyneuropathy or "ADAPT" study), which is investigating the effect of supervised exercise versus standard care counseling on polyneuropathy, as measured by IENFD and change in quality of life, is currently underway (Clinical trials identifier NCT02341261).

Sarcoiditis

ARA 290 (Cibinetide), an erythropoietin derivative that activates the innate repair receptor and initiates anti-inflammation, cytoprotection, and healing, has been well tolerated and showed benefit in treating sarcoidosis associated neuropathic pain in two phase II clinical trials.[18 249]

Sjögren's syndrome

Like all polyneuropathies that are associated with Sjögren's syndrome, studies of the disease specific treatment of Sjogren's associated SFN are sparse. A small uncontrolled trial of intravenous immunoglobulins in Sjögren's syndrome found a reduction in neuropathic pain in SFN,[250] but in other series the response to corticosteroids has been poor.[150 251 252] A small prospective, phase III clinical trial testing the benefit of intravenous immunoglobulins in patients with painful large fiber sensory polyneuropathy will soon be enrolling and could potentially inform treatment choices in patients with SFN that is associated with Sjögren's syndrome (Clinical trials identifier NCT03700138).

Sodium channelopathies

The discovery of the SCN9A, SCN10A, and SCN11A genetic mutations has opened the door to potential therapeutic options for painful SFN.[88 253 254] Lacosamide, a blocker of Nav1.3, Nav1.7, and Nav1.8 that stabilizes channels in the slow inactivation state, has been studied in SCN9A associated SFN, although the results have not yet been published[255] (Clinical trials identifier NCT01911975).

Current management of neuropathic pain

Neuropathic pain and positive sensory disturbances contribute greatly to the morbidity associated with sensory polyneuropathy. Most studies have focused on the treatment of painful neuropathy secondary to diabetes or chemotherapy induced painful neuropathy. A large meta-analysis published in 2015 updated recommendations on the pharmacologic treatment of neuropathic pain.[256] This review found moderate to high quality of evidence for the use of serotonin-norepinephrine reuptake inhibitors (SNRIs), pregabalin and gabapentin, tricyclic antidepressants (TCAs), opioids, botulinum toxin, and capsaicin. SNRIs, TCAs, gabapentin, and pregabalin were given a strong recommendation and proposed as first line agents, whereas topical capsaicin or lidocaine and tramadol were given a weaker recommendation and proposed as second line. Strong opioids and botulinum toxin A were recommended as third line.

A recent large retrospective systematic review of 106 randomized controlled trials examined the effect of various drugs for diabetic neuropathy on pain and quality of life. Anticonvulsants including pregabalin and oxcarbazepine; SNRIs including duloxetine and venlafaxine; TCAs; atypical opioids including tramadol and tapentadol; and botulinum toxin A were determined to be more effective than placebo. The strength of evidence was considered moderate for SNRIs and low for the other listed agents. The review concluded that other commonly used agents including gabapentin, topical capsaicin, typical opioids, dextromethorphan, and mexiletine were no more effective than placebo.[257]

A large multicenter double blind parallel group study of diabetic neuropathic pain studied whether patients who did not respond to standard dose monotherapy with duloxetine (60 mg/day) or pregabalin (300 mg/day) would respond to high dose duloxetine (120 mg/day), high dose pregabalin (600 mg/day), or a combination

Table 5 | Drugs used to treat neuropathic pain*†

Recommended drug	Strength of evidence (AAN)	Strength of evidence (EFNS)	Recommended dose	Common adverse effects	Mechanism of action
Pregabalin	Strong: level A	Strong: level A	150-600 mg/d in 3 doses	Weight gain, dizziness, sedation, edema	Decreases central sensitization by acting on voltage gated calcium channels
Gabapentin	Moderate: level B	Strong: level A	300-3600 mg/d in 3 doses	Weight gain, dizziness, sedation, edema	Decreases central sensitization by acting on voltage gated calcium channels
Venlafaxine	Moderate: level B	Strong: level A	75-225 mg/d (XR formulation available); may be divided into 2-3 doses	Nausea, vomiting, headache, dizziness	Inhibits serotonin and norepinephrine reuptake
Duloxetine	Moderate: level B	Strong: level A	60-120 mg/d; may be divided into 2 doses	Nausea, vomiting, headache, dizziness	Inhibits serotonin and norepinephrine reuptake
Tricyclic antidepressants (amitriptyline, nortriptyline, desipramine, imipramine)	Moderate: level B (amitriptyline);Insufficient evidence to support use: level U (desipramine, imipramine	Strong: level A	25-150 mg qhs	Weight gain, sedation, anticholinergic effects	Inhibits serotonin and norepinephrine reuptake, blocks sodium channels, anticholinergic
Tramadol	Moderate: level B	Strong: level A	100-400 mg/d in up to 4 doses	Nausea, vomiting, constipation, somnolence, dizziness	Mu-receptor agonist, Inhibits serotonin and norepinephrine reuptake
Oxycodone	Moderate: level B	Strong: level A	Up to 120 mg/d	Nausea, vomiting, constipation, somnolence, dizziness	Mu-receptor agonist
Morphine sulfate	Moderate: level B		Up to 120 mg/d	Nausea, vomiting, constipation, somnolence, dizziness	Mu-receptor agonist
Sodium valproate	Moderate: level B	Inefficacious: level B	500-1200 mg/d; may be in 3 doses	Weight gain, headache, tremor, sedation, alopecia, nausea, vomiting, thrombocytopenia	Enhances action of GABA or mimics action at postsynaptic receptor sites
Dextromethorphan	Moderate: level B	Moderate: level B	400 mg/d	Dizziness, sedation, restlessness, nausea	Sigma receptor stimulation
Capsaicin	Moderate: level B	Inefficacious: level B	0.075% cream up to 4 times daily	Allodynia, erythema, hypertension	Transient receptor potential villanoid-1 agonist depletes substance P
Isosorbide dinitrate spray	Moderate: level B			Hypotension, flushing, local erythema	Forms HO, acts as vasodilator, potentially increases microvascular flow
Topical lidocaine 5%	Weak: level C		Up to 12 h	Local erythema	Sodium channel inhibition
Percutaneous electric nerve stimulation	Moderate: level B		15-60 min/session	Local pain, bruising, temporary exacerbation of pain	Unclear; potentially blocks transmission of pain signals, enhances release of endorphins, serotonin
Botulinum toxin		Moderate: level B	50 U intradermally over dorsum of foot at 12 sites	Pain, bleeding, local reaction, muscle weakness	Unclear; potentially blocks nociceptor transduction
Carbamazepine		Weak: level C	100-200 mg every 4-6 h; maximum 1200 mg daily	Dizziness, sedation, nausea, vomiting, rash, blurred vision	Decreases sodium channel conductance
α-lipoic acid	Insufficient evidence to support use: level U		600 mg/d in 2 doses	Nausea, vomiting, rash	Antioxidant

*Abbreviations: AAN=American Academy of Neurology; bid=twice daily; EFNS=European Federation of Neurological Societies; qhs=every night at bedtime; XR=extended release.
†On the basis of either AAN or EFNS guidelines, the following agents are considered inefficacious: serotonin and norepinephrine reuptake inhibitors, zonisaminde, menantine, mexilitine, pentoxifylline, clonidine, lacosamide, lamotrigine, and oxcarbazepine.

of both (duloxetine 60 mg/day and pregabalin 300 mg/day). Eight hundred and four patients were evaluated for initial monotherapy, and the 339 who were considered non-responders were treated with high dose monotherapy or combination therapy. The primary outcome measure was the Brief Pain Inventory Modified Short Form (BPI-MSF) 24 hour average pain change after starting high dose monotherapy or combination therapy. No statistically significant differences in the BPI-MSF average pain score were seen between the combination and high dose monotherapy groups (P=0.370). When the initial standard monotherapy doses were compared, 60 mg/day of duloxetine was superior to 300 mg/day of pregabalin (P<0.01).[258]

A prospective interventional study conducted in an Indian diabetic clinic enrolled 100 patients who had never been treated with drugs for neuropathic pain to receive either pregabalin (50 patients) or duloxetine (50 patients). Comparative efficacy was determined by the Neuropathic Pain Scale (NPS) and the Neuro-QOL, a quality of life instrument. On the basis of NPS and Neuro-QOL scores, the efficacy of duloxetine was 1.27 and 1.44 times that of pregabalin, respectively. Cost effectiveness was calculated using cost consequence analysis, the average cost effectiveness ratio and the incremental cost effectiveness ratio. This analysis demonstrated that duloxetine, while slightly more expensive, demonstrated a significant improvement in quality of life.[259]

The use of opioids for the management of chronic neuropathic pain is generally discouraged. Although these drugs are efficacious in the short term, evidence to support their longer term use is weaker, and serious safety concerns exist.[260] A recent meta-analysis of 96 randomized placebo controlled trials investigating the efficacy of opioids for chronic non-cancer pain found that opioid use was associated with significant but small improvements in pain and physical functioning. When opioids were compared with non-opioid alternatives the benefit for pain and physical functioning seemed to be similar.[261]

Neuropathic pain management guidelines

Both the European Federation of Neurological Societies (EFNS) and American Academy of Neurology (AAN) (updated 2010 and 2011, respectively) have published guidelines on the pharmacologic management of painful diabetic peripheral neuropathy (table 5).[262 263] Both guidelines support the use of TCAs, pregabalin, gabapentin, various opioids, SNRIs,

QUESTIONS FOR FUTURE RESEARCH

- Because impaired glucose tolerance and type 2 diabetes are highly associated with neuropathy, further study into the best way to treat hyperglycemia (and other risk factors such as central obesity and hypertriglyceridemia) is needed. This is extremely important given the morbidity and disability associated with diabetic neuropathy, the most common cause of neuropathy worldwide.
- In transthyretin familial amyloidosis with polyneuropathy further studies are needed to determine the effect of inotersen and patisiran on the cardiomyopathy. In addition, we need to find a way to identify this rare subset of patients early in the disease course to avoid delays in start of treatment.
- Advances in understanding the role of antiganglioside antibodies in the sensory neuropathies have recently been made. How will an even greater understanding of the underlying pathomechanisms of these ganglioside antibodies translate to more targeted therapies?

and topical lidocaine for the treatment of neuropathic pain. The AAN guidelines also recommend the use of topical capsaicin and valproate with level B evidence and only pregabalin was supported by level A evidence. Each of these guidelines recommend against the use of oxcarbamazepine, lamotrigine, lacosamide, clonidine, and mexiletine in the symptomatic management of painful neuropathy.

Emerging treatments for neuropathic pain

Chemodenervation with botulinum toxin A is thought to inhibit the release of peripheral neurotransmitters such as acetylcholine and nociceptive peptides (substance P, glutamate, calcitonin gene related peptide) from sensory nerves.[264] In addition, botulinum toxin inhibits vanilloid receptor TRPV1 expression on the surface of peripheral nociceptors. It has been supported by multiple studies as described in a recent review for the treatment of neuropathic pain.[265]

A 2015 meta-analysis evaluating the use of several treatments for neuropathic pain gave botulinum toxin A a weak recommendation.[256] In the same year, a meta-analysis looking at chemodenervation in diabetic peripheral polyneuropathy supported its use as a result of finding clinically significant improvements in pain scores.[264] Most recently, in 2017, a large systematic review found that botulinum toxin was more effective than placebo, although the strength of evidence was low.[257]

There is some evidence from small studies to support the use of acupuncture as a non-pharmacologic treatment for neuropathic pain. A randomized placebo controlled partially blinded trial in Germany is currently looking at the effect of needle acupuncture, laser acupuncture, and placebo laser acupuncture on electrophysiologic parameters, neurologic deficits, and symptoms.[266]

Conclusions

The sensory polyneuropathies are heterogeneous conditions with distinct clinical phenotypes defined by the type of nerve fibers involved and the time course. Although many of the small fiber, pain predominant and large fiber, ataxia predominant neuropathies discussed are relatively uncommon, those reviewed have the shared feature of being potentially

HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE

Two patients provided their experience of having sensory neuropathy in their own words. They were given the option to review the manuscript but declined.

treatable and even reversible. The recognition of these distinctive presentations is of utmost importance to enable treatment to be started before permanent nerve damage occurs.

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PROVA NON ESTRATTA

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TOGM RAMORA
24/02/2021 Romina Gori

CONCORSO PUBBLICO, PER TITOLI ED ESAMI, PER N. 1 POSTO DI COLLABORATORE PROFESSIONALE SANITARIO – TECNICO DI NEUROFISIOPATOLOGIA - CAT. D DA ASSEGNARE ALLA UOC NEUROLOGIA 6 - NEUROFISIOPATOLOGIA

PROVA ORALE C

Valutazione pre-operatoria e monitoraggio intraoperatorio in corso di chirurgia per correzione di cifoscoliosi cervico-dorsale ed emivertebrectomia T2-T3

a. Esami preoperatori indicati per la tipologia di intervento
b. Indicazioni al monitoraggio, tecniche di monitoraggio e mappaggio applicabili (pess, pem, onda d, mapping viti toraciche, …)
c. Criteri di warning e considerazioni di base sul regime anestesiologico
d. Pitfalls relativi a posizionamento, eventuali manovre correttive in corso di IOM (ottimizzazione dipolo cefalico, ripresa baseline, wait and see..)

INFORMATICA

Descrivi come ordinare una determinata selezione in ordine crescente o decrescente su foglio di lavoro excel.

INGLESE:

Lettura e traduzione di uno stralcio di articolo allegato

ALLEGATO DOMANDA C

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Auditory mismatch detection, distraction, and attentional reorientation (MMN-P3a-RON) in neurological and psychiatric disorders: A review

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ABSTRACT

Involuntary attention allows for the detection and processing of novel and potentially relevant stimuli that lie outside of cognitive focus. These processes comprise change detection in sensory contexts, automatic orientation toward this change, and the selection of adaptive responses, including reorientation to the original goal in cases when the detected change is not relevant for task demands. These processes have been studied using the Event-Related Potential (ERP) technique and have been associated to the Mismatch Negativity (MMN), the P3a, and the Reorienting Negativity (RON) electrophysiological components, respectively. This has allowed for the objective evaluation of the impact of different neuropsychiatric pathologies on involuntary attention. Additionally, these ERP have been proposed as alternative measures for the early detection of disease and the tracking of its progression. The objective of this review was to integrate the results reported to date about MMN, P3a, and RON in different neurological and psychiatric disorders. We included experimental studies with clinical populations that reported at least two of these three components in the same experimental paradigm. Overall, involuntary attention seems to reflect the state of cognitive integrity in different pathologies in adults. However, if the main goal for these ERP is to consider them as biomarkers, more research about their pathophysiological specificity in each disorder is needed, as well as improvement in the general experimental conditions under which these components are elicited. Nevertheless, these ERP represent a valuable neurophysiological tool for early detection and follow-up of diverse clinical populations.

1. Introduction

Attention can be understood as a neurophysiological regulation system that influences the effectiveness of other cognitive processes such as perception, memory, learning, and executive function (Posner and Petersen, 1989; Estévez-González et al., 1997; Broadbent, 2013; Schröger et al., 2015). A typical way of classifying attentional mechanisms is in terms of how does the information enter the system. One of the ways can be by means of a top-down mechanism, that is, through an active, hierarchical and focalized selection process, organized by priorities that the Central Nervous System (CNS), particularly the prefrontal cortex, establishes on incoming stimuli. Other ways are summed up under the umbrella term of bottom-up mechanisms, referring to a passive selection of stimuli determined largely by their novelty, saliency, or distracting features (Escera et al., 2000).

Involuntary attention is directly associated with the bottom-up mechanism, and is defined as an automatic, non-intentional process of selection of stimuli that are potentially relevant to the organism though initially out of cognitive focus. This allows for further focused processing of these stimuli to achieve better behavioral regulation (Escera et al., 2000; Deouell and Knight, 2009). While involuntary attention is less associated with cognitive effort, it represents a behavioral cost that is expressed as a decrease in performance on tasks with voluntary or intentional components after the onset of the distracting stimulus

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(Friedman et al., 2001).

The balance and interaction between the voluntary –top-down– and involuntary –bottom-up– attentional processes, allow for conceptualizing the latter in a three-phase model, that includes (1) the automatic monitoring and detection of changes in the sensory environment outside of the current cognitive focus, (2) the orientation toward these changes (which comprises distraction in the case of task-irrelevant stimulation), and (3) the selection of adaptive responses to them, including reorientation to the original goal in case they are not relevant for the current task (Escera et al., 2000; Friedman et al., 2001; Horváth et al., 2008b). This model has been supported by Event-Related Potentials (ERP) studies. ERP are defined as brief voltage changes in the brain's electrical activity that are associated in time and phase with diverse sensory, motor, and cognitive processes (Fabiani et al., 2000).

Each of the stages of this model has been associated to specific ERP components that can be observed in either active or passive oddball paradigms, typically in the auditory domain, which include regularities in the sensory context and deviant stimuli that break these regularities by modifying some physical characteristic of the target stimuli. Typically, differential waveforms are calculated by subtracting the ERP waveform elicited by the frequent standard stimuli from the one elicited by the infrequent deviant stimuli in order to extract the change detection effects from the electrical potential (Schroger and Wolff, 1998). This differential waveform has been called the "distraction potential" (Fig. 1) and it comprises three sequential components –the Mismatch Negativity (MMN), the P3a, and the Reorientation Negativity (RON). These electrophysiological components coincide with each stage of the conceptual model mentioned above and will be reviewed in this context below.

1.1. MMN

The Mismatch Negativity (MMN) is typically elicited between 100 and 150 ms after the onset of a deviant, typically auditory stimulus and has been associated with the first stage of involuntary attention (Näätänen et al., 1978). It includes the modeling and constant monitoring of the context of sensory stimulation (Cowan, 1999). This state of "attunement" with the environment is independent from voluntary control (Näätänen and Winkler, 1999). According to Horváth et al. (2008b), the extraction of regularities from the sensory environment promotes efficiency in cognitive terms, since it promotes stable representations of context and reduces additional demands for attentional resources. In turn, discrete deviations from this sensory context are automatically detected, promoting an updated version of such representations (Näätänen and Winkler, 1999). In this way, the MMN does not reflect a simple process of detection, but rather provides a measurement of how sensory information is structured in memory (Sussman, 2007).

The MMN typically shows a frontocentral distribution (Näätänen et al., 2007), and it is believed to emerge from two neural generators: a superior temporal source, related with a pre-attentional change detection, and a frontal generator, which has been mainly associated with attentional capture (Cacioppo et al., 2007). It has been shown that the integrity of the glutamatergic system, especially of the N-Methyl-D-Aspartate (NMDA) receptors, exerts great influence on this component (Javit et al., 1994; Javitt et al., 1995; Bickel and Javitt, 2009). It has also been proposed that other neurotransmission systems, including the dopaminergic (Kähkönen et al., 2002), serotoninergic (Ahveninen et al., 2002), cholinergic (Inami et al., 2005), GABAergic (Nakagome et al.,

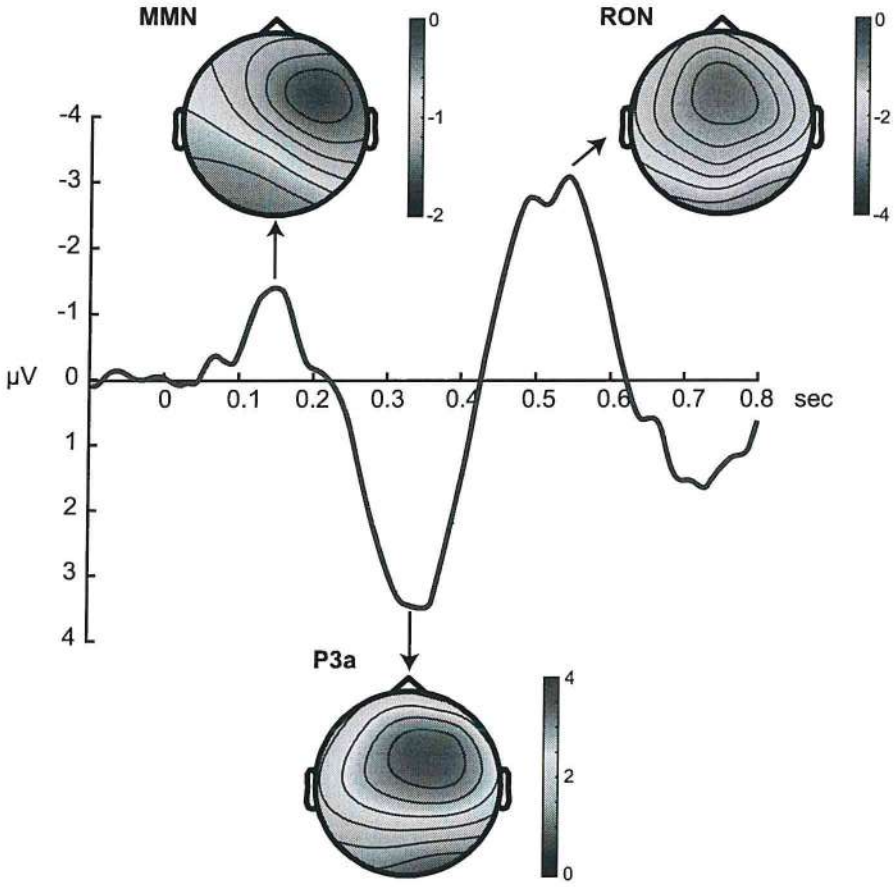

Fig. 1. The distraction potential.

1998), and histaminergic (Serra et al., 1996), can play a role in the modulation of this component despite some inconsistent results (Leung et al., 2007). In a recent work, Naatanen et al. (2011) extensively reviewed the MMN and its implications for different clinical conditions.

1.2. P3a

In cases where the disparity or deviation from the sensory context is extensive or relevant, other superior processes of greater complexity whose main function consist on the assignment of cognitive resources to the disparity processing are also triggered, and therefore, a change in the direction of the attention is elicited (Escera et al., 1998; Näätänen et al., 2007). This effect is more evident when the changes are produced suddenly rather than gradually (Horváth et al., 2008b). When this happens, cognitive resources are assigned to the efficient processing of the new event, which in turn can represent a cost in task performance. That is, the CNS allows task-irrelevant distractions to be processed (Escera et al., 2000; Horváth et al., 2008b). This second stage has been associated to the P3a component, elicited between 250 and 350 ms after the onset of a deviant, novel or unexpected stimulus (Squires et al., 1975; Luck and Kappenman, 2011). The P3a is part of the so called P300 family, which is associated with the engagement of attention and memory (Polich, 2007) and indexes an update of mental representations of novel stimuli (Donchin, 1981). The initial processing of such stimuli has been associated with the P3a. It is worth highlighting that the different P300 subcomponents have been related to attentional allocation at different functional levels (Polich, 1989; Kok, 1997; Rushby et al., 2005). Also, the so called Novelty P3 is thought to be functionally and anatomically analogous to the P3a component described here (Polich, 2007).

Two main neurophysiological sources have been proposed for the generation of the P3a: one responsible for its early portion, localized in the superior temporal cortex including the hippocampus (Knight, 1996), and a second source responsible for the late portion, embedded in the prefrontal cortex (Halgren et al., 1995).

It has been consistently reported that dopamine promotes the novelty processing associated to the P3a. Pharmacological studies suggest that the dopaminergic system modulates P3a features as an inverted U shape function, in which both poor and excessive dopamine availability can yield to a reduction of the P3a amplitudes (Apitz and Bunzeck, 2013). Polich (2007) may be consulted for an extensive review of the P3a.

1.3. RON

The third stage of the involuntary attention model includes the ability of the system to reassign cognitive resources, namely attention, to the original task, allowing for performance to be restored (Horváth et al., 2008b). This stage is denominated attention re-orientation, it occurs between 450 and 700 ms after the onset of the novel or distracting stimulus and it has been associated to the Reorienting Negativity (RON) component. The RON is mainly observed at frontal scalp regions and its amplitude is proportional to the magnitude of the deviation (i.e., a greater frequency deviation in Hz) (Polich, 2003). Current-density topographical maps have depicted generators in centroparietal regions for this component (Berti and Munka, 2006). According to Schröger et al. (2000), the RON reflects two distinct functional processes of the attentional reorientation after distraction: the re-focusing on task relevant information within working memory, and a general attentional reorientation or preparation for the next stimulus. The functional role of RON is supported by the fact that this component is not present when the deviations are task relevant, nor when the auditory stimuli are ignored (Schroger and Wolff, 1998). Nevertheless, the key factor to observe RON seems to be the presence of a well-defined primary task that requires reorienting (Correa-Jaraba et al., 2016). Additionally, it has been proposed that RON may in part reflect motor or response- preparation activity (Horváth et al., 2008a).

The neurotransmission systems involved with this component have been scarcely investigated. Manipulations with Haloperidol, a dopamine D2 receptor antagonist, have shown decreases in the amplitude and increases in the latencies of RON (as in P3a). The latter probably indicates an influence from basal ganglia and prefrontal cortices circuitry regulated by dopamine (Kähkönen et al., 2002).

In recent years, ERP have been useful for the identification of cognitive alterations in different neurological and psychiatric disorders (Solís-Vivanco et al., 2009). As an example, a large amount of studies supports MMN and P3a as feasible markers of schizophrenia (Javitt et al., 2008; Light et al., 2015). While for other illnesses some studies have reported changes in one or two of the previously mentioned ERP, we consider that the electrophysiological analysis of involuntary attention in clinical conditions should consider all three aspects of involuntary attention processing in its temporal sequence, given that it is possible to obtain the three ERP described above from a single auditory oddball task. This would allow for a more nuanced knowledge about the affected stage of processing for each of these pathologies, in turn allowing for a better understanding of the involved cognitive alterations in each case.

To date, there are detailed reviews that concentrate knowledge about MMN or P3a in clinical samples (Näätänen et al., 2007; Raggi et al., 2010; Naatanen et al., 2011; Maekawa et al., 2012; Seer et al., 2016). Their main purpose is related to the description of early auditory processing, sensory memory function, or the potential role of each ERP as a biomarker. Nevertheless, the reorientation phase, (i.e. what happens after a distraction) is still unclear even in healthy subjects (Horváth et al., 2008b; Horváth, 2014), and the research conducted in this field has been scarce. Moreover, the MMN, P3a, and RON are not necessarily directly linked as a single process (Horváth et al., 2008b). In this review, we propose that the exploration by means of the three-phase conceptual model and the three electrophysiological components associated to it, portray a wider overview of involuntary attention, its potential dysfunction in clinical populations and its association with cognitive and psychosocial function (Corbetta et al., 2008; Higuchi et al., 2014). Since it has been reported that the ERP from the distraction potential are feasible biomarkers of cognitive dysfunction, but at the same time, the temporal and functional role of P3a and RON have been challenged (Horváth et al., 2008b; Horváth, 2014), here we looked for experimental studies that reported at least 2 of the three components using the same auditory paradigm. This allowed for a description of changes on involuntary attention in temporal terms for different neurologic and psychiatric illnesses. We suggest that using this framework, more nuanced hypotheses can be drawn about attentional impairment in different clinical populations, in contrast to the more conventional strategies exploring each component in isolation.

2. Methods

2.1. Systematic literature review

2.1.1. Inclusion criteria

We considered scientific articles for inclusion if they (1) were experimental reports that contained inferential statistics; (2) were conducted in human adults; (3) were published between 1990 and 2019; (4) were published in English; and (5) at least two of the three components from the distraction potential were analyzed.

2.1.2. Search strategy

We carried out a search using the digital platforms ScienceDirect, PubMed, PsycINFO, Google Scholar, and Scopus, with two strings (String1: Involuntary attention psychiatric neurological auditory oddball novelty illness OR disorder OR ADHD OR schizophrenia OR Parkinson OR TBI OR multiple OR sclerosis OR bipolar OR depression OR autism OR substance OR Huntington's "event related potential"

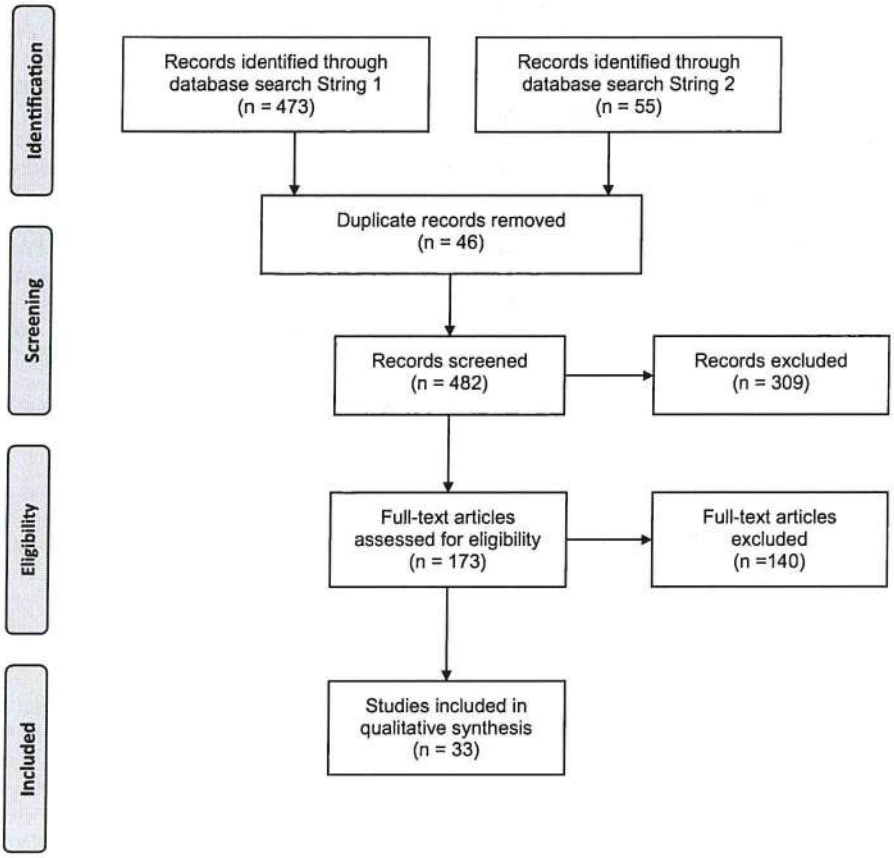

Fig. 2. Research items selection diagram.

-children –animal; String 2: MMN P3 P300 P3a RON psychiatric neurological auditory oddball novelty illness OR disorder OR ADHD OR schizophrenia OR Parkinson OR TBI OR multiple OR sclerosis OR bipolar OR depression OR autism OR substance OR Huntington's -children –animal). A first selection process was based on the presence of the keywords on title and abstracts. Following this, the articles identified as potentially relevant were downloaded and reviewed in full text.

3. Results

We identified 482 articles: 473 using search string 1 and 55 using search string 2. Of these, 46 were excluded because they were duplicates (Fig. 2).

Another 309 were excluded because they did not make explicit the exploration of clinical populations in the title or abstract, and 141 because they did not analyze two of the three components. With the purpose of facilitating the exploration of this work, Table 1 summarizes the main findings in the different pathologies reviewed herein based on the 33 studies finally selected.

4. Neurological disorders

4.1. Parkinson's disease

Parkinson's disease (PD) is an incurable, chronic and systemic disease that results mainly from the degeneration of the dopaminergic neurons in the substantia nigra (Forno, 1996). The resulting affectation of the nigro-striatal pathways causes the characteristic movement alterations of the disease, such as tremor, rigidity, restless legs syndrome, bradykinesia, and postural instability (APA, 2013; Pringsheim et al., 2014). Additionally, patients with PD may show difficulties for shifting the focus of attention, and adapting to environmental changes (Rustamov et al., 2014). In the last decade, there has been increasing interest to investigate cognition-based biological markers for the early identification and progression tracking of PD, among which ERP have been included (Solís-Vivanco et al., 2009; Solís-Vivanco et al., 2011; Sharma et al., 2013).

Tsuchiya et al. (2000) showed reduced amplitudes of P3a in frontal electrodes associated with the characteristic executive function deficiencies in these patients, especially verbal fluency and cognitive flexibility. Also, in contrast with healthy participants, patients with PD did not show differences in P3a amplitude elicited early in the task versus late, probably indicating a reduced habituation to novelty in this disease. Additionally, it has been reported that these patients are characterized by an increase in MMN latencies, which may imply subtle impairments of pre-attentive phases in these patients (Ebmeier, 1992).

To date, the majority of the studies that have explored the components of the distraction potential in PD have reported them individually. Seer et al. (2016) performed an extensive review of ERP in PD and, according to these authors, only Solís-Vivanco et al. (2011 and 2015) reported all three of them. In the first of these works Solís-Vivanco et al. (2011), the authors reported changes in P3a and RON from early disease stages. In the second (Solís-Vivanco et al., 2015), these changes were analyzed with regard to disease severity and progression. In both studies, the MMN was similar among the groups, while the P3a of the patients was inversely related with progression of the disease. The authors suggested that the reduction of P3a amplitudes could be used as a marker of disease progression, given that the association was significantly maintained even after controlling by pharmacological, clinical, and demographic variables. In addition, these

Table 1
Studies investigating involuntary attention in neurologic and psychiatric disease.

Disorder	Authors	Subjects	Paradigm	MMN	P3a	RON
Parkinson's disease	Solís-Vivanco et al. (2011)	25 medicated patients 17 non-medicated patients 20 controls	Auditory duration discrimination Oddball Task	→	↓	↓
	Solís-Vivanco et al. (2015)	55 patients 24 controls	Auditory duration discrimination Oddball Task	→	↓	→
Multiple sclerosis	Jung et al. (2006)	46 patients 46 controls	Auditory passive Oddball Task	↓	↓	-
Lateral amyotrophic sclerosis	Hanagasi et al. (2002)	20 patients 13 controls	Auditory Oddball Task under passive and target detection conditions	→	↓	-
	Raggi et al. (2008)	10 patients 10 controls	3 stimulus auditory passive Oddball Task	↓	↓	-
	Volpato et al. (2016)	15 patients 15 controls	Auditory target discrimination Oddball Task	-	↓	↓
Huntington disease	Beste et al. (2008)	26 patients with motor symptoms 13 patients without motor symptoms 12 controls	Auditory duration discrimination Oddball Task	↑	→	↑
Sleep obstructive apnea syndrome	Gosselin et al. (2006)	12 patients 12 controls	Auditory duration discrimination Oddball Task	→	↓	→
Traumatic brain injury and mild head injury	Potter et al. (2001)	24 patients 24 controls	3 stimulus target discrimination auditory Oddball Task	-	→	↑
	Kaipio (2016)	11 patients 10 controls	3 stimulus auditory Oddball Task with 3 passive conditions and a visuomotor Task condition	↑	↑	-
Schizophrenia	Grzella et al. (2001)	20 patients 20 controls	Auditory passive Oddball Task	→	↓	-
	Kiang et al. (2009)	253 patients 147 controls	Auditory passive Oddball Task	↓	↓	-
	Fisher et al. (2010)	12 patients with hallucinations 12 patients without hallucinations 12 controls	vocal sounds auditory passive Oddball Task	→	↓	-
	Takahashi et al. (2012)	410 patients 247 controls	Auditory passive Oddball Task	↓	↓	-
	Rissling et al. (2012)	428 patients 258 controls	Auditory passive Oddball Task	↓	↓	↓
	Jahshan et al. (2012a, 2012b)	26 patients at risk of mental state 31 recent-onset patients 33 patients with chronic schizophrenia 28 controls	Auditory passive Oddball Task	↓	↓	↓
	Atkinson et al. (2012)	30 patients at risk of mental state 10 patients first episode psychosis 20 controls	Auditory passive Oddball Task	↓	↓	-
	Mondragón-Maya et al. (2013)	20 patients at risk of mental state 20 patients first episode psychosis 24 controls	Auditory passive Oddball Task	→	↓	-
	Rissling et al. (2013)	20 patients 20 controls	Auditory Oddball Task under passive and target detection conditions (the difficulty: high and low and the sensory modality of directed attention (visual vs. auditory)) were experimentally varied.	↓	↓	-
	Fisher et al. (2014)	10 patients with hallucinations 13 controls	3 stimulus auditory passive Oddball Task	↓	↓	-
	Solís-Vivanco et al. (2014)	20 patients at risk of mental state 20 patients first episode psychosis 23 controls	Auditory passive Oddball Task	↓	→	-
	Higuchi et al. (2014)	19 patients at risk of mental state 19 patients first episode psychosis 19 patients with chronic schizophrenia 19 controls	Auditory passive Oddball Task	↓	→	↓
	Light et al. (2015)	966 patients 824 controls	Auditory passive Oddball Task	↓	↓	-
	Atkinson et al. (2017)	102 patients at risk of mental state 61 controls	Auditory passive Oddball Task	→	→	-

(continued on next page)

Table 1 (*continued*)

Disorder	Authors	Subjects	Paradigm	MMN	P3a	RON
Bipolar disorder	Andersson et al. (2008)	25 patients 28 controls	Auditory Oddball Task under passive and target detection conditions	↓	→	-
	Paris et al. (2018)	14 patients 14 controls	3 stimulus auditory passive Oddball Task in two conditions: with emotionally spoken syllables and acoustically matched non-vocal tones.	→	↓	-
Moderate Intermittent Explosive Disorder	Koelsch (2009)	21 patients 39 controls	3 stimulus target detection auditory Oddball Task	→	↓	→
Obsessive Compulsive Disorder	Ischebeck et al. (2011)	20 patients 20 controls	Auditory passive Oddball Task in combination with an emotional recognition Visual Task	→	↑	-
Substance dependence	Polo et al. (2003)	15 patients with chronic alcoholism 17 controls	3 stimulus auditory passive Oddball Task in combination with visual Discrimination Task	→	↑	↓
	Kivisaari (2008)	23 patients with opioid dependence 18 controls	auditory passive Oddball Task	→	→	-
Depression	Chen et al. (2014)	45 first episode major depression 40 recurrent major depression 46 controls	auditory passive Oddball Task	↓	↓	-
Autism	Clery et al. (2013)	30 adults with autism 30 controls	Visual passive Oddball Task in combination with Visual Distraction Task	→	↑	-
	Fan and Cheng (2014)	20 adults with autism 20 controls	Auditory passive Oddball Task with emotional syllables and non-vocal sounds	↓	↓	-

→ same amplitude in comparison with control group, ↑ increase of amplitude in comparison with control group, ↓ decrease of amplitude in comparison with control group, - not tested

authors described that the reduction in P3a amplitudes in this clinical population was independent of age, age at onset, laterality of the predominant motor symptoms, or antiparkinsonian treatment. RON showed a smaller amplitude only in a non-medicated group in comparison with the control group, suggesting a probable dopaminergic modulation of this component (Solís-Vivanco et al., 2011). In addition, an inverse relationship was found between RON amplitude and percentage of errors, probably due to deficiencies in working memory capacity or an increase in impulsivity (Solís-Vivanco et al., 2015). Recently, this same group reported that novelty detection was already deficient in these patients from the initial stages of the disease (less than 5 years of evolution) as evidenced by the phase-linked electroencephalographic activity within the time range of the P3a (Solís-Vivanco et al., 2018).

4.2. Multiple sclerosis

Multiple sclerosis (MS) is an autoimmune, demyelinating, and degenerative disease. Its causes are unknown, although a combination of genetic, metabolic, viral, and environmental factors has been proposed (Goldenberg, 2012).

Jung et al. (2006) compared the MMN and P3a of 46 patients with MS vs. 46 control participants. The MS group showed smaller amplitudes (area under the curve) and longer latencies for both MMN and P3a. These authors concluded that MS affects not only the processes of controlled attention, as has been shown with P3b (Aminoff and Goodin, 2001; Azcarraga-Guirola et al., 2017), but also the processing of information in pre-attentional stages. A subsample of 18 patients was evaluated with neuropsychological tests and was subdivided according to whether cognitive dysfunction was present. In the subgroup of patients with cognitive impairment, the MMN amplitudes elicited were of approximately one half of that obtained in the group without impairment. In this respect, Jung et al. (2006) postulated the hypothesis that the MMN could be associated with a global cortical dysfunction rather than with an affectation restricted to the auditory cortex. Interestingly, ERP were not affected significantly by the progression of the disease nor by the structural alterations noted using magnetic resonance imaging (MRI). Thus, the MMN could provide an index of the cognitive status of these patients, independent of disease progression.

The literature reviewed above is in line with the consistent reports of attentional and executive deficiencies in MS (Kujala et al., 1995; Foong et al., 1999). This supports the hypothesis that the frontal networks that sustain attention are frequently affected in patients with MS in general, and that this in turn is reflected in the amplitudes of the MMN and P3a components.

4.3. Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis ALS is a neurodegenerative disease that affects the motor neurons of the spinal cord, brainstem, and neocortex, gradually causing motor paralysis. As in MS, in ALS, cognitive impairment has been described in at least one subpopulation of patients (Goldstein and Abrahams, 2013). However, motor affectations from early disease stages can decisively affect performance on neuropsychological tests. For this reason, it has been highlighted the need to count on evaluations that do not require a verbal or motor response, as is the case with ERP (Raggi et al., 2010).

Hanagasi et al. (2002) reported that a pattern of subclinical impairment of executive and attentional functions related with the frontal network is evident even in non-demented patients at early stages of ALS. The authors used a battery of neuropsychological tests and an oddball paradigm in both passive and active conditions to compare 20 patients to 13 paired healthy adults. While the MMN was similar in patients and controls, the P3a had reduced amplitudes and longer latencies in the clinical group, which also correlated with worse performance in the neuropsychological assessments. Due to the absence of significant differences in MMN, they discarded that this impairment could be attributable to primary vigilance or arousal failures.

Raggi et al. (2008) compared 10 patients to 10 controls performing an oddball paradigm with standard, deviant, and novel stimuli. The authors reported similar MMN amplitudes when considering the difference waveform resulting from deviant minus standard stimuli. On the other hand, the subtraction of novel minus standard stimuli showed decreased amplitudes and longer latencies in both the MMN and P3a elicited in patients. Moreover, the latencies of MMN were negatively correlated with the scores of disability and severity in patients. P3a

latencies were positively correlated with the duration of the disease.

Volpato et al. (2016) compared the N200, P300, and RON obtained from 15 ALS patients and 15 healthy participants, elicited by two types of infrequent stimuli: *relevant*, which would require a response, and *irrelevant*, which should be ignored. The authors reported that all of the components elicited in the clinical group showed reduced amplitudes and longer latencies compared to those of healthy controls. Specifically, the P300 elicited after deviant and irrelevant stimuli showed decreased amplitudes and longer latencies in the ALS patients, while the P300 that was elicited after targets was similar between the groups. The authors interpreted their findings as evidence of reduced available attentional resources derived from a specific degradation of prefrontal networks. In agreement with this, patients with ALS also obtained lower scores in tests such as the Wisconsin Card Sorting Test (WCST) and Raven's Progressive Matrices, which have been closely related with frontal lobe function (Fuster, 2001). These authors concluded that ALS exerts an impact on cognitive function, including deficiencies in auditory processing at all levels of the three-phase model, that is, from novelty detection to attentional reorientation.

While other ERP seem to be adequate to explore motor deficiencies in these patients (Raggi et al., 2010), the studies reported here support the idea that the distraction potential provides an additional sensitive tool for the assessment of cognitive change (Hanagasi et al., 2002; Raggi et al., 2008; Volpato et al., 2016).

4.4. Huntington's disease

Huntington's disease (HD) is a hereditary, progressive, and fatal disease that is characterized by motor alterations, dementia, and behavioral changes, which result from the profound degeneration of the basal ganglia and the cerebral cortex (Bear et al., 2007). At the molecular level, an overexpression of NMDA receptors has been described, and has been related to the presence of the disease's characteristic motor symptoms (Stack et al., 2007). Beste et al. (2008) explored the MMN in this population. The authors compared 26 HD patients who were carriers of the huntingtin gene (13 with motor symptoms and 13 without them) against 12 healthy participants, all with comparable educational background. Their results revealed that the HD group with motor symptoms was differentiated from the other two groups by having better execution in neuropsychological tests of attention, lower reaction times for frequent and infrequent stimuli, and a MMN with greater amplitude and shorter latency. There were no differences in the characteristics of P3a between the groups, while the group of patients with motor symptoms showed a RON with greater amplitude in central and left electrodes.

The authors discussed that in the case of HD, in contrast with other neurodegenerative diseases such as PD and Alzheimer's disease, the mismatch detection, orientation, and attentional reallocation are not affected in symptomatic patients, and also, that the laterality observed in RON could be related to an asymmetric pattern of degeneration, restricted to specific brain areas. The authors proposed that the paradoxical improvement of attention in HD patients with advanced disease could occur due to increased NMDA activity, which might enhance signal propagation within the striatum and enable more efficient mismatch detection and executive performance.

4.5. Obstructive sleep apnea syndrome

Obstructive sleep apnea syndrome (OSAS) is characterized by sleep fragmentation and frequent awakenings due to impaired breathing rhythm. Although it has commonly been treated as a respiratory disease, it can be classified as a neurological illness that is frequently comorbid to others (Broderick and Guilleminault, 2008). It has been shown that the poor quality of sleep in persons with this syndrome can affect some cognitive functions, mainly those associated with frontal areas of the brain (Naegele et al., 1998). Gosselin et al. (2006) utilized an auditory distraction paradigm to investigate involuntary attention in 12 patients with OSAS in comparison to 12 healthy participants. They reported that there were no differences between the groups in reaction times, MMN, or RON. The P3a of the group of patients showed decreased amplitudes and a non-significant tendency for greater latencies. The authors conclude that frontal regions integrity appears to be compromised in these patients, who also showed worse execution in neuropsychological tests (Beebe and Gozal, 2002).

4.6. Traumatic brain injury and mild head injury

Traumatic brain injury (TBI) is the result of the impact on the brain by an external force than can produce decrease or loss of consciousness and failures on cognitive function and/or physical capacities (Menon et al., 2010). It has been conceptualized as a disease that, in the long term, has potential neuroinflammatory consequences and increased risk of age-related cognitive decline (Tremblay et al., 2014). Deficiencies in memory, emotional regulation, self-monitoring, cognitive flexibility, planning, and social skills are commonly present (Menon et al., 2010; Levine et al., 2013).

Kaipio (2016) reported increased amplitudes in the MMN and the late portion of the P3a in these patients, which was interpreted as hyper-reactivity in the involuntary attention mechanisms and abnormal distractibility. However, on an intertrial analysis, MMN diminished drastically as the task progressed in comparison with the controls, which suggests fast vigilance decrements in TBI patients. Interestingly, this reduction was independent of abnormalities in the MRI obtained in the patient group (Hynd et al., 1991).

Other studies in which involuntary attention has been evaluated with MMN, P3a or RON separately show that the relationship between these ERP and TBI might not be so simple. As an example, Rugg et al. (1993) compared 16 patients with 16 healthy controls under an oddball paradigm that included targets and novel stimuli. The authors found a P3a with greater amplitudes and latencies in the TBI group for the novel stimuli, while no difference was found in the early processing (N2) of the relevant stimuli. After eliminating one patient with extreme values and subtracting the activity of the frequent stimuli, significant differences were only maintained for latencies. The authors concluded that orientation remained intact in the majority of patients but that, under some circumstances (e.g. increased difficulty for tone discrimination), it operated more slowly. In a recent review of ERP in TBI which include MMN and P3a, Duncan et al. (2011) postulated that in general, smaller amplitudes and/or a greater latencies of both ERP has been reported after a TBI. These authors highlighted inconsistencies among studies possibly due to the variety of methods employed and of some clinical variables, such as the localization of the insult. In support to this, it has been described that injuries in the anterior cingulum tend to produce amplitude reductions of P3a, in contrast with orbitofrontal damage, which has been associated with amplitude increments (Elting et al., 2005).

Around 80% of TBI are classified as a Mild Head Injury (MHI). Clinical symptoms and cognitive impairments are similar to those of TBI, but expressed to a lesser degree (Duncan et al., 2011). In general, the P3b component has been postulated as a sensitive measure for deficits in cortical synaptic function that follow TBI, even for MHI (Cecchi, n.d.; Dupuis et al., 2000; Witt et al., 2010). Potter et al. (2001) reported no differences in reaction times or in the characteristics of the P3a in this clinical group compared to healthy controls. However, patients showed an increased RON, which was interpreted as a greater activation of the frontal networks of attention. This "frontal over-activation" could be the result of less inhibition even from earlier processing stages, since the clinical group showed a tendency for a larger amplitude of N2. In light of this evidence, RON could be further explored to inquire about attentional deficits in this population.

5. Psychiatric disorders

5.1. Schizophrenia, first psychotic episode and subjects at risk

Schizophrenia is a psychiatric disorder characterized by the appearance of positive (e.g., delusions and hallucinations) and negative symptoms (e.g., abulia and anhedonia), that exert an impact on several cognitive functions and daily activities (Mondragón-Maya et al., 2011). One diagnostic criterion for schizophrenia is that the symptoms must be present for at least 6 months. When the symptoms manifest as attenuated or for less than 6 months, patients can be classified as at-risk or prodromal (APA, 2013). Due to its prevalence and complexity, the study of schizophrenia has established as one of its main goals, the promotion of early diagnosis based on objective neurophysiological and psychological measures (Javitt et al., 2008; Rissling and Light, 2010; Rissling et al., 2010; Takahashi et al., 2012; Higuchi et al., 2014; Solís-Vivanco et al., 2014). Specifically, ERP have been suggested as biomarkers of early detection and cognitive impairment in this disorder (Javitt et al., 2008; Roach and Mathalon, 2008; Rissling et al., 2010; Rissling et al., 2012; Light et al., 2015).

5.1.1. MMN

A reduction in frontocentral MMN amplitude has been consistently described in schizophrenia patients, especially for duration deviances (Kiang et al., 2009; Rissling and Light, 2010; Jahshan et al., 2012a; Rissling et al., 2012; Takahashi et al., 2012; Rissling et al., 2013; Higuchi et al., 2014). It has been reported that antipsychotic drugs do not affect consistently this ERP; thus, it has been proposed as a biological marker of the disease (Korostenskaja et al., 2005; Umbricht and Krljes, 2005; Rissling et al., 2012).

In a study with 253 patients and 147 healthy controls with an age range of 18–65 years, Kiang et al. (2009) reported that while there was an overall reduction of MMN amplitudes in patients, MMN amplitudes declined as a function of age in both patients and controls. These decrements were manifested slightly less steeply in patients. These authors proposed that the observed pattern might represent an early disease-related deterioration of MMN, with a subsequent decline product of normal aging.

The amplitude reductions of this component are evident even from at-risk phases and have been associated with the probability of transitioning to schizophrenia approximately 2 years before fulfilling the criteria for diagnosis (Atkinson et al., 2012; Jahshan et al., 2012a; Shaikh et al., 2012; Higuchi et al., 2014). Furthermore, it has been proposed that a reduced MMN could reliably indicate an increased risk of conversion to schizophrenia rather than the presence of a single psychotic episode. Higuchi et al. (2014) reported that, after following up patients at risk for 2.2 years, those who converted to schizophrenia presented, from the onset, smaller MMN amplitudes. In contrast, those who did not convert were not differentiated from healthy participants similar in gender and age. In contrast, there are also studies that have failed to find a significant reduction of MMN in subjects at risk, with a first psychotic episode, and even with diagnosis of schizophrenia in comparison to healthy subjects (Grzella et al., 2001; Fisher et al., 2010; Mondragón-Maya et al., 2013; Atkinson et al., 2017).

Takahashi et al. (2012) analyzed MMN and P3a generator sources through exact Low Resolution Electromagnetic Tomography Analyses (eLORETA) in a sample of 410 patients with schizophrenia in comparison to 247 controls. The authors described smaller amplitudes of MMN and P3a in patients, while the analysis of neural sources revealed similar distributions between patients and controls. The main MMN generators in the control group were found bilaterally in the precentral gyrus, and in the superior temporal gyrus, the medial frontal gyrus, the paracentral lobule, the cingulate gyrus, the superior temporal gyrus, and maximally in the left upper frontal gyrus. The clinical group was characterized by a reduction in the current density of MMN in the right medial frontal gyrus, the right cingulate gyrus, and in the right paracentral lobule, with maximal differences in the medial frontal gyrus as compared to the control group.

Fujiwara et al. (2007) reported a smaller volume of the cingulate cortex, as well as abnormalities in the morphology of the grey and white matter in schizophrenia, which were related to less ability in social cognition and less ability to recognize emotions. In line with this background, Takahashi et al. (2012) proposed that the discrepancies found in MMN amplitudes, as well as in its generating sources, could reflect the onset of a cascade of deficiencies, ranging from the detection of novelty to high-order attentional operations in these patients. Likewise, Solís-Vivanco et al. (2014) found differences in the topographic distribution of MMN, in which both at-risk patients and those with a first psychotic episode, showed asymmetries in MMN, with smaller amplitudes in left and central regions as compared to the control group. These authors suggested that this effect could continue throughout the progression of the disease, given that structural abnormalities have been reported in the left temporal lobule, including the transversal temporal gyrus (the Heschl gyrus) in subjects with a first psychotic episode and in patients with chronic schizophrenia (Kasai et al., 2003; Salisbury et al., 2007; Rasser et al., 2009). A similar reduction in amplitudes has been observed in patients with depression and those within the bipolar spectrum. Nevertheless, patients with schizophrenia are distinguished by an additional reduction at temporal electrode sites as well as stronger neuropsychological impairment (Kaur et al., 2011b; Jahshan et al., 2012b).

With respect to MMN latencies, it has been proposed that the basic processes of detection could be slower in patients with schizophrenia even at early stages (Shin et al., 2009). Using an oddball paradigm with novel sounds, Fisher et al. (2014) reported that patients experiencing auditory hallucinations showed decreased amplitudes and increased latencies of MMN. They concluded that MMN is a functionally relevant index of altered auditory processing in schizophrenia that might reflect reduced cortical resources available to process incoming auditory stimuli. Also, these results support the hypothesis that the auditory cortices of patients with persistent auditory hallucinations are "tuned" to preferentially process internally generated auditory signals (such as auditory hallucinations) at the expense of external auditory processing (Ford et al., 2008). However, some of the reviewed studies obtained just tendencies toward greater latencies of MMN for duration deviants, without significant differences between patients and healthy controls (Grzella et al., 2001; Kiang et al., 2009; Fisher et al., 2010; Kaur et al., 2011a; Atkinson et al., 2012; Jahshan et al., 2012a; Rissling et al., 2012; Takahashi et al., 2012; Mondragón-Maya et al., 2013; Rissling et al., 2013; Fisher et al., 2014; Higuchi et al., 2014; Solís-Vivanco et al., 2014; Atkinson et al., 2017).

Some studies have explored additive clinical effects of substance use in these patients. In the case of marijuana, it has been reported that its consumption in subjects at risk for psychosis leads to longer MMN latencies as compared to subjects at risk and controls who were not consumers (Pesa et al., 2012). Additionally, Dulude (2008) compared a group of patients with schizophrenia against a control group, who were not significantly differentiated in terms of demographic characteristics or on tobacco –consumption. The group of patients was evaluated after nicotine was administered by means of chewing gum or after consuming a placebo, while the control group was only evaluated during a 3-h abstinence period. Utilizing a passive auditory distraction paradigm and two visual number- and letter-recognition paradigms with distractor sounds, it was reported that the MMN of the patients after administration of the placebo was smaller in amplitude on average than that of the control group. This effect was not present in the nicotine-administration condition. These results support the hypothesis that nicotine, under certain conditions and at certain doses, can improve involuntary attention in patients with schizophrenia. However, more studies with proper controls groups that replicate these results are necessary.

In addition to the proposal that MMN might be used as a biomarker

of conversion to psychosis, this ERP has been tested regarding its sensibility to disease severity and daily functioning. Higuchi et al. (2014) found a negative association between the Index of Attention Disorder score measured by the Scale of the Assessment of Negative Symptoms (SANS) (Andreasen, 1990) and the amplitude of MMN at frontal electrodes. In patients with psychotic symptoms (schizoaffective disorder, schizophreniform disorder, bipolar disorder and major depressive disorder) a reduced MMN at temporal electrodes and the presence of positive symptoms appear to have important links to higher-order cognitive and psychosocial functioning (Hermens et al., 2010; Kaur et al., 2011a; Kaur et al., 2011b; Jahshan et al., 2012b; Kaur et al., 2012). Additionally, a recent inter-site study that compared 824 healthy controls to 966 patients with schizophrenia (Light et al., 2015) reported that MMN deficits predicted worse cognitive and social function in patients. The authors highlighted that the effect of MMN amplitudes reduction was comparable in magnitude across laboratories. Nevertheless, in the case of subjects-at-risk, some studies agree that the positive and negative symptoms are not directly related with MMN amplitudes or latencies (Atkinson et al., 2012; Solís-Vivanco et al., 2014; Atkinson et al., 2017).

5.1.2. P3a

In patients with schizophrenia and at-risk patients, it has been described that the P3a component shows deficiencies that could be associated with anatomic and functional changes at frontal regions (Grzella et al., 2001; Kiang et al., 2009; Kaur et al., 2011a; Takahashi et al., 2012; Mondragón-Maya et al., 2013; Rissling et al., 2013; Fisher et al., 2014; Light et al., 2015). Kiang et al. (2009) reported a reduction in the amplitudes of P3a in a sample of 253 schizophrenia patients aged between 18 and 65 years. In agreement with this, Takahashi et al. (2012) reported smaller P3a amplitudes at frontal and parietal areas in a sample of 410 chronic patients in comparison with 247 controls. These authors propose that the observed reductions might be due to anatomic differences in the anterior-posterior cingulate and medial frontal gyri, given their role for novelty detection and attentional orientation. However, their study does not answer whether it is the onset of the disease that promotes the reduction in P3a amplitude, or whether this reduction is present at premorbid stages. Mondragón-Maya et al. (2013) reported that the reduction in P3a could be present years before meeting schizophrenia diagnostic criteria, given that patients with a first psychotic episode and at-risk subjects exhibited smaller P3a amplitudes at right regions during a passive oddball paradigm.

Overall, the results regarding changes in the P3a component in schizophrenia are not so straightforward. Atkinson et al. (2012) showed evidence of reduced P3a amplitudes at prodromic phases but just a tendency for reductions during the first psychotic episode. In a subsequent study with a bigger sample size, they did not find changes in this component even at prodromal states (Atkinson et al., 2017). Similarly, Higuchi et al. (2014) failed to find differences after comparing at-risk subjects, patients with a first psychotic episode, and patients with chronic schizophrenia. Given the different results for MMN and P3a in schizophrenia, Takahashi et al. (2012) suggested to explore the generator sources of each component and its association with some of the anatomic regions usually affected in the disease, such as the auditory cortex, the inferior and medial frontal gyri, and the anterior cingulate cortex. In addition, Rissling et al. (2013) argue that due to the importance of identifying biomarkers that are sensitive to cognitive systems in schizophrenia patients, it is pertinent to challenge the malleability of MMN and/or P3a under different experimental conditions. The main question of their study was whether directed attention can improve pre-attentive function in schizophrenia patients, even if deficient at baseline. They evaluated 20 patients with schizophrenia and 20 healthy paired participants. All participants underwent 4 EEG recordings where attentional demand (low vs. high) and modality (visual, auditory) of directed attention were experimentally manipulated. Consistent with other studies, they found reduced MMN and P3a amplitudes in the group of patients in comparison to the control group. P3a responses were larger in the high attentional demand conditions, with no group by demand interaction. Amplitudes obtained for both MMN and P3a were larger when attention was directed to the auditory vs. visual modality, with no group by modality interaction. They also found high correlations between P3a amplitude deficits with both positive symptoms and psychosocial functioning in the schizophrenia group. The authors suggested that changes in early automatic sensory processes are strongly associated with selective attention and may therefore serve as a gateway to higher cognitive and psychosocial functioning.

Some variables that could affect attentional orientation in schizophrenia are the presence of hallucinations, in which the P3a amplitude is further reduced (Fisher et al., 2010; Fisher et al., 2014), or the consumption of marijuana, in which the P3a peak is delayed in comparison to non-consuming patients and healthy participants (Pesa et al., 2012). For the latter results, the authors propose that this effect might arise from early processing, given that the latencies of both the P3a and the MMN showed a positive correlation with years of consumption.

P3a latency in schizophrenia has yielded contrasting results. Besides the study by Pesa et al. (2012), Grzella et al. (2001) found a delayed P3a in a group of 20 patients with schizophrenia compared to 21 healthy controls. In contrast with these results, several authors agree that the latency of P3a does not undergo changes in patients with schizophrenia, including prodromal stages (Kiang et al., 2009; Fisher et al., 2010; Atkinson et al., 2012; Jahshan et al., 2012a; Rissling et al., 2012; Takahashi et al., 2012; Mondragón-Maya et al., 2013; Fisher et al., 2014; Higuchi et al., 2014; Solís-Vivanco et al., 2014; Light et al., 2015; Atkinson et al., 2017). Furthermore, there is no evidence to our knowledge regarding a difference in latency between patients with schizophrenia and patients with bipolar or affective disorders, with which they share symptomatology and genetic vulnerability (Kaur et al., 2011a; Jahshan et al., 2012b; Kaur et al., 2012).

Many studies have sought a relationship between the characteristics of P3a (amplitude and latency) and distinctive symptoms of schizophrenia. Reductions of P3a amplitudes have been associated with earlier ages of illness onset and worse psychosocial functional status (Light et al., 2015). In contrast, there are studies that have failed to find a relation between P3a and scales of positive and negative symptoms in schizophrenia (Kaur et al., 2011a; Pesa et al., 2012; Higuchi et al., 2014). These discrepancies could be the result of inclusion criteria utilized in each study (Mondragón-Maya et al., 2013). From a longitudinal study in which there were no differences in the latencies of MMN or P3a between at-risk patients and controls, Atkinson et al. (2017) concluded that the electrophysiological components held no relation to the neuropsychological variables. These authors propose that the subjective report is a better instrument for predicting the probability of converting to schizophrenia; however, as the authors note, their sample size was rather small, and their study is statistically underpowered.

It should be noted that while reductions in P3a amplitudes can also be observed in other pathologies such as BD, patients with schizophrenia are differentiated by a greater reduction in the amplitude of this component at frontal and central electrode recording sites (Kaur et al., 2011a; Jahshan et al., 2012b; Kaur et al., 2012).

5.1.3. RON

There are only three studies, to our knowledge, that have reported the effects of RON on schizophrenia using auditory oddball paradigms. First, Jahshan et al. (2012a) explored differences in the three components of the distraction potential along the course of the illness by comparing groups of patients who were at risk, with a recent diagnosis, or with chronic schizophrenia. Interestingly, only the patients with chronic schizophrenia were differentiated from the other groups based on a reduction in RON amplitude. The authors proposed that RON expresses changes until schizophrenia becomes chronic. Therefore, this

component could be understood as a marker of disease progression.

In a study with 428 patients and 285 healthy controls, Rissling et al. (2012) reported a reduction of the amplitudes of the three components in patients. Although the topographic distribution was similar between the groups, the amplitude reductions in the patients were specific to frontocentral electrodes. Importantly, while the type of antipsychotic drug was a modulator of MMN and P3a amplitudes at frontal electrodes, this was not the case for RON. Additionally, age-at-onset of schizophrenia and the number of hospitalizations were not good predictors of the amplitude of this ERP. Higuchi et al. (2014) also reported that RON amplitudes were significantly affected in a group with a first psychotic episode and in another group with chronic schizophrenia at frontal regions (Fz and F4), further supporting RON's potential value for the diagnosis and follow-up of the disease. None of the three studies mentioned above found any differences in RON latencies (Jahshan et al., 2012a; Rissling et al., 2012; Higuchi et al., 2014).

Regarding the relationship to the symptoms, Higuchi et al. (2014) found a correlation between the severity of aberrant formal thought (e.g. disorganized language, lack of logic, delirium, and incoherence), measured by the Scale of Assessment of Positive Symptoms (SAPS) (Andreasen, 1990) and the reduction of RON amplitudes at frontal recording sites. The authors proposed that RON could also be used as a marker of the progression of cognitive disturbances in patients with schizophrenia.

Whether the components of the triphasic model of distraction form a dependent response chain or whether they are dissociated has been challenged in healthy adults (Horváth et al., 2008b) as well as in schizophrenia (Atkinson et al., 2012). Rissling et al. (2012) concluded that, contrary to the cascade models in which deficiencies in early processing affect high-order processing, each of these processes contribute independently to the cognitive and social deficiencies that are present in schizophrenia. Consequently, it is crucial to further explore the relationship among each of the three components and the neurocognitive deficits that characterize this pathology.

In sum, reductions of MMN amplitude can be seen as a marker of risk for developing schizophrenia, including an association between its amplitude and the cognitive and social deficits that are characteristic of the disease. The impact of the deficiencies of MMN on the later high-order processes remains under debate. P3a findings in schizophrenia are varied, and the results could be modulated by the comorbidity with other clinical entities and severity of the symptoms, such as hallucinations and marijuana consumption, which are not present in all patients. P3a is not sensitive to changes from prodromal stages, as in the case of MMN, and it has been suggested that the reduction of its amplitude is a result of a cascade effect that occurs once the MMN is affected and the disease has been established. However, differences have been found in the RON without changes in the preceding ERP, for which it has been suggested that the changes in each component may be independent from each other and could represent diverse deficits in neuronal communication. Two of the three studies that, to our knowledge, analyze the distraction potential, confirmed that the amplitude reduction of the RON is related to symptoms of chronic schizophrenia. For this reason, this component could be useful as a marker informing clinical follow-up.

5.2. Bipolar disorder

Bipolar Disorder (BD) is an affective disorder with two variations: while BD type I is characterized by marked periods of extreme mania and can also include depression, the BD type II is distinguished by hypomania (a less severe mania) and is accompanied with episodes of severe depression; both types alternate with symptom-free periods of euthymia (APA, 2013). BD usually shows deficiencies in a broad range of cognitive functions including verbal memory, sustained attention, and executive function (Andersson et al., 2008). Studies using twins have shown that this disorder constitutes a highly heritable entity, and imaging studies have showed that this pathology is related with metabolic and neuroanatomic changes (APA, 2013). The bipolar spectrum shares symptomatology with schizophrenia, including attentional deficiencies. For this reason, ERP have also been explored as markers of predisposition, progression, and differential diagnosis (Kaur et al., 2011a). Although research with ERP in BD is scarce, it has been suggested that the type of medication has no impact on MMN and P3a, therefore this technique is able to exhibit deficiencies in the processing of attention in spite of other clinical variables (Andersson et al., 2008).

5.2.1. MMN

Andersson et al. (2008) compared 25 patients with BD II with 28 healthy controls; they reported that the group of patients showed difficulties in the detection of novelty from preattentional stages as evidenced by smaller amplitudes and an increased MMN latency. Paris et al. (2018) suggested that the decreased ability to detect changes in auditory stimuli and to recognize emotions that are present in BD should be evident in the ERP. By means of an oddball paradigm that included syllables and tones denoting emotions, they compared a group of 14 patients with BD I and II (7 of each one) with 14 healthy paired controls. Contrary to their hypothesis and to other studies that included patients with BD (Kaur et al., 2011a; Jahshan et al., 2012b; Kaur et al., 2012), the MMN of the BD group was similar in amplitude to the healthy subjects. This suggests that the neural mechanisms underlying the initial change detection in emotional speech prosody is unimpaired. However, in the BD group the MMN was delayed in latency. This delay was present equally in both the vocal and non-vocal conditions. The authors propose that this could be a reflection of global auditory change detection deficits instead of a specific impairment for emotional prosody.

5.2.2. P3a

Andersson et al. (2008) did not describe any differences in the amplitudes or latencies of P3a between patients and healthy participants. In contrast, Jahshan et al. (2012b) explored a bigger sample of patients with BD and schizophrenia. They found reduced P3a amplitudes in the patients with BD (in comparison to healthy subjects), suggesting an impaired covert orienting response or an inability to shift attention to meaningful auditory stimuli. Moreover, Paris et al. (2018) did not find changes in a non-vocal condition, but the BD group presented reduced amplitudes in P3a obtained from vocal emotional syllables. These results have clinical implications, since the emotional cues may not be recognized to be salient by individuals with BD, resulting in fewer attentional resources allocation to further processing of this type of information. This may contribute to the poor interpersonal outcomes typically observed in these patients.

To our knowledge, there are no studies that have explored RON in BD. Future research assessing the relationship of the distraction potential in this disorder with clinical symptoms, higher-order cognitive processes, and social functioning are especially needed to clarify its boundaries with schizophrenia (Andersson et al., 2008; Kaur et al., 2011a; Jahshan et al., 2012b; Kaur et al., 2012).

5.3. Moderate Intermittent Explosive Disorder

Patients with Intermittent Explosive Disorder (IED) are characterized by impulsivity, drastic mood changes, and behavioral disinhibition. These symptoms are not explained by another mental disorder nor as a consequence of the physiological effects of substance use or general medical conditions. IED is one of the two unique disorders in the DSM-V that are focused on the presence of anger and aggressiveness. When episodes of aggressiveness affect health, social life, or work life but are not judicially relevant (e.g., door slamming, shouting, or throwing things), it is diagnosed as moderate Intermittent Explosive Disorder (mIED) (APA, 2013). Inhibition –like attention– is thought to be mediated by the prefrontal cortex; thus, it has been proposed that

changes could be observed in ERP during involuntary attentional paradigms in these patients (Fuster, 2001; Jung et al., 2006; Koelsch, 2009).

Following the hypothesis that the disinhibition present in these patients proceeds from very early stages of the sensory processing of novelty, Koelsch (2009) expected that the MMN amplitudes would be of greater magnitude in patients with mIED; however, the amplitudes and latencies were of similar magnitudes between patients and healthy controls. In contrast, the author reported smaller P3a amplitudes in the group with mIED. Additionally, the P3a was not observed in 25% of the patients. Even after exclusion of these patients from the analysis, the results remained statistically significant. Similar amplitude reductions have been found in other samples with impulsivity, or with additional cocaine or alcohol use (Biggins et al., 1997).

Koelsch (2009) suggests that there is a link between the mechanisms related to impulsivity and those related to involuntary attentional orientation, but not for those related to automatic change detection (MMN) or voluntary attention (measured with P3b). This assertion assumes that the P3a reflects frontal (executive) activity, while MMN derives mainly from temporal areas. However, it is noteworthy that other authors have found an association between impulsivity traits (measured by self-report scales and motor-response inhibition) and reduced MMN amplitudes (Franken et al., 2005). To clarify this association, future research might explore mIED not only with involuntary attentional tasks, but also with others involving inhibition, such as Go/noGo paradigms, from which ERP can also be obtained (Falkenstein et al., 1995). To our knowledge, there are no studies studying RON in mIED.

5.4. Obsessive Compulsive Disorder (OCD)

Obsessive Compulsive Disorder (OCD) is an anxiety disorder characterized by intrusive and obsessive thoughts and compulsions, which are defined by repetitive behaviors or rituals (APA, 2013). In these pathologic anxiety states, hyperactivity is observed in areas such as the orbitofrontal cortex, the cingulate cortex, and fronto-striatal networks as shown by neuroimaging (Graybiel and Rauch, 2000). These same regions have also been associated with involuntary attentional orientation (Polich, 2007). Ischebeck et al. (2011) explored ERP for frequent, infrequent, and novel sounds during a visual recognition task in two conditions: a threat context and a neutral context. While the elicited MMN did not show any differences between the groups (20 patients with OCD and 20 healthy controls), OCD patients showed increased P3a amplitudes that were modulated by the effect of novelty, but not context. The differences did not have a relation with the type of drug or with affective state. The authors suggested that the findings of this study can serve to modify behavioral therapies used for these patients, directly treating their hypersensitivity to novel stimulation. The RON was not analyzed in this study, however, it would be desirable to explore the reorientation process and whether habituation to novel stimuli is deficient in this population.

5.5. Substance abuse and dependence

The DSM-V criteria for diagnosing substance dependence are related with the duration and frequency of consumption, tolerance to the substance, the adverse effects that occur when consumption is stopped, withdrawal from daily life activities, as well as the consequent social, physical, and legal problems (APA, 2013). These criteria have been widely discussed for diagnosing, treating, and investigating substance dependence as a unitary illness (Hasin et al., 2012; Hasin et al., 2013), and it has been proposed that it is necessary to include biomarkers for this set of disorders. However, the latter has not been achieved, due among other factors, to the complexity of differentiating these patients in terms of anatomic changes and brain function, and to the differential effects produced by each substance. There are a few studies on substance dependence that analyze the distraction potential with auditory paradigms. However, there are more publications that investigate the attentional effect of substance consumption in healthy subjects without abuse or dependence (Kähkönen et al., 2005; Gabbay et al., 2010; Knott et al., 2011; Mathalon et al., 2014). In consonance with the purpose of this review, consumption in healthy adults will be not described. However, the results of those studies indicate that both the use and dependence to substances is related with attentional deficiencies and changes in ERP.

5.5.1. MMN

Polo et al. (2003) analyzed a sample of adults aged between 25 and 56 years with 12-years alcoholism on average. They confirmed, as did other similar studies (Pekkonen et al., 1998; Polo et al., 1999; Grau et al., 2001), that the mechanisms of change detection reflected by the MMN are not impaired in this disease. MMN with longer latencies were observed in a visual task with auditory distractors in opium-dependent patients (Kivisaari, 2008). This effect may reflect changes in dopaminergic and GABAergic regulation in frontal areas.

5.5.2. P3a

In contrast with MMN, P3a appears to be vulnerable to the abuse of and dependence on specific substances. Alcoholism has been characterized by a P3a of greater amplitudes at prefrontal areas (Polo et al., 2003). This enhancement might represent a greater attentional allocation to novel stimuli, resulting in more distraction than that of healthy subjects. In opium-dependent patients, longer P3a latencies were found. This result was associated with fronto-temporal atrophy as confirmed by MRI and with poorer performance in tests measuring attention, executive function and fluid intelligence (Kivisaari, 2008).

5.5.3. RON

In patients with chronic alcoholism, a posterior parietal positive deflection has been observed instead of RON (Polo et al., 2003). The authors clarify that, although they were not able to identify RON in these patients, the performance accuracy and reaction times were similar to those of the control group, meaning that the process of reorientation is not necessarily abolished. Polo et al. (2003) suggested that the positivity observed in the group with alcoholism is similar to the $P3_2$ described in healthy adults by Friedman et al. (1993). $P3_2$ is a parietal positivity between 500 and 600 ms that is attributed to a more in-depth processing of the stimuli that, despite the irrelevance of the latter, attract the attention of the participants. Polo et al. (2003) suggest that, due to the similarities between the latency and topographic distribution of the positivity found in the group of patients with alcoholism and the study of Friedman et al. (1993), both responses could reflect a common neural process.

5.6. Depression

According to the World Health Organization (WHO), depression is the most common affective disorder at the worldwide level (WHO, 2017). It is characterized by a prolonged feeling or emotional state of suffering that, in the majority of cases, is not linked with an obvious external cause (APA, 2013). Symptoms include lack of appetite, insomnia, feelings of uselessness and guilt, thoughts of death, and a diminished ability to concentrate (Bear et al., 2007).

In the majority of the studies on depression using ERP, the P3a has been explored separately, and to a lesser extent, the MMN. In a review on ERP in depression, Bruder et al. (2012) suggested that it is necessary to separate subcomponents (such as the P3a of the P300 and the MMN of the N1) in order to acquire a better understanding of the impact of the pathology along specific phases of cognitive processing.

To our knowledge, there is one study that reported two of the three phases of the distraction potential (MMN and P3a) using an auditory paradigm in adults. Chen et al. (2014) studied 45 patients with First

Episode of Major Depression (FMD), 40 with Recurrent Major Depression (RMD) and 46 healthy controls. Their results are summarized below.

5.6.1. MMN

Both groups of patients (RMD and FMD) presented smaller MMN amplitudes compared to the control group, while the latencies were similar among the three groups. Other studies had also previously reported that depression can affect the processes of automatic deviance detection (Takei et al., 2009; Naismith et al., 2012; Qiao et al., 2013). Chen et al. (2014) proposed that these results could be explained by deficiencies in the prediction of incoming auditory information at the preconscious level, which later affects the online updating of the schema established by the frequent stimuli. It must be noted that no MMN differences were found between the clinical groups, so recurrence did not show to have an additive effect of mismatch detection. In addition, the amplitude reduction was not associated with the severity of the depression measured by the Hamilton Depression Rating Scale (Hamilton, 1960). Thus, the authors proposed that MMN could be a marker for the diagnosis of the onset of depression.

5.6.2. P3a

Both groups of patients with depression showed lower P3a amplitudes and longer latencies at frontocentral electrodes compared to the control group. Also, the RMD group showed even smaller amplitudes and greater latencies than the FMD group. The severity of the depression measured by the Hamilton scale (Hamilton, 1960) was correlated with decrease in amplitude of the P3a in both groups. Additionally, in the RMD group, the reductions in amplitude and the increases in latency of the P3a were related to the number of previous depressive episodes. Thus, while MMN could be a marker of illness onset, P3a might be a useful index of recurrence. Chen et al. (2014) mentioned that one of the major disadvantages of their study was that the effect of the drug on the ERP of the patients is unable to be discarded, and given that it has been reported that antidepressants can influence the amplitude of the P3a (Luck, 2005) their results are to be taken with caution.

Although patients with depression could have deficiencies in focalization and attentional reorientation, more studies are necessary to demonstrate this more clearly. In their review on different ERP in patients with depression, Bruder et al. (2012) emphasize that, despite the fact that auditory distraction paradigms from which MMN and P3a are obtained are of great value for understanding the cognitive alterations associated with depression, studies on this area are too few and have used small samples. Thus, future studies using ERP should inquire into how components are modulated by heterogeneity among patients, related neurotransmission systems, and treatment response, among other variables.

To our knowledge, there are no studies that report RON in adults with depression. Nevertheless, Lepistö et al. (2004) explored a sample of children with mayor depression and described MMN, P3a, and a Late Discriminative Negativity (LDN), which was delayed compared with the control group. LDN is registered within the time range of RON; however, its role with respect to attention in adults has not been yet defined. Studies using MRI reported that the severity of the symptoms of patients with mild states of depression is related to a decrease in connectivity of the resting state in areas such as the dorsolateral prefrontal cortex and the temporoparietal junction (Hwang et al., 2015). These areas have been related to the reorientation system (Corbetta et al., 2008). For this reason, future studies should consider the use of oddball paradigms to explore attentional reorientation in depression.

5.7. Autism

Autism is described as a spectrum of neurodevelopmental disorders with three core diagnostic features: impaired social interaction, impaired verbal and nonverbal communication, and restricted or circumscribed interests with stereotyped behaviors (Amaral et al., 2011). It has been argued that similar to ADHD, autism is characterized by reduced maturation of prefrontal cortex circuitry that could underlie the inability to react adequately to the affective expressions of others (Fuster, 2001).

Neuroimaging studies have shown the activation of the prefrontal dorsolateral cortex of healthy subjects in attention and working memory tasks as well in tasks of mentalization or theory of mind. In turn, autistic patients present a lesser degree of prefrontal activation in these tasks and in others in which the integrity of the frontal lobules is evaluated (e.g., Wisconsin Card Sorting Test, verbal fluidity, and Go-noGo) as compared to control groups (Shallice, 2001). Currently there are no known diagnostic biological markers and diagnosis is still based solely on behavioral criteria (Kandel et al., 2000).

Clery et al. (2013) found a non-significant tendency of the MMN to be reduced in amplitude and the P3a to be increased after the onset of infrequent (tone deviant) rather than novel stimuli (environmental sounds) in adults with autism (aged 18–30 years). In contrast, the P3a was elicited with greater amplitudes when faced with novel rather than infrequent stimuli in healthy controls. Based on this and other studies, the authors suggested that attentional orientation toward deviations of low magnitude could contribute to the typically observed intolerance to change in these patients (Happé and Frith, 2006).

Fan and Cheng (2014) proposed that in autism, deficiencies are expressed at both the sensory and social levels. Similar to faces, voices express important information that patients with autism may not process efficiently. These authors compared 20 patients (aged between 18 and 29 years) with a diagnosis of autistic spectrum to 20 matched healthy controls using a passive auditory oddball paradigm involving emotionally spoken syllables, either happy or angry, that deviated from an otherwise neutral speech sound. A second condition involved acoustically matched non-vocal sounds. The group of patients exhibited smaller MMN amplitudes for both vocal and non-vocal types of stimuli, without interactions between the group and the type of deviation. Furthermore, smaller amplitudes of MMN obtained from angry syllable deviants were related to a greater index of autistic symptoms on the *Autism Spectrum Quotient* scale in the patient group (Baron-Cohen et al., 2001). Thus, the authors proposed the exploration of the MMN as a marker of severity. Moreover, a P3a component was also reported for emotional syllable deviants in both groups, but not for non-vocal sounds. Patients exhibited smaller amplitudes of P3a obtained from angry syllable deviants in comparison to the control group. This result was interpreted as a consequence of less attentional orientation to salient emotional events. It has been reported that attention is more easily oriented toward stimuli that implicate threat (Pratto and John, 1991); thus, the observed lower amplitudes for MMN and P3a in these patients could imply that deficiencies in the processing of emotional stimuli could occur even from early or automatic sensory processing stages. The previously mentioned studies demonstrate that involuntary attention is modified in patients with autism; however, future studies are necessary to explore the relationship between deficits at the sensory level and their interaction with the emotional factor. This can be implemented by means of auditory distractors, such as syllables that are emotional in tone (as in the study of Fan and Cheng), aversive everyday sounds, and harmonic and non-harmonic musical sequences (Koelsch et al., 2005).

6. Conclusions

The objective of this review was to explore the three phases of involuntary attention in different neurological and psychiatric pathologies. With this information, we report the usefulness of corresponding ERP as indicators of cognitive failures along the evolution of the disease, their association with symptomatology, the comorbid variables that can be their modulators, and their viability as biomarkers. The ERP

comprise a technique with many advantages, including ease-of-extraction, low cost, and optimal temporal resolution. In addition, ERP as a tool in cognitive neuroscience facilitates the investigation of clinical populations, diminishing bias due to learning and the evaluator's subjectivity for interpretation of the corresponding cognitive failures, in addition to allowing comparisons and correlations with the pathologies' own symptoms.

Given the frequency with which attention is affected in different neurological and psychiatric groups (Mirsky, 1987; Naatanen et al., 2011), various studies have explored the different components of the distraction potential in these populations, although in a separate manner in the majority of the cases.

The distraction potential has shown sensitivity to premorbid phases in some illnesses, as in the case of MMN in patients at risk for psychosis and has allowed to differentiate among pathologies that share symptoms, such as bipolar disorder and schizophrenia. Similarly, this ERP complex could serve in a complementary manner the follow-up of some disorders due to its sensitivity to severity and evolution in Parkinson's disease (reduction of P3a amplitude), psychosis (reduction of RON amplitude) and autism (reduction of MMN amplitude); to the number of episodes in depression (reduction of P3a amplitude); and to cognitive dysfunction in schizophrenia (reduction of RON amplitude) and multiple sclerosis (reduction of MMN amplitude). Interestingly, the features of each ERP have been also linked with the phenomenology of each pathology; for example, an increase in subjective distraction with an increased P3a in alcoholism, or impulsivity with RON amplitude and latency in Parkinson's disease.

The changes in this ERP complex have also permitted to establish the additive effects of other comorbidities, such as the effects of marijuana in patients with schizophrenia. On the other hand, these ERP could also serve as a source of information with respect to psychosocial functioning (MMN and P3a in psychosis). It is important to emphasize that several of the studies reported here emphasize the need to include ERP in the clinical and cognitive evaluation of some illnesses, given that, from a hierarchical point of view, it is important to analyze involuntary attention to understand and provide a prognosis on more complex cognitive functions.

One of the major challenges for ERP to be used as biomarkers includes the exclusion of the effects of other individual factors, such as age of the participants, duration of the disease, and drugs administered. This would promote replicability and generalization of the findings among studies. Various authors (Polo et al., 2003; Lepistö et al., 2004; Duncan et al., 2011; Bruder et al., 2012; Seer et al., 2016) agree in that the differences among paradigms comprise a difficulty at the time of comparing results and elaborating conclusions.

We suggest that the RON should be explored in greater depth. Although this ERP has allowed for the establishment of more structured hypotheses on the dynamics of involuntary attention, it also represents the least investigated component in different neurological and psychiatric pathologies.

Finally, the high frequency with which the involuntary attention is affected in neurological and psychiatric pathologies highlights the importance of this function within the clinical context. Moreover, given the similarities among the alterations of these ERP in different pathologies, it is important to situate the changes in amplitude, latency, and topographic distribution within the specific context of each disease and their relationship with the symptoms. Thus, an amplitude similar to or greater than that of the healthy subjects in components such as MMN and P3a could be due to processes of compensation (e.g., Huntington's disease) or to underlying structural changes (e.g., Traumatic brain injury), even when, in both cases, the physiological basis of these processes is of pathological nature.

6.1. Points to highlight

6.1.1. Limitations

Differences between paradigms create distinct evaluation conditions that have increased the variability of conclusions among authors and, in the majority of the studies, the distraction potential (MMN-P3a-RON) is not explored in its three phases. Furthermore, the high variability typically found across participants when extracting electrophysiological measures in hand with the small samples typically used make it hard to generalize findings across studies. We tried to overcome this difficulty by including at least 2 of the 3 components, which allowed us to relate them in a more coherent way.

Also, the absence of differences at behavioral level between participants with pathology and controls in some studies does not allow to clearly identify the functional role of the ERP, even when significant differences are found between groups. In this situation, the involvement of compensatory mechanisms for effective behavior, as in the case of alcoholism, should be considered.

In cases where a great part of the sample does not show some of the components of the distraction potential, such as RON in alcoholism, it is difficult to assert any conclusive arguments.

6.1.2. Highlights

It is important to conduct more investigation on the sources of each ERP of the distraction potential, as well as its functional role, especially in the case of RON.

The different components of the distraction potential have been proposed as biomarkers (especially MMN and P3a). However, studies with larger sample sizes are required to associate this ERP with clinical symptomatology. Additionally, studies that explore not only the sensitivity, but also the specificity of each component for each disease compared to similar pathologies are needed (i.e. Parkinson's disease versus other parkinsonian disorders).

As a final summary, the MMN has been proposed with greatest frequency as a biomarker of risk for psychosis. P3a has been proposed as a marker of frontal and striatal dysfunction, and it exhibits sensitivity to the presence of neurological and psychiatric pathology in general. Finally, RON has been scarcely explored, even though it has been postulated as a marker of the integrity of frontal areas and high-order functions. Nevertheless, the functional role for this ERP is still to be fully understood in healthy subjects as well as in patients.

Finally, there is a need to delve deeper into the degree of association between these ERP and the rest of the cognitive functions. In general, these ERP could be a reliable index of: a) anatomic and functional changes linked with the detection of changes in attentional networks, and b) markers of risk, severity, and evolution of some neurological and psychiatric diseases. Therefore, they could be explored from both perspectives. As ERP continue to demonstrate their usefulness under valid and systematic experimental conditions, they could be used in the future for the timely detection and cognitive follow-up of different pathologic entities.

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Declaration of competing interest

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