PROVA ORALE A

1) Valutazione della funzionalità visiva:
    a. Pattern ERG e pattern PEV
        i. Modalità di registrazione
        ii. Modalità di stimolazione
        iii. Identificazione e Significato delle principali componenti

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

PROVA NON ESISTENTE

DISEGNO BONFOCO

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Dario Bal

PROVA A

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ISCEV STANDARDS

ISCEV guide to visual electrodiagnostic procedures

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Abstract Clinical electrophysiological testing of the visual system incorporates a range of noninvasive tests and provides an objective indication of function relating to different locations and cell types within the visual system. This document developed by the International Society for Clinical Electrophysiology of Vision provides an introduction to standard visual electrodiagnostic procedures in widespread use including the full-field electroretinogram (ERG), the pattern electroretinogram (pattern ERG or PERG), the multifocal electroretinogram (multifocal ERG or mfERG), the electrooculogram (EOG) and the cortical-derived visual evoked potential (VEP). The guideline outlines the basic principles of testing. Common clinical presentations and symptoms are described with illustrative examples and suggested investigation strategies.

Keywords ISCEV standards · Clinical electrophysiology · Electrooculogram (EOG) · Electroretinogram (ERG) · Pattern ERG · Multifocal ERG (mfERG) · Visual evoked potential (VEP) · Optic neuropathy · Maculopathy · Retinopathy

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Introduction

Clinical electrophysiological testing of the visual system incorporates a range of tests based upon the recording of electrical potentials evoked by visual stimuli, using electrodes situated on the surface of the eyes, the peri-orbital skin or scalp. The tests are noninvasive and provide an objective indication of function relating to different locations and cell types within the visual system. This document developed by the International Society for Clinical Electrophysiology of Vision (ISCEV) provides an introduction to standard visual electrodiagnostic procedures in widespread use and describes the common clinical indications for which these tests are applicable. Detailed specifications for each procedure may be found in the appropriate ISCEV standards [1–5]. The basic principles of electrodiagnostic testing are outlined in this document, but the document is not intended to be prescriptive or to address every clinical scenario and is not a mandate for specific procedures on individual patients. Clinical electrophysiological testing has the greatest utility when performed in conjunction with clinical assessment by specialist eye care professionals. Clinical context is essential to enable appropriate clinical management.

This guideline describes the basic methods and underlying principles of testing for each of the standard tests including the full-field flash electroretinogram (ERG), the pattern electroretinogram (pattern ERG or PERG), the multifocal electroretinogram (mfERG), the electrooculogram (EOG) and the cortical-derived visual evoked potential (VEP). The principal focus is to place these tests in clinical context. Common clinical presentations and symptoms are described with illustrative examples and suggested investigation strategies.

The electrophysiological tests

ISCEV publishes and regularly updates standards for clinical tests of the visual system. The most recent publications are listed on the ISCEV Web site www.iscev.org/standards and are freely accessible. In addition to these basic tests, extended protocols may support differential diagnosis or functional monitoring. Below is a brief description of normal waveforms resulting from the ISCEV standard tests and the physiologic implications of abnormal responses. Users should consult the relevant standard or extended protocol for detailed testing protocols.

Fig. 1 Representative full-field and pattern ERGs in a normal subject (**a**), in a case of macular dystrophy (**b**), cone-rod dystrophy (**c**), rod-cone dystrophy with relative sparing of macular function (**d**), complete CSNB (**e**), incomplete CSNB (**f**) and birdshot retinochoroidopathy (BRC) before treatment (**g**) and after treatment illustrating full recovery of the ERG and PERG (**h**). Recordings showed a high degree of inter-ocular symmetry except in BRC (data from other eye are not shown). Note there is a 20-ms pre-stimulus delay in all single flash ERG recordings. Two responses for each stimulus condition are superimposed to illustrate reproducibility. Broken lines replace blink artefacts occurring after the ERGs, for clarity

The full-field ERG

The ISCEV standard full-field ERGs (Fig. 1a) are global responses of the retina to brief flashes of light and provide an assessment of generalized retinal function under light- and dark-adapted conditions. A ganzfeld (German for "whole field") stimulator, which provides a uniformly illuminated field, is used to deliver a range of flash stimuli that evenly illuminate the maximal area of retina. The ERGs are recorded with electrodes in contact with the cornea or conjunctiva or with skin electrodes attached to the lower eyelids. Several types of corneal electrode may be used including contact lens, fiber, jet and gold foil electrodes. The pupils are dilated to maximize retinal illumination and to minimize inter-subject and inter-visit variability. Reliable interpretation of recordings requires comparison with electrode-specific and age-matched normative data. The normal test–retest variability of ERG parameters is also an important consideration if used to monitor disease progression or the safety or efficacy of treatments.

The ISCEV standard protocol includes dark-adapted (DA) recordings after 20-min dark adaptation to flash strengths of 0.01, 3.0 and 10.0 cd s m^{-2} (DA 0.01; DA 3.0; DA 10.0). The weak flash (DA 0.01) ERG arises in the inner retinal rod bipolar cells and is the only standard test that selectively monitors rod system function. Abnormality of the DA 0.01 ERG can be caused by either rod photoreceptor dysfunction or selective dysfunction occurring post-phototransduction or at the level of the inner retinal rod bipolar cells. The DA 3.0 (standard flash) and DA 10.0 (strong flash) ERGs have input from both rod and cone

a
normal
b
macular
dystrophy
c
cone-rod
dystrophy
d
rod-cone
dystrophy
DA 0.01
DA 3.0
DA 10.0
LA 30Hz
LA 3.0
PERG
amplitude (μV)
time (ms)

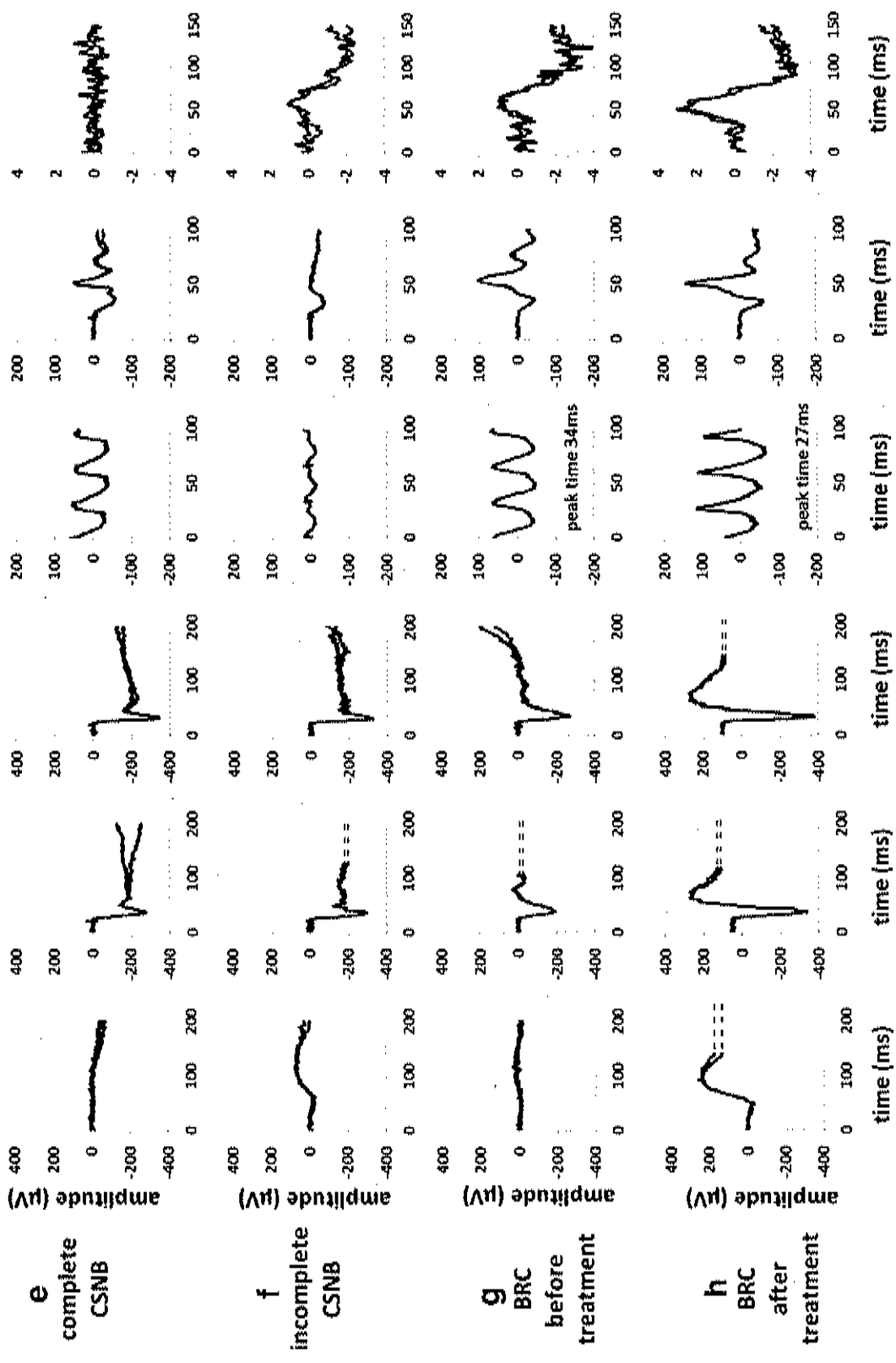

Fig. 1 continued

systems, but the DA rod system contribution dominates in a normal retina. Approximately the first 8 ms of the cornea-negative a-wave reflects rod hyperpolarizations, and as the a-wave in the DA 10.0 ERG is of shorter peak time and larger than in the DA 3.0 ERG, it provides a better measure of rod photoreceptor function. The subsequent cornea-positive b-wave arises largely in the rod On-bipolar cells and reflects function that is post-phototransduction. Thus, the DA strong flash ERG enables localization of dysfunction to the rod photoreceptors (a-wave reduction and concomitant b-wave reduction) or to a level that is post-phototransduction or inner retinal (sparing of the a-wave with b-wave reduction). The DA oscillatory potentials (OPs) are small high-frequency components normally visible on the rising limb of the DA 3.0 and DA 10.0 ERG b-waves and are thought to reflect amacrine cell signaling. Reduction in the OPs is often associated with other ERG abnormalities but may occur selectively in some disorders. The cone system contribution to both DA ERG a- and b-waves is minor in a normal retina but can be of greater significance in patients with disease primarily or exclusively affecting the rod system.

Standard light-adapted (LA) ERGs provide two measures of generalized cone system function; both are obtained to a flash strength of 3.0 cd s m^{-2}, after a standard period of 10-min light adaptation in the Ganzfeld with a constant background luminance of 30 cd m^{-2}. A 30 Hz flash stimulus, superimposed on the background, is used to elicit the LA 30 Hz flicker ERG, generated largely by post-receptoral retinal structures. The single flash cone (LA 3.0) ERG consists mainly of a- and b-waves. The LA 3.0 ERG a-wave arises in the cone photoreceptors and Off-bipolar cells; the b-wave is dominated by a combination of cone On- and Off-bipolar cell activity, and a reduced b/a ratio suggests cone system dysfunction that is post-phototransduction or post-receptoral.

The full-field ERG enables the distinction between generalized outer and inner retinal dysfunction and predominant rod or cone system dysfunction. Symptoms and/or clinical signs may suggest a retinopathy, but the presence, severity and nature of retinal dysfunction cannot always be inferred from the clinical findings and ERGs can help differentiate between a wide range of disorders when appropriately placed in clinical context (see below and Table 1). It is stressed that the full-field ERG is largely generated by the retinal periphery and there is minimal contribution from the macula. Electrophysiological assessment of macular function requires the use of different techniques such as the pattern ERG or multifocal ERG.

The pattern ERG

The ISCEV standard PERG is derived largely from the macular retinal ganglion cells and complements the full-field ERG, in differentiating between maculopathy and generalized retinopathy. PERG also enables a more meaningful evaluation of a VEP, to exclude a macular cause of VEP abnormality and to provide an additional assessment of retinal ganglion cell involvement (see below). The PERG is recorded to an alternating high-contrast checkerboard using a corneal electrode. PERGs are attenuated by poor refraction and ocular media opacity, and care must be taken to optimize the optical quality of the checkerboard stimulus; for this reason, contact lens electrodes are not suitable.

The transient PERG has two major components of diagnostic value: a positive polarity P50 and a negative polarity N95 (Figs. 1a and 2). Both components reflect macular retinal ganglion cell function, but there is an additional more distal retinal contribution to the P50 component. Both P50 and N95 depend on the function of the macular cones, and P50 reduction and/or delay can characterize macular dysfunction. Selective reduction in N95 with preservation of P50 suggests dysfunction at the level of the retinal ganglion cells. In severe or chronic retinal ganglion cell dysfunction, there may be P50 reduction, but in such circumstances P50 usually shortens in peak time, reflecting loss of the retinal ganglion cell contribution to P50. Preservation of P50 helps to establish the effective stimulus quality and contrast of the checkerboard in patients who may have poor visual acuity for reasons other than maculopathy. Comparison of responses to a standard and additional large-field stimulus may help characterize the area of macular dysfunction, although spatial resolution is lower than for the mfERG.

The multifocal ERG

The ISCEV standard mfERG (Fig. 3a) provides a measure of cone system function over 61 or 103 discrete hexagonal retinal areas, within the central

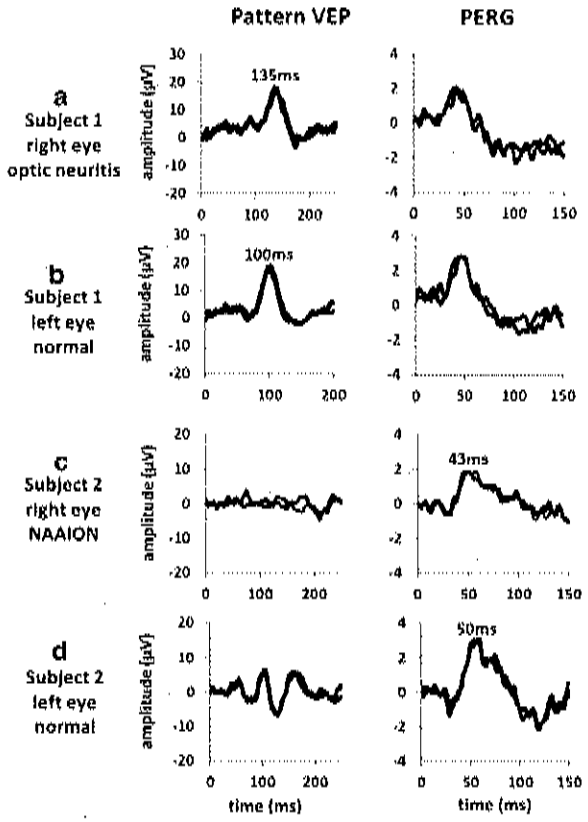

Fig. 2 Representative pattern-reversal VEPs and PERGs in the affected (**a**, **c**) and fellow (**b**, **d**) eyes in a patient with non-acute optic neuritis (Subject 1; **a**, **b**) and in an elderly patient with a severe non-arteritic anterior ischemic optic neuropathy (Subject 2; **c**, **d**). The P100 component of the pattern VEP in optic neuritis shows a 35-ms delay compared with the normal fellow eye, without significant amplitude reduction, consistent with optic nerve conduction delay; pattern ERGs are normal in this case and reveal no evidence of macular or retinal ganglion cell dysfunction. The pattern VEP P100 component in **c** is undetectable, and PERG shows a reduced N95:P50 ratio and shortening of P50 peak time (inter-ocular difference 7 ms) compared with the fellow eye, indicating severe optic nerve dysfunction with retinal ganglion cell involvement. Two responses for each stimulus condition are superimposed to illustrate reproducibility

40°–50° of the posterior pole centered on the macula. The hexagons of the ISCEV standard stimulus array are scaled to elicit comparable response amplitudes from each stimulus region, resulting in larger hexagons with increasing eccentricity. Reliable recording requires good patient fixation, and corneal electrodes are required as signals are small.

Each hexagonal stimulus element is modulated rapidly to display white or black frames according to an irregular but predetermined binary sequence known as a "pseudorandom" or "m-sequence." The signal associated with a particular hexagon is extracted from a single continuous recording from each eye, using automated cross-correlation analysis. The responses can be mathematically stratified into components associated with single illumination events (the first-order kernel), used for ISCEV standard testing. The optical quality of the stimulus is important, and patients should be optimally refracted and must fixate accurately on a central target or cross-hairs throughout the recording period. There is a compromise between spatial resolution (smaller, more numerous hexagons) and the recording duration necessary to obtain responses with a satisfactory signal-to-noise ratio. There are two major response components; an early negative polarity N1 component is derived from cone bipolar cells with a cone photoreceptor contribution and a later positive polarity P1 component that arises in cone bipolar cells.

The spatial resolution of the mfERG is better than for the PERG and full-field ERGs, and this enables improved characterization of focal central, annular, hemifield or discrete paracentral areas of posterior pole dysfunction, but reliable recording requires good patient fixation. If the area of dysfunction shows reasonably good radial symmetry, interpretation may be facilitated by averaging waveforms from all the hexagons in each concentric ring in the stimulus pattern (ring-averaging). Illustrative examples of mfERG recordings are shown in a case of retinitis pigmentosa (RP) with central macular sparing (Fig. 3b), in macular dystrophy (Fig. 3c) and in a patient with an enlarged blind spot (Fig. 3d). The mfERG is also a useful adjunct to the VEP and is less affected by optical factors than the PERG; there is no retinal ganglion cell contribution to the mfERG, and a normal response excludes primary macular photoreceptor dysfunction as cause of VEP abnormality or central visual loss. However, in some conditions such as cystoid macular edema (CME), the mfERG may be preserved or less affected than the PERG.

The electrooculogram

The ISCEV standard EOG is used to assess generalized retinal pigment epithelium (RPE) function. There is a potential difference between the apical and basal surfaces of the RPE that results in a dipole across the eye, with the cornea being positive with respect to the

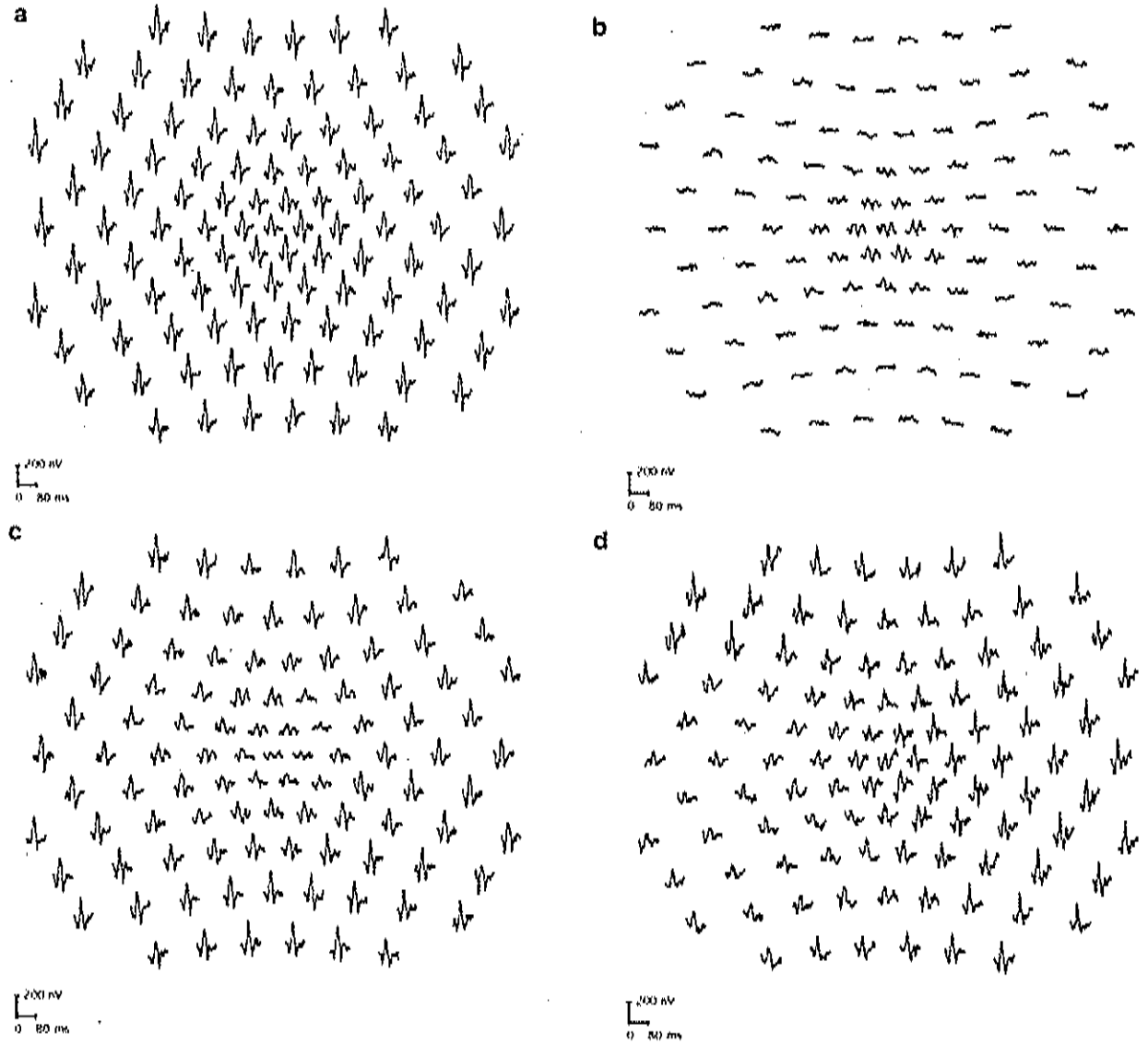

Fig. 3 Multifocal ERGs recorded to a 103-element stimulus array in a representative normal subject (**a**), in a case of retinitis pigmentosa showing relative sparing of central macular function (**b**), in a case of macular dystrophy showing reduction over a central area (**c**) and in a patient with an eccentric nasal area of retinal dysfunction consistent with an enlarged blind spot extending inferiorly in the right eye (**d**). MfERGs in cases **a**–**c** showed a high degree of inter-ocular symmetry; abnormalities were unilateral in **d**. Traces are shown in retinal view

back of the eye. This potential difference, the standing potential of the eye, is recorded using skin electrodes placed at the medial and lateral canthus of each eye during uniform 30-degree horizontal saccades, made periodically during dark and then light adaptation. During the standard 15-min period of dark adaptation, there is a fall in the recorded standing potential, typically reaching a minimum at 10–15 min, referred to as the dark trough (DT). The dark phase is followed by a 15-min period of continuous light adaptation to a standard white background (100 cd m^{-2}), provided by a Ganzfeld stimulator. Following light onset, there is an increase from the standing potential resulting in the EOG light peak (LP). The LP/DT ratio (Arden ratio) provides a measure of the generalized function of the RPE/photoreceptor complex. The development of a normal EOG light peak requires not only a normally functioning RPE, but also normally functioning rod photoreceptors, with the degree of EOG abnormality broadly corresponding to the degree of rod-derived

ERG abnormality. An EOG assessment of generalized RPE/photoreceptor function is most useful when interpreted in the context of normal or only mildly subnormal rod-mediated ERG findings. In the presence of severe rod dysfunction from any cause, the EOG will be abnormal, and not additionally informative about the function of the RPE. Common causes of generalized RPE dysfunction are outlined below.

Visual evoked potentials

The ISCEV standard VEPs provide an important objective test in the investigation of suspected optic nerve disease or post-retinal visual pathway dysfunction. The VEPs are electrical potentials recorded from the scalp derived from electrical currents generated in the visual cortex in response to visual stimulation. The VEP indicates the function of the entire visual pathway from the retina to area V1 of the visual cortex and primarily reflects the central retinal projection to the occipital poles. Recording electrodes are positioned on the scalp according to anatomical landmarks using a standardized "International 10/20 system" measurement method. The recording montage includes at least one occipital electrode (Oz) referred to a mid-frontal reference (Fz). Computerized signal averaging is used to extract the time-locked VEP from spontaneous brain activity (the electroencephalogram or EEG).

The ISCEV standard for VEP testing describes three stimulus modalities: pattern-reversal, pattern onset–offset and diffuse flash stimulation. A reversing checkerboard is used to record the pattern-reversal VEP, generally most useful for the assessment of optic nerve function, but requiring an adequate level of fixation and compliance. The normal pattern-reversal VEP has a prominent positive component at approximately 100 ms (P100; Fig. 2), although normal ranges differ and are age and laboratory dependent. Pattern onset–offset (pattern appearance) stimulation is less commonly used in the diagnosis of optic nerve disease than pattern reversal, but has the advantage of being less affected by nystagmus. Flash VEPs are generally less sensitive to dysfunction than pattern VEPs, but may be used in young children or when patients cannot fixate or comply with testing. They are also useful in the presence of media opacity when the use of stronger non-standard flashes may be helpful to establish the integrity of the visual pathway. There is wider variability in normal ranges than for pattern VEPs, and an inter-ocular comparison is often most useful. Flash VEPs may occasionally reveal abnormalities in the presence of normal pattern VEPs, and this can occur in rare cases of optic neuritis, in some cases of optic nerve sheath pathology or due to unsuspected retinopathy.

Multichannel VEPs, in excess of the current ISCEV standard, are needed to detect optic nerve misrouting or to detect and characterize chiasmal or retrochiasmal dysfunction. Multichannel flash VEPs can also reveal the visual pathway misrouting associated with albinism in children, but flash VEPs are usually normal in adults with albinism.

The timing, amplitude and waveform shape of the P100 component are used to evaluate pattern-reversal VEPs, which provide an important objective test in the investigation of suspected optic nerve disease or post-retinal visual pathway dysfunction. However, abnormalities are not specific and can reflect, for example, optic nerve or macular dysfunction and can also be caused by poor compliance or sub-optimal refraction. Reliable interpretation of pattern VEP abnormality usually requires complementary assessment to exclude a macular cause. Similarly, a flash ERG may exclude a retinal cause of flash VEP abnormality. There are numerous causes of optic nerve disease, and VEPs may suggest or support a suspected diagnosis when interpreted in clinical context. Common causes of optic neuropathy are outlined below.

Clinical indications for visual electrophysiology

Symptoms, signs and circumstances that frequently prompt referral for visual electrophysiology are outlined below, with selected examples illustrated in Figs. 1, 2 and 3, chosen to illustrate the underlying principles of testing. Accurate localization of dysfunction within the visual pathway may require complementary testing with different techniques, and a suggested test strategy is outlined in Fig. 4. It is stressed that multiple tests may not be needed in all patients and that electrophysiological findings and accurate diagnosis require interpretation in the context of the clinical findings. A comprehensive list of all conditions that may prompt visual electrophysiological examination is beyond the scope of this guideline,

but diagnoses that commonly benefit from testing and typical findings are summarized in Table 1.

Visual acuity loss

Visual acuity loss may be caused by inherited and acquired causes of maculopathy (with or without retinopathy), optic nerve and visual pathway disease, but this may not be obvious on clinical grounds alone and the distinction is enabled by electrophysiological testing.

Retinal and RPE disorders

The pattern ERG and mfERG may be used to assess the severity of macular dysfunction (Figs. 1 and 3) in the presence of fundus abnormality or used to detect dysfunction in occult cases of maculopathy or macular dystrophy. If there is visible evidence of maculopathy on fundus examination, a full-field ERG will determine whether there is peripheral retinal involvement, e.g., differentiating between macular dystrophy (normal full-field ERG; Fig. 1b) and cone and cone-rod dystrophy (see below and Fig. 1c). Common reasons for referral include bull's eye lesions, which may be associated with macular dystrophy, cone or cone-rod dystrophy, or acquired dysfunction, for example, caused by hydroxychloroquine toxicity. In Stargardt disease (ABCA4 retinopathy), the most common monogenic cause of inherited macular/retinal dystrophy, there is usually visible maculopathy and fleck

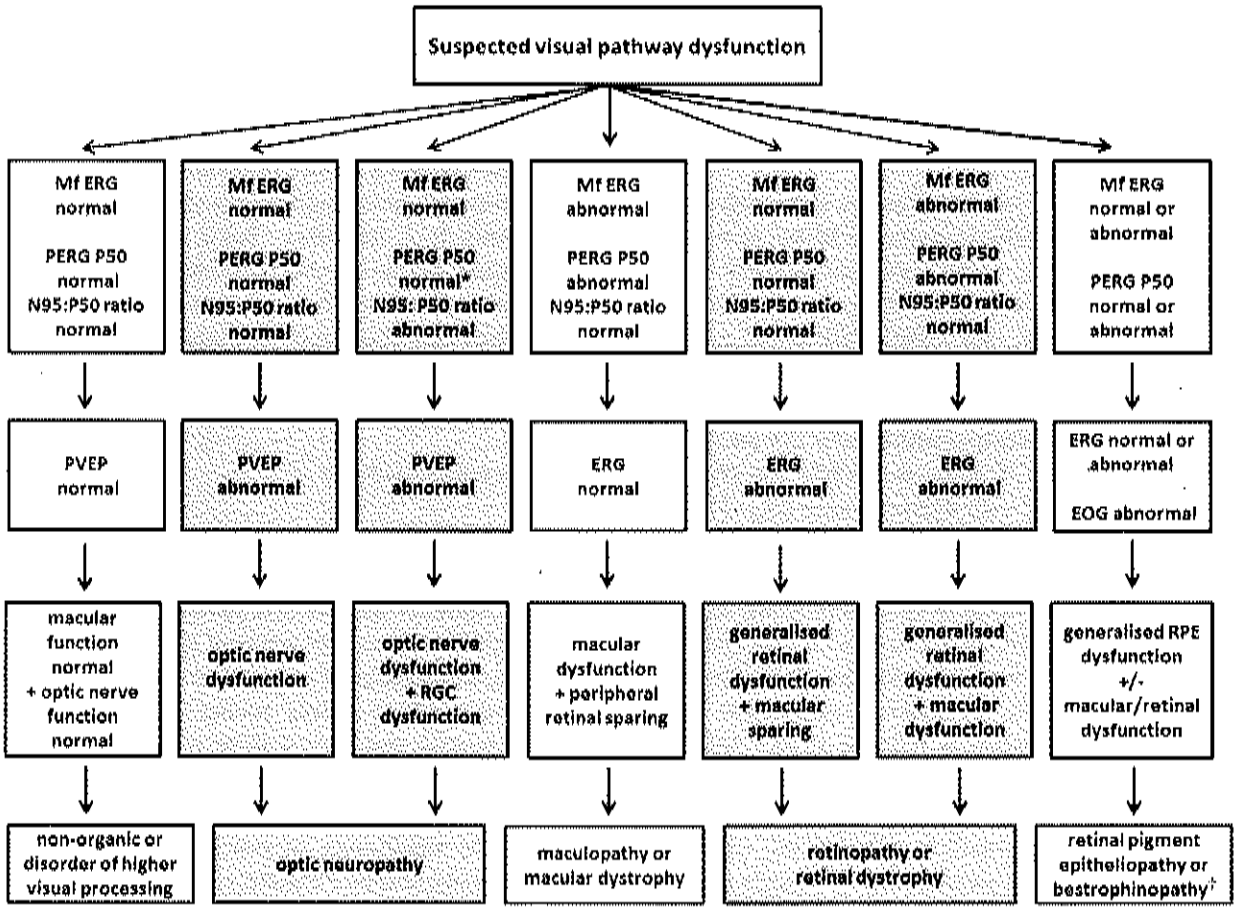

Fig. 4 Suggested test strategy for cases of suspected visual pathway dysfunction, illustrating how complementary tests can localize dysfunction within the visual system. Asterisk (*): in cases of retinal ganglion cell dysfunction, the PERG N95:P50 ratio is subnormal, but in severe disease P50 may additionally show reduction with shortening of peak time. Dagger (†): bestrophinopathies: Best disease is associated with a normal ERG and abnormal EOG; autosomal recessive bestrophinopathy causes severe EOG reduction and later onset progressive retinopathy with relatively mild ERG abnormality; in ADVIRC, the EOG is abnormal and the ERG abnormal. See Table 1 for details. After; [6, 7]

lesions (not always present in children or early disease) and ERGs establish whether dysfunction is confined to the macula or whether there is generalized cone or cone and rod involvement.

Rapid loss of visual acuity may occur in acquired disorders such as paraneoplastic (carcinoma associated retinopathy; CAR) or autoimmune retinopathy (AIR), which are often without fundus abnormality at presentation and are typically associated with pronounced rod and cone photoreceptor dysfunction, evident on ERG testing. In cases of vitelliform macular lesions, an ERG and EOG are indicated; Best vitelliform macular dystrophy is characterized by a severely reduced EOG light peak to dark trough ratio in the absence of ERG abnormality, confirming generalized RPE dysfunction and largely excluding other disorders that may resemble Best disease on fundus examination, including some pattern dystrophies such as adult-onset vitelliform macular dystrophy.

Optic nerve/post-retinal disorders

In the absence of obvious fundus abnormality, the pattern VEP in combination with a PERG or mfERG distinguishes optic nerve dysfunction from occult macular disease. The pattern VEP is usually abnormal in macular disease, and PERG P50/central mfERG preservation largely excludes macular dysfunction as a cause of pattern VEP abnormality.

Acute visual acuity loss with pain on eye movement is typical of optic neuritis, and VEPs are typically delayed in keeping with demyelination (Fig. 2), with or without amplitude reduction; the VEP abnormality usually persists even if visual acuity improves. VEP abnormalities may occur in an asymptomatic eye and in visually asymptomatic patients with multiple sclerosis, consistent with subclinical demyelination. Approximately 35% of patients with optic nerve demyelination manifest a reduced PERG N95:P50 ratio, in keeping with retrograde involvement of the retinal ganglion cells and occurring a minimum of 4–6 weeks after presentation, although this can occur in any form of optic neuropathy. A sudden painless and irreversible loss of vision is typical of non-arteritic anterior ischemic optic neuropathy (NAION), and unlike demyelination, pattern VEPs typically show amplitude reduction without significant delay (Fig. 2). In arteritic anterior ischemic optic neuropathy (AAION), there is usually severe visual loss and gross VEP abnormality. Leber hereditary optic neuropathy (LHON) typically presents with sudden sequential, painless visual loss, and pattern VEPs are usually undetectable or severely abnormal at presentation; PERG P50 amplitude is typically normal providing fixation is adequate, but there may be marked reduction in N95 in the acute stages, in keeping with primary ganglion cell dysfunction.

Compressive lesions of the visual pathways are associated with progressive or insidious visual acuity loss, although if unilateral this may be noticed suddenly by the patient. If a unilateral optic nerve lesion is anterior to the optic chiasm, there will be unilateral pattern VEP abnormality. Localization of dysfunction posterior to the optic nerves requires multichannel VEP recordings. Chiasmal dysfunction results in a "crossed asymmetry," such that the VEP from each eye is abnormal over a different hemisphere. Retrochiasmal dysfunction results in an "uncrossed" asymmetry such that monocular VEPs from both eyes are abnormal over the same hemisphere. Progressive visual loss is also a feature of dominant optic atrophy and nutritional optic neuropathies such as that caused by vitamin B12 deficiency. Toxic etiology includes ethambutol, methyl-alcohol poisoning (also associated with retinopathy) and rare cases of tobacco toxicity. Visual loss may also result from injury to the occipital cortex usually resulting in both pattern and flash VEP waveform degradation or distortion.

Non-organic visual loss

In cases of unexplained or suspected "functional" visual loss, normal electrophysiology helps to exclude an organic cause. A well-formed pattern-reversal VEP is incompatible with a visual acuity of approximately 6/36 or worse, although care must be taken to ensure adequate patient compliance during testing. Flash VEPs are usually normal, and even if there is dysfunction with non-organic overlay, it is difficult to reconcile a detectable flash VEP with "no perception of light" vision. The significance of pattern VEP abnormality depends on the results of macular testing with PERG P50 or mfERG, and the importance of flash VEP abnormality may similarly depend on the absence of significant full-field ERG abnormality. Normal visual electrophysiology does not preclude the presence of underlying organic disease, and particular caution must be exercised if there is a possibility of higher cortical dysfunction.

Night blindness

Night blindness (nyctalopia) can result from generalized rod system dysfunction, and this may be confirmed or excluded using a full-field ERG. The DA 3.0 and DA 10.0 ERGs enable localization of dysfunction to the rod photoreceptors (a-wave reduction and concomitant b-wave reduction) or to a level that is post-phototransduction or inner retinal (sparing of the a-wave; b-wave reduction).

Night blindness due to rod photoreceptor dysfunction

In progressive retinal degenerations such as retinitis pigmentosa, which in mild cases may be associated with a normal or near-normal fundus appearance, there is ERG evidence of a rod-cone dystrophy (Fig. 1d). The severity of generalized retinal dysfunction in RP varies, but there may be preserved visual acuity and relative preservation of macular function until the late stages in many cases, as revealed by PERG P50 (Fig. 1d) or mfERG (Fig. 3b). Progressive degeneration encroaching upon the macula may lead to eventual blindness, and it is important to distinguish from other causes of rod system dysfunction. In RP, the DA 0.01 ERG is typically reduced and the bright flash (DA 3.0 and DA 10.0) ERGs show a-wave reduction. The reduction in the a-wave confirms rod photoreceptor dysfunction; there is concomitant b-wave reduction because the b-wave is generated "downstream" from the abnormal rod photoreceptors. The LA 30 Hz and LA 3.0 ERGs are typically delayed and/or reduced, but dysfunction is milder than in the rod system. The reduction in the a-wave makes the distinction from the two common forms of congenital stationary night blindness (complete and incomplete CSNB; see below). There are other rare forms of CSNB that cause severe rod-driven ERG abnormalities (DA 3.0 and DA 10.0 ERG a-wave reduction) but with spared cone system function, and these include "Riggs-type" CSNB, Oguchi disease and fundus albipunctatus. In the latter two disorders, there are usually characteristic fundus abnormalities and improvement or recovery of rod system function after prolonged DA (see Table 1 for a summary). The fundus appearance in fundus albipunctatus may be similar to patients with retinitis punctata albescens (Bothnia dystrophy); patients with Bothnia dystrophy may also show partial ERG recovery following prolonged dark adaptation, but the phenotype is more severe than in fundus albipunctatus and evolves to a progressive rod-cone dystrophy.

Acquired night blindness with a normal fundus can occur in vitamin A deficiency and CAR, although in rare cases of CAR there may be an electronegative ERG. The ERGs in vitamin A deficiency are characterized by severe rod system dysfunction and normal or near-normal cone system function, similar to the ERGs in "Riggs-type" CSNB. However, the ERGs in vitamin A deficiency usually return to normal following treatment.

Night blindness due to dysfunction occurring post-phototransduction

Complete and incomplete CSNB are associated with a normal fundus and generalized retinal dysfunction that is post-phototransduction (Fig. 1e, f), with normal (or near-normal) a-waves and electronegative DA 3.0 and DA 10.0 ERG waveforms (b/a ratio < 1). In complete CSNB, the DA 0.01 ERG is undetectable. The LA 30 Hz ERG, although often of normal amplitude, may have a slightly broadened trough and often shows borderline or mild peak time delay. The LA 3.0 ERG has normal a-wave amplitude but with a broadened bifid trough and a b-wave with a sharply rising peak with no oscillatory potentials; the b/a ratio varies but is usually mildly subnormal. The shape of the DA and LA ERG waveforms are characteristic of loss of On-pathway function with Off-pathway preservation, also evident in the long-duration On–Off ERG, which reveals an electronegative On response and a normal Off response. Complete CSNB is caused by a defect in 1 of 5 genes (Table 1), expressed by On-bipolar cells and consistent with the ERG abnormalities. In incomplete CSNB, the DA0.01 ERG is present but subnormal. LA 30 Hz ERGs are markedly reduced and have a bifid shape. The LA3.0 ERG is markedly subnormal with a low b:a ratio. Long-duration stimulation reveals reduction in both the On b-wave and Off d-wave. It is noted that the 2 genes implicated in incomplete CSNB (Table 1) are involved in neurotransmitter release from the photoreceptor presynaptic membrane, consistent with ERG evidence of both On- and Off-bipolar cell dysfunction.

Acquired night blindness with a normal fundus and electronegative ERG can occur in melanoma-associated retinopathy (MAR) and rarely in CAR (see

above). MAR is rare but is associated with malignant melanoma, and the ERG findings are identical to those in complete CSNB (Fig. 1e). The ISCEV standard ERG features in MAR, CAR and vitamin A deficiency are different to each other, but are indistinguishable from some of the inherited disorders mentioned above, highlighting the importance of clinical context in the interpretation of ERGs.

Photophobia

Photophobia is commonly associated with generalized cone system dysfunction and can be an early symptom in cone and cone-rod dystrophies. In cone dystrophies, the LA 30 Hz and LA 3.0 ERGs show delay and/or amplitude reduction, and in cone-rod dystrophy, there is additional abnormality of the DA ERGs (Fig. 1c). In both conditions, there is usually severe macular dysfunction evident on PERG (Fig. 1c) or mfERG testing. Rod monochromacy (achromatopsia) is characterized by severe cone system dysfunction from early infancy; the LA ERGs are typically undetectable, but the DA 0.01 ERG, selective for the rod system, is normal, and the DA 10.0 ERG is normal or shows mild reduction in the a- and b-waves, due to a loss of the normal dark-adapted cone system contribution. The ERG findings in S-cone monochromacy (a form of "X-linked incomplete achromatopsia") are similar, but DA ERGs may be additionally attenuated due to high myopia; there may be a markedly abnormal (but detectable) LA 3.0 ERG and the short-wavelength ("blue") flash ERG is relatively preserved. Congenital photophobia may also be a feature of albinism. Photophobia is rarely caused by dysfunction confined to the macula. Acquired causes of photophobia include retinal inflammatory disease such as uveitis and birdshot retinochoroidopathy (BRC), both associated with a high incidence of generalized cone system dysfunction, AIR and CAR. Photophobia is a rare feature of optic nerve disease but can also occur in neurological disorders such as migraine, meningitis and in carotid artery or vertebral artery disease.

Visual field loss

Peripheral visual field constriction is a common feature of rod-cone dystrophy (RP), and this can occur without classical intraretinal pigment deposition, particularly in children. Cone and cone-rod dystrophies may present with visual field defects including central scotomata, generalized depression of sensitivity, ring scotomata and peripheral field loss if there is relative sparing of central macular function. Peripheral visual field loss may also occur in inflammatory retinal disorders such as BRC, associated with variable retinal dysfunction but often characterized by generalized cone system dysfunction, manifest as delay in the LA 30 Hz ERG, and sometimes associated with additional inner retinal rod system involvement (reduction in DA 10.0 ERG b:a ratio) which may be reversible following treatment (Fig. 1g, h). In acute zonal occult outer retinopathy (AZOOR), there is usually field loss disproportionate to visible fundus changes and persistent photopsia within the scotoma. Full-field ERG abnormalities are common, and some may show a reduction in the EOG light peak-to-dark trough ratio, not explained by abnormalities in rod function. Autoimmune disorders, such as CAR and AIR, may also present with rapid visual field constriction and marked ERG abnormality (see above). Homonymous hemianopic visual field defects usually reflect chiasmal or retrochiasmal brain lesions, and these may be detected by multichannel VEP recordings and require prompt further investigation. Field loss may also be seen in shallow retinal detachments and retinoschisis with concomitant full-field ERG changes, and clinical or ultrasound eye examination is essential.

Disk pallor

Disk pallor may be a feature of optic neuropathy or retinopathy, including cone and cone-rod dystrophies. In central retinal artery occlusion (CRAO), there may be unilateral retinal edema and a "cherry red" spot at the fovea in the acute phase, but after a few weeks, this resolves as disk pallor develops. The subacute and chronic phases may be mistaken for ischemic optic neuropathy, and the electrophysiology enables the distinction. The ERG in CRAO has an electronegative DA 3.0 or DA 10.0 ERG, and there is usually marked involvement of the LA ERGs, in keeping with generalized inner retinal dysfunction. There are several other potential masquerades of optic neuropathy including occult maculopathy (inherited or acquired) and central serous chorioretinopathy (CSR); both may manifest PERG P50 or central mfERG abnormalities. In acute idiopathic blind spot syndrome (AIBSS), the

mfERG may characterize the nasal area of reduced function (Fig. 3d). Occult retinopathy (including AZOOR), autoimmune and paraneoplastic retinopathies typically show marked ERG abnormalities, and in posterior scleritis, which like optic neuritis may be accompanied by pain on eye movement, there may be inflammatory changes affecting the retina that cause ERG abnormality.

Glaucoma

Glaucoma is a progressive optic neuropathy associated with injury to retinal ganglion cell axons, frequently due to elevated intraocular pressure. Common signs include a characteristic pattern of optic atrophy (enlargement of the optic nerve cup), sectoral nerve fiber layer defects, often best visible with red-free light and evident on optical coherence tomography (OCT). There are often characteristic visual field defects, including arcuate "nerve fiber bundle defects" which reflect the distribution of optic nerve fibers emanating from the optic nerve, and "nasal steps" at the horizontal raphe.

The pattern ERG is sensitive to macular ganglion cell dysfunction and nerve fiber layer loss in glaucoma and can be of value in the evaluation of "glaucoma suspects" with glaucomatous risk factors such as elevated intraocular pressure, or optic nerve head changes, prior to the measureable loss of visual field. There may be reduction in the N95 (and also the P50) component in transient recordings, but steady-state PERG recordings are more affected. Traditional full-field ERG parameters, such as a-wave and b-wave amplitudes, are insensitive to ganglion cell injury, but there is increasing interest in the photopic negative response (PhNR). This is a late, cornea-negative deflection in the full-field ERG which is often recorded to red flashes presented on a blue background. The PhNR reflects global retinal ganglion cell function and offers the possibility of detecting and monitoring glaucomatous progression. ISCEV standard multifocal ERGs (first-order kernels) are driven primarily by photoreceptor and bipolar cells and are thus relatively insensitive to ganglion cell damage, although subtle effects of glaucoma have been described in the second-order kernels or with special stimulation paradigms. Multifocal recording technology has also been adapted to produce low-resolution visual field-like maps of VEP responses to spatial stimuli for eccentricities out to approximately 20° (e.g., dartboards), although standardization and clinical utility have yet to be established.

Nystagmus

Congenital nystagmus is a feature of several ocular and neurological disorders. Isolated idiopathic congenital motor nystagmus (CMN) is not associated with other ocular or neurological abnormalities, and although pattern-reversal VEP and PERG may be difficult or impossible to record due to eye movements, flash VEPs and full-field ERGs are normal. Common retinal causes of nystagmus include Leber congenital amaurosis (LCA), associated with severe generalized photoreceptor dysfunction (DA and LA ERGs are severely reduced or undetectable), cone and cone-rod dystrophy, rod and S-cone monochromacy and complete and incomplete CSNB, characterized by different ERG phenotypes (see above). Nystagmus is also associated with ocular and oculo-cutaneous albinism (see above), and diagnosis in the former may be difficult in the absence of obvious skin depigmentation.

Acquired nystagmus may result from drug toxicity or medication that impairs the function of the labyrinth, thiamine or vitamin B12 deficiency, head injury, stroke, multiple sclerosis or any disease or injury of the brain that affects neural centers that control eye movements. Exclusion of afferent visual pathway dysfunction with electrophysiology may provide an important contribution to the management of such cases.

Vascular retinopathies or ischemic status of retina

The full-field ERG is sensitive to retinal ischemic disorders affecting the inner retina. There may be reductions in the DA 3.0 and DA 10.0 ERG b:a ratios, the DA oscillatory potentials are usually abnormal or extinguished, and LA 30 Hz ERGs show prolonged peak times and waveform distortions. The ERG may be invaluable in detecting ischemic central retinal vein occlusion (CRVO), progression of non-ischemic to ischemic CRVO and in the diagnosis of ocular ischemic syndrome especially when the carotid Doppler scans are normal or equivocal. The ERG has advantages over commonly used fluorescein angiography in being safe and noninvasive, providing information on deeper layers and peripheral areas of retinal blood supply and may be informative in patients with systemic co-morbidities or pregnancy, in patients

allergic to fluorescein dye or in cases of vitreous hemorrhage obscuring the fundus view. Prolonged LA 30 Hz ERG peak times are frequently seen in diabetic retinopathy and are associated with increased risk of disease progression. Peak time delays can be useful for screening, and loss of oscillatory potentials can occur in some diabetic patients without diabetic retinopathy and may identify patients at increased risk.

Ocular media opacity

Full-field ERGs and flash VEPs can provide valuable information in patients with suspected retinal or visual pathway disease when the fundus is obscured or when the use of retinal imaging techniques is precluded by an opaque ocular media. Integrity of retinal and visual pathway may be important considerations prior to treating patients with corneal lesions, cataracts or vitreous hemorrhage, particularly if there is a history of retinal detachment, retinal or neurological involvement. A normal or relatively preserved ERG or flash VEP may suggest a better prognosis for improved vision. An abnormal full-field ERG may suggest generalized retinal dysfunction but may also occur in vitreous hemorrhage. An abnormal ERG does not exclude central visual recovery because it does not assess macular function. It is noted that the ERG is usually abnormal in the presence of intraocular silicone oil tamponade (for retinal detachment), but interpretation is confounded because the oil impedes conduction of the electrical signals from the retina to the corneal surface.

Family history of visual pathway disease

Visually asymptomatic patients with a family history of retinal or optic nerve disease or suspected cases of syndromic retinal dystrophy may require electrophysiological testing for evidence of subclinical disease. For example, visually asymptomatic obligate carriers of X-linked RP usually manifest abnormal and asymmetrical ERG abnormalities, irrespective of whether there is fundus abnormality, whereas the ERGs in carriers of X-linked choroideremia are usually normal until late in life. Carriers of X-linked ocular albinism and patients with rubella retinopathy may also have abnormal fundus pigmentation; the ERGs are normal in the former and normal or near-normal in the latter. There is variable expressivity in (autosomal dominant) Best disease such that some heterozygotes have a normal fundus and an EOG may be needed to confirm the diagnosis. Similarly, VEP and PERG N95 abnormalities may indicate optic nerve and retinal ganglion cell dysfunction in cases of suspected dominant optic atrophy.

Monitoring of disease progression, treatment efficacy and safety

Serial testing may assist the distinction between stationary and progressive conditions, important for diagnosis and patient counseling. Pattern and flash VEPs have diverse applications and may be used to monitor visual pathway maturation in infants with poor vision or amblyopia or to monitor optic nerve function in patients with known neurological disease. In inflammatory retinal diseases such as BRC, the ERGs can be used to monitor efficacy of treatment objectively (Fig. 1g, h), thus informing clinical management and titration of potentially toxic medication. Worsening VEPs may prompt the need for surgical intervention in dysthyroid eye disease or in neurological disorders, irrespective of stable neuroradiology. Several medications commonly administered systemically for non-ocular conditions are potentially toxic to the macula, retina or optic nerves, and pre-treatment assessment and monitoring may be considered. The multifocal ERG, for example, may reveal annular or parafoveal macular dysfunction that can manifest as an early stage of hydroxychloroquine toxicity, before the development of a visible "bulls-eye" lesions and before structural changes are evident or obvious on retinal imaging. Intraocular drugs, intraoperative dyes and bright lights of ophthalmic surgical equipment have become another source of toxic/phototoxic maculopathy that may need retinal and macular electrophysiology testing for monitoring, for clinical evaluation or for diagnosis. ERG evaluations are also becoming an integral part of various clinical trials comparing outcome efficacies of various surgical or medical procedures involving the macula such as macular holes, epiretinal membranes, anti-VEGF treatments, macular detachments and central serous chorioretinopathy. Similarly, ERGs may be used to monitor retinal safety of new treatments and as objective outcome measures in clinical trials that aim to restore visual function or arrest disease progression.

Special considerations and indications for ERG and VEP testing in infants and children

Accurate diagnosis may be difficult in young children who are unable to describe their visual symptoms or who are difficult to examine. The objective data provided by electrophysiological testing are fundamental to the management of the child with suspected visual pathway dysfunction, but there are important considerations relating to maturation of responses, ability to comply with testing and causes of visual pathway dysfunction more specific to the pediatric population. Both ERG and VEP responses show profound developmental changes during infancy and childhood, and although all visual electrophysiological values are considered in relation to age, it is even more important in young patients. Infants up to the age of about 2 years can frequently undergo successful ERG testing without general anesthesia, while being held in a parent's lap, either by using only topical anesthetic eye drops and corneal electrodes or by using surface electrodes on the lower eyelids. It may be appropriate to shorten the standard ERG protocol, and many practitioners start with light-adapted ERGs and perform limited dark adaptation, dependent upon the compliance and comfort of the child. VEP testing in infants is equally feasible, but may require simple flash stimulation, if steady fixation on the center of the VEP pattern stimulus cannot be induced with a moving toy, jangling keys or similar to encourage central fixation.

Examination under anesthesia may enable the use of corneal electrodes in the non-compliant child, but anesthesia usually alters ERG timing and amplitudes, and interpretation requires caution. Similarly, the use of skin electrodes limits sensitivity since the signal amplitude is lower, but in this age group there is rarely a need to detect subtle abnormalities and most clinically appropriate questions may be easily addressed. For example, is there a detectable ERG, is there a functioning cone system, is there a response after dark adaptation and is there an electronegative ERG waveform? The cortical neurons which drive the VEP are much more susceptible to general anesthesia than the retina, precluding reliable VEP recordings.

Unexplained visual loss

Absent or impaired visually mediated behavior may indicate a disorder affecting any level of the visual system. Babies who do not fix and follow and presumed amblyopic patients that fail to respond to treatment may require testing to confirm or exclude pathology. Early diagnosis of retinal dystrophy may be essential to identify young candidates who are potentially amenable to future experimental treatments. A normal ERG may also prompt the need for further investigations such as VEPs or neuroradiology. Non-organic visual loss is relatively common in older children, and in such circumstances, the electrophysiological data are usually normal even though there may be reported profound visual loss.

Congenital nystagmus

The differential diagnosis includes several retinal disorders such as Leber congenital amaurosis, congenital stationary night blindness, and rod and S-cone monochromacy. The ERG will help differentiate these conditions. Young children with albinism show multichannel flash VEP evidence visual pathway misrouting, although with increasing age (above about 5 years) this may be best demonstrated with pattern onset–offset VEPs. Flash VEPs and ERGs are normal in idiopathic CMN. Clinical examination is also needed to investigate or exclude TORCH infections like viral retinitis that result in nystagmus and variable ERG abnormalities.

Known or suspected hereditary disorders

The ERG may be helpful in advising families with patients at risk of hereditary retinal disorders. The extent to which the various retinal dystrophies are detectable in early infancy is frequently not known, but a normal ERG at age 7 or 8 years of age largely excludes X-linked RP. Night blindness may be associated with RP or CSNB and ERGs help differentiate between progressive and stationary disorders. In young cases of suspected Best disease, children may be unable to comply with EOG testing, but testing of the parents will almost invariably identify the parent carrying the mutation, irrespective of whether the fundi are normal.

Perinatal infections

Perinatal infections, particularly the "TORCH" agents, may attack ocular tissues, with possible profound associated dysfunction. The most common

perinatal infection is probably rubella retinopathy, which frequently results in mottled RPE pigmentation ad a "salt and pepper" appearance, but in such cases the ERG is usually normal or near-normal.

Perinatal brain injury

Perinatal brain damage may lead to severe visual impairment. VEPs enable objective determination of the nature of the deficit and may help grade the severity of cortical dysfunction. However, it is important to recognize that VEPs do not reflect higher processing required for normal vision.

Trauma

In children who have suffered head/orbital trauma or suspected visual pathway injury, complementary retinal and VEP testing may localize dysfunction and help to confirm, exclude or distinguish between retinopathy and optic nerve or post-retinal dysfunction, particularly in those unable or too young to communicate verbally.

Delayed visual maturation

Infants often present with "visual indifference," showing little or no reaction to visual stimuli for several months. If the eye examination, ERG, and VEP are normal or near-normal, this provides reassurance, and the prognosis for development of normal or near-normal vision is reasonably good.

Monitoring for retinal drug toxicity

The most common indication in this category is vigabatrin, which is used for the treatment of infantile spasms (West syndrome). The drug causes peripheral visual field constriction in approximately 30% of adults. The ERG is helpful in monitoring patients who are too young or lack the ability to perform visual field testing.

Amblyopia

Children suspected of having amblyopia are often referred for electrophysiology to exclude other causes of poor vision, for example when visual acuity has not improved with patching and the fundi are normal or when visual acuity is reduced bilaterally. In amblyopic eyes, pattern-reversal VEPs may show amplitude reduction; delays in the major positive (P100) component can occur, but this tends to be more prominent in strabismic rather than anisometropic amblyopia. Pattern VEPs may also be used to monitor the efficacy of occlusion therapy in amblyopic and fellow eyes, but subjective assessment of vision (if possible) should generally take priority.

Complementary testing

Electrophysiological testing complements routine ophthalmic examination, subjective tests of visual function and retinal imaging methods commonly employed in the assessment of patients with visual impairment. Electrophysiological methods are objective and uniquely assess aspects of function and dysfunction. Ophthalmic examination and imaging techniques may be normal in the presence of retinal and visual pathway dysfunction or may reveal abnormalities that do not correlate with the nature or severity of dysfunction. Optimal assessment is obtained with judicious use of widely used techniques including those outlined below.

Subjective assessment of function

Visual acuity

Visual acuity (VA) testing is a long established method of assessing central visual function in almost any form of visual system pathology, from ptosis of the eyelids and corneal epithelial edema to retinal degenerations and optic neuropathies. However, VA loss is non-specific and cannot be used to localize dysfunction within the visual pathway. The VA does not give an indication of peripheral retinal function and may also be relatively or completely preserved in the presence of macular or optic nerve dysfunction. VA may be normal, for example, in paracentral and peripheral retinal derangements, nerve fiber bundle defects (as in glaucoma), in subacute optic neuritis and lesions of the posterior visual pathways which spare the projections of the central retina.

Visual fields

Visual field testing is widely available and, with the advent of automated static perimetry, highly

standardized and reproducible. Visual fields allow localization of visual impairment, with classic patterns of visual field loss associated with localized and generalized retinal disorders, macular and optic nerve disease, chiasmal disruptions, lesions of the lateral geniculate body and optic radiations, and cortical lesions. Pattern ERG and multifocal ERG can be of great value in distinguishing between macular and optic nerve disease, often associated with similar visual field abnormalities and often indistinguishable by VEP alone. Full-field ERG abnormalities are a leading indicator of degenerative retinal disorders such as retinitis pigmentosa. Peripheral visual fields are important in the adequate assessment of degenerative retinal diseases such as retinitis pigmentosa, in which the extent of scotomas and the presence of residual temporal islands of vision are of great importance to the patient but cannot be adequately assessed by central Humphrey visual fields and peripheral automated visual field protocols. It is highlighted that visual fields do not always correlate with objective suprathreshold electrophysiological measures of function.

Contrast sensitivity

Loss of contrast sensitivity is readily documented with special eye charts designed for the task, or CRT-based vision testing devices, and can occur in the absence of significant VA reduction. The causes of reduced contrast sensitivity include optical problems such as corneal haze or cataract, and complementary use of different electrophysiological tests (Fig. 4) can differentiate these from a wide range of visual pathway disorders.

Color vision testing

Color vision is an important visual faculty, and abnormalities may derive from retinal, optic nerve or (rarely) cortical pathology. Commonly used Ishihara plates are highly sensitive to even minor dyschromatopsias, but detect only red-green (protan or deutan axis) abnormalities. Other sets of test plates, such as the H-R-R plates, also detect tritan axis problems. The common X-linked protan and deutan color vision defects are rarely associated with abnormalities in the ISCEV standard ERG, but can be detected with nonstandard chromatic stimuli. Absence or severe loss of normal color vision suggests more severe pathology, such as achromatopsia or optic nerve disease, which are readily detected by ERG or VEP.

Dark adaptometry

Abnormalities of dark adaptation are difficult for patients and physicians to assess without formal testing, as normal difficulties seeing in dim light may be reported as abnormally impaired night vision. Formal dark adaptometry can be performed with specialized instruments, such as the Goldmann–Weekers Dark Adaptometer. Qualitative assessment can be readily obtained with much simpler materials, such as the Hyvarinen cone adaptation test, in which an examiner with normal dark adaptation compares his/her adaptation with that of the patient, who is asked to sort colored plastic tiles in a very dim room. Abnormalities of dark adaptation generally imply retinal pathology, including CSNB, vitamin A deficiency, paraneoplastic retinopathies and degenerative disorders such as retinitis pigmentosa, usually readily differentiated by full-field ERG in clinical context.

Retinal imaging

Fundus photography has been available as a clinical tool since 1926, and fluorescein angiography was introduced in 1959. More recently, advances in fundus imaging have appeared with increasing frequency, not only documenting ophthalmoscopic findings, but extending the range of clinical perception in depth (ICG angiography) and resolution; spectral domain OCT now approaches the resolution of low-power microscopy, without the need to remove tissue from the eye for histologic processing. However, the enhanced capability of fundus imaging has not displaced electrophysiological methods of testing function. The need to complement anatomical methods with studies of visual function is as keen as ever and perhaps more so as increasing detail in fundus imaging allows ever finer diagnostic distinctions to be made, for which the functional consequences must be determined.

Fundus photography

Fundus photography documents the appearance of the retina and allows rapid estimation of the size and

characteristics of fundus lesions. Digital photography has improved resolution and enabled more objective assessments as well as multi-spectral imaging. Newer cameras provide a wider-field image far greater than the 30°–40° fields of traditional fundus cameras, revealing important pathology of the peripheral retina which was previously unappreciated or more difficult to assess, especially in children.

Fluorescein angiography

Fluorescein angiography documents the extent and integrity of the retinal vasculature and remains an important tool even in the era of advanced OCT imaging, which lacks the dynamic aspect of the evolving fluorescein angiogram. ICG angiography extends the range of angiographic imaging deeper into the choroid, demonstrating vascular structures and abnormalities that may be less evident or undetectable using other methods.

Fundus autofluorescence

Fundus autofluorescence imaging (FAF) can reveal otherwise invisible manifestations of disrupted RPE metabolism. The main fluorophore to short-wavelength excitation is lipofuscin, derived from the phagocytosis of shed photoreceptor outer segments in the RPE. The distribution of FAF across the posterior pole and abnormal accumulations or depletions of the FAF signal can detect or accentuate the appearance of lesions in a wide range of disorders, and the technique has largely replaced fluorescein angiography in the assessment of inherited retinal and macular dystrophies. Since the technique was introduced in the early 1990s, methods such as PERG and mfERG have helped establish the functional significance of common FAF abnormalities and the value of FAF in monitoring disease progression.

Optical coherence tomography

Optical coherence tomography (OCT) has revolutionized retinal evaluation. It is far superior to even the most careful ophthalmoscopy at detecting anatomical disruptions of the posterior pole, such as cystoid edema, vitreomacular traction or shallow serous detachments of the retina or RPE. Moreover, the recognition of the role of the line of photoreceptor inner segment ellipsoid (or inner segment/outer segment junction) as an indicator of the integrity of the photoreceptors has clarified the diagnosis of many retinal disorders. For example, in many cases of "occult macular dystrophy" OCT may expose subtle or localized outer retinal loss. Focal OCT abnormalities do not always correlate with the severity of dysfunction or the function of surrounding retinal tissues.

Adaptive optics

Adaptive optics (AO) techniques use active optical elements to compensate for the optical aberrations of the eye and provide a noninvasive method for extending spatial resolution and studying the micromorphology of the retina in vivo. Clinical implications are only beginning to emerge, but otherwise invisible disruptions in the photoreceptor mosaic have been documented in different retinal and macular disorders.

Genetic testing

Electrophysiology has a pivotal role to characterize disorders and the phenotypic variability associated with a known genotype or to guide the screening of genes associated with a known electrophysiological phenotype. Advances in molecular biology have enabled genotyping of many inherited retinal and macular dystrophies, but the functional consequences remain difficult to predict due to allelic heterogeneity, genetic modifiers and other factors. In rare retinal dystrophies, ERGs can be used to identify the gene responsible, e.g., in enhanced S-cone syndrome (NR2E3), "cone dystrophy with supernormal ERG" (KCNV2) and RGS9/R9AP-retinopathy, as outlined in Table 1. It is more usual for the ERGs to suggest a range of disorders or possible genotypes, e.g., in complete CSNB, the ERG phenotype is common to X-linked and autosomal recessive forms with mutations in 1 of several different genes and ERGs are additionally identical to those in melanoma-associated retinopathy, highlighting the importance of interpretation in clinical context. The emergence of unbiased whole exome and whole genome sequencing may reveal novel or unexpected genetic alterations and electrophysiological interrogation likely to prove increasingly important to establish the functional consequences and genotype–phenotype correlations.

Table 1 Typical electrophysiological abnormalities in selected retinal and visual pathway disorders

	Typical or common fundus/ocular abnormalities	Acquired disorder or gene/s implicated[a]	Macular function	Rod system function		Cone system function		Comments including VEP, EOG and other electrophysiological findings where relevant
			PERG P50 or MfERG	DA 0.01	DA10.0	LA 30 Hz	LA 3.0	
Adult vitelliform macular dystrophy	Small vitelliform foveal lesion due to a sub-retinal cyst with or without paracentral drusen and mild RPE changes	PRPH2, BEST1, IMPG1, IMPG2	N/A	N	N	N	N	The EOG is normal or mildly subnormal and distinguishes most cases from Best vitelliform macular dystrophy
Albinism	Blonde fundus and foveal hypoplasia are common. There may be iris transillumination and nystagmus	TYR, OCA2, TYRP1, SLC45A2, GPR143	A	N	N	N	N	Multichannel VEPs show bilateral contralateral predominance to pattern onset–offset (adults) or flash stimulation (young children). Assessment of macular function may be precluded by the effects of nystagmus; in the absence of nystagmus there may be evidence of mild macular dysfunction in some cases
Autosomal dominant vitreoretinochoroidopathy (ADVIRC)	Liquefied vitreous. Preretinal white dots and neovascularization often present. Peri-papillary atrophy can occur. Abnormal pigment often extends to an equatorial demarcation line at the posterior border	BEST1	A	A	A	A	A	The EOG light peak-to-dark trough ratio is severely abnormal
Autosomal recessive bestrophinopathy (ARB)	Diffuse RPE irregularity extending to the vascular arcades associated with patchy RPE atrophy and punctate white dots	BEST1	A/N	A/N	A/N	A/N	A/N	The EOG light peak-to-dark trough ratio is severely abnormal. ERG is initially normal but mild abnormalities usually develop in late childhood or adolescence and then worsen progressively
Batten disease (Juvenile onset neuronal ceroid lipofuscinosis)	Normal or Bull's eye lesion	CLN3	A	A	A (-ve)	A	A (-ve)	Electronegative ERG may be detected before fundus changes. LA 3.0 ERG may have a low b:a ratio
Birdshot retinochoroidopathy (BRC)	Multiple pale sub-retinal lesions. Inflammatory signs such as vitritis, vasculitis and CME are common	Acquired	A/N	A/N	A(-ve)/N	A/N	A/N	Variable. Mf ERG and PERG often reveal macular dysfunction, especially if there is CME. ERG is normal to abnormal depending on severity and efficacy of treatment. LA 30 Hz ERG commonly delayed and DA strong flash ERGs in some cases have a low b:a ratio

Table 1 continued

	Typical or common fundus/ocular abnormalities	Acquired disorder or gene/s implicated[a]	Macular function	Rod system function		Cone system function		Comments including VEP, EOG and other electrophysiological findings where relevant
			PERG P50 or MfERG	DA 0.01	DA10.0	LA 30 Hz	LA 3.0	
Best vitelliform macular dystrophy (Best disease)	Variable but often characterized by a vitelliform yellow macular lesion due to a sub-retinal cyst, which may evolve in some to become vitelliruptive with eventual atrophy. Fundus can be normal	BEST1	N/A	N	N	N	N	The EOG light peak-to-dark trough ratio is abnormal. Macular dysfunction occurs as macular lesions become vitelliruptive
Bulls-eye maculopathy (BEM)	Concentric paracentral changes with foveal sparing	Acquired or Genetic	A	N	N	N	N	Maculopathy or macular dystrophy
			A	N	N	A	A	Cone dystrophy
			A	A	A	A+	A+	Cone-rod dystrophy
								PERG/mfERG evidence of macular dysfunction; mfERG may reveal paracentral dysfunction with localized or relative foveal sparing
Carcinoma Associated Retinopathy (CAR)	Fundus initially normal. RPE atrophy, mottling and vessel attenuation may develop	Acquired	A	A+	A+	A+	A+	Often severe photoreceptor dysfunction causing an undetectable ERG or severe a-wave reduction. Cone system is most affected in some. In rare cases there is an electronegative ERG
Central retinal artery occlusion (CRAO)	Inner retinal edema and a cherry red spot at the macula in the early stages. Eventual arteriolar attenuation and disk pallor	Acquired	A (variable)	A	A (-ve)	A	A	Decreased oscillatory potentials. Relative sparing of visual acuity and of the PERG/central mfERGs if there is a cilioretinal artery
Central retinal vein occlusion (CRVO)	Dilatation and tortuosity of retinal veins, dot and flame hemorrhages, cotton wool spots, optic disk and macular edema, hyperemia. Ischemic form may result in severe vascular leakage and rubeosis	Acquired	A (variable)	A	A(-ve)	A	A	Reduced oscillatory potentials. Ischemic CRVO associated with more severe ERG changes and a more reduced DA ERG b:a ratio than non-ischemic disease. ERG a-wave involvement in severe cases
Choroideremia	Loss of RPE and choriocapillaris. Inner retina and optic disk normal. Late involvement of macula.	REP1	A	A+	A+	A	A	Severe (+) rod > cone or undetectable ERGs. Late macular involvement.
	Female heterozygotes may show mild pigmentary changes or patchy RPE degeneration		N	N	N	N	N	ERG is usually normal in female heterozygotes but worsening can occur from middle age
Cone dystrophy	Fundus may be normal. Disk pallor, granular RPE, bull's eye lesion, central atrophy	see Ret Net (many)	A	N	N	A	A	See text. PERG and MfERG usually show evidence of severe and early macular involvement
Cone-rod dystrophy	Fundus may be normal. Disk pallor, granular RPE, bull's eye lesion, central atrophy.		A	A	A	A+	A+	

Table 1 continued

	Typical or common fundus/ocular abnormalities	Acquired disorder or gene/s implicated[a]	Macular function	Rod system function		Cone system function		Comments including VEP, EOG and other electrophysiological findings where relevant
			PERG P50 or MfERG	DA 0.01	DA10.0	LA 30 Hz	LA 3.0	
CSNB								
1. Schubert–Bornschein								
(a) complete	Fundus normal (± myopic changes).	NYX, GRM6, TRPM1, LRIT3, GPR179	A	U	A (−ve)	A	A	See text for details
(b) incomplete	Fundus normal (± myopic changes).	CACNA1F, CABP4	A	A	A (−ve)	A+	A+	
2. Riggs-type	Fundus normal	PDE6B, RHO, GNAT1, SLC24A1	N	A	A	N	N	See also fundus albipunctatus and Oguchi disease (forms of CSNB with abnormal fundi and delayed dark adaptation)
Dominant optic atrophy (DOA)	Disk pallor typically wedge shaped and temporal but may be diffuse	OPA1, OPA3, OPA4, OPA5, OPA8	PERG P50 N or mildly subnormal and of short peak time MfERG N	N	N	N	N	PERG N95 may be abnormal in early stages. In severe cases PERG P50 may be reduced with shortening of P50 peak time. Pattern VEP often shows delay and reduction but abnormalities can be mild in the early stages
Enhanced S-cone syndrome (Goldman Favre disease)	Normal to nummular pigment clumping in RPE in vicinity of vascular arcades. Macular schisis can occur	NR2E3	A	U	A	A+	A	Pathognomonic ERG abnormalities. DA3, DA10 and LA3 ERGs are severely delayed with a simplified waveform. LA3 ERG a-wave is larger than the severely abnormal LA 30 Hz ERG. S-cone ERG is enlarged
Fundus albipunctatus	Multiple small white/yellow spots with sparing of the macula	RDH5	A/N	A	A	A/N	A/N	See text. DA ERGs improve or normalize after prolonged dark adaptation. Approximately 50% have mild LA ERG abnormalities
Glaucoma	Disk cupping, nerve fiber loss	Acquired	PERG abnormal MfERG normal	N/A	N/A	N/A	N/A	VEP may be normal or mildly abnormal unless severe/advanced disease. Steady-state PERG more sensitive than transient PERG for monitoring purposes. PhNR may be used to assess global retinal ganglion cell function

Table 1 continued

	Typical or common fundus/ocular abnormalities	Acquired disorder or gene/s implicated[a]	Macular function	Rod system function		Cone system function		Comments including VEP, EOG and other electrophysiological findings where relevant
			PERG P50 or MfERG	DA 0.01	DA10.0	LA 30 Hz	LA 3.0	
Ischemic optic neuropathy.	In arteritic form optic disk swelling, disk pallor ± flame hemorrhages	Acquired	PERG P50 N or mildly subnormal and of short peak time MfERG N	N	N	N	N	Pattern VEPs show reduction without significant delay. More severe in arteritic (AAION) than non-arteritic (NAION) cases. There may be eventual PERG N95 reduction in keeping with retinal ganglion cell dysfunction and with reduction/shortening of P50 peak time in some. Usually unilateral
KCNV2-retinopathy ("Cone dystrophy with supernormal rod ERG")	Normal in young but BEM and macular RPE atrophy may develop. Disk pallor in some. Peripheral retina normal	KCNV2	U	A	A	A	A	Pathognomonic ERG abnormalities. Generalized cone system dysfunction with unusual rod system involvement; DA ERGs to dim flashes are small and delayed and ERG b-waves to strong flashes large. DA 10 ERG a-wave has a distinctive broad trough with a late negative component
Leber congenital amaurosis (LCA)	Pigmentary & atrophic changes with age. Hypoplastic/swollen disks common	see Ret Net (many)	A	A+	A+	A+	A+	ERG typically undetectable or severely reduced from early infancy
Leber hereditary optic neuropathy (LHON)	Nerve fiber layer swelling in acute stages. Enlarged or telangiectatic and tortuous peri-papillary vessels. Optic atrophy	G11778A, T14484C, G3460A	PERG P50 N or mildly subnormal and of short peak time MfERG usually N	N	N	N	N	PERG N95 may be abnormal in acute stage. Pattern VEPs are undetectable or severely abnormal. Absence of fluorescein leakage from the swollen disk, distinguishing LHON from other forms of disk swelling.
Melanoma-associated retinopathy (MAR)	Fundus usually normal. Vitreous cells, vessel attenuation and disk pallor may develop in some	Acquired	A	U	A(-ve)	A	A	Long-duration On–Off ERG shows On response b-wave reduction with sparing of the Off -response. Full-field ERGs identical to those in complete CSNB
Oguchi disease	Golden fundus sheen which resolves following prolonged dark adaptation (Mizuo–Nakamura phenomenon)	SAG, rhodopsin kinase	N	U	A	N	N	DA ERGs show severe rod dysfunction after 20 min in the dark. LA ERGs are normal. After prolonged DA a single strong flash elicits a normal ERG; subsequent flashes elicit subnormal responses and further prolonged DA is needed to recover

Table 1 continued

	Typical or common fundus/ocular abnormalities	Acquired disorder or gene/s implicated[a]	Macular function	Rod system function		Cone system function		Comments including VEP, EOG and other electrophysiological findings where relevant
			PERG P50 or MfERG	DA 0.01	DA 10.0	LA 30 Hz	LA 3.0	
Optic neuritis	Disk pallor and thinning of retinal nerve fiber layer may be evident	Acquired	PERG P50 N or mildly subnormal and of short peak time MfERG N	N	N	N	N	Pattern VEP is usually delayed with or without amplitude reduction. PERG P50 is usually normal but in 35% cases there is PERG N95 reduction in keeping with retinal ganglion cell dysfunction and with reduction/shortening of P50 peak time in some. May be subclinical involvement of the other eye
Pattern dystrophy	Various patterns of pigment deposition within the macula including adult-onset vitelliform macular dystrophy, butterfly-shaped, reticular, multifocal pattern dystrophies and fundus pulverentulus	PRPH2	A/N	N	N	N	N	The EOG is normal or mildly subnormal. The ERG is usually normal although there can be marked variability in fundus appearance and ERG phenotype within families with PRPH2 mutation
Retinitis Pigmentosa (RP; Rod-cone dystrophy)	Classically bone-spicule formation. RPE atrophy, attenuated vessels, disk pallor. Normal or near-normal in some	see Ret Net (many).	A/N	A+	A+	A	A	See text. Rod-cone dystrophy of variable severity. Variable macular involvement. In X-linked pedigrees, female heterozygotes usually have ERG abnormalities with inter-ocular ERG asymmetry
Rod monochromacy ("Achromatopsia")	Usually normal, macular granularity may develop	CNGA3, CNGB3, GNAT2, PDE6C, PDE6H, ATF6	A	N	N/sl. A	U	U	See text. There may be mild reduction in DA strong flash ERGs due to loss of the normal cone system contribution to the a- and b-waves
Retinal toxicity (selected examples)	Chloroquine/Hydroxychloroquine	Acquired	A	N/A	N/A	N/A	N/A	MfERG shows annular macular dysfunction in early stages with later central involvement. ERG abnormal in severe cases
	Desferrioxamine		A	N/A	N/A	N/A	N/A	Macular dysfunction most common; PERG/mfERG ± ERG abnormality. ERG may be normal but ranges from showing mild rod dysfunction to severe cone-rod dysfunction
	Quinine		A	A	A(-ve)	A	A	On response electronegative; Off d-wave has an abnormal shape

Table 1 continued

	Typical or common fundus/ocular abnormalities	Acquired disorder or gene/s implicated[a]	Macular function	Rod system function		Cone system function		Comments including VEP, EOG and other electrophysiological findings where relevant
			PERG P50 or MfERG	DA 0.01	DA10.0	LA 30 Hz	LA 3.0	
Retinitis punctata albescens (Bothnia dystrophy; rod-cone dystrophy)	Multiple small white/yellow spots with sparing of the macula. Diffuse RPE degeneration, scalloped peripheral atrophy and pigment deposition in late stages	RLBP1	A/N	A	A	A	A	Resembles fundus albipunctatus in early stages and DA ERGs may show partial improvement after prolonged dark adaptation. Eventual progressive rod-cone dystrophy
RGS9 / R9AP – retinopathy ("Bradyopsia")	Fundus normal	RGS9, R9AP	PERG U	N	Sl. A	U	A+	DA 10 ERG mildly abnormal unless inter-stimulus interval is increased e.g. to 1-2 mins. Scotopic red flash ERG reveals normal rod and good DA cone function, in spite of severe LA ERG abnormalities.
S-cone monochromacy ("X-linked incomplete achromatopsia")	Usually normal, macular granularity may develop	OPN1LW, OPN1MW	A	N	N/sl. A	U	A	A preserved S-cone ERG distinguishes the disorder from rod monochromacy. There may be relatively mild reduction in DA 0.01 and DA10 ERG a-waves due to high myopia and loss of cone system contribution to the strong flash ERG a- and b-waves
Stargardt disease/fundus flavimaculatus (ABCA4-retinopathy)	Central atrophy with flecks or widespread flecks across posterior pole with peri-papillary sparing. Extensive RPE atrophy in severe cases	ABCA4	A	N	N	N	N	Macular dystrophy
			A	N	N	A	A	Cone dystrophy
			A	A	A	A	A	Cone-rod dystrophy
								In all 3 phenotypes there is PERG/ mfERG evidence of macular dysfunction
Vitamin A deficiency	Normal or white spots across the fundus	Acquired	N	A	A	N	N	See text.
X-linked retinoschisis	Macular cysts common; may progress to macular atrophy in older men. Peripheral schisis occurs in about 50% of cases	RS1	A	A	A(-ve)	A	A	On b-wave ± OFF d-wave subnormal. Inner retinal dysfunction of variable severity. PERG and mfERG usually abnormal

"-ve" signifies an electronegative ERG; b-wave that is smaller than a normal or near-normal a-wave (b:a < 1)

N normal, *A* abnormal, *sl. A* slightly abnormal, *A+* severely abnormal, *U* undetectable

[a]See RetNet, the Retinal Information Network for details of disease genes and updates on disease genes; RetNet, http://www.sph.uth.tmc.edu/RetNet/

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Compliance with ethical standards

Conflict of interest All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements) or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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Statement of human rights This article does not contain any research studies with human participants performed by any of the authors.

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References

1. McCulloch DL, Marmor MF, Brigell MG, Hamilton R, Holder GE, Tzekov R, Bach M (2015) ISCEV standard for full-field clinical electroretinography (2015 update). Doc Ophthalmol 130:1–12
2. Bach M, Brigell MG, Hawlina M, Holder GE, Johnson MA, McCulloch DL, Meigen T, Viswanathan S (2013) ISCEV standard for clinical pattern electroretinography (PERG): 2012 update. Doc Ophthalmol 126:1–7
3. Constable PA, Bach M, Frishman LJ, Jeffrey BG, Robson AG (2017) International society for clinical electrophysiology of vision. ISCEV standard for clinical electro-oculography (2017 update). Doc Ophthalmol 134:1–9
4. Hood DC, Bach M, Brigell M, Keating D, Kondo M, Lyons JS, Marmor MF, McCulloch DL, Palmowski-Wolfe AM (2012) ISCEV standard for clinical multifocal electroretinography (mfERG) (2011 edition). Doc Ophthalmol 124:1–13
5. Odom JV, Bach M, Brigell M, Holder GE, McCulloch DL, Mizota A, Tormene AP (2016) ISCEV standard for clinical visual evoked potentials—(2016 update). Doc Ophthalmol 133(1):1–9
6. Carr RE, Siegel IM (1990) Electrodiagnostic testing of the visual system: a clinical guide. FA Davis Company, Philadelphia, pp 134–147
7. Holder GE (2001) The pattern electroretinogram and an integrated approach to visual pathway diagnosis. Prog Ret Eye Res 20:531–561

PROVA ORALE B

1) Valutazione elettroneurografica:
    a. Risposte ricorrenti
    b. Risposte riflesse
    c. Modalità di registrazione e stimolazione
    d. interpretazione

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

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DEBORAH BOUROO

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Diagnosis and management of sensory polyneuropathy

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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.[41]

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.[45-46] 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)[2]	In 2015, 9.4% of the US population were estimated to have diabetes[3]	Lifetime incidence of neuropathy is 37-45% in type 2 diabetes and 54-59% in type 1 diabetes[3]. Prevalence of diabetic neuropathy is 5-54% depending on the criteria and methods used to define neuropathy and age of included patients[4-7]
Prediabetic small fiber neuropathy		In 2015, 33.9% of the US population over the age of 18 years had prediabetes[3]	Prevalence IGT and neuropathic pain: 8.7-14.8% IFG and neuropathic pain: 4.2-5.7%[8 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[16-18]
Sjögren's syndrome associated sensory neuropathies	Globally, 6.92/100 000[21]	Globally, 60.87/100 000[21]	Prevalence of "pure sensory neuropathy": 9.2% Prevalence of neuronopathy 0.6% (in a French population)[17]
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[31]	
Miller Fisher syndrome	0.1/100 000 in UK; 15-20% of all GBS in Asia and 1-7% in the West[32]		
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[41]		

*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.[50-54] 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
Sjogren'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 antibodies; 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.[66 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 71 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.[24 76 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,[76] although some researchers report that paresthesia and autonomic involvement may predict the presence of small fiber dysfunction.[76] 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.[94]

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.[75] That said, the identification of the presence of small fiber dysfunction in fibromyalgia enables screening for other causes of SFN, such as diabetes.[91 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=Sjogren's syndrome A; SSB=Sjogren'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.[28] Given the scarcity of such reports in the literature, the existence of sensory GBS has been called into question.[29]

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[36 127]; 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.[136-146] 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.[28 150 151] 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).[62 154] 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).

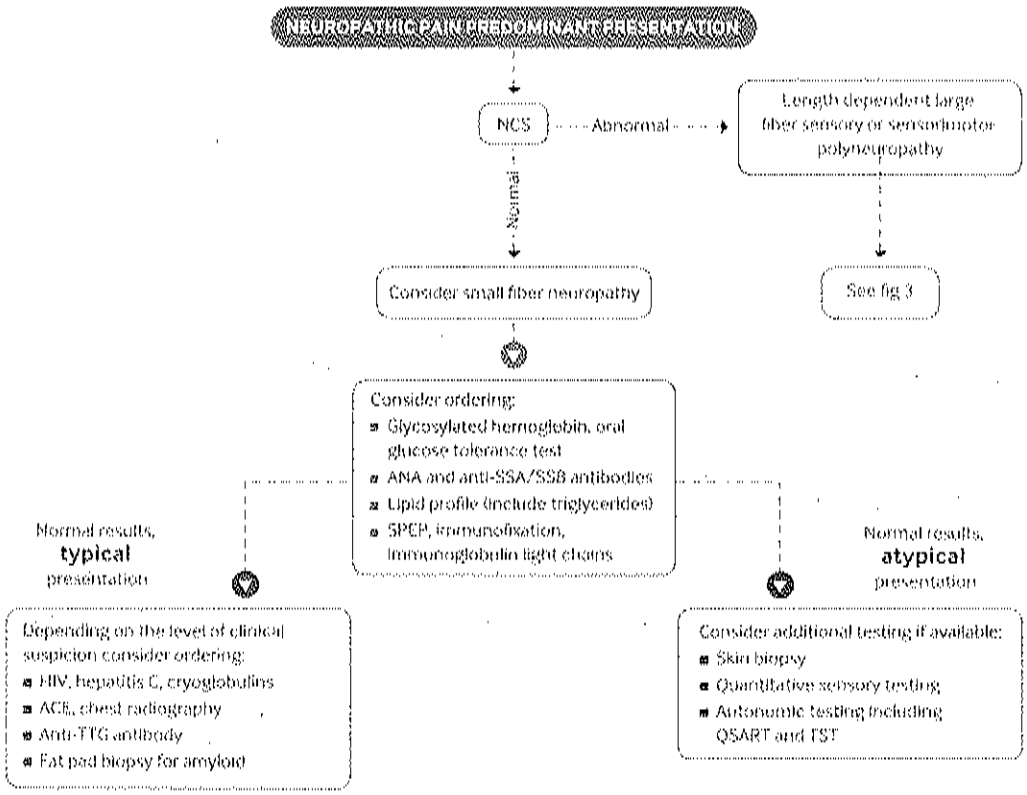

Fig 1 | Diagnostic algorithm for neuropathic pain predominant presentations. Abbreviations: ACE=angiotensin converting enzyme; ANA=antinuclear antibody; NCS=nerve conduction studies; QSART=quantitative sudomotor axon reflex test; SPEP=serum protein electrophoresis; SSA=Sjögren's syndrome A; SSB=Sjögren's 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 6), 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.[121]

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.

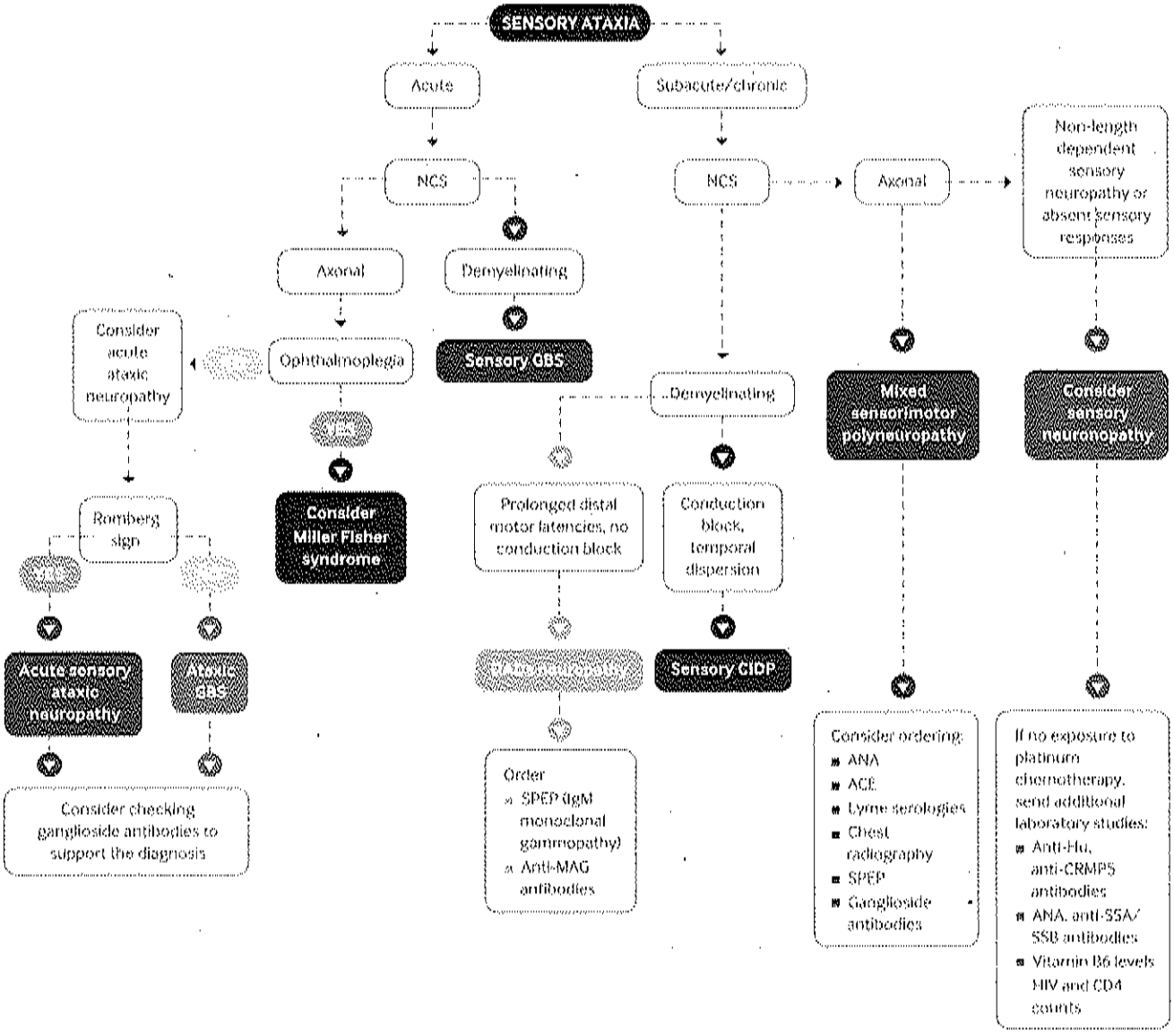

Fig 2| Diagnostic algorithm for sensory ataxic presentations. Abbreviations: ACE=angiotensin converting enzyme; ANA=antinuclear antibody; CRMP-5=collapsing response mediator protein-5; DADS=distal acquired demyelinating symmetric neuropathy; GBS=Guillain-Barré syndrome; MAG=myelin associated glycoprotein; 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.[56 171-176]

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

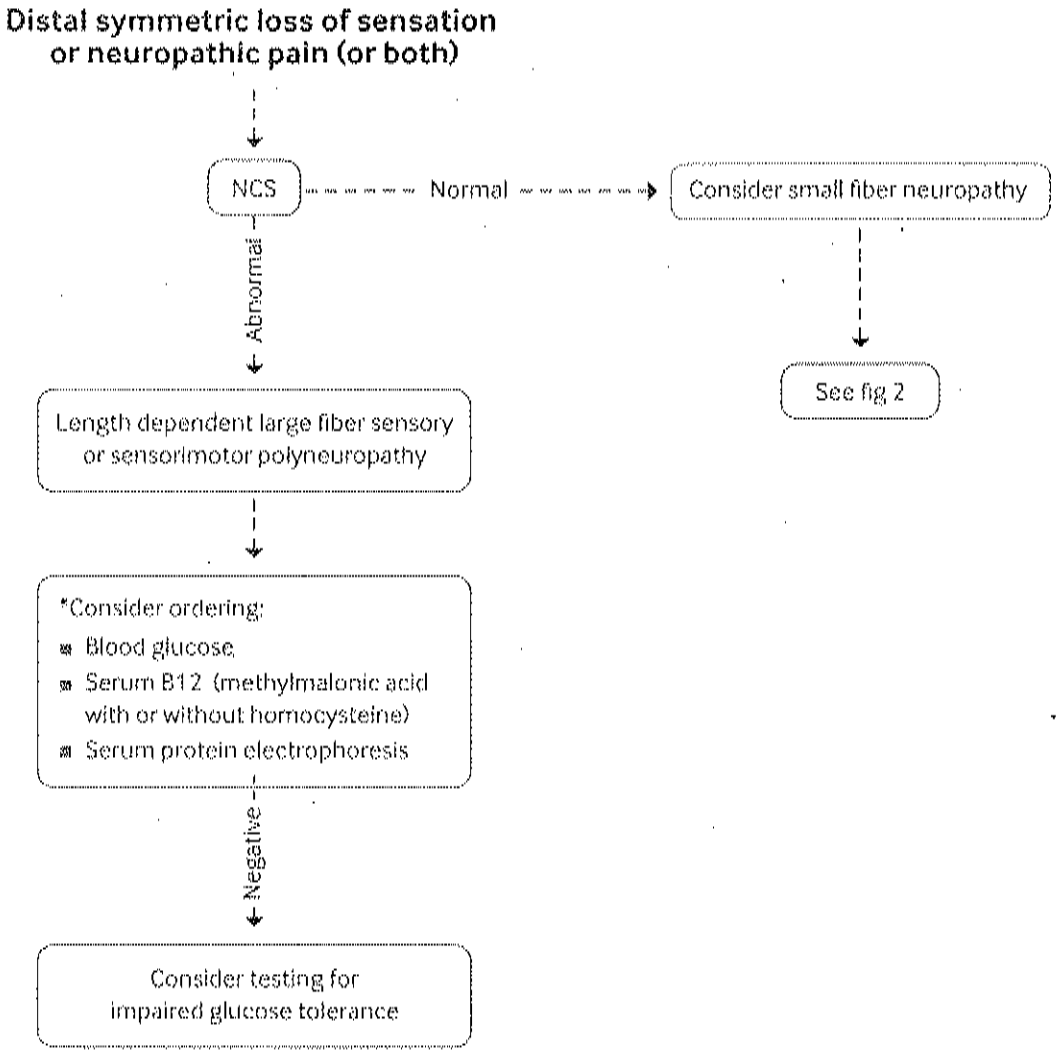

Fig 3| Diagnostic algorithm for distal symmetric loss of sensation or neuropathic pain (or both). Abbreviations: NCS=nerve conduction studies. *Based on American Academy of Neurology guidelines.[154]

shown to detect early small nerve fiber damage in many disorders.[174 177-182] 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

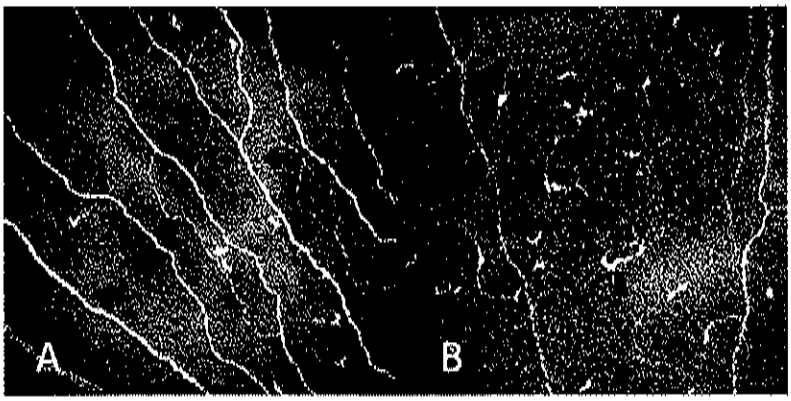

Fig 4 | Corneal nerve fiber analysis using corneal confocal microscopy showing (A) healthy control with normal nerve fiber density (arrows) and (B) a patient with diabetic polyneuropathy who has markedly reduced sub-basal nerve fiber density (arrow) and Langerhans cells (arrowheads).

measurement of IENFD adds little diagnostic value for SFN.[186] 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.[188]

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.[1 202-204] 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

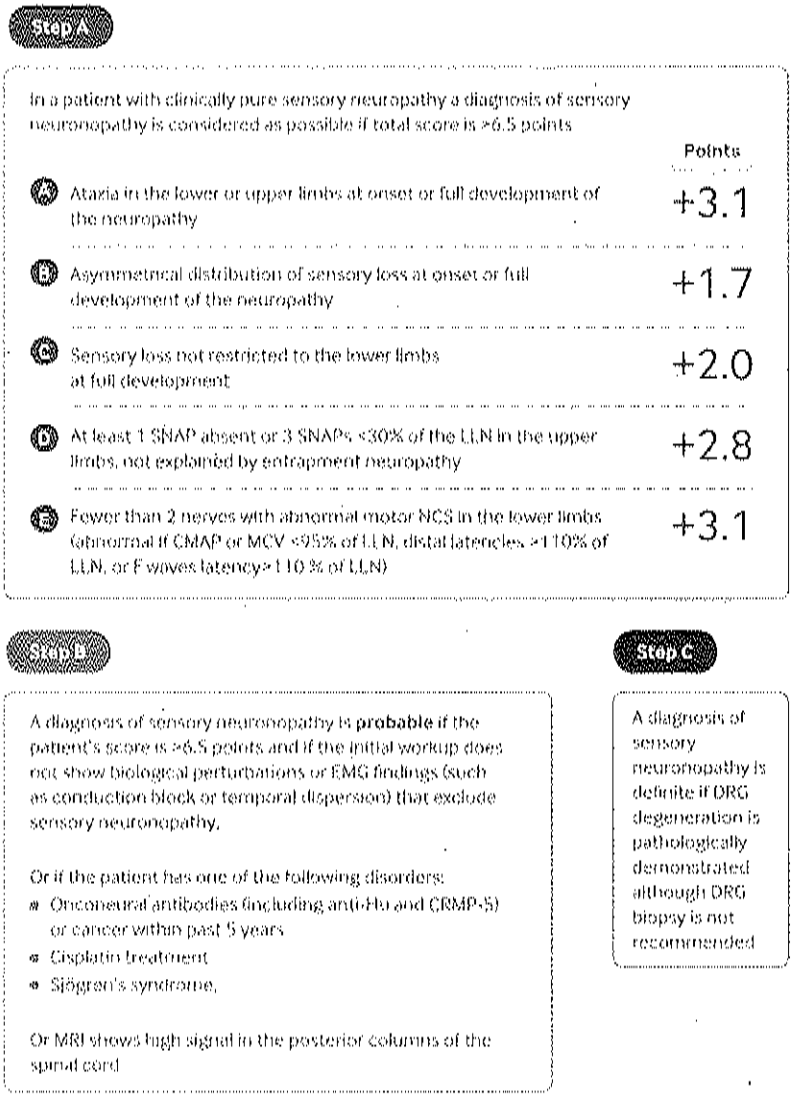

Fig 5 | Diagnostic criteria for sensory neuropathy. CMAP=compound motor action potential; DRG=dorsal root ganglion; EMG=electromyography; LLN=lower limit of normal; MCV=motor nerve conduction velocity; MRI=magnetic resonance imaging; NCS=nerve conduction studies; SNAP=sensory nerve action potential. Adapted, with permission, from Camdessanché and colleagues.[56]

formation, as well as mononuclear cell infiltrates in the interstitial tissue.[124] 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.[70] 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

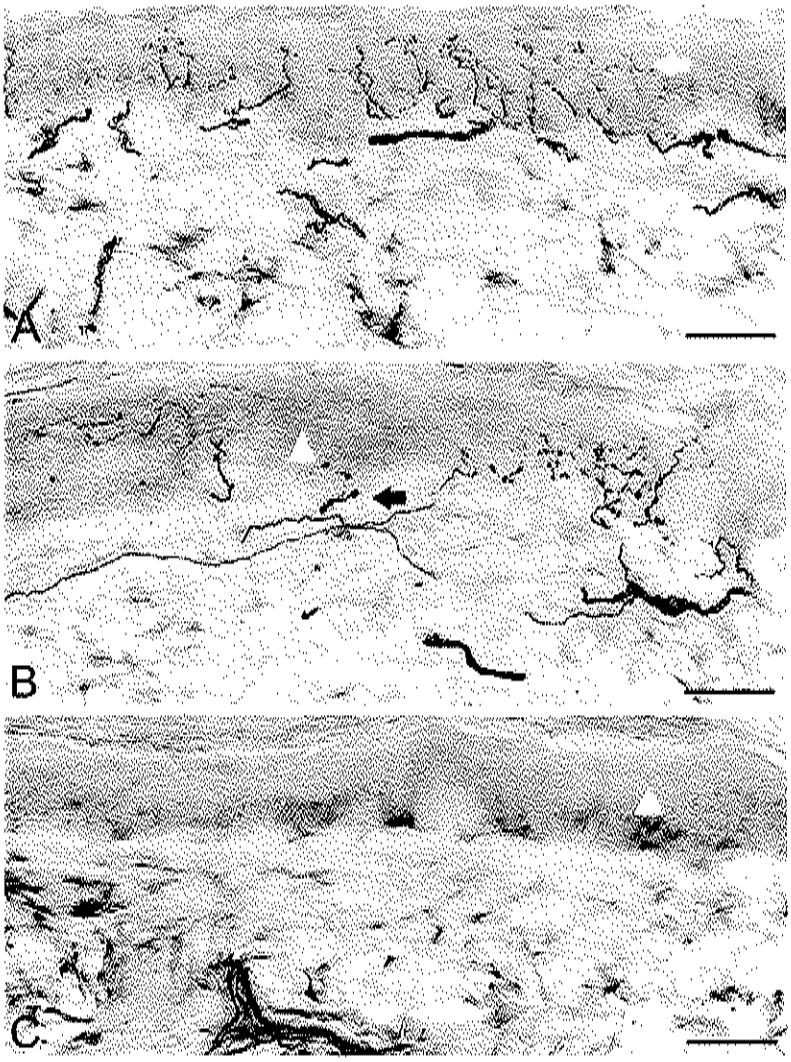

Fig 6 | Skin biopsy (scale bars equate to 50 µM). (A) Healthy control with normal intraepidermal nerve fiber density (white arrow). (B) Patient with diabetic polyneuropathy who has reduced intraepidermal nerve fiber density (white arrowhead) and axonal swellings (black arrow), a common finding in such 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.[138 225] 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.[226 227] 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,[241] rituximab,[206] and sirolimus[205] 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	Ineffacacious: 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	Ineffacacious: level B	0.075% cream up to 4 times daily	Allodynia, erythema, hypertension	Transient receptor potential vallanoid-1 agonist depletes substance P
Isosorbide dinitrate spray	Moderate: level B			Hypotension, flushing, local erythema	Forms NO, 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 ineffacacious: serotonin and norepinephrine reuptake inhibitors, zonisamide, memantine, mexiletine, 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.[266] 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.[267]

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 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.

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.

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1 Terkelsen AJ, Karlsson P, Lauria G, Freeman R, Finnerup NB, Jensen TS. The diagnostic challenge of small fibre neuropathy: clinical presentations, evaluations, and causes. *Lancet Neurol* 2017;16:934-44. 10.1016/S1474-4422(17)30329-0 pmid:29029847

2 Chan ACY, Wilder-Smith EP. Small fiber neuropathy: Getting bigger! *Muscle Nerve* 2016;53:671-82. 10.1002/mus.25082 pmid:26872938

3 Grant G. The 1932 and 1944 Nobel Prizes in physiology or medicine: rewards for ground-breaking studies in neurophysiology. *J Hist Neurosci* 2006;15:341-57. 10.1080/09647040600638981. pmid:16997767

4 Centers for Disease Control and Prevention (US) of H and HS. Centers for Disease Control and Prevention. National diabetes statistics report. 2017. https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf

5 Zilliox L, Russell JW. Treatment of diabetic sensory polyneuropathy. *Curr Treat Options Neurol* 2011;13:143-59. 10.1007/s11940-011-0113-1 pmid:21274758.

6 Vinik AI, Nevoret M-L, Casellini C, Parson H. Diabetic neuropathy. *Endocrinol Metab Clin North Am* 2013;42:747-87. 10.1016/j.ecl.2013.06.001 pmid:24286949.

7 Herman WH, Kennedy L. Underdiagnosis of peripheral neuropathy in type 2 diabetes. *Diabetes Care* 2005;28:1480-1. 10.2337/diacare.28.6.1480 pmid:15920071.

8 Young MJ, Boulton AJ, MacLeod AF, Williams DR, Sonksen PH. A multicentre study of the prevalence of diabetic peripheral neuropathy in the United Kingdom hospital clinic population. *Diabetologia* 1993;36:150-4. 10.1007/BF00400697 pmid:8458529

9 Dyck PJ, Kratz KM, Karnes JL, et al. The prevalence by staged severity of various types of diabetic neuropathy, retinopathy, and nephropathy in a population-based cohort: the Rochester Diabetic Neuropathy Study. *Neurology* 1993;43:817-24. 10.1212/WNL.43.4.817 pmid:8469345.

10 Ziegler D, Rathmann W, Meisinger C, Dickhaus T, Mielck A. KORA Study Group. Prevalence and risk factors of neuropathic pain in survivors of myocardial infarction with pre-diabetes and diabetes: The KORA Myocardial Infarction Registry. *Eur J Pain* 2009;13:582-7. 10.1016/j.ejpain.2008.07.007 pmid:18782671.

11 Ziegler D, Rathmann W, Dickhaus T, Meisinger C, Mielck A. KORA Study Group. Neuropathic pain in diabetes, prediabetes and normal glucose tolerance: the MONICA/KORA Augsburg Surveys S2 and S3. *Pain Med* 2009;10:393-400. 10.1111/j.1526-4637.2008.00556.x pmid:19207736.

12 Moore JX, Chaudhary N, Akinyemiju T. Metabolic Syndrome Prevalence by Race/Ethnicity and Sex in the United States, National Health and Nutrition Examination Survey, 1988-2012. *Prev Chronic Dis* 2017;14:E24. 10.5888/pcd14.160287 pmid:28301314

13 Valeyre D, Prasse A, Nunes H, Uzunhan Y, Brillet P-Y, Muller-Quernheim J. Sarcoidosis. *Lancet* 2014;383:1155-67. 10.1016/S0140-6736(13)60680-7 pmid:24090799

14 Rybicki BA, Major M, Popovich J Jr, Maliarik MJ, Iannuzzi MC. Racial differences in sarcoidosis incidence: a 5-year study in a health maintenance organization. *Am J Epidemiol* 1997;145:234-41. 10.1093/oxfordjournals.aje.a009096 pmid:9012596.

15 Cozier YC, Berman JS, Palmer JR, Boggs DA, Serlin DM, Rosenberg L. Sarcoidosis in black women in the United States: data from the Black Women's Health Study. *Chest* 2011;139:144-50. 10.1378/chest.10-0613 pmid:20595459.

16 Hoitsma E, Marziniak M, Faber CG, et al. Small fibre neuropathy in sarcoidosis. *Lancet* 2002;359:2085-6. 10.1016/S0140-6736(02)08912-2 pmid:12086764

17 Tavee J, Culver D. Sarcoidosis and small-fiber neuropathy. *Curr Pain Headache Rep* 2011;15:201-6. 10.1007/s11916-011-0180-8. pmid:21298560.

18 Heij L, Niesters M, Swartjes M, et al. Safety and efficacy of ASA 200 in sarcoidosis patients with symptoms of small fiber neuropathy: a randomized, double-blind pilot study. *Mol Med* 2013;18:1430-6. 10.2119/molmed.2012.00112. pmid:23168581

19 Oudejans LC, Niesters M, Brines M, Dahan A, van Velzen M. Quantification of small fiber pathology in patients with sarcoidosis and chronic pain using cornea confocal microscopy and skin biopsies. *J Pain Res* 2017;10:2057-65. 10.2147/JPR.S142683 pmid:28894389.
20 Drent M, Strookappe B, Hoitsma E, De Vries J. Consequences of Sarcoidosis. *Clin Chest Med* 2015;36:727-37. 10.1016/j.ccm.2015.08.013 pmid:26593145.
21 Qin B, Wang J, Yang Z, et al. Epidemiology of primary Sjogren's syndrome: a systematic review and meta-analysis. *Ann Rheum Dis* 2015;74:1983-9. 10.1136/annrheumdis-2014-205375 pmid:24938285.
22 Carvajal Alegria G, Guellec D, Mariette X, et al. Epidemiology of neurological manifestations in Sjogren's syndrome: data from the French ASSESS Cohort. *RMD Open* 2016;2:e000179. 10.1136/rmdopen-2015-000179 pmid:27110384.
23 Collin SM, Bakken IJ, Nazareth I, Crawley E, White PD. Trends in the incidence of chronic fatigue syndrome and fibromyalgia in the UK, 2001-2013: a Clinical Practice Research Datalink study. *J R Soc Med* 2017;110:231-44. 10.1177/0141076817702530 pmid:28358988.
24 Heidari F, Afshari M, Moosazadeh M. Prevalence of fibromyalgia in general population and patients, a systematic review and meta-analysis. *Rheumatol Int* 2017;37:1527-39. 10.1007/s00296-017-3725-2 pmid:28447207.
25 Üçeyler N, Zeller D, Kahn A-K, et al. Small fibre pathology in patients with fibromyalgia syndrome. *Brain* 2013;136:1857-67. 10.1093/brain/awt053 pmid:23474848.
26 Oaklander AL, Herzog ZD, Downs HM, Klein MM. Objective evidence that small-fiber polyneuropathy underlies some illnesses currently labeled as fibromyalgia. *Pain* 2013;154:2310-6. 10.1016/j.pain.2013.06.001 pmid:23748113.
27 Inês M, Coelho T, Conceição I, Duarte-Ramos F, de Carvalho M, Costa J. Epidemiology of transthyretin familial amyloid polyneuropathy in Portugal: a nationwide study. *Neuroepidemiology* 2018;51:177-82. 10.1159/000490553 pmid:30153683.
28 Gertz MA. Hereditary ATTR amyloidosis: burden of illness and diagnostic challenges. *Am J Manag Care* 2017;23(Suppl):S107-12.pmid:28978215.
29 de Greef BTA, Hoeijmakers JGJ, Gorissen-Brouwers CML, Geerts M, Faber CG, Merkies ISJ. Associated conditions in small fiber neuropathy - a large cohort study and review of the literature. *Eur J Neurol* 2018;25:348-55. 10.1111/ene.13508 pmid:29112785.
30 Faber CG, Hoeijmakers JGJ, Ahn H-S, et al. Gain of function Nav1.7 mutations in idiopathic small fiber neuropathy. *Ann Neurol* 2012;71:26-39. 10.1002/ana.22485 pmid:21698661.
31 Sejvar JJ, Baughman AL, Wise M, Morgan OW. Population incidence of Guillain-Barré syndrome: a systematic review and meta-analysis. *Neuroepidemiology* 2011;36:123-33. 10.1159/000324710 pmid:21422765
32 Willison HJ, Jacobs BC, van Doorn PA. Guillain-Barré syndrome. *Lancet* 2016;388:717-27. 10.1016/S0140-6736(16)00339-1 pmid:26948435.
33 Teener JW. Miller Fisher's syndrome. *Semin Neurol* 2012;32:512-6. 10.1055/s-0033-1334470 pmid:23677659.
34 Rajabally YA, Simpson BS, Beri S, Bankart J, Gosalakkal JA. Epidemiologic variability of chronic inflammatory demyelinating polyneuropathy with different diagnostic criteria: study of a UK population. *Muscle Nerve* 2009;39:432-8. 10.1002/mus.21206 pmid:19260065.
35 Laughlin RS, Dyck PJ, Melton LJ 3rd, Leibson C, Ransom J, Dyck PJB. Incidence and prevalence of CIDP and the association of diabetes mellitus. *Neurology* 2009;73:39-45. 10.1212/WNL.0b013e3181aaea47 pmid:19564582.
36 Nobile-Orazio E. Chronic inflammatory demyelinating polyradiculoneuropathy and variants: where we are and where we should go. *J Peripher Nerv Syst* 2014;19:2-13. 10.1111/jns5.12053 pmid:24612201
37 Viala K, Maisonobe T, Stojkovic T, et al. A current view of the diagnosis, clinical variants, response to treatment and prognosis of chronic inflammatory demyelinating polyradiculoneuropathy. *J Peripher Nerv Syst* 2010;15:50-6. 10.1111/j.1529-8027.2010.00251.x pmid:20433605.
38 Dalakas MC. Rituximab in anti-MAG neuropathy: More evidence for efficacy and more predictive factors. *J Neurol Sci* 2017;377:224-6. 10.1016/j.jns.2017.04.016 pmid:28477700
39 Antoine J-C, Camdessanché J-P. Paraneoplastic neuropathies. *Curr Opin Neurol* 2017;30:513-20. 10.1097/WCO.0000000000000475 pmid:28682959.
40 Tavee J, Zhou L. Small fiber neuropathy: A burning problem. *Cleve Clin J Med* 2009;76:297-305. 10.3949/ccjm.76a.08070 pmid:19414545
41 Khoshnoodi MA, Truelove S, Burakgazi A, Hoke A, Mammen AL, Polydefkis M. Longitudinal assessment of small fiber neuropathy: evidence of a non-length-dependent distal axonopathy. *JAMA Neurol* 2016;73:684-90. 10.1001/jamaneurol.2016.0057 pmid:27065313.
42 Iqbal Z, Azmi S, Yadav R, et al. Diabetic peripheral neuropathy: epidemiology, diagnosis, and pharmacotherapy. *Clin Ther* 2018;40:828-49. 10.1016/j.clinthera.2018.04.001 pmid:29709457.
43 Truini A, Spallone V, Morganti R, et al. A cross-sectional study investigating frequency and features of definitely diagnosed diabetic painful polyneuropathy. *Pain* 2018;159:2658-66. 10.1097/j.pain.0000000000001378 pmid:30161042
44 Gwathmey KG. Sensory neuronopathies. *Muscle Nerve* 2016;53:8-19. 10.1002/mus.24943 pmid:26467754.
45 Kuntzer T, Antoine J-C, Steck AJ. Clinical features and pathophysiological basis of sensory neuronopathies (ganglionopathies). *Muscle Nerve* 2004;30:255-68. 10.1002/mus.20100 pmid:15318336
46 Camdessanché J-P, Jousserand G, Ferraud K, et al. The pattern and diagnostic criteria of sensory neuronopathy: a case-control study. *Brain* 2009;132:1723-33. 10.1093/brain/awp136 pmid:19506068.
47 Riggins S, England JD. Ataxias related to sensory neuropathies. *Handb Clin Neurol* 2012;103:605-17. 10.1016/B978-0-444-51892-7.00043-7 pmid:21827921.
48 Cho TA, Bhattacharyya S. Approach to Myelopathy. *Continuum (Minneap Minn)* 2018;24(2, Spinal Cord Disorders):386-406. 10.1212/CON.0000000000000583 pmid:29613892.
49 Levine TD. Small fiber neuropathy: disease classification beyond pain and burning. *J Cent Nerv Syst Dis* 2018;10:1179573518771703. 10.1177/1179573518771703 pmid:29706768
50 Peters MJH, Bakkers M, Merkies ISJ, Hoeijmakers JGJ, van Raak EPM, Faber CG. Incidence and prevalence of small-fiber neuropathy: a survey in the Netherlands. *Neurology* 2013;81:1356-60. 10.1212/WNL.0b013e3182a8236e pmid:23997150
51 Hoffman EM, Staff NP, Robb JM, St Sauver JL, Dyck PJ, Klein CJ. Impairments and comorbidities of polyneuropathy revealed by population-based analyses. *Neurology* 2015;84:1644-51. 10.1212/WNL.0000000000001492 pmid:25832668.
52 Visser NA, Notermans NC, Linssen RSN, van den Berg LH, Vrancken AFJE. Incidence of polyneuropathy in Utrecht, the Netherlands. *Neurology* 2015;84:259-64. 10.1212/WNL.0000000000001160 pmid:25503982.
53 Farhad K, Traub R, Ruzhansky KM, Brannagan TH 3rd. Causes of neuropathy in patients referred as "idiopathic neuropathy". *Muscle Nerve* 2016;53:856-61. 10.1002/mus.24969 pmid:26561790.
54 Sopacua M, Hoeijmakers JGJ, Merkies ISJ, Lauria G, Waxman SG, Faber CG. Small-fiber neuropathy: Expanding the clinical pain universe. *J Peripher Nerv Syst* 2019;24:19-33. 10.1111/jns.12298 pmid:30569495.
55 Lang M, Treister R, Oaklander AL. Diagnostic value of blood tests for occult causes of initially idiopathic small-fiber polyneuropathy. *J Neurol* 2016;263:2515-27. 10.1007/s00415-016-8270-5 pmid:27730378.
56 Pop-Busui R, Boulton AJM, Feldman EL, et al. diabetic neuropathy: a position statement by the American Diabetes Association. *Diabetes Care* 2017;40:136-54. 10.2337/dc16-2042 pmid:27999003.
57 Singleton JR, Smith AG, Russell JW, Feldman EL. Microvascular complications of impaired glucose tolerance. *Diabetes* 2003;52:2867-73. 10.2337/diabetes.52.12.2867 pmid:14633845
58 Little RR, England JD, Wiedmeyer HM, et al. Relationship of glycosylated hemoglobin to oral glucose tolerance. Implications for diabetes screening. *Diabetes* 1988;37:60-4. 10.2337/diab.37.1.60 pmid:3335278.
59 Cortez M, Singleton JR, Smith AG. Glucose intolerance, metabolic syndrome, and neuropathy. *Handb Clin Neurol* 2014;126:109-22. 10.1016/B978-0-444-53480-4.00009-6 pmid:25410218.
60 Sumner CJ, Sheth S, Griffin JW, Cornblath DR, Polydefkis M. The spectrum of neuropathy in diabetes and impaired glucose tolerance. *Neurology* 2003;60:108-11. 10.1212/WNL.60.1.108 pmid:12525727.
61 Hoffman-Snyder C, Smith BE, Ross MA, Hernandez J, Bosch EP. Value of the oral glucose tolerance test in the evaluation of chronic idiopathic axonal polyneuropathy. *Arch Neurol* 2006;63:1075-9. 10.1001/archneur.63.8.noc50336 pmid:16769858
62 Bongaerts BWC, Rathmann W, Kowall B, et al. Postchallenge hyperglycemia is positively associated with diabetic polyneuropathy: the KORA F4 study. *Diabetes Care* 2012;35:1891-3. 10.2337/dc11-2028 pmid:22751964
63 Dyck PJ, Clark VM, Overland CJ, et al. Impaired glycemia and diabetic polyneuropathy: the OC IG Survey. *Diabetes Care* 2012;35:584-91. 10.2337/dc11-1421 pmid:22355020.
64 Pourhamidi K, Dahlin LB, Englund E, Rolandsson O. No difference in small or large nerve fiber function between individuals with normal glucose tolerance and impaired glucose tolerance. *Diabetes Care* 2013;36:962-4. 10.2337/dc12-1331 pmid:23223347.
65 Ylitalo KR, Herman WH, Harlow SD. Serial anthropometry predicts peripheral nerve dysfunction in a community cohort. *Diabetes Metab Res Rev* 2013;29:145-51. 10.1002/dmrr.2367 pmid:23161607
66 Gordon Smith A, Robinson Singleton J. Idiopathic neuropathy, prediabetes and the metabolic syndrome. *J Neurol Sci* 2006;242:9-14. 10.1016/j.jns.2005.11.020 pmid:16448668.
67 Gordon Smith AG. Impaired glucose tolerance and metabolic syndrome in idiopathic neuropathy. *J Peripher Nerv Syst* 2012;17(Suppl 2):15-21. 10.1111/j.1529-8027.2012.00390.x pmid:22548618.
68 Singleton JR, Smith AG, Bromberg MB. Painful sensory polyneuropathy associated with impaired glucose tolerance. *Muscle Nerve* 2001;24:1225-8. 10.1002/mus.1136 pmid:11494277
69 Kassardjian CD, Dyck PJB, Davies JL, Carter RE, Dyck PJ. Does prediabetes cause small fiber sensory polyneuropathy? Does it matter? *J Neurol Sci* 2015;355:196-8. 10.1016/j.jns.2015.05.026 pmid:26049659.
70 DeFronzo RA, Abdul-Ghani MA. Preservation of β-cell function: the key to diabetes prevention. *J Clin Endocrinol Metab* 2011;96:2354-66. 10.1210/jc.2011-0246 pmid:21697254.

71 Smith AG, Russell J, Feldman EL, et al. Lifestyle intervention for pre-diabetic neuropathy. *Diabetes Care* 2006;29:1294-9. 10.2337/dc06-0224 pmid:16732011.

72 Smith AG, Singleton JR. Obesity and hyperlipidemia are risk factors for early diabetic neuropathy. *J Diabetes Complications* 2013;27:436-42. 10.1016/j.jdiacomp.2013.04.003. pmid:23731827.

73 Burns TM, Dyck PJB, Aksamit AJ, Dyck PJ. The natural history and long-term outcome of 57 limb sarcoidosis neuropathy cases. *J Neurol Sci* 2006;244:77-87. 10.1016/j.jns.2006.01.014 pmid:16524595.

74 Bakkers M, Merkies ISJ, Lauria G, et al. Intraepidermal nerve fiber density and its application in sarcoidosis. *Neurology* 2009;73:1142-8. 10.1212/WNL.0b013e3181bacf05 pmid:19805731

75 Tavee JO, Karwa K, Ahmed Z, Thompson N, Parambil J, Culver DA. Sarcoidosis-associated small fiber neuropathy in a large cohort: Clinical aspects and response to IVIG and anti-TNF alpha treatment. *Respir Med* 2017;126:135-8. 10.1016/j.rmed.2017.03.011 pmid:28318820.

76 Pavlakis PP, Alexopoulos H, Kosmidis ML, et al. Peripheral neuropathies in Sjogren's syndrome: a critical update on clinical features and pathogenetic mechanisms. *J Autoimmun* 2012;39:27-33. 10.1016/j.jaut.2012.01.003 pmid:22318209

77 Birnbaum J. Peripheral nervous system manifestations of Sjögren syndrome: clinical patterns, diagnostic paradigms, etiopathogenesis, and therapeutic strategies. *Neurologist* 2010;16:287-97. 10.1097/NRL.0b013e3181ebe59f pmid:20827117

78 Mori K, Iijima M, Koike H, et al. The wide spectrum of clinical manifestations in Sjogren's syndrome-associated neuropathy. *Brain* 2005;128:2518-34. 10.1093/brain/awh605. pmid:16049042

79 Berkowitz AL, Samuels MA. The neurology of Sjogren's syndrome and the rheumatology of peripheral neuropathy and myelitis. *Pract Neurol* 2014;14:14-22. 10.1136/practneurol-2013-000651. pmid:24307005.

80 Liu X, Treister R, Lang M, Oaklander AL. IVIg for apparently autoimmune small-fiber polyneuropathy: first analysis of efficacy and safety. *Ther Adv Neurol Disord* 2018;11:1756285617744484. 10.1177/1756285617744484 pmid:29403541

81 Paticoff J, Valovska A, Nedeljkovic SS, Oaklander AL. Defining a treatable cause of erythromelalgia: acute adolescent autoimmune small-fiber axonopathy. *Anesth Analg* 2007;104:438-41. 10.1213/01.ane.0000252965.83347.25. pmid:17242106.

82 Gorson KC, Ropper AH. Idiopathic distal small fiber neuropathy. *Acta Neurol Scand* 1995;92:376-82. 10.1111/j.1600-0404.1995.tb00150.x pmid:8610490

83 Dabby R, Gilad R, Sadeh M, Lampl Y, Watemberg N. Acute steroid responsive small-fiber sensory neuropathy: a new entity? *J Peripher Nerv Syst* 2006;11:47-52. 10.1111/j.1085-9489.2006.00062.x. pmid:16519781.

84 Yuki N, Chan AC, Wong AHY, et al. Acute painful autoimmune neuropathy: A variant of Guillain-Barré syndrome. *Muscle Nerve* 2018;57:320-4. 10.1002/mus.25738. pmid:28667708.

85 Hoeijmakers JG, Faber CG, Lauria G, Merkies IS, Waxman SG. Small-fibre neuropathies—advances in diagnosis, pathophysiology and management. *Nat Rev Neurol* 2012;8:369-79. 10.1038/nrneurol.2012.97 pmid:22641108.

86 Faber CG, Lauria G, Merkies ISJ, et al. Gain-of-function Nav1.8 mutations in painful neuropathy. *Proc Natl Acad Sci U S A* 2012;109:19444-9. 10.1073/pnas.1216080109 pmid:23115331.

87 Huang J, Han C, Estacion M, et al. PROPANE Study Group. Gain-of-function mutations in sodium channel Na(v)1.9 in painful neuropathy. *Brain* 2014;137:1627-42. 10.1093/brain/awu079 pmid:24776970

88 Waxman SG, Merkies ISJ, Gerrits MM, et al. Sodium channel genes in pain-related disorders: phenotype-genotype associations and recommendations for clinical use. *Lancet Neurol* 2014;13:1152-60. 10.1016/S1474-4422(14)70150-4 pmid:25316021.

89 Planté-Bordeneuve V. Transthyretin familial amyloid polyneuropathy: an update. *J Neurol* 2018;265:976-83. 10.1007/s00415-017-8708-4. pmid:29249054

90 Rowczenio DM, Noor I, Gillmore JD, et al. Online registry for mutations in hereditary amyloidosis including nomenclature recommendations. *Hum Mutat* 2014;35:E2403-12. 10.1002/humu.22619 pmid:25044787.

91 Planté-Bordeneuve V, Said G. Familial amyloid polyneuropathy. *Lancet Neurol* 2011;10:1086-97. 10.1016/S1474-4422(11)70246-0. pmid:22094129.

92 Oaklander AL, Klein MM. Evidence of small-fiber polyneuropathy in unexplained, juvenile-onset, widespread pain syndromes. *Pediatrics* 2013;131:e1091-100. 10.1542/peds.2012-2597 pmid:23478869

93 Lawson VH, Grewal J, Hackshaw KV, Mongiovi PC, Stino AM. Fibromyalgia syndrome and small fiber, early or mild sensory polyneuropathy. *Muscle Nerve* 2018;58:625-30. 10.1002/mus.26131 pmid:29572887

94 Farhad K, Oaklander AL. Fibromyalgia and small-fiber polyneuropathy: What's in a name? *Muscle Nerve* 2018;58:611-3. 10.1002/mus.26179. pmid:29938813.

95 Lodahl M, Treister R, Oaklander AL. Specific symptoms may discriminate between fibromyalgia patients with vs without objective test evidence of small-fiber polyneuropathy. *Pain Rep* 2017;3:e633. 10.1097/PR9.0000000000000633. pmid:29430562.

96 Leinders M, Doppler K, Klein T, et al. Increased cutaneous miR-let-7d expression correlates with small nerve fiber pathology in patients with fibromyalgia syndrome. *Pain* 2016;157:2493-503. 10.1097/j.pain.0000000000000668. pmid:27429177.

97 Saperstein DS, Levine TD, Levine M, Hank N. Usefulness of skin biopsies in the evaluation and management of patients with suspected small fiber neuropathy. *Int J Neurosci* 2013;123:38-41. 10.3109/00207454.2012.723652 pmid:22947232

98 Asbury AK. Diagnostic considerations in Guillain-Barré syndrome. *Ann Neurol* 1981;9(Suppl):1-5. 10.1002/ana.410090703 pmid:7224610.

99 Windebank AJ, Blexrud MD, Dyck PJ, Daube JR, Karnes JL. The syndrome of acute sensory neuropathy: clinical features and electrophysiologic and pathologic changes. *Neurology* 1990;40:584-91. 10.1212/WNL.40.4.584 pmid:2157173

100 Oh SJ, LaGanke C, Claussen GC. Sensory Guillain-Barré syndrome. *Neurology* 2001;56:82-6. 10.1212/WNL.56.1.82 pmid:11148240

101 Mori M, Kuwabara S, Fukutake T, Yuki N, Hattori T. Clinical features and prognosis of Miller Fisher syndrome. *Neurology* 2001;56:1104-6. 10.1212/WNL.56.8.1104 pmid:11320188

102 Schabet M. Miller Fisher syndrome. *Pract Neurol* 2009;9:289-91. 10.1136/jnnp.2009.182113. pmid:19762889.

103 Weiss JA, White JC. Correlation of 1a afferent conduction with the ataxia of Fisher syndrome. *Muscle Nerve* 1986;9:327-32. 10.1002/mus.880090408. pmid:3713737

104 Kornberg AJ, Pestronk A, Blume GM, Lopate G, Yue J, Hahn A. Selective staining of the cerebellar molecular layer by serum IgG in Miller-Fisher and related syndromes. *Neurology* 1996;47:1317-20. 10.1212/WNL.47.5.1317 pmid:8909449

105 Lo YL. Clinical and immunological spectrum of the Miller Fisher syndrome. *Muscle Nerve* 2007;36:615-27. 10.1002/mus.20835 pmid:17657801.

106 Jacobs BC, Endtz H, van der Meché FG, Hazenberg MP, Achtereekte HA, van Doorn PA. Serum anti-GQ1b IgG antibodies recognize surface epitopes on Campylobacter jejuni from patients with Miller Fisher syndrome. *Ann Neurol* 1995;37:260-4. 10.1002/ana.410370218. pmid:7531419.

107 Jacobs BC, Hazenberg MP, van Doorn PA, Endtz HP, van der Meché FG. Cross-reactive antibodies against gangliosides and Campylobacter jejuni lipopolysaccharides in patients with Guillain-Barré or Miller Fisher syndrome. *J Infect Dis* 1997;175:729-33. 10.1093/infdis/175.3.729 pmid:9041356.

108 Schwerer B. Antibodies against gangliosides: a link between preceding infection and immunopathogenesis of Guillain-Barré syndrome. *Microbes Infect* 2002;4:373-84. 10.1016/S1286-4579(02)01550-2 pmid:11909748.

109 Fross RD, Daube JR. Neuropathy in the Miller Fisher syndrome: clinical and electrophysiologic findings. *Neurology* 1987;37:1493-8. 10.1212/WNL.37.9.1493 pmid:2819783

110 Wakerley BR, Uncini A, Yuki N. GBS Classification Group. Guillain-Barré and Miller Fisher syndromes—new diagnostic classification. *Nat Rev Neurol* 2014;10:537-44. 10.1038/nrneurol.2014.138. pmid:25072194

111 Yuki N, Uncini A. Acute and chronic ataxic neuropathies with disialosyl antibodies: a continuous clinical spectrum and a common pathophysiological mechanism. *Muscle Nerve* 2014;49:629-35. 10.1002/mus.24192 pmid:24477738.

112 Rojas-García R, Querol L, Gallardo E, et al. Clinical and serological features of acute sensory ataxic neuropathy with antiganglioside antibodies. *J Peripher Nerv Syst* 2012;17:158-68. 10.1111/j.1529-8027.2012.00407.x pmid:22734901

113 Richter RB. The ataxic form of polyradiculoneuritis (Landry-Guillain-Barré syndrome). Clinical and pathologic observations. *J Neuropathol Exp Neurol* 1962;21:171-84. 10.1097/00005072-196204000-00001 pmid:14492053

114 Yuki N, Susuki K, Hirata K. Ataxic Guillain-Barré syndrome with anti-GQ1b antibody: relation to Miller Fisher syndrome. *Neurology* 2000;54:1851-3. 10.1212/WNL.54.9.1851 pmid:10802797

115 Ito M, Matsuno K, Sakumoto Y, Hirata K, Yuki N. Ataxic Guillain-Barré syndrome and acute sensory ataxic neuropathy form a continuous spectrum. *J Neurol Neurosurg Psychiatry* 2011;82:294-9. 10.1136/jnnp.2010.222836. pmid:21252265

116 Uncini A, Susuki K, Yuki N. Nodo-paranodopathy: beyond the demyelinating and axonal classification in anti-ganglioside antibody-mediated neuropathies. *Clin Neurophysiol* 2013;124:1928-34. 10.1016/j.clinph.2013.03.025 pmid:23639374

117 Garcia-Santibanez R, Zaidman CM, Sommerville RB, et al. CANOMAD and other chronic ataxic neuropathies with disialosyl antibodies (CANDA). *J Neurol* 2018;265:1402-9. 10.1007/s00415-018-8853-4 pmid:29633012

118 Willison HJ, O'Leary CP, Veitch J, et al. The clinical and laboratory features of chronic sensory ataxic neuropathy with anti-disialosyl IgM antibodies. *Brain* 2001;124:1968-77. 10.1093/brain/124.10.1968 pmid:11571215

119 Attarian S, Boucraut J, Hubert AM, et al. Chronic ataxic neuropathies associated with anti-GD1b IgM antibodies: response to IVIg therapy. *J Neurol Neurosurg Psychiatry* 2010;81:61-4. 10.1136/jnnp.2009.185736. pmid:19726417.

120 Oh SJ, Joy JL, Kuruoglu R. "Chronic sensory demyelinating neuropathy": chronic inflammatory demyelinating polyneuropathy presenting as a pure sensory neuropathy. *J Neurol Neurosurg Psychiatry* 1992;55:677-80. 10.1136/jnnp.55.8.677 pmid:1326601

121 Oh SJ, Joy JL, Sunwoo I, Kuruoglu R. A case of chronic sensory demyelinating neuropathy responding to immunotherapies. *Muscle Nerve* 1992;15:255-6. 10.1002/mus.880150219. pmid:1549147
122 Simmons Z, Tivakaran S. Acquired demyelinating polyneuropathy presenting as a pure clinical sensory syndrome. *Muscle Nerve* 1996;19:1174-6. 10.1002/(SICI)1097-4598(199609)19:9<1174::AID-MUS16>3.0.CO;2-V. pmid:8761278
123 Ayrignac X, Viala K, Koutlidis RM, et al. Sensory chronic inflammatory demyelinating polyneuropathy: an under-recognized entity? *Muscle Nerve* 2013;48:727-32. 10.1002/mus.23821. pmid:23424105
124 Rajabally YA, Wong SL. Chronic inflammatory pure sensory polyradiculoneuropathy: a rare CIDP variant with unusual electrophysiology. *J Clin Neuromuscul Dis* 2012;13:149-52. 10.1097/CND.0b013e31822484fb. pmid:22538310.
125 Sinnreich M, Klein CJ, Daube JR, Engelstad J, Spinner RJ, Dyck PJB. Chronic immune sensory polyradiculopathy: a possibly treatable sensory ataxia. *Neurology* 2004;63:1662-9. 10.1212/01.WNL.0000142507.12763.58. pmid:15534252.
126 Saperstein DS, Katz JS, Amato AA, Barohn RJ. Clinical spectrum of chronic acquired demyelinating polyneuropathies. *Muscle Nerve* 2001;24:311-24. 10.1002/1097-4598(200103)24:3<311::AID-MUS1001>3.0.CO;2-A. pmid:11353415.
127 Larue S, Bombelli F, Viala K, et al. Non-anti-MAG DADS neuropathy as a variant of CIDP: clinical, electrophysiological, laboratory features and response to treatment in 10 cases. *Eur J Neurol* 2011;18:899-905. 10.1111/j.1468-1331.2010.03312.x. pmid:21199182.
128 Dalakas MC. Advances in the diagnosis, immunopathogenesis and therapies of IgM-anti-MAG antibody-mediated neuropathies. *Ther Adv Neurol Disord* 2018;11:1756285617746640. 10.1177/1756285617746640. pmid:29403542.
129 Katz JS, Saperstein DS, Gronseth G, Amato AA, Barohn RJ. Distal acquired demyelinating symmetric neuropathy. *Neurology* 2000;54:615-20. 10.1212/WNL.54.3.615. pmid:10680792.
130 Dalakas MC, Teravainen H, Engel WK. Tremor as a feature of chronic relapsing and dysgammaglobulinemic polyneuropathies. Incidence and management. *Arch Neurol* 1984;41:711-4. 10.1001/archneur.1984.04050180033012. pmid:6743059.
131 Pedersen SF, Pullman SL, Latov N, Brannagan TH 3rd. Physiological tremor analysis of patients with anti-myelin-associated glycoprotein associated neuropathy and tremor. *Muscle Nerve* 1997;20:38-44. 10.1002/(SICI)1097-4598(199701)20:1<38::AID-MUS5>3.0.CO;2-I. pmid:8995581.
132 Kaku DA, England JD, Sumner AJ. Distal accentuation of conduction slowing in polyneuropathy associated with antibodies to myelin-associated glycoprotein and sulphated glucuronyl paragloboside. *Brain* 1994;117:941-7. 10.1093/brain/117.5.941. pmid:7953603.
133 Lupu VD, Mora CA, Dambrosia J, Meer J, Dalakas M, Floeter MK. Terminal latency index in neuropathy with antibodies against myelin-associated glycoproteins. *Muscle Nerve* 2007;35:196-202. 10.1002/mus.20678. pmid:17068765
134 Monaco S, Bonetti B, Ferrari S, et al. Complement-mediated demyelination in patients with IgM monoclonal gammopathy and polyneuropathy. *N Engl J Med* 1990;322:649-52. 10.1056/NEJM199003083221002. pmid:1689461.
135 Antoine J-C, Camdessanché J-P. Paraneoplastic disorders of the peripheral nervous system. *Presse Med* 2013;42:e235-44. 10.1016/j.lpm.2013.01.059. pmid:23608019.
136 Taieb G, Renard D, Deverdal M, Honnorat J, Labauge P, Castelnovo G. Pure monomelic sensory neuronopathy associated with anti-yo antibodies. *Muscle Nerve* 2012;45:297-8. 10.1002/mus.22168. pmid:22246892.
137 Antoine JC, Mosnier JF, Absi L, Convers P, Honnorat J, Michel D. Carcinoma associated paraneoplastic peripheral neuropathies in patients with and without anti-onconeural antibodies. *J Neurol Neurosurg Psychiatry* 1999;67:7-14. 10.1136/jnnp.67.1.7. pmid:10369814.
138 Graus F, Keime-Guibert F, Reñé R, et al. Anti-Hu-associated paraneoplastic encephalomyelitis: analysis of 200 patients. *Brain* 2001;124:1138-48. 10.1093/brain/124.6.1138. pmid:11353730.
139 Côté-Mantha E, Savard M. Paraneoplastic anti-HU syndrome associated with uterine tumor. *Can J Neurol Sci* 2012;39:254-5. 10.1017/S0317167100022198. pmid:22506291.
140 Fournier CN, Kalra A, Lachance DH, Zaevan C, Srinivasan J. ANNA-1 (anti-Hu) associated sensory neuronopathy with malignant mixed mullerian tumor. *Muscle Nerve* 2013;47:776-7. 10.1002/mus.23764. pmid:23536385.
141 Saso T, Tanaka K, Ito N. Anti-Hu-antibody-associated paraneoplastic neurological syndrome accompanying testicular cancer. *Int J Urol* 2010;17:99. 10.1111/j.1442-2042.2009.02422.x. pmid:20377832
142 Lukacs S, Szabo N, Woodhams S. Rare association of anti-hu antibody positive paraneoplastic neurological syndrome and transitional cell bladder carcinoma. *Case Rep Urol* 2012;2012:724940. 10.1155/2012/724940. pmid:23320243.
143 Cowley A, Pascoe S. Paraneoplastic subacute sensory neuronopathy in association with adenocarcinoma of the prostate. *BMJ Case Rep* 2011;2011:bcr0420114077. 10.1136/bcr.04.2011.4077. pmid:22689835
144 Matsui T, Hori Y, Nagano H, et al. Poorly differentiated hepatocellular carcinoma accompanied by anti-Hu antibody-positive paraneoplastic peripheral neuropathy. *Pathol Int* 2015;65:388-92. 10.1111/pin.12304. pmid:25961021.
145 Oh SJ, Gurtekin Y, Dropcho EJ, King P, Claussen GC. Anti-Hu antibody neuropathy: a clinical, electrophysiological, and pathological study. *Clin Neurophysiol* 2005;116:28-34. 10.1016/j.clinph.2004.07.012. pmid:15589180.
146 Ogawa M, Nishie M, Kurahashi K, Kaimori M, Wakabayashi K. Anti-Hu associated paraneoplastic sensory neuronopathy with upper motor neurone involvement. *J Neurol Neurosurg Psychiatry* 2004;75:1051-3. 10.1136/jnnp.2003.024265. pmid:15201371.
147 Voltz R, Dalmau J, Posner JB, Rosenfeld MR. T-cell receptor analysis in anti-Hu associated paraneoplastic encephalomyelitis. *Neurology* 1998;51:1146-50. 10.1212/WNL.51.4.1146. pmid:9781545
148 Tomita M, Koike H, Kawagashira Y, et al. Clinicopathological features of neuropathy associated with lymphoma. *Brain* 2013;136:2563-78. 10.1093/brain/awt193. pmid:23884813.
149 Dalmau J, Graus F, Cheung NK, et al. Major histocompatibility proteins, anti-Hu antibodies, and paraneoplastic encephalomyelitis in neuroblastoma and small cell lung cancer. *Cancer* 1995;75:99-109. 10.1002/1097-0142(19950101)75:1<99::AID-CNCR2820750117>3.0.CO;2-I. pmid:7804984.
150 Griffin JW, Cornblath DR, Alexander E, et al. Ataxic sensory neuropathy and dorsal root ganglionitis associated with Sjogren's syndrome. *Ann Neurol* 1990;27:304-15. 10.1002/ana.410270313. pmid:2327738
151 Damasceno A, França MC Jr, , Cury H, Nucci A. Autonomic dysfunction in non-paraneoplastic sensory neuronopathy: beyond sensory abnormalities. *J Neurol* 2011;258:231-7. 10.1007/s00415-010-5730-1. pmid:20820798.
152 Mellgren SI, Göransson LG, Omdal R. Primary Sjogren's syndrome associated neuropathy. *Can J Neurol Sci* 2007;34:280-7. 10.1017/S0317167100006697. pmid:17803024
153 Berger JR, Dean D. Neurosyphilis. *Handb Clin Neurol* 2014;121:1461-72. 10.1016/B978-0-7020-4088-7.00098-5. pmid:24365430
154 England JD, Gronseth GS, Franklin G, et al. American Academy of Neurology. Practice Parameter: evaluation of distal symmetric polyneuropathy: role of laboratory and genetic testing (an evidence-based review). Report of the American Academy of Neurology, American Association of Neuromuscular and Electrodiagnostic Medicine, and American Academy of Physical Medicine and Rehabilitation. *Neurology* 2009;72:185-92. 10.1212/01.wnl.0000336370.51010.a1. pmid:19056666.
155 Bodofsky EB, Carter GT, England JD. Is electrodiagnostic testing for polyneuropathy overutilized? *Muscle Nerve* 2017;55:301-4. 10.1002/mus.25464. pmid:19056666
156 Kothari MJ, Preston DC, Plotkin GM, Venkatesh S, Shefner JM, Logigian EL. Electromyography: do the diagnostic ends justify the means? *Arch Phys Med Rehabil* 1995;76:947-9. 10.1016/S0003-9993(95)80072-7. pmid:7487436.
157 Kothari MJ, Blakeslee MA, Reichwein R, Simmons Z, Logigian EL. Electrodiagnostic studies: are they useful in clinical practice? *Arch Phys Med Rehabil* 1998;79:1510-1. 10.1016/S0003-9993(98)90411-7. pmid:9862291
158 Cho SC, Siao-Tick-Chong P, So YT. Clinical utility of electrodiagnostic consultation in suspected polyneuropathy. *Muscle Nerve* 2004;30:659-62. 10.1002/mus.20119. pmid:15389656
159 Callaghan BC, Burke JF, Kerber KA, Albers JW, Feldman EL. Electrodiagnostic tests are unlikely to change management in those with a known cause of typical distal symmetric polyneuropathy. *Muscle Nerve* 2017;56:E25. 10.1002/mus.25713. pmid:28561909
160 Pereira PR, Viala K, Maisonobe T, et al. Sjogren sensory neuronopathy (Sjogren ganglionopathy): long-term outcome and treatment response in a series of 13 cases. *Medicine (Baltimore)* 2016;95:e3632. 10.1097/MD.0000000000003632. pmid:27175675
161 Antoine J-C, Robert-Varvat F, Maisonobe T, et al. French CIDP study group. Testing the validity of a set of diagnostic criteria for sensory neuronopathies: a francophone collaborative study. *J Neurol* 2014;261:2093-100. 10.1007/s00415-014-7423-7. pmid:25108558.
162 Zis P, Hadjivassiliou M, Sarrigiannis PG, Barker ASJE, Rao DG. Rapid neurophysiological screening for sensory ganglionopathy: A novel approach. *Brain Behav* 2017;7:e00880. 10.1002/brb3.880. pmid:29299392.
163 Auger RG, Windebank AJ, Lucchinetti CF, Chalk CH. Role of the blink reflex in the evaluation of sensory neuronopathy. *Neurology* 1999;53:407-8. 10.1212/WNL.53.2.407. pmid:10430436
164 Alam T, Barker ASE, Alix JJP, Hadjivassiliou M, Rao DG. Sensory ganglionopathy and the blink reflex: electrophysiological features. *Can J Neurol Sci* 2016;43:385-9. 10.1017/cjn.2015.361. pmid:26795714
165 Cruccu G, Aminoff MJ, Curio G, et al. Recommendations for the clinical use of somatosensory-evoked potentials. *Clin Neurophysiol* 2008;119:1705-19. 10.1016/j.clinph.2008.03.016. pmid:18486546.
166 Cierici AM, Nobile-Orazio E, Mauri M, Squellati FS, Bono GG. Utility of somatosensory evoked potentials in the assessment of response to IVIG in a long-lasting case of chronic immune sensory polyradiculopathy. *BMC Neurol* 2017;17:127. 10.1186/s12883-017-0906-2. pmid:28668085.
167 Di Stefano G, La Cesa S, Leone C, et al. Diagnostic accuracy of laser-evoked potentials in diabetic neuropathy. *Pain* 2017;158:1100-7. 10.1097/j.pain.0000000000000889. pmid:28267059.

168 Lefaucheur J-P, Wahab A, Planté-Bordeneuve V, et al. Diagnosis of small fiber neuropathy. A comparative study of five neurophysiological tests. *Neurophysiol Clin* 2015;45:445-55. 10.1016/j.neucli.2015.09.012. pmid:26596193

169 Backonja MM, Attal N, Baron R, et al. Value of quantitative sensory testing in neurological and pain disorders: NeuPSIG consensus. *Pain* 2013;154:1807-19. 10.1016/j.pain.2013.05.047. pmid:23742795

170 Selim MM, Wendelschafer-Crabb G, Hodges JS, et al. Variation in quantitative sensory testing and epidermal nerve fiber density in repeated measurements. *Pain* 2010;151:575-81. 10.1016/j.pain.2010.06.034. pmid:20851518

171 Maier C, Baron R, Tölle TR, et al. Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): somatosensory abnormalities in 1236 patients with different neuropathic pain syndromes. *Pain* 2010;150:439-50. 10.1016/j.pain.2010.05.002. pmid:20627413.

172 Dyck PJ, Dyck PJ, Kennedy WR, et al. Limitations of quantitative sensory testing when patients are biased toward a bad outcome. *Neurology* 1998;50:1213. 10.1212/WNL.50.5.1213. pmid:9595965.

173 Shy ME, Frohman EM, So YT, et al. Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Quantitative sensory testing: report of the therapeutics and technology assessment subcommittee of the American Academy of Neurology. *Neurology* 2003;60:898-904. 10.1212/01.WNL.0000058546.16985.11. pmid:12654951.

174 Hansson P, Backonja M, Bouhassira D. Usefulness and limitations of quantitative sensory testing: clinical and research application in neuropathic pain states. *Pain* 2007;129:256-9. 10.1016/j.pain.2007.03.030. pmid:17451879.

175 Tavakoli M, Marshall A, Thompson L, et al. Corneal confocal microscopy: a novel noninvasive means to diagnose neuropathy in patients with Fabry disease. *Muscle Nerve* 2009;40:976-84. 10.1002/mus.21383. pmid:19902546.

176 Perkins BA, Lovblom LE, Bril V, et al. Corneal confocal microscopy for identification of diabetic sensorimotor polyneuropathy: a pooled multinational consortium study. *Diabetologia* 2018;61:1856-61. 10.1007/s00125-018-4653-8. pmid:29869146

177 Bönes M, Culver DA, Ferdousi M, et al. Corneal nerve fiber size adds utility to the diagnosis and assessment of therapeutic response in patients with small fiber neuropathy. *Sci Rep* 2018;8:4734. 10.1038/s41598-018-23107-w. pmid:29549285.

178 Alam U, Jeziorska M, Petropoulos IN, et al. Diagnostic utility of corneal confocal microscopy and intra-epidermal nerve fibre density in diabetic neuropathy. *PLoS One* 2017;12:e0180175. 10.1371/journal.pone.0180175. pmid:28719619.

179 Chen X, Graham J, Dabbah MA, et al. Small nerve fiber quantification in the diagnosis of diabetic sensorimotor polyneuropathy: comparing corneal confocal microscopy with intraepidermal nerve fiber density. *Diabetes Care* 2015;38:1138-44. 10.2337/dc14-2422. pmid:25795415.

180 Bucher F, Schneider C, Blau T, et al. Small-fiber neuropathy is associated with corneal nerve and dendritic cell alterations: an in vivo confocal microscopy study. *Cornea* 2015;34:1114-9. 10.1097/ICO.0000000000000535. pmid:26186372

181 Ferdousi M, Azmi S, Petropoulos IN, et al. Corneal confocal microscopy detects small fibre neuropathy in patients with upper gastrointestinal cancer and nerve regeneration in chemotherapy induced peripheral neuropathy. *PLoS One* 2015;10:e0139394. 10.1371/journal.pone.0139394. pmid:26430773

182 Kemp HI, Petropoulos IN, Rice ASC, et al. Use of corneal confocal microscopy to evaluate small nerve fibers in patients with human immunodeficiency virus. *JAMA Ophthalmol* 2017;135:795-800. 10.1001/jamaophthalmol.2017.1703. pmid:28594979

183 Scarr D, Lovblom LE, Lovshin JA, et al. Lower corneal nerve fibre length identifies diabetic neuropathy in older adults with diabetes: results from the Canadian Study of Longevity in Type 1 Diabetes. *Diabetologia* 2017;60:2529-31. 10.1007/s00125-017-4439-4. pmid:28971222.

184 Kass-Iliyya L, Javed S, Gosal D, et al. Small fiber neuropathy in Parkinson's disease: A clinical, pathological and corneal confocal microscopy study. *Parkinsonism Relat Disord* 2015;21:1454-60. 10.1016/j.parkreldis.2015.10.019. pmid:26578039.

185 Scarr D, Lovblom LE, Ostrovski I, et al. Agreement between automated and manual quantification of corneal nerve fiber length: Implications for diabetic neuropathy research. *J Diabetes Complications* 2017;31:1066-73. 10.1016/j.jdiacomp.2016.07.024. pmid:28347694.

186 England JD, Gronseth GS, Franklin G, et al. American Academy of Neurology. Practice Parameter: evaluation of distal symmetric polyneuropathy: role of autonomic testing, nerve biopsy, and skin biopsy (an evidence-based review). Report of the American Academy of Neurology, American Association of Neuromuscular and Electrodiagnostic Medicine, and American Academy of Physical Medicine and Rehabilitation. *Neurology* 2009;72:177-84. 10.1212/01.wnl.0000336345.70511.0f. pmid:19056667.

187 Buchmann SJ, Penzlin AI, Kubasch ML, Illigens BM-W, Siepmann T. Assessment of sudomotor function. *Clin Auton Res* 2019;29:41-53. 10.1007/s10286-018-0530-2. pmid:29737432

188 Abuzinadah AR, Kluding P, Wright D, et al. Less is more in diabetic neuropathy diagnosis: comparison of quantitative sudomotor axon reflex and skin biopsy. *J Clin Neuromuscul Dis* 2017;19:5-11. 10.1097/CND.0000000000000150. pmid:28827483.

189 Novak V, Freimer ML, Kissel JT, et al. Autonomic impairment in painful neuropathy. *Neurology* 2001;56:861-8. 10.1212/WNL.56.7.861. pmid:11294922.

190 Carroll MS, Reed DW, Kuntz NL, Weese-Mayer DE. Novel methods of imaging and analysis for the thermoregulatory sweat test. *J Appl Physiol (1985)* 2018;125:755-62. 10.1152/japplphysiol.01086.2017. pmid:29878873.

191 Castro J, Miranda B, Castro I, de Carvalho M, Conceição I. The diagnostic accuracy of Sudoscan in transthyretin familial amyloid polyneuropathy. *Clin Neurophysiol* 2016;127:2222-7. 10.1016/j.clinph.2016.02.013. pmid:27072093.

192 Low VA, Sandroni P, Fealey RD, Low PA. Detection of small-fiber neuropathy by sudomotor testing. *Muscle Nerve* 2006;34:57-61. 10.1002/mus.20551. pmid:16718689

193 Gordon Smith AG, Lessard M, Reyna S, Doudova M, Singleton JR. The diagnostic utility of Sudoscan for distal symmetric peripheral neuropathy. *J Diabetes Complications* 2014;28:511-6. 10.1016/j.jdiacomp.2014.02.013. pmid:24661818.

194 Rajan S, Campagnolo M, Callaghan B, Gibbons CH. Sudomotor function testing by electrochemical skin conductance: does it really measure sudomotor function? *Clin Auton Res* 2019;29:31-9. 10.1007/s10286-018-0540-0. pmid:29956008.

195 Wilder-Smith EP, Guo Y, Chow A. Stimulated skin wrinkling for predicting intraepidermal nerve fibre density. *Clin Neurophysiol* 2009;120:953-8. 10.1016/j.clinph.2009.03.011. pmid:19375384

196 Ping Ng KW, Ong JJY, Nyein Nyein TD, et al. EMLA-induced skin wrinkling for the detection of diabetic neuropathy. *Front Neurol* 2013;4:126. 10.3389/fneur.2013.00126. pmid:24032026.

197 Teoh HL, Chow A, Wilder-Smith EP. Skin wrinkling for diagnosing small fibre neuropathy: comparison with epidermal nerve density and sympathetic skin response. *J Neurol Neurosurg Psychiatry* 2008;79:835-7. 10.1136/jnnp.2007.140947. pmid:18270233.

198 Birnbaum J, Lalji A, Piccione EA, Izbudak I. Magnetic resonance imaging of the spinal cord in the evaluation of 3 patients with sensory neuronopathies: Diagnostic assessment, indications of treatment response, and impact of autoimmunity: A case report. *Medicine (Baltimore)* 2017;96:e8483. 10.1097/MD.0000000000008483. pmid:29245216.

199 Ebadi H, Siddiqui H, Ebadi S, Ngo M, Breiner A, Bril V. Peripheral nerve ultrasound in small fiber polyneuropathy. *Ultrasound Med Biol* 2015;41:2820-6. 10.1016/j.ultrasmedbio.2015.06.011. pmid:26318562.

200 Walker FO, Cartwright MS, Alter KE, et al. Indications for neuromuscular ultrasound: Expert opinion and review of the literature. *Clin Neurophysiol* 2018;129:2658-79. 10.1016/j.clinph.2018.09.013. pmid:30309740.

201 Lauria G, Hsieh ST, Johansson O, et al. European Federation of Neurological Societies Peripheral Nerve Society. European Federation of Neurological Societies/Peripheral Nerve Society Guideline on the use of skin biopsy in the diagnosis of small fiber neuropathy. Report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society. *Eur J Neurol* 2010;17:903-12, e44-9. 10.1111/j.1468-1331.2010.03023.x. pmid:20642627

202 Lauria G, Bakkers M, Schmitz C, et al. Intraepidermal nerve fiber density at the distal leg: a worldwide normative reference study. *J Peripher Nerv Syst* 2010;15:202-7. 10.1111/j.1529-8027.2010.00271.x. pmid:21040142

203 Collongues N, Samama B, Schmidt-Mutter C, et al. Quantitative and qualitative normative dataset for intraepidermal nerve fibers using skin biopsy. *PLoS One* 2018;13:e0191614. 10.1371/journal.pone.0191614. pmid:29370274

204 Lauria G, Cornblath DR, Johansson O, et al. European Federation of Neurological Societies. EFNS guidelines on the use of skin biopsy in the diagnosis of peripheral neuropathy. *Eur J Neurol* 2005;12:747-58. 10.1111/j.1468-1331.2005.01260.x. pmid:16190912.

205 Provitera V, Gibbons CH, Wendelschafer-Crabb G, et al. A multi-center, multinational age- and gender-adjusted normative dataset for immunofluorescent intraepidermal nerve fiber density at the distal leg. *Eur J Neurol* 2016;23:333-8. 10.1111/ene.12842. pmid:26493160

206 Devigili G, Tugnoli V, Penza P, et al. The diagnostic criteria for small fibre neuropathy: from symptoms to neuropathology. *Brain* 2008;131:1912-25. 10.1093/brain/awn093. pmid:18524793.

207 Blackmore D, Siddiqi ZA. Diagnostic criteria for small fiber neuropathy. *J Clin Neuromuscul Dis* 2017;18:125-31. 10.1097/CND.0000000000000154. pmid:28221302.

208 Takatsu M, Hays AP, Latov N, et al. Immunofluorescence study of patients with neuropathy and IgM M proteins. *Ann Neurol* 1985;18:173-81. 10.1002/ana.410180203. pmid:2412485

209 Hays AP, Lee SS, Latov N. Immune reactive C3d on the surface of myelin sheaths in neuropathy. *J Neuroimmunol* 1988;18:231-44. 10.1016/0165-5728(88)90101-4. pmid:2452830

210 Mendell JR, Sahenk Z, Whitaker JN, et al. Polyneuropathy and IgM monoclonal gammopathy: studies on the pathogenetic role of anti-myelin-associated glycoprotein antibody. *Ann Neurol* 1985;17:243-54. 10.1002/ana.410170305. pmid:2581496.

211 Jacobs JM, Scadding JW. Morphological changes in IgM paraproteinaemic neuropathy. *Acta Neuropathol* 1990;80:77-84. 10.1007/BF00294225. pmid:2163186.

212 Latov N. Diagnosis and treatment of chronic acquired demyelinating polyneuropathies. *Nat Rev Neurol* 2014;10:435-46. 10.1038/nrneurol.2014.117 pmid:24980070

213 Wiczek HF, Larsson M, Ericzon B-G, FAPWTR. Long-term data from the Familial Amyloidotic Polyneuropathy World Transplant Registry (FAPWTR). *Amyloid* 2011;18(Suppl 1):193-5. 10.3109/13506129.2011.574354072. pmid:21838484.

214 Adams D, Gonzalez-Duarte A, O'Riordan WD, et al. Patisiran, an RNAi therapeutic, for hereditary transthyretin amyloidosis. *N Engl J Med* 2018;379:11-21. 10.1056/NEJMoa1716153. pmid:29972753

215 Benson MD, Waddington-Cruz M, Berk JL, et al. Inotersen treatment for patients with hereditary transthyretin amyloidosis. *N Engl J Med* 2018;379:22-31. 10.1056/NEJMoa1716793. pmid:29972757

216 Berk JL, Suhr OB, Obici L, et al. Diflunisal Trial Consortium. Repurposing diflunisal for familial amyloid polyneuropathy: a randomized clinical trial. *JAMA* 2013;310:2658-67. 10.1001/jama.2013.283815. pmid:24368466.

217 Coelho T, Maia LF, Martins da Silva A, et al. Tafamidis for transthyretin familial amyloid polyneuropathy: a randomized, controlled trial. *Neurology* 2012;79:785-92. 10.1212/WNL.0b013e3182661eb1. pmid:22843782.

218 Mori M, Kuwabara S, Fukutake T, Hattori T. Intravenous immunoglobulin therapy for Miller Fisher syndrome. *Neurology* 2007;68:1144-6. 10.1212/01.wnl.0000258671.11824.61 pmid:17404197

219 Overell JR, Willison HJ. Recent developments in Miller Fisher syndrome and related disorders. *Curr Opin Neurol* 2005;18:562-6. 10.1097/01.wco.0000178256.25581.2f pmid:16155441

220 Patwa HS, Chaudhry V, Katzberg H, Rae-Grant AD, So YT. Evidence-based guideline: intravenous immunoglobulin in the treatment of neuromuscular disorders: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* 2012;78:1009-15. 10.1212/WNL.0b013e31824de293. pmid:22454268

221 Siddiqui K, Cabalane E, Keogan M, Hardiman O. Chronic ataxic neuropathy with cold agglutinins, atypical phenotype and response to anti-CD20 antibodies. *Neurology* 2003;61:1307-8. 10.1212/WNL.61.9.1307 pmid:14610153.

222 Loscher WN, Woertz A, Wallnofer M, Wanschitz JV, Luef G. Successful treatment of CANOMAD with IVIg and rituximab. *J Neurol* 2013;260:1168-70. 10.1007/s00415-013-6867-5. pmid:23400502.

223 Delmont E, Jeandel PY, Hubert AM, Maruo L, Boucraut J, Desnuelle C. Successful treatment with rituximab of one patient with CANOMAD neuropathy. *J Neurol* 2010;257:655-7. 10.1007/s00415-009-5412-z. pmid:19960199.

224 Kam C, Balaratnam MS, Purves A, et al. Canomad presenting without ophthalmoplegia and responding to intravenous immunoglobulin. *Muscle Nerve* 2011;44:829-33. 10.1002/mus.22167. pmid:22006700.

225 Dalakas MC. Rituximab in anti-MAG neuropathy: More evidence for efficacy and more predictive factors. *J Neurol Sci* 2017;377:224-6. 10.1016/j.jns.2017.04.016. pmid:28477700.

226 Dalakas MC, Rakocevic G, Salajegheh M, et al. Placebo-controlled trial of rituximab in IgM anti-myelin-associated glycoprotein antibody demyelinating neuropathy. *Ann Neurol* 2009;65:286-93. 10.1002/ana.21577. pmid:19334068.

227 Ianca Ferfoglia R, Guimarães-Costa R, Viala K, et al. Long-term efficacy of rituximab in IgM anti-myelin-associated glycoprotein neuropathy: RIMAG follow-up study. *J Peripher Nerv Syst* 2016;21:10-4. 10.1111/jns.12156. pmid:26748872

228 Gazzola S, Delmont E, Franques J, et al. Predictive factors of efficacy of rituximab in patients with anti-MAG neuropathy. *J Neurol Sci* 2017;377:144-8. 10.1016/j.jns.2017.04.015. pmid:28477606.

229 Svahn J, Petiot P, Antoine J-C, et al. Francophone anti-MAG cohort Group. Anti-MAG neuropathies in 202 patients: clinicopathological and therapeutic features. *J Neurol Neurosurg Psychiatry* 2018;89:499-505. 10.1136/jnnp-2017-316715 pmid:29070644.

230 Joint Task Force of the EFNS and the PNS. European Federation of Neurological Societies/Peripheral Nerve Society Guideline on management of paraproteinemic demyelinating neuropathies. Report of a joint Task Force of the European Federation of Neurological Societies and the Peripheral Nerve Society—first revision. *J Peripher Nerv Syst* 2010;15:185-95. 10.1111/j.1529-8027.2010.00278.x. pmid:21040140.

231 Rakocevic G, Martinez-Outschoorn U, Dalakas MC. Obinutuzumab, a potent anti-B-cell agent, for rituximab-unresponsive IgM anti-MAG neuropathy. *Neurol Neuroimmunol Neuroinflamm* 2018;5:e460. 10.1212/NXI.0000000000000460 pmid:29629397

232 Antoine J-C, Robert-Varval F, Marsonobe T, et al. French Neuromuscular Network FILNEMUS. Identifying a therapeutic window in acute and subacute inflammatory sensory neuronopathies. *J Neurol Sci* 2016;365:187-91. 10.1016/j.jns.2015.12.044. pmid:26810539

233 Takahashi Y, Takata T, Hoshino M, Sakuma M, Kanazawa I. Benefit of IVIG for long-standing ataxic sensory neuronopathy with Sjogren's syndrome. IV immunoglobulin. *Neurology* 2003;60:501-5. 10.1212/01.WNL.0000046680.47883.7D pmid:12578938.

234 Chen WH, Yeh BI, Chiu HC. Plasmapheresis in the treatment of ataxic sensory neuropathy associated with Sjögren's syndrome. *Eur Neurol* 2001;45:270-4. 10.1159/000052142 pmid:11385268

235 Santosa A, Lim AYN, Vasoo S, Lau EC, Teng GG. Neurosjogren: early therapy is associated with successful outcomes. *J Clin Rheumatol* 2012;18:189-92. 10.1097/RHU.0b013e318277169e pmid:23188203.

236 Pertovaara M, Korpela M. Sustained response to rituximab in a patient with Sjögren's syndrome and severe refractory polyneuropathy. *Clin Exp Rheumatol* 2012;30:808-9.pmid:22992382

237 Martinez ARM, Nunes MB, Nucci A, França MC Jr. Sensory neuropathy and autoimmune diseases. *Autoimmune Dis* 2012;2012:873587. 10.1155/2012/873587. pmid:22312482

238 Caroyer J-M, Maalo MU, Stenfeld SD. Severe sensory neuronopathy responsive to infliximab in primary Sjögren's syndrome. *Neurology* 2002;59:1113-4. 10.1212/WNL.59.7.1113 pmid:12370480

239 Oh SJ, Dropcho EJ, Claussen GC. Anti-Hu-associated paraneoplastic sensory neuropathy responding to early aggressive immunotherapy: report of two cases and review of literature. *Muscle Nerve* 1997;20:1576-82. 10.1002/(SICI)1097-4598(199712)20:12<1576::AID-MUS13>3.0.CO;2-2 pmid:9390671.

240 Rosenfeld MR, Dalmau J. Diagnosis and management of paraneoplastic neurologic disorders. *Curr Treat Options Oncol* 2013;14:528-38. 10.1007/s11864-013-0249-1 pmid:23900965

241 Uchuya M, Graus F, Vega F, René R, Delattre JY. Intravenous immunoglobulin treatment in paraneoplastic neurological syndromes with antineuronal autoantibodies. *J Neurol Neurosurg Psychiatry* 1996;60:388-92. 10.1136/jnnp.60.4.388 pmid:8774401.

242 Keime-Guibert F, Graus F, Fleury A, et al. Treatment of paraneoplastic neurological syndromes with antineuronal antibodies (anti-Hu, anti-Yo) with a combination of immunoglobulins, cyclophosphamide, and methylprednisolone. *J Neurol Neurosurg Psychiatry* 2000;68:479-82. 10.1136/jnnp.68.4.479 pmid:10727484.

243 Graus F, Vega F, Delattre JY, et al. Plasmapheresis and antineoplastic treatment in CNS paraneoplastic syndromes with antineuronal autoantibodies. *Neurology* 1992;42:536-40. 10.1212/WNL.42.3.536 pmid:1312683.

244 Shams'ili S, de Beukelaar J, Gratama JW, et al. An uncontrolled trial of rituximab for antibody associated paraneoplastic neurological syndromes. *J Neurol* 2006;253:16-20. 10.1007/s00415-005-0882-0. pmid:16444604

245 de Jongste AH, van Gelder T, Bromberg JE, et al. A prospective open-label study of sirolimus for the treatment of anti-Hu associated paraneoplastic neurological syndromes. *Neuro Oncol* 2015;17:145-50. 10.1093/neuonc/nou126. pmid:24994790.

246 Singleton JR, Smith AG, Marcus RL. Exercise as therapy for diabetic and prediabetic neuropathy. *Curr Diab Rep* 2015;15:120. 10.1007/s11892-015-0682-6. pmid:26538074

247 Singleton JR, Marcus RL, Jackson JEK, Kitsteard M, Graham TE, Smith AG. Exercise increases cutaneous nerve density in diabetic patients without neuropathy. *Ann Clin Transl Neurol* 2014;1:844-9. 10.1002/acn3.125. pmid:25493275.

248 Kluding PM, Pasnoor M, Singh R, et al. The effect of exercise on neuropathic symptoms, nerve function, and cutaneous innervation in people with diabetic peripheral neuropathy. *J Diabetes Complications* 2012;26:424-9. 10.1016/j.jdiacomp.2012.05.007 pmid:22717465

249 van Velzen M, Heij L, Niesters M, et al. ARA 290 for treatment of small fiber neuropathy in sarcoidosis. *Expert Opin Investig Drugs* 2014;23:561-50. 10.1517/13543784.2014.892072. pmid:24555851.

250 Morozumi S, Kawagashira Y, Iijima M, et al. Intravenous immunoglobulin treatment for painful sensory neuropathy associated with Sjogren's syndrome. *J Neurol Sci* 2009;279:57-61. 10.1016/j.jns.2008.12.018. pmid:19168191

251 Mori K, Koike H, Misu K, Hattori N, Ichimura M, Sobue G. Spinal cord magnetic resonance imaging demonstrates sensory neuronal involvement and clinical severity in neuronopathy associated with Sjogren's syndrome. *J Neurol Neurosurg Psychiatry* 2001;71:488-92. 10.1136/jnnp.71.4.488 pmid:11561032.

252 Wakasugi D, Kato T, Gono T, et al. Extreme efficacy of intravenous immunoglobulin therapy for severe burning pain in a patient with small fiber neuropathy associated with primary Sjögren's syndrome. *Mod Rheumatol* 2009;19:437-40. 10.1007/s10165-009-0180-2. pmid:19458906.

253 Dib-Hajj SD, Binshtok AM, Cummins TR, Jarvis MF, Samad I, Zimmermann K. Voltage-gated sodium channels in pain states: role in pathophysiology and targets for treatment. *Brain Res Rev* 2009;60:65-83. 10.1016/j.brainresrev.2008.12.005 pmid:19150627

254 Dib-Hajj SD, Waxman SG. Translational pain research: lessons from genetics and genomics. *Sci Transl Med* 2014;6:249. 10.1126/scitranslmed.3007017. pmid:25122661.

255 de Greef BTA, Merkies ISJ, Geerts M, Faber CG, Hoeijmakers JGJ. Efficacy, safety, and tolerability of lacosamide in patients with gain-of-function Nav1.7 mutation-related small fiber neuropathy: study protocol of a randomized controlled trial—the LENSS study. *Trials* 2016;17:306. 10.1186/s13063-016-1430-1. pmid:27363506.

256 Finnerup NB, Attal N, Haroutounian S, et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. *Lancet Neurol* 2015;14:162-73. 10.1016/S1474-4422(14)70251-0. pmid:25575710.

257 Waldfogel JM, Nesbit SA, Dy SM, et al. Pharmacotherapy for diabetic peripheral neuropathy pain and quality of life: A systematic review. *Neurology* 2017;88:1958-67. 10.1212/WNL.0000000000003887 pmid:28341643

258 Tesfaye S, Wilhelm S, Lledo A, et al. Duloxetine and pregabalin: high-dose monotherapy or their combination? The "COMBO-DN study"—a multinational, randomized, double-blind, parallel-group study in patients with diabetic peripheral neuropathic pain. *Pain* 2013;154:2616-25. 10.1016/j.pain.2013.05.043 pmid:23732189

259 Roy MK, Kudiakose AS, Varma SK, Jacob LA, Bregum NJ. A study on comparative efficacy and cost effectiveness of Pregabalin and Duloxetine used in diabetic neuropathic pain. *Diabetes Metab Syndr* 2017;11:S1-5. 10.1016/j.dsx.2016.07.003. pmid:27484440

260 Ballantyne JC. Opioids for the treatment of chronic pain: mistakes made, lessons learned, and future directions. *Anesth Analg* 2017;125:1769-78. 10.1213/ANE.0000000000002500 pmid:29049121

261 Busse JW, Wang L, Kamaleldin M, et al. Opioids for chronic noncancer pain: a systematic review and meta-analysis. *JAMA* 2018;320:2448-60. 10.1001/jama.2018.18472. pmid:30561481

262 Attal N, Cruccu G, Haanpaa M, et al. EFNS Task Force. EFNS guidelines on pharmacological treatment of neuropathic pain. *Eur J Neurol* 2006;13:1153-69. 10.1111/j.1468-1331.2006.01511.x pmid:17038030.

263 Bril V, England J, Franklin GM, et al. American Academy of Neurology American Association of Neuromuscular and Electrodiagnostic Medicine American Academy of Physical Medicine and Rehabilitation. Evidence-based guideline: treatment of painful diabetic neuropathy: report of the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. *Neurology* 2011;76:1758-65. 10.1212/WNL.0b013e3182166ebe. pmid:21482920

264 Lakhan SE, Velasco DN, Tepper D. Botulinum toxin-A for painful diabetic neuropathy: a meta-analysis. *Pain Med* 2015;16:1773-80. 10.1111/pme.12728 pmid:25800040.

265 Oh H-M, Chung ME. Botulinum toxin for neuropathic pain: a review of the literature. *Toxins (Basel)* 2015;7:3127-54. 10.3390/toxins7083127 pmid:26287242.

266 Meyer-Hamme G, Friedemann T, Greten HJ, Plaetke R, Gerloff C, Schroeder S. ACUDIN-ACU puncture and laser acupuncture for treatment of Diabetic peripheral Neuropathy: a randomized, placebo-controlled, partially double-blinded trial. *BMC Neurol* 2018;18:40. 10.1186/s12883-018-1037-0. pmid:29653569.

PROVA ORALE C

1) Valutazione Mismatch negativity (MMN)
    a. Modalità di stimolazione
    b. Modalità di registrazione
    c. Significato delle principali componenti
    d. Applicazioni cliniche

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

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PROVA 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; Dowell 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.,

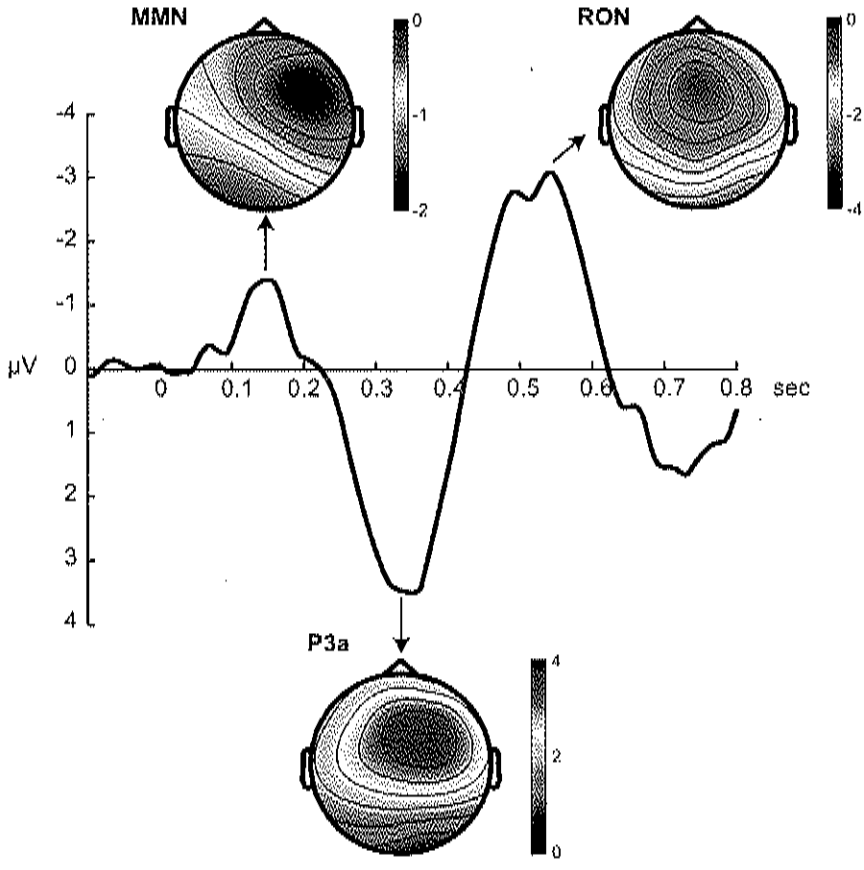

Fig. 1. The distraction potential.

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; Ruggi et al., 2010; Naatanen et al., 2011; Mackawa 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"

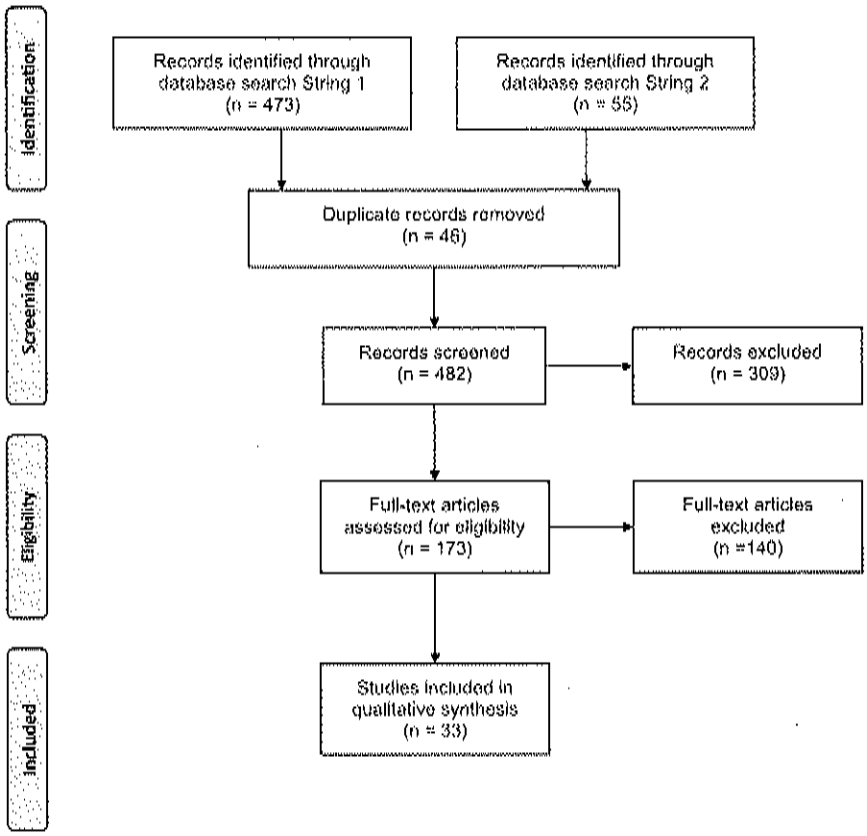

Fig. 2. Research items selection diagram.

-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 (Rustanov 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 10 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	Gezelli 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	↓	↓	↓
	Lahstein 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	↓	→	-
	Poels 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	Roelsch (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 (Rojala 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).

Hamagosi 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). Porter 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 $P3_a$ described in healthy adults by Friedman et al. (1993). $P3_a$ 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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References

Ahveninen, J., Kähkönen, S., Pennanen, S., Liesivuori, J., Ilmoniemi, R.J., Jääskelainen, I.P., 2002. EEG and MEG measurements after tryptophan depletion suggest serotonergic modulation of auditory involuntary attention. Neuroimage 16, 1052–1061.

Amaral, D., Geschwind, D., Dawson, G., 2011. Autism Spectrum Disorders. Oxford University Press.

Arnnoff, J.C., Goodin, D.S., 2001. Long-latency cerebral event-related potentials in multiple sclerosis. J. Clin. Neurophysiol. 18, 372–377.

Andersson, S., Barder, H.E., Hellvin, T., Lovdahl, H., Malt, U.F., 2008. Neuropsychological and electrophysiological indices of neurocognitive dysfunction in bipolar II disorder. Bipolar Disord. 10, 888–899.

Andreasen, N.C., 1990. Methods for assessing positive and negative Symptoms1 *Schizophrenia: positive and negative symptoms and syndromes*. Karger Publishers, pp. 73–88.

APA (2013) Diagnostic and Statistical Manual of Mental Disorders (DSM-5®). In Association, A.P. (ed). American Psychiatric Pub.

Apitz, T., Bunzeck, N., 2013. Dopamine controls the neural dynamics of memory signals and retrieval accuracy. Neuropsychopharmacology 38, 2409.

Atkinson, R.J., Michie, P.T., Schall, U., 2012. Duration mismatch negativity and P3a in first-episode psychosis and individuals at ultra-high risk of psychosis. Biol. Psychiatry 71, 98–104.

Atkinson, R.J., Fulham, W.R., Michie, P.T., Ward, P.B., Todd, J., Stain, H., Langdon, R., Thienel, R., Paulik, G., Cooper, G., Min, T.C., Schall, U., 2017. Electrophysiological, cognitive and clinical profiles of at-risk mental state: the longitudinal minds in transition (MinT) study. PLoS One 12, e0171657.

Azcarraga-Guirola, E., Rodriguez-Agudelo, Y., Velazquez-Cardoso, J., Rito-Garcia, Y., Solis-Vivanco, R., 2017. Electrophysiological correlates of decision making impairment in multiple sclerosis. Eur. J. Neurosci. 45, 321–329.

Baron-Cohen, S., Wheelwright, S., Skinner, R., Martin, J., Clubley, E., 2001. The autism-spectrum quotient (AQ): evidence from asperger syndrome/high-functioning autism, malesand females, scientists and mathematicians. J. Autism Dev. Disord. 31, 5–17.

Bear, M.F., Connors, B.W., Paradiso, M.A., 2007. Neuroscience. Lippincott Williams & Wilkins.

Beebe, D.W., Gozal, D., 2002. Obstructive sleep apnea and the prefrontal cortex: towards a comprehensive model linking nocturnal upper airway obstruction to daytime cognitive and behavioral deficits. J. Sleep Res. 11, 1–16.

Berti, Munka, 2006. Examining task-dependencies of different attentional processes as reflected in the P3a and reorienting negativity components of the human event-related brain potential. Neurosci. Lett. 396, 177–181.

Beste, C., Saft, C., Gruendken, O., Falkenstein, M., 2008. Increased cognitive functioning in symptomatic Huntington's disease as revealed by behavioral and event-related potential indices of auditory sensory memory and attention. J. Neurosci. 28, 11695–11702.

Bickel, S., Javitt, D.C., 2009. Neurophysiological and neurochemical animal models of schizophrenia: focus on glutamate. Behav. Brain Res. 204, 352–362.

Bigglas, C.A., MacKay, S., Clark, W., Fein, G., 1997. Event-related potential evidence for frontal cortex effects of chronic cocaine dependence. Biol. Psychiatry 42, 472–485.

Broadbent, D.E., 2013. Perception and Communication. Elsevier.

Broderick, M. & Guilleminault, C. (2008) Neurological aspects of obstructive sleep apnea. *Annals of the New York Academy of Sciences*, 1142, 44–57.

Bruder, G.E., Kayser, J., Tenke, C.E., 2012. Event-related brain potentials in depression: clinical, cognitive and neurophysiologic implications. The Oxford handbook of event-related potential components 2012, 563–592.

Cacioppo, J.T., Tassinary, L.G., Berntson, G.G., 2007. Psychophysiological science: Interdisciplinary approaches to classic questions about the mind. In: Handbook of Psychophysiology. pp. 1–16.

Cecchi, M., ERP for Diagnosis and Prognosis of Traumatic Brain Injury.

Chen, J., Zhang, Y., Wei, D., Wu, X., Fu, Q., Xu, F., Wang, H., Yu, M., Ma, W., Yang, L., 2014. Neurophysiological handover from MMN to P3a in first-episode and recurrent major depression. J. Affect. Disord. 174, 173–179.

Clery, H., Roux, S., Houy-Durand, E., Bonner-Jolibault, F., Brunvan, N., Gomot, M., 2013. Electrophysiological evidence of atypical visual change detection in adults with autism. Front. Hum. Neurosci. 7, 62.

Corbetta, M., Patel, G., Shulman, G.L., 2008. The reorienting system of the human brain: from environment to theory of mind. Neuron 58, 306–324.

Correa-Jaraba, K.S., Cid-Fernández, S., Lindín, M., Díaz, F., 2016. Involuntary capture and voluntary reorienting of attention decline in middle-aged and old participants. Front. Hum. Neurosci. 10, 129.

Cowan, N., 1999. An embedded-processes model of working memory. Models of working memory: Mechanisms of active maintenance and executive control 20, 506.

Dennett, Knight, 2009. Executive function and higher-order cognition: ERP studies. Encyclopedia of Neuroscience 4, 105–109.

Donchin, E., 1981. Surprise!... surprise? Psychophysiology 18, 493–513.

Dulude, L. (2008) Effects of Nicotine on Brain Event-Related Potential and Behavioural Performance Indices of Auditory Distraction in Schizophrenia. University of Ottawa (Canada).

Duncan, C.C., Summers, A.C., Perla, E.L., Coburn, K.L., Mirsky, A.F., 2011. Evaluation of traumatic brain injury: brain potentials in diagnosis, function, and prognosis. Int. J. Psychophysiol. 82, 24–40.

Dupuis, F., Johnston, K.M., Lavoie, M., Lepore, F., Lassonde, M., 2000. Concussions in athletes produce brain dysfunction as revealed by event-related potentials. Neuroreport 11, 4087–4092.

Flumeier, K.P., 1992. A quantitative method for the assessment of overall effects from a number of similar electrophysiological studies: description and application to event-related potentials in Parkinson's disease. Electroencephalography and Clinical Neurophysiology/Evoked Potentials Section 84, 440–446.

Elting, J.-W., van der Naalt, J., van Weerden, T.W., De Keyser, J., Maurits, N.M., 2005. P300 after head injury: peak-delay caused by reduced P3A amplitude. Clin. Neurophysiol. 116, 2606–2612.

Escera, Alho, Winkler, Naatanen, 1998. Neural mechanisms of involuntary attention to acoustic novelty and change. *Journal of cognitive neuroscience* 10, 590–604.

Escera, Alho, Schröger, Winkler, 2000. Involuntary attention and distractibility as evaluated with event-related brain potentials. *Audiology and Neurotology* 5, 151–166.

Estévez-González, A., García-Sánchez, C., Junqué, C., 1997. La atención: una compleja función cerebral. Rev. Neurol. 25, 1989–1997.

Fabiani, M., Gratton, G., Coles, M., 2000. Event-related brain potentials: methods, theory. Handbook of psychophysiology 53–84.

Falkenstein, M., Koshlykova, N.A., Kiroj, V.N., Hoormann, J., Hohnsbein, J., 1995. Late ERP components in visual and auditory Go/Nogo tasks. Clin. Neurophysiol. 96, 36–43.

Fan, Y.-T., Cheng, Y., 2014. Atypical mismatch negativity in response to emotional voices in people with autism spectrum conditions. PLoS One 9, e102471.

Fisher, D.J., Labelle, A., Knott, V.J., 2010. Auditory hallucinations and the P3a: attention-switching to speech in schizophrenia. Biol. Psychol. 85, 417–423.

Fisher, D.J., Smith, D.M., Labelle, A., Knott, V.J., 2014. Attenuation of mismatch negativity (MMN) and novelty P300 in schizophrenia patients with auditory hallucinations experiencing acute exacerbation of illness. Biol. Psychol. 100, 43–49.

Foong, J., Rozewicz, L., Davie, C.A., Thompson, A.J., Miller, D.H., Ron, M.A., 1999. Correlates of executive function in multiple sclerosis: the use of magnetic resonance spectroscopy as an index of focal pathology. The Journal of neuropsychiatry and clinical neurosciences 11, 45–50.

Ford, J.M., Roach, B.J., Jorgensen, K.W., Turner, J.A., Brown, G.G., Notestine, R., Bischoff-Grethe, A., Greve, D., Wible, C., Lauriello, J., 2009. Tuning in to the voices: a multisite FMRI study of auditory hallucinations. Schizophr. Bull. 35, 58–66.

Forno, L.S., 1996. Neuropathology of Parkinson's disease. J. Neuropathol. Exp. Neurol. 55, 259–272.

Franken, I.H.A., Nijs, I., Van Strien, J.W., 2005. Impulsivity affects mismatch negativity (MMN) measures of preattentive auditory processing. Biol. Psychol. 70, 161–167.

Friedman, D., Simpson, G., Hamberger, M., 1993. Age-related changes in scalp topography to novel and target stimuli. Psychophysiology 30, 383–396.

Friedman, Cycowicz & Gaeta (2001) The novelty P3: an event-related brain potential (ERP) sign of the brain's evaluation of novelty. *Neuroscience and biobehavioral reviews*, 25, 355–373.

Fujiwara, H., Hirao, K., Namiki, C., Yamada, M., Shimizu, M., Fukuyama, H., Hayashi, T., Murai, T., 2007. Anterior cingulate pathology and social cognition in schizophrenia: a study of gray matter, white matter and sulcal morphometry. Neuroimage 36, 1236–1245.

Fuster, J.n.M., 2001. The prefrontal cortex—an update: time is of the essence. Neuron 30, 319–333.

Gabbay, F.H., Duncan, C.C., McDonald, C.G., 2010. Brain potential indices of novelty processing are associated with preference for amphetamine. Exp. Clin. Psychopharmacol. 18, 470.

Goldenberg, M.M., 2012. Multiple sclerosis review. Pharmacy and Therapeutics 37, 175.

Goldstein, L.H., Abrahams, S., 2013. Changes in cognition and behaviour in amyotrophic lateral sclerosis: nature of impairment and implications for assessment. The Lancet Neurology 12, 368–380.

Gosselin, N., Mathieu, A., Mazza, S., Petit, D., Malo, J., Montplaisir, J., 2006. Attentional deficits in patients with obstructive sleep apnea syndrome: an event-related potential study. Clin. Neurophysiol. 117, 2228–2235.

Grau, C., Polo, M.D., Yago, E., Gual, A., Escera, C., 2001. Auditory sensory memory as indicated by mismatch negativity in chronic alcoholism. Clin. Neurophysiol. 112, 728–731.

Graybiel, A.M., Rauch, S.L., 2000. Toward a neurobiology of obsessive-compulsive disorder. Neuron 28, 343–347.

Grzella, I., Müller, B.W., Oades, R.D., Bender, S., Schall, U., Zerbin, D., Wolstein, J., Sartory, G., 2001. Novelty-elicited mismatch negativity in patients with schizophrenia on admission and discharge. J. Psychiatry Neurosci. 26, 235.

Halgren, E., Baudena, P., Clarke, J.M., Heit, G., Liégeois, C., Chauvel, P., Musolino, A., 1995. Intracerebral potentials to rare target and distractor auditory and visual stimuli. I. Superior temporal plane and parietal lobe. Electroencephalogr. Clin. Neurophysiol. 94, 191–220.

Hamilton, M., 1960. A rating scale for depression. J. Neurol. Neurosurg. Psychiatry 23, 56.

Hanagasi, H.A., Gurvit, I.H., Ermutlu, N., Kaptanoglu, G., Karamursel, S., Idrisoglu, H.A., Emre, M., Demiralp, T., 2002. Cognitive impairment in amyotrophic lateral sclerosis: evidence from neuropsychological investigation and event-related potentials. Cogn. Brain Res. 14, 234–244.

Happé, F., Frith, U., 2006. The weak coherence account: detail-focused cognitive style in autism spectrum disorders. J. Autism Dev. Disord. 36, 5–25.

Hasin, D.S., Fenton, M.C., Beseler, C., Park, J.Y., Wall, M.M., 2012. Analyses related to the development of DSM-5 criteria for substance use related disorders: 2. Proposed DSM-5 criteria for alcohol, cannabis, cocaine and heroin disorders in 663 substance abuse patients. Drug Alcohol Depend. 122, 28–37.

Hasin, D.S., O'Brien, C.P., Auriacombe, M., Borges, G., Bucholz, K., Budney, A., Compton, W.M., Crowley, T., Ling, W., Petry, N.M., 2013. DSM-5 criteria for substance use disorders: recommendations and rationale. Am. J. Psychiatr. 170, 834–851.

Heinrichs, D.F., Ward, P.B., Hodge, M.A.R., Kaur, M., Narsimhi, S.L., Hickie, I.B., 2010. Impaired MMN/P3a complex in first-episode psychosis: cognitive and psychosocial associations. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 34, 822–829.

Higuchi, Y., Seo, T., Miyanishi, T., Kawasaki, Y., Suzuki, M., Sumiyoshi, T., 2014.

Mismatch negativity and p3a/reorienting complex in subjects with schizophrenia or at-risk mental state. Front. Behav. Neurosci. 8, 172.

Horváth, J., 2014. Sensory ERP effects in auditory distraction: did we miss the main event? Psychol. Res. 78, 339–348.

Horváth, J., Maess, B., Berti, S., Schröger, E., 2008a. Primary motor area contribution to attentional reorienting after distraction. Neuroreport 19, 443–446.

Horváth, J., Winkler, I., Bendixen, A., 2008b. Do N1/MMN, P3a, and RON form a strongly coupled chain reflecting the three stages of auditory distraction? Biol. Psychol. 79, 139–147.

Hwang, J.W., Egorova, N., Yang, X.Q., Zhang, W.Y., Chen, J., Yang, X.Y., Hu, L.J., Sun, S., Tu, Y., Kong, J., 2015. Subthreshold depression is associated with impaired resting-state functional connectivity of the cognitive control network. Transl. Psychiatry 5, e683.

Hynd, G.W., Semrud-Clikeman, M., Lorys, A.R., Novey, E.S., Eliopulos, D., Lyytinen, H., 1991. Corpus callosum morphology in attention deficit-hyperactivity disorder: morphometric analysis of MRI. J. Learn. Disabil. 24, 141–146.

Inami, R., Kirino, E., Inoue, R., Arai, H., 2005. Transdermal nicotine administration enhances automatic auditory processing reflected by mismatch negativity. Pharmacol. Biochem. Behav. 80, 453–461.

Ischebeck, M., Endrass, T., Simon, D., Kathmann, N., 2011. Auditory novelty processing is enhanced in obsessive-compulsive disorder. Depression and anxiety 28, 915–923.

Jahshan, C., Cadenhead, K.S., Rissling, A.J., Kirihara, K., Braff, D.L., Light, G.A., 2012a. Automatic sensory information processing abnormalities across the illness course of schizophrenia. Psychol. Med. 42, 85–97.

Jahshan, C., Wynn, J.K., Mathis, K.I., Altshuler, L.L., Glahn, D.C., Green, M.F., 2012b. Cross-diagnostic comparison of duration mismatch negativity and P3a in bipolar disorder and schizophrenia. Bipolar Disord. 14, 239–248.

Javitt, D.C., Steinschneider, M., Schroeder, C.E., Vaughan Jr., H.G., Arezzo, J.C., 1994. Detection of stimulus deviance within primate primary auditory cortex: intracortical mechanisms of mismatch negativity (MMN) generation. Brain Res. 667, 192–200.

Javitt, D.C., Steinschneider, M., Schroeder, C.E., Arezzo, J.C., 1995. Intracortical mechanisms underlying mismatch negativity (MMN) generation in monkeys: implications for working memory and the PCP/NMDA model of schizophrenia. Schizophr. Res. 15, 179.

Javitt, D.C., Spencer, K.M., Thaker, G.K., Winterer, G., Hajós, M., 2008. Neurophysiological biomarkers for drug development in schizophrenia. Nat. Rev. Drug Discov. 7, 68.

Jung, J., Morlet, D., Mercier, B., Confavreux, C., Fischer, C., 2006. Mismatch negativity (MMN) in multiple sclerosis: an event-related potentials study in 46 patients. Clin. Neurophysiol. 117, 85–93.

Kähkönen, S., Ahveninen, J., Pekkonen, E., Kaakkola, S., Huttunen, J., Ilmoniemi, R.J., Jääskeläinen, I.P., 2002. Dopamine modulates involuntary attention shifting and reorienting: an electromagnetic study. Clin. Neurophysiol. 113, 1894–1902.

Kähkönen, S., Rossi, E.M., Yamashita, H., 2005. Alcohol impairs auditory processing of frequency changes and novel sounds: a combined MEG and EEG study. Psychopharmacology 177, 366–372.

Kaipio, M.-L., 2016. Mismatch negativity (MMN) and P3a abnormalities in traumatic brain injury. Stud. Psychol. 116, 2016.

Kandel, E.R., Schwartz, J.H., Jessell, T.M., Department of, B., Molecular Biophysics Thomas, J., Siegelbaum, S. & Hudspeth, A.J. (2000) Principles of neural science. McGraw-Hill New York.

Kasai, K., Shenton, M.E., Salisbury, D.F., Hirayasu, Y., Onitsuka, T., Spencer, M.H., Yurgelun-Todd, D.A., Kikinis, R., Jolesz, F.A., McCarley, R.W., 2003. Progressive decrease of left Heschl gyrus and planum temporale gray matter volume in first-episode schizophrenia: a longitudinal magnetic resonance imaging study. Arch. Gen. Psychiatry 60, 766–775.

Kaur, M., Battisti, R.A., Lagopoulos, J., Ward, P.B., Hickie, I.B., Hermens, D.F., 2011a. Neurophysiological biomarkers support bipolar-spectrum disorders within psychosis cluster. Journal of psychiatry & neuroscience: JPN 37, 313.

Kaur, M., Battisti, R.A., Ward, P.B., Ahmed, A., Hickie, I.B., Hermens, D.F., 2011b. MMN/P3a deficits in first episode psychosis: comparing schizophrenia-spectrum and affective-spectrum subgroups. Schizophr. Res. 130, 203–209.

Kaur, M., Lagopoulos, J., Ward, P.B., Watson, T.L., Naismith, S.L., Hickie, I.B., Hermens, D.F., 2012. Mismatch negativity/P3a complex in young people with psychiatric disorders: a cluster analysis. PLoS One 7, e51871.

Kiang, M., Braff, D.L., Sprock, J., Light, G.A., 2009. The relationship between preattentive sensory processing deficits and age in schizophrenia patients. Clin. Neurophysiol. 120, 1949–1957.

Kivisaari, R. (2008) Opioid dependence; Brain Structure and Function: a Magnetic Resonance Imaging, Neuropsychological, and Electromagnetic Study.

Knight, R.T., 1996. Contribution of human hippocampal region to novelty detection. Nature 383, 256.

Knott, V., Heenan, A., Shah, D., Bolton, K., Fisher, D., Villeneuve, C., 2011. Electrophysiological evidence of nicotine's distracter-filtering properties in non-smokers. J. Psychopharmacol. 25, 239–248.

Koelsch, S., 2009. P3a and mismatch negativity in individuals with moderate Intermittent Explosive Disorder. Neurosci. Lett. 460, 21–26.

Koelsch, S., Gunter, T.C., Wittfoth, M., Sammler, D., 2005. Interaction between syntax processing in language and in music: an ERP study. J. Cogn. Neurosci. 17, 1565–1577.

Kok, A., 1997. Event-related-potential (ERP) reflections of mental resources: a review and synthesis. Biol. Psychol. 45, 19–56.

Korostenskaja, M., Dapsys, K., Siurkute, A., Maciulis, V., Ruksenas, O., Kähkönen, S., 2005. Effects of olanzapine on auditory P300 and mismatch negativity (MMN) in schizophrenia spectrum disorders. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 29, 543–548.

Kujala, P., Portin, R., Revonsuo, A., Ruutiainen, J., 1995. Attention related performance in two cognitively different subgroups of patients with multiple sclerosis. J. Neurol. Neurosurg. Psychiatry 59, 77–82.

Lepistö, T., Soininen, M., Čeponien, R., Almqvist, F., Näätänen, R., Aronen, E.T., 2004. Auditory event-related potential indices of increased distractibility in children with major depression. Clin. Neurophysiol. 115, 620–627.

Leung, S., Croft, R.J., Baldeweg, T., Nathan, P.J., 2007. Acute dopamine D 1 and D 2 receptor stimulation does not modulate mismatch negativity (MMN) in healthy human subjects. Psychopharmacology 194, 443–451.

Levine, B., Kovacevic, N., Nica, E.I., Schwartz, M.L., Gao, F., Black, S.E., 2013. Quantified MRI and cognition in TBI with diffuse and focal damage. Neuroimage Clin. 2, 534–541.

Light, G.A., Swerdlow, N.R., Thomas, M.L., Calkins, M.E., Green, M.F., Greenwood, T.A., Gur, R.E., Gur, R.C., Lazzeroni, L.C., Nuechterlein, K.H., 2015. Validation of mismatch negativity and P3a for use in multi-site studies of schizophrenia: characterization of demographic, clinical, cognitive, and functional correlates in COGS-2. Schizophr. Res. 163, 63–72.

Luck (2005) An introduction to the event-related potential technique (cognitive neuroscience).

Luck, Kappenman, 2011. The Oxford Handbook of Event-Related Potential Components. Oxford university press.

Maekawa, T., Hirano, S., Onitsuka, T., 2012. Auditory and visual mismatch negativity in psychiatric disorders: a review. Curr. Psychiatr. Rev. 8, 97–105.

Mathalon, D.H., Ahn, K.-H., Perry Jr., E., Cho, H.-S., Roach, B.J., Blais, R., Bhakta, S., Ranganathan, M., Ford, J.M., D'Souza, D.C., 2014. Effects of nicotine on the neurophysiological and behavioral effects of ketamine in humans. Frontiers in psychiatry 5, 3.

Menon, D.K., Schwab, K., Wright, D.W., Maas, A.I., 2010. Position statement: definition of traumatic brain injury. Arch. Phys. Med. Rehabil. 91, 1637–1640.

Mirsky, A.F., 1987. Behavioral and psychophysiological markers of disordered attention. Environ. Health Perspect. 74, 191.

Mondragón-Maya, A., Bernal-Hernández, J., Yáñez-Téllez, G., Rodríguez-Agudelo, Y., 2011. Mismatch negativity (MMN) and schizophrenia: a revision. Actas españolas de psiquiatría 39, 363.

Mondragón-Maya, A., Solís-Vivanco, R., León-Ortiz, P., Rodríguez-Agudelo, Y., Yáñez-Téllez, G., Bernal-Hernández, J., Cadenhead, K.S. & de la Fuente-Sandoval, C. (2013) Reduced P3a amplitudes in antipsychotic naïve first-episode psychosis patients and individuals at clinical high-risk for psychosis. J. Psychiatr. Res., 47, 755-761.

Näätänen, R., Winkler, I., 1999. The concept of auditory stimulus representation in cognitive neuroscience. Psychol. Bull. 125, 826.

Näätänen, R., Gaillard, A.W.K., Mäntysalo, S., 1978. Early selective-attention effect on evoked potential reinterpreted. Acta Psychol. 42, 313–329.

Näätänen, R., Paavilainen, P., Rinne, T., Alho, K., 2007. The mismatch negativity (MMN) in basic research of central auditory processing: a review. Clin. Neurophysiol. 118, 2544–2590.

Näätänen, R., Kujala, T., Kreegipuu, K., Carlson, S., Escera, C., Baldeweg, T., Ponton, C., 2011. The mismatch negativity: an index of cognitive decline in neuropsychiatric and neurological diseases and in ageing. Brain: a journal of neurology 134, 3435–3453.

Naegele, B., Pepin, J.-L., Levy, P., Bonnet, C., Pellat, J., Feuerstein, C., 1998. Cognitive executive dysfunction in patients with obstructive sleep apnea syndrome (OSAS) after CPAP treatment. Sleep 21, 392–396.

Naismith, S.L., Mowszowski, L., Ward, P.B., Diamond, K., Paradise, M., Kaur, M., Lewis, S.J.G., Hickie, I.B., Hermens, D.F., 2012. Reduced temporal mismatch negativity in late-life depression: an event-related potential index of cognitive deficit and functional disability? J. Affect. Disord. 138, 71–78.

Nakagome, K., Ichikawa, I., Kanno, O., Akaho, R., Suzuki, M., Takazawa, S., Watanabe, H., Kazamatsuri, H., 1998. Overnight effects of triazolam on cognitive function: an event-related potentials study. Neuropsychobiology 38, 232–240.

Paris, M., Mahajan, Y., Kim, J., Meade, T., 2018. Emotional speech processing deficits in bipolar disorder: the role of mismatch negativity and P3a. J. Affect. Disord. 234, 261–269.

Pekkonen, E., Ahveninen, J., Jääskeläinen, I.P., Seppä, K., Näätänen, R., Sillanaukee, P., 1998. Selective acceleration of auditory processing in chronic alcoholics during abstinence. Alcohol. Clin. Exp. Res. 22, 605–609.

Pesa, N., Hermens, D.F., Battisti, R.A., Kaur, M., Hickie, I.B., Solowij, N., 2012. Delayed preattentional functioning in early psychosis patients with cannabis use. Psychopharmacology 222, 507–518.

Polich, J., 1989. Habituation of P300 from auditory stimuli. Psychobiology 17, 19–28.

Polich, 2003. Detection of Change. *Event Related Potential and fMRI Findings* Kluwer Academic Publishers, Massachusetts.

Polich, 2007. Updating P300: an integrative theory of P3a and P3b. Clinical neurophysiology: official journal of the International Federation of Clinical Neurophysiology 118, 2128.

Polo, M.D., Escera, C., Gual, A., Grau, C., 1999. Mismatch negativity and auditory sensory memory in chronic alcoholics. Alcohol. Clin. Exp. Res. 23, 1744–1750.

Polo, M.D., Escera, C., Yago, E., Alho, K., Gual, A., Grau, C., 2003. Electrophysiological evidence of abnormal activation of the cerebral network of involuntary attention in alcoholism. Clin. Neurophysiol. 114, 134–146.

Posner, M.I., Petersen, S.E., 1989. The Attention System of the Human Brain. (DTIC Document).

Potter, D.D., Bassett, M.R., Jory, S.H., Barrett, K., 2001. Changes in event-related potentials in a three-stimulus auditory oddball task after mild head injury. J. Psychophysiol. 14, 190–191.

Pratto, F., John, O.P., 1991. Automatic vigilance: the attention-grabbing power of negative social information. J. Pers. Soc. Psychol. 61, 380.

Pringsheim, T., Jette, N., Frolkis, A., Steeves, T.D.L., 2014. The prevalence of Parkinson's

disease: a systematic review and meta-analysis. Mov. Disord. 29, 1583–1590.
Qiao, Z., Yu, Y., Wang, L., Yang, X., Qiu, X., Zhang, C., Ning, N., Shi, J., Chen, L., Li, Z., 2013. Impaired pre-attentive change detection in major depressive disorder patients revealed by auditory mismatch negativity. Psychiatry Res. Neuroimaging 211, 78–84.
Raggi, A., Consonni, M., Iannaccone, S., Perani, D., Zamboni, M., Sferrazza, B., Cappa, S.F., 2008. Auditory event-related potentials in non-demented patients with sporadic amyotrophic lateral sclerosis. Clin. Neurophysiol. 119, 342–350.
Raggi, A., Iannaccone, S., Cappa, S.F., 2010. Event-related brain potentials in amyotrophic lateral sclerosis: a review of the international literature. Amyotroph. Lateral Scler. 11, 16–26.
Rasser, P.E., Schall, U., Todd, J., Michie, P.T., Ward, P.B., Johnston, P., Helmbold, K., Case, V., Soyland, A., Tooney, P.A., 2009. Gray matter deficits, mismatch negativity, and outcomes in schizophrenia. Schizophr. Bull. 37, 131–140.
Rissling, A.J., Light, G.A., 2010. Neurophysiological Measures of Sensory Registration, Stimulus Discrimination, and Selection in Schizophrenia Patients *Behavioral Neurobiology of Schizophrenia and Its Treatment*. Springer, pp. 283–309.
Rissling, A.J., Makeig, S., Braff, D.L., Light, G.A., 2010. Neurophysiologic markers of abnormal brain activity in schizophrenia. Current psychiatry reports 12, 572–578.
Rissling, A.J., Braff, D.L., Swerdlow, N.R., Hellemann, G., Rassovsky, Y., Sprock, J., Pela, M., Light, G.A., 2012. Disentangling early sensory information processing deficits in schizophrenia. Clin. Neurophysiol. 123, 1942–1949.
Rissling, A.J., Park, S.H., Young, J.W., Rissling, M.B., Sugar, C.A., Sprock, J., Mathias, D.J., Pela, M., Sharp, R.F., Braff, D.L., 2013. Demand and modality of directed attention modulate "pre-attentive" sensory processes in schizophrenia patients and nonpsychiatric controls. Schizophr. Res. 146, 326–335.
Roach, B.J., Mathalon, D.H., 2008. Event-related EEG time-frequency analysis: an overview of measures and an analysis of early gamma band phase locking in schizophrenia. Schizophr. Bull. 34, 907–926.
Rugg, M.D., Pickles, C.D., Potter, D.D., Doyle, M.C., Pentland, B., Roberts, R.C., 1993. Cognitive brain potentials in a three-stimulus auditory "oddball" task after closed head injury. Neuropsychologia 31, 373–393.
Rushby, J.A., Barry, R.J., Doherty, R.J., 2005. Separation of the components of the late positive complex in an ERP dishabituation paradigm. Clin. Neurophysiol. 116, 2363–2380.
Rustanov, N., Rodriguez-Raecke, R., Timm, L., Agrawal, D., Dressler, D., Schrader, C., Tacik, P., Wegner, F., Dengler, R., Wittfoth, M., 2014. Attention shifting in Parkinson's disease: an analysis of behavioral and cortical responses. Neuropsychology 28, 929.
Salisbury, D.F., Kuroki, N., Kasai, K., Shenton, M.E., McCarley, R.W., 2007. Progressive and interrelated functional and structural evidence of post-onset brain reduction in schizophrenia. Arch. Gen. Psychiatry 64, 521–529.
Schroger, E., Wolff, C., 1998. Behavioral and electrophysiological effects of task-irrelevant sound change: a new distraction paradigm. Brain Res. Cogn. Brain Res. 7, 71–87.
Schroger, E., Giard, M.H., Wolff, C., 2000. Auditory distraction: event-related potential and behavioral indices. Clin. Neurophysiol. 111, 1450–1460.
Schröger, E., Marzecová, A., SanMiguel, I., 2015. Attention and prediction in human audition: a lesson from cognitive psychophysiology. Eur. J. Neurosci. 41, 641–664.
Seer, C., Lange, F., Georgiev, D., Jahanshahi, M., Kopp, B., 2016. Event-related potentials and cognition in Parkinson's disease: an integrative review. Neurosci. Biobehav. Rev. 71, 691–714.
Serra, J.M., Escera, C., Sánchez-Turet, M., Sánchez-Santre, J., Grau, C., 1996. The H1-receptor antagonist chlorpheniramine decreases the ending phase of the mismatch negativity of the human auditory event-related potentials. Neurosci. Lett. 203, 77–80.
Shaikh, M., Valmaggia, L., Broome, M.R., Dutt, A., Lappin, J., Day, F., Woodley, J., Tabraham, P., Walshe, M., Johns, L., 2012. Reduced mismatch negativity predates the onset of psychosis. Schizophr. Res. 134, 42–48.
Shallice, T., 2001. Theory of mind and the Prefrontal Cortex. Oxford University Press.
Sharma, S., Moon, C.S., Khogali, A., Haidous, A., Chabenne, A., Ojo, C., Jelebinkov, M., Kordi, Y., Ebadi, M., 2013. Biomarkers in Parkinson's disease (recent update). Neurochem. Int. 63, 201–229.
Shin, K.S., Kim, J.S., Kang, D.-H., Koh, Y., Choi, J.-S., O'Donnell, B.F., Chong, C.K., Kwon, J.S., 2009. Pre-attentive auditory processing in ultra-high-risk for schizophrenia with magnetoencephalography. Biol. Psychiatry 65, 1071–1078.
Solís-Vivanco, R., Ricardo-Garcell, J., Rodríguez-Agudelo, Y., 2009. Un Atención involuntaria: Aspectos clínicos y electrofisiológicos. Rev. Ecuat. Neurol. 18, 94–104.
Solís-Vivanco, R., Ricardo-Garcell, J., Rodríguez-Camacho, M., Prado-Alcalá, R.A., Rodríguez, G., Rodríguez-Violante, M., Rodríguez-Agudelo, Y., 2011. Involuntary attention impairment in early Parkinson's disease: an event-related potential study. Neurosci. Lett. 495, 144–149.
Solís-Vivanco, R., Mondragón-Maya, A., León-Ortiz, P., Rodríguez-Agudelo, Y., Cadenhead, K.S. & de la Fuente-Sandoval, C. (2014) Mismatch negativity reduction in the left cortical regions in first-episode psychosis and in individuals at ultra high-risk for psychosis. Schizophr. Res., 158, 58-63.
Solís-Vivanco, R., Rodríguez-Violante, M., Rodríguez-Agudelo, Y., Schilmann, A., Rodríguez-Ortiz, U., Ricardo-Garcell, J., 2015. The P3a wave: a reliable neurophysiological measure of Parkinson's disease duration and severity. Clin. Neurophysiol. 126, 2142–2149.
Solís-Vivanco, R., Rodríguez-Violante, M., Cervantes-Arriaga, A., Justo-Guillén, E., Ricardo-Garcell, J., 2018. Brain oscillations reveal impaired novelty detection from early stages of Parkinson's disease. NeuroImage: Clinical 18, 923–931.
Squires, N.K., Squires, K.C., Hillyard, S.A., 1975. Two varieties of long-latency positive waves evoked by unpredictable auditory stimuli in man. Electroencephalogr. Clin. Neurophysiol. 38, 387–401.
Stack, E.C., Ludeogh, A., Smith, K.M., Cormier, K., Kubilus, J.K., Bogdanov, M., Matson, W.R., Yang, L., Jenkins, B.G., Luthi-Carter, R., 2007. Neuroprotective effects of synaptic modulation in Huntington's disease R6/2 mice. J. Neurosci. 27, 12908–12915.
Sussman, E.S., 2007. A new view on the MMN and attention debate. J. Psychophysiol. 21, 164.
Takahashi, H., Rissling, A.J., Pascual-Marqui, R., Kirihara, K., Pela, M., Sprock, J., Braff, D.L., Light, G.A., 2012. Neural substrates of normal and impaired preattentive sensory discrimination in large cohorts of nonpsychiatric subjects and schizophrenia patients as indexed by MMN and P3a change detection responses. Neuroimage 66, 594–603.
Takei, Y., Kumano, S., Hattori, S., Uehara, T., Kawakubo, Y., Kasai, K., Fukuda, M., Mikuni, M., 2009. Preattentive dysfunction in major depression: a magnetoencephalography study using auditory mismatch negativity. Psychophysiology 46, 52–61.
Tremblay, S., Henry, L.C., Bedetti, C., Larson-Dupuis, C., Gagnon, J.-F., Evans, A.C., Theoret, H., Lassonde, M., Beaumont, J.-D., 2014. Diffuse white matter tract abnormalities in clinically normal ageing retired athletes with a history of sports-related concussions. Brain: a journal of neurology 137, 2997–3011.
Tsuchiya, H., Yamaguchi, S., Kobayashi, S., 2000. Impaired novelty detection and frontal lobe dysfunction in Parkinson's disease. Neuropsychologia 38, 665–654.
Umbricht, D., Krljes, S., 2005. Mismatch negativity in schizophrenia: a meta-analysis. Schizophr. Res. 76, 1–23.
Volpato, C., Prats Serlano, M.A., Silvoni, S., Segato, N., Cavinato, M., Merico, A., Piccione, F., Palmieri, A., Bichsumer, M., 2016. Selective attention impairment in amyotrophic lateral sclerosis. Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration 17, 236–244.
WHO (2017) Depression and Other Common Mental Disorders: Global Health Estimates. In Organization, W.H. (ed).
Witt, S.T., Lovejoy, D.W., Pearlson, G.D., Stevens, M.C., 2010. Decreased prefrontal cortex activity in mild traumatic brain injury during performance of an auditory oddball task. Brain imaging and behavior 4, 232–247.