Nystagmus Therapies:
Types, Sites, and Measures

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Current therapies for nystagmus fall into two major categories, *central* and *peripheral*. Central therapies may be neurosurgical or pharmacological; each is directed at the central source of the nystagmus and its aim is to directly reduce the initiating, brain-stem nystagmus signal (the motor command). Peripheral therapies may be pharmacological, optical, or surgical; each is directed at a peripheral mechanism to directly reduce the resulting eye oscillation without affecting the brain-stem nystagmus motor command. One additional, new therapy that may affect nystagmus is *afferent* therapy. An example is gene therapy applied to the retina to correct genetic deficits that impair vision directly and may facilitate the development of nystagmus (e.g., RPE65 deficiency and infantile nystagmus syndrome (INS)) (1). The accompanying Figure illustrates the anatomical sites of: each type of therapy; the neurophysiological signals present; and the measurements of each therapy's direct and indirect effects. The ocular motor system is centered in the brain stem with multiple connections to the cerebellum and cortex.

The most accurate measure of any therapy is a measure of its *direct* effects, not an indirect measure of a neurophysiological function that is dependent on other intervening functions, each subject to idiosyncratic deficits. Therefore, the primary outcome measure of a therapy should be a measure of the therapy's direct effects—regardless of a desired medical outcome, which is usually only indirectly related to those effects. Unfortunately, evaluations of the effectiveness of nystagmus therapies commonly substitute one medically desirable, indirect outcome (i.e., improved primary-position visual acuity) for more direct measures of each therapy. Succumbing to that temptation is neither good science nor good medicine—the results are not a valid measure of therapies whose direct effects do not lie in the pathway from afferent input to visual discrimination. It also eliminates other, often more important, measures of visual function. Many patients with INS have one or more afferent visual deficits that limit potential visual acuity, whether or not they were related to the series of events in the motor system that resulted in ocular

motor instability. Finally, even for those with no afferent deficits, mental status (stress) often results in a measured visual acuity that is lower than the acuity achieved during normal life. Therefore, using indirect measures far downstream from a nystagmus therapy's direct effects will result in confounded measurements reflecting variations in the patient population's afferent systems or stress levels rather than the effectiveness of the therapies (e.g., measured primary-position visual acuity improvement is *not* a valid measure of the effectiveness of nystagmus surgery).

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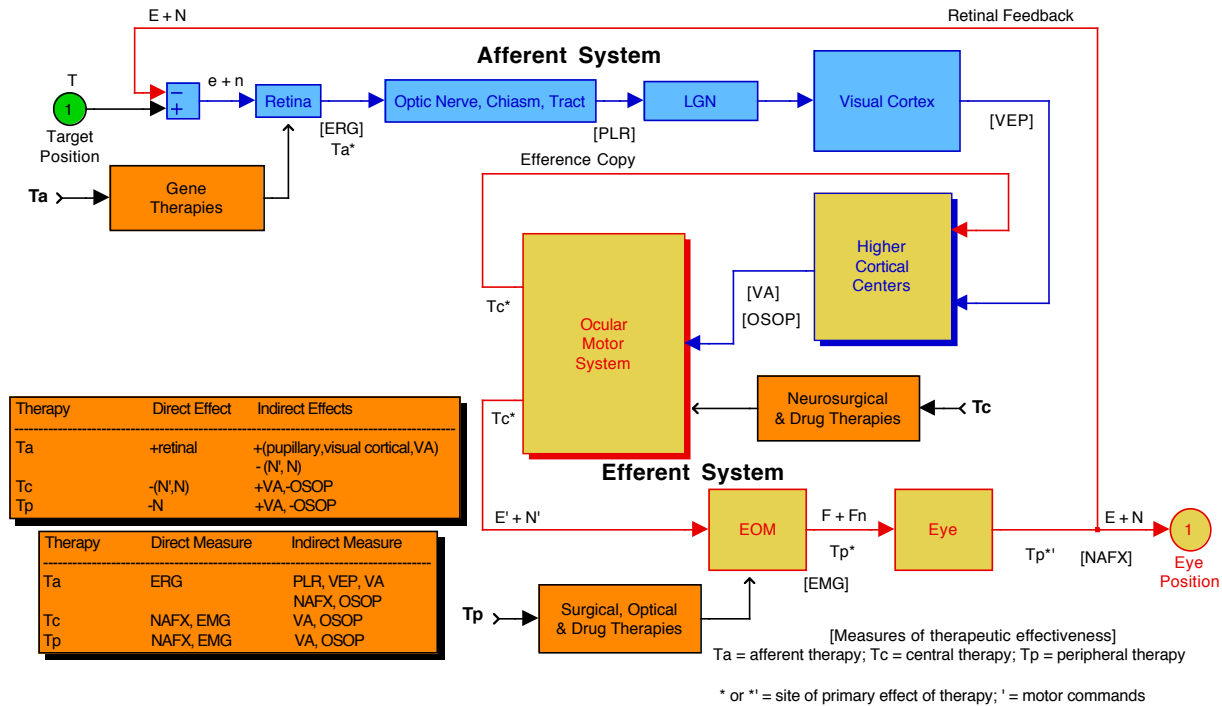
Tp damps the nystagmus (N) which improves potential acuity [NAFX] and may improve measured acuity [VA] or oscillopsia [OSOP]
Tc damps the nystagmus signal (N') which damps the nystagmus (N), improves potential acuity [NAFX], and may improve measured acuity [VA] or oscillopsia [OSOP]
Ta improves retinal function which improves [ERG, PLR, VEP, and VA] and damps both the nystagmus signal (N') and the nystagmus (N), improving potential acuity [NAFX]

Figure. A block diagram of the ocular motor system indicating the types of therapeutic intervention for nystagmus, their anatomic sites, and direct and indirect measurements of their effectiveness. Ta is afferent therapy for deficits in the visual system (shown here is gene therapy for retinal deficiencies), Tc is central (neurosurgical or drug) therapy for nystagmus, and Tp is peripheral (surgical, optical, or drug) therapy for nystagmus. Shown in square brackets are the sites of therapeutic tests of visual and ocular motor function. The direct and indirect effects of each type of therapy and the direct and indirect outcome measures for each are listed in the Legend Boxes. e=retinal error; n=nystagmus error; E=eye position; N=nystagmus; F=extraocular muscle force; Fn=extraocular muscle nystagmus force; ERG=electroretinogram; PLR=pupillary light reflex; VEP=visual evoked potential; EMG=electromyogram; NAFX=expanded nystagmus acuity function; +=improved, higher, or better; -=diminished, lower, or less; blue/light-blue blocks=afferent sensory; blue/yellow block=afferent-efferent sensorimotor; red/yellow blocks=efferent motor; and black/orange blocks=therapies.

The ideal measure of any nystagmus therapy is one that is both a direct outcome measure of that therapy and, if possible, a predictive measure of the medical goals of improved primary-position acuity and *improved visual function*. As the Figure shows, the electroretinogram, pupillary light reflex, and visual evoked potential are the most direct measures for afferent therapies. Each is predictive of visual acuity, which is determined slightly upstream, albeit requiring higher cortical function. In animal studies, where visual acuity is not easily measured, the eXpanded Nystagmus Acuity Function (NAFX) (2) provides an easily obtainable, *in vivo* measure of gene therapy's effectiveness by measuring nystagmus waveform improvements (3). Although an indirect measure of afferent therapy, the NAFX predicts potential acuity. For central and peripheral therapies, the best and least invasive direct measure is the NAFX; the electromyogram is both invasive and not easily related to visual acuity. Because the NAFX both predicts acuity improvements and measures increases in the range of gaze angles over which those improvements are present, it was chosen as the primary outcome measure of two masked clinical trials of the effectiveness of tenotomy (4,5) in the treatment of infantile nystagmus in adults (6) and children (7). In many patients with INS, increasing the effective high-acuity visual field does far more to improve visual function than simply increasing Snellen acuity in one small region of the visual field—unfortunately, this is neither appreciated nor commonly measured in the physician's office. It does explain why a given therapy may result in a patient reporting that he can "see better" even when the pre- and post-therapeutic primary-position Snellen acuities are essentially equal.

As the Figure illustrates, peripheral surgical therapy acts at the muscle to damp the resulting nystagmus; it does not change the brain-stem nystagmus signal itself. Also, it is equally effective in damping both infantile and acquired nystagmus (the muscle cannot determine the origin of the nystagmus signal). Central pharmacological therapy is administered to damp the brain-stem nystagmus signal. Because of their independence, if both central and peripheral therapies are applied together (in either order), the result will be the multiplicative damping from both therapies. This type of 'dual-mode' therapy has been shown to maximally damp the nystagmus and maximally improve visual function.

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