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# Principles and Practice of Clinical Electrophysiology of Vision

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# Amblyopia and Clinical Electrophysiology

J. Vernon Odom

Amblyopia means blunt or reduced vision and is generally defined by reduced visual acuity. It may be organic or functional. Organic amblyopia is attributable to some detectable retinal or higher dysfunction, e.g., toxic amblyopia, alcohol amblyopia, and nutritional amblyopia. Functional amblyopia is not identifiable by fundus examination or other standard ophthalmic procedures and is usually associated with a childhood history of abnormal visual experience.<sup>82</sup> Bilateral functional amblyopia is a consequence of severely abnormal visual experience in both eyes, e.g., bilateral cataracts, ptosis, hemangioma, or uncorrected high refractive error.<sup>54</sup>

Unilateral functional amblyopia or reduced visual acuity in one eye is the most common form of amblyopia and affects 1% to 3% of the adult population. It will be referred to as amblyopia in the remainder of this section. The precise definition of reduced acuity is somewhat arbitrary. Frequent criteria are a reduction of two or more lines on an acuity chart, 0.5 (20/40 or 6/12) or worse acuity in one eye, or an acuity difference of 1 octave or more between the eyes. Amblyopia is usually associated with a childhood history of abnormal visual experience in one eye: (1) monocular deprivation due to monocular cataract, hemangioma, ptosis, or extreme monocular patching (deprivation amblyopia); (2) a difference of refractive error between the two eyes of 1 D or more (anisometropic amblyopia); or (3) strabismus (strabismic amblyopia). Strabismic amblyopia can be subdivided into as many categories as one chooses to divide strabismus. Subgroups of amblyopes have different visual characteristics.<sup>15, 24, 54, 66</sup> Stereopsis and normal binocular vision are impaired in amblyopia. Early detection and

treatment, usually by patching therapy, can often correct amblyopia.

Because amblyopia is a treatable disease of childhood, the challenge is to develop an electrophysiological test or tests that (1) would detect amblyopia, (2) could be used to monitor patching therapy, and (3) would predict therapeutic success. To be useful clinically the tests must be reliable in children. Two aspects of visual function that are closely related to amblyopia and also appropriate for electrophysiological study are visual acuity and binocularity. There are several reviews of the electrophysiological deficits in amblyopia.<sup>39, 46, 71</sup>

In general, visual evoked potential (VEP) amplitudes in amblyopic eyes are smaller than in the fellow eyes or the eyes of normals.<sup>6, 10, 26, 48, 74</sup> One characteristic of amblyopes is the large interocular difference in VEP amplitudes as compared with the typical 10% difference observed in normals.<sup>1, 70</sup> However, the magnitude of the effect varies as a function of the individual, temporal frequency, and spatial frequency.<sup>46, 48, 74</sup> For example, luminance-elicited VEPs are not reduced in some amblyopes,<sup>75</sup> and VEP amplitude is more reduced in amblyopes with central fixation than in those with deviations of 2 to 4 prism diopters.<sup>77</sup> The reduced VEP from an amblyopic eye may be attributable to a reduction in the number of cortical neurons being activated by the amblyopic eye as compared with the normal eye.<sup>45</sup>

Several studies have evaluated the effectiveness of interocular differences in VEP amplitudes elicited by a single, high-contrast pattern in detecting amblyopia.<sup>23, 52, 72, 86</sup> Estimates of the normalcy of interocular amplitude differences have a test-retest reliability

of about 85%.<sup>23, 52</sup> The overall accuracy in identifying patients and normals is about 80%,<sup>23, 52, 72, 83, 86</sup> 46% to 85% of amblyopes are correctly identified (sensitivity),<sup>23, 52</sup> and 82% to 94% of normals are correctly identified (specificity).<sup>23, 52</sup> In a good clinical test one expects the sensitivity to be greater than 46% to 85%. Comparing interocular VEP amplitude differences elicited by a single pattern is not a satisfactory method of detecting amblyopia.<sup>23, 83</sup>

VEPs of amblyopic eyes that are elicited by pattern reversal have altered latencies or implicit times. The prominent P<sub>1</sub> component is delayed in the amblyopic eye as compared with the fellow eye or normal eyes.<sup>6, 24, 69</sup> The later P<sub>2</sub> component is decreased in latency in the amblyopic eye.<sup>69</sup> Although statistically significant, P<sub>1</sub> delays are not reliable enough to detect individual amblyopes.<sup>24, 83</sup> The use of interocular latency differences in conjunction with interocular amplitude differences improves the detection of amblyopes slightly.<sup>72</sup>

Because one of the defining characteristics of amblyopia is reduced acuity, electrophysiological assessment of visual acuity is an appealing strategy for identifying young amblyopes. VEP-estimated acuity is reduced in the amblyopic eye.<sup>17, 22, 49, 57, 58, 61, 65, 80</sup> However, VEP acuity and Snellen acuity are not equivalent.<sup>17, 22</sup> The relationship of extrapolated acuities to observed Snellen acuities depends on the scales used in performing the extrapolations.<sup>33</sup> Sweep VEP acuity tends to overestimate poor acuity in amblyopic eyes and to underestimate the good acuity of fellow eyes in amblyopia.<sup>17</sup> Therefore, sweep VEP acuity might fail to detect mild amblyopia or small changes in acuity with patching therapy.

During patching therapy, VEP acuity can undergo large changes that reflect the effects of patching and/or natural deprivation.<sup>36</sup> With patching in infants and young children, the acuity of the patched eye declines, and that of the other eye improves.<sup>51, 58</sup> Patching also results in a reduction of amplitude in the patched eye and a prolongation of its P<sub>1</sub> latency.<sup>25</sup> As with patching-induced VEP acuity changes, VEP latency and amplitude changes are not necessarily permanent.<sup>5, 6, 25, 66, 86</sup> VEP acuity and other changes frequently precede changes in fixation preference<sup>54, 58, 86</sup> and add potentially useful information. VEP acuity and possibly amplitude and latency changes can be useful in detecting significant amblyopia,<sup>25, 33, 86</sup> adjusting patching therapy to maximum efficiency (i.e., minimum patching required to improve the acuity of the deprived eye),<sup>25, 36, 37, 54, 58</sup> or timing surgical decisions (e.g., performing stra-

bismus surgery when the acuities in the two eyes are equal). However, the time involved to record even sweep VEP acuities is considerable by clinical standards. Despite the time involved, in children less than 3 years of age, 75% of the attempted VEP acuity tests are completed.<sup>55</sup>

Several categories of experiments have examined the interocular interactions in amblyopia: binocular summation, interocular suppression, purely binocular processes, and stereopsis. Studies of binocular summation<sup>1-4, 12-14, 18-20, 41, 53, 62, 67, 78, 79, 84</sup> consist of three stimulus conditions: stimulation of each eye and both eyes. The amplitude of the binocular response is compared with one of the monocular responses: the smaller, the larger, or the mean monocular response. If one assumes that the two eyes are independent with independent noise sources, one would expect a binocular summation of about 1.4 (square root of 2). This is a commonly obtained value.<sup>1, 6, 66, 84</sup> Alternatively, one might argue that the expected summation is the sum of the two monocular responses and that only responses greater than the sum of the monocular responses or twice the mean monocular response (i.e., facilitation) represent a truly binocular response.<sup>2-4, 53</sup> Even in normals, binocular summation is a very ephemeral characteristic.<sup>2-4, 12-14, 18-20, 41, 44, 53, 62, 67, 78, 79, 84</sup>

The amount of binocular summation varies with (1) the stimulus characteristics,<sup>2-4, 19, 20, 41, 84</sup> (2) the response component measured,<sup>20, 62</sup> and (3) the electrode location.<sup>44, 62</sup> In general, an ideal stimulus for eliciting summation in normals would be of low contrast (<40%) and/or mean luminance, with a spatial frequency lower than 5 cycles per degree and a frequency less than 8 Hz.<sup>8</sup>

Binocular summation elicited by high-contrast patterns alone does not reliably identify amblyopes.<sup>83</sup> Patients with anomalous retinal correspondence (ARC) show binocular summation, while patients with small angle deviations and suppression do not.<sup>12</sup> The variation in summation cannot be accounted for by the depth of amblyopia.<sup>77</sup> Binocular summation is eliminated in normals and strabismics if a neutral-density filter is placed in front of one eye.<sup>79</sup> The density at which summation is eliminated is less in strabismics with ARC,<sup>13, 14, 18</sup> 0.4 neutral density (nd) as compared with 1.6 nd for normals. A sequence of tests has been proposed to detect abnormal binocularity<sup>14</sup>; however, the tests have not been examined to determine clinical utility.

If different stimuli are presented to the two eyes (dichoptic stimulation), one may elicit a number of sensory phenomena, including suppression, rivalry,

and summation, depending on the precise stimulus conditions.<sup>21, 29, 68, 76, 85</sup> Suppression is most easily observed if the stimuli are higher in mean luminance or contrast (>50%) and of the same spatial frequency.<sup>18</sup> Size-specific suppression is abnormal in patients with abnormal binocularity<sup>30, 42, 43, 50, 56</sup> and amblyopia.<sup>87</sup> While suppression identifies patients better than binocular summation does, it is not reliable enough to detect anomalies in individual patients.<sup>34, 87</sup>

Recently, several new VEP tests of binocular vision have been proposed.<sup>9, 38, 59, 60, 64, 81</sup> They demonstrate a response that could occur only if the input of the two eyes were combined. Typically, dichoptic stimuli are presented.<sup>34, 42, 43</sup> The VEP undergoes Fourier analysis, and a frequency is found in the response that is not present in either stimulus.<sup>9, 38, 59, 60, 64, 81</sup> Various linear<sup>60</sup> and nonlinear<sup>9, 38, 59, 60, 64, 81</sup> mechanisms of binocular interaction may be identified. Their clinical use has not been examined.

Stereopsis is a uniquely binocular response; VEP-determined stereoacuity identifies adult stereoanomalous observers with amblyopia.<sup>16</sup> However, determining stereoacuity is time-consuming.

A number of studies have attempted to identify the location of the amblyopic defect. A continuing debate has been whether there is retinal involvement in amblyopia. Flash-elicited electroretinograms (ERGs) are generally normal in amblyopia<sup>35, 51, 88</sup>, however, the ERG second-harmonic amplitude is abnormal in some amblyopes,<sup>31</sup> as is the impulse response obtained with pseudorandom binary sequences.<sup>47</sup> Lateral interaction anomalies in amblyopes that are determined by using VEP estimates of Westheimer functions suggest an anomaly prior to the cortex.<sup>40</sup> Some studies have observed a reduced pattern ERG (PERG) amplitude in amblyopic eyes even after controlling for fixation errors.<sup>7, 47, 63, 73</sup> Others have found no PERG amplitude reduction if patterns are presented at the retinal locus that elicits the largest PERG amplitude.<sup>27, 28, 32</sup> The utility of PERG amplitude reduction in identifying amblyopes in the clinic has not been examined.

In summary, electrophysiological assessment of amblyopia has proved interesting theoretically but has not proved itself in the clinic. Experimental researchers have often ignored the diversity of the amblyopic conditions, and clinicians have often failed to employ stimulus conditions or combinations of stimulus conditions that optimally distinguish the visual processes affected by amblyopia. In the absence of a short, proven clinical test, we caution the

clinical electrophysiologist not to rely on the results of one measure of one stimulus condition in evaluating amblyopia and suggest that VEP acuity assessment seems the safest strategy if the time constraints permit it.

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