Psychophysical Evaluation for Visual Prosthesis

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Abstract
Vision restoration through retinal, optic nerve, and cortical implants is no longer just the stuff of fantasy. The design and development of visual prostheses rapidly move from the engineering phase toward preclinical and clinical trials, yet the benchmarks to determine their efficacy in blind research subjects have received very little attention, and likewise the selection criteria and preparation of early recipients of these devices. This article examines the aspects of vision for which prostheses may be of help, the selection of early prosthesis wearers, and the pre- and postimplant evaluations required to assess safety and efficacy. I concentrate on the functional assessment, and particularly on psychophysical methodology, but also address other measures of safety and efficacy, as well as approaches to vision rehabilitation with visual prostheses. Finally, I speculate what roles the first few generations of visual prostheses may play, and emphasize the importance of using simulations to support the development and rehabilitation process.
1. THE CHALLENGE OF PROSTHETIC VISION

Restoring vision to the blind is a technological challenge on a scale biomedical engineering has not previously encountered. This is immediately obvious when comparing the challenge of restoring sight to that of restoring hearing. For the detection and transmission of sounds in our environment, the human auditory system relies on approximately 15,000 hair cells in the cochlea and a similar number of acoustic nerve fibers, and modern cochlear implants are successful at conveying useful hearing with 16–20 electrodes. For a retinal, optic nerve, or cortical prosthesis to transmit a similar fraction of the information carried by the 120 million retinal photoreceptors or 1.2 million optic nerve fibers in the healthy human eye, it would have to contain over 1000 electrodes, even without considering the 100-fold sampling excess of the photoreceptor layer and the extensive signal preprocessing performed by neuronal circuits in the retina. Even the most advanced visual prostheses now being considered, using a few hundred electrodes to transmit signals to the visual pathway, limits sensory function by an order of magnitude more than the cochlear prosthesis. The Argus 2 retinal implant, the only device currently in long-term clinical tests, has 60 electrodes, thus greatly restricting the information that can be conveyed.

A second, equally daunting, challenge is the likely inability of visual prosthetic devices to provide even a fraction of the extensive image-processing power provided by the retina and early visual pathways. A retinal implant is unlikely to harness any of the spatial, temporal, and chromatic analytical power provided by the intact visual system because retinal degeneration leads to
dramatic reorganization of local retinal networks (1, 2). By their very location, optic nerve and cortical implants do not benefit from any of the preprocessing power provided by the retina. All three devices, then, may provide visual information by eliciting multiple phosphenes at a large number of electrodes, but the percepts produced by such stimulation are unlikely to bear much resemblance to vision as we know it. Just as with cochlear implants, one cannot appreciate the challenges faced by the prosthesis wearer until one realizes this fundamental disparity between normal sensory function and the stimulation provided by electrodes implanted along the sensory afferent pathway.

In the heyday of prewar German scientific discovery, Foerster (3) established that electrical stimulation of the visual cortex in an awake patient during a neurosurgical intervention produced the percept of dots of light, called phosphenes, and that the location of a phosphene changed with that of the electrical stimulus. The field of vision restoration then lay silent for several decades, until research in both the United Kingdom and the United States brought the possibility of implanting cortical electrodes for vision restoration back into the limelight, through the theoretical consideration of the number of phosphenes required for tasks such as reading (4) and form recognition (5), as well as through acute and chronic stimulation experiments, first and foremost by Brindley and colleagues (6–8). Continued attempts by Dobelle and colleagues (9, 10) and others (11) notwithstanding, further developments of prosthetic vision through cortical implants have made only modest progress in the past four decades, hampered primarily by the limitations in resolution and long-term stability of the epicortical electrode arrays used by Brindley and Dobelle and by the slow development of reliable chronic intracortical stimulating electrodes. Recent developments in this area (12, 13) may now be bringing cortical vision restoration close to the clinical trial stage (14, 15).

In the intervening decades, for the first time, vision restoration through electrical stimulation of the retina became a feasible objective. As recently as 1970, the only surgical access to the retina was through an open sky technique, in which the entire cornea was opened and the crystalline lens removed to reach the retina through the dilated iris. The introduction of the pars plana approach (16, 17), in which instruments and infusion cannulas are inserted through ports behind the crystalline lens and ciliary body yet anterior to the retinal margin, allowed intraocular pressure to be maintained throughout surgery. This made retinal surgery safer and more precise and opened the opportunity to insert permanent implants in the posterior chamber of the eye with relative ease. Yet even then, the retina was considered by most too delicate a structure to serve as the substrate for an implanted electrode array.

There was also a more fundamental reason not to attempt vision restoration through an intraocular implant: The consensus among neuroscientists was that the degeneration of the retinal photoreceptors must lead to the trans-synaptic degeneration (18, 19) of all proximal cells (i.e., bipolar and retinal ganglion cells); that a similar proximal degeneration process would follow any blinding condition of the distal visual system; and that for this reason the optic nerve, the visual pathway connecting the eye and the brain, would not be capable of serving as a conduit for signals from an intraocular implant.

Two factors were responsible for the development of intraocular electrical stimulation over the past 25 years: the clinical success of the cochlear implant (20) and the stubborn refusal of a few eye surgeons and researchers in the United States and Germany to accept conventional wisdom. The cochlear implant proved that at least some secondary neurons survive the threat of trans-synaptic degeneration and can successfully transfer sensory information from an implanted device. Potts and Inoue recorded electrically evoked responses to electrical stimulation of the globe. Alan Chow in Chicago, Eberhard Zrenner in Tuebingen, and Eugene de Juan and Mark Humayun in Durham, North Carolina, more or less independently interpreted these findings as evidence that reports of
phosphenes elicited through electrical or pressure stimulation of the eyelids in profoundly blind patients were not mere anecdotes, but rather indications of the survival of at least some retinocortical connections; their insights laid the foundations for three of the most active groups in retinal prosthesis research.

Although some long-held tenets of neuroscience have had to yield to the reality of phosphenes elicited through intraocular stimulation (21, 22), others stand unchallenged. There is broad consensus that functional vision restoration is predicated on prior visual experience (23, 24). Although it is true that cochlear implants have now proven successful in bringing auditory function to congenitally deaf children implanted within the first year of life (25–27), it is not clear that visual prostheses will have the same benefit when implanted in early childhood: The intricate development potential of the normal visual system that starts at birth and extends over approximately a decade (28, 29) cannot be realized through an input device with a few hundred channels. Conversely, implantation in young children may guarantee the best potential for effective prosthetic vision—although radically different from normal vision: At an age when neuronal circuits are maximally plastic, retinal and cortical circuitry organizes itself to make optimal use of the input signals provided, whereas a previously developed and then degenerated system can respond to an implant and provide function only to the extent permitted by the remaining plasticity of the degenerated circuitry. For researchers and clinicians to gain a clear understanding of these mechanisms, it is essential to document with the greatest possible detail the implant recipient’s history of vision loss, remaining preoperative vision level, interventions provided in the form of training (e.g., type, duration, and intensity), and the development of visual function and daily activity performance over the rehabilitation period. Below I briefly address each of these issues.

A thorough review of visual prostheses currently under development would justify a separate publication, but a brief overview may be of help. There are at the present time at least 20 distinct research groups in at least 8 countries actively engaged in visual prosthesis development. In addition, there are laboratories (e.g., several of the national laboratories within the United States Department of Energy) working on subsystems, such as electrode technologies, usually in collaboration with one or more groups working on system development and integration. The work can be roughly categorized into three areas: retinal, optic nerve, and cortical approaches. The retinal approach aims at stimulating secondary neurons in the inner retina, typically by means of an electrode array placed on the inner retinal surface or inserted under the retina. A few groups pursue electrical stimulation of the retina with stimulating electrodes placed on the outer wall of the eye, and some labs use neurotransmitters or engineered photopigments as the signal carrier activating the retina. Optic nerve approaches pursue two forms of stimulation: through cuff electrodes that activate many optic nerve fibers at once (and thus elicit large phosphenes) and penetrating microelectrodes that contact small groups of fibers. The cortical approach seeks to place electrodes over the central visual field projection in primary visual cortex; typically, these are penetrating electrodes that are thought to provide better short-term and long-term stability of tissue stimulation than the subdural electrodes used by Brindley & Dobelle. For those interested in recent reviews of the technology and state of visual prosthetics development, I recommend References 30–32. The listing of active groups, project specifications, and Web sites given in Reference 30 remains largely accurate. For an updated list of Web sites, see Related Resources.

2. A HIERARCHY OF VISUAL ABILITIES

To most people, vision loss is a simple, discrete variable: There is normal vision, low vision, and blindness. Yet to those who experience progressive vision loss, personally or in people to whom they are close, there is a near-endless gradation of ever-decreasing vision levels. Retinitis pigmentosa
The World Health Organization's International Classification of Functioning, Disability, and Health (33), applied to visual impairment and blindness, and examples of their manifestations, assessments, and treatments. (First column) The overall health levels that govern an individual's visual functioning and independence. (Second column) Ways in which functional deficits at each level manifest themselves. (Third column) Outcome measures used to assess each aspect of function. (Fourth column) The available interventions at each level. The top of the diagram emphasizes disease state, whereas below we see the effects at the sensory, functional, daily living, and existential levels. ADL, activities of daily living; CCTV, closed-circuit television; O&M, orientation and mobility. The shaded areas in the “Measurement” column are discussed in greater detail in subsequent sections.

<table>
<thead>
<tr>
<th>Function level</th>
<th>Manifestation</th>
<th>Measurement</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual system disorders</td>
<td>Retinal degeneration, Glaucoma, Diabetic retinopathy, Refractive errors</td>
<td>Blurry and/or distorted vision, Blind spots, Glare, Diplopia</td>
<td>Physical: Retinal thickness, Corneal curvature, Cup-to-disk ratio, Psychophysical: Visual acuity, Contrast sensitivity, Color discrimination</td>
</tr>
<tr>
<td>Functional limitations</td>
<td>Daily living activities, Social activities, Recreational activities, Vocational activities</td>
<td>Self-report: Daily goals, Functional independence, Quality of life</td>
<td>Treatment: ADL training, O and M training, Eccentric viewing training</td>
</tr>
<tr>
<td>Activities/ (dis)abilities</td>
<td>Survival skills: Self care, Communication, Mobility, Safety</td>
<td>Well-being: Social support, Isolation, Depression</td>
<td>Treatment: Sensory substitution, Dog guide, Visual prosthetics, Vocational retraining</td>
</tr>
<tr>
<td>Participation/ handicap</td>
<td></td>
<td></td>
<td>Social services, Assisted living</td>
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patients may mourn the loss of the vision level they had in childhood or even a year ago, yet they realize the vision that is left is far better than total blindness. From a functional perspective, both for the purposes of measuring vision and establishing treatment outcomes, and in terms of rehabilitation objectives, one can define a hierarchy of visual and functional attributes, each of which can be quantified using appropriate measures.

Using the World Health Organization's 2001 International Classification of Functioning, Disability, and Health (33), one can distinguish chronic deficits in visual function (impairment) as leading to deficits in performance (disability), and persistent disability as leading to chronic dependence (handicap) (Figure 1). From Figure 1, it becomes clear that what or how the person sees is less important than how well the visual information gained serves the performance of daily activities. Blind persons can participate in life and many of its activities through a variety of
Table 1  Examples of measurable aspects of vision, ordered from simplest to most complex

<table>
<thead>
<tr>
<th>Function</th>
<th>Measurable aspects of vision</th>
</tr>
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<tbody>
<tr>
<td>Light</td>
<td>Orienting</td>
</tr>
<tr>
<td>Projection</td>
<td>Pointing</td>
</tr>
<tr>
<td>Movement</td>
<td>Following</td>
</tr>
<tr>
<td>Color</td>
<td>Selecting</td>
</tr>
<tr>
<td>Shape and pattern</td>
<td>Classifying</td>
</tr>
<tr>
<td>Three-dimensional structure</td>
<td>Navigating, manipulating</td>
</tr>
<tr>
<td>Hyperacuity</td>
<td>Aligning</td>
</tr>
<tr>
<td>Stereoaucity</td>
<td>Threading</td>
</tr>
</tbody>
</table>

Each cell in the left column lists a visual function; the corresponding cell in the right column lists a visual task for which this function is a prerequisite.

nonvisual alternate strategies and support services, and low vision patients can minimize the effects of functional limitations through rehabilitation that teaches them the use of assistive devices so they can make optimal use of their remaining vision (34). Between these two levels, at the point at which natural vision provides no useful function, substitution devices or visual prosthetics can maximize blind persons' ability to reach daily goals and be functionally independent, and help them avoid isolation and depression.

For all the items listed in the measurement column in Figure 1, quantitative assessment of remaining function is possible. The following sections discuss the visual function and performance measures that are most directly related to establishing the person's function without and with a prosthesis. Table 1 shows measurable attributes of visual function and performance, in increasing order of complexity. The performance activities listed in Table 1 can be envisaged as representative abilities mediated by the visual function in the same row. Both aspects can be measured, as demonstrated below. For the purpose of this review, I briefly elaborate on the three most elementary levels of vision because they are rarely thought of as measurable entities.

### 2.1. Light Detection

The ability to tell light from dark (without additional cues such as heat from an incandescent source or the sun) can be as crude as distinguishing day from night, or as precise as deciding which among a pair of intervals contained a flash just above absolute threshold. Dark-adapted rod sensitivity thresholds for a full-field flash can be as low as $10^{-8}$ cd s m$^{-2}$; normal cone threshold sensitivity is roughly $10^{-3}$ cd s m$^{-2}$; and patients with bare light perception from end-stage retinal degeneration may have thresholds of $100$ cd s m$^{-2}$ or more.

One should not confuse the ability to detect light with the abilities to rate and discriminate brightness, which in addition to light sensitivity require a dynamic range wide enough to distinguish among brightness levels. Well-trained observers can reliably distinguish flashes with a brightness ratio of 1 dB (26% difference) over many log units (35), but the test-retest reliability of brightness ratings and absolute threshold detection can be as large as 4–8 dB between visits, depending on the nature of vision loss (36–38). Still, given the 10 orders of magnitude over which light-detection thresholds can vary, this measure has a greater ability to classify vision loss than almost any other single measure. Note that illumination levels, just as auditory and tactile sensory stimuli, are measured on a logarithmic (decibel) scale.
Visual performance based on light detection alone is obviously limited. Besides the maintenance of a circadian rhythm—which can be severely disrupted in individuals with total blindness (39)—light detection can serve jointly with nonvisual abilities, such as tactile information in cane travel. Tests of visual performance based on light detection can thus measure subjects’ ability to find the window or doorway that is the source of the light, by virtue of increasing brightness as one approaches them rather than by perceiving the direction from which the light originates.

### 2.2. Light Localization

The ability to indicate from which direction a light originates is critically dependent on crude retinal image projection and on the area of functional retina: As long as the ocular media are clear, light projection in the eye follows the laws of geometric optics, but a patient with a blind retinal area (scotoma) either does not perceive a light projected onto that area or misperceives its location owing to stray light scattered onto intact retinal areas. The simple properties of light projection and localization have traditionally been used to assess the viability of the retina in patients with dense cataract, as a prognostic indicator for the outcome of cataract surgery; more often, however, they are combined with pattern projection to obtain a measure of visual acuity, as well as retinal integrity (40).

In normally sighted observers, localization of small lights is correlated with the density of ON-Pβ retinal ganglion cells and saccade accuracy (41), but it is affected by positional uncertainty in the stimulus and neural deficits such as amblyopia (42). In fact, although the relative position estimation of two stimuli in space can be highly accurate (43), absolute localization of a single stimulus is much cruder and may be severely compromised, even without complete loss of functional vision. A prime example of such a condition is retinitis pigmentosa: Patients commonly have fairly good central vision while their remaining visual field may have shrunk to as little as 5° in diameter. Localization of stimuli outside of the central island of vision obviously becomes impossible. Yet a projection test in these patients may reveal the presence of substantial spared retinal areas in the far periphery (so-called temporal islands), allowing them to perceive light or movement off to the side, without being able to attribute a shape to such percepts (44, 45). Conversely, patients with intact peripheral retinas but a macular scotoma due to age-related macular degeneration have poor saccadic refixation and hence poor localization accuracy for eccentric stimuli (46).

Visual performance based on light projection and nonvisual abilities can include tasks such as pointing and grasping. The proficiency that can be attained depends on the extent and layout of the patient’s intact visual field. In most cases, the small amount of vision available is used only to guide tactile or auditory task performance; no pattern or form vision is involved.

### 2.3. Movement Perception

Perceiving a light as moving and correctly assigning direction to this movement require not only intact projection and detection over an extended retinal area, but also intact temporal processing, allowing signals from adjacent retinal areas to be transmitted to the visual cortex and processed in the correct order. Although this may seem self-evident in the intact visual system, variable delays due to severely compromised retinal neurons and processing may cause the signal sequence at the cortical level to become ambiguous. To further complicate matters, the degenerating retina—and crude visual prostheses, for that matter—may only convey large-scale spatial and slow temporal information, whereas cortical motion detectors are known to be selective for fine patterns (high spatial frequencies) (47). Movement perception is thus likely to become severely impaired as part of the retinal degeneration process.
There is a rich literature reporting movement perception and speed and direction discrimination in normally sighted observers and the extent to which these measures are affected by blurring, presentation of composite stimuli with multiple motion vectors, and so on, but the relevance of such results for patients with severe vision loss is minimal: These results all presume adequate form perception. Motion discrimination without form perception in cortically blind patients has been demonstrated (48), but this most likely involves selective use of extracortical mechanisms that is not available to patients with retinal degeneration. Specific reports in retinal degeneration patients are limited to the areas of displacement thresholds (49), heading direction (50), and mobility (51) but are restricted to patients with usable form vision.

Performance tasks served by the visual perception of light movement, other sensory cues, and motor skills may involve tracking (gaze), tracing (marker), and following (walking). Once again, no true form or pattern vision is required to perform such tasks; light perception alone can provide sufficient guidance.

3. SCREENING METHODS AND CRITERIA

The initial step in any experimental rehabilitation program is a careful screening and selection of candidates. This is particularly important at a stage where safety and efficacy of a new category of devices have not been established unambiguously. Inclusion and exclusion criteria need to be clearly defined, and patient’s disease background and retinal/optic nerve/cortical status should be carefully documented. For retinal implants, standard imaging techniques such as fundus photos, fluorescein angiograms, and optical coherence tomography of the implant area and the retinal nerve fiber layer around the optic disc are important benchmarks for intact function of the inner retina; the latter of these is the best available predictor for optic nerve status, and thus for the prospects of a successful optic nerve implant. Similarly, contrast angiograms of the cerebral vasculature are important indicators for neurosurgeons planning the placement of a cortical visual prosthesis. Collected at baseline in both eyes—and, for a unilateral cortical prosthesis, using CT and MRI imaging of both hemispheres—they can be repeated during follow-up to document any differential changes between the implanted and control structures; they also help guide the surgeon in determining the safest and most promising implant location. To ascertain minimal retinal and optic nerve functionality, one can attempt electrophysiology—especially multifocal visually evoked potentials, which yield a map of retinal areas from which the light-evoked signal reaches the visual cortex (52)—and functional imaging; however, there is no experience in the use of such techniques in patients with minimal light perception. A full-field visually evoked potential, although less informative about the remaining function of specific retinal areas, is more likely to yield a recordable response, especially because (contrary to the multifocal technique) it does not require the patient to maintain a stable direction of gaze during several minutes of recording. In patients without appreciable light perception, one can use an electrically evoked potential through a contact lens, DTL (after the inventors Dawson, Trick, and Lutzkow), or skin electrode (53, 54). There is scant published literature regarding the application of such techniques, and an urgent need exists for the collection of normative data. In the case of cortical prostheses, no comparable light or electrical stimulation technique can be applied (because the choice for such a system is generally based on the unavailability of the retina for stimulation), but it is conceivable that newer techniques such as transcranial magnetic stimulation can be used to elicit phosphenes (55, 56) and possibly evoked responses, and ascertain at least a minimal level of functionality. Again, we urgently need validation studies for most of the above-mentioned techniques in functionally blind subjects, as few studies in such patients have been done.
Although there are no major safety concerns stemming from the pilot clinical trials carried out to date (57–59), the risks of the surgical procedures involved are not negligible. Damage to the delicate retinal, optic nerve, or cortical tissue is possible, and the effectiveness of the implant is not guaranteed. Therefore, it is extremely important that prospective implant recipients undergo thorough screening for their willingness to accept no effective improvement or further loss of function as a possible outcome of their participation, including an evaluation by a licensed psychologist. There has been no formal analysis of these patients’ motivations to participate in early clinical trials, but findings in cochlear implant and other prosthesis recipients should serve as a warning: A recent University of Iowa study characterized a majority of candidates seeking a cochlear implant as showing “elevations in depression, social introversion, suspiciousness, and social anxiety and loneliness,” (60) obviously not desirable characteristics for those about to undergo a novel procedure with uncertain outcome. Conversely, the presence of other disabilities is not necessarily a barrier for successful prosthetic rehabilitation: A study of deaf children and adults with severe visual, mental, or social comorbidities receiving cochlear implants demonstrated improved quality of life (61). In general, however, the early phase of visual-prosthesis trials should give preference to otherwise healthy individuals. Moreover, psychosocial factors such as supportive caregivers, employers, and educators are known to be conducive to successful recovery and rehabilitation (62).

In view of the known importance of patients’ character traits and support systems in other forms of disability and rehabilitation (63, 64), it is remarkable how few published reports are available of desirable psychological attributes in early-prosthesis-trial participants, even for well-established devices with a slow rehabilitation time course, such as lower-limb and cochlear prostheses. Instead, the available literature concentrates on easily quantifiable predispositions, such as the locus of impairment and history of disability, remaining function, and cognitive and education status. The success of lower-limb rehabilitation in older patients is strongly predicted by their score on a simple pictorial learning test, in addition to factors such as the amputation site (65). A cochlear implant–population study showed that the duration of hearing loss and preoperative word recognition, rather than residual hearing in the implanted and fellow ear (66) or age (67, 68), predicted postoperative outcomes and that a statistical model based on these measures can serve as a predictor of cost-effectiveness (69). A recent study indicates that verbal-learning scores and working memory are better predictors of cochlear implant success in previously hearing adults than general cognitive measures (70). Formal assessment tools considering factors such as preimplant language and speech ability, duration of deafness, and learning style are available for use in children (71), but the corresponding tools in vision evaluation do not yet exist.

Even with this experience from studies involving cochlear implant wearers, the prerequisites for an ideal visual prosthesis recipient are not a priori clear. We can make some educated guesses, however. Prior visual experience (at least in terms of shape recognition, spatial/temporal relationships between visible objects and events, and movement) appears to be a minimum requirement for the interpretation of prosthetic visual input. In addition to having this experience, candidates should be able to accurately describe their previous and current visual experiences. Particular visual skills such as the ability to create mental maps can be important assets for postoperative rehabilitation: Someone who is an independent cane traveler with the demonstrated ability to negotiate both familiar and unfamiliar territory is more likely to be able to interpret and apply prosthetic visual input to everyday tasks. Preoperative screening of such skills (e.g., by asking patients to draw the layout of their home) or of an object or environment explored by tactile or auditory means is of great importance.

It is crucial that candidates are prepared to engage in a long-term rehabilitation process and are willing to learn using even crude visual information. Prior experience with functional rehabilitation, either for low vision or to remedy another functional deficit, may improve the patient's
understanding of, and stamina during, the learning process. As an example, patients with Usher syndrome—who suffer from both a retinal degeneration and neurosensory hearing loss, and who compose the majority of those commonly referred to as the deaf-blind—may benefit from the previous experience of learning to use a cochlear implant when becoming early visual prosthesis recipients. Conversely, the presence of important coexisting conditions that limit normal function can be a negative factor: If too much effort is devoted to compensation for a coexisting impairment, effective visual prosthetic rehabilitation may be harder to accomplish. Thus Usher patients may be good visual prosthesis candidates only once they have become fully proficient cochlear implant users. Finally, as learned from other types of prosthetic rehabilitation, the emotional and cognitive robustness of the prospective recipient is likely to be another important determinant of success with early visual prostheses. The finding that those seeking a prosthetic cure from a cochlear implant are not necessarily well balanced and resilient is likely to hold equally for visual prostheses.

In view of these reports and expectations, early applicants to visual prosthesis trials clearly need to undergo thorough physical, psychological, and cognitive evaluations prior to acceptance as program participants, at least until the potential and limitations of the technology have been explored in more detail. The probability of limited benefit of these devices is high. More importantly, however, the value of highly motivated study participants capable of relating detailed, precise, and reproducible experiences to the investigators cannot be emphasized strongly enough. As in any high-risk endeavor, it takes true pioneers to break new ground, and the patients participating in early clinical trials are as critical to progress as any of the inventors, engineers, and clinicians.

4. PREOPERATIVE PSYCHOPHYSICAL ASSESSMENT: VISUAL FUNCTION AND PERFORMANCE

Psychophysical tests almost invariably measure the subject’s ability to detect a stimulus or discriminate between similar stimuli; such judgments can include a decision among several templates (N-alternative forced choice), relative to a reference stimulus, or presence versus absence. If a strength metric can be assigned to the stimulus, the result of such experiments generally follows what is known as a psychometric function; for stimuli far below the reference or threshold, performance (expressed as percent correct or percent seen) is at chance, and as stimulus strength increases, performance improves to asymptote at a ceiling accuracy. Commonly, especially in untrained subjects, a lapse rate \(\delta\) of 1\%–6\% is observed, so the upper asymptote is set at \(1 - \delta\) rather than 100\%. The psychometric function is an ogive of the form depicted in Figure 2, with \(P_0\) as the chance level, \(1 - \delta\) as the ceiling, \(\alpha\) as the stimulus strength at the inflection point—which is commonly chosen as the threshold because performance is midway between chance and ceiling (higher threshold criteria can be set if higher performance levels are required)—and \(\beta\) as an additional parameter reflecting how rapidly performance improves as a function of stimulus strength. Other functions (cumulative normal, Weibull) are used to model psychometric performance in specific test situations, but most studies seem to agree that the precise form is relatively unimportant as long as these basic parameters are included.

There is an extensive literature regarding techniques to measure the psychometric function in visual psychophysics (for a thorough review, see 72). In the present context, it is sufficient to say that for clinical assessment, it is extremely important to choose a method that balances rapid convergence with fault tolerance. One can obtain rapid convergence with methods based on Bayesian statistics (73–76); in other words, a new threshold estimate is calculated after each trial by fitting the psychometric function to the previously accumulated responses, and the new stimulus strength is set on the basis of this fit, typically at or near the expected threshold. However, these techniques typically presume an ideal observer (i.e., a subject who makes neither false positive nor...
false negative errors). Clinically useful variants of these techniques should contain catch trials—no stimulus is presented, so a false positive response rate can be determined—and thresholds placed far above threshold to determine the lapse rate. One should note that most automated clinical test instruments (such as the Humphrey visual field analyzer) do not use Bayesian estimation techniques, but rely on variants of up-down staircase methods (77) in which the stimulus strength is increased following an error and decreased following one or more correct responses.

With this general framework in mind, let us consider the approaches currently used to measure visual function in patients with end-stage vision loss. We restrict ourselves to light detection, light localization, and movement perception, the three most basic aspects of vision listed above.

1. Light detection: As noted above, absolute thresholds can vary over many orders of magnitude, and thus the source used for testing requires an equally large range. One may use several sources with overlapping ranges, provided their spectral composition is sufficiently similar—to avoid different matches in subjects with selective photoreceptor loss. For qualitative demonstration of light sensitivity, any light source suffices: Exposing the eye to be tested to a night light, room lights, or a penlight or scleral transilluminator held close to the eye allows for 4–5 log units of brightness. It is almost impossible, however, to obtain any precision with such tools commonly used in the clinic.

As part of a simple set of well-controlled tests named Basic Light Measurement (BaLM), Bach and colleagues (78) perform simple two-alternative forced-choice light on-off tests on a flat panel display in a completely darkened room; the brightness of the light can be adjusted to determine the psychophysical threshold. The subject is dark-adapted for 30 min.
to reach a stable sensitivity level. Many patients with end-stage retinal degeneration who have no useful form vision or light projection still have sufficient light sensitivity to detect these stimuli. The potential disadvantage of this test is that, with further vision loss, patients may no longer be able to reach threshold. A major advantage is that it can be performed on widely available equipment.

A different set of light-sensitivity tests, also performed after dark adaptation, uses a white (Xenon or LED) flash in the ganzfeld dome of clinically used ERG systems such as the UTAS-3000 (LKC, Gaithersburg, Maryland) and the Espion ColorDome (Diagnosys, Lowell, Massachusetts). A description of these tests and their reproducibility has been published by our lab (37) and by Jacobson and colleagues (36, 38). The tests were first used in an experimental trial of retinal cell transplantation in end-stage retinitis pigmentosa in the late 1990s (79), and their test-retest reliability was sufficient to demonstrate initial improvements and later relapse of the vision levels in some of these recipients, presumably caused by neurotrophic factors released by the transplanted cells. Although not every clinic participating in future clinical trials of retinal implants may have access to an ERG ganzfeld dome, such systems are commonplace at academic centers and larger retina practices. Moreover, a dedicated instrument can easily be developed as the demand increases.

2. Light localization: The standard test for light localization, the clinical visual field, is in almost all cases useless for projection verification in prospective implant recipients: Not only does a visual field test require stable fixation, but the stimulus sizes and brightness range available in most of these instruments fall short of most patients’ light-detection thresholds, and the field area tested does not include far-peripheral locations such as the temporal islands. The BaLM test can increase the brightness and extent of the stimulus, but not the eccentricity. For this reason, the use of much simpler confrontation perimetry methods is required. In these tests, the experimenter holds a flashlight or trans-scleral illuminator bright enough for the patient to see and shines it directly at one of the patient’s eyes in a fully darkened room, with the untested eye covered. Because many patients have poor fixation ability, it is important to monitor the patient’s gaze while performing the test. There is no standard protocol for this type of test. When performed in the clinic, the outcomes are noted in terms of intact or compromised quadrants and eccentricities. In the experimental trial of retinal cell transplantation, we adopted a clock hour system with 37 presentation points, 1 centrally and 36 in rings of 12 at approximately 10°, 30°, and 70° eccentricity (Figure 3a). The patient responded with “central” or with a clock hour followed by “close,” “middle,” or “far;” thus a stimulus presented in point 25 should elicit the response “1 o’clock, far.” In patients with less practice or more advanced vision loss, responses can be elicited according to the keys on a telephone pad or compass directions (N, NE, E, etc.) (Figure 3b).

3. Movement perception: As was the case for light detection, the BaLM test protocol was designed to measure motion detection thresholds in patients with sufficiently low brightness thresholds. In patients with poor brightness sensitivity, one can use a flashlight technique similar to that for localization, albeit that the light must be kept on long enough to allow movement to be perceived. Four- (cardinal directions) or eight-alternative (including diagonals) forced-choice procedures can be used, and the number of alternatives can be further doubled by presenting movements toward and away from, rather than across, fixation. In our laboratory, we have obtained good reproducibility with this technique, provided it was used within the remaining intact visual field areas (79).

Psychophysical techniques for localization and movement assessment that so heavily depend on the human operator are far from ideal. At this time there is no practical substitute for the
Figure 3
Stimulus presentation and scoring schemes for confrontation perimetry in patients with severe vision loss: (a) a 37-point scheme and (b) a 9-point scheme.

operator-managed approach: There is standard eyetracking technology, designed to provide feedback or adjust stimulus location on computer displays if the subject is not properly fixating, but such displays have insufficient brightness for most patients. This again shows the clear need for dedicated stimulus presentation equipment that can overcome these limitations.

If the need for calibrated measures of elementary visual functions may seem obvious, visual performance measures at these vision levels are almost nonexistent: Individuals without functional form vision simply do not rely on what they see, but use alternate strategies. The Minnesota Rate of Manipulation Test (80), originally designed to test dexterity in patients with functional vision but poor grip strength and/or fine motor control, can be adapted for the reverse situation, but as soon as the tactile element (a well in which a round peg is placed) is replaced by a strictly visual target, the task becomes impossible to someone without form vision. Occupational therapists and orientation and mobility (O&M) instructors familiar with the problems of severely visually impaired clients are in the best position to assess patients’ use of rudimentary vision in task performance, but there is a need for test courses, materials, and scoring methods that are reliable and sensitive to changes in performance; the beginnings of such tools exist (see Section 6), but they need to be expanded, refined, and validated for lower levels of vision. Studies with low vision patients in the areas of wayfinding (81), eye-hand coordination (82), visual search (83), driving (84), and reading (85) are available, and a few clinical trial protocols include visual performance evaluations, but there are no accepted standards; moreover, most of these studies were performed in patients with substantial remaining vision. Blind individuals tend to be highly skilled at task performance with minimal visual guidance (e.g., by memorizing the layout of a mobility course or by using tactile cues). There is a clear need for the development of a few simple, validated visually guided tasks for the nearly blind.

The need for tests of patients’ internal visual representations (mental maps) is mentioned above as a preoperative selection criterion. Correlating this ability with early recipients’ postoperative results may allow the prediction of success in future prosthesis patients; to do so, quantification
of this skill is necessary. Existing tests have been calibrated primarily in sighted individuals; a few reports in patients with severe vision loss are available (83, 86).

Over the course of the past decade, the field of rehabilitation has developed a new approach to performance assessment through the use of patient-reported outcomes. Standardized questionnaires are used to collect patients’ judgments regarding the level of difficulty involved in the performance of a wide range of tasks of varying complexity. The approach and analysis are based on item response theory (34, 87)—simply put, that tasks can be ordered according to difficulty along one or a few dimensions and that subjects’ abilities can be ordered and quantified along those same dimensions—and the computer-driven administration often limits the tasks sampled to those within the patient’s ability range and interest. Based on a sufficient number of patients and tasks sampled, a so-called Rasch analysis can be performed that establishes the dimensionality of the scales, ranks tasks and patients along each scale, and uses the score distributions within patients to determine whether any tasks need to be eliminated (e.g., those having different connotations for different patients) and, conversely, uses the distributions within tasks to determine whether any patients do not match the expected scale (e.g., those with comorbidities that impose separate limits on the task).

Several well-calibrated visual functioning questionnaires are available (88), but only two have been tested in patient populations with a range of vision loss, including (near-)blindness (89, 90). Even in these, the number of items scored as manageable by nearly blind patients is small, and responses may be based on nonvisual task performance. Future work will have to expand this set of items and the population in which they have been calibrated.

5. POSTOPERATIVE ASSESSMENT: BASIC SAFETY AND FUNCTIONALITY

Postoperative assessment of visual prostheses follows a trajectory similar to that used elsewhere in neurosensory prosthetics, especially the cochlear implant. The principal outcome variables of interest for a visual prosthesis may be the wearer’s visual function and performance with the device, but a number of more basic measures are of key importance, especially during the early development phase. I briefly list these as a reminder of the many aspects involved in developing this new field.

5.1. Device Safety

It will be important to document the condition of the recipient’s eye in the immediate postoperative period to assure that any adverse effects of the implantation are minimal and to obtain records needed if later complications arise. Most of this evidence involves the anatomical/physiological tests and exams previously used in preoperative evaluation. After an initial monitoring period, there should be no need for frequent repetition of these tests and exams, except in the case of (suspected) adverse events: The stability of basic device functionality (see below) can serve as an adequate indicator of long-term safety.

5.2. Effects on Remaining Vision

Because all visual prostheses currently envisaged, including those where the image-acquisition camera is implanted, require an external power supply, the effects of the implant on the remaining vision can be ascertained by turning off the power and repeating the preoperative light, location, and movement tests and any other visual function tests the implant wearer may have been able to accomplish. It is true that the implant may physically interfere with vision (e.g., by reducing
the amount and distribution of light that can reach the retina), but because most implants only affect part of the retina, optic nerve, or cortex, native vision in the remaining areas should be unchanged, and the amount of change to be expected owing to simple mechanical or optical effects of the implant can be estimated even prior to implantation. If (negative) changes exceed those in the fellow eye, this may indicate a negative effect of the implant, and the changes should be closely monitored to distinguish between transient postoperative effects and long-term adverse effects.

5.3. Basic Functionality

In the early stage of postoperative testing, it is most important to establish for each of the implanted electrodes whether its activation elicits a phosphene and, if so, to measure its perceptual range (i.e., the interval between threshold visibility and discomfort level). Because of the upper limit of safe stimulation (91), a threshold may not be reached for some electrodes, or the dynamic range may be restricted. Regular repetition of this measurement is needed to examine the stability of the electrode-tissue interface and of the wearer’s percepts. One can use basic strength-duration curve parameters—rheobase and chronaxie (92)—to detect changes at the electrode-tissue interface, whereas perceptual changes (e.g., reduction of the threshold due to practice) are more likely to result in scaling of the strength-duration curve amplitude. Even if the basic stimulus is kept constant—a charge-balanced cathodic-anodic pulse with equal pulse width and amplitude in either phase—at least three pulse durations (e.g., 0.1, 1, and 100 ms) and three different amplitudes (e.g., at 80% and 125% of the previously established threshold and at the previously established upper limit of comfort) are required for monitoring purposes. For an array with up to 100 electrodes, this amounts to fewer than 1000 observations (i.e., achievable within a single session), but for larger arrays, even this elementary verification exceeds the wearer’s endurance. Monitoring strength-duration curve parameters and scaling can then be done in a carefully chosen subset of electrodes, whereas a single trial at a standard pulse duration and 125% of threshold amplitude can be used to monitor the basic functionality of the remaining electrodes. Objective techniques, such as recording of the electrically evoked potential, may seem attractive but are impractical because of the low signal-to-noise ratio, hence the need to average many (typically up to 100) responses.

5.4. Spatiotemporal Interactions

Simultaneous in-phase stimulation of neighboring electrodes may lower the perceptual threshold—or yield a combined threshold where no individual thresholds could be obtained—whereas asynchronous stimulation may raise it. In general, nearest-neighbor interactions between electrodes are likely and need to be mapped. Even assuming that, near threshold, the system can be approximated as linear, additive, and spatiotemporally separable (i.e., the exploration of parameter space near each electrode can be kept to eight neighbors, three amplitudes, and three delays), this represents a formidable task when performed for all electrodes. Just as for basic functionality, a subset of electrodes can be selected for full parameterization, whereas the remaining electrodes can be sampled with two to four combinations each to verify their conformity with the chosen subset. During the early postoperative phase, test-retest reliabilities and learning effects need to be established in each recipient and in each of these functionality areas to estimate the amount of change necessary to establish significance for both safety and efficacy outcomes.
6. POSTOPERATIVE PSYCHOPHYSICAL ASSESSMENT: FUNCTION AND PERFORMANCE

Even if the implant is stable and provides reliable phosphenes at many electrodes, with well-behaved interactions in time and space, the wearer’s central visual system has to be able to interpret the signals and apply them to meaningful visual tasks. Functional outcome measures ultimately determine the efficacy of a visual prosthesis, and it is important to establish careful benchmarks for efficacy. The greatest challenge may be to define outcomes that cover a wide range of functioning because it is not known in advance how much functionality future prosthetics will provide. This section reviews well-established efficacy measures and outlines the development work needed to accomplish the goal of a comprehensive range of outcome measures. It follows the hierarchy outlined in Figure 1 and Table 1, but fills in the higher functional levels that matter in the wearer’s daily life, while retaining the distinction among information transfer (e.g., movement detection and shape discrimination), information processing/integration (e.g., three-dimensional object recognition and eye-hand coordination), and self-reported functional outcomes (e.g., task-performance ratings on daily living activities).

6.1. Information Transfer (Perception)

In information transfer, visual function is measured along the dimensions indicated in Table 1. Test procedures for light, projection, and movement can be adapted from existing tests, such as the BaLM (78). Because these are computer-generated tests, with stimuli displayed on a screen, they can be applied in almost any setting, collect response data to run efficient psychometric procedures, present results instantaneously, and retain complete log files for post hoc analysis and report generation to regulatory agencies. Of the more complex aspects of visual function listed in Table 1, color is unlikely to be perceived in the conventional manner: The highly localized retinal circuitry underlying color discrimination in normal vision is lost as part of the retinal degeneration process (1) and, even if intact, cannot be activated with large-scale electrodes. Similar considerations hold for hyperacuity and stereoacuity, which require high resolution at the retinal level to serve as input for cortical processing.

This leaves us with the perception of shape, pattern, and three-dimensional structure as the most important functional measures. The single basic ability underlying these three functions is shape perception: Even three-dimensional structure is more commonly inferred by viewing objects from different vantage points than from stereoscopic viewing. Vision measures such as acuity, contrast sensitivity, and visual field can be used to specify the ability to see shape. They can be determined using the charts and perimeters found in every eye clinic, but the range of these tests is inadequate for most near-term prostheses. Electrode spacing (typically 300–800 μm along the retinal surface or 1°–3° of visual angle) limits visual acuity to 20/2400 or worse, according to Shannon’s theorem, although scanning-induced temporal gradients likely can be used to correctly discern patterns above the Nyquist limit (93). Admittedly, cortical resolution with similar electrode distances may be much better: The cortical magnification factor can be as high as 23 mm per degree (equivalent to 20/60 for 300-μm electrode spacing) at the center of fixation (94), but it falls to 3 mm per degree at 5°, and this high resolution is limited to some local areas if electrodes are placed in clusters. Device size (typically less than 8 mm over the retina, or 25°) limits the visual field area covered, although it is considerably wider than the tunnel vision experienced by patients with advanced retinitis pigmentosa. For optic nerve and cortical implants with multiple electrode clusters, the visual field area covered is likely to be wider, but it may contain many gaps.
When it comes to creating visual function tests with specialized requirements, no tool is as flexible as the personal computer (PC). PC-based vision tests have been developed in several laboratories, and some are being marketed. More recently, even manufacturers of clinical vision test equipment have started promoting the use of screen-based versions of their visual acuity tests. Few, however, have expanded such tests to include contrast sensitivity, visual field, hue discrimination, and other tests, in part because they demand careful screen calibration (contrast sensitivity and color) and monitoring of test conditions such as subject-to-screen distance (visual field, typically performed at close range to obtain a wider angular subtense) and room illumination. We have demonstrated that, when these conditions are controlled, PC-based tests can be as reliable as standard clinical tests (95, 96), and viewing angles can be large enough to create test stimuli corresponding with 20/4000 visual acuity. Therefore, PC-based tests such as those developed in our laboratory and the Freiburg Acuity Test can easily accommodate the large optotypes required for prosthetic visual acuity testing, whereas chart-based visual acuity tests are limited by the largest optotypes they contain (20/1600 at 0.5 m for the ETDRS chart, so named after the Early Treatment Diabetic Retinopathy Study for which it was designed). In addition, other stimulus types besides letters can be created when using screen-based tests. Infant vision studies (97) and a clinical trial involving late-stage retinitis pigmentosa patients (98) have used square-wave gratings as a visual acuity–test stimulus, in a two- (cardinal orientations) or four- (including diagonals) alternative forced-choice task; compared with a 10% chance level in the 10-alternative letter-based test, the 50% or 25% chance level requires a larger number of trials to reach the same confidence level, but because the trials tend to be quicker owing to the more uniform stimulus, the total test time remains similar.

Contrast sensitivity testing has limited applicability in the context of visual prosthetics because scene contrast presented to a visual prosthesis can be boosted as part of real-time image pre-processing. Contrast discrimination, or the ability to distinguish simultaneous gray levels, is of greater importance because most live images contain both high- and low-contrast features. One can use the results of such tests to limit the range of contrast enhancement. Note that there are no chart-based contrast discrimination tests, and most labs use sine-wave gratings, Gabor patches, and similar patterns (99), which may not be optimal for use in prosthetic vision wearers unfamiliar with such patterns. Thus there is a need for the development of a simple contrast discrimination test with optotypes or square-wave gratings.

Visual field tests with the Humphrey visual field analyzer and other commercial perimeters can be programmed to present stimuli in specific locations and areas, but their flexibility is unlikely to be adequate to accommodate the levels of vision provided by early visual prostheses. The PC-based visual field test developed in our laboratory (95, 96) can bridge the gap between the crude localization of a large light and standard perimetry, but further development and validation of all visual field tests for this population are required.

Only for a single implant, the 16-electrode retinal prosthesis created by Second Sight Medical Products (Sylmar, California), has a report on visual function tests been published at this time (59). Rather than using standard visual function tests, the investigators sought to quantify performance on meaningful three- or four-alternative forced-choice tasks. Three subjects located and counted objects such as common household items, discriminated among such items, determined the orientation of a large letter L, and identified the direction of object motion; success rates varied from 40% to 100% but were mostly in the 60%–75% range, i.e., well above chance. Stimulating individual electrodes (i.e., a multiphoton image) versus all electrodes together (i.e., a single large phosphene) yielded a modest improvement in success rate and response time, suggesting the effective use of the (limited) resolution afforded by the array. Although these tests may not withstand rigorous scrutiny in terms of validation, scaling, reproducibility, and so on, they can...
certainly be adapted to meet such criteria or at the very least can form the beginnings of a rehabilitation curriculum (see Section 7). For validated visual function measures, reviewers at regulatory agencies, sponsors, and peer-reviewed journals are likely to demand traditional visual function measures, however.

6.2. Information Processing/Integration (Perception and Action)

Information processing and integration encompass activities during which visual information is either combined with other sensory information or used to guide actions. This may be as simple as using visual information to guide the search for a pattern or object or to redirect gaze during reading, or it may be as complex as guiding fine (writing, small-parts assembly) or coarse (walking, wayfinding) motor activities. In the case of visual prosthetics, these activities are not only limited by the low resolution and limited extent of the implant, but in most cases (e.g., head-mounted camera) they are also limited by the need to perform head rather than eye movements to collect information and inspect the target of the planned action. This places two burdens on the prosthesis wearer that are not shared by other individuals, whether fully or partially sighted, performing visually guided actions.

Prosthesis-mediated vision levels are expected to be well above the wearers’ preoperative vision, yet they severely limit the range of visually guided tasks that can be managed in daily life. As noted above, many daily activities can be accomplished by tactile or other means. For these reasons, most daily activities do not qualify as good practice or test activities for prosthetic vision wearers. Below I present some activities that can and have been used, although their use has been limited to simulated rather than real prosthetic vision (see Section 9).

Visual search testing for a single common household object was reported for the Second Sight 4 × 4 retinal implant (59) and was explored in prosthetic vision simulations for a checkerboard inspection task (86, 100). In the first case, only a single object had to be located but not identified, whereas subjects performing the second task had to count up to 16 white checks on an otherwise black checkerboard. In principle, one can design many variants of search tasks, and these can easily be adapted to measure performance (time to completion, errors) as a function of parameters such as object size and the presence of distracters or occluders. There is a large body of literature on visual search to guide the design of these tasks, although few test paradigms have been applied to partially sighted individuals. Adapting search tasks to a population with profound vision loss (<20/500) will be a useful first step in preparation for prosthetic vision testing.

Reading is the most common visual search and information processing task in daily life. Although sustained reading may be beyond the capability of near-term visual prostheses, spot reading of single words or numbers may be feasible sooner. Single-digit reading with simulated prosthetic vision has been included in a virtual wayfinding task (101) (see below), whereas several groups have explored reading with pixelized vision (102–109) (see Section 9). Most reading studies used regular arrays of either square abutting or small round phosphenes (i.e., a highly idealized representation of what may be perceived by a retinal prosthesis wearer, and very different from what may be expected for an optic nerve or cortical prosthesis) and may therefore have limited predictive value of what prosthesis wearers can accomplish. Conversely, several studies used standardized words and sentences (110) and can thus be further adapted for future prosthetic vision testing, assuming the required resolution (at least 16 resolvable phosphenes per character) can be achieved.

Eye-hand coordination tasks without tactile feedback that may guide performance are rare. For this reason, our laboratory has designed several tasks specifically for testing under simulated prosthetic vision conditions, with the possibility of adapting them to real prosthetic vision conditions in the future. In one such test (Figure 4a) subjects are asked to place black checkers on
Scenes and data from performance evaluation tasks developed in the author's laboratory. Scenes are passed through a pixelizing filter in real time when presented to sighted subjects. Scenes in panels a and b are observed through a head-mounted camera; the scene in panel d is computer-generated (virtual reality). (a) A 12-field example of the checkers-playing task. Subjects first count the white fields, and then place a black checker on each of them. (b, c) Meander-maze tracing and scoring. The maze is displayed on a tablet computer, and the subject traces from the filled to the open circle; tracing speed is indicated by color (blue denotes a fast speed), and the red areas are summed to compute an error score. (d) First room in a 10-room maze traversed using a game controller in a virtual wayfinding experiment.

In the checkerboard task, parameters such as the number and size of the checkers can be adjusted, whereas the maze-tracing task can have varying widths, number and sharpness of angles, and so on. This flexibility allows the task to be used across a wide range of implant properties.

Wayfinding has been a longstanding area of low vision research, but owing to safety concerns (obstacles, drop-offs that may lead to falls and injuries), this research has concentrated on two areas: cane-assisted travel in everyday environments and visually guided travel in the laboratory. There is one report in the literature of a flexible setup created in the laboratory to test wayfinding with (simulated) prosthetic vision, including steps up and down and physical objects to be avoided.
Although this setup was designed with enough variability to create a half-dozen different routes, and similar precautions can be taken for tests in real buildings or outdoors, subjects in such real-world situations tend to learn the layout of any given course after a few trials, so the range of available options for practice and for calibrated test routes is severely limited. Real-world wayfinding tasks are subject to variability in lighting conditions and traffic flow, among other things, and may require the presence of a licensed O&M professional. They are certainly useful for assessment purposes, but the need for an O&M instructor greatly limits their use in daily practice. Incidentally, O&M instructors are used to working with functionally blind individuals and with those who still have usable vision, but working with a population that regains limited vision places new demands on their expertise (see Section 7).

To overcome the need for an O&M professional and to expand the range of available test routes, wayfinding in a virtual environment may be the best solution. In our laboratory we have created a simple wayfinding task (Figure 4d) in which subjects use a game controller to find their way through 10 concatenated rooms, arranged according to many different floor plans. Large numbers on the wall help the subject keep track of the proper order, and travel time and errors (returning to a previous room) are used as performance measures; in a more advanced version, contacts with the wall and with strategically placed virtual obstacles could be scored as an additional measure, but because prosthesis wearers are likely to be cane travelers, we did not consider this critical in our design. The most important feature of this virtual setup is that the wayfinding task is learned, but the layout remains unpredictable.

6.3. Self-Reported Functional Outcomes

As discussed in Section 4, the application of item-response theory and Rasch analysis to the field of low vision rehabilitation has added a new dimension to the assessment of visual task performance by including the client’s individual judgment, yet deriving a calibrated quantitative measure of the person’s ability from the combined scores on a number of tasks. Presently, the validated questionnaires used in low vision rehabilitation contain relatively few items that can be accomplished solely visually with only rudimentary form vision. Table 2 shows the 16 least visually demanding tasks in the 48-item Veterans Administration Low Vision Visual Functioning Questionnaire (VALVFQ-48) (113) according to scores from a low vision population of well over 1000 individuals (R.W. Massof, personal communication). For the prosthetic vision population even this questionnaire has limitations: A number of the tasks in Table 2 can be accomplished primarily by tactile means, although some clearly rely on vision only. Moreover, there is a substantial gap between the two tasks deemed easiest and the next group, indicating a need for additional tasks to fill this gap. One can identify such activities by querying a patient population with profound (<20/500) visual impairment, asking in particular for activities where they feel their limited vision still makes a difference. It is not a priori certain that enough patients share such activities to obtain precise calibrations, but as these items are added to the questionnaire, the cumulative responses collected over time will further narrow down the estimates.

The postoperative assessment of prosthesis functionality is not only important to the wearer, researcher, clinician, and device manufacturer, but it also serves as one of the major criteria on which regulatory agencies such as the U.S. Food and Drug Administration (FDA) base decisions for premarket approval. In past clinical trials, the FDA has strongly relied on visual function measures, most strongly on visual acuity. It will require a concerted effort from many sides to convince these agencies that visual performance measures and self-reported outcomes deserve serious consideration, along with traditional visual function measures, if only because these nontraditional measures tie in most closely with the wearer’s own experience. For this to happen, however, a body
Table 2  Least visually demanding tasks from the set of 48 included in the VALVFQ-48 questionnaire

<table>
<thead>
<tr>
<th>Task</th>
<th>Logit scorea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Travel indoors/familiar places</td>
<td>−2.88</td>
</tr>
<tr>
<td>Get dressed</td>
<td>−2.74</td>
</tr>
<tr>
<td>Fix snack</td>
<td>−1.93</td>
</tr>
<tr>
<td>Keep clothes clean</td>
<td>−1.64</td>
</tr>
<tr>
<td>Eat/drink neatly</td>
<td>−1.36</td>
</tr>
<tr>
<td>Travel outdoors/familiar places</td>
<td>−1.28</td>
</tr>
<tr>
<td>Groom oneself</td>
<td>−1.25</td>
</tr>
<tr>
<td>Tell time</td>
<td>−0.92</td>
</tr>
<tr>
<td>Avoid bumping into things</td>
<td>−0.84</td>
</tr>
<tr>
<td>Take a message</td>
<td>−0.7</td>
</tr>
<tr>
<td>Match clothes</td>
<td>−0.62</td>
</tr>
<tr>
<td>Clean the house</td>
<td>−0.59</td>
</tr>
<tr>
<td>Visit public restroom</td>
<td>−0.58</td>
</tr>
<tr>
<td>Sign name</td>
<td>−0.53</td>
</tr>
<tr>
<td>See food on plate</td>
<td>−0.43</td>
</tr>
<tr>
<td>Identify money</td>
<td>−0.39</td>
</tr>
</tbody>
</table>

*Logit scores are derived from a population of over 1000 patients with severe visual impairment.

of high-quality research must be accumulated that increases the standing of these nontraditional measures in the literature and their acceptance among professionals.

7. REHABILITATION STRATEGIES

A prosthetic device is only as good as the wearers’ ability to put it to use in daily activities. However, that ability depends on long and persistent hard work by both the wearers and the rehabilitation researchers and staff who help them learn the device’s operation and its application in all the different situations where it may be of benefit. In other words, if prosthesis design and hardware are crucial for reliable operation, its ergonomics and a thorough rehabilitation program are the key ingredients to successful use by the target population. This section briefly outlines the role of professionals in the fields of rehabilitation engineering and low vision rehabilitation who can draw on their years of experience working with severely impaired patients to guide prosthesis wearers toward the optimal and judicious integration of the prosthesis into their daily lives.

A prerequisite for any functionality is proficiency in device operation (the ability to adjust device settings to optimize processing for a given task or situation), which is in part a matter of design ergonomics and good operator instruction. We assume that the device developers and manufacturers have provided the wearer and professionals with technical instructions and operational training, so they are aware of the capabilities and limitations of the device. This is in no way sufficient, however, to guarantee that the wearer receives optimal benefits from the device. First of all—especially in the early phase of visual prosthesis introduction, but possibly for several decades if the experience with cochlear prosthesis is any indication—implant surgery is followed by a period of fine-tuning of and adjustment to the individual electrode gain and timing characteristics, and most likely also spatial and temporal filter characteristics, to adjust for interactions among neighboring electrodes that may depend on the condition of the individual’s tissue substrate.
and on implant position. This adjustment process may require multiple sessions and may have to be repeated from time to time. It also requires the availability of specifically trained prosthesis technicians, a profession for which the training curriculum needs to be developed in parallel with early clinical trials. Most likely this will initially be the joint responsibility of design engineers and psychophysicists and will then gradually be transferred to the newly trained prosthesis technicians on the basis of accumulated experience.

Only after the setup process is at least substantially completed can the actual rehabilitation training process begin, mediated by several specialists currently involved in low vision rehabilitation. If past experience with low vision aids is an indication, the major role in this process will be played by vision rehabilitation instructors (certified low vision specialists, teachers for the blind and visually impaired, and occupational therapists). These specialists are used to training patients in device proficiency, in other words, basic operation and adjustments to meet the requirements of particular tasks (e.g., lighting conditions, working distance, and scanning techniques). Moreover, they are familiar with situations where a device differs in specific ways from normal viewing: A prime example is the use of the tray to move reading materials under the camera of a closed-circuit television reader. In the case of visual prosthesis, the principal differences in viewing method are related to the attachment of the camera and the electrode array. The camera will in most cases be mounted on the wearer's forehead, prompting the need to use head movements to redirect one's gaze, for which eye movements would normally be used (114). Eye movements, conversely, are counterproductive to stable viewing because the rigid attachment of an electrode array to the underlying tissue stabilizes the phosphenes in a stationary position, giving the wearer the impression that the entire scene follows the eye movement (101). One way to limit this effect is to learn to suppress eye movements, in particular those normally associated with head movements (vestibulo-ocular reflex); our experience in prosthetic vision simulations is that subjects tend to voluntarily adopt this suppression (100). A second, more elegant way would be to monitor the wearer's eye position and accordingly remap the scene area presented through the prosthesis; a wide-angle scene camera could easily span an angle normally covered by eye movements.

A second category of professionals that will undoubtedly play a major role in prosthetic vision rehabilitation comprises O&M teachers. Their principal task will be to help the client integrate the use of a visual prosthesis into a set of previously existing travel skills. This last point is extremely important: Safe travel is a skill that is methodically taught, and slowly acquired, and the limited capabilities of early prosthetic vision cannot substitute for those skills. The building across the street may be visible to the prosthesis wearers, but whether all the cars, pedestrians, and other stationary and moving obstacles on the way there are also visible is doubtful. The previous familiarity with cane travel, echo localization, and other O&M techniques is indispensable. Conversely, O&M instructors working with prosthetic vision wearers must have a thorough understanding of what the device can and cannot accomplish. For this reason, they need to work in close cooperation with rehabilitation engineers and vision rehabilitation specialists.

Vision rehabilitation and O&M instructors not only are familiar with solutions to daily activity performance with a variety of low vision aids, but their principal strength may be in analyzing new tasks, breaking them down into manageable components, and working with the client to acquire the dexterity needed for each component. Thus, as a simple example from eccentric viewing training that may apply to future visual prosthetics, training on a reading task needs to proceed in a highly structured manner: finding the optimal text position and viewing ergonomics, learning to identify single letters, then short words, longer words, and finally short phrases. Previous reading experience may transfer, but only to the extent of putting together words and sentences. Letters and letter combinations may look unfamiliar at first, just as all phosphene vision is likely to be different from natural vision; this is one important lesson learned from the cochlear implant.
For the first several years after prosthetic implants become a clinical tool, and again as major
changes in the technology are introduced, there will be a need for coordinated efforts in developing
the training materials for rehabilitation specialists working with new implant recipients. Given the
wide availability of remote-access technology, web conferencing, and other tasks over the Internet,
there is an excellent opportunity for this prosthetic vision training curriculum to be developed in
a collaborative environment. The only limitation imposed may be by competing manufacturers
reluctant to share device-specific information, making it unlikely that they will initiate such a
design group. A dedicated core group of low vision researchers and rehabilitation engineers,
vision rehabilitation teachers, and O&M instructors working with early prosthesis wearers will be
in an excellent position to start such a group. A meeting held at the Smith-Kettlewell Institute in
San Francisco in October 2007 laid a foundation in one topic area, i.e., prosthetic vision outcomes
measurement.

8. GOALS OF NEAR-TERM VISUAL PROSTHESES

The development of visual prosthetics is clearly presently in its infancy, and it is hard to predict
the development of technical capabilities. Yet early attempts at vision restoration through cortical
(6, 9–11), optic nerve (115–117), and retinal (57, 59, 118) prosthesis prototypes have provided a
hint of what the visual system can accomplish, even with the most primitive implants. From the
technical specifications of prototype visual prostheses discussed at recent conferences and reports
in the literature, we can estimate the vision levels the improved implants of the next 5–10 years
may allow. In doing so, we have to distinguish among the three substrates because each entails its
own strengths and challenges.

The retinal prosthesis is the most straightforward in its geometric properties: The layout of per-
ceived phosphenes should closely match that of the electrode grid by virtue of the geometric nature
of the eye’s optics, with the exception of the central 2°–3° in which the bipolar and ganglion cells are
displaced outward. However, it has the drawback of large electrodes and interelectrode distances
relative to the native resolution, approximately a factor of 50 lower than that afforded by foveal
cones and inner retinal neurons. This greatly limits the details that can be resolved for higher-order
tasks, such as reading and face recognition, that many retinitis pigmentosa patients hope to regain.

The cuff electrodes of the optic nerve prosthesis currently in use can only be used to activate
many nerve fibers simultaneously, and perceived phosphenes will inevitably be amorphous and lack
specific localization. A penetrating electrode array for optic nerve fiber stimulation currently being
developed by a group in Shanghai (119) may overcome this limitation and yield smaller and more
distinct phosphenes, but as with the cortical prosthesis, these are likely to assume a wide geometric
distribution, even if the general organization of the optic nerve (120) is taken into account.

Contrary to expectation, phosphenes elicited by cortical stimulation may not result in
phosphene patterns that match the known retinotopic projection (94, 121). With both subdu-
ral (122) and intracortical (11) implants, phosphenes from adjacent electrodes were reported at
disparate locations, presumably because the implant straddled striate and prestriate cortex and/or
because of intervening sulci. These findings signal a need for accurate and efficient phosphene-
mapping methods, a problem that has received some attention in the early days of cortical implants
(122, 123) but only limited systematic investigation (124, 125). Creating an accurate phosphene
map addresses just the first stage of the problem, however. An inverse map transform needs to be
applied to the visual scene, and even then it may be difficult to convey structure and meaning if
the phosphene map has substantial gaps.

This brings us to a crucial question: How can we know what tasks a visual prosthesis wearer will
be able to accomplish? The specifications of the device can only tell us the theoretical optimum,
but whether the neuronal substrate can fully utilize that information is unclear. The difference in performance between single-phosphene and multiphosphene operation of the Second Sight 4 × 4 array is only modest, suggesting that at least at the retinal level, signals from multiple electrodes are not processed independently. It is certainly possible, however, that long-term use will allow further improvements, as has been reported repeatedly for cochlear implants. If visual prostheses fulfill the requirements of long-term stability and basic functionality, then the wearers themselves will become the teachers of what can be accomplished. If the expression “mind over matter” holds anywhere in the biomedical field, it is in the ability of prosthesis wearers to exceed the designers’ expectations and push the limits of the technology.

9. ROLE OF PROSTHETIC VISION SIMULATIONS

In the research field of prosthetic vision, psychophysics simulations play a somewhat unusual role. Originally intended to answer questions such as the number of phosphenes it takes to recognize a person’s face (109) or the resolution required to read four-letter French words in the periphery (104), they have gradually been refined by including more realistic intensity profiles (126) and gaze stabilization (100, 127). We still do not know whether the current crop of advanced simulations1 comes close to the experience of implant wearers, but as that information becomes available the next set of simulation designs will be waiting to incorporate it.

Rather than being mere toys for visualization and speculation, simulations can play many roles:

1. They can be used in normally and partially sighted individuals to study their adaptation to the severely impoverished visual condition experienced by prosthesis wearers. For the foreseeable future, such sighted subjects will more readily available than prosthesis wearers.
2. They can be adapted to include phenomena reported by early prosthesis wearers and help researchers understand those phenomena and suggest ways to compensate for them.
3. They can be used to instruct prosthesis designers and rehabilitation specialists in identifying bottlenecks and adjust designs to compensate for those.
4. They can help implant wearers’ physicians and relatives gain an appreciation for the challenges faced by the wearer.

It is interesting to note that the importance of simulations is unlikely to wane over time. Twenty-five years after the clinical introduction of the cochlear implant, simulations of cochlear implant function are playing a more prominent role than ever, as judged by the number of PubMed entries on the topic. It stands to reason that prosthetic vision simulations will continue to play a prominent role in visual prosthesis development as well, at the technical design, psychophysics, and rehabilitation levels alike.

1A series of representative simulation videos can be found at http://lions.med.jhu.edu/lvrc/gd.htm.

10. CONCLUDING REMARKS

It is remarkable how many groups and laboratories have joined the field of visual prosthesis development over the past 1–2 decades, and how many publications about methodology, design, and engineering of visual prosthetics have appeared at professional conferences and in the peer-reviewed literature. Maybe even more remarkable have been the media attention and the level of interest among the general public. On one hand, this interest is understandable: Seeking to cure blindness is an endeavor of literally biblical proportions, and even the first baby steps toward that goal are bound to attract attention. On the other hand, it places tremendous responsibilities on the shoulders of
those working in this field: to tone down the rhetoric and emphasize the need for realistic expectations; to point out that what has been accomplished thus far is promising, yet very modest; and to minimize competition and maximize collaborative efforts in order to shorten the time needed to overcome the enormous hurdles of which we are aware, and those still lurking behind the horizon.

I hope this article makes it clear that it is none too soon to broaden the ranks of those working toward a functional visual prosthesis. The days of prosthetic vision rehabilitation are here, and it is time to benefit from the expertise of those who have brought low vision rehabilitation to a much higher standard over the past few decades, and who continue to advance that field. But along with the rehabilitation specialists it also is time to bring in the specialists in outcome measurement and functional assessment. We will need their help to tell regulatory agencies and society at large how much we are actually accomplishing. We may not always like what they have to tell us, at first, but it is only by being critical of our own accomplishments that we will make true progress.

There is an urgent demand for the miracle cure for blindness. Visual prosthetics are unlikely to be that cure, just like hearing with a cochlear implant is far from normal hearing. But if we can bring the visual prosthesis to a level where it can measure up to today’s cochlear prosthesis, that will be a tremendous accomplishment. For the time being, this can be a tangible and very worthwhile goal.

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**LITERATURE CITED**


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**RELATED RESOURCES**

List of Web sites for active visual prosthesis groups, April 2008:

- [http://www.bostonretinalimplant.org/](http://www.bostonretinalimplant.org/)
- [http://bmes-erc.usc.edu/brl](http://bmes-erc.usc.edu/brl)
- [http://www.2-sight.com](http://www.2-sight.com)
- [http://www.med.wayne.edu/kresgeeye/ligon/](http://www.med.wayne.edu/kresgeeye/ligon/)
- [http://www.stanford.edu/~palanker/lab/retinalpros.html](http://www.stanford.edu/~palanker/lab/retinalpros.html)
- [http://www.svec.uh.edu/BIONIC.html](http://www.svec.uh.edu/BIONIC.html)
- [http://www.eyenet-aachen.de/05-07-1-implants.html#epi_ret](http://www.eyenet-aachen.de/05-07-1-implants.html#epi_ret)
- [http://www.retna-implant.de/](http://www.retna-implant.de/)
- [http://nanobio.snu.ac.kr/eng/index.html](http://nanobio.snu.ac.kr/eng/index.html)
- [http://bionic.gsbme.unsw.edu.au/](http://bionic.gsbme.unsw.edu.au/)
- [http://www.ophthal.med.osaka-u.ac.jp/www/artificial/index_e.html](http://www.ophthal.med.osaka-u.ac.jp/www/artificial/index_e.html)
- [http://www.jsav.jp/eng/index_e.htm](http://www.jsav.jp/eng/index_e.htm)
- [http://www.bioen.utah.edu/cni/projects/blindness.htm](http://www.bioen.utah.edu/cni/projects/blindness.htm)
- [http://neural.iit.edu/index.htm](http://neural.iit.edu/index.htm)
- [http://cortivis.umh.es/](http://cortivis.umh.es/)
- [http://www.polystim.ca/](http://www.polystim.ca/)
- [http://lions.med.jhu.edu/lvrc/gd.htm](http://lions.med.jhu.edu/lvrc/gd.htm)
- [http://biophotonics.sjtu.edu.cn](http://biophotonics.sjtu.edu.cn)

* A page on this Web site keeps an updated list of visual prosthesis projects around the world.
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