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Rehabilitation of visual perception in cortical blindness

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Abstract

Blindness is a common sequela after stroke affecting the primary visual cortex, presenting as a contralesional, homonymous, visual field cut. This can occur unilaterally or, less commonly, bilaterally. While it has been widely assumed that after a brief period of spontaneous improvement, vision loss becomes stable and permanent, accumulating data show that visual training can recover some of the vision loss, even long after the stroke. Here, we review the different approaches to rehabilitation employed in adult-onset cortical blindness (CB), focusing on visual restoration methods. Most of this work was conducted in chronic stroke patients, partially restoring visual discrimination and luminance detection. However, to achieve this, patients had to train for extended periods (usually many months), and the vision restored was not entirely normal. Several adjuvants to training such as noninvasive, transcranial brain stimulation, and pharmacology are starting to be investigated for their potential to increase the efficacy of training in CB patients. However, these approaches are still exploratory and require considerably more research before being adopted. Nonetheless, having established that the adult visual system retains the capacity for restorative plasticity, attention recently turned toward the subacute poststroke period. Drawing inspiration from sensorimotor stroke rehabilitation, visual training was recently attempted for the first time in subacute poststroke patients. It improved vision faster, over larger portions of the blind field, and for a larger number of visual discrimination abilities than identical training initiated more than 6 months poststroke (i.e., in the chronic period). In conclusion, evidence now suggests that visual neuroplasticity after occipital stroke can be reliably recruited by a range of visual training approaches. In addition, it appears that poststroke visual plasticity is dynamic, with a critical window of opportunity in the early postdamage period to attain more rapid, more extensive recovery of a larger set of visual perceptual abilities.

BACKGROUND

Cortical blindness (CB) is a common cause of morbidity in humans resulting from damage to the primary visual cortex (V1) or its immediate afferents (Duncan et al., 2005; Zhang et al., 2006; Pollock et al., 2019). Here, “cortical blindness” is used as an umbrella term, to include all homonymous visual field defects resulting from postchiasmal lesions. This

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includes left- and right-sided homonymous hemianopias, as well as superior and inferior homonymous quadrantanopias and scotomas of the right and left visual hemifields. While most cases of cortical blindness are unilateral, they can also present bilaterally. Demographic studies are few for this condition. The Blue Mountains Eye Study in Australia revealed CB to afflict approximately 0.8% of the noninstitutionalized population over 49 years of age (Gilhotra et al., 2002). In the United Kingdom, two studies found visual impairments to occur in a majority of new stroke survivors, with 28–52% exhibiting visual field loss (Rowe et al., 2013, 2019b). Similarly, in the United States, Pollock and colleagues (Pollock et al., 2019) estimated a 27–57% incidence of visual field defects following ischemic brain injury. Since the 2009 National Hospital Discharge Survey reported the incidence of stroke in the United States as approaching 1 million per year, this equates to approximately a quarter to half a million new individual cases of stroke-induced CB annually. Together with other possible causes of CB—traumatic brain injury, brain tumors, demyelinating diseases, and congenital conditions (Pollock et al., 2019)—this amounts to a substantial disease burden on three different continents, and likely worldwide. We should also note here that in this chapter, our discussions will focus on adult-acquired CB, rather than childhood cortical visual impairment. In addition, we will deal only with stroke-induced CB, both because it represents the most common etiology of this disease (Pollock et al., 2019; Rowe et al., 2019b) and because most rehabilitation approaches to date have been tested in this particular group of patients.

Patients with cortical blindness are impaired in many activities of daily living, including reading, navigating, driving, and recognizing people and objects (Dombovy et al., 1986; Jongbloed, 1986; Jones and Shinton, 2006; Papageorgiou et al., 2007; Gall et al., 2009; Goodwin,2014). As such, the burden of disease from this condition is high, causing a significant and measurable impact on quality of life (Warren, 2009; Rowe et al., 2019a). Patients report that their cortical blindness is very distressing (Kischka, 2019; Falkenberg et al., 2020; Hanna et al., 2020), which is compounded by the paucity of vision care that they receive (Falkenberg et al., 2020; Hanna et al., 2020). With the incidence of stroke rising among younger people (Béjot et al., 2016), this situation should only be expected to worsen in coming years.

APPROACHES TO VISUAL REHABILITATION FOR CORTICAL BLINDNESS

In contrast to physical therapy for motor stroke, there are currently no standardized, validated, or widely accepted vision restoration treatments for cortically blind patients (Pollock et al., 2019). Therapies typically focus on aspects of occupational therapy that involve teaching compensatory strategies or using substitution, whereby the goal is to teach patients to maximize the use of their remaining vision (Fig. 25.1A). This is similar to how a patient with an amputated limb might use occupational therapy or, in some cases, a prosthesis, to learn to adapt and accomplish activities of daily living such as getting dressed.

Visual substitution therapy aims to reposition the visual world so that objects that normally fall within the blind field instead fall within intact portions of the visual field. While work is being done on developing digital, wearable, “augmented reality” technology for this purpose (Sayed et al., 2020), the most common current methods involve the use of eyeglasses with

prisms attached to one lens (Rossi et al., 1990; Bainbridge and Reding, 1994; Peli, 2000; Szlyk et al., 2005; Bowers et al., 2014; Rowe et al., 2017; Houston et al., 2018). The prisms shift images so that what would normally project onto the hemianopic retina is instead seen by portions of the retina projecting to the intact visual cortex. Although most patients must be trained to interpret the shifted visual world, the use of prism lenses allows them to capture visual information they might otherwise miss, improving mobility (Bowers et al., 2014), visual functioning, and quality of life (O'Neill et al., 2011). Unfortunately, many patients are never able to learn to properly integrate this information or disambiguate it from the image directly in front of them, thus failing to benefit from these lenses (Rowe et al., 2017; Pollock et al., 2019). In particular, users encounter challenges when attempting tasks exercising near vision, walking downstairs, or gazing through the prisms themselves (Giorgi et al., 2009). The optical quality of a particular set of prisms may also limit its utility, and some patients may experience adverse effects such as headaches and diplopia (Pollock et al., 2019). Overall, only a third to a half of patients who begin a rehabilitation program with prisms end up continuing to wear their lenses long-term (Bowers et al., 2008; Giorgi et al., 2009).

Compensation therapy similarly aims to reposition the visual world, but instead of using lenses, patients are taught to capture the visual information that would normally fall in the deficit area by moving their eyes and head to more systematically sample their blind field (Weinberg et al., 1977; Zihl, 1980; Kerkhoff et al., 1992; Kerkhoff, 1999; Kerkhoff, 2000; Nelles et al., 2001; Pambakian et al., 2004; Spitzyna et al., 2007; Roth et al., 2009; Mannan et al., 2010; Trauzettel-Klosinski, 2010; Ong et al., 2015; Sahraie et al., 2016). Strategies include increasing the number of saccades toward the impaired visual field, varying the amplitude of saccades to increase sampling efficiency, developing organized patterns of scanning, and increasing the number and amplitude of head movements (Lane et al., 2010; Schuett et al., 2012; Aimola et al., 2014; Goodwin, 2014). This can be particularly helpful for reading, visual search, and obstacle avoidance (Zihl, 1995; Bouwmeester et al., 2007; Goodwin, 2014; de Haan et al., 2015). Interestingly, without coaching, many patients do not learn to make appropriate, compensatory eye and head movements toward their blind field on their own. In fact, cortically-blind patients, who lack feedback from their visual periphery on the affected side, can exhibit very different visual search strategies compared to visually intact participants; this includes ineffective scanning, abnormal saccade patterns, and trouble estimating how far they need to scan to capture relevant visual information (Ishiai et al., 1987; Zangemeister et al., 1995; Zihl, 1995; Hildebrandt et al., 1999; Kerkhoff, 1999; Pambakian et al., 2000; Martin et al., 2007; Iorizzo et al., 2011). As such, CB patients can benefit from explicit instruction and repetitive training, for instance, on how to use physical landmarks, in order to properly sample different areas of their visual field defect (Bowers et al., 2014).

Both substitution and compensation techniques improve quality of life and activities of daily living by teaching patients how best to use their remaining vision (Weinberg et al., 1977; Spitzyna et al., 2007; Roth et al., 2009; Rowe et al., 2017; Pollock et al., 2019). However, they are neither designed nor aim to recover any of the vision lost (Campion et al., 1983; Pollock et al., 2019). Restoring vision and shrinking the size of the visual field defect have been holy grails of the field for many decades. The remainder of this chapter will provide

an updated review of vision restoration approaches to CB (Fig. 25.1B–D), and will critically evaluate their relative merits. First, however, we will start with a short discussion of methods employed to measure visual field defects in CB, followed by an outline of the natural history of this condition.

MEASURING VISION LOSS AFTER OCCIPITAL STROKE

To appropriately target rehabilitation efforts, stroke survivors must have an accurate diagnosis of their visual sequelae, including accurate and reliable measurements of the size and borders of areas of vision loss. Also, key to ultimately developing individualized treatment plans is the ability to define what specific aspects of visual perception are impaired, and the extent of impairment across different regions of the visual field (i.e., across different retinotopic locations). These deficits can vary dramatically between patients, across retinotopic locations, and they also often appear in combination, including impaired central vision, eye movement abnormalities, visual field loss, visual inattention/neglect, and other visual “perceptual” disorders (Rowe et al., 2019b). Many of these abnormalities are first identified at the bedside or in neurology/ophthalmology/optometry clinics. However, some of these determinations require more sophisticated, detailed testing than is possible in the clinic. Both procedural and technologic limitations currently relegate such testing to basic research laboratories, which can perform psychophysical measurements under controlled stimulus conditions and with controlled fixation.

Nonetheless, the first assessment of visual field loss after occipital stroke is often confrontation, which involves the clinician using hand gestures to ascertain the presence and general location of visual field deficits. During typical confrontation testing, the examiner asks the patient to focus on the examiner’s nose or face, and to make a series of judgments monocularly and/or binocularly, such as counting fingers presented in each quadrant of the visual field or indicating when the examiner has moved their finger(s) into the field of view (Elliott et al., 1997; Pandit et al., 2001; Kerr et al., 2010).

Once confrontation confirms a suspected visual field defect, the clinical gold standard for measuring the extent of visual field loss in adult-onset CB is automated perimetry, most commonly using the Humphrey perimeter (Townend et al., 2007; Hepworth and Rowe, 2018). The test presents small stationary lights of varying luminance monocularly to determine detection thresholds at retinotopically determined test points throughout the visual field. Patients fixate centrally, and their head position is controlled using a forehead/chin rest. Eye-tracking in the Humphrey is optional, but whether or not it is used, the gaze is interrogated by presenting some of the lights to be detected inside the optic disc representation (which should normally lack visual sensation, and thus represents a means of assessing false-positive responses). Patients indicate visual detection by pressing a handheld button; false positives (pressing the button during a blind spot check), false negatives (failing to detect light of previously-detected threshold brightness or lower), and fixation losses are monitored throughout testing to estimate test reliability and fixation accuracy. While standard static automated perimetry is limited to the central visual field (typically a radius of the central 10, 24, or 30 degrees of vision), it is more sensitive for detecting poststroke homonymous visual field loss than confrontation (Pandit et al., 2001;

Townend et al., 2007; Kerr et al., 2010; Hanna et al., 2017). The device measurement error for Humphrey perimetry is reported by the manufacturer to be within 3 dB at individual test spots. However, test–retest variability can be influenced by many factors, including patient motivation and focus, time of day, season, as well as the technician's experience, instruction of the patient, and monitoring, along with adjustments and feedback during testing (Montolio et al., 2012). In addition to Humphrey static perimetry, several kinetic perimetry options are available, in which small lights are moved, usually from the visual periphery toward the center, and patients indicate when they first detect each light. These options include the Goldmann manual kinetic perimeter, which outputs hand-drawn visual fields (Hepworth and Rowe, 2018; Pollock et al., 2019), the Tubingen kinetic perimeter (Pollock et al., 2019), and the Octopus kinetic perimeter, which can be viewed as an automated version of the Goldmann test (Hepworth and Rowe, 2018; Pollock et al., 2019). Although there are few guidelines for exactly how visual fields should be assessed in neurologic conditions (Hepworth and Rowe, 2018), in common practice, kinetic perimetry appears to be used less often than Humphrey static perimetry for stroke patients.

As mentioned earlier, in addition to luminance detection deficits assessed by perimetric methods, many other visual abilities are impaired within cortically-blinded fields, although their full extent is rarely captured clinically. Laboratory psychophysical measures across a range of different tasks (including detection, identification, discrimination, comparison, etc.) and incorporating fixation control with eye trackers, are generally needed to properly characterize impairments across the spectrum of visual abilities. Such studies have revealed specific deficits in motion direction discrimination, motion integration, and other, more complex motion computations (Hess and Pointer, 1989; Azzopardi and Cowey, 2001; Huxlin et al., 2009; Das et al., 2014; Vaina et al., 2014; Saionz et al., 2020).In the visual form domain,V1damage impairs simple functions such as orientation discrimination of static shapes (Hess and Pointer, 1989; Das et al., 2014;Saionz et al., 2020), as well as higher-order functions such as face and object recognition (Riddoch, 1917; Zeki and Ffytche, 1998; Stoerig, 2006; Cowey, 2010).

Despite a deficit of conscious vision in cortically-blinded fields, it has been noted since Riddoch's original observations in soldiers with battlefield wounds (Riddoch, 1917) that some patients with occipital damage retain partial visual processing within their perimetrically-defined visual field defect. Weiskrantz further detailed this phenomenon, dubbing it "blindsight" (Weiskrantz et al., 1974). Blindsight is broadly defined as a deficit in conscious vision with concomitant, limited, weak visual processing abilities. It is most commonly elicited during forced-choice behavioral testing when upon presentation of a stimulus inside the blind field, the participant is asked to "guess" the response even if they are uncertain that they can perform the task. In most cases of blindsight, this results in better-than-chance performance (i.e., better than pure guessing). Blindsight also appears to require large, coarse, moving, orflickering visualstimuli (Weiskrantz et al., 1995), containing high luminance contrasts, low spatial frequencies, and high temporal frequencies (Sahraie et al., 2008)—e.g., a very large, well-defined object moving or flickering at a moderate to high speed/rate, on a clear background. Patients with bilateral CB can use blindsight to perform such remarkable feats as successfully navigating an obstacle course in a hallway (de Gelder et al., 2008). It is also possible for them to recognize emotions (de Gelder et

al., 1999; Tamietto and de Gelder, 2010) and even to exhibit fear conditioning using visual cues (Hamm et al., 2003). Yet, while blindsight has been documented for many facets of visual processing (Stoerig, 2006; Cowey, 2010), it is not always reliably elicited, even within the same individual, and it captures only a subset of normal human vision (Campbell and Robson, 1968; Robson, 1993; Azzopardi and Cowey, 1997). In more common cases, when the visual field defect poststroke is unilateral, the intact hemifield provides information that is so much more salient to the person than information processed in the blind field, that the functional relevance of blindsightis questionable (Weiskrantz, 2009; Sahraie et al., 2013). Thus, it may be safe to assume that patients with unilateral CB place little reliance on blindsight for visual functioning in daily life.

NATURAL HISTORY OF OCCIPITAL STROKE: RECENT INSIGHTS INTO THE DYNAMICS OF VISION LOSS

Few studies to date have characterized the natural history of vision loss after occipital stroke, and the extant literature has focused on deficits in luminance detection as measured by clinical perimetry tests. Two large, longstanding, prospective studies indicated that spontaneous improvements in the size of visual fields are most likely to occur within the first 2 weeks after stroke; the first used confrontation assessment (Gray et al., 1989), and the second used manual kinetic perimetry (Tiel and Kolmel, 1991). A third study, also using manual kinetic perimetry, followed patients over 3 years after stroke and found that the majority experienced improvements, which were restricted to the first 6 months poststroke (Messing and Ganshirt, 1987). The largest prospective study that utilized automated perimetry examined a mixed group of stroke, trauma, and tumor patients with damage to the occipital lobe (Zhang et al., 2006); the authors found that roughly 40% of their participants exhibited some spontaneous improvement. However, the probability of improvement was highest (affecting approximately 60% of patients) in the first 3 months postdamage, dropping precipitously from 3 to 6 months (only about 20% penetrance during this time frame). Beyond 6 months postdamage, the likelihood of any further improvement was essentially null (Zhang et al., 2006). The time course of spontaneous visual recovery in perimetrically defined blind fields after occipital stroke matches nicely the reported time course for motor recovery after motor cortex stroke (Duncan et al., 1992, 1994). Together, these studies have informed the general belief among both clinicians and scientists that, after a brief period of possible spontaneous improvement in the visual field defect in the first 6 months after adult-onset occipital damage, vision loss becomes stable and permanent.

However, recent work using more stringent approaches to patient selection and more refined, quantitative analyses of visual defects (both perimetrically and psychophysically defined) suggest that the natural history of stroke-induced CB may differ from current dogma. Psychophysical testing of a small group of subacute occipital stroke patients within the first 3 months of their stroke revealed that half or more retained *conscious* visual discrimination abilities for some classes of targets presented fully within their perimetrically-defined blind field (Saionz et al., 2019, 2020). Preserved abilities included fine direction discrimination, coarse direction discrimination, and contrast sensitivity, but they all disappeared by the onset of the chronic poststroke period, i.e., 6 months poststroke (Saionz et al., 2019, 2020).

Notably, preserved vision in subacute blind fields was distinct from blindsight in that it was consciously accessible. The strength of these visual discriminations varied across the blind field, signifying that vision loss immediately after occipital stroke is neither complete nor uniform. Instead, *V1 damage appears to initiate a process of gradual vision loss, beginning with small-spot luminancedetection (such asused duringperimetry) and progressing to include larger targets, and more complex, higher-order visual functions.* The precise timescale of loss for different visual functions initially preserved in the early poststroke period is currently unknown. However, in all cases examined to date, by 6 months poststroke, preserved visual discrimination abilities within the field defect degraded and blindness became profound (Saionz et al., 2019, 2020). Importantly, in contrast with perimetrically-defined blind fields, which spontaneously shrank in a large proportion of patients in the first few months poststroke, discrimination abilities inside the blind field never recovered spontaneously (Saionz et al., 2020). Thus, there are major differences in the types of "*vision*" measured by visual perimetry (whether static, kinetic, automated, or manual), as opposed to psychophysical approaches (which rely on forced-choice tasks and threshold levels of performance). These differences are key to properly characterize both residual vision in the blind field, as well as the properties of vision that can be recovered with therapeutic interventions such as visual training.

Beyond the subacute poststroke period, new research also challenges the notion that chronic blind fields are stable in the absence of an intervention. In one small, but detailed, prospective study, chronic patients who received standard-of-care treatment after occipital stroke actually showed slight worsening of their perimetrically-defined visual field defect, measured by Humphrey automated perimetry (Cavanaugh and Huxlin, 2017). This finding was confirmed by a larger retrospective review of stroke-induced CB, which noted that from 6 months poststroke onward, the visual field defect tends to worsen slowly over time (Wang et al., 2017; Saionz, 2020). These studies identified worsening of the perimetric visual field defect in the chronic period by using a novel, quantitative approach to the analysis of Humphrey automated perimetry, combined with rigorous inclusion/exclusion criteria for patient type and reliability indices of the perimetric fields themselves (Cavanaugh and Huxlin, 2017). It is hoped that future studies will continue to apply rigorous inclusion criteria, as well as quantitative and modeling approaches to the analysis of visual perimetry data so as to attain greater precision and sensitivity for changes in visual function, both spontaneous and following therapeutic interventions.

PRESERVED VISUAL PATHWAYS: SUBSTRATES FOR VISUAL REHABILITATION

Insights into the natural history of vision loss after V1 stroke, including the new perspectives outlined in the previous section, can be gained from reviewing the anatomic and physiologic consequences of V1 damage. In the classical, image-forming pathway (Kandel et al., 2012), information is first collected and processed by the retina, the visual sensory organ, whose only output is via the axons of retinal ganglion cells. These axons carry information through the optic nerve to the rest of the brain. At the optic chiasm, retinal ganglion cell axons originating from each nasal retina decussate, so that information reorganizes from

segregation by eye to segregation by visual hemifield. Retro-chiasmatic fibers thus carry information about the contralateral visual hemifield, from both eyes, and form their first synapse with neurons in the dorsal lateral geniculate nucleus (dLGN) of thet halamus, where 6 cell layers sort, process, and ultimately transmit the information further up the system. The optic radiations carry this feedforward visual information to a second, postretinal synapse in the primary or striate visual cortex (V1), the major target of the early, classical, image-forming pathway. V1 further processes information and distributes it to multiple extra-striate visual cortical areas, each of which performs specialized processing of the received visual information. While lesions to any of the retro-chiasmatic structures up to and including V1 can cause CB, visual information is also relayed to extra-striate visual areas through pathways that bypass V1. These include projections from the retina to the superior colliculus to the pulvinar of the thalamus and on to the extra-striate cortex, and from the dLGN directly to the extra-striate cortex (Tamietto et al., 2010; Das et al., 2014; Ajina et al., 2015a; Tamietto and Morrone, 2016; Ajina and Bridge, 2019).

Another important consideration is that when V1 is damaged by a stroke (or other means), neuronal death is not limited to cells in V1. The damage initiates a process of trans-synaptic retrograde degeneration of afferent neurons—something that has been observed in both humans and nonhuman primates (Porrello and Falsini, 1999; Jindahra et al., 2009; Bridge et al., 2011; Cowey et al., 2011; Jindahra et al., 2012; Patel et al., 2016; Millington et al., 2017; Rajanala et al., 2019; Schneider et al., 2019). This occurs sequentially, with neurons in the dLGN being the first to die (Mihailović et al., 1971; Wong-Riley, 1972), followed by retinal ganglion cells in the lesion projection zone (Cowey et al., 2011). The time course of retrograde degeneration has been most carefully documented in animal studies (Mihailović et al., 1971; Wong-Riley, 1972; Atapour et al., 2017). In humans, our information is less precise, with best estimates coming from imaging studies—magnetic resonance imaging of the brain and optical coherence tomography of the retina. Data obtained with both of these techniques suggest that early retinogeniculate portions of the visual system begin to show measurable signs of retrograde degeneration by 6 months after injury (Jindahra et al., 2009; Bridge et al., 2011; Cowey et al., 2011; Jindahra et al., 2012; Patel et al., 2016; Schneider et al., 2019). These anatomic findings support the psychophysical observation that the evolution of vision loss after V1 stroke is gradual—at least for many visual discrimination abilities. The residual vision preserved in the subacute poststroke period (Saionz et al., 2020) may well be mediated by regions of the striate cortex that survive the incident stroke (indeed such regions have been proposed to underlie blindsight/residual visual processing in the chronic period (Kleiser et al., 2001; Morland et al., 2004; Radoeva et al., 2008; Das and Huxlin, 2010; Papanikolaou et al., 2014; Barbot et al., 2021)). The disappearance of subacute residual vision by the onset of the chronic period could be caused by some of the surviving V1 regions becoming quiescent due to progressing atrophy from a persistent lack of normal feedforward and feedback input (Fendrich et al., 1992; Wessinger et al., 1997; Das and Huxlin, 2010). The psychophysical properties of subacute residual vision—namely, preservation of some but not all visual abilities across regions of the blind field (Saionz, 2020; Saionz et al., 2020)—are also consistent with the notion of possible “spared islands of visual cortex” (Albrecht and Hamilton, 1982; Tootell et al., 1995; Boynton et al., 1999; Ajina et al., 2015b; Niemeyer et al., 2017; Pawar et al., 2019). However, emerging

data suggest that these islands lose the ability to mediate conscious visual perception sometime within the first 6 months poststroke. We posit here that this could occur through a combination of progressing retrograde degeneration and lack of normal feed forward and feedback inputs. Infact, this combination of factors could lead to a form of “visual disuse atrophy” (Saionz et al., 2020), where by the activity of weak, surviving connections becomes down-weighted over time, as patients learn to ignore the abnormal visual signals originating from their blind field. Many questions naturally emerge from this, but the ones we will focus on in the remainder of this chapter are (1) can vision be recovered in stroke-induced cortical blindness and (2) when is the most optimal time to administer treatment?

USE OF VISION RESTORATION TRAINING IN CORTICAL BLINDNESS (FIGS. 25.1B AND 25.2)

Despite evidence of residual visual processing in cortically blind fields, it has been repeatedly suggested that the adult visual system may not be capable of functional recovery after V1 stroke in adulthood (Horton, 2005a, 2005b). Yet an abundance of basic research into poststroke visual plasticity has shown that visual training can recover certain visual functions in long-standing, chronic, CB (reviewed in Melnick et al., 2016). Because these original studies were conducted beyond the window of spontaneous visual recovery, the investigators were able to establish that vision improvements were exclusively the result of training and not spontaneous plasticity. These training studies were based on principles of perceptual learning, an umbrella term for a form of neuroplasticity within sensory systems whereby repeated stimulation improves processing of stimuli across the lifespan (Ahissar and Hochstein, 1997; Dosher and Lu, 1998; Gilbert et al., 2009; Lu et al., 2011; Sagi, 2011; Lu et al., 2016; Dosher and Lu, 2017). A prevailing hypothesis about the mechanism of visual perceptual learning is that it is a form of Hebbian neuroplasticity (Dosher and Lu, 2009). The evidence we detail here suggests that this mechanism is functioning quite effectively in the residual visual system of V1-damaged patients, both in the chronic and subacute poststroke periods.

As mentioned earlier, most of the data demonstrating the efficacy of visual perceptual training as a vision restoration tool has come from research studies performed in chronic occipital stroke patients (summarized in Fig. 25.2). Few of these scientific research studies have been validated and published as randomized, placebo-controlled, double-blinded trials (Pollock et al., 2019) and this remains a gap in the field. Kasten and Sabel’s visual restitution therapy (VRT, Fig. 25.2A) was claimed to improve luminance detection in CB fields (Kasten et al., 1998) and became clinically available in Europe and the United States for vision restitution, marketed by NovaVision. However, it was later shown to suffer from insufficient fixation control (Reinhard et al., 2005), light scatters (Pelak et al., 2007), and problems induced by using the same task for both training and evaluation of vision restoration. Sabel’s group later tested many variants on VRT (Kasten et al., 1998; Poggel et al., 2004; Kasten et al., 2007; Jobke et al., 2009; Poggel et al., 2010; Gall et al., 2014; Turco et al., 2015; Alber et al., 2017). These included a high-contrast, moving spiral that occupied the entire blind field (Fig. 25.2B) and was dubbed an “extrastriate” stimulus (Jobke et al., 2009). However, fixation remained un-enforced and it was unclear if patients were required

to perform a motion task or just passively view this moving stimulus. Unfortunately, the high-profile failure of VRT in clinical circles, together with the general lack of randomized, controlled, clinical trials for most of the other visual restoration approaches developed by other research groups (see below), have thrown significant doubt on the feasibility and usefulness of visual restitution in adult-onset CB (Horton, 2005a, 2005b; Pollock et al., 2019). Thankfully, however, efforts to attain solutions for this patient population have persisted.

Fundamentally, such efforts should start with a better understanding of the basic science of training-induced plasticity and perceptual learning in CB patients. Below, we will review the basic, neuroscientific approaches used to date in this population. As shown graphically in Fig. 25.2C–N, these can be subdivided into the following categories: (1) training to *detect* the presence of a visual target, (2) training to *discriminate or identify* specific aspects of a visual target, (3) repeated presentation of a *single stimulus* at the same blind-field location in each training session, until improvement is attained (Fig. 25.2D–H), or (4) presentation of *stimuli at different locations* on each trial within a session, either in the intact or blind field (Fig. 25.2A–C, J–N). In (3), stimulus location is predictable from trial to trial; in (4), the patient needs to deal with location uncertainty for the stimulus to be detected or discriminated.

Chokron and colleagues (Chokron et al., 2008) attained encouraging results with a multilocation spot detection task that resembled VRT but seemed to better address light scatter and task-specificity issues (Fig. 25.2C). Subsequent attempts to improve upon this shifted the field toward visual psychophysics performed with online fixation control using an eye tracker (thus ensuring gaze-contingent stimulus presentation), as well as manipulations of stimulus and task difficulty (pushing the visual system to its perceptual limits and allowing measurement of threshold performance in the blind field).

These studies demonstrated recovery of a range of visual abilities within cortically-blinded fields, including detection of flickering sinusoidal gratings and detection contrast sensitivity (Sahraie et al., 2006, 2010; Trevethan et al., 2012), flicker sensitivity (Raninen et al., 2007), relative target localization (Chokron et al., 2008; Elshout et al., 2016), letter identification (Raninen et al., 2007; Chokron et al., 2008), direction integration (Huxlin et al., 2009; Das et al., 2014), motion coherence (Vaina et al., 2014), coarse and fine [translational] direction discrimination (Cavanaugh et al., 2015, 2019), rotational direction discrimination (Elshout et al., 2016), and contrast sensitivity for both static orientation and motion direction discriminations (Das et al., 2014). Most of the psychophysical training regimens listed above also caused reductions in the size of visual field defects measured with clinical perimetry (Sahraie et al., 2006; Chokron et al., 2008; Huxlin et al., 2009; Bergsma et al., 2012; Trevethan et al., 2012; Vaina et al., 2014; Elshout et al., 2016; Cavanaugh and Huxlin, 2017). Importantly, the improved/restored vision appeared to be consciously accessible (Sahraie et al., 2013; Saionz et al., 2020) and recovery did not always seem to represent a simple enhancement of blindsight (Das et al., 2014). Indeed, in many cases, the stimuli used to retrain vision could not elicit blindsight—e.g., static nonflickering Gabors with slow temporal cosine envelopes (Hess and Pointer, 1989; Weiskrantz et al., 1991; Morland et

al., 1996; Sahraie et al., 2008) or random-dot stimuli with complex motion (Azzopardi and Cowey, 2001).

In summary, patients with longstanding, adult-onset CB retain the potential for visual neuroplasticity and this potential can be recruited by intensive, repeated detection or discrimination training to recover conscious visual perception in the blind field. Fixation control during stimulus presentation appears to be important for training to be most effective, but this is beyond the capacity of most current systems to incorporate. However, what is more realistic to implement with current technology is real-time fixation control using eye-trackers during pre- and post-training tests that are usually performed in laboratories or clinics. This is key for the accurate assessment of changes in visual functions, whether measured with perimetry or psychophysics. As such, it would be good to see this implemented routinely for visual testing in this patient population.

LIMITATIONS OF TRAINING IN THE CHRONIC PERIOD AFTER OCCIPITAL STROKE

While visual training does recover chronic stroke patients' ability to perform a range of detection and discrimination tasks in their blind field, recovery generally requires several weeks to months of daily practice at each blind field location (Huxlin et al., 2009; Sahraie et al., 2010; Das et al., 2014; Cavanaugh et al., 2015; Larcombe et al., 2018; Cavanaugh et al., 2019). Indeed, several studies have shown that the amount of improvement in chronic CB (both psychophysically-measured and perimetrically-derived) is directly proportional to the number of training sessions performed (Cavanaugh et al., 2015; Cavanaugh and Huxlin, 2017). Even so, recovered vision in chronic CB patients is not as accurate or sensitive as normal vision, appearing coarser and exhibiting lower contrast (Huxlin et al., 2009; Das et al., 2014; Cavanaugh et al., 2015). At some level, the inability of therapy to restore normal vision in CB is not entirely surprising. After all, V1 damage kills a large portion of neurons selective for fundamental visual attributes, such as orientation and direction. In addition, it has been postulated that V1 lesions shift the excitation/ inhibition balance in the residual visual circuitry toward excessive inhibition (Spolidoro et al., 2009). High levels of intracortical inhibition can limit plasticity and would be expected to increase the threshold for activation of relevant circuits. This may explain why visual training started more than 6 months after stroke is reported by patients to be arduous and slow, something that was confirmed empirically in a recent study comparing training-induced recovery in chronic and subacute CB (Saionz et al., 2020).

MOUNTING EVIDENCE FOR BENEFITS OF EARLIER INTERVENTION AFTER V1 STROKE

The approach to rehabilitation used in vision stroke research to date has largely involved delaying intervention until the chronic poststroke period, when visual fields have stabilized, making it easier to isolate the impact of the intervention from spontaneous improvements. This stands in stark contrast to sensorimotor stroke therapy, which has been systematically investigated as early as the first week poststroke (Bernhardt et al., 2017). Current treatment

guidelines for sensorimotor stroke recommend initiating early rehabilitation to promote faster, greater recovery (Krakauer, 2006; Winstein et al., 2016; Bernhardt et al., 2017; Dromerick et al., 2021). These clinical observations are supported by scientific evidence suggesting that the damaged brain may have increased neuroplastic potential early after injury (Rossini et al., 2003; Bavelier et al., 2010; Hensch and Bilimoria, 2012; Seitz and Donnan, 2015). The early poststroke period is characterized by resolution of peri-lesional inflammation and edema, variability in vascular perfusion, upregulation of growth and injury-response factors (especially brain-derived neurotrophic factor), changes in neurotransmitter modulation (especially GABA, glutamate, and acetylcholine), an overall shift in the excitation/inhibition balance to favor excitation, and possibly even the re-emergence of acritical-period-likestate (Rossini et al., 2003; Bavelier et al., 2010; Hensch and Bilimoria, 2012; SeitzandDonnan,2015).Moreover, structural barriers to plasticity in the form of myelin-related proteins inhibiting axonal sprouting, perineuronal nets of chondroitin sulfate proteoglycans, and fibrotic tissue have yet to form (Rossini et al., 2003; Bavelier et al., 2010; Hensch and Bilimoria, 2012). It is conceivable that these processes underlie the spontaneous improvements in detection perimetry observed in the first few months after an occipital stroke. Recent work has now begun to investigate whether these processes can also be recruited by early administration of visual training to facilitate greater and faster recovery of visual discriminations (not just detection) in cortically blind fields.

In addition to enhanced neuroplastic potential early poststroke, the specter of trans-synaptic retrograde degeneration further motivates administering training during the subacute period. Degeneration is likely well underway by 6 months poststroke (Bridge et al., 2011; Bridge and Plant, 2012; Jindahra et al., 2012; Schneider et al., 2019) and, once it happens, it will deprive chronic patients of important sensory substrates, and can only limit training-induced visual recovery. For instance, loss of parvocellular neurons, which are especially susceptible to retrograde degeneration (Cowey et al., 1989; Yu et al., 2018), will impair responses of the remaining visual circuitry (and of the person) to fine detail (mediated by sensitivity to high spatial frequencies), tasks involving form recognition or discrimination (mediated by neural orientation and shape preferences) and low luminance contrasts (due to loss of the sufficient number of sensitive neurons), among others. As detailed above, preserved, blind-field contrast sensitivity and orientation discrimination are key differences between early subacute and chronic CB patients (Saionz et al., 2020).

With these motivations, the question becomes: does identical training initiated in the subacute poststroke period lead to greater recovery than training in the chronic period? In one of the first, systematic, psychophysical studies of subacute vision rehabilitation (Saionz et al., 2020), patients recovered visual discriminations in a fraction of the number of training sessions needed by chronic patients. Subacute patients also showed transfer of learning to deeper, untrained areas of the blind field and they exhibited substantial enhancements of Humphrey perimetry, even greater than those attained spontaneously. Early data also suggest that subacute patients may be able to train on a wider range of stimuli than chronic patients; in particular, they can recover the ability to discriminate low-contrast, stationary stimuli—something very few chronic patients are able to do (Saionz et al., 2019; Saionz, 2020). Importantly, in these studies, untrained subacute patients, who served as a control group, experienced the expected spontaneous improvements in their perimetrically-

measured [Humphrey] visual fields, but they did not show any spontaneous improvements in visual discrimination abilities. This observation highlighted a dissociation between the type of vision that could improve spontaneously poststroke (luminance detection, a.k.a. perimetry) and that which required deliberate training (discriminationtasks).Spontaneous improvements in perimetry are hypothesized to be the result of subsiding peri-lesional edema and inflammation, restoration of blood flow to the penumbra, and some degree of spontaneous reorganization (Krakauer, 2006). In contrast, subacute improvements in visual discrimination abilities seemed to occur only as a result of specific, training-dependent neuroplasticity. The dissociation between luminance detection and discrimination tasks also suggests a need to develop more comprehensive clinical assessments of vision loss after stroke, beyond perimetry (Saionz et al., 2020)—current clinical assessments fail to capture so many key aspects of visual function, including those which are preserved in the first few months after a stroke, or which are recovered following directed blindfield training using complex visual stimuli/tasks.

All in all, results of psychophysical testing and training in subacute patients support the notion that occipital stroke may reopen a sensitive or maybe even critical period for vision (Bavelier et al., 2010; Hensch and Bilimoria, 2012; Voss, 2013). In this poststroke sensitive period, the neuroplastic potential is enhanced but environmental input is required to guide optimal, functional tuning of relevant circuits. If it turns out that the early poststroke period is actually a critical period (i.e., a period with the exclusive potential to develop specific functions), this will have important implications for the field. As is true of all critical periods, it would mean that if residual circuits are not appropriately stimulated during this limited period of time, then their function could be permanently and negatively altered. It is therefore key for future research to determine whether the early period after an occipital stroke is a sensitive or a critical period, and for what visual functions. It will also be important to better define the temporal extent of this early sensitive/critical period and to identify factors that control its closing—factors that could perhaps be manipulated to prolong its duration.

SAFETY OF VISION TRAINING EARLY AFTER STROKE

In sensorimotor stroke, where more research has been conducted on early rehabilitation, concerns have emerged that very early rehabilitation may actually be harmful. Animal studies have found that exercise beginning less than 24 hours after motor cortex stroke led to an increase in inflammatory cytokines (Li et al., 2017) and enlargement of the ischemic lesions (Risedal et al., 1999), but neither study found behavioral consequences. Two animal studies initiating exercise at 24hours did find worse outcomes, along with tissue-level effects such as reduced neuronal proliferation (Kozlowski et al., 1996; Komitova et al., 2005). In humans, a large multicenter, randomized, control trial (AVERT) reported that patients who received very early (within 24hours poststroke) mobilization had worse outcomes than patients who received standard of care, of which the majority were mobilized 24–48hours poststroke (Bernhardt et al., 2015). Another smaller trial found similar results (Sundseth et al., 2012), but other studies of early rehabilitation beyond the first 24-hour window did not find significant harm or worse outcomes (reviewed in Coleman et al., 2017; Dromerick et al., 2021). An important caveat here is that the AVERT trial focused on out-of-bed

mobilization. This is relevant because negative results seen with very early mobilization could be due to hemodynamic effects of upright posture on the brain areas at risk for further ischemic damage, and may not be relevant for interventions that can be done in-bed (Ward and Kitago, 2016).

In studies of early visual restoration training (Saionz et al., 2019; Saionz, 2020; Saionz et al., 2020), participants started training no less than 14 days poststroke, which falls well beyond the window for safety concerns in sensorimotor stroke rehabilitation; none of the trained patients reported adverse events, and none experienced worsening of vision. Moreover, while a motor stroke patient may avoid using an affected limb, a vision stroke patient cannot selectively refrain from exposing the affected visual field to light or other visual stimulation; the only recourse would be visual deprivation, which is not the current standard of care. As such, it is in fact universal practice that vision stroke patients receive immediate, constant exposure to visual sensory stimulation in the affected hemifield (except while sleeping). This prompts the consideration that it may be possible to *enhance* recovery potential—even spontaneous recovery in untrained individuals—with a short (less than24hour) period of vision *deprivation* immediately after an occipital stroke. Indeed, animal studies have shown that dark adaptation can re-open a critical period window (He et al., 2006; Montey and Quinlan, 2011; Duffy and Mitchell, 2013; Mitchell et al., 2016), and this approach has even been considered for augmenting treatment of adult human amblyopes (He et al., 2007; Eaton et al., 2016). Thus, while subacute visual training is not likely to cause additional harm over no training, it may be worth investigating whether very early poststroke visual exposure can be manipulated to further improve recovery.

ADJUVANTS TO BEHAVIORAL TRAINING FOR VISION REHABILITATION

An important question is whether pharmacologic or other tools can be used to enhance rehabilitation after vision stroke, either alone or in combination with a visual training program. The goal of such an adjuvant is to aid neuroplasticity and speed learning, perhaps by prolonging the duration of the poststroke sensitive/critical period or reopening a sensitive period after it has closed (Bavelier et al., 2010; Ng et al., 2015).

Noninvasive brain stimulation hasbeen used by many research groups as an adjuvant to training for vision recovery, albeit primarily in the chronic poststroke period. Transcranial random noise stimulation (tRNS) applies a current of defined amplitude and randomly variable direction within a frequency range. tRNS has been shown to enhance cortical excitability in the motor cortex (Terney et al., 2008) and improve perception in the visual cortex (Pirulli et al., 2013; Campana et al., 2014; van der Groen and Wenderoth, 2016).When administered during vision training sessions, it was found to improve learning in both visually intact and chronic cortically-blind adults (Herpich et al., 2019). Chronic, cortically-blind participants receiving tRNS were able to recover motion discriminations far faster than would normally be expected from training alone. Transcranial direct current stimulation (tDCS) applies unidirectional current and can cause excitatory or inhibitory responses depending on electrode positioning and, thus, the current direction (Nitsche et al., 2003). Investigators using NovaVision's VRT have also reported success combining their program with tDCS in a small number of chronic cortically blind patients, showing

that VRT in conjunction with tDCS improves perimetric visual fields and activities of daily living (Plow et al., 2011, 2012) as well as blind field motion perception (Olma et al., 2013) more than sham stimulation. A follow-up study suggested that tDCS may be safe to use in subacutes, and may lead to greater improvement in visual fields than sham stimulation (Alber et al., 2017). However, these results have not been replicated by others using visual training other than VRT (Herpich et al., 2019), suggesting that this approach needs further investigation before its efficacy can be reliably claimed. Investigators have also studied the use of transorbital alternating current stimulation (rtACS) for CB, with case reports indicating possible improvement in perimetric sensitivity of the spared visual field (Gall et al., 2014) and increased area of BOLD activation in fMRI (Sabel et al., 2020). As further evidence emerges, noninvasive brain stimulation may become a promising tool for enhancing visual restoration in the chronic period, warranting further investigations into its mechanisms of action, safety, and efficacy if administered in the subacute period.

The use of pharmacology in vision recovery poststroke has not yet been systematically evaluated (although one pilot trial is currently ongoing: NCT02737930). Animal studies have suggested that serotonin reuptake inhibitors such as fluoxetine, as a stand-alone agent, could improve plasticity in the adult visual system by reopening a critical period (Maya Vetencourt et al., 2008). Results from a rodent model (Ng et al., 2015) suggested that serotonin reuptake inhibitors may improve recovery and may prolong the transient period of increased plasticity poststroke. However, human studies have shown mixed results. The FLAME trial, a moderately sized randomized controlled trial, found that 20mg of fluoxetine for 3 months poststroke enhanced motor recovery. Unfortunately, several large-scale, follow-up trials (FOCUS, EFFECTS, and AFFINITY) failed to confirm these results (Dennis et al., 2019; Hankey et al., 2020; Lundström et al., 2020). One reason for this may be that these larger trials had less selective inclusion criteria than FLAME and did not ensure that all participants received physical therapy during the treatment period (which may be relevant if the beneficial effects of fluoxetine are activity-dependent). However, all three of the larger trials also found a significantly increased risk of bone fractures in the fluoxetine group. As such, fluoxetine is unlikely to become routinely recommended for augmenting poststroke recovery. It remains to be seen if other agents may have the potential to modulate neuro-recovery without significant side effects.

CONCLUSIONS

The intact adult visual system is capable of neuroplasticity throughout the lifespan, as evidenced by visual perceptual learning and its ability to dynamically process ever-changing visual inputs. An expanding body of research now shows this potential to persist even after strokes that damage large regions of the primary visual cortex. Emerging evidence suggests that aspects of vision loss immediately after stroke are neither sudden nor complete. Instead, vision loss is a gradual, spatially, and functionally uneven process that, without intervention, continues well into the chronic poststroke period. Recent work suggests that early visual restoration training can interrupt this process, preserving and then enhancing residual vision within the perimetric blind field. The stroke may even open up a new sensitive period of visual plasticity, in which deliberate visual stimulation provided by training (possibly enhanced by adjuvants such as noninvasive brain stimulation or pharmacology) is required

to optimize the function of residual visual circuits. Early training likely takes advantage of enhanced neuroplasticity and a visual system that has yet to suffer the consequences of retrograde degeneration. Results to date suggest that when training is administered in the first few months' poststroke, subacute CB patients are able to recover vision much faster than chronic patients. In addition, they are able to recover a larger range of visual discrimination abilities, over larger regions of their blind field, than patients who begin identical training in the chronic, poststroke period. However, even when interventions are not administered until the chronic poststroke period, benefits in terms of visual recovery—albeit more limited—can still be elicited. In conclusion, recent advances in visual restoration research suggest that, paralleling sensorimotor stroke, visual neuroplasticity is dynamic after visual cortex stroke. Importantly, research highlights the benefits of using psychophysical approaches to probe the complexities of visual processing in CB fields, and the importance offixation control for attaining accurate measures of the magnitude of change in visual perception whether spontaneously or as a function of rehabilitation. Finally, it remains true, as recommended by the latest Cochrane review (Pollock et al., 2019), that the basic scientific studies described presently still need to be validated by randomized, placebo-controlled, double-blinded trials, contrasting the interventions proposed with the standard of care (which sadly remains doing nothing), as well as appropriate "control" training interventions. Nonetheless, this body of work provides both new hope and opportunity to revise our theoretic and therapeutic approach in this growing clinical population, employing accumulating evidence from basic neuroscientific studies that vision can indeed be restored after permanent damage to the primary visual cortex.

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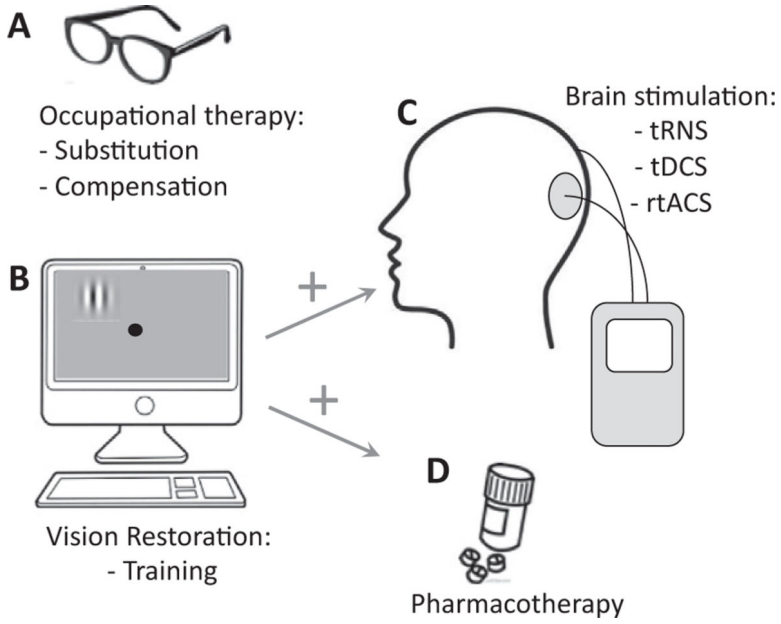

Fig. 25.1.

Main experimental and clinical therapies attempted to date for vision rehabilitation after occipital stroke. (A) Occupational therapy includes both substitution (prisms or other lenses) and compensation (teaching eye and head movement) strategies. These therapies may improve quality of life but do not restore lost vision. (B) Visual restoration approaches may be accomplished through home computer-based vision training using a range of psychophysical tasks. The effectiveness of restitution therapy may depend on the timing poststroke, the specific training task used, and patient compliance, especially for fixation control. (C) Visual training could potentially be enhanced with noninvasive electric brain stimulation, of which there are many strategies currently under investigation as a potential adjuvant to training. tRNS, transcranial random noise stimulation; tDCS, transcranial direct current stimulation, rtACS, repeated transorbital alternating current stimulation. (D) Finally, visual training could also potentially be paired with pharmacotherapy to promotegreater recovery, although this approach remains to be vetted both experimentally and clinically.

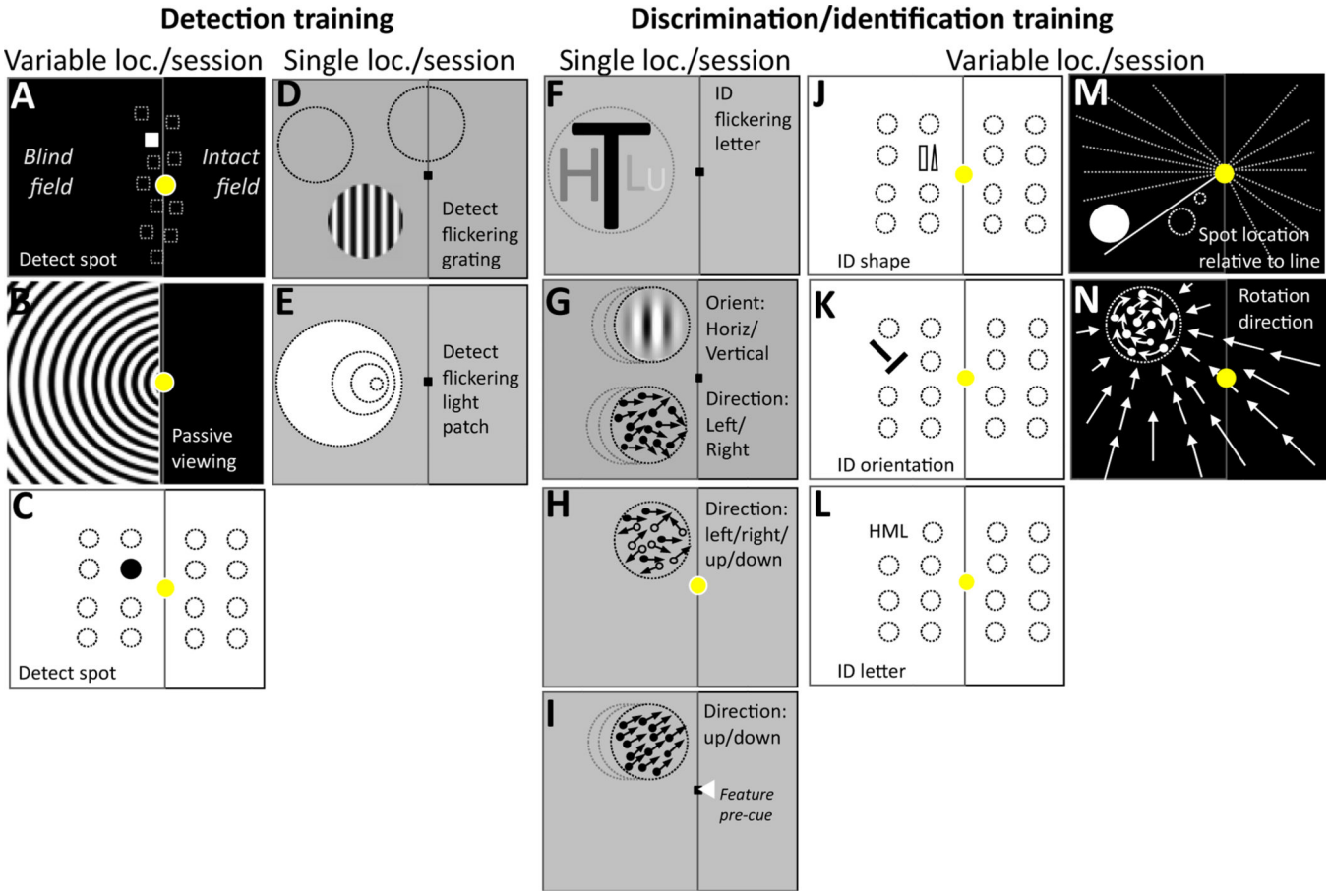

Fig.25.2.

Simplified, schematic representation of visual training tasks administered to restore vision in cortically-blinded portions of the visual field after occipital stroke. Each rectangular aperture represents the computer display in front of the putative patient, with a fixation spot (yellow in paradigms that did not use an eye tracker, and a small black square in paradigms that used an eye tracker for fixation enforcement at least during pre-and posttests). For illustrative purposes, the putative blind field is considered to be on the left side of the vertical centerline in each aperture. Tasks the patients were asked toperform are notedin each aperture and are separated according to whether they involved stimulus detection or discrimination/identification (ID), as well as according to whether they stimulated single or variable/multiple locations in a given training session. (A) Original VRT task, Kasten et al. (1998). (B) Extrastriate VRT task, Jobke et al. (2009). (C). Spot detection task, Chokron et al. (2008). (D) Detection of 10 Hz-flickering, contrast-varying sinusoidal grating, Sahraie et al. (2006, 2010), Trevethan et al. (2012). (E) Detection of flickering light patch of different sizes, Raninen et al. (2007). (F) Identify flickering letters (4 possibilities) of different sizes, Raninen et al. (2007). (G) Discriminate the orientation (horizontal/vertical) of high-contrast, static, nonflickering Gabors, or the global motion direction (left/right) and integration of random-dot stimuli, Huxlin et al. (2009), Das et al. (2014). (H) Discriminate the direction of motion (4 possibilities: up/down/right/left) of noisy, random-dot stimuli, Vaina et al. (2014). (I) Fine direction discrimination with feature-based attentional pre-cues, Cavanaugh

et al. (2019). (J) Shape identification task (rectangle/triangle), Chokron et al. (2008). (K) Orientation identification task (2 choices: left/right of vertical), Chokron et al. (2008). (L) Letter identification task (3 choices: H, M or L), Chokron et al. (2008). (M) Spot location is relative to the line (2 choices: clockwise/ anticlockwise), Elshout et al. (2016). (N) Rotation direction of circular target at the center of flow-field (2 choices: clockwise/anti-clockwise), Elshout et al. (2016).