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Visual Prosthesis

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Abstract:

There are more than 40 million blind individuals in the world whose plight would be greatly ameliorated by creating a visual prosthetic. We begin by outlining the basic operational characteristics of the visual system as this knowledge is essential for producing a prosthetic device based on electrical stimulation through arrays of implanted electrodes. We then list a series of tenets that we believe need to be followed in this effort. Central among these is our belief that the initial research in this area, which is in its infancy, should first be carried out in animals. We suggest that implantation of area V1 holds high promise as the area has a large volume and can therefore accommodate extensive electrode arrays. We then proceed to consider coding operations that can effectively convert visual images viewed by a camera to appropriately stimulate electrode arrays to yield visual impressions that can provide shape, motion and depth information. In realizing this quest we advocate experimental work that mimics electrical stimulation

effects non-invasively in sighted subjects using a camera from which the images collected are converted into displays on a monitor akin to those created by electrical stimulation.

1. Introduction

When Pope Benedict the 12th set out to have the walls of the great cathedral of St. Peter redecorated in the 12th century, he sent messengers all over Italy to obtain samples from the best artists. When a messenger came to Ambrogio Bondone Giotto (1267-1337), who had not heard of the contest, he did not have a sample painting prepared. So he took a sheet of paper and a pencil dipped into red ink, and drew a perfect circle. "Here is your drawing," he said. The Pope, upon examining all the productions submitted, some of which were quite fancy and elaborate, chose Giotto. To this day in Tuscany there is the saying "The round O of Giotto" (Broos, 1971).

Turning this story around, we can pose the question central in considering prosthetic devices for the blind: how is it possible for us to identify a perfect circle? Answers to this question, which relate to how the brain processes shape information, are central to the quest of creating a functional prosthetic device for the blind.

In the United State there are over one million blind individuals (Leonard, 2002). In the world the number exceeds 40 million. A variety of strategies have emerged to aid the blind, which involve both invasive and noninvasive approaches. Creating devices that can convey visual impressions through non-visual modalities is one of the more successful strategies, one outcome of which is the ability of blind individuals to read using the somatosensory system by palpating raised dots that form shapes of letters as in the case of Braille as devised by Louis Braille in 1881 (Mellor, 2006). In this paper we shall deal with the question of how effective methods could be that recreate visual images by virtue electrical stimulation of various regions in the visual system. In doing so three central questions need to be posed to define workable strategies:

A. What aspects of vision are most important to realize through a prosthetic device? We believe that the four most important aspects of vision that a prosthetic device needs to provide are (1) the perception of shape, (2) the perception of motion, (3) the perception of depth, and (4) the ability to localize objects in space relative to the body (Albright and Stoner, 2002; Howard, 2002; Kandel et al., 2000; Sekuler and Blake, 2006).

B. Which animal species would be the most desirable choice for testing such devices implanted directly into the brain for the delivery of electrical stimulation? We believe that the animal most highly suited to study the feasibility of a visual prosthetic device is the rhesus monkey whose visual system is similar to that of man (Cowey, 1979; Felleman and van Essen, 1991; Golomb et al., 1985; Jacobs, 1981; Polyak, 1957; Sereno et al., 1995; Tootell et al., 2003).

C. Which visual areas are best suited for such implantation? We believe that a most promising visual area for implantation of a prosthetic device is the striate cortex, area V1, as recently proposed by Troyk and colleagues (2003). Other areas under study are the retina, the lateral geniculate nucleus of the thalamus (LGN) and higher cortical areas (Marg and Diersen, 1965; Murphey and Maunsell, 2007; Pezaris and Reid, 2007; Zrenner, 2002). Since research examining the feasibility of a visual prosthetic device is in its infancy, research must be carried out exploring each of these areas.

The first step in developing a prosthetic device based on electrical stimulation is to have a thorough understanding of the workings of the visual system. A prosthetic device has to operate in harmony with the principles that underlie the operation of the visual system. We shall therefore begin by describing the basics of this system and will then proceed to examine how one might come up with a satisfactory prosthetic device that can successfully process shape, motion and depth information, and provide viable cues about the location of objects in space relative to the body. We shall then proceed to examine considerations essential for the creation of a functioning prosthetic device, some of which so far have received little attention.

2. The basics of the visual system:

The attributes of the visual system that are essential for developing strategies to produce a workable prosthetic device for implantation in the brain are described in what follows. These attributes are based predominantly on experimental work. Living organisms have evolved over millions of years and have undergone dramatic changes induced by ever changing environmental pressures. As a result of this, organisms did not evolve in an expected, predictive fashion (Dawkins, 1986). Therefore, experimental work has been the most fruitful and informative approach to understanding the visual system, as exemplified by several Nobel prizes awarded to anatomists and neuroscientists for their discoveries (e.g. Cajal and Golgi, 1906; Hartline, 1967; Hubel and Wiesel 1981). Most of these discoveries are based on work carried out in organisms other than man.

a. Retina

Two of the most important research strategies in uncovering the workings of the brain, which will provide the foundation for building a neuro-prosthetic device for the blind, are the development of new techniques and the choice of appropriate species for study. In elucidating the structure and function of the retina, the development of histological techniques, particularly the Golgi stain that labels not only the cell bodies of neural tissue but also their dendritic and axonal processes, was central. In the latter part of the 19th Century, Max Johann Sigismund Schultze succeeded in labeling the photoreceptors of the retina and discovered that they were of two major types, the rods and the cones (Schultze, 1873). Initially, there was major resistance to this claim, but once established beyond doubt, the question arose as to their function. Schultze noticed that in central retina the fovea contained only cones. So he posed the question of how this area is different from other regions of the retina where both cones and rods reside. The first difference he noted is that one can see much more detail in the fovea due to the high packing density of the photoreceptors. Each cone in the fovea is approximately 2.4 μm in diameter, which represents 0.7 minutes of arc of the visual field. Another difference Schultze noted is that the fovea is night blind. Capitalizing on this latter observation he concluded that rods, unlike cones, are for night vision. His discoveries would have surely earned him the Nobel Prize had it been in existence at that time.

In 1906 the Nobel Prize did go to Ramon y Cajal and Camillo Golgi for the discoveries they had made about the nervous system utilizing the Golgi stain (Cajal, 1937). Cajal did a great deal of work on the retina characterizing the various cells types therein. Ironically, Golgi, looking through the microscope at brain tissue he had stained with the method he invented, concluded that the nervous system is composed of an elaborately intertwined continuous network, whereas Cajal, uncovering the synapse, developed the neuron model: individual cells talking to each other through synaptic connections. The neuron model, of course, prevailed and subsequent work has succeeded is specifying the biochemistry of neurotransmitters and the receptor sites (Rodieck, 1973). Cajal, and later many other investigators, have established that in the retina one can distinguish five major classes of cells (Rodieck, 1973). The first class is the photoreceptors: the rods and cones. The cones in many primates, including humans, form three subclasses that are sensitive to different wavelengths and can therefore provide color vision. Figure 1A shows a head-on view of the photoreceptors. The upper segment shows the arrangement of the cones in the fovea. In this region there are approximately 200,000 cones per square millimeter. The tight hexagonal array optimizes the packing density of these receptors thereby assuring high acuity vision. The lower segment shows the arrangement at a 5 degree eccentricity. Here we can see the rods interspersed between the cones whose diameter at this level has more than doubled (2.4 to 5.6 µm in diameter). The packing density of the cones drops 10 fold from the center of the fovea to 5 degrees out. In primates each eye has about one million retinal ganglion cells that send one million axons into the brain (Barlow, 1981; Rodieck, 1973).

Of the five major classes of cells in the retina, the second set forms the horizontal cells, the third the bipolar cells, the fourth the amacrine cells and the fifth the ganglion cells. The ganglion cells send their axons to the central nervous system. Their axons course along the inner surface of the retina as can be seen in Figure 1C and exit from the eye at the optic disk that appears in Figure 1B and C.

Cajal had speculated about how the information provided by the rods and cones is processed. He concluded that there must be separate sets of ganglion cells, one set driven by the rods and the other by the cones (Cajal, 1937). Subsequent work established, however, that the information from the rods and cones, where they coexist on the retina, converges on the ganglion cells through different retinal pathways.

Another counterintuitive arrangement in the retina is that the photoreceptors face away from the light, being placed closest to the pigment epithelium that is right against the inner wall of the sclera. Thus all the other cells, as well as the retinal ganglion cell axons, are more central in the eye than are the receptors; this means that the photons have to travel through the cells and fibers to activate the photoreceptor molecules. To minimize interference with the incoming photons, these cells and axons are transparent. To further improve vision in the fovea, in this region the cells and their processes are placed sideways, radially thereby making for clear access of light to the foveal photoreceptors. This arrangement is shown in Figure 1D. Because of this and because of the high density of the photoreceptors, the retinal ganglion cells that receive inputs from the foveal receptors are stacked on top of one another in regions beyond the foveal area thereby forming several sub-layers as shown in Figure 1D; with increasing eccentricities and the concomitant decrease in the density of the photoreceptors, eventually the ganglion cells are reduced to a single sublayer.

A major advance around the turn of the last century was the invention of the microelectrode. The finest microelectrode made from drawn glass tubes was small enough to have a tip less than a micron in diameter. This made it possible to record from individual cells intracellularly, which is an important requirement for the detailed characterization of neuronal activity. Furthermore, techniques had also been developed that made it possible to inject a labeling substance into cells, so that, subsequent to characterizing them with recordings from the microelectrode, they could be examined anatomically. Thus it became possible to establish structure and function relationships.

In characterizing the structure and function of the neurons in the retina, one of the problems was that in most species these cells are tiny and the lack of stability made it impossible to keep the tip of the microelectrode inside a cell for long enough to study it and to then inject it with a labeling agent. To circumvent this problem two approaches had been taken, most notably by Werblin and Dowling (1969) who have published some of the most important papers on retinal organization. They selected a species for study in which the retinal cells are unusually large, the mud puppy (*Necturus maculosus*). The dissected eye was placed into a dish with a solution that kept it healthy. These procedures enabled them to record intracellularly and to inject dyes to label the cells after the recording. They established that (1) all photoreceptors hyperpolarize to light, which was totally counterintuitive, and that they produce only graded potentials. The neurotransmitter in the receptors is glutamate (Bloomfield and Dowling, 1987), (2) horizontal cells also all hyperpolarize and have only graded potentials, (3) some bipolar cells hyperpolarize and some depolarize; they all produce only graded potentials, (4) some of the amacrine cells produce only graded potentials, but some also generate action potentials, and (5) retinal ganglion cells, whose axons exit from the eye to central brain structures, yield action potentials.

Further work has established a number of other central facts that need to be taken into account for the creation of a prosthetic device for the blind. It has been shown that there are several different classes of retinal ganglion cells that perform different analyses of the visual scene. Notable among these are the ON and OFF retinal ganglion cells.

The ON and OFF cells were discovered by Keffer Hartline in the 1930s, a discovery that yielded him a Noble Prize in 1967 (Rodieck, 1973). He was the first to record from the axons of retinal ganglion cells. He showed that some cells discharged when light was shone into their receptive fields and some discharged when the light was terminated. He therefore called them the ON and OFF retinal ganglion cells. The receptive field of a ganglion cell is comprised of a small area on the retina or, more appropriately put, a small region in the visual field from which light activates a cell.

Subsequent work has established that the ON and OFF systems arise at the level of the cone bipolar cells by virtue of bipolar cells that have either sign-conserving or sign-inverting neurotransmitter receptor sites. The OFF bipolar cells have non-NMDA receptor sites and hyperpolarize to light just as do the photoreceptors. The ON bipolars, on the other hand, have a different neurotransmitter receptor called mGluR6 that inverts the signal; when the photoreceptors hyperpolarize, the ON bipolar cells depolarize (Rodieck, 1973; Schiller, 1996). These cells therefore depolarize when the photoreceptors hyperpolarize. The ON and OFF bipolar cells connect to the ON and OFF ganglion cells. As a consequence of this arrangement, an excitatory signal in the form of action potentials can be generated for light decrement in OFF ganglion cells and for light increment in ON ganglion cells.

To further complicate matters, in many primates the rod photoreceptors connect with a separate class of bipolar cells, the rod bipolars, which all have neurotransmitter receptors that are sign conserving. In the rod system these bipolar cells connect to the same ganglion cells as do the cones. They do this through a series of steps that involves amacrine cells and yields sign conserving and sign inverting signals for the ganglion cells. Thus under daylight conditions the ganglion cells are driven predominantly by the cones whereas at night they are driven by the rods in those portions of the retina where the rods and cones coexist. Thus it appears that there are no separate pathways to the brain for rods and cones, a fact that may have bearing on how retinal prosthetic devices might need to be constructed.

A subclass of retinal ganglion cells, the ON/OFF cells, is activated transiently by any sign of contrast change as first shown by Hartline (1938). This is apparently accomplished by virtue of a convergent input from the ON and OFF bipolar cells onto ganglion cells (Schiller, 1996; Wässle and Boycott, 1991).

These considerations raise the question as to why we have ON and OFF systems originating in the retina. Studies now suggest that this arrangement enables organisms to rapidly detect and process both light incremental and light decremental information (Schiller, 1996). Vision is notably different from other senses in this regard. There is virtually always light out there, and different objects in the visual scene vary in the amount of light they reflect. Objects that absorb light appear dark and objects that reflect light appear as bright. We see print in newspapers and books by virtue of light decrement. Text that appears on monitors may be set up to be seen either by virtue of light decrement with black letters on a gray background, or by virtue of light increment by having bright letters on the same background. Fish in the ocean perceive looming predatory birds, like pelicans, by virtue of being able to rapidly process the dark, shadowy object in the sky. Thus it is believed now that these two systems have evolved to be able to process both light incremental and light decremental cues rapidly using an excitatory processes for both in the retina.

As we move our eyes about in exploring the visual scene, with each shift in gaze there is either an increment or decrement in illumination at any single point on the retinal surface. The ON cells discharge when there is an increment in illumination and the OFF cells discharge when there is a decrement. Light increment and decrement are mutually exclusive; as we move our eyes about exploring a pattern-rich visual scene, changes in illumination at any point on the retinal surface will be either incremental or decremental. It has been discovered that the ON and OFF systems in the retina actually provide independent coverage of the visual field. Accordingly, in the inner retina the dendritic processes of the ON and OFF cells form separate sub layers (Wässle and Boycott, 1991).

It should be noted at this point that there are conditions that occasionally arise, as we explore the visual scene, when light reflected from objects produces neither light increment nor decrement to which ganglion cells can respond. Such objects would be invisible were it not for the fact that in most cases under such conditions there is a change in wavelength composition. To deal with this kind of situation, color vision has evolved, as a result of which objects in the visual scene can be perceived when there is a change in color but not in luminance contrast. It has been proposed that color vision has emerged over time to defeat camouflage, as many animals have developed protective surfaces to make themselves "invisible". One line of study of our visual capacities examines how we see under "isoluminant" conditions, namely when only chrominance and no luminance cues are provided (Kaiser and Boynton, 1996). Under such conditions perception is still possible, but is notably degraded (Logothetis et al., 1990; Schiller et al., 1991). The ability to process chrominance cues in humans and many primates is accomplished by having three kinds of cones, those that are most sensitive to short wavelengths (blue), medium wavelengths (green) and long wavelengths (red). Individuals in whom there is an abnormality in the composition of these cones are referred to as color blind. Color blindness is not uncommon, and is much more prevalent in males than females (Kaiser and Boynton, 1996). Yet such individuals can see quite well and can have drivers' licenses. It is almost as if color vision were a luxury yielding a small, if significant, improvement in our abilities to process the visual scene.

Another major discovery about the organization of retinal ganglion cells, first made by Kuffler in the cat retina, is that the receptive fields of these cells have circular center/surround organization (Kuffler, 1953). The surround is inhibitory. Consequently a small spot of light (or darkness) placed into the center of the receptive field of ganglion cells produces a vigorous response, whereas a large spot produces greatly attenuated activity. It is believed that the inhibitory surround of retinal ganglion cells is brought about predominantly by the horizontal cells of the retina. The manner in which ON and OFF retinal ganglion cells discharge to light incremental and light decremental spots is shown schematically in Figure 2A. In the upper portion of the figure small spots confined to the excitatory center of the receptive fields are used. The ON cell shown discharges vigorously to the bright spot, whereas the OFF cell discharges to the dark spot. When large spots, which act on both the center and the antagonistic surround of the receptive fields, are used instead, the response is much attenuated.

Why retinal ganglion cells have developed this antagonistic center/surround organization has been extensively debated. One compelling hypothesis is that this arrangement optimizes sensitivity; these cells discharge to *changes* in contrast, not to absolute levels of illumination (Rodieck, 1973; Schiller, 1996).

Retinal ganglion cells have a relatively limited range of discharge rates from 0 to about 400Hz. But illumination levels vary over almost 10+ log units and the pupil diameter can change only over roughly a 16-fold range in humans and most primates. Hence adaptation, much of which takes place in the photoreceptors themselves, is of central importance. In short order, most retinal ganglion cells cease to respond at any level of maintained light. Thus it appears that these types of retinal ganglion cells, which are believed to play a central role in pattern, motion and depth perception, can best be described as *local illumination change detectors*.

This view is supported by a remarkable series of experiments in which images were stabilized on the retina (Pritchard, 1961). One approach was to attach a tiny projector to a contact lens which subjects were asked to wear while lying down. It was found that images disappeared in a matter of just a few seconds when they were "fixed" on the retina. This can actually be demonstrated in a simpler way using gaussian stimuli that lack sharp edges, so the normal slight tremor of the eye, that keeps images alive on the retina, is not a factor. An example of this is shown in Figure 2B. If one fixates on the upper central square spot for about 10-30 seconds, both gaussian smudges disappear because the retinal ganglion cells adapt and become silent. If one now shifts the center of gaze to the lower fixation spot, complementary afterimages appear; the area of the retina that had been exposed to the dark gaussian on the right now yields the afterimage of a light spot by virtue of the discharge of ON ganglion cells. The reason this happens is that, due to adaptation during the first fixation the region exposed to the dark gaussian becomes more sensitive so that after shifting the gaze the photons reflected from the gray background that impinge on this more sensitive region activate ON-center ganglion cells thereby creating the complementary afterimage. The opposite situation arises for the area exposed to the bright gaussian during initial fixation; the portion of the retina exposed to this bright spot becomes less sensitive. Consequently, after the gaze shift the photons from the gray background activate a less sensitive region of the retina, which in turn activates the OFF cells yielding the percept of a (non-existing) dark spot.

Another interesting fact about afterimages is that their apparent size changes as a function of viewing distance, a fact that has bearing on visual prosthetics. To experience this, fixate on the little white center square within the black disk in Figure 2C with the figure at a comfortable viewing distance. Maintain rigorous fixation for about 30 seconds and then shift your gaze to the cross in the right of Figure 2C. As soon as the negative afterimage appears, move your head toward or away from the page. The size of the afterimage will change as a function of viewing distance; the closer your head to the page, the smaller the afterimage becomes. A more dramatic way of perceiving this size change is to reestablish the afterimage and then look at a clear region on the wall in the room. The image will appear to be quite large. The scaling of the afterimage is fully lawful. If the image created at a viewing distance of 57.3 centimeters is 1 centimeter in diameter, which corresponds to a one degree of visual angle; doubling the viewing distance to 114.6 centimeters increases the size of the afterimage to 2 centimeters in diameter; halving the distance decreases it to a diameter of 0.5 centimeters. The visual angle is a constant.

These observations raise the point that under normal viewing conditions we have a very strong sense of size constancy. The perceived size of a quarter, for example, remains the same irrespective of the distance at which it is viewed, although the size of its image on the retina changes lawfully with viewing distance. Several mechanisms contribute to size constancy. Object familiarity is an important factor as is the comparison provided with other objects in the scene. Seeing that same quarter with some pennies and nickels around it helps in this regard. Also important is the information available in the brain regarding the accommodative state of the lens and the degree of vergence of the two eyes. The importance of these cues can be seen when one puts prisms in front of the eyes, something like a 5-10 degree prism in front of each eye, with the angles arranged in opposition, and views one's thumb against a featureless background at a fixed distance. The eye adjusts to the prism by changing the vergence angle thereby keeping the images in the two eyes in register. When this is done, increased convergence produced by the prisms makes the thumb look smaller; decreased convergence, achieved by reversing each prism, makes the thumb look larger.

Another important factor of note, however obvious, is that while normal objects in the visual scene appear stationary when the eye moves about, afterimages move with the eyes. Thus the information available in the brain regarding the position of the eye in orbit, the state of vergence of the eyes, and the accommodative state of the lens play a central role in enabling us to determine the location of objects in three-dimensional space relative to our bodies and to perceive a stable world.

Further work examining the retina has established that there are several additional classes of ganglion cells that deal with different aspects of visual analysis (Schiller & Logothetis, 1990; Schiller et al., 1990a,b; Wässle and Boycott, 1991). Most studied among these in the primate are the so called midget and parasol retinal ganglion cells. The midget cells, as the name implies, are small and have medium conduction velocities to the central nervous system. The parasol cells, which are less numerous, are large, and have dendritic arbors that look like umbrellas, hence the name. The midget system, the cells of which are especially numerous in central retina, can process fine detail as well as color. Cells of the parasol system have much larger receptive fields, are very sensitive to changes in luminance contrast, and play an important role in motion processing. They respond transiently to illumination changes, producing brief bursts of action potentials. Midget cells produce more sustained activity, but following each illumination change their activity returns to baseline in a few seconds. Overall, the receptive fields of ganglion cells increase in size with increasing eccentricity from the fovea, with the parasol cells having receptive sizes three times the diameter of midget cells (Rodieck, 1973). The midget and parasol cells both come in ON and OFF sub-varieties. The midget cells, furthermore, also process color in separate subclasses; the receptive fields of these cells are tiny, with the center in most composed of but a single cone. By contrast, the parasol cells receive a mixed input from the three cone types both in the center and surround regions of their receptive fields; as a result, this highly sensitive system can respond to color exchanges but cannot specify what the colors are.

Another class of retinal ganglion cells is the cells of Dogiel, which are highly distinct anatomically. They are directionally selective, meaning that they respond to stimuli that move in one direction of motion better than to movement in the opposite direction. These cells are part of the accessory optic system (AOS). This system ties in with the vestibular and oculomotor systems and plays a central role in stabilizing the eye with respect to the world (Karten et al., 1977; Simpson et al., 1979). In the rabbit, where each eye has about 350,000 retinal ganglion cells there are approximately 7,000 cells of Dogiel (Schiller, 1986).

Yet an additional class of retinal ganglion cells, believed to be relatively small in number, can provide information about overall levels of illumination (Barlow and Levick, 1969). Were such cells absent, we could not tell day from night, since most other ganglion cells in the retina, as already noted, respond not to steady illumination but to changes in contrast.

Given these various classes of retinal ganglion cells that perform largely different jobs in analyzing the visual scene, one can appreciate the fact that creating a prosthetic device that can activate them selectively is a daunting task. If a prosthetic device were to be based on electrical stimulation of the retina, most of these different classes of cells likely would be activated indiscriminately with largely unknown sensory and motor consequences.

Several other problems must be overcome for a retinal prosthetic device to become workable. A central one of these is the fact that there are a million fibers coursing to the optic disk where the retinal ganglion cells exit the eye. As a result, there is a tightly packed plexus of fibers on the inner surface of the retina as shown in Figure 1. Were these fibers activated by electrical stimulation through a metal microelectrode with its tip on the inner retinal surface, the receptive fields of the activated ganglion cells of origin would form a banana-like swath (Schiller and Malpeli, 1977). This fact is best realized by the finding that microstimulation of the retina using currents between 200 and 400μA (with extraordinarily long pulse durations up to 8 ms) produces phosphenes whose characteristics could not be predicted by simply noting the site of stimulation within the retina (Rizzo et al., 2003a,b; but see Humayun et al., 1999). This results when the stimulation activates fibers-of-passage and when the position of the electrode within the substrate is not stable (Tehovnik, 1996; Tehovnik et al., 2006). Even if these problems were to be solved (Humayun et al., 2003), several other concerns would need to be addressed: Given that there are several distinct classes of retinal ganglion cells that perform different analyses on the visual scene, their indiscriminate activation would likely yield confusing precepts and undesirable motor acts such as eye movements generated by the cells of Dogiel and pupillary changes (Simpson et al., 1979). Notable also is the fact that the density of the receptors and ganglion cells changes dramatically with eccentricity (Rodieck, 1973). In central retina, ganglion cells can be stacked on top of each other radially five deep, as already noted, whereas in the periphery they form just a single layer. Selective activation of ganglion cells in the foveal representation is therefore a taxing problem. Also, selective activation of ganglion cells would require extremely tightly spaced stimulating electrodes with the capacity of delivering different current levels for different locations. Also problematic is the fact that the movement of our eyes is taken into account by the accessory optic system as well as the vestibular system; the information so provided keeps track of the position of the eye in orbit that thereby enables us to localize objects in space relative to our bodies. It is doubtful that electrical stimulation of the retina could provide this information. This problem is also present when the lateral geniculate nucleus (LGN) and area V1 are electrically stimulated; we shall discuss this in more detail below.

How to keep the retinal implant securely attached to the eye is yet another major problem. To solve this, some investigators have tried to eliminate eye movements that could dislodge the device. One approach is to inject botox to inactivate the eye muscles (Humayun et al., 2003; Rizzo et al., 2003a,b). To remain effective, injections would have to be made about every 4-6 months.

Yet another problem with using a retinal prosthetic is that, in many cases, the retinae of blind individuals undergo dramatic changes over time. The retina can degenerate to a level that forecloses the effective stimulation of neurons (Bartlett et al., 2005; Santos et al., 1997; Stone et al., 1992).

Degeneration is also of concern in the LGN. Several studies have established that in this structure significant changes occur after deprivation and enucleation (Hendry, 1991; Matthews et al., 1960; Mize et al., 1992; Sloper at al., 1987a, b; Tigges and Tigges, 1991). By contrast, several studies have established that area V1 remains an effective site for eliciting phosphenes by electrical stimulation in individuals who have been blind for many years (e.g. Dobelle et al., 1976; Schmidt et al., 1996).

An important consideration for development of a visual prosthesis is to assess what the layout is of visual images on the retinal surface and in subsequent visual areas. In a remarkable set of experiments Balkema and Dräger (1985) have provided a striking demonstration of this for the retina. These investigators have developed a monoclonal antibody that could selectively label those rods of the retina in the mouse that had been exposed to light. First, the words FIAT LUX (let there be light) were flashed on in the visual scene. The retina was then processed disclosing the words FIAT LUX imprinted on it. Ursula Dräger had presented these findings some years ago at MIT and showed a photograph of the retinal surface with these words inscribed on it. An agitated listener raised his hand and, when acknowledged, asked loudly, "But were the words right side up on the retina?" Ursula Dräger assured him that they were upside down but that she had rotated the slide 180 degrees so the audience could readily read the words. The first author of this paper was also relieved to hear her reply. It just so happened he had recently been asked to review a puzzling paper that had proclaimed that everyone had been wrong and that images are actually right-side up on the retina. The proof? Cleverly, the author of the submitted manuscript had taken an eye from a slaughtered ox. On the back side of the eye he made a small cutout over which he had placed a tiny translucent plastic screen. He found that the images presented to the eye appeared right side up on the little screen. So what was wrong here? Unlike in cameras, in living organisms the focal length of the lens in the eye is changed by a set of muscles that can vary the thickness of the lens and hence its focal length. This arrangement allows accommodation to take place so that objects appearing at various distances from the eye can be brought to focus on the retina surface. The experimenter did not realize that when an animal is slaughtered, the focal length of the lens lengthens dramatically since the muscles controlling it cease to be operational. Consequently the images on the retinal surface remained right side up much as they do when one looks through a magnifying lens. Once an image is viewed beyond the focal length of the lens, however, the images immediately turn upside down in accordance with the physical principles of lenses. Thus we can rest be reassured; images on the retina *are* upside down, as they also are in the brain areas that receive projections from the retina. Prosthetic devices must take this fact into account; if images are to be collected with a camera, they must be inverted before they are sent to the implanted electrode arrays to be in consonance with the inverted layout of the retinal projections.

b. The central projections from the retina

In animals with eyes placed on the side of the head, each eye sees a different part of the world with only limited binocular overlap. In such animals, which include most fish and reptiles, the optic nerve crosses over at the optic chiasm so that the images from the left eye make impressions in the right hemisphere and from the right eye on the left hemisphere. At one time, in Cajal's days, there raged quite a debate as to whether the fibers at the chiasm really cross over. Cajal established that fibers do cross and argued that this arrangement preserved the spatial integrity of the visual scene by "forming a continuous whole" across the hemispheres. With the eyes moving to the front in many species, including primates, the connections from the retina changed dramatically as depicted in Figure 3. With the eyes focusing on a central spot, the visual field can be divided into two halves. The right visual field projects to the left and the left visual field to the right hemisphere. This is accomplished by having the temporal hemiretinae project ipsilaterally and the nasal hemiretinae project contralaterally. This arrangement allows local visual activation from punctate locations in space in each eye to end up at corresponding locations in the brain thereby preserving the spatial integrity of the system.

The projections from the various cell types in the retina have considerable order. The cells of Dogiel project to the so-called terminal nuclei, and yet another class of cells, often referred to as w-cells, project extensively to the superior colliculus (Rodieck, 1973; Schiller and Malpeli, 1977; Simpson et al., 1979). The most robust projection in the primate, however, is to the lateral geniculate nucleus of the thalamus, a cross section of which appears in Figure 4A. The anterior portion of the LGN has six layers as shown in this figure. Beyond approximately 17 degrees of eccentricity the LGN is reduced to four layers (Malpeli and Baker, 1975). Overall the LGN is a rather small structure measuring about 6 millimeters anterio-posteriorly as well as dorsoventrally and 5 millimeters laterally in the monkey.

The LGN is a beautiful, laminated structure in which there is an orderly topography. The upper, parvocellular layers, receive input from the midget cells whereas the lower, magnocellular layers receive input from the parasol cells. In central retina, and in the central representation of the visual field in the

LGN, the midget cells outnumber the parasol cells approximately 8 to 1; in peripheral representation their respective numerosity becomes nearly equal (Malpeli and Baker, 1975). Yet another group of cells, the koniocellular cells, project to the intralaminar layers, some of which are believed to play a role in processing information from the blue cones (Chatterjee and Callaway, 2003; Martin et al., 1997). The input from the left and right eyes is layer specific. The arrangement of the connections is such that the left LGN process information from the right half of the visual field with the obverse being the case for the right LGN.

The receptive field properties of LGN cells in the monkey are quite similar to those found in the retina (Schiller and Malpeli, 1977; Wiesel and Hubel, 1966). Due to the much higher packing density of retinal ganglion cells in central vision, a higher volume of tissue in the LGN is devoted to central vision.

At this stage we have only limited knowledge of what visual percepts are created by electrical stimulation of the LGN as few studies have been conducted on humans (Marg and Dierssen, 1965), but some recent work is ongoing in animals (Pezaris and Reid, 2007). Marg and Dierssen (1965) found that stimulation of the LGN evoked spots and disks of light exhibiting particular colors of blue, green, yellow, or red. Lined visual streaks were also elicited. This might be related to the fact that fibers of passage between and LGN and cortex were activated and that the eyes of the subjects were not controlled. Much like the retina, the receptive fields of the cells in the LGN are anchored to the eyes. Marg and Dierssen (1965) found that stimulation of the LGN produced a strong desire to move the eyes in the direction of the evoked percept.

Animal studies have shown that electrical microstimulation of the LGN for the most part produces a punctate percept (Pezaris and Reid 2006, 2007). The topographic arrangement of the LGN makes it feasible but difficult to place arrays of electrodes in an orderly fashion into this structure. Although the volume of tissue in the LGN is significantly greater than in the retina, the relatively small overall size of this structure, its location deep in the brain, and the laminar separation of cells types raises concerns about the feasibility of proper electrode array placement (Cohen 2007). Selective activation of different classes of cells is quite difficult as is the orderly placement of electrodes that can preserve the spatial integrity of the system. Worrisome also is the stability that can be achieved when such long electrodes are used and the possible damage they might cause in the overlying tissue.

c. The striate cortex (V1)

In primates the information provided by the retinal ganglion cells and the cells of the LGN is transformed in several notable ways in area V1 as first established by Hubel and Wiesel (1977). The majority of cells in V1 are orientation and direction specific. Many receive convergent input from the midget and parasol ON and OFF cells (Schiller et al., 1976a,b). Cells also receive an orderly, convergent input from the two eyes that gives rise to stereoscopic depth perception (Barlow et al., 1967; Freeman and Ohzawa, 1990; Poggio and Fischer, 1977).

A prime distinction Hubel and Wiesel made in studying single cells in area V1 is that two distinct types are what they called simple and complex cells. Complex cells receive convergent input from ON and OFF cells that originate in the retina. Because of this convergence, these cells respond to both light increment and decrement and hence seem unable to specify sign of contrast. The majority of simple cells also receive convergent input from the ON and OFF systems, but a subgroup of them does receive selective input from either the ON or the OFF cells that project from the LGN to V1. Yet another group of cells in V1 responds in a selective and tonic fashion to either light increment or light decrement, variously called T-cells or luxotonic cells (Bartlett and Doty, 1974; Kayama et al. 1979; Schiller et al., 1976 a, b). Thus the subgroup of simple cells and the T, or luxotonic cells, have the attributes necessary to specify the sign of contrast of objects that appear in their receptive fields. Since these various groups of cells are largely intermingled in V1, they cannot be selectively stimulated using methods we presently have at our disposal.

The gray matter in the striate cortex is relatively uniform, measuring about 2 millimeters in thickness as shown in Figure 4B. The packing density of cells is high and is also quite uniform throughout area V1 (O'Kusky and Colonnier, 1982; Peters, 1987, 1994; Rockel et al., 1980). This is not true for the retina and LGN. For the retina in particular, there is a higher density of cells for central vision as compared to peripheral vision and the overall density of cells is less when compared to area V1 (Barlow, 1981; Perry and Cowey, 1985; Schein, 1988). This difference has serious implications for the use of electrical stimulation: a non-uniform density means that different current levels would need to be used to activate a fixed number of cells (Tehovnik, 1996). This is not a major problem for area V1 since a fixed current will activate a fixed number of cells throughout; the delivery of 2.0 µA of current is estimated to have a spread of 50 micra in V1 (Tehovnik and Slocum, 2007a).

In the rhesus monkey the central 6-8 degrees of the visual field is laid out on the surface of the occipital lobe. The region for the most part is lissencephalic meaning that it is quite smooth with the exception of the shallow *external calcarine fissure* as shown in Figure 4D. Also shown is the topographic layout of this region with much more area allocated to central than peripheral representation of the visual field. The projection is such that the images on the cortical surface of the monkey are actually upside down, with the lower visual field represented in the upper portion of area V1 and the upper visual field represented in the lower portion. As already noted, the left visual field projects to the right hemisphere and the right visual field to the left. The sizes of the receptive fields in the fovea are very small (< 0.5 degrees) and increase with increasing eccentricity (Dow et al. 1981).

The gray matter of V1 has both a laminar and columnar organization. Inputs from the LGN terminate most extensively in layer 4C, with layer 4Cβ receiving input mostly from the magnocellular layers whose input from the retina is from the parasol cells, whereas the input to layer 4c□ is from the parvocellular layers of the LGN to which the midget cells project from the retina (Fitzpatrick et al., 1985; Hubel and Wiesel, 1972; LeVay et al., 1975). The koniocellular cells, which from the retina project to the intralaminar layers of the LGN, terminate in the uppermost layers of V1 (Hendry and Yoshioka, 1994).

The columnar organization of the cortex is one of the central discoveries that had been made in neuroscience (Mountcastle, 1997). In area V1 the two major kinds of columns distinguished are orientation and the alternating left and right ocular inputs, which are well defined in layer 4 (Hubel and Wiesel, 1977). The columns representing the left and right eyes alternate so that when this input is labeled from one of the eyes, which yields dark stripes, a top view of the cortex gives the appearance of zebra stripes. This orderly separation of left and right eye inputs is most evident in layer 4. In the upper and lower layers the majority of cells receive a convergent input from the two eyes thereby integrating their input. One aspect of this integration involves the processing of stereoscopic depth information. The columnar organization as seen in layer 4 looks much like a thumb imprint. Interestingly, the width of the columns is constant, about 500 µm, in spite of the fact that progressively less volume of tissue is allocated to increasing eccentricities of visual field representation.

The representation of various orientations is also quite orderly. Just how these columns are laid out in area V1 is still not fully settled. Several models have been proposed, the earliest of which is often called the "ice-cube" model according to which alternating left and right eye inputs form one axis and the various orientations form an orthogonal axis (Hubel and Wiesel, 1977). It now appears that this arrangement may not be as orderly as suggested in this proposed model, although the columns themselves are indeed well defined. If one passes an electrode through the cortex at right angles to the surface, the cells encountered from top to bottom of gray matter all have the same orientation. If on the other hand an electrode is passed through the tissue at an angle, there is an orderly progression of different orientations. Other attributes of the visual cortex, which include direction specificity, color selectivity and spatial frequency selectivity, do not appear to have the well-defined columnar arrangement of orientation and ocular dominance (Hubel and Wiesel, 2005).

The organization of area V1, its sizable volume (e.g. about 2000 mm^3 per hemisphere—Felleman and van Essen, 1991) with over 100 times as many neurons as the LGN (Barlow, 1981), and the effects of local electrical stimulation, which creates a small image (Brindley and Lewin, 1968; Dobelle and Mladejovsky, 1974; Schmidt, 1996; Tehovnik and Slocum, 2007a), suggest that this area is well suited for studying the feasibility of a prosthetic device. V1 in monkeys is immediately below the skull and the dura mater in the occipital region. Therefore, electrodes can be placed accurately and with relative ease (e.g. Bradley et al., 2005; Troyk et al., 2003). The large volume of tissue representing the visual field in area V1 is an important consideration. It allows for selective activation of tissue representing areas just a fraction of a degree apart, thereby allowing reasonable re-creation of shapes. The volume of gray matter allocated for spatial representation in V1 is over 30 times greater than in the LGN and over 100 times greater than in the retina (Felleman and van Essen, 1991; Perry and Cowey, 1985; Schein, 1988; Winter et al., 1969).

Most of the neurons of V1 also respond relatively transiently to static changes in illumination as do the retinal ganglion cells (Hubel and Wiesel, 1977). The V1 cells can also be thought of as local illumination difference detectors but with the additional restrictions pertaining to the orientation of edges, direction of motion and spatial frequency of objects in the visual scene.

Extensive work has been carried out in humans and to a lesser extent in monkeys showing that electrical stimulation of area V1 creates a punctate image much like a star (Brindley and Lewin, 1968; Dobelle and Mladejovsky, 1974; Schmidt, 1996; Tehovnik and Slocum, 2007a). The size of the image varies with eccentricity, being very small in the fovea and growing in size with increasing distance from central vision in accordance with magnification factor and/or receptive field size in humans as well as monkeys (Tehovnik and Slocum, 2007a). When a region in V1 coding for a visual-field eccentricity of 3 degrees was stimulated in a monkey, the contrast of the image created with 20 -120 μA pulses delivered at 200 Hz and for 80-100 ms, was 6 to 12% with size of 15 to 20 minutes of visual angle (Schiller et al., 2006).

In discussing the retina, we had noted that one of the major problems in this area is that the tissue degenerates over time (Matthews et al., 1960; Sloper et al., 1987a,b). In advocating area V1 as the target of a visual prosthesis, one needs to address to what extent this area undergoes degeneration or changes over time after retinal damage. One set of studies examining this issue showed some significant changes in area V1 following damage to the retina (Chino et al., 1992; Darian-Smith and Gilbert, 1995; Gilbert et al., 1990; Gilbert and Wiesel, 1992; Heinen and Skavenski, 1991; Kaas et al., 1990). Another set of studies, however, showed little change in the organization of V1; particularly notable among these studies is the finding that humans blind for a decade or more experience phosphenes when their area V1 is electrically stimulated. (Dobelle et al., 1976; Schmidt et al., 1996; Smirnakis et al., 2005). These latter studies suggest that the stability of area V1 over time is significantly greater than what has been found in the retina and the LGN.

3. Processing of the visual scene in three dimensions:

The visual scene projected into the eye forms a two dimensional image on the retina. One of the prime tasks of the visual system is to reconstruct the third dimension from this image. This is such an essential requirement that even the most primitive living organisms have developed mechanisms to achieve it. For example, a frog, to survive, has to flick its tongue out to catch the flies that flit about in its immediate space. Several neural mechanisms have evolved to enable us to recreate the third dimension. The mechanisms for depth processing include stereopsis, motion parallax, perspective and shading. Stereopsis is achieved by having neurons in the cortex receive convergent input from the two eyes that enables the system to convert disparity cues into depth information. This is a remarkable process as made evident when one views displays in Magic Eye books. The neural mechanisms involved are both intricate and complex as has been established in numerous studies (Casagrande and Boyd, 1996; Howard, 2002; McKee and Harris, 1999; Roe et al., 2007). At this stage it is unlikely that a prosthetic device based on electrical stimulation can be devised that can selectively stimulate neurons in the visual system that specify different depths based on disparity. The representation of different depths does not appear to be arranged in columns or layers that could be selectively activated by electrical stimulation. While stereopsis is indeed a major mechanism for depth perception, it should be noted here that 5 to 10% of the population in the USA is stereo blind; yet these individuals have little trouble analyzing the visual scene in three dimensions and are awarded drivers' licenses even without being tested for stereoscopic vision. People who lack stereopsis rely on other depth cues the brain can process. Among these, motion parallax is perhaps the most prominent mechanism. This is a very robust system as deficits in this capacity are extremely rare. Motion parallax is a monocular cue and takes advantage of the physical fact that when there is movement, objects at different distances from the observer move at different rates across the retinal surface. This differential rate of motion is processed by the brain to provide information about the relative location of objects in depth. A prosthetic device that can accurately activate successive elements in an array based on the visual input from a camera should be able to provide this information reasonably well. Other available depth cues, as we had noted in section 2a, include shading, perspective, vergence and accommodation.

4. Eye movements and spatial localization:

The visual system as we had described so far, is organized in retinocentric coordinates. Such organization is well suited to represent what is often called allocentric space -- how objects in three-dimensional space are arranged relative to one other (Klatzky, 1998). An additional task for the brain is to compute where objects are located in space *relative* to the body, often referred to as egocentric space. This is an essential requirement, without which organisms that locomote in space would not be able to do so with any degree of accuracy. To properly orient in space, information about the position of the limbs and head relative to the body and the position of the eye in orbit need to be accurately computed and integrated.

The movement of the eyes and the signals needed to keep track of them, involves several rather elaborate processes in the brain. Since one of the prime tasks of eye movements is to be able to accurately direct the fovea to desired spatial locations so that they can be analyzed in fine detail, the saccadic system, which accomplishes this for the most part, is coded in retinocentric coordinates. This is the case in several brain structures including V1, portions of the superior colliculus and the frontal eye fields. Electrical stimulation at any given site in these areas elicits a saccadic eye movement that has a constant vector; when the electrical stimulation is delivered, the same saccadic vector is generated no matter where the eye is in orbit (Schiller and Tehovnik, 2001). In V1 and the superior colliculus the vector depends on where within the structure one stimulates. If one first plots out the receptive field location of the neurons relative to the foveal area, their activation results in a saccadic eye movement that shifts the center of gaze into the receptive field. Further proof that these areas code constant vectors comes from the observation that prolonged electrical stimulation produces a staircase of saccades with similar successive vectors (Robinson, 1972; Schiller and Stryker, 1972).

This arrangement works extremely well to shift the center of gaze to desired locations in visual space. What it does not do directly is to provide all the necessary information regarding where the eye is in orbit. Several areas provide this information. One of them is the medial eye fields of the frontal lobes (Lee and Tehovnik, 1995; Tehovnik and Lee, 1993). Electrical stimulation of this area shifts the eye to specific orbital locations. Maintained stimulation holds the eye at that location. To keep the eye stabilized with respect to the world we have the vestibulo-ocular reflex. If the head is rotated, the semicircular canals send a signal to the oculomotor complex that with great rapidity counter-rotates the eye to keep it stable with respect to the visual scene. Doing so is essential for being able to process visual information when we are in motion. Many of us have seen movies made with cameras attached to the head of skiers. The hills and trees vibrate wildly on the trip downhill and we are impressed by the incredible skiing abilities of these skiers. The fact is, however, that what the skiers see is nothing like what the camera sees. The skiers, as most of us, have a wonderful vestibular system that stabilizes the eye with respect to the ski slopes, whereas a regular camera does not have such a system. Indeed, people whose vestibular system is compromised have major difficulties in processing the visual scene when they are in motion (Leigh and Zee, 1980; Sherman and Keller, 1986).

One of the interesting findings research has generated in this area is that the vestibulo-ocular reflex is readily modifiable, due apparently in part to the visual inputs from the accessory optic system we had already discussed (Simpson et al., 1979). A basic experiment of this sort first establishes how well an experimental subject's reflex operates under normal conditions. A simple way of doing this is to take a rotating chair, something like what they have in a barber shop, and place the person in it. Eye movements are recorded in total darkness. When the body and head are rotated, the eye counter rotates. When this is done in most subjects the magnitude of the counter rotation of the eyes equals the body rotation. When this is measured quantitatively and performance is perfect, it can be said that the gain of the oculomotor reflex equals 1 (Jones, 1977; Jones et al., 1984). If one now proceeds to have a subject wear magnifying or minifying lenses for a few days, the gain of the reflex changes to accommodate to the change. If the gain is halved by the lens system, the vestibulo-ocular reflex changes to 0.5; if it is doubled, it changes to 2. It is believed that the visual input from the accessory optic system has the power to modify the gain, with the cerebellum playing a significant role in this process (Demer at al., 1985). The vestibulo-ocular reflex and its adaptability need to be integrated into the creation of a prosthetic device.

5. Phosphenes created by electrical stimulation and their relationship to eye movements:

As we had already noted, electrical microstimulation of area V1 creates a small, star-like image the size of which increases as increasingly eccentric representations are stimulated. The eye, the LGN, and V1 utilize a retinocentric code as delineated in Figures 4, 5 and 6. The computation of the spatial location of visual images relative to the body, as described above, is accomplished by utilizing signals that define the location of the eyes in orbit, their vergence and the accommodation of the lens. The image created by electrical stimulation is not privy to this information. Hence the perceived size and the spatial location of the phosphene elicited by electrical stimulation of a given site is not invariant as are real images; the phosphene moves with the eyes and changes in size as a function of vergence and accommodation (Brindley and Lewin, 1968; Cowey and Walsh, 2000; Dobelle and Mladejovsky, 1974; Grèusser, 1991; Richards, 1971; Rushton and Brindley, 1977; Schmidt et al., 1996). The rules that govern the spatial location and size of the phosphene follow the same rules as do afterimages (Grèusser, 1991). For example: in sighted individuals, electrical stimulation of area V1 in a region a few degrees from the fovea produces a star-like image with a diameter of approximately 0.2 degrees of visual angle. This means that when a subject views a sheet of paper at a distance of 57.3 centimeters from the eye, the star-like image has a diameter of 2 mm. This is equivalent to the lower case letter "a" using a size 12 Ariel font. As in the case of afterimages, doubling the distance of the sheet of paper from the eyes doubles the apparent size of the phosphene to 4 mm and halving the distance reduces its apparent size to 1 millimeter. Such size changes apply throughout, so that when an array of electrodes is activated, as described in Figures 7-10, the pattern produced remains the same but its overall apparent size and its location in space change as a function of eye movements, vergence and accommodation; the position of the phosphene relative to the fovea is constant and hence moves about when the eye moves just as do afterimages.

One major problem in creating an effective prosthetic device based on electrical microstimulation is that eye movements are compromised in most blind individuals. Eye movements are often uncoordinated, multidirectional, disjunctive, and the gain of the vestibulo-ocular reflex is less than 1. Some blind individuals have a persistent nystagmus. These conditions are more pronounced in the congenitally blind than in individuals who become blind later in life (Bartels, 1928; Hall and Ciuffreda, 2002; Kömpf and Piper, 1987; Leigh and Zee, 1980; Sherman and Keller, 1984). There are several possible solutions to this problem, depending to the nature of the eye-movement control problem in each individual, all of which necessitate bringing eye-movements under control. Some possible solutions will be discussed below.

6. The basic tenets for producing a visual prosthetic for the blind:

In this section we list what we believe are essential basic tenets that must be taken into account for the creation of an effective, long-lasting prosthetic device.

a. Must use an appropriate animal model

Exploration of the feasibility of a visual prosthetic device is in its infancy. In setting up strategies for the research to examine this question, it is wise to take a close look at the development of the cochlear implant, which has been a tremendous success. Tens of thousands of profoundly and severely deaf people today in over 70 countries have cochlear implants that successfully provide information to the auditory centers of the brain (Clark, 2006). The multichannel auditory prosthetic device pioneered by Graeme Clark was developed over a period of many years starting in the late 60s. Most of the work was carried out in Australia. An effective device that was ready for implantation in human subjects occurred only after Clark and colleagues had performed 10 years of animal experimentation perfecting their device by conducting electrophysiological and psychophysical experiments on behaving as well as anesthetized cats (Clark, 2003). Since funding for Clark's work was limited at the beginning, Clark and his staff had to seek donations from the general public (e.g. the Rotary, Lions, and Apex clubs) to continue their work. These funds led to the eventual implantation of a multichannel cochlear device into a deaf patient in 1978.

Following the strategy of the development of the cochlear prosthetic, it is our belief that the first step in developing a visual prosthetic for blind humans is to use an animal model. This belief is not shared by all investigators; Weiland and Humayun (2003) have suggested that major device verification of effectiveness should be done on humans only. We believe that adopting this approach in the absence of animal experimentation will, at best, significantly delay progress; more likely, this approach will likely end in failure. So far, the field of visual prosthetics has opted for an approach that is antithetical to the one adopted by Graeme Clark. A recent example of this is the work of Ed Schmidt and colleagues who in

1996 tested the effects of stimulating through an array of electrodes implanted in V1 of a blind patient (Schmidt et al., 1996). This work ended abruptly due to complications (Wagenaar, 2004, pg. 4). The work was followed nine years later by the implantation in a monkey of a similar device that had previously been implanted in the blind patient (Bradley et al., 2005). Some five months after the electrodes had been implanted in the monkey the animal became lethargic due to fluid build-up around the electrodes. Following recovery, the animal was left with a persistent upward nystagmus and visual field defects. Subjecting blind humans to an implant that has not been perfected in animals should be deemed unethical at this time. Some hundreds of monkeys may be required to perfect a visual cortical prosthesis for blind. Getting FDA approval to test even one patient with an implant will be a major achievement given the experiences of Schmidt, Bradley and colleagues. Nevertheless, humans should be used in entirely noninvasive procedures to test some of the basic assumptions and limitations of possible prosthetic devices before a visual prosthetic device has been perfected in animals.

b. Stimulation at each brain site must provide a punctate percept

As noted above, there is quite a bit of evidence, both in humans and monkeys, that electrical stimulation of area V1 produces a punctate, star-like image. The size of this image increases with increasing eccentricity of visual field representation in accordance with magnification factor and/or receptive field size (Tehovnik and Slocum, 2007a,b). This suggests that area V1 is a promising candidate for exploring the feasibility of a prosthetic device based on electrical stimulation. Extrastriate cortical areas appear to be less well suited for implantation of a prosthetic device for several reasons: (1) The receptive fields of single cells become progressively larger in the extrastriate areas (Felleman and Van Essen 1991); in V3 they are three times larger on the average; in V4 and MT they are much larger than that. (2) The topography in extrastriate areas is significantly less well defined than in V1. (3) The overall volume of tissue in most higher visual areas is less than in V1. (4) The behavioral state of the organism can influence electrical stimulation effects progressively more in these higher visual areas (Penfield and Perot, 1963).

c. Must select a brain region in which a large area is devoted to visual processing

We believe that area V1 of the monkey meets this tenet exceptionally well. We therefore advocate that this area should be extensively studied in assessing the feasibility of a prosthetic device for the blind. Area V1, as already noted, is quite uniform in thickness and cell density. The visual field is laid out in a neat topographic order and, in monkeys, the region representing the central 6-7 degrees of the visual field on the lissencephalic cortical surface; this fact makes for relatively easy placement of electrode arrays. Since the effort of creating a visual prosthetic device is in its infancy, the study of other areas, notably the retina, the LGN, and higher cortical areas should continue to be explored.

d. Must preserve the spatial integrity of the system

The orderliness with which the visual cortex has evolved over millions of years has resulted in being able to process shape information with remarkable accuracy and rapidity. To enable images to be identified, we believe that a central effort must be made to preserve the spatial integrity of the system. Surprisingly, efforts to develop a prosthetic device have often not made this a central tenet.

This concern brings us back to the Giotto story: How can we create a prosthetic device that, using appropriate electrical stimulation, can create images that correspond to real objects in the visual scene such as a circle? To deal with this question we need to take a closer look at the layout and topography of area V1 where the problem of preserving the spatial integrity of the system is more manageable than in the retina and the LGN.

To better understand how images are represented in area V1, a set of simple dotted images is shown in the upper portion of Figure 5 using the scheme of Schwartz (1994). Dots are used because, as already noted, electrical stimulation at each site in V1 produces a star-like image. The areas activated in area V1 of the monkey are depicted below in the figure. The images in the left visual field project to the right hemisphere and those in the right visual field to the left. The images are reversed and upside down on the retinal surface and on the surface of V1. Figure 5A shows how a set of dots forming an arrow placed in the center of the visual field is laid out in the cortex of the monkey. In Figure 5B a circular array of dots is presented in the right visual field. The areas activated in V1 form a roughly circular array with the area activated by each dot varying notably in size due to the magnification factor. Figure 5C shows what the activation is like when the identical circular array of dots is centered along the vertical meridian. The activation in the cortex now becomes bilateral. Being equidistant from the center point, which impinges on the center of the foveal representation, the size of each region activated in V1 is therefore the same. However, the activated region bears no resemblance to a circle; two curved lines are created. The equivalent percept, however, is a perfect circle. This curious arrangement has evolved enabling us to veridically analyze the visual scene in spite of it not really making good logical sense. We believe that a prosthetic device must factor in this organizational principle if it is going to be effective for creating veridical visual images.

The spatial integrity of the system can be preserved in two basic ways. The first is to create an electrode array system that is proportional as will be described below. The second is to use a dense array of equally spaced electrodes which are selectively activated utilizing a computer program that factors in magnification for appropriate stimulation of electrodes within the array. The advantage of using a proportional array is that it requires significantly fewer electrodes for equal acuity and is quicker and simpler to operate. These points will be examined in detail in the sections that follow.

We propose that a proportional array, which creates a visual image of a rectangular group of dots when all elements are activated, is an advantageous arrangement. We shall present several lines of evidence to support this point. In Figure 6A a square array of 256 equally-spaced dots is shown, with 128 in the left and 128 in the right visual hemifield. The area of the visual field occupies 4 degrees of visual angle. The corresponding regions activated in area V1 of the monkey are shown schematically below. Were one to place an electrode at each of these locations in V1, as shown in the bottom of Figure 6B, the images created upon brief electrical stimulation of all 256 electrodes would presumably look like those shown on the top of Figure 6B. The overall layout of the square is similar to the image shown on the top of Figure 6A. However, due to the fact that the receptive-field size of the neurons increases with increasing eccentricity, as does the magnification factor, the dots created by the electrical stimulation would be smaller near the center than in the periphery. We shall call this arrangement the “proportional” array.

How effective such a device might be for pattern perception under static conditions is approximated in Figure 7. A camera views the visual scene, as shown in the center. On the bottom left a rear view of the monkey brain is shown with an array 128 electrodes placed into each hemisphere as had been described in Figure 6. Activating all electrodes creates the image shown above on the left in Figure 7. Shown in the center is the visual field upon which the words FIAT LUX are flashed on briefly. The image in the camera is broken up into 256 sections with the aid of a computer, each of which is connected to a corresponding electrode. The connections are inverted and the right half of the visual field is connected with the electrode array on the left and the left visual field to the right, thereby preserving the integrity of the system. The letters in the visual field shown in the center of the figure are set up optimally to activate the electrodes as shown on the bottom right. The electrodes activated are shown in red. The visual image assumed to be created appears on the top right. The words are reasonably readable.

Next, let us examine two other possible bilateral electrode arrays. Figure 8 shows a circular array, which is arranged according to the magnification factor in V1. Again, on the left the image is shown when all the electrode elements are activated. The electrodes that FIAT LUX activates are shown in red. The resultant image created appears on the top right of the figure. The quality of this stationary image is quite good.

Let us now compare what kinds of images are created by electrical stimulation of an array of electrodes that are equally spaced as shown in Figure 9. In this case each array consists of 256 elements, twice as many as those used in Figures 7 and 8. Figure 9 on the bottom shows the layout of the electrode arrays placed bilaterally. When all are activated, as on the left, a butterfly image is created. Hence we shall refer to this arrangement as the "butterfly array." The electrodes activated by FIAT LUX and the image created appears on the right. The words are not nearly as readable as with the proportional array.

As a further examination of the images created by the square proportional array and the equally spaced array in Figure 10, we show the percepts we believe would be created when squares at different locations in the visual field are flashed on. As can be seen, the proportional square array, shown on the left (A & C), yields squares of equal sizes but with the size of the individual phosphenes larger in the peripheral representation as already noted. With the butterfly array, shown on the right (B & D), the squares vary both in shape and size.

<u>e. Must take into account the operation of the ON and OFF systems</u>

The existence of the ON and OFF systems and their convergence onto single cells in area V1 raises some intriguing questions as to how to create a prosthetic device for the blind that can effectively process both light incremental and light decremental information.

As we had noted earlier, the ON and OFF systems have emerged in the course of evolution to enable living organisms to process both light incremental and light decremental information rapidly and efficiently. From the single-ended system of the photoreceptors, which all hyperpolarize to light, a double ended system has been created which yields largely separate excitatory signals for light increment (the ON system) and for light decrement (the OFF system). Notably, the majority of neurons in area V1 receive a convergent input from these two systems. Therefore, such cells do not seem to be able to provide viable information about the sign of contrast of objects in the visual scene. Figure 11A shows data collected from multiple units in area V1 of the monkey when a small white or black spot is flashed on for 500 milliseconds in the center of their receptive fields and when a large white spot is flashed on. The response is similar to the small white and black spots. The large spot elicits no response.

We make about three saccades per second as a result of which images at specific retinal locations are present only for about a third of a second. Due to the relatively transient nature of the neural responses and the movement of the eyes, it may be said that with each shift in gaze the slate is wiped clean, ready to accept and analyze the image that falls on the retina during the subsequent fixation. Because of this state of affairs, signals from a putative prosthetic device using a camera, from which signals pass through a computer, need to be transient, thereby essentially mimicking the manner in which neurons are normally activated.

It is a well known fact that in blind subjects who lack a functional retina, electrical stimulation of individual sites in the LGN and V1 creates a star-like image on a black background. In such subjects stimulation does not appear to produce dark spots. It may be said then that electrical stimulation in the blind is single ended. The stimulation of selected regions in an array of electrodes hooked up to a camera always creates a batch of star-like images on a dark background. So how can one provide information about dark objects?

Given these basic facts, the question arises as to what the best approach is for converting visual images into electrical stimulation of implanted electrodes. We shall consider three possibilities. The first approach is to use what may be called a *sustained activator* with which the frequencies and/or current levels are set to be proportional to the light level within the cells of the camera unit, each of which connects to a specific electrode in the array. There are several reasons why such a system is undesirable: (1) Sustained activation does not appear to produce a constant star-like image; it has been shown that when electrical stimulation is prolonged, images in area V1 fade away (Schmidt et al., 1996). (2) Varying frequency and current levels produces changes in perceived contrast over only a relatively narrow range as has already been noted (Schiller et al., 2006). (3) Most neurons in area V1 actually do not respond in a sustained fashion to light; instead, they respond relatively briefly to changes in illumination. (4) To assure the longevity of implanted electrode arrays, duration of activation should be minimized. Taking these considerations into account a sustained activator system would seem most undesirable.

Another approach is to set up the prosthetic device as a *transient luminance difference* detector that activates the electrode array briefly whenever a change occurs within the individual cells of the camera that activates the individual electrodes. This arrangement would greatly reduce the extent to which electrodes are activated over time. A major problem that arises, however, is that a response is elicited both when a stimulus appears and when it disappears thereby interfering with the proper analysis of temporal events. An example demonstrating this appears in **Display 1** (cross15). This dynamic display, and subsequent ones, can be viewed on the journal's website. On the left of **Display 1** the visual image is shown that consists of a horizontal and vertical line appearing repeatedly in succession. Shown on the right are the star-like images created by the activation of the electrodes in V1. Due to the fact that the *luminance difference detector* responds both when a stimulus appears and when it disappears, instead of seeing alternating horizontal and vertical lines, a stationary cross is perceived. In a more general way, this arrangement would do a poor job in handling motion.

A solution that overcomes these problems is to create a system in which each cell is turned into what we call an *intracell comparator* (Dobelle, 2000). This is a procedure used in various forms in a number of routines for visual processing in computer vision; it is often referred to as an edge detector system. The general idea is that each cell in the camera unit activates a corresponding electrode only when a change in illumination occurs *within* the elements of a cell. This arrangement is similar to how the majority of V1 cells respond, an example of which appears in Figure 11A. Here data are shown as obtained from an alert monkey trained to fixate. After mapping the receptive field of the multiple units from which we recorded, data were collected under three conditions: (1) flashing on a small white spot for 500 milliseconds within the receptive field, (2) flashing on a small dark spot, and (3) flashing on a white spot that was larger than the receptive field. Each condition was presented 40 times. The neurons respond in a similar fashion to the small light and dark spots and do not respond at all to the large spot. Thus as a group these cells behave like *intracell comparators*.

The basic algorithm involved in creating an *intracell comparator* is depicted in Figure 11B. In this arrangement each cell is hooked up to an electrode as had been described in Figures 7-10. When a change in illumination occurs that affects all elements *within* a cell equally, no response is elicited as depicted in b in Figure 11B since there is no differential activation *within* the cell. By contrast, when a luminance difference arises *within* the cell, as shown in d, f and h, a short-lasting activation results. The system has the option of providing different levels of activation based on magnitude of the contrast difference that arises within cells; the greater the contrast change within a cell, as shown in Figure 11 d, f, and h, the higher the frequency or current produced. Since overall changes in perceived contrast as a function of frequency and current level fall within a narrow range as we had noted, only a limited number of levels could be used effectively. We believe that the *intracell comparator* system is one which is in consonance with the basic operational principles of neurons in V1 as shown on top of Figure 11A.

The *intracell comparator* system is single ended: A response is elicited to any sign of contrast change. Thus the response produced by black letter on a white background or white letters on a dark background produce similar activation. This arrangement is in consonance with the response characteristics of the majority of V1 cells. The response is made transient by having the activation occur only briefly, adjustable between perhaps 200 to 500 milliseconds to fit personal needs and situations.

Based on mimicking procedures it appears that the *intracell comparator* system works reasonably well. **Display 2** (cross25) shows this. Unlike in the previous display (Display 1), the alternating horizontal and vertical lines are reproduced quite faithfully. A more complex example of this appears in Displays 3 and 4 (fiatlux24 and 14). Both displays show the words FIAT LUX drifting across visual space, with **Display 3** using the *temporal difference detector* scheme and **Display 4** showing the *intracell comparator* system. The latter does a rather decent job in displaying the moving image.

The limitations of the *intracell comparator* system for processing images in two-dimensional space should be acknowledged, however. While outline forms with relatively well-defined edges or lines work quite well, smooth, extended surfaces are not visible, as indicated in Figure 11Bb. A dynamic example of this is shown in **Display 5** (squaresample3c) in which the image created by a moving outline square is presented. The percept created corresponds nicely with the actual image. However, when a solid square is used, this is not the case, as shown in **Display 6** (squaresampler4b). Instead of a solid square, an outline square is perceived since the solid regions do not activate the cells except for the edges. One way to remedy this problem is to break up solid surfaces into grained surfaces. **Display 7** (squaresampler5) shows the arrangement when a solid area in the display is changed to a crosshatched one. As a result of this the image created appears more like a solid surface because the cross hatched regions keep activating the cells over which they course.

It should be instructive at this juncture to examine what kind of image is created using the *intracell comparator* system when an outline square is moved across the visual field using the butterfly array. The moving square arrangement is identical to the one shown in Display 5 for which the proportional array was used. **Display 8** (butterfly3) shows the images elicited using the equally spaced butterfly array depicted in Figure 9. The percept created only remotely resembles the actual display. What is seen instead is an object that changes shape and size rather than being constant. It would seem unlikely that even extensive training could overcome this problem and enable a blind subject implanted with the butterfly array to perceive a square of a constant size moving across the visual field. Because of this, we believe that it is highly desirable to use proportional arrays that can provide unchanging images of objects as they move across the visual field successively activating different regions of area V1.

<u>f. Procedures must be created to provide egocentric spatial cues</u>

As we had noted, one central requirement for a visual prosthetic device is to provide information about where objects are in the visual scene relative to the body. Due to the noted fact that eye movements, accommodation and the vestibulo-ocular reflex are compromised in most blind patients, the incorporation of eye-movement signals in a prosthetic device is unlikely to solve the problem. Another, perhaps more promising approach, is to train blind subjects to minimize their eye movements and, in addition, to provide a *reference signal*. One such possible signal would be the differential activation of a region in area V1 that represents the center of the fovea. To make it differential, the electrical stimulation of this area could occur in brief bursts, thereby making it appear as a flickering phosphene. It would be activated, as needed, by the subject, perhaps by pushing a button. This independent signal, always denoting the same retinal location, could then be utilized to move the eyes to desired locations. For example, were a blind subject to place one of his fingers in front of the camera, the pulsing reference signal could be shifted by the movement of the eyes to be superimposed on the finger. The somatosensory system provides information about position of the finger relative to the body. As a result, the location of visual objects processed by the camera activating the implanted electrode array could be linked to the position of the finger, thereby providing cues about the location of objects in the visual scene relative to the body.

g. Arrangements must be made to optimize the processing of fine detail

There are two prime ways of optimizing fine detail. The first is to use a camera with a zoom. The second is to increase the number of electrodes implanted into the brain.

Using a zoom camera is extremely effective in improving fine detail as it has properties on a small scale similar to that of a microscope or telescope. A simple, obvious example is to prop up a book a few feet away and look at it through a camera. By zooming in the words will become readable. This procedure can therefore significantly enhance acuity when such a camera is hooked up to activate implanted electrode arrays as described in Figures 7-11.

To improve acuity by varying the density and numerosity of electrodes in implanted arrays, there are two major limitations need to be noted. The first is that large arrays are likely to cause tissue damage either already upon implantation or subsequently with the passage of time. The second is that the density of electrode placement is limited by the size of the phosphenes created. Very closely spaced electrodes would not create spatially distinguishable spots and therefore would be unlikely to improve acuity. When at a four degree eccentricity electrodes are placed 1.3 millimeters apart in monkey V1, we estimate that the phosphenes created have only a small degree of overlap as shown in Figures 6-8. Because more tissue is allocated for central vision, and because the phosphenes created become smaller when regions near the foveal representation are stimulated, in this region electrodes can be profitably placed closer to each other without the stimulation creating overlapping phosphenes.

So the question that arises then is how one can optimize resolution most effectively by proper electrode placing. Figure 12 shows two schemes. On the left, a proportional array is shown that is enhanced for the central 2 degrees of the visual field by doubling up on the number of electrodes in this region as indicated by the electrodes marked in blue in the bottom of Figure 12A. The electrode placements marked in red are the same as for the proportional arrays shown in Figure 7. This arrangement increases the number of electrodes from 128 per side to 224 per side. The improvement in resolution in this central area is shown in Figure 12B showing the activation produced by the word FIAT LUX that occupies just over a two degree region in the visual field viewed by the camera. To obtain similar resolution at eccentricities between 2 and 4 degrees from the center of the fovea with and equally spaced array, 2.85 times as many electrodes would be needed: 610 per side as depicted in Figure 12C. In the proportional array further resolution could be gained by doubling up the electrodes for the central one degree of foveal vision which would produce spatially separate phosphenes within this region. Such placement would require 96 more electrodes but could double acuity within this region.

When an enhanced array of the sort described is used in concert with the zooming option we believe visual acuity can be significantly improved.

h. The prosthetic device must be able to provide information in three dimensions

As we had noted in section 2, one of the essential requirements for a prosthetic device is to be able to provide information about the relative location of objects in depth. Without such information locomotion in space would be next to impossible. We had also noted that a prosthetic device that relies on electrical stimulation should be capable of providing motion parallax cues for the extraction of depth information.

Here we provide two basic examples to indicate that the enhanced proportional array of 448 elements using the *intracell comparator* system is capable of providing a modicum of depth cues based on motion parallax. In **Display 9** (oval8) eight short vertical lines are displayed on the left which are rotated in steps to provide the impression of movement in depth. On the right is shown the manner in which visual impressions are presumed to be created by the electrical stimulation elicited by the camera viewing the display on the left. Although the image is degraded, most viewers can derive a sense of depth from the right display.

The second example is shown in **Display 10** (threed14). The image shown is a little bit more complex than the previous one. A drifting truncated pyramid is rocked back and forth across the visual field along its vertical axis. The sense of depth created with the enhanced proportional array reproduces the three-dimensional impression reasonably well.

While the high contrast images comprised of relatively thin lines reproduce reasonably well, this may not be the case for low contrast images, especially when they have extended, homogeneous surfaces. To asses how well a proportional array set up with the intracell comparator system works for depth processing in natural settings, the mimicking procedures we describe in the next section will have to be used.

i. Mimicking of the presumed effects must be carried out in sighted subjects to provide insights about the manner in which electrodes should be spaced and activated in an array

Quite a number of studies have simulated a visual prosthetic environment using a camera mounted to the head to simulate pixelized phosphene vision (Cha et al., 1992a,b,c; Chen et al., 2004, 2005a,b, 2006, 2007; Dagnelie, 2006; Dagnelie et al., 2006, 2007; Fu et al., 2006; Hayes et al., 2003; Thompson et al., 2003). None of these studies has put the eyes under experimental control. In all cases, one or both eyes, are allowed to view a pixelized screen that could be as small as 1.6 by 1.6 degrees^2 of visual angle (e.g. Cha et al. 1992a,b,c) or as large as 19 by 19 degrees of visual angle (e.g. Thompson et al., 2003). The field of view of the camera is adjusted according to the need of the task: acuity tests require a smaller field than whole-body navigation and subjects are often allowed to scan the field with the camera using head movements. The most commonly studied topics using pixelized vision via a head-mounted camera include visual acuity (Cha et al. 1992a, Chen et al. 2004, 2005a, 2006, 2007; Hayes et al. 2003), reading (Cha et al. 1992b; Dagnelie et al. 2006; Fu et al. 2006; Hayes et al. 2003), object and face perception (Hayes et al. 2003; Thompson et al. 2003), eye-hand coordination (Hayes et al., 2003), and whole-body navigation (Cha et al., 1992c, Dagnelie et al., 2007). The critical variables studied have been (a) pixel number, size, and spacing, (b) pixel dropout rate, and (c) number of contrast levels. The most important factors have been pixel number and size and the pixel dropout rate (which is studied since not every implanted electrode remains functional). For reading it has been found that 4 pixels are required per letter (Dagnelie et al., 2006; Fu et al., 2006) and between 2 and 6 characters must be visible for efficient reading (Cha et al., 1992b; Dagnelie et al., 2006; Fu et al., 2006; Legge et al., 1985). A few studies have actually used a camera to send signals directly to the retina or V1 of blind patients (e.g. Dobelle et al., 1976; Dobelle, 2000; Humayun et al., 2003).

To study the visual impressions that might be created using a prosthetic device based on electrical stimulation of area V1, we have devised a system that converts the input from a camera mounted on the head into visual images viewed on a monitor in a bezel (as shown in Figure 13) that mimic the images created by electrical stimulation as described in Figure 7-10. The program is flexible and allows for the manipulation of various array configurations. Two possible arrangements are shown in Figure 13. On the left is the proportional array shown earlier, and on the right the proportional circular array. The camera views a display that consists of a large circle and a small square. The electrodes activated to produce the phosphenes appear in the top left and right sections. The resultant images created appear on the bottom.

With this arrangement we can proceed to determine how effective a prosthetic device might be in a real life situation when free movement is allowed and when the visual scene is dynamic. Subjects are free to move their heads about so they can optimize the process of deciphering the visual scene. To learn about how they move their heads, a laser is attached to the camera; consequently the location of the laser spot in the visual scene can be traced enabling the experimenter to determine what strategies subjects use to decipher the visual scene (e.g. Dobelle, 2000). Furthermore, subjects can be provided with a controller for the camera zoom which enables them to optimize the resolution of the images viewed.

Using this mimicking system one can address the following central questions: (1) How well can the system process stationary images? (2) How can head movement improve processing? (3) How can acuity be optimized by manipulating the zoom feature on the camera and by mimicking different array configurations, (4) How can moving objects be analyzed best? (5) How can depth perception be realized? (6) How can one effectively minimize the amount of activation of brain tissue yet effectively process visual displays? Our preliminary tests show that the percepts created using the mimicking device depicted in Figure 13 set to convert the camera image with the *temporal intracell comparator* yields images similar to those shown in Displays 4-11.

7. A brief description of one experimental session:

Here is an excerpt from our protocol from one subject:

The subject we tested had volunteered for the experiment eagerly and found the project most interesting once it was explained to him. The helmet with the camera and the bezel with the small monitor was placed on his head. We used the proportional square array described in Figure 7 and the *temporal intracell comparator*. The subject was instructed to direct his head toward the wall on which was pasted the famous statement made by John F. Kennedy at his inaugural address in 1961. The words appeared in a single line and the subject was asked to first activate the camera zoom to optimize resolution and to then scan the display by slowly moving his head from left to right:

ASK NOT WHAT YOUR COUNTRY CAN DO FOR YOU – ASK WHAT YOU CAN DO FOR YOUR COUNTRY

The image created looked similar to what is shown in **Display 11**. The subject recited the words clearly. As he spoke, the experimenter detected a slight accent, so he asked where he was from. "I am Italian," he said. "From Tuscany," he added.

"All right, in that case I would like to show you one more display," said the experimenter. “Just keep your head still and I will flash on a figure. You tell me what you see.” The experimenter flashed on a circle using the proportional circular array (Figures 8 and 13) which then appeared on the monitor; the image created looked like the one shown in **Display 12.**

"Okay, what do you see?" the experimenter inquired.

"I see a circle. The round O of Giotto," the subject added.

THE END

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STATIC FIGURES:

Figure 1: The retina: A. Head-on view of the rods and cones in the fovea and at an eccentricity of 5 degrees. B. Head-on view of the retina showing the fovea, the optic disk and the blood vessels. C. Head-on view of the retina showing the course of the axons to the optic disk. D. Cross section of the retina at the foveal pit demonstrating that this region is free of retinal cells other than the photoreceptors; this is achieved by having cell processes course away from this central area.

Figure 2: A: Schematic of the responses of ON and OFF-center ganglion cells to spots presented in the center of their receptive field and large spots that impinge on both the center and the surround of their receptive fields. The vertical lines represent the action potentials created by the stimulation. Center-surround organization in these ganglion cells is antagonistic as a result of which a more vigorous response is elicited when a small spot is presented than a large one. ON-center ganglion cells are excited by light increment (the white spot on the gray background) whereas OFF-center cells are excited by light decrement (black spot on the gray background). B. Demonstration of the effects of adaptation. Fixating on the little white square in the center between the two gaussian disks for 10-20 seconds will result in the disappearance of these disks due to the adaptation process that takes place in the retina. At this point, when one shifts the center of gaze to the lower little white square. Two negative afterimages will appear as a result of the photons from the homogeneous background impinging on more and less sensitive areas in the retina at the adapted locations. C. The scaling of afterimages. Fixate on the white dot in the center of the black disk in the left for 20-30 seconds, then shift your gaze to the black cross in the center of the right. Once the afterimage appears move the sheet toward and away from you. The afterimage will scale in size.

Figure 3: The basic wiring diagram of the visual system. Ganglion cells from the nasal hemiretinae cross over at the optic chasm whereas those from the temporal hemiretinae project ipsilaterally. As a result, punctate images in the visual field activate corresponding points in the visual system when they are presented along the horopter where an image activates corresponding points on the retinal surface. Images from the left visual hemifield (in blue) project to the right hemisphere and images from the right visual hemifield (green) project to the left hemisphere. The major projection sites from the retina are the lateral geniculate nucleus, the superior colliculus, the terminal nuclei. In the cortex there are numerous visual area (shown are V1, V2, V3, V4, and MT). These areas send both feed forward and feed back connections to many areas of the brain. Images appear outside the horopter impinge on retinal non-corresponding points.

Figure 4: Layout of the lateral geniculate nucleus and primary visual cortex (V1). A. A Nissyl-stained cross section of the lateral geniculate nucleus which for the central 17 degrees of the visual field representation has six layers. The top four layers (3-6) receive input from the retinal midget cells. The bottom two layers (1-2) receive input from the parasol cells. The intralaminar layers receive input mostly from the retinal koniocellular cells (which contain the calcium-binding protein calbindin-D28k). B: A Nissyl-stained cross section of area V1. The thickness of gray matter and density of neurons is quite constant though out this area. The layers in the gray matter are designated. The prime input of the midget and parasol cells from the LGN goes to layers 4cα and 4cβ. The inputs from the koniocellular cells terminate in layers 1 and 2. C: Layout of the central five degrees of the visual field. The left hemifield (blue) projects to the right hemisphere and the right hemifield (green) projects to the left visual field. D: A rear view of the monkey brain showing the central 6-8 degrees of the visual field layout. This region in the monkey is lissencephalic except for the external calcarine sulcus, which is quite shallow. The visual field is laid out in a topographic fashion with much more area allocated for central than peripheral representation. The visual field is laid out upside down in the cortex with the upper part of the visual field

in the lower region of V1 and the lower visual field in the upper portion of V1 using the conformal mapping scheme of Schwartz (1994) for the macaque monkey.

Figure 5: The basic manner in which images activate various regions of area V1 in the monkey. Dotted figures are presented in the visual field in accordance with the fact that electrical stimulation of area V1 produces star-like images. A: A dotted arrow is placed in into the visual field centered on the vertical meridian. The areas activated in V1 are shown below. The tail of the arrow projects into the right and the head of the arrow to the left hemisphere. Due to the magnification factor that results in more space allocated per unit area for central than for peripheral vision, the size of the area activated by each dot is progressively larger the closer the dots are to the foveal representation. Due to center/surround antagonism in retinal and LGN cells and due to the greater responses elicited to edges in the cortex, the dots drive neurons more vigorously at the outer periphery of each dot than in the center, which is depicted by the shading of the dots on the cortical surface. B: The dotted circle placed in the right visual hemifield activates the marked regions in the left hemifield; the dot in the center of the fovea activates the foveal representation in both hemispheres. The activation in the left hemifield forms a pretty good circle but the size of each dot representation changes as a function of eccentricity. C: The same circle is presented in the visual field centered on the vertical meridian. The activation in the cortex forms two crescents yet what we perceive is a perfect circle. The size of the areas activated is constant as these locations are equidistant from the fovea.

Figure 6: A: An array of 256 dots arranged in the shape of a square and the corresponding brain regions activated in area V1. B: An array of 256 electrodes placed proportionally on the cortical surface taking magnification factor into account, with 128 in each hemisphere. Electrical stimulation under these conditions presumably activates an array or star-like images whose size increases with increasing eccentricity. The white lines show schematically the correspondence of points in the visual field and with the electrodes in the cortex.

Figure 7: The presumed effects of electrical stimulation using a proportional square array. On the bottom left is shown the rear view of a monkey brain with the electrodes placed bilaterally as had been shown in Figure 6. When electrical stimulation is applied to all electrodes, as indicated by the red-centered electrodes, it presumably yields the square array of dots shown in the visual field above. The center section of the figure shows a digital camera that looks at the display FIAT LUX centered in the visual field. The camera is hooked up to a computer and a stimulator arranged to activate the appropriate points in the cortex. The regions activated by the letters are shown by the red filled dots in the bottom right panel. The resultant image created by the selective activation of the subregions in the camera unit is shown in the upper right panel. The electrodes activated in the brain are shown in red.

Figure 8: Examination of the percept yielded when, instead of a proportaional square array a proportional circular array is placed on the cortical surface. When all electrodes are activated a radial display comprised of an array of near-perfect circles is produced as shown in the upper left. When the same words, FIAT LUX are presented as in Figure 7, this arrangement yields an image shown on the top right as are the electrodes activated (red dots), shown bottom right.

Figure 9: The images created when equally spaced electrode arrays are placed onto the visual cortex as shown on the bottom left. The arrays consist of 256 element spaced 1.3 mm apart for each side thus making for twice the overall number of electrodes as in the previous figures. When all electrodes are activated the presumed image, as shown on the left, looks like a butterfly due to the manner in which the visual field is laid out on the cortical surface. Presenting the words FIAT LUX, as in the previous figures,

produces a rather distorted image as shown on the top right. The electrodes activated by the words are shown in red.

Figure 10: Comparing two electrode arrays when three identical squares are presented at three locations in the visual field. A: With the proportional array, the squares created by electrical stimulation are approximately equivalent in size although the size of the individual dots becomes larger with increasing eccentricities as already noted for Figures 6-9. B. The equally spaced array, shown in B, yields distorted squares that are much larger in the periphery than near the fovea.

Figure 11: A. Post stimulus time histograms of multiunit data obtained from a fixating alert monkey when the receptive fields of the V1 cells were stimulated with a small white spot, a small black spot and a white spot larger than their receptive fields. The data are based on 40 trials for each condition. The small light and dark spots elicited similar responses whereas the large spot elicited no response at all. B. The activation of a single cell in the recording system that is set up to have the same number of units as the number of implanted electrodes. Each unit is activated only when a difference in activation occurs *within* its elements as shown in d. Changes in illumination that affect all elements within a unit equally, as in b, produce no activation**.** This arrangement mimicks the basic characteristics of V1 neurons.

Figure 12: An enhanced proportional display system. A: Ninety-six electrodes are added to each array shown in Figures 6 and 7 thereby making for a total of 448 elements. The added electrodes are placed in-between the central 8 by 8 portion of the electrode array shown in Figure 6 yielding a 16 by 16 array. The image elicited by stimulating all sites appears on top. B: The images created by the 256 and 448 element arrays when the words FIAT LUX are confined largely to the central two degrees of the visual field appear on the right top demonstrating the higher resolution reaped by the addition of the 96 electrodes. C: Evenly spaced electrode array that allows for proportional activation using a program that corrects for magnification factor. The arrangement of 610 electrodes per side provides approximately the same resolution as the proportional array in A that has 224 electrodes per side.

Figure 13: Procedures for mimicking a prosthetic device non-invasively. A video camera is attached to the head with a laser so head movements can be tracked. The image in the camera is converted as in Figure 12. The resultant image is displayed on a small monitor inside a bezel that is attached to the head, which is the only visual signal provided to the observer. Shown are the layouts for the proportional square and circular arrays when a small central square and a large circle are presented in the visual field. The small square is reproduced well with the proportional array; the large circle is produced extremely well with the circular array.

DYNAMIC DISPLAYS:

Display 1: The responses elicited in a proportional square array to an alternating horizontal and vertical line using the *transient luminance difference* detector system. The visual stimulus appears on the left and the activation producing the visual impression created by the electrical stimulation is shown on the right. Each line is shown for 180 ms. Activation duration is set to last 90 milliseconds. Due to a response elicited both when the stimulus appears and is terminated, a persistent cross is seen instead of alternating lines.

Display 2: The responses elicited in a proportional square square array to an alternating horizontal and vertical line using the *temporal intracell comparator* system. The visual stimulus appears on the left and the activation producing the visual impression created by the electrical stimulation is shown on the right. Each line is shown for 180 ms. Activation duration is set to last 90 milliseconds. The alternating lines are reproduced quite well.

Display 3: The responses elicited in a proportional square array to the drifting words FIAT LUX using the *temporal difference detector* system. The visual stimulus appears on the left and the activation producing the visual impression created by the electrical stimulation is shown on the right. The letters move across the visual field in 90 millisecond steps. Activation duration is set to 90 milliseconds.

Display 4: The responses elicited in a proportional square array to the drifting words FIAT LUX using the *temporal intracell comparator* system. The visual stimulus appears on the left and the activation producing the visual impression created by the electrical stimulation is shown on the right. The letters move across the visual field in 90 millisecond steps. Activation duration is set to 90 milliseconds. The reproduction using this scheme is superior to the one shown is superior to the one shown in Display 3 that uses the *temporal difference detector* system.

Display 5: The responses elicited in a proportional array to a drifting outline square using the *temporal intracell comparator* system. The visual stimulus appears on the left and the activation producing the visual impression created by the electrical stimulation is shown on the right. The display moves across the visual field in 90 millisecond steps. Activation duration is set to 90 milliseconds. The square is reproduced quite faithfully.

Display 6: The responses elicited in a proportional square array to a drifting solid square using the *temporal intracell comparator* system. The display moves across the visual field in 90 milliseconds steps. Activation duration is set to 90 milliseconds. This system produces an outline square instead of a solid square.

Display 7: The responses elicited in a proportional square array to a drifting cross-hatched square using the *temporal intracell comparator* system. The display moves across the visual field in 90 millisecond steps. Activation duration is set to 90 milliseconds. The cross hatching in the drifting visual display now produces what is pretty much a solid square.

Display 8: The responses elicited in an equally spaced (butterly) array to a drifting outline square using the *temporal intracell comparator* system. The display moves across the visual field in 90 millisecond steps. Activation duration is set to 90 milliseconds. Instead of a square moving in space an object is seen that undergoes notable changes in shape from which it would be difficult to infer the movement of a single, invariant moving object.

Display 9: The responses elicited in a proportional square array to a group of rotating lines using *temporal intracell comparator* system. The impression of three dimensions is reasonably well preserved.

Display 10: The responses elicited in a proportional square array to a rocking pyramid using the *temporal intracell comparator* system. The impression of three dimensions is reasonably well preserved.

Display 11: The image created when the text of John F. Kennedy's famous remark, pasted on the wall, was scanned by a subject. The camera was set to use the *temporal inrarcell comparator system* with the proportional square array as shown in Figure 7.

Display 12: The image created when a circle is flashed on after central fixation using the camera set to use the proprotional circular array system.

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