Postmortem investigation of a human cortical visual prosthesis that was implanted for 36 years

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Abstract

Objective. Postmortem analysis of the brain from a blind human subject who had a cortical visual prosthesis implanted for 36 years (Dobelle 2000 Asaio J. 46 3–9) Approach. This provided insight into the design requirements for a successful human cortical visual prosthesis by revealing, (a) unexpected rotation of the electrode array 25 to 40 degrees away from the midsagittal plane, thought to be due to the torque of the connecting cable, (b) degradation of the platinum electrodes, and (c) only partial coverage of the primary visual cortex by the rectangular array. The electrode array only overlapped with the anterior 45% of primary visual cortex (identified by the line of Gennari), largely missing the posterior foveal representation of visual cortex. Main results. A significantly greater proportions of electrodes outside of V1 elicited phosphenes than did electrodes within of V1. Histology did not reveal appreciable loss of neurons in cortex that surrounded the migrated array, perhaps due to the very slow rotation of this implant. Significance. This pioneering effort to develop a cortical visual prosthesis suggests that to maximize efficacy, the long-term effects of implanted alien materials on nervous tissue, and vice versa, need to be considered in detail, and that electrode array design considerations need to optimally match the electrodes to the patient’s cortical anatomy. Modern pre-implant imaging can help optimize future implants by identifying the location and extent of bridging veins with MRI and even map the location of the V1/V2 border in vivo with PET.

1. Introduction

It was nearly 30 years after Hermann Monk demonstrated that occipital lesions in monkeys and dogs caused blindness (Monk 1881) that the Japanese ophthalmologist, Tatsugi Inouye, reported that occipital wounds in soldiers also caused predictable visual loss (Inouye 1909, Holmes and Lister 1916, Holmes 1918). Within a decade, the Breslau/Wroclaw neurosurgeon, Otfrid Foerster, first reported that visual phosphenes could be elicited by electrical stimulation of the human occipital lobe (Foerster 1929, Kraus and Schum 1931, Penfield and Boldrey 1937, Penfield and Rasmussen 1950, Button and Putnam 1962, Chapanis et al 1973, Dobelle et al 1974, Dobelle and Mladejovsky 1974). It was a neurologist, Wendell Dobelle (Krieg 1953) who was the first to suggest that electrical cortical stimulation could form the basis for a visual prosthesis. Giles Brindley systematically mapped multiple phosphenes (Brindley and Lewin 1968, Brindley et al 1972, Brindley 1973, 1982, Brindley and Rushton 1974, 1977) by implanting the first multielectrode array in a blind subject. William Dobelle was the first to implement Krieg’s idea to connect implanted electrodes to a video camera, creating the first visual prosthetic (Dobelle et al 1974, 1976, Dobelle 2000, reviewed by Hambrecht 1995, Greenberg 2000). Subsequent to the first vision prosthetic, between 2000–2005, Dobelle implanted his prosthesis into 16 individuals that were blind (Lane 2015). The second generation of Dobelle implants had between 140–512 electrodes implanted.
Figure 1. Photograph of the occipital/parietal region of the specimen as received, with a notch-shaped indentation in the medial right hemisphere created by the stimulating array.

on the surface of the cortex in a butterfly array (Lane and Troyk 2016). The vision prosthesis was connected to an external processor and camera by way of cables. The connection site of the pedestals was often infected leading to medical complications, with the exception of one participant who received round-the-clock nursing care (Lane and Troyk 2016). Some of the implants were removed due to complications from infection while others remain implanted. The first Dobelle implantee remained implanted longer than any of the other participants. We describe here the postmortem findings for the first Dobelle visual prosthesis that was implanted in a blind person for 36 years, and subsequently migrated (Dobelle 2000) to glean design requirements for a useful cortical visual prosthesis.

2. Methods

In 1978 a rectangular stimulator grid was implanted over the right medial occipital cortex of a 41 year-old blind subject in New York City. Communication with a video camera was through a percutaneous cable and pedestal attached to the right parietal skull. Twenty-one phosphenes were reported over a two-decade period. He died in March, 2014, 36 years after implantation. The subject and his family were extensively interviewed by one of our group (FL, personal communication) in 2012, and later donated his brain for study by our group. The brain was removed by the local medical examiner and that brain and a portion of the hardware were shipped to us (figure 1).

After fixation in 10% buffered formalin, the brain was dissected and analyzed grossly and histologically, as well as by MR imaging. The two hemispheres were separated by a mid-sagittal cut after the initial examination of the specimen. The parietooccipital region of each hemisphere was cut off by a second coronal cut. Subsequently, the parieto-occipital regions were imaged separately by MRI as described below. After MR imaging the parieto-occipital portions of the hemispheres were cut into a series of slices of approximately 5–10 mm thickness in a plane perpendicular to the notch left by the electrode grid (figure 2). Representative histologic sections were taken from the region around the cleft-like space left by the electrode grid as well as the corresponding region of the contralateral hemisphere. These were processed for paraffin embedding and histologic sectioning. H&E stained and Bielschowsky stained slides were prepared for examination. Immunohistochemical stains were performed for GFAP as a marker of gliosis and CD68 as a marker of reactive histiocytic infiltrates.

2.1. Torque of cable

Because the rotation of the implanted grid may have been due to the torque caused by the twist in the intracerebral connecting cable, we computed the
Figure 2. (a) Medial view of the right occipital lobe, which was sliced in a plane that was perpendicular to the notch in which the electrode array was located. (The apparent defect in one of the slices corresponds to the tissue that was sampled in the tissue block shown in figure 6). (b) This cutting plane has been transferred to the sagittal MRI brain slices. (c) A comparison of the virtual brain slices in the occipital region of the MRI with the actual brain slices of the occipital lobes.

2.2. Line of Gennari
Each resulting occipital slice was photographed to trace the line of Gennari. Areas including primary visual cortex (V1, BA-17) were identified by determining the location and extent of the line of Gennari by direct visual inspection. These parieto-occipital slices were photographed on both sides, and the photographs were examined in detail. Perhaps the cortical stripe became less visible due to compression by the grid, since we could only appreciate its presence on the medial face of the hemisphere on two of six right-hemisphere slices.

2.3. Imaging
Before slicing, each hemisphere of the brain was placed in saline and scanned independently in vitro in a 3.0 T Phillips scanner using a T1 pulse sequence. A 3D model of the cortex was created with FreeSurfer (Dale et al 1999, Fischl et al 1999), following the ‘Ex Vivo Recon’ instructions given at https://surfer.nmr.mgh.harvard.edu/fswiki/ExvivoRecon. Freesurfer’s white matter segmentation was refined using MATLAB’s ‘area opening’ algorithm, bwareaopen, to remove extraneous visual noise from saline bubbles, and additional manual correction of white matter boundaries abutting against the cortical gray matter, subcortical structures, and ventricles. The slicing planes were identified in the MRI, and the location and extent of visible portions of the line of Gennari were transferred in to the 3D model. This was compared to the location of primary visual cortex as indicated by the probabilistic map of normal V1 included in FreeSurfer (Hinds et al 2008, Desikan et al 2006).

2.4. Electrode registration
A virtual $8 \times 8$ grid was created using electrode-to-electrode spacing as measured using a mechanical caliper on the physical grid. This virtual grid
was manually positioned in the right hemisphere cleft of the 3D MRI model using 3D Slicer (Fedorov et al 2012, Kikinis et al 2014). The final position was determined by comparing the distance between all possible electrodes, and the relative distance between his 21 phosphenes (figure 3(b)). The final position was chosen so that adjacent electrodes that elicited widely separated phosphenes in the visual field were juxtaposed across the calcarine and other sulci.

3. Results

3.1. Specimen

The received fixed autopsy brain from the local medical examiner weighed 1227 g. The electrode grid was fixed to the skull and separated from the brain. We do not know the post-mortem latency of the removal of the brain. Except for a 2.5 × 3.5 cm 'J' shaped-notch in the medial face of the right hemisphere, it did not show any observable abnormalities; no atrophy, mass effect, swelling, softening or cavitation was noted. The meninges were unremarkable without overt gross fibrosis or features suggestive of cellular infiltrates.

The region of the right hemisphere where the electrode grid was implanted was easily identified because a cleft-like space was observed on the medial face that was angled about 40 degrees from the mid-sagittal plane (figure 1). The adjacent occipital cortex posterior to the grid appeared pushed medial and forward into a bulge that accentuated the 3 cm cleft-like space holding the electrode grid. The portion of occipital bone in which the electrode grid was embedded (figure 3(a)) could be positioned in a way to make the 3.8 × 2.8 × 0.64 cm rigid electrode grid easily slide into this cleft-like space. When we received the specimen, the grid was rigidly attached to the skull at the point of insertion, via fixation of the grid connecting cable. The rostral edge of the grid was spaced 0.5 cm from the inner table of the skull. The pass-through section of the cable was encapsulated with bone. Electrodes were 2.4 (±0.5 mm) in diameter with a center-to-center spacing of 2.5 mm. The grid’s connecting wires entered the skull near the occipital/parietal midline, and upon exiting the skull followed a sub-galeal course, connecting to a 64 contact, 2 cm diameter pedestal attached to the parietal skull above and behind the right ear (See Dobelle 2000, figure 2). Successive axial slices of the right hemisphere showed the relationship of the grid to the Line of Gennari (figure 4). In the anterior-posterior direction, the electrodes covered the anterior 45% of Area 17 on the medial face. The posterior 55% of Area 17 was not covered by the rectangular stimulating array. As has been described by (Stensaas et al 1974), V1 for this subject extended onto the outer surface of the posterior pole by about 1 cm on both hemispheres.

3.2. Registration to 3D MRI model

Analysis of the MRI model suggested that the rotation of the grid was closer to 25 degrees from the sagittal plane, in contrast with figure 1. The locations of the brain slices were identified in the MRI so that visible portions of the line of Gennari could be marked in the 3D model (figures 3(c) and (d)). The virtual grid was registered to the brain based on anatomical considerations (i.e. the shape and orientation of the medial cleft produced by the electrode array) (figure 3), and the idea that physically adjacent electrodes associated with phosphenes that were widely separated in the visual field (Dobelle 2000) (e.g. electrodes 1:10, 26:33, 28:29, 58:60) must be located across the calcarine fissure or other sulci (figures 3(c) and (d)). The resulting physical localizations of the electrodes that elicited phosphenes all fell within the flat region of the notch (figure 3(c)). When the cortex model was inflated using FreeSurfer, the electrodes were found to be on the exposed medial face, and not within the calcarine fissure (figure 3(d)).

When mapped to the 3D model, the regions where the line of Gennari were observed were smaller, but generally agreed with FreeSurfer’s estimate of the extent of V1 based on the Hind’s V1 atlas (figures 3(c)–(d); Hinds et al 2008). Except in the most anterior and posterior regions, the edges of the FreeSurfer V1 estimate largely fell between slices where the subject’s line of Gennari was observed (figures 3(c)–(d), red) versus not observed (figure 3(d), yellow). Based on the FreeSurfer estimate, 16 of the 57 (28%) electrodes located within V1 and 5 of the 7 electrodes located outside of V1 elicited phosphenes, yielding a statistically significant increased proportion of phosphenes from extrastriate stimulation (χ² = 23, df = 63, p < .05). Given the spatial resolution of the slices, it is also possibly that the subject’s V1 is slightly smaller than the FreeSurfer estimate, particularly in the more posterior regions where the line of Gennari’s vertical extent is less clear. As seen in figure 4, the majority of line of Gennari was within the calcarine fissure, and was only identified on the surface of the medial face of either hemisphere in two of the 12 slices.

3.3. Electrode surfaces

In examining the grid, an obvious darkening of electrodes was visible on half of the array as can be seen in figure 3(a), (most obvious in the lower right portion of the array in figure 3(a)). Microscopic examination revealed that all but two of the electrodes in this half were notably darkened in appearance, whereas the electrodes in the opposite half had a bright, shiny, appearance.

3.4. Histology

Overall, neuronal density and organization did not appear altered on the hematoxylin and cosin stained section (H&E) (figure 5), with the exception of very
Figure 3. (a) The Teflon-platinum stimulating array attached to the occipital skull. It could easily be slid into the notch in the right hemisphere. (b) Scatterplot of inter-electrode distances and associated inter-phosphenes distances. Nearby electrodes with widely separated phosphenes (grey oval) are likely fall on opposite sides of the calcarine fissure. (c) Realistic three-dimensional reconstruction of the medial occipital lobe showing the location of the 21 electrodes that elicited phosphenes placed within the notch (upper visual field: grey; lower visual field: black). Portions of the line of Gennari that were visible in the occipital slices are shown in red. The probabilistic estimate of V1 inherent to FreeSurfer falls within the white line. (d) Inflated cortex showing the relationship between the electrodes (dots), the same probabilistic location of V1 (white line), and the extent of the line of Gennari. Slices where the line of Gennari was not observed are shown in yellow. The FreeSurfer length coefficient factor was set to 5.

focal mild encephalomalacia with focal hemosiderin deposition (figure 6). No significant infiltration by macrophages was visualized by CD68 staining which supports the absence of recent tissue damage. Beyond that, a histologic comparison of the two hemispheres revealed uniform chronic gliosis on the side of the implant with fibrillary astrocytes that are not easily visualized on the H&E sections, but highlighted by the performed labeling for GFAP (figure 5). The location of the line of Gennari was confirmed histologically on several serially submitted blocks with Bielschowsky staining (figure 6).

3.5. Cable torque
The force required to rotate the grid to a position that was parallel to the mid-sagittal plane was 115 g. This corresponds to a torque of 15.8 mNm. Because this force was probably exerted over a long period, this post-mortem measurement should be considered as an upper bound.

4. Discussion
Post-mortem examination of a visual prosthesis grid and cable revealed post-implant migration of the array and partial degradation of the platinum electrodes. The most surprising finding was that the electrode array had rotated 25–40 deg away from the mid-sagittal plane. Migration of implanted devices has been reported in the past (Cook et al 2013). Because the cortex touching the surface of the grid appeared relatively normal, we suspect that these changes were due to a slow migration process to which part of the cortex could adapt, and part could not. This was likely caused by the rotational elastic torque of the connecting cable. Beginning around the late 1970s into the 1980s, novel techniques for transcranial embedding of wiring into the skull/brain using various durable acrylics were tried. However, after long (several years) implantation in/around a conduit, the acrylic surfaces would often become encapsulated by new bone.
growth after the acrylic wore away due to assumed micromotions of the cable. This is supported by our microscope examinations in which no boundary between an artificial material and bone was observed. This may have happened early on after implantation, because at some point the cable became encapsulated by the skull at the point close to where the cable connected to the grid.

4.1. Rotational dynamics
Considering how much the gross anatomy of the right medial visual cortex in the region of the electrode grid was altered, the histological findings were remarkably intact. We did not observe cell loss near the electrodes due to electrical stimulation, as others have reported (Agnew et al 1986, 1990, McCreaery et al 1994). We imagine that this might have been due to the slow rotation of this grid over many years, but we have little direct information relative to the speed of rotation or its cause in this subject. We suspect that the cable pass-through was slowly encapsulated with bone tissue. In addition to the torque of the implanted cable, perhaps the continuous CSF circulation and cardiac pulsations, or occasional sneezing, coughing, and head movements may have caused rotation over many years.

There is a general consensus that rigid arrays such as this one (Dobelle 2000) cause greater compression than flexible silicone rubber (Brindley and Lewin 1968), or soft pliable cellophane-like etched arrays (Kaiju et al 2017). Such flat surface electrodes are different from penetrating electrodes (Bak et al 1990, Schmidt et al 1996), which move with the cortex, provided they are not tethered with stiff cables or encapsulated or adhered to the dura. Our own experience with cabled arrays in a non-human primate model revealed many problems (Bradley et al 2005). In addition to providing a vector for serious extra-corporeal infection, we found that the rotational torque and elasticity of the wires and insulation tended to displace our needle electrodes and cause small hemorrhages. The proliferation of rigid cables connected to large numbers of electrodes were difficult to manage during implantation and due to their elasticity, may have had a tendency to return to their pre-implantation shapes. For the implanted array that we described here, the evidence shows that rotational forces caused notable deformation of the brain tissue. For more recently implanted cortical array designs, we are not aware of associated studies that consider any rotational effects upon brain tissue. One might speculate that smaller sizes and more pliable cables
would tend to mitigate the rotational forces exerted by cables even in these modern devices. However, lateral tethering forces of cables in modern implanted arrays are generally known to cause damage to cortical tissue. The results from this post-mortem study suggest that more attention should be paid, and additional studies performed, to understand the effects of cables in all dimensions, upon the physical stability of implanted electrode arrays. One solution to cabling problems is to eliminate the cabling and communicate energy and stimulation instructions via transcutaneous telemetry (Troyk et al 2003, Rush et al 2011).

4.2 Electrode degradation
The majority of the electrodes (30 out of 33) on the high-numbered half of the grid showed visual changes in their surface reflectivity, suggesting some form of electrochemical degradation. Although the

Figure 5. Histopathologic changes. HE morphology, panels (A) through (D): The basic light-microscopic examination of the cerebral cortex under the implant shows little alteration of the cortical architecture at low power ((A)—side of implant, (B)—comparable cortex from the contralateral hemisphere; scale bar 200 micrometers). (C) There was no evidence of any significant neuronal changes at higher magnification. (D)—comparable cortex from the contralateral hemisphere; scale bar 50 micrometers). The black ink seen on some of the images was applied to mark the location of the implant. It was applied at the time of the gross examination to ensure proper identification of this region on the histologic preparations. GFAP staining, panels (E) through (H): Immunohistochemical staining for GFAP highlights the presence of relatively uniform chronic gliosis in the cortex ((E)—side of implant, (F)—comparable cortex from the contralateral hemisphere; scale bar 200 micrometers) with fibrillary astrocytes ((G)—side of implant, (H)—comparable cortex from the contralateral hemisphere; scale bar 50 micrometers). CD68, panels (I) and J: Immunohistochemical staining for CD68 confirms the absence of any significant infiltration by histiocytic/microglial cells ((I)—side of implant, (J)—comparable cortex from the contralateral hemisphere; scale bar 200 micrometers).
Figure 6. Histologic changes: (A) (Bielschowsky stain—black bar corresponds to 2 mm): The low power examination shows region adjacent to the electrode grid. The estimated position of the electrode grid is marked by the open triangles. The arrows mark the Line of Gennari that is highlighted on this stain as distinct line of white matter type tissue within the primary visual cortex. Part of the primary visual cortex would have abutted the electrode grid. (B) (H&E—black bar corresponds to 5 mm): H&E stained serial section of the same region shown in panel (A). (C) (H&E—black bar corresponds to 50 micrometer): Higher power shows superficial with black ink marking the cortical surface that would have abutted the electrode grid. Focally in the area shown in this image the superficial cortex showed mild gliosis and hemosiderin deposition. Other areas appeared normal at the level of the H&E stained sections. The available meningeal tissue was devoid of any significant inflammatory reactive changes. (D) (H&E—black bar corresponds to 20 micrometer): Higher power view of the area shown in panel (C).

4.3. Histopathology
The surface of the cortex underlying the electrode grid showed very focal mild encephalomalacia with hemosiderin and gliosis. The histopathology does not allow timing of the injury that led to these focal changes. They may indeed date back to the time of the electrode grid placement. Otherwise, though, cortex and meninges did not show any significant alterations of basic histopathology in response to the electrode grid that had remained in place for 36 years. The lack of overt fibrosis or inflammatory changes is arguably promising for future studies that plan on placing long-term cortical implants (Xia and Ren 2013).

4.4. Personalization of grid placement
Like many normal subjects, this subject’s V1 extended onto the outer surface of the occipital pole (Brindley 1972, Stensaas et al 1974). This rigid midline array did not reach posterior enough to stimulate the fovea, but somehow did elicit three phosphenes seemingly
across the central meridian of the visual field. The grid was only in contact with the anterior 45% of primary visual cortex, as identified by the line of Gennari, precluding the possibility of eliciting many phosphenes in the foveal region. We suspect that future implantations will employ anatomy-inspired flexible arrays that more closely match the anatomy of the visual cortex, with special consideration for coverage of the foveal region near the occipital pole. The finding that there was a significantly higher proportion of phosphenes obtained from extra-striate electrodes on the medial face than striate electrodes was surprising, given the emphasis early researchers have placed on striate stimulation.

Recent investigations of lateral occipital stimulation have found comparable proportions of phosphenes (Schmidt et al 1996, Lee et al 2000, Kaido et al 2004, Larson and Heeger 2006, Murphey et al 2009, Cicmil and Krug 2015, Bosking et al 2017a, 2017b). Although many extrastriate phosphenes are punctate in nature, more anterior stimulation sites may elicit more complex experiences, such as primate MT stimulation altering primate movement perception (Salzman et al 1990), and fusiform face area stimulation disrupting human face perception (Mundel et al 2003).

A possible explanation for the unusual spatial pattern of phosphenes generated from stimulation via this grid is that the patient had an unusual post-morbid cortical anatomy, and many phosphenegenerating electrodes were located outside of V1. However, neuropathologic examination suggested that the subject’s anatomy was within the normal range of variation, and some phosphenegenerating electrodes were likely located over V1, ruling out the possibility that the spatial distribution of the perceptions could be explained on an anatomic basis. Spatial uncertainty in the mapping of the subject’s phosphene location also may have contributed to the unusual spatio-topic pattern. We suspect that primary visual cortex and its V1/V2 border could be identified in vivo for blind subjects with PET receptor imaging studies (radioligand [11C]flumazenil) to reveal the relatively high concentration of GABA\(_A\) receptors in primary visual cortex (Zilles et al 2002). It is likely that the use of wireless floating microelectrode arrays will make it possible to avoid occipital bridging blood vessels and accommodate to the complex anatomical topography of the occipital pole, allowing dense coverage of the foveal projection region.

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