Vision Research[1]

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Summary

This paper discusses claims that the use of non-human animals in vision research has led to our understanding and treatment of various ocular conditions in humans. It is shown that such use is not necessary and that the most important means of understanding vision is through ethical and humane studies on humans. Results of research using non-human animals confuses the situation because of differences between species.

Keywords: alternative, ethics, eye, humane research, morality, non-human animal, research, sight, species differences, vision

Because I am a vision scientist, I am keenly aware of the exaggerated nature of the claims that non-human animals (animals[3]) are indispensable in vision research. Much of this work is neurophysiological, dealing with single cell recordings. This work does not measure vision, which has a large psychological component in humans, and the work has little to do with vision in terms of behaviour and function. This is alluded to by some investigators in their own publications[4]. Vision cannot be studied reliably in non-human animals because one cannot communicate adequately with them, and cellular recordings do not provide any information on whether and how the animals see. Although the information derived may be interesting, there are potential problems in relying upon it and there are other, more reliable ways of obtaining it.

It is only in the human that we can learn about what is being experienced under whatever conditions. A good example of this involves the phenomenon of blindsight[5]. With other animals, we cannot ever know just whether and what is being seen or how it is being perceived. Lack of direct communication, an inability to 'ask' the right questions or placing the individuals in confounding situations prevent us from adequately and reliably assessing vision in them. A case in point involves Helen, a rhesus macaque who had had her visual cortex surgically removed[6]. The researcher had this to say about her situation:

> "*Some years ago I made a discovery which brought home to me dramatically the fact that, even for an experimental psychologist, a cage is a bad place in which to keep a monkey. I was studying the recovery of vision in a rhesus monkey, Helen, from whom the visual cortex had been surgically removed (Humphrey, 1974[7]). In the first four years I'd worked with her Helen had regained a considerable amount of visually guided behaviour, but she still showed no sign whatever of three-dimensional spatial vision. During all this time she had, however, been kept within the confines of a small laboratory cage. When, at length, five years after the operation,*

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1 The intent of this brief review is to demonstrate that reliance on animal research is unnecessary to understand or treat vision disorders in humans. Due to the substantial number of published studies that substantiate the various assertions I make, I have limited the citations to just a few in each case.

This document is not being regularly updated. Although some of the references may be considered by some to be 'dated', this only serves to show just how much understanding and management has remained unchanged over the decades despite thousands, perhaps millions, of animals having been subjected to some of the worst privation imaginable. In addition to the lack of scientific credibility or necessity, there are strong moral arguments against subjecting non-consenting beings to harm and death; this subject is addressed in another manuscript (Buyukmihci 2022-12-01).

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3 Purely for the sake of convenience, I may refer to animals other than humans as "animals", recognising that all are animals of one kind or another; there is no intention to imply that any, even a human, is morally superior or intrinsically more valuable than another.

4 Blakemore & Vital-Durand 1979

5 Stoerig & Cowey 2007

6 Humphrey 1976

7 Humphrey 1974

she was released from her cage and taken for walks in the open field at Madingley her sight suddenly burgeoned and within a few weeks she had recovered almost perfect spatial vision. The limits on her recovery had been imposed directly by the limited environment in which she had been living."

There are major differences in the development, function, reaction and structure of the visual systems of humans and other animals[8]. Consider this in the case of amblyopia, for example[9]. Amblyopia is a severe loss of visual acuity due to lack of proper stimulation of the developing visual system. The cat, who had been widely used to study this condition, does not have a macula or fovea. These regions, which *are* present in humans, account for essentially all useful vision and it is the lack of development of their connections in the brain which are of the utmost importance in this disease[10]. The cat 'model' of amblyopia, therefore, cannot reliably predict what changes may occur in humans when vision is deprived. Furthermore, the experimental situation in the cat and other non-human animals is entirely artificial, a perturbation of an otherwise normal animal. Spontaneously occurring visual deprivation in human children, however, often is associated with other developmental defects which tend to modify and confound the situation.

Non-human primates are increasingly being used in vision research. Although there are many structural and physiological similarities between certain species of non-human primates and humans, there still may be problems in extrapolating the information to the human situation. For example, in order to study myopia or nearsightedness, one could induce it artificially in macaques by depriving them of vision after birth. Different species of macaques, however, have markedly different reactions to the same experimental procedure[11]. The mechanism of eye elongation appears to be different between rhesus and stump-tailed macaques. One must question, therefore, which species, if any, mimics the human condition? A circular argument becomes apparent: unless human studies corroborate the hypotheses derived from non-human animal studies, one cannot determine the relevance to the human condition. If, however, one can do studies on humans to derive the data to make this corroboration, then there can be no justification for the non-human animal studies. Apropos to this issue, many of the studies I cite to document research using humans also involved the concurrent use of non-human primates[12]. Because the important information was derivable using human volunteers, it seems clear that there was no need to use the non-human primates in order to learn about humans.

It would be much more rewarding and scientifically credible to study people who have had natural afflictions which fit the design of the experiment. I call these 'nature's experiments' and they comprise the subject of many studies[13]. Iatrogenic situations created by the treatment or other manipulation of human patients are also scientifically rigorous means of obtaining information to understand the anatomy of the human visual system and treat related diseases[14]. See each citation for a brief mention of the nature of the various types of visual system abnormalities in these situations (natural and iatrogenic).

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8 Arcaro et al 2022; Balslev et al 2022; Bito 1990; Flessert et al 2022; Henkind 1978; Jacobs & Harwerth 1989; McKeon et al 2022; Packwood & Gordon 1975; Palmer & King 1982; Rodieck 1979; Van Essen 1979

9 I discuss amblyopia in greater depth elsewhere (Buyukmihci 2022-12-17).

10 von Noorden 1978

11 Raviola & Wiesel 1985

12 Arcaro et al 2022; Cowey & Alexander 2012; Cowey et al 2011; Crawford et al 1983; Fehring et al 2022; Flessert et al 2022; Henry & Kohn 2020; McKeon et al 2022; Mohl et al 2020; Sablé-Meyer et al 2021; Santos-Mayo et al 2021; Schmitt et al 2021; Solomon et al 2021; Westerberg et al 2022

13 Cowey & Alexander 2012; Cowey et al 2011; Crawford et al 1983; Johnson et al 1982; Kiyosawa et al 1989; Korczyn 1975; Miyake et al 1990; Moran & Gordon 1982; Singh & Schulz 1984; Wright et al 1987; Zimmermann et al 2020

14 Adams et al 2007; Gabel & Birngruber 1981; Haglund et al 1992; Tso et al 1977; Wallow et al 1977; Werner et al 1989

There has been considerable concern expressed by vision scientists other than just myself that experimental work on non-human animals either is not relevant or may be misleading with respect to the human condition and its treatment. Those relating specifically to amblyopia are referenced elsewhere[15]. Murphy and co-workers criticised the chick 'model' of human juvenile myopia because of its severe shortcomings based upon species differences in anatomy and responses to experimental manipulations[16].

von Noorden and Maumenee were critical of the classic work of Wiesel and Hubel using cats because of the substantial differences in neuroanatomy and neurophysiology between cats and humans[17]. von Noorden later commented on how data from non-human animals could not be applied directly to humans, and that there were differences between monkeys and cats in the various studies done[18]. In his Jackson Memorial Lecture[19], he again was critical of non-human animal experiments with regard to infantile esotropia or convergent strabismus. He pointed out that the experimental work done in monkeys was not analogous. He concluded that there was no non-human animal 'model' for infantile esotropia, despite all the experimental work which had been done making infant monkeys strabismic.

The present level of sophistication using humans to understand brain function in general and the visual system in particular is considerable[20]. For example, Kiyosawa and co-workers, using human volunteers and positron emission tomography, demonstrated a regional reduction in cerebral glucose metabolism in patients with optic neuropathy[21]. Others have studied patients with refractory seizure disorders and who were undergoing evaluation for therapeutic brain surgery[22]. These patients had had subdural electrode grids implanted. Cortical mapping was done by electrical stimulation of the cerebral cortex in order to learn important neuroanatomical details of the human motor cortex, information virtually impossible to derive from other animals.

Others have used positron emission tomography or magnetic resonance imaging to measure activity-related changes in regional cerebral blood flow to identify brain regions which are active in human subjects during reading or playing the piano[23]. There are numerous other examples of elegant or critical work done using human volunteers[24]. This combination of cognitive and neurobiological approaches has provided information about the functional anatomy of perception, attention, motor control and language in the human, something not possible with non-human subjects.

Studies on humans provide us with information about the *human* visual system which will be invaluable in understanding and treating *human* disorders. They also demonstrate that claims that non-human animals are absolutely necessary are not true. These and other methods can be used in numerous other disciplines. I mention these not just to point out specific examples of alternatives

15 Buyukmihci 2022-12-17
16 Murphy et al 1992
17 von Noorden & Maumenee 1968
18 von Noorden 1978
19 von Noorden 1988
20 Arcaro et al 2022; Balslev et al 2022; Demer et al 1988; Gofas-Salas et al 2022; Haglund et al 1992; Larsson et al 2010; Nunez et al 2022; Phamnguyen et al 2022; Ramirez et al 2022; Roth et al 2020; Sugiyama et al 2022
21 Kiyosawa et al 1989
22 Uematsu et al 1992
23 Petersen et al 1988,1990; Posner et al 1988; Sergent et al 1992
24 Barbosa et al 2020; Busch et al 2009; Candy et al 2001; Fehring et al 2022; Hafed & Krauzlis 2006; Hsu et al 2021,2022; Hudak et al 2011; Larsson et al 2010; Mathewson et al 2009; Miladinovic et al 2022; Mohl et al 2020; Norcia et al 2020; Nunez et al 2022; Petrov et al 2005; Pilz et al 2020; Roth et al 2020; Santos-Mayo et al 2021; Schmitt et al 2021; Solomon et al 2021; Westerberg et al 2022; Yue et al 2020

to non-human animals. More importantly, they provide evidence on what could be done if there was a change in mind-set, a change from one which views other animals as mere ‘tools’ to one which considers them to be deserving of the same respect as humans. If we did this, then we could concentrate our efforts on improving available alternatives and developing new ones. Necessity then would become the mother of invention. We could begin the journey out of the dark ages of violence and destruction perpetrated on non-consenting and unwilling individuals in the name of science.

When contemplating or discussing the issue of non-human animals used in research, the most important point to consider is that these animals are not ‘things’, they are living beings who have feelings and share with us the drive to live. They are not here *for* us. They are not our tasters, we are not their kings. Their value does not depend upon their utility to us. Humans are not the only ones deserving of freedom and the pursuit of their interests. Other animals have just as much right to share the experience we call life. Harming or killing these individuals in the name of science does not make it noble or right. We do to these individuals what we do because we are *capable* of doing so, operating under the morally reprehensible 'principle' of “might makes right”, something that should be anathema to our own sense of morality.

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   “...across species, the underlying eccentricity representations corresponding to these macroanatomical structures differ strikingly across humans and macaques. Thus, the correspondence between retinotopic representation and cortical folding for an evolutionarily old structure like V1 is species-specific and suggests potential differences in developmental and experiential constraints across primates.”
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25 The list of references is not intended to be exhaustive on any particular subject. Rather, I have provided just a few examples to emphasise certain points.

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   "These studies have indicated that positron emission tomography is feasible for the investigation of brain function in human amblyopia. ...the greatest value of this technique probably lies in its use in locating and characterizing the poorly understood extrastriate regions involved in vision. This technique has great potential for further

research."

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    "As a model for human juvenile myopia, the chick model has several shortcomings (eg, the magnitude of myopia in the chicken far exceeds that found in human juvenile myopia, the model requires physical disruption of the visual image, the chicken eye can recover after myopia induction if normal vision is restored, and there are marked differences between the anatomy and physiologic optics of avian and human eyes)..."
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    "The feline limits of fusion and qualitative stereopsis reported here are quite different from those reported from human psychophysical experiments."
    The cat's visual acuity is "...about one-sixth that of..." the human.
    The experiment also was repeated, in essence, on human subjects to determine if the difference between the results in the cats and those previously reported for humans was due to species differences. Those results argued that it was due to species differences.
    "[W]e attempted to measure the limits of fusion and qualitative stereopsis on human subjects, using the same procedures we used in the cat experiments."
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    "We have used recent advances in the precision of positron emission tomography (PET) for measuring activity-related changes in regional cerebral blood flow to identify brain regions active during three levels of single-word processing."
    "The combination of cognitive and neurobiological approaches, of which this study is an example, has given us information about the functional anatomy of perception, attention, motor control, and language. As these endeavours proceed, solutions to the

problem of mind-brain interaction that have intrigued us for so long should be illuminated."
"The use of positron emission tomography to measure regional changes in average blood flow during processing of individual auditory and visual words provides support for multiple, parallel routes between localized sensory-specific, phonological, articulatory and semantic-coding areas."

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    "...the experiments with atropine administration suggest that the mechanism of eye elongation is different in rhesus and stump-tailed macaques: accommodation seems to have a role in M. arctoides but not in M. mulatta."
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"The studies were performed on 35 patients with refractory seizure disorders who were undergoing evaluation for ablative brain surgery."
"...we examined in detail the records of cortical mapping done by electrical stimulation of the cerebral cortex via implanted subdural electrode grids in 35 patients with seizure disorders. ... Our study reconfirmed that a significant number - at least one-third - of motor responses are distributed outside the classic narrow cortical strip. In patients with brain lesions, the motor representation is further displaced outside the narrow strip. This finding indicates that primary motor cortex may extend beyond the gyrus immediately anterior to the [Rolandic fissure]."
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"Amblyopia has now been produced successfully in models of various species, but data from cats, squirrels, and dogs cannot be applied automatically to man. There are differences in the anatomic and functional organization of the visual system of cats and primates. Human amblyopia involves primarily foveal vision rather than peripheral vision..."
"Moreover, in spite of many similarities of the visual deprivation syndrome in the different species, results from our studies in monkeys are different in some respects from those obtained in cats. For instance, unlike in the cat, unilateral lid closure in the monkey affects not only the binocularly innervated portion of the lateral geniculate nucleus but also the monocular portion...In addition, we have been unable thus far to show that the morphology of different classes of neurons in the lateral geniculate nucleus of the monkey is selectively affected by visual deprivation as it is in cats..."
"Amblyopia is now defined as a unilateral or bilateral decrease of visual acuity caused by form vision deprivation, abnormal binocular interaction, or both, for which no organic cause can be detected by the physical examination of the eye and which, in appropriate cases, is reversible by therapeutic measures."
"Research in amblyopic animal models has confirmed many older concepts regarding human amblyopia based solely on clinical observation and psychophysical experimentation."
66. von Noorden, G.K. 1988-01-01 "A reassessment of infantile esotropia: XLIV Edward Jackson Memorial Lecture" American Journal of Ophthalmology 105(1):1-10 https://doi.org/10.1016/0002-9394(88)90113-4
"...advances in our knowledge can be expected from the rapidly emerging discipline of infant psychophysics."
"Finally, we must ask whether animal experiments have helped us to better understand the pathophysiology of essential infantile esotropia. It is true that the so-called binocular cells in the striate cortex are permanently lost in infant monkeys after artificial strabismus...However, these cells also disappear in nonstrabismic monkeys after eyelid suture...or after experimentally induced anisometropia...Thus far the loss of binocularly innervated striate neurons has only been linked to an absence of stereopsis...There is no evidence from animal research that binocular functions other than stereopsis, such as sensory and motor fusion, are similarly affected by abnormal visual experience early in life. There is currently no animal model for essential infantile esotropia."
67. von Noorden, G.K. and Maumenee, A.E. 1968-02-01 "Clinical observations on stimulus-

deprivation amblyopia (amblyopia ex anopsia)" American Journal of Ophthalmology 65(2):220-224 https://doi.org/10.1016/0002-9394(68)93590-3

One patient in this report had corneal scarring of the right eye at two years of age. Penetrating keratoplasty was done at 26 years of age, but visual acuity did not improve and convergent strabismus was present when left eye was occluded. The other patients had similar types of histories.

"Juler [1921] emphasized the close relation between the functional result and the age at occurrence of cataract. Similar observations have been reported by Broendstrup [1944]..."

"It has been known for a long time that normal development of the visual system depends to a certain extent on adequate stimulation of the retina during early infancy and childhood."

Concerning the experiments of Wiesel and Hubel, "...it is not appropriate to transfer these data uncritically, to similar situations in humans, since the morphologic and functional organization of the visual system in cats is substantially different from that in man."

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    Used humans who were to have an eye removed due to intraocular neoplasia; exposed retinas to the light one to three days before enucleation.

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    Each person had IOL in each eye: one transmitted UV, the other absorbed it. There was selective loss in sensitivity of the short-wave cone photoreceptors after five years. Supports hypothesis that UV light may damage human retina.

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    "A 2-day-old polycythemic infant was found to have bilateral total hyphemas, presumably related to birth trauma. ... At four weeks of age...no retinal details could be visualized. ... Bilateral total occlusion was prescribed to prevent amblyopia until the hemorrhages spontaneously resolved."

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    Aspects of vision function, including fixation and eye movement, were studied in patients who had medial or lateral thalamic lesions.