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Health: Enhancement and Technology

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An independent academic psychologist, based in England, who has written extensively on different areas of psychology with an emphasis on the critical stance towards traditional ideas.

A complete listing of his writings at http://psychologywritings.synthasite.com/. See also material at https://archive.org/details/orsett-psych.

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1.1. INTRODUCTION

Jotterand (2024) began: "Throughout history, humans have used various techniques to augment and alter cognitive capacities, behaviour, and physical capabilities. Recent progress in pharmacology, neuroscience, genetics, regenerative medicine, artificial intelligence, and bioengineering has allowed the development of drugs, procedures, and devices not only to treat various disorders but also to use the same technologies to enhance human capabilities, if not possibly alter the very notion of what it means to be human" (p1).

This author continued: "The development of these technologies is on the verge of redesigning the boundaries of human existence. Brain–computer interfaces (BCIs), CRISPR Cas9, synthetic biology, radical life extension, neuro-enhancements, neuroprostheses, and bionics constitute only a few instances of technological trends that could potentially allow redefining and transcending human biological limitations" (Jotterand 2024 p1).

Agar (2024) argued that "we should consider ourselves to be entering an age of human enhancement" (p9). The upshot is a need for a more sophisticated approach to the philosophical and ethical issues.

As well as the philosophical issue of what human enhancement will mean for human nature, and the legal, social, political, and ethical implications, Jotterand (2024) outlined four areas of enhancement - physical, cognitive, mood, and medicine.

Advocates of enhancement argue that "not only should we implement enhancement from a practical point of view, but we also have a moral duty to do so because acting otherwise (hence not benefiting our society by 'bettering' ourselves as individuals) would be unwise and

go against the very essence of human nature. As a species, we are inclined to better ourselves and shape nature to our needs and dreams" (Garasic and Lavazza 2024 p320).

1.2. TREATMENT VS ENHANCEMENT

Garasic and Lavazza (2024) observed: "Clinical practice (ie: therapy or care) is generally the restoration (or preservation) of a previous (or average) condition in the population. Enhancement concerns an improvement with respect to average conditions. But it appears overly difficult to draw a line between the two (eg: think of the physiological decay of the elderly)" (p319). A compromise is "therapeutic enhancement, which Jensen (2020) defined as "those interventions that are often performed to return an individual's health/ performance to their baseline but may also increase health/performance beyond the baseline" (quoted in Garasic and Lavazza 2024). Bionics is an example of this (ie: "the replacement or enhancement of organs or other body parts by mechanical versions"; Garasic and Lavazza 2024 p320) (eg: prostheses).

Garasic and Lavazza (2024) described two paradigms relevant to the debate about therapy/treatment versus enhancement. First, the "paradigm of availability", which takes the view that "once a drug, medical technique, device or prosthesis is available, one sees no reason why it should not be used since it has been presumptively made for the purpose of human well-being" (Garasic and Lavazza 2024 p321). This can be described as the user's point of view. Second, the "paradigm of possibility of therapy", which is the researcher's point of view. This is the idea that the motivation of biomedical research is "to find applicable solutions in medicine" (Garasic and Lavazza 2024 p321).

The distinction between using technological developments to treat existing disease versus the enhancement of healthy individuals is seen by many as a cut-off point, but this is blurred if technology is used in disease prevention. Talking about human gene-editing, Juengst et al (2018) noted the issue (not a new one) of whether it "should restrict itself to medical goals or also seek ways to improve on normal human traits" (p351). These authors continued: "Society has been debating the ethics of enhancement as a boundary problem for medicine for decades. Cosmetic surgery, using biosynthetic growth

hormone to increase children's stature, or the use of steroids to improve athletic performance have all raised similar concerns. These practices pose the question of whether they stray from the goals of proper medicine to implicate physicians in different social vices, from sexism and unfair competition to unnecessary health risks" (Juengst et al 2018 p351).

One problem for the therapeutic use of technologies is what is normal that is being restored. For example, Grover et al (2022) found that transcranial stimulation improved the memory of older adults (in their 60s to 80s), while the "greatest effects occurred in individuals starting from a lower baseline. These results, obtained with an inexpensive and easy-to-use tool, are prompting many people who do not have cognitive deficits to turn to devices developed as clinical tools to improve their intellectual or even sport performance... The very possibility of improving the average cognitive abilities without risk or excessive effort is also prompting the conception of new social scenarios in which enhancement becomes commonly accepted or even required in some specific contexts" (Garasic and Lavazza 2024 p324).

Garasic and Lavazza (2024) ended: "A universalistic principle of therapy (ie: the possibility for everyone to receive treatment when needed) as opposed to enhancement, which is selective and less inclusive, may ultimately be a good compass to guide ethical analysis and operational decisions at the boundary between clinical practice and individual improvement" (p328).

1.3. ETHICS OF GENETIC ENHANCEMENT

"Human enhancement occurs when we improve an existing capacity, or create a new capacity, so that we can perform a task better or our lives as a whole go better. Depending on how we define the term, enhancement can be intentional or accidental" (Anomaly and Johnson 2024 p145) [1]. This definition allows a story of human

[1] Anomaly and Johnson (2024) stated: "According to Allen Buchanan, 'A biomedical enhancement is a deliberate intervention, applying biomedical science, which aims to improve an existing capacity that most or all normal human beings typically have, or to create a new capacity, by acting directly on the body or brain' (2011...). This is a useful general account. But whether we want to define enhancements as merely attempts to improve existing capacities or as successful attempts at improvements will probably depend on the context of debate. We might also want to distinguish between improvements in performing a task that are incidental to the main goal of the enhancement, and those that are fully intended. For instance, the same change to a gene that can confer resistance to HIV (which me might

progress and enhancement from the first use of fire and tools onwards. "Modern debates over enhancement usually focus on intentionally altering ourselves through medicine, surgery, or genetic engineering" (Anomaly and Johnson 2024 p145). In the latter case, selection of eggs or sperm, and gene editing are the main forms of enhancement [2].

Anomaly and Johnson (2024) considered the the ethics of genetic enhancement. The concepts of a "positional good" and an "all-purpose good" are important here. The former is "one whose value depends on how many other people have it, and how much of it they have. For example, height is a positional good in the sense that not everyone can be tall, and taller men (up to some threshold) are often considered more attractive to women than shorter men. Height may be a possible genetic enhancement that some parents would pursue for their children" (Anomaly and Johnson 2024 p146). An all-purpose good is "one whose value does not depend on how it is distributed in a population. For example, a healthy heart is good for us regardless of whether other people's hearts work well" (Anomaly and Johnson 2024 p146). Positional goods can be purchased by those with money and so creates inequalities as poorer individuals cannot afford them.

One solution would be to restrict the purchase of the positional goods (in this case, genetic enhancements). But this may mean the development of a "black market", which is even more based on who can pay, and so inequalities would increase (Anomaly and Johnson 2024).

Alternatively, state subsidies could be offered for enhancement technologies where individuals cannot afford them [3]. "Deciding which procedures to subsidise (or penalise) would probably require us to sort out which are likely to produce positive externalities – benefits for other people in a population – and which are likely to have negative externalities" (Anomaly and Johnson 2024 p147).

Genetic enhancement is often distinguished from treatment with genetic technologies. The latter refers to the "reduction" of a disease, whereas enhancement is the

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term a 'genetic immunisation' enhancement) can also improve memory function" (p152).

[2] Pre-natal gene editing (ie: gene editing while the foetus is in the uterus) was reported in monkeys in late 2024 for a specific inherited condition that affected tissues (but this condition could not be diagnosed until well into the pregnancy) (Le Page 2024).

[3] Silver (1997) speculated about the future of genetic engineering leading to two distinct human species - "Genrich" (who have made use and benefitted from the technology) and "Naturals" (who have not) (Agar 2024).

improvement of a "healthy" trait. Medical ethics tend to favour gene editing for treatment rather than enhancement, but "both types of genetic manipulation might improve how well a person's life goes, or their capacity to perform a certain task" (Anomaly and Johnson 2024 p147). Resnick (2000), for example, found the treatment-enhancement distinction unhelpful. Daniels (2000), however, favoured the distinction. "For example, he thinks that certain disabilities tend to have an especially deleterious effect on people's prospects and that 'fair equality of opportunity' requires that we prioritise eliminating these deprivations more than implementing enhancements when governments design a health care system. Daniels does not oppose enhancement, and he does not think treatments of serious disabilities should always trump enhancements. Instead, Daniels argues that the treatment-enhancement distinction often tracks how scarce medical resources should be allocated in a government healthcare system in which allocation decisions must be made" (Anomaly and Johnson 2024 pp148-149).

When parents make the decision in relation to their child or future child, there is an issue of consent. "Embryos are not decision-makers – they cannot conceive of their own interests, make decisions, or communicate their decisions to consent to an enhancement. Informed consent is usually considered a core principle of medical ethics. Living people can usually give informed consent about whether to enhance themselves. To secure the interests of future people, however, we might rely on proxy consent. Proxy consent occurs when a representative accepts or refuses an intervention on behalf of someone who cannot" (Anomaly and Johnson 2024 p149). But can an embryo be represented by another person? The principle of "procreative beneficence" has been introduced to deal with this question. It holds that "couples should select the child, of the possible children they could have, who is expected to have the best life... based on the relevant, available information" (Savulescu 2001 quoted in Anomaly and Johnson 2024) [4].

Selective genetic enhancement can be viewed as a form of eugenics. This is a "loaded term" because of its

[4] "Changing genes as a parental decision can undermine the child's autonomy. As the child cannot have a say in the matter, this can be a difficult matter. The values the child might choose or the life they might want might not be the same as what their parents imagined. Parents cannot limit their child's future opportunities through enhancements – let alone, as Habermas [2003] warned us, through a designed genetic makeup" (Garasic and Lavazza 2024 p323).

history and its association with "weeding out" certain individuals from the population as a whole [5]. This has been called "classical" or "old" eugenics to distinguish it from "liberal" eugenics, which tends to "focus on individuals and their free pursuit of genetic changes that will improve their or their offspring's lives" (Anomaly and Johnson 2024 p149) [6]. Also genetic enhancement of intelligence, say, for certain individuals may improve society as a whole through the inventions of these individuals (Anomaly and Johnson 2024) (table 1.1).

- Much debate about enhance can be speculative, but sex selection has been a reality for a while. Sparrow (2024) used sex selection as a model for enhancement, making a number of general points, including:

- i) It is not clear generally what each gene or set of genes actually does. Biological males have a Y chromosome, which biological females do not (as a general rule), but what behaviours emerge from the genes on this chromosome? This is a debate about sex differences. "The fact that we are still arguing about sex differences gives us reason to pause when it comes to the confidence with which pundits pronounce that the presence of this or that gene constitutes – or would constitute – an enhancement. If we cannot agree on the nature and classification of the differences associated with sex, what hope do we have of agreeing on whether some proposed new gene or set of genes would constitute an enhancement?" (Sparrow 2024 p105).

- ii) If it is possible to change the genetic sex of an embryo (eg: replacing a Y chromosome with an X chromosome), is that enhancement? From a biological point of view, female humans have health advantages over males (eg: live longer; the ability to become pregnant), but from a social point of view, "most societies are systematically unjust when it comes to the treatment of, and opportunities available to women, there are a number of advantages associated with being born male" (Sparrow 2024 pp108-9).

Table 1.1 - Sex selection.

[5] "According to Allen Buchanan et al (2000...), 'Eugenics is mostly remembered for the outrages committed in its name. Terrible as they were, however, these wrongs do not, in themselves, tell us about the validity of eugenic moral thinking…For the history of eugenics to be instructive in ensuring social justice in a society with greater knowledge about genes, and perhaps some ability to alter them, the key question is whether eugenics was wrong in its very inception. Our review finds that much of the bad reputation of eugenics is traceable to attributes that, at least in theory, might be avoidable in a future eugenic program'" (Anomaly and Johnson 2024 p152).

[6] Eugenics had strong support in the early 20th century. For example, geneticist Charles Davenport founded the "Eugenics Record Office" in the USA in 1910 "to improve the natural, physical, mental, and temperamental qualities of the human family" (quoted in Chiong and Austriaco 2024).

There is a concern that this points to selection against embryos perceived as having a disability. Shakespeare (eg: 2014) has written particularly about this concern, both in terms of how disability is conceptualised in society, and the impact on individuals living with disability. The latter has been called the "expressivist objection", and "it claims that selecting against disabilities expresses a disvalue of the lives of those living with a disability. The potential effects of reducing the number of people living with disabilities are important to consider, but the objection rests on a controversial foundation: that a disability is part of a person's identity, thus that eliminating disabilities expresses disvalue toward those identities. Where disability is a state and not a part of identity, this objection to pursuing enhancement may not apply" (Anomaly and Johnson 2024 p151).

To understand public attitudes towards enhancement, Bostrom and Ord (2006) developed the "reversal test". The aim was to see if attitudes are biased towards the present. They explained: "When a proposal to change a certain parameter is thought to have bad overall consequences, consider a change to the parameter in the opposite direction. If this is also thought to have bad overall consequences, then the onus is on those who reach these conclusions to explain why our position cannot be improved through changes to this parameter. If they are unable to do so, then we have reason to suspect that they suffer from status quo bias" (Bostrom and Ord 2006 quoted in Anomaly and Johnson 2024).

Anomaly and Johnson (2024) gave this example: "Suppose a couple is using IVF [in vitro fertilisation] and selecting from multiple embryos. Suppose also that the embryos are identical except that one has below-average intellectual capacities ('intelligence' for short), one has average intelligence, and the other has above-average intelligence. If they select the embryo with average intelligence, they are selecting against both high and low intelligence. Unless they can provide a reason for doing so, they seem to be exhibiting status quo bias. They might be motivated by a heuristic that leads them to believe average capacities are ideal for living a good human life. Or they might think deviations away from the average tend to be bad for human welfare (which could, of course, be true, given some uncertainty about what large changes will bring). Either way, they need a theory of why they are selecting in one direction

or another" (p148).

1.4. CRISPR

The CRISPR genome editing technology allows for the genetic manipulation of offspring, "thus fulfilling the aspirations of liberal eugenicists" (Chiong and Austriaco 2024 p154). Agar (2004) argued for such "design" of humans. Chiong and Austriaco (2024) countered that "a liberal society that seeks not to harm anyone should reject germline genome editing with CRISPR because we can never perform the appropriate benefit-risk analysis that would prevent parents from harming their enhanced offspring with germline gene editing" (p154).

"Clustered regularly interspersed short palindromic repeats" (CRISPR) is "a family of DNA sequences that are found in the genomes of single-celled bacteria. In nature, these DNA sequences are derived from the genomes of bacterial viruses called bacteriophages that had previously infected the bacterial cell. This preserved copy of viral DNA enables the bacteria to detect and defend themselves from future bacteriophage attacks using a molecule called Cas9, an acronym for 'CRISPR-associated protein 9'" (Chiong and Austriaco 2024 p155). The upshot is the ability to alter DNA by "programming" Cas9 to target particular DNA sequences.

It can be used to genetically engineer non-reproductive or somatic cells with an inherited mutation as well as reproductive cells or gametes that produce offspring [7]. The latter is germline gene therapy. "In principle, a couple could now use the CRISPR molecular machine to edit the genomes of their sperm or their egg or their embryo to conceive a child with a set of desired characteristics" (Chiong and Austriaco 2024 pp155-156) [8].

Agar's (2004) argument in favour of this therapy revolved around parental choice, as long as it does not cause harm - ie: cause suffering or to infringe on the

[7] It was predicted that CRISPR therapies will be too expensive for ordinary use after the first treatment was developed for sickle cell disease by Vertex Pharmaceuticals in 2023 (The leader 2023). One solution to keep costs down is to take cells from a single donor and gene edit them to use with different patients. This is the idea of "off-the-shelf" cells (Le Page 2023). Cheaper therapies would encourage their use more generally, but Matthew Porteus of Stanford University noted that "rolling out CRISPR cures en masse would also require everything from training people to building infrastructure to industrialising the manufacture of the required components to having regulations that ensure safety without being too onerous" (quoted in Le Page 2023).

[8] Using CRISPR to fix mutations in sperm stem cells could overcome infertility, and Ephrat Levy-Lahad of Shaare Zedek Medical Centre in Jerusalem saw this as "a compelling reason for heritable genome editing" (quoted in Le Page 2023).

freedom of choice in the future of offspring (Chiong and Austriaco 2024).

The arguments for and against germline gene therapy with CRISPR centre around a number of points, including (Chiong and Austriaco 2024):

a) Whether experiments with non-human animals and germline gene editing give sufficient information for a proper risk-benefit analysis in relation to children.

b) IVF is a good model to follow. It was adopted with limited benefit-risk assessment at the beginning, but it is now common and well accepted.

c) The fear of "underground" or "rogue" use of human germline gene editing [9]. This should encouraged regulated use.

There are also "unintended or inadvertent enhancements" (Agar 2024). For example, "gene-editing efforts to prevent Alzheimer's disease by controlling the species typical rate of senescence" (Juengst et al 2018 p353). Juengst et al (2018) preferred the term "incidental enhancement", explaining in more detail the about the Klotho protein research: "The stated goal of this research is to develop somatic human gene-editing interventions to prevent age-associated degenerative neurological conditions such as Alzheimer's disease by controlling and reversing neurological demyelination. However, upregulating the Klotho gene has also been shown to enhance cognition in mice and to increase murine life-span by as much as 30%. If the same pleiotropic effects were predictable for Klotho editing in humans, it might mean that in the course of preventing neurological decline, we could also improve people's cognitive capacities, as well as extend their lifespans" (pp352-353).

Agar (2024) pointed out also that "[T]he age of human enhancement brings the possibility of enhancements that may be intended but where, for political reasons, the intention to enhance may be disclaimed. This could mean that enhancements in the early stages of the age of human enhancement are more likely to evade ethical scrutiny" (p15).

[9] A real-life cautionary tale was that of He Jiankui, who in 2018 used CRISPR-Cas9 to modify a gene in female twins while still embryos in order to create more resistance to HIV. He was fined and jailed in China. Subsequent research has suggested that the changes in the gene in question shortens lifespan (Garasic and Lavazza 2024).

1.5. AGEING ENHANCEMENT

"Ageing enhancement" is a term describing the application of scientific advances to human ageing. Considering the bioethics involved, Farrelly (2024) asked: "Is it morally permissible, indeed even morally obligatory, to aspire to alter human ageing by retarding the biological processes that make human bodies and minds susceptible to chronic disease, frailty, and disability in late life?" (p162).

This author summarised the ethical issues into four specific questions:

i) "Is extending life natural?" - Life expectancy has increased over the recent centuries through better diet, and disease control, for example ("natural" ways), but the specific application of scientific advancement to lengthen life is presented as "unnatural" by critics.

Concepts like "slowing ageing" and "conquering death" are often used by advocates. But "pursuing immortality, counter critics, "in taking the ageing of the body as itself a kind of disorder to be corrected, it treats man's mortal condition as a target for medicine, as if death were indeed rather like one of the specific (fatal) diseases. There is no obvious end-point to the quest for ageless bodies: after all, why should any lifespan, however long, be long enough?" (President's Council on Bioethics 2003 quoted in Farrelly 2024). Furthermore, there are concerns about "succumbing to the seductive promises of biotechnology, the promises of 'a perfect, better-than-human future, in which we shall all be as gods, ageless and blissful' [Kass 2003]" (Farrelly 2024 p164).

Farrelly (2024) viewed the argument around immortality as unhelpful. He stated: "Death is inevitable, but it is deeply problematic to suggest that attempts to prevent specific causes of death (eg: cancer, starvation, or automobile accidents) – which would have the effect of 'extending life' – are objectionable because they are in some sense 'unnatural'" (Farrelly 2024 p165).

ii) "How long should humans live?" or "How long is enough life?" - Callahan (1998) took a clear stance: "The average person in good health in the developed countries of the world (and living in a reasonably safe environment), already lives long enough to accomplish most reasonable ends... Neither the human species as a whole, nor most individuals, need more than the present

average life expectancy in the developed countries (the mid-seventies to low-eighties) for a perfectly satisfactory life. This idea of a steady-state life expectancy at its present level would establish, happily, a finite and attainable goal: 'Enough, already'" (quoted in Farrelly 2024).

There is a difference between prolonging life in any state of health, and prolonging healthy life. The latter seems a more desirable goal.

iii) "Can we justify trying to extend the lives of those who have more already?" or "What about equality?" - Whatever the aims of those who attempt to prolong life, the reality is that ageing enhancement benefits individuals in rich countries (not poor), and rich individuals within those countries. In this sense, ageing enhancement becomes a global justice issue.

Two counter-arguments are that health inequalities are based on genetic and physiological differences rather than socio-economic ones, and an "anti-ageing pill" could be cheap and widely available for all (Farrelly 2024). Farrelly (2024) argued that research on ageing should not stop, rather equal access should be the debate.

iv) "Should we aspire to prevent disease (eg: cancer, heart disease, and stroke), frailty, and disability at all stages of the human lifespan?" or "Why promote public health?" - Farrelly (2024) asserted: "To help protect persons from infectious and chronic diseases in late life, public health must prioritise the effort to alter the rate of biological ageing so that the average person can enjoy more healthy years of life, and compress the period of time spent with multi-morbidity, frailty, and disability. An ageing enhancement is likely to be among one of the most important advances in public health in the 21st century" (p173).

DiPaola and Garasic (2013) imagined a "feasible" life extension to 500 years. Garasic and Lavazza (2024) outlined "two deeply problematic scenarios" as a consequence: "First, we would damage the planet and future generations with a drastic increase of the world population. Second, we would likely find ourselves in a situation in which only a few wealthy individuals might have access to a biotechnologically induced longevity, and this would worsen discrimination. The impact would affect future generations as well as the distribution of resources across already existing individuals on the planet. Notably, a single person living 500 years would

consume resources such as air, water, and food in the same amount that would have otherwise supported the existence of six or more generations of people" (pp326-327).

1.6. COGNITIVE ENHANCEMENT

Cognitive enhancement (CE) [10] can be defined as the "[A]mplification or extension of core capacities of the mind through improvement or augmentation of internal or external information processing systems" (Sandberg and Bostrom 2006 quoted in Forlini 2024). Forlini (2024) pointed out: "This definition accommodates a range of interventions that can be behavioural such as sleep, nutrition, and education, or technological, such as pharmacology, supplements, and brain stimulation... However, it is mainly the technological interventions that are at the centre of ethical controversy as to whether they are coercive, fair, safe, and align with an individual's authentic self" (p202) [11] [12] [13].

Artificial intelligence (AI) can be used to achieve human enhancement through, what Erler and Muller (2024) called, "intellectual augmentation" (IA). This is distinct from AI as a tool. For example, a calculator, "while helping us reach the correct result when performing a complex multiplication, nevertheless does not do so by improving our mathematical abilities or general cognitive functioning. Rather, the calculator relieves us of the need to engage in mathematical reasoning by performing that task for us" (Erler and Muller 2024 p189).

Erler and Muller (2024) laid out the issues related

[10] Wu (2024) noted more than one thousand academic papers on CE since 1990.

[11] "It is intuitively appealing to ingest pharmaceuticals to make ourselves better at doing things efficiently and correctly. Roughly speaking, there has been a long history of using drugs to enhance cognition such as memory, attention, response speed, decision-making correctness, etc of healthy people in different cultures. For example, ephedrine was used in China, khat in North America, and coca in South America... Around the early 20th century, amphetamine and cocaine were deemed good medicines for treating depression and enhancing cognition in Western countries" (Wu 2024 p340).

[12] Common substances can produce some degree of CE, like nicotine and caffeine, while pharmaceuticals for specific conditions can be "repurposed" with healthy individuals (eg: acetylcholine inhibitors for dementia; amphetamine-based medications for ADHD) (Wu 2024).

[13] Wu (2024) commented that common pharmaceuticals "could have prominent effects in helping those with cognitive deficits to recover or maintain their neurotypical cognitive functions, but their cognitive enhancement effects are often modest and non-linear in healthy persons. The human brain has limited resources and energy; when one cognitive function is enhanced, another might be suppressed (eg: focus vs flexibility). Therefore, it is certain that no magic pill with comprehensive enhancement effects exists" (p351).

to AI as IA:

i) "Devices not performing as expected" - "AI advisors" vary "virtual assistants" on smartphones that provide information for everyday decisions through to "robo-advisors", algorithms that make decisions based on large sets of data. With such advisors "the quality of the advice provided by such a system could in principle fail to meet the standards promised by its manufacturer. This could happen either because of inadequate design, over-hyping of existing technical capabilities, or because the company selling the device had purposefully programmed it to nudge users toward courses of action that were favourable to its own interests, or those of its business partners, even when these were not fully in line with a user's ethical commitments" (Erler and Muller 2024 p193).

ii) Safety - eg: invasive brain-computer interfaces (BCIs) (table 1.2) where implanted electrodes in the brain connect to a computer.

iii) Coercion - eg: bi-directional BCI allows control of a computer, but also electrical stimulation of the brain. Or requiring employees to wear non-invasive BCI headsets to monitor their performance.

iv) "Privacy and cognitive liberty" - eg: the collection of data whether the manufacturer's of virtual assistants recording conversations to improve the AI's performance or the measuring of brainwave patterns of BCIs. Also devices can be "hacked" by unauthorised parties.

v) "Authenticity and mental atrophy" - Outsourcing moral decisions, say, to AI does not necessarily improve our moral reasoning because "it would be delivering the end result of such reasoning 'on a plate', circumventing the need to effortfully work things out for ourselves. In fact, one might fear that regularly outsourcing moral and prudential reasoning to AI advisors would cause our own capacity to engage in such reasoning to atrophy due to insufficient practice. IA would then entail a form of regression..." (Erler and Muller 2024 p196).

vi) Fairness - There is already signs of a "digital divide" (Ragnedda and Muschert 2013), which is furthered between those who have AI for enhancement and those who do not. But also fairness is an issue in AI decision-

making because an algorithm has to learn from existing data, at least initially, and the original data could lead to "algorithmic bias". "Even without any intention on the part of their designers, AI advisors could exhibit biases in their recommendations that unfairly disadvantaged certain social groups, whether as a result of the procedure used to issue those recommendations, or of the data on which they would be relying. A health AI advisor, for instance, might not provide equally reliable input to users from ethnic minorities, if the data used to train its algorithms did not feature enough members of those under-represented groups" (Erler and Muller 2024 p198).

- BCI is part of the concept of symbiosis between humans and AI, which, Furlanis and Gilbert (2024) argued, has three characteristics - the relationship is more than humans have with tools; the relationship allows humans to transcend normal limitations; and the human's sense of self is changed.

- In relation to the latter, "the human subject can experience the device becoming part of them, a part of their bodies and their personal selves" (Furlanis and Gilbert 2024 p228). Kenneally (2021 quoted in Furlanis and Gilbert 2024) described the experience of BCI as "we were calibrated together", "we became one".

Table 1.2 - BCI.

What do individuals feel about CE, and AI and IA? There have been studies to measure attitudes, and views on ethical issues, as well as actual use. For example, Schelle et al (2014) reviewed a number of studies, and found that "medical safety, coercion, and fairness are the most recurrent and ethically contentious topics across a range of stakeholders (eg: students, professionals, and the general public). Indeed, these three topics continue to be discussed in subsequent empirical research" (Forlini 2024 p205) (table 1.3).

Ambivalence in attitudes towards CE has been observed in research. For example, students finding caffeine to boost cognitive performance acceptable, but not prescription stimulants (Forlini 2024).

One problem with the research on CE is the limited representation of diverse communities. "The range of social, racial, professional, economic, and geographical contexts represented is narrow. There are prevalence studies from Africa, Asia, Europe, North America,

- Garasic and Lavazza (2024) gave the example of surgeons improving their performance through cognitive enhancement: "If cognitive enhancers were optional, considering the ubiquitous quantifications of performance in our society, good surgeons unwilling to use cognitive enhancers would either be pushed to use them under peer pressure or be ostracised for not being 'as committed' as their enhanced colleagues (with the risk of losing many excellent and valuable professionals)... If the use were instead to be compulsory, the problem would be related to the impact on society more broadly. Would people be forced to cognitively enhance themselves so as to be able to be more alert during longer shifts (while being paid the same)? (Garasic and Lavazza 2016)" (Garasic and Lavazza 2024 p326).

Table 1.3 - What if everybody else is enhancing?

Oceania, and South America, which confirm that CE happens in many parts of the world... However, existing prevalence data remain piecemeal across the globe leaving the extent to which CE needs to be a global concern currently unanswerable. From an empirical ethics perspective, the type of stakeholders recruited for studies is repetitive. A review of literature on the social context of CE, 'found that research efforts have chiefly targeted college students, yet there is a lack of knowledge concerning other social groups likely to use these pharmaceuticals non-medically, such as persons with high strain employment' (Robitaille and Collin 2016...)" (Forlini 2024 p207). Convenience samples recruited online is also a problem here.

Forlini (2024) added another problem in that the data were collected "in an anticipatory fashion based on what ethical issues might arise rather than the major problems that individuals and institutions are grappling with" (p210).

What is it that is being cognitively enhanced? Controlled studies with pharmaceuticals tend to restrict the scope to measurable and standardised tests. Wu (2024) noted that emotional enhancement (eg: increased motivation) can be as important as CE, as well as moral enhancement effects in such studies.

The fear that neurotechnology will take over our brains is some way can be challenged by the "extended mind hypothesis" (eg: Carter and Pritchard 2019), which likens CE to external tools, like calculators and notepads. Gligorov (2024) pointed out that "the use of cognitive enhancers that cause changes to cognition within the boundaries of the human organism can be properly incorporated into cognition and do not violate

cognitive character or undermine knowledge acquisition" (pp214-215).

Clark and Chambers (1998) described the case of "Otto" who carries a notebook to compensate for a waning memory. "When he needs to, Otto utilises his notebook to gain access to facts that aid him in making decisions regarding what to do next, such as how to get to the grocery store. Clark and Chalmers argue that Otto's notebook becomes part of his cognition" (Gligorov 2024 p218). The "extended mind hypothesis" takes "the view that tools external to the person's biological organism can become incorporated into their cognitive function. This argument can then be used to argue that certain types of cognitive enhancers can become incorporated into an individual's cognitive character, rebuffing the view that the use of enhancers in some way undermines cognitive agency" (Gligorov 2024 p218). The issues then becomes what is meant by "cognitive agency".

The alternative view (eg: Harris 2011) is summed up by the "axiological objection" (Carter and Pritchard 2019). This is that "cognitive enhancement removes the obstacles required for cognitive achievement in a way that renders the acquisition of knowledge trivial... Based on the axiological objection, cognitive enhancers diminish cognitive achievement by improving our biological ability to remember or by supplementing memory through the use of smart technology and thereby removing the difficulty inherent in mastering any given subject" (Gligorov 2024 p217).

Whatever can be achieved now, there is always speculation about the future of CE. Higgins et al (2024) applied "anticipatory ethics" with the aim "to identify and prevent harmful consequences before they emerge" (p237). They continued: "It can be difficult to regulate or unwind practices once they have been established in society. Anticipatory ethics encourages researchers and developers to engage in a design process that considers ways in which harms can be minimised or prevented. Harms are often realised only after a technology has been disseminated, by which time addressing or mitigating these harms can be expensive or impossible. It is imperative that ethical harms be vigilantly anticipated in the development of novel products with an eye toward who these harms might affect" (Higgins et al 2024 p238).

At the same time, exaggerated claims and speculations are not helpful. One area of CE that is prone to much speculation is BCI. In a review of media articles on BCI, Gilbert et al (2019) found that around

three-quarters were positive, with the most positive using terms like "super brains" and "thought control". "Gilbert et al's findings suggest some journalists are too quick to embrace the notion of a transparent mind that can be read by a BCI, which 'reduces our utmost secretive thoughts to a mere package of exportable and importable qualia'. In reality, invasive closed-loop BCIs that decode and respond to an individual's unique brain signals are largely being explored in the therapeutic realm" (Higgins et al 2024 p242).

Higgins et al (2024) were clear: "Ethicists must express realistic concerns about the potential harms of emerging technologies. Critics of speculative ethics have argued that 'rather than credulity, we should employ scepticism; rather than taking a paper's conclusions for granted, we should interrogate them; rather than detaching from the science, we should engage with it' (Wexler 2019)" (p244). Adherence to the current scientific data is important as the basis of where we can go with neurotechnology. Wexler's (2019) article was entitled, "separating neuroethics from neurohype"; good advice.

1.7. MORAL ENHANCEMENT AND TRANSHUMANISM

The belief that the body and mind can be improved is the foundation of transhumanism, which Bostrom (2005 quoted in Ach and Beck 2024) defined as "an interdisciplinary approach to understanding and evaluating the opportunities for enhancing the human condition and the human organism opened up by the advancement of technology". While Loh (2020 quoted in Ach and Beck 2024) pointed out: "The transhumanist method is technological transformation of the human being into a post-human being. [...] Human evolution is regarded as generally uncompleted" [14]. Fukuyama (2004 quoted in Ach and Beck 2024), however, was critical of transhumanism as "the world's most dangerous idea".

Transhumanists' desire is to completely change humans, which means to change "human nature" (whatever

[14] Advocates of enhancement can fall into "moral marketing" (an overselling of the benefits for the future), particularly if a date not far off is added (eg: 2045 for "optional immortality", according to Kurzweil 2005) (Agar 2024). Agar (2024) responded: "On the face of it, there's nothing wrong with offering an exciting vision of the way the world could be in the future. Kurzweil's story about optional immortality and magnificently enhanced intellects does not seem to violate any law of physics or logic. It describes a thrilling way things could turn out. We should nevertheless recognise such stories as moral marketing rather than as enabling the dispassionate assessment of the likely benefits of enhancement that we need in the age of human enhancement" (p14).

that might be). Supporters take a perspective that could be called the "creativity framework" - ie: there is no pre-given human nature and so we can create ourselves (Ach and Beck 2024). Critics might be said to take the perspective of the "gratitude framework" - "human nature consists in a pre-given, essential 'true self' which can and must be identified and nurtured – both on an individual level and on a collective level of human existence – and must not be interfered with. The transhumanist aim of improving or even overcoming (biological) human properties and capacities by technological means obviously contradicts this assumption. Since human nature is a precious gift, we must be true to it and value its giftedness..., instead of trying to interfere with nature and 'playing God'" (Ach and Beck 2024 p270).

Ach and Beck (2024) framed the debate about changing human nature in this way: "In the end, the whole debate about transhumanism may be regarded as much ado about nothing – or at least little: if one understands human nature in terms of our current biological condition, the idea of overcoming this nature is of little normative interest... If, on the contrary, one conceives of human nature in metaphysical terms, the question arises, whether transhumanism is not just the idea of a radical, technologically shifted realisation of this very nature" (p270).

Moral enhancement is a core idea in transhumanism.

"Moral enhancement" is "the endeavour to improve (moral) behaviour through direct brain intervention" (Muller 2024 p253) [15]. This could vary from methods to reduce and remove negative aspects of humanity (eg: sadism; prejudice) to improving altruism and other positive characteristics. Many such ideas are theoretical, and the debate has "shifted from grandoise, humanity-saving goals to crime control" (Muller 2024 p254). The methods used include drugs and neurosurgery.

Muller (2024) considered the ethics of moral enhancement through neurosurgery. The first problem is what moral enhancement is changing [16]. The idea of "moral

[15] Wiseman (2024) preferred the term "moral bioenhancement (MBE), which was defined as "the use of any technology or pharmacology on human biology in order to produce some morally-relevant effect. The targets of enhancement are generally taken to be human drives, capacities, and powers of any sort, and the ideal would be to diminish the morally problematic things persons do and to facilitate the morally good things persons do" (p293). James Hughes (2006 quoted in Wiseman 2024) used the phrase "virtue engineering".

[16] DeGrazia (2014) distinguished between "motivational improvement", "improved insight", and "behavioural improvement" (Ach and Beck 2024).

intelligence" (eg: Tanner and Christen 2013) could be used, and this includes skill-based aspects like moral problem-solving, moral sensitivity, and moral commitment (Muller 2024). The assumption is that moral dysfunctions are caused by brain dysfunctions (eg: Fumagalli and Priori 2012 talked of a brain network called the "moral brain"). Thus, neurosurgery to rectify the brain dysfunction would rectify the moral dysfunction.

A practical example would be reducing hyper-aggression by removal of the amygdala, which has been tried with humans and non-humans. There have been some successes (Muller 2024).

Another use is neurosurgery on the hypothalamus, say, to reduce or control pathological sexuality. There are historical cases with paedophilia, and, now viewed negatively, with homosexual men (eg: "conversion therapy"; Moen and Heath 1972) (Muller 2024).

A third area of use is with psychopathy (eg: "moral reconditioning"; De Ridder et al 2009).

Muller (2024) stated: "All of the neurosurgical interventions proposed to date are intended to improve the ability to behave in a morally correct manner despite external or internal resistances or temptations. This is to be achieved in two fundamentally different ways: (1) temptations are to be reduced by attenuating aggressive or sexual impulses, or 'immoral stimuli', or by automatically suppressing them in a situation-specific manner (interventions in the limbic system, particularly in the amygdalae or in the hypothalamus). (2) The self-control (resistance to temptation and suppression of impulsive responses) is to be improved (by interventions in the DLPFC [dorso-lateral prefrontal cortex])" (pp259-260). She recommended the second way to "improve steadfastness", but whether it is possible with current knowledge is another issue. Muller (2024) lamented the lack of empirical evidence.

This is the "can", what about the "ought" ("is moral enhancement through neurosurgery ethically justifiable?") (Muller 2024). "Whether and to what extent neurosurgical interventions for moral enhancement are ethically justifiable depends, among other things, on whether the person concerned is of age, capable of giving consent, and living in freedom (ie: not in custody, forensic placement, or preventive detention). Furthermore, it depends on whether the intervention is chosen by the patient, forced upon him or her, or even carried out forcibly against his or her will. [...] A person may have reasonable and rational reasons to undergo neurosurgery to make certain socially or morally problematic

behaviours less likely in the future... Examples that can be considered include the notorious adulterer who desperately wants to be faithful, the hot-tempered father who repeatedly beats his children even though he does not want to, or the paedophile who morally condemns his sexual preference and fears committing crimes" (Muller 2024 p260).

Where the moral behaviour is penalised by society (eg: imprisonment), stopping the individual performing the behaviour could enhance their life. "According to humanistic ethics, moral enhancement would only be acceptable if it not only increased the individual's freedom of action (eg: thanks to release from prison) but also his or her freedom of will or capacity for self-determination. The latter would be increased if impulse control and thus moral steadfastness were improved but not if merely aggressive or sexual impulses were reduced or automatically downregulated" (Muller 2024 p262).

Wiseman (2024) proposed a number of arguments for and against moral enhancement/MBE (table 1.4).

FOR:

- i) "Wouldn't it be nice if" the bad side of humans could be curbed.
- ii) "Enhance or die" - The belief that humans are innately self-destructive, and failure to enhance will lead to extinct.
- iii) "Free to enhance" - A libertarian position that individuals should be free to improve themselves if they want.
- iv) "Evil is a disease to be treated" - Extreme immoral behaviour is a sickness to be treated like any other disease.

AGAINST:

- i) "MBE is not desirable" - For example: "Thinking of moral issues as biological defects and regarding persons as mechanical devices whose moral errancy is nothing more than a technical problem serves to reduce the human person to the level of machines" (Wiseman 2024 p299).
- ii) "Ought implies can" - It is one thing to argue in favour of MBE, but it is another as to whether MBE is possible. Persson and Savulescu (2008) observed: "A moral enhancement of the magnitude required to ensure that this [ultimate harm] will not happen is not scientifically possible at present and is not likely to be possible in the near future" (quoted in Wiseman 2024).

- iii) Context - "what is morally good in one context can be morally problematic in another. Mercy is a clear example of how context in part constitutes what makes for moral goods, the manner in which some moral goods stand in a necessary relation to others. Mercy, if shown in the right circumstances, shows excellence of character. However, when a parole board, for example, is considering the case of a sadistic, predatory sex offender, questions of mercy become more problematic. Mercy is not good in and of itself, and it does not have some unique definition or singular expression through which it can be wisely deployed. Depending on context, mercy takes different meanings and different forms, and sometimes needs to be withheld" (Wiseman 2024 p300).

- iv) "Biologising morality" - "there is no direct link between biological processes and the concrete expression of a moral good. This is a crucial point. There is just too much variation in what counts as empathy, generosity, compassion, and so on, to directly map these expressions onto some imagined biological source – as if to say: here is the gene for empathy, here is the neuronal pathway for compassion (whose version of empathy? Whose version of compassion? In what time and in what place?). Concrete expressions of moral goods do not map onto biology in this way at all – there is just too much conceptual mediation between biological source and concrete expression" (Wiseman 2024 p301).

Table 1.4 - Key arguments for and against moral enhancement/MBE.

Wiseman (2024) favoured a "realistic MBE" that tinkered in a small way with certain behaviours, while taking account of social, personal, and biological dimensions of the problem.

1.7.1. Future Generations

Crutchfield (2024) argued that future generations are more likely to suffer from the current generations' collective action (eg: harming the planet) than current generations have suffered from past generations' actions. Therefore, enhancing current generations will benefit not only ourselves but future generations. Crutchfield (2024) stated that "we (currently living adults) have a moral duty to protect the well-being of future generations and can only do so by undergoing widespread enhancement of our cognitive and moral capacities" (p283).

One issue is around the duty current living individuals have to future generations. This can be seen as a duty to protect as well as a duty to non-maleficence (eg: not to harm future generations by depleting

resources). The duty to protect can be expressed in the "vulnerability model" (Goodin 1985). "According to the vulnerability model, one person has a duty to protect another when the latter's interests and their satisfaction are vulnerable to the former's actions. A child's interests are vulnerable to the actions of their caregivers. An elderly parent's interests are vulnerable to the action of their adult children. Adult children thus have a duty to protect their elderly parents (and, arguably, the adult child never voluntarily assumes that relation). Passengers on a ship are vulnerable to the actions of the captain, so the captain has a duty to protect her passengers" (Crutchfield 2024 p285).

It is assumed that moral enhancement now will help us to understand the issues for future generations (ie: this is the knowledge), and to "co-operate" with them. Also it will help in the discipline needed to change behaviours that influence global warming, say, and impact future generations.

Crutchfield (2024) ended: "It is beyond most currently living individuals' capacity to contribute to the satisfaction of the duty to protect future generations. Rather than excuse everyone from the obligation, it is better to change what these individuals can do. What they need to do is beyond their reach. Thus, an intervention is required" (p290). Moral enhancement is the intervention recommended by Crutchfield (2024).

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2. ELECTRONIC HEALTH RECORDS

2.1. CLOZAPINE

Clozapine is an anti-psychotic medication with supportive evidence that it is "the most effective drug for treatment-resistant schizophrenia in adults" (Balbuena et al 2024 p572). In fact, it is recommended as the "gold standard" in this situation in some countries. But "the role of clozapine in early-onset schizophrenia (EOS) remains less understood" (Balbuena et al 2024 p572).

Real-world data are crucial in understanding the effectiveness of a drug. Rather than administration of the drug under controlled conditions as in a trial, there is the everyday use as prescribed. One way to study this is the "electronic cohort" (ie: looking back at the electronic health records (EHRs) of patients).

Balbuena et al (2024) did this in Canada with reference to relapses and adverse events with clozapine. The data came from British Columbia, Manitoba, and Saskatchewan provinces for the period 2008 to 2018, and included children, adolescents and adults. The total sample was 45 616 adults and 1476 children and adolescents. The primary outcome measure was relapse (defined as "mental health visits or admissions after being discharged from the initial visit"; p573), while the secondary outcome was adverse events/side effects of clozapine.

Compared to other anti-psychotic medications, relapse was lower with clozapine for both adults, and children and adolescents, but adverse events were comparatively higher for adults.

Balbuena et al (2024) accepted the following limitations to their data: "There were no clinical variables such as age of illness onset, severity of illness and how soon treatment was initiated due to limitations of administrative data on hospitalisations – that is, they do not contain clinician assessments of patient function or validated rating scales. As such, it was not possible to tell how well patients functioned independent of relapse. This also applies to adverse

events: without the benefit of clinical notes, it was not possible to tell if these were caused by clozapine (or other drugs) and what other conditions may have contributed to the hospitalisation. The medication data were not ideal because the number of days' supply of medications was fixed at one month. The study was restricted to three provinces because these provinces enabled a linkage of hospitalisations and pharmacy redemption. Unfortunately, not all the hospitals in these provinces are required to submit all emergency and inpatient admissions to CIHI [Canadian Institute of Health Information]" (pp576-577).

2.2. YOGA

Another study using EHRs, but a different area of health was performed by Penrod and Moore (2022), and their study of the anti-hypertensive effects of yoga. The data were taken from EHRs in the USA - hospitals and outpatient centres in Pennsylvania. The design of the study was case-control method.

The cases were patients who had had regular yoga sessions (n = 1355) and the controls were matched non-yoga patients (n = 8682).

Yoga was associated with lower blood pressure than non-yoga, and the yoga group was more likely to have normal blood pressure for their age. The researchers concluded: "Yoga, as used by patients in their daily lives, may be an effective strategy for blood pressure control and the prevention of hypertension at the population level" (Penrod and Moore 2022 p1).

EHRs are a source of large-scale, real-world data, but researchers who use them as data are dependent on their accuracy (as reported by patients and recorded by medical staff and administrators). This is true of any medical records. It is also secondary data, ie: not collected by the researchers.

The yoga group was based on the inclusion of "yoga" on the EHR, and Penrod and Moore (2022) admitted that "most mentions of yoga are ambiguous, few notes include quantitative indicators like sessions per week or minutes per session, even fewer describe the type of yoga practice which may be important as meditation, independent of other aspects of a yoga practice, has a potential role in cardiovascular risk reduction. An additional limitation of the yoga mentions is the possibility of social desirability bias, individuals may exaggerate their health behaviours to satisfy a

conscious or subconscious need to be viewed favourably by their health care providers" (p7). The researchers explained further: "Yoga is not a single entity, it is a broad term used to encompass many styles and evolutions of an ancient practice, and the effects of any yoga variation on any individual patient will be subjective. By using retrospective, observational data, we presume the patients reporting a regular yoga practice to their health care providers have adopted a style of yoga, a teacher, and a practice environment that resonates with them" (Penrod and Moore 2022 p7).

2.3. PREDICTING SUICIDALITY WITH AI

Predicting future behaviour is a goal of much research, but practically more so with suicidality. Wiest et al (2024) investigated the use of AI and machine learning applied to EHRs in this area.

One hundred randomly selected text-based admission notes of in-patients at a psychiatric hospital in Germany in 2023 were analysed by a large language model. The patients were mostly admitted for diagnoses of major depressive disorder, psychotic disorders, and dementia. The aim was to predict suicidal intention compared to human experts. The algorithm showed around 80-90% accuracy in identifying suicidality (ie: both true positives (risk) and true negatives (no-risk)). A false negative is an individual rated as no-risk when they are at risk, while a false positive is an individual rated at risk when they are no-risk. The researchers commented: "For a clinical application such as suicide risk detection, where false negatives are likely to lead to detrimental outcomes, sensitivity should approach 100%, even at the cost of detecting more false positives, which can be resolved with further human evaluation to ensure no case is missed" (Wiest et al 2024 p535).

This was a proof-of-concept study, which used a binary variable of suicide risk or not, whereas reality may be more nuanced (eg: low, medium, high risk of suicide).

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3. CONSENT AND BIOBANKS

Thompson et al (2025) outlined the situation related to biobanking: "As the collection and interrogation of population-scale data is increasingly positioned as the route to new understandings of health and disease, large-scale biobanks have emerged as essential elements of research infrastructure. While these repositories are designed to collect, store, and manage bio-samples and data to facilitate a broad range of research applications over time, their longitudinal nature (often extending over decades) presents challenges for governance. Health research governance typically relies on a one-off consent model, where participants agree to specific research activities at the outset. Yet, as technological advancements continue to enable new kinds of data collection and analyses, it may not be possible to foresee all future research applications at the time participants join a biobank" (pp1-2).

Using the example of the UK Biobank (set up in 2006), Thompson et al (2025) explored the idea of consent. At the time of enrolment participants gave consent for their medical records to be accessed about their future health (including tissue samples) as well as detailed biographical information and biological samples provided at the time.

Thompson et al (2025) ran twelve focus groups for 94 UK Biobank participants in 2022 and 2023 to discuss consent and data storage and sharing. A vignette about a skin biopsy was used "to discuss cellular tissue that might be stored following a procedure and then discussed in general terms the acceptability of UK Biobank access to health data and samples and the differences between them" (Thompson et al 2025 p3).

Analysis of the transcripts of the group discussions showed that "participants locate responsibility for research decisions with the biobank, rather than seeking control through their consent. They perceive their consent not as a one-off agreement but as the `opening act' for a research relationship with the biobank that can be continued through communication" (Thompson et al 2025 p1). The building of a relationship between participants and research institution was key for these authors.

The fact that tissue samples could be added to the biobank was a surprise to some of the participants, but the majority view was summed up by this quote: "as far as I'm concerned, whatever has been kept and recorded,

whether it's information, pictures, or that little bit of bone marrow, it's all stuff that's on my medical record and I'm happy for Biobank to access it if it's going to be useful" (p4).

However, there was some reservation around pregnancy, as one participant said: "I think there may be things, say you'd had a miscarriage or something like that, I know there has been stuff about babies, parts of unborn children, things like that, that can upset people [refers to both stored tissue and data about such events that would be held in the health record]" (p5). While subjective opinions on medical records was a concern as in this quote: "It could be, I don't know, a sample taken, a cervical smear taken of a young person, and in this written report it says shows promiscuity or something like that... Hope it wouldn't happen now, but 20 odd years ago" (p6).

Note that the volunteers who agreed to participate in the biobank, and who participated in the focus groups may view the issues differently to individuals who did not participate in one or either cases.

REFERENCE

Thompson, R et al (2025) The research relationship: Participant perspectives on consent in biobanking BMC Medical Ethics 26, article 47

4. NEUROFEEDBACK AND TREATMENT OF MENTAL DISORDERS

4.1. INTRODUCTION

Sitaram et al (2023) defined neurofeedback (NF) as "an experimental technique for closed-loop brain training for animals and human participants to self-manipulate their brain signals. NF provides an explicit sensory indicator of a neurophysiological process to enable individuals to modulate activation levels in specific ways to observe its effect on brain function and behaviour" (p1).

NF has the potential to be a non-pharmacological and non-invasive treatment for physical and mental problems (Sulzer et al 2024) (appendix 4A). Underlying NF is the "concept of voluntary control over neural function" (or "endogenous neuromodulation of circumscribed brain circuitry", to use more technical language) (Sulzer et al 2024 p1).

Human NF tends to be "explicit" or "implicit" in the main. Explicit NF involves the participant using a feedback signal of the biological changes that need to be controlled, whereas implicit NF might be, for example, "as part of an experiment, participants can be asked to play a video game whose parameters (level of difficulty, the number of points won etc) change according to the brain activity. Implicit feedback does not provide information about the biological signal to the participant but incorporates indirect interactivity with the participant, thereby influencing the control of brain

activity" (Sitaram et al 2024 p2). "Decoded neurofeedback" (Decnef) is an example of a technique inbetween implicit and explicit NF. During its use "participants know an NF experiment is taking place and receive explicit feedback about the targeted brain activity on each trial; however, they do not know what the feedback and/or how the feedback is related to their task performance" (Sitaram et al 2024 p2).

Sulzer et al (2024) outlined four areas relevant to this topic:

i) Methodological advancements - eg: increased precision of neural targeting.

ii) Mechanisms of action - "How NF works is as yet an open question" (Sulzer et al 2024 p3).

iii) Applications of NF - Studies have investigated the use with depression, tinnitus, brain injury rehabilitation, pain relief, and obsessive-compulsive disorder, for example (Sulzer et al 2024).

iv) Ethical and regulatory issues.

NF has led to the development of brain-computer interfaces (BCIs) and brain-machine interfaces (BMIs). The former are non-invasive techniques, whereas BMIs involved implanted electrodes in the brain. Both BCIs and BMIs are concerned with the control of external devices by neural activity (eg: a cursor on a computer screen) (Sitaram et al 2024).

4.2. METHODOLOGICAL ADVANCEMENTS

Allam et al (2024) outlined a proof-of-concept study using non-invasive, individualised functional magnetic resonance imaging (fMRI) closed-loop neuromodulation (iNM), which has the possibility of application to neuro-rehabilitate cerebral visual impairment (eg: deficits in the perception of complex motion leading to navigational problems).

To explain, "following a lesion, brain regions that previously played the main role to perform visual and cognitive tasks can no longer support this role. iNM is based on using neural plasticity to bypass lesioned visual pathways that can no longer perform visual and cognitive tasks by training intact brain regions to

perform these functions. iNM aims to induce changes by boosting supportive brain regions and/or 'islands' of intact tissue with the goal to at least partially fulfil the brain function previously led by the now-damaged areas. Thus, iNM uses the brain's inherent redundancy..." (Allam et al 2024 p4).

In this study, eight healthy volunteers were asked to discriminate up or down direction of movement of stimuli in the central or peripheral visual field with or without iNM. Initially, fMRI was used to show the brain activity (measured by blood flow to different areas) during the discrimination task. Then a magnetic pulse was administered to particular active areas during neuromodulation.

Functional near-infra-red spectroscopy (fNIRS) is an alternative to fMRI in NF, first developed in the 1990s. Both techniques are haemodynamic in that the learning in response to NF is seen in blood flow to different areas of the brain (Klein et al 2024). Table 4.1 lists the key strengths and weaknesses of fNIRS in NF (Klein et al 2024).

STRENGTHS	WEAKNESSES
1. Lower discomfort in use makes it suitable for sensitive populations. 2. Lower technology level means the equipment is cheaper. 3. Body-posture independence which does not force the user to lie still, for example. 4. Easier application requiring less skilled operators.	1. Similar to fMRI, it is only an indirect measure of brain activity. 2. Limited spatial resolution. 3. Limited brain coverage. 4. The cap or headband worn during use can become uncomfortable.

Table 4.1 - Key strengths and weaknesses of fNRIS in NF.

Impairments in executive functions (EFs) can be addressed by NF; for example, cognitive rehabilitation after stroke, and in dementia. But there are "non-responders" to NF (Enriquez-Geppert et al 2024).

One possibility is the use of microdoses of psilocybin (a psychedelic drug) and NF (eg: learning to relax and change the brainwave patterns), which Enriquez-Geppert et al (2024) investigated in a feasibility study. Thirty-seven adults (mostly students, and regular

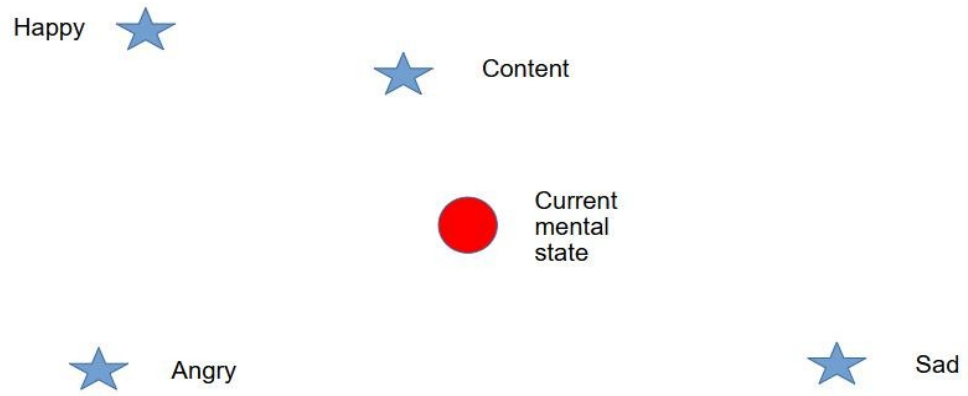
recreational drug users) in the Netherlands participated in the experimental or control group. Self-rated and computerised task-based EFs (eg: fast categorisation of pictures into land or sea animals; response to one colour but no response to another (Go/No-go task)) were the outcome measures.

"Placebo effects were consistent across groups, with no tasks-based EF improvements, but significant self-reported gains in daily EFs — working memory, shifting, monitoring and inhibition — showing medium and high effect sizes" (Enriquez-Geppert et al 2024 p1).

The researchers ended: "Potential candidates for psilocybin-assisted NF are individuals who face deficits in EFs and experience diminished neuroplasticity, such as those with psychiatric conditions (particularly depression) and the elderly, as such populations could particularly benefit from interventions that include a neuroplasticity enhancer" (Enriquez-Geppert et al 2024 p14).

Semantic NF (sNF) is a new approach which uses brain activity patterns from areas that code semantic information. Goebel et al (2024) argued that "providing semantic information to participants about the similarity of their current mental state (CMS) to other related mental states, instead of merely providing the strength of activation, enables more specific and effective self-regulation training" (p2). As, for example, in the case of individuals with mood disorders.

In "conventional activation-based fMRI NF", as Goebel et al (2024) called it, a thermometer-like display provides the feedback, and the individual can alter this display by specific mental tasks (eg: recalling emotional autobiographical memories). sNF uses "representational similarity analysis" which presents the feedback as a semantic map (or representational space) of mental states (eg: happy, sad, angry). The individual indicates their CMS on the map and learns to change brain activity to move around the representational space to the desired position (figure 4.1). Specific mental tasks like evoking certain feelings are used.



(After Goebel et al 2024 figure 4)

Figure 4.1 - Hypothetical example of sNF.

4.3. MECHANISMS OF ACTION

Sitaram et al (2024) outlined the mechanisms of brain self-regulation, including:

i) Cognitive processes - Two processes are key: discrimination and self-maintenance. "Discrimination is the ability to perceive and identify the neural variable associated with the feedback signal. Self-maintenance is the ability to affect/influence the neural variable and change it in the intended manner. The hypothesis is that, when the above two skills are acquired through NF training, they would allow the participant to regulate the neural variable through a volitional psychosomatic process" (Sitaram et al 2024 p2).

ii) Psychological factors - The feedback contingency (eg: continuous or intermittent feedback) and reward type (eg: food, money, encouragement) are key, and they link to attention, motivation, mood, and personality, which are all relevant in NF, particularly if NF training takes time and requires attention to detail.

Sitaram et al (2024) described two major models of brain self-regulation - "the reinforcement learning model" and "the active inference model". The former is based on associative learning, "by which an association between two stimuli or between a behaviour and a stimulus

is learned. Associative learning states that the probability of a physiological response is increased when a reinforcing stimulus follows that response" (Sitaram et al 2024 p6).

The active inference model asserts that "organisms constantly minimise surprise or uncertainty in their environment by making predictions and actions. This is achieved by the brain constructing internal representations (models) of the environment and generating predictions about incoming sensory information. When the internally generated predictions do not match reality, a prediction error arises, requiring the brain to update its internal models, to improve future predictions, thus reducing future surprise or uncertainty" (Sitaram et al 2024 p7). NF learning is seen as "a process of minimising uncertainty" (Sitaram et al 2024 p7).

Gurevitch et al (2024) stated the obvious fact that "not all individuals respond equally to NF training, possibly owing to varying self-regulation abilities. This underscores the importance of understanding the mechanisms behind successful neuromodulation (ie: capacity)" (p1).

Neuromodulation of the amygdala has been proposed to help in psychiatric conditions, and success in real-time sessions have been reported in individuals with depression, anxiety, and post-traumatic stress disorder (PTSD) (Goldway et al 2020). But the individual differences in "regulation success" (or "neuromodulation capacity") may be only half of individuals (Gurevitch et al 2024).

Gurevitch et al (2024) found that individual differences in amygdala reactivity was associated with neuromodulation success in a study with 97 participants from three groupings - healthy controls, individuals with PTSD, and fibromyalgia patients. The researchers defined the term "neuromodulation capacity" as "the degree of successful volitional self-regulation of a specific neural signal through NF training" (Gurevitch et al 2024 p9).

The self-evaluation of performance in NF and the confidence in accuracy were studied by Munoz-Moldes et al (2024). The participants were eight healthy adults in the Netherlands with no prior experience of NF. The task was presented as to "learn how to achieve different levels of brain activation by modulating a mental drawing task" (p2). At each trial, of ten, participants were asked to

rate their performance, and the confidence of their rating (before receiving the NF).

Self-regulation of brain activity improved with training, and so did their performance prediction, but confidence did not change nor did it correlate with better or worse performance predictions. The findings showed "a dissociation between predictions of performance and confidence reports in the presence of feedback" (Munoz-Moldes et al 2024 p1).

There is evidence that NF can be used to "alter and combine memories" (Peng et al 2024 p1). The memory phenomenon of "hippocampal overlap" is relevant here.

"Unlike a hard drive that stores files in dedicated blocks, the brain partially re-uses neurons that already store existing memories when forming a new memory. Because of the resulting overlap, when we later attempt to retrieve one memory, other related memories can come to mind. The competition between these co-activated memories can cause interference and behavioural errors in the moment. At the same time, such co-activation can also induce learning, with consequences for how the target and competitor memories are subsequently represented. Namely, this learning can increase the amount of subsequent overlap between the neural populations representing each memory (integration), or it can reduce overlap (differentiation)" (Peng et al 2024 p1).

Peng et al (2024) used NF as twenty healthy volunteers viewed one item of furniture while imagining another item of furniture. After five sessions of NF, there was "memory integration in behaviour and the brain: the trained objects became harder for participants to discriminate behaviourally in a categorical perception task and harder to discriminate neurally from patterns of fMRI activity in their hippocampus as a result of losing unique features" (Peng et al 2024 p1).

On the positive side, NF used in this way could help with traumatic memories, say. While, on the negative side, it raises concerns about changing memories in a "brainwashing" way.

4.4. APPLICATIONS OF NF

Kim et al (2024) investigated the use of NF to help with cravings during smoking cessation. Thirty-one US adult smokers were recruited for the study. Firstly, baseline brain activity was measured in response to

smoking-related images. Then the participants were instructed to think about cigarettes in a positive way ("craving condition") or a negative way ("don't crave condition"). Individual brain activity patterns were collected for these states.

This small-scale study was enable to show potentially that participants could learn strategies to change the craving brain patterns. This study focused on whole brain activity whereas previous studies had been on regions and connections of brain areas (Kim et al 2024).

NF has the potential for application with individuals with attention-deficit hyperactivity disorder (ADHD) to help with impulsive behaviour and deficits in executive functions. Two small-scale trials (Alegria et al 2017 and Criaud et al 2020) found some benefits (though they had no placebo control condition) (Lukito et al 2024).

Lukito et al (2024) built upon these studies with a larger randomised controlled trial. Eighty-eight boys and adolescents aged 10-18 years in the UK diagnosed with ADHD were the participants. They were involved in four one-hour active or sham (placebo control) fMRI-NF sessions where controlling a gamified rocketeer displayed on a screen was the aim (which was the NF on right inferior frontal cortex (rIFC) activity) during Go/NoGo tasks. Put simply, the purpose was to learn to control impulsive reactions. There was no significant difference found in task performance between the active and sham conditions, but left IFC activity increased with training in the active condition.

Though this study had a sham-control, on the positive side, there were limitations including the involvement of males only, and that most of the participants were taking medications for their ADHD.

In gaming disorder individuals "display attentional biases, unconsciously turning their attention towards gaming-related stimuli" (Oka et al 2024 p1). Specific areas of the brain, like the insula, are involved in the attentional biases. Oka et al (2024) developed "decoded attentional bias training" (DecABT), a technique using NF to change activity in the insula (in this case), and so reduce the attraction of gaming. Twenty-one participants with "probable gaming disorder" were involved in this study.

Berman et al (2024) reported a proof-of-concept study to show that subjective pain perception could be

reduced with NF. There were sixteen participants (Canadian adult volunteers without baseline pain) given a painful thermal stimulation to the left forearm, who learned to up- or down-regulate certain brain activity patterns.

The researchers explained: "Before neurofeedback therapy can be easily and widely implemented, several objectives must be achieved. Firstly, we need a clear target for neurofeedback as the intervention's success depends directly upon our capacity to correctly identify the relevant pattern of brain activity. Most previous decoded neurofeedback approaches aimed at training new brain decoders for each individual participant. This approach probably affords the most individualised interventions but also presents the disadvantage of being lengthy, as many experimental trials need to be acquired for each subject in order to build new individualised decoders [patterns of brain activity]. With reduced data, individualised brain targets tend to be more 'noisy' and less accurate" (Berman et al 2024 p2).

But Berman et al (2024) made use of two standardised pain "signatures" - the neurologic pain signature, and the stimulus intensity independent pain signature.

4.5. ETHICAL AND REGULATORY ISSUES

"In recent years, in tandem with the growing capacity of neurotechnology to access neural information, concern has grown among certain scientists and political groups that neural data could be used for purposes other than medical or scientific advances. This current of thought warns us that, without regulation, further developments in decoding brain activity could open a Pandora's box, and that 'we must act to protect the human mind, before it is too late' [Yuste 2021 in Ruiz et al 2024]" (Ruiz et al 2024 p1).

Ienca and Adorno (2017b in Ruiz et al 2024) stated that "new neuroimaging technologies pose a fundamental ethical and legal and social challenge: determining whether, or under what conditions, it is legitimate to gain access to or to interfere with another person's neural activity" (quoted in Ruiz et al 2024).

This has led to the development of "neuroethics", which Saffre (2002) defined as "the examination of what is right and wrong, good and bad about the treatment of, perfection of, or unwelcome invasion of and worrisome manipulation of the human brain" (quoted in Ruiz et al 2024).

The idea of "neurorights" (Ienca and Adorno 2017a) has been used, but should these be seen as "rights in the philosophical sense (moral rights), as rights in the sense of international human rights law (legal rights), or all the above" (Ienca 2021 quoted in Ruiz et al 2024)? Chile enshrined neurorights in the Constitution in 2021 (Ruiz et al 2024). Table 4.2 summarises the main arguments around neurorights.

Concern about the misuse of NF is behind these concerns and ideas, and Ruiz et al (2024) noted two relevant points. Firstly, NF is unlike methods of studying the brain, like neuroimaging and electroencephalography (EEG), because it is "a form of endogenous brain stimulation and it sits alongside other (exogenous) stimulation neurotechnologies (both non-invasive and invasive) such as transcranial direct current stimulation, transcranial magnetic stimulation, spinal cord stimulation, implanted brain stimulation, electroconvulsive therapy, optogenetics, among many others" (Ruiz et al 2024 p2).

Secondly, "alongside the scientific and clinical use of these neurotechnologies, a growing private industry-led market has appeared. Commercial NF uses include neural information from a subject that promises to track workers' fatigue levels and mood swings, among other cognitive processes" (Ruiz et al 2024 p3). At the same time, NF currently has a number of limitations that mean that "dystopian misuse" is not a reality. For example, that brain changes do not persist over time, and that NF requires the participant of the individual. Therefore, although the scenario of a malicious implementation of NF or BCI in an unsuspected participant is not impossible, the successful implementation of such a complex technology (particularly out of the research environment), and its use to produce significant behavioural modifications are quite difficult" (Ruiz et al 2024 p3).

Ruiz et al's (2024) position on legal neurorights can be summarised by their concluding sentence: "Just as the maxim 'primum non nocere' (first, do not harm) is applied to medicine, we believe that the same logic should govern laws on health and that extreme care should be taken to protect personal rights without delaying scientific progress" (p8).

Furnari et al (2024) considered the ethics of NF in relation to influencing the decision-making of others. They outlined three characteristics of NF that could be problematic:

PRO	CON
Bublitz (2022) outlined three drivers for neurorights: 1. "Neuroessentialism" - Concern around the reductionism of explaining behaviour at the level of neural processes. 2. "Neuroexceptionalism" - The view that data related to the brain is "something exceptional, thus deserving a unique ethical and legal consideration" (Ruiz et al 2024 p5). 3. "Neurosciencefictionism" or "neurohype" - The fear of "dystopian misuse".	1. Legislation on neurorights politicises NF, and "neurorights lies at the crossroads of science and politics, and what is at stake is the influence the former should have on the latter and vice versa" (Ruiz et al 2024 p5). 2. Neurorights are just human rights: "'Some of these rights — personal identity, freedom from algorithmic bias — do not seem to stand in any closer relation to neurons. The prefix 'neuro' is thus a misnomer... Most neurorights are variations of rights to the person' [Bublitz 2022]. Indeed, human rights are more than sufficient since they deal with the human being as a whole" (Ruiz et al 2024 p6). 3. A key question is "should we turn everything we consider morally good into law (or, better, a human right)? Indeed, 'a central worry is the inflation of rights and their resulting devaluation. Human rights are powerful tools, they transform the legal landscape and potentially the lives of billions of people... If every important interest or legitimate concern became a matter of human rights, they may lose their distinction, significance, and effectiveness, it is widely feared... A parsimonious approach in loose analogy to Occam's Razor should be adopted: human rights should not be multiplied without necessity" (Bublitz 2022 quoted in Ruiz et al 2024).

Table 4.2 - Arguments around neurorights.

i) Precision - The ability to manipulate specific mental activity. For example, one study manipulated the liking and disliking of faces initially viewed as neutral (Shibata et al 2016).

ii) Covertness - The use of NF without the individual's conscious awareness (eg: during a video game).

iii) Persistence - The induction of "habits of mental activity" (p2) that persist over time.

Furnari et al (2024) emphasised their concerns with reference to commercial and political contexts, and the

need for regulations. Two types of regulations exist generally - threshold-based laws (where something becomes illegal when it passes a certain threshold), and feature-based laws (that make specific features illegal). The former might be when there is "unfair manipulation" of behaviour by NF, and the latter, covert NF use as illegal.

4.6. APPENDIX 4A - NEWER AND INNOVATIVE TREATMENTS

4.6.1. Transcranial Direct Current Stimulation (tDCS)

This involves weak direct electrical stimulation to parts of the brain via scalp electrodes.

Woodham et al (2025) reported benefits in a ten-week controlled trial for individuals with major depressive disorder (MDD). A total of 174 adults (from England and Wales, and Texas, USA) with at least moderate severity current episode MDD received active or sham tDCS over the left (and right) dorsolateral prefrontal cortex for five 30-minute sessions per week for three weeks, then three sessions per week for seven weeks.

At the end of ten weeks, the active group showed a significant improvement compared to the sham group. The mean Hamilton Depression Rating Scale score at baseline was 19 overall, and the active tDCS group had a mean reduction to 9.5 compared to 11.7 for the shame group.

4.6.2. Transcranial Magnetic Stimulation

Tozzi et al (2024) reported promising results for transcranial magnetic stimulation (TMS) to the left dorsolateral prefrontal cortex (dLPFC) with treatment-resistant depression (TRD). The researchers concentrated on specific cognitive impairments found in individuals with depression (eg: cognitive control). This "cognitive biotype" (reported in 27% of individuals with depression; Hack et al 2023) has been linked to poor connectivity between the dLPFC and the dorsal anterior cingulate cortex. Such individuals responded better to TMS, and showed improved cognitive performance.

The participants were forty-three US military veterans with TRD [17], of which 26 were classed as the "cognitive biotype-positive". Depression severity was

[17] The "BiomarkerS for Transcranial Magnetic Stimulation Anti-depressant Response to Treatment fMRI" (B-SMART-fMRI) study.

measured pre-treatment, post-early treatment, and post-treatment, and cognitive control by a Go-NoGo task. Tozzi et al (2024) used "a Go–NoGo task in which a word (press) is frequently presented in the colour green (Go) and infrequently in the colour red (NoGo). Veterans were asked to respond with a keypress when the word was presented in green and inhibit a keypress when it was presented in red" (p994).

4.6.3. Invasive Techniques

In a pilot study with men with treatment-resistant PTSD (TR-PTSD), Gill et al (2023) found that electrodes implanted in the amygdala (intra-cranial electroencephalography; iEEG) showed the electrical activity during recall of trauma-related memories. Theta waves (at 5-9 Hz) increased at this time, and stimulation of the amygdala (with the "NeuroPace RNS system" implanted neurostimulator) "led to significant reductions in TR-PTSD symptoms... following one year of treatment as well as reductions in aversive-related amygdala theta activity" (Gill et al 2023 p1).

This was closed-loop or state-dependent neurostimulation, and it has the following key advantages, according to Gill et al (2023): "the ability to record electrophysiological signals over time, on-demand therapy delivery, and potentially extended battery life (and thereby fewer device replacement surgeries) depending on the programmed settings" (p5).

The eight participants were recruited in the USA from two hospitals, and they had agreed to have the brain implants for either TR-PTSD or epilepsy. Trauma memories were triggered by the "Emotion Image Task" and the "Script-Driven Imagery Task". The former involved pictures that triggered an emotional response, while the latter used an audio recording of an actor describing the listener's traumatic event (constructed from previous interviews with the patient).

4.6.4. Repurposing Substances

(1) Cannabidiol (CBD) (the non-intoxicating constituent of cannabis) has the potential to help individuals with anxiety disorders. The anxiolytic (or calming) effect is key.

In order to produce a medication based on CBD that can be licensed for use, testing is required, initially

on animals, and then trials with humans. Dahlgren et al (2023) reported an open-label trial in New England, USA.

Fourteen outpatients at a local hospital classified as showing moderate-to-severe anxiety were the participants. Two standard self-report measures of anxiety were used - the "Beck Anxiety Inventory" (BAI) (Beck 1990), and the "Overall Anxiety Severity and Impairment Scale" (OASIS) (Norman et al 2006). The trial lasted four weeks and involved a CBD-based solution. Anxiety was significantly reduced at Week 4 compared to the baseline scores (a mean reduction of around 15%) (and even as early as at Week 1). "The study drug is well-tolerated, with high adherence/patient retention and no reported intoxication or serious adverse events. Minor side effects, including sleepiness/fatigue, increased energy, and dry mouth are infrequently endorsed" (Dahlgren et al 2023 p1).

In terms of limitations of this trial, both patients and staff were unblinded, meaning it was known that a treatment as being used, and so there was a risk of "expectancy effects" [18]. The sample was volunteers, primarily higher educated White women. "Regression to the mean" was a general problem faced by this study (and any trial) - ie: repeated rating of the same behaviour (in this case, anxiety symptoms) can produce extreme values that trend towards the mean with time. This is irrelevant of improvements, and "has been hypothesised to markedly contribute to placebo effects" (Dahlgren et al 2023 p8).

(2) Psychedelic drugs are being repurposed as potential treatments for "all sorts of health issues" ("New England Journal of Medicine" podcast 2023 quoted in Colloca and Fava 2024), including depression, PTSD, and untreatable pain (Colloca and Fava 2024).

Clinical trials to test these substance face a number of challenges including the nature of a control or placebo condition. Ideally, a trial will include an "active placebo" condition - ie: "a placebo that mimics some side effects or sensations of the active treatment to maintain blinding in clinical trials" (Colloca and Fava 2024 p1153).

The "placebo effect" (which includes expectations) is where an inert substance ("passive placebo") (or an active substance that has no direct therapeutic benefit;

[18] Or "expectation effects" - "the influence of patient expectations about treatment outcomes on their actual response to the treatment, which can substantially impact therapeutic effects" (Colloca and Fava 2024 p1153).

"active placebo") (table 4.3) presented as an active drug produces an effect. For example, Olson et al (2020) found that some students given a placebo of psilocybin in a setting to enhance expectations (a "psychedelic party") reported alterations in consciousness.

The placebo effect can result from informing the participant before the trial begins, general public health knowledge, past experiences, and verbal suggestion (Colloca and Fava 2024).

Trials establish the effectiveness of a drug through the principle of additivity. "Additivity refers to the summation of placebo and active treatment effects. The problem of the assumption of additivity is that it does not take into account the fact that the higher the placebo response rate, the smaller the effect size..." (Colloca and Fava 2024 p1154). The difference between placebo and drug will also vary whether the placebo is active or inert/passive.

	ADVANTAGES	DISADVANTAGES
ACTIVE PLACEBO	* Less risk of unblinding by participants. * Better comparison group than inert placebo.	* Ethical concerns around deliberate inducing of side effects. * Greater risk of expectation effects.
PASSIVE/INERT PLACEBO	* Traditional control or comparison group for the drug. * No ethical concerns as with active placebo that mimics side effects of the drug.	* Risk of unblinding as participants can recognise no treatment effects or side effects. * Not a good comparison with the drug.

(After Colloca and Fava 2024 table 1 p1155)

Table 4.3 - Key advantages and disadvantages of active and passive placebo conditions.

Colloca and Fava (2024) offered some ways to manipulate expectations in placebo conditions of psychedelic drug trials, including:

a) Balanced placebo design - Developed by Ross et al (1962), this design involves four types of groups - "true drug" (given drug and told so), placebo (given placebo and told drug), "hidden drug" (given drug but told

placebo), and control (given placebo and told so). It involves deception of some participants.

b) Sequential parallel comparison design - Participants are initially randomised to the placebo or drug group in Stage 1. "Those who do not respond to the placebo in Stage 1 are re-randomised in Stage 2 to either continue with the placebo or switch to the treatment. This design helps to control for placebo responses and minimises participant expectations by ensuring that non-responders to the placebo are given another chance to receive the active treatment" (Colloca and Fava 2024 p1167). It is more complex (and expensive) than the average trial.

c) Overt-covert design - Participants given a placebo initially are told that they will receive the drug in the future, but not when it will start (covert condition), while another group receives the drug from the start and is told so (overt condition). There is a higher risk of unblinding.

Other strategies to deal with "functional unblinding" include giving the drug with permission to participants when asleep, giving all participants the drug but at different doses, or deceiving the participants about the trial (eg: telling them that there were many different drugs being used when there was only a placebo and a psychedelic) (Couzin-Frankel 2025).

(3) Ibogaine is a plant-derived compound that has been used successfully with substance use disorders (eg: Brown and Alper 2018), but there have been rare instances of fatal cardiac arrhythmia. The co-administration of magnesium with ibogaine overcomes this potential risk (Cherian et am 2024).

Cherian et al (2024) explained further: "Ibogaine is derived from the root bark of the Tabernanthe iboga shrub and related plants and is traditionally used in African religious, spiritual and healing ceremonies. Therapeutic dosing leads to dream-like states of consciousness that facilitate a longer period of self-reflection and evaluation. Pharmacologically, ibogaine and its principal metabolite noribogaine demonstrate moderate-to-weak affinity for a number of neurotransmitter receptors... Ibogaine also increases the transcription of neurotrophic factors including brain-derived neurotrophic factor and glial cell line-derived neurotrophic factor and increases

cortical neuron dendritic arbour complexity in vitro. This unique pharmacology results in ibogaine's classification as an atypical psychedelic and the aforementioned nature of the experience has led to it being termed an 'oneirogen' [eg: Brown et al 2019]" (p374).

Cherian et al (2024) reported a clinical trial of ibogaine (and magnesium) with thirty male US Special Operations Forces veterans with mild traumatic brain injury (TBI) (eg: caused by exposure to repeated blasts leading to changes in the brain's structure, functional connectivity, and blood flow). The trial is known as the "Stanford Traumatic Injury to the CNS protocol" (MISTIC). Significant improvements were found in functioning (ie: a reduction in functional impairments caused by the TBI) with combined magnesium and ibogaine.

Ibogaine has potential "to rapidly interrupt opioid drug dependence, as measured by a dramatic reduction in opioid withdrawal symptoms. Although rigorous demonstration of clinical efficacy via controlled clinical trials is pending, the profound anti-addiction effects of ibogaine have been amply documented in anecdotal reports and open-label clinical trials, including rapid and long-lasting relief of drug cravings, increased duration of abstinence, as well as long-term reduction of anxious and depressive symptoms in subjects with drug dependence, PTSD, and traumatic brain injury (TBI)" (Havel et al 2024 p1).

An "edited" version of ibogaine (to deal with cardiac safety) has been produced ("Oxa-Iboga"), and found to reduce opioid use disorder-like behaviour in male rats (eg: opioid self-administration) with no safety concerns by Havel et al (2024).

(4) Evidence is emerging that ketamine can have rapid-onset anti-depressant properties, particularly useful with TRD (eg: Nikolin et al 2023). Glue et al (2024) reported a proof-of-concept trial of extended-release ketamine tablets.

Initially, 231 adults with TRD received ketamine over five days in an open-label phase of the trial. The individuals who showed remission in their depression (n = 118) were then included in the double-blind phase: twelve weeks of placebo or one of four dose levels of ketamine. The highest dose group showed statistically significant improvements in depression compared to the placebo group.

The researchers concluded: "Use of an extended-release oral dosage ketamine formulation may be advantageous compared with intra-nasal or intra-venous dosing, in terms of reduced intensity of dissociation, lower risk of abuse, reduced frequency and intensity of sedative and cardiovascular side effects, and improved convenience for administration in the community" (Glue et al 2024 p2008). Specifically in relation to abuse, Glue et al (2024) explained that the "extended-release ketamine tablets used in this study are exceptionally hard and difficult to shatter, due to annealing of polyethylene oxide during their manufacturing process. This property may make this formulation less likely to be diverted for abuse, due to difficulty in manipulation of the tablets" (p2008).

The removal of non-responders in the open-label phase can be seen as isolating those individuals who will benefit from the treatment (positive view) or "cherry-picking" participants to show an effect (negative view). The researchers admitted that a likely overestimation of numbers of those responding to the drug with this "enriched design". An unenriched clinical trial would include all participants throughout (unless they chose to drop-out).

(5) "Psilocybin-assisted psychotherapy" (PAP) (ie: drug and therapy together) has potential for psychiatric symptoms, like anxiety and depression. Specifically, a single session for individuals with cancer experiencing psychiatric problems. Petridis et al (2024) pooled results from two clinical trials in 2016 (Ross et al 2016; Griffiths et al 2016).

Eighty-seven patients were randomised in a crossover trial to receive psilocybin then placebo or vice versa. The "Brief Symptom Inventory" (Derogatis and Melisaratos 1983) was used as the outcome measure. Significant improvements were found with PAP in the following six months.

Psilocybin works at different levels - at the biochemical level of the neurotransmitter serotonin, and psychologically "the profound psycho-spiritual experiences that are commonly occasioned during dosing sessions" (Petridis et al 2024 p1411).

Table 4.4 lists the key limitations of Petridis et al's (2024) study.

- Pooled data from two clinical trials with slightly different protocols.
- Over 90% of participants were White (Americans), and almost all had higher education qualifications, which limited the generalisability of the findings.
- Nearly half of participants had previous psychedelic experience.
- Only one self-reported measure of psychiatric symptoms used. Independent raters of the outcome variables would be ideal.
- The placebo was an inert pill and unblinding occurred (at least among the therapists in the PAP). An active placebo (eg: another drug) would be better.

Table 4.4 - Key limitations of Petridis et al (2024).

4.6.5. Biomarkers

Around one-third of individuals diagnosed with schizophrenia are classed as treatment-resistant schizophrenia (TRS) (Cheng et al 2024). "Studies suggest that TRS may have a higher heritability compared to schizophrenia, indicating that TRS may be a more familial phenotype and distinguishable from non-TRS cases based on its genetic underpinnings. Patients with TRS have poorer prognosis and worse functional outcomes compared to patients with other severe psychiatric disorders" (Cheng et al 2024 pp1-2).

Cheng et al (2024) used UK Biobank cohort data to investigate potential biomarkers of TRS. Biomarkers (ie: biochemicals) in the blood and urine, say, could give clues to underlying genetic bases and to illnesses (table 4.5) [19]. The UK Biobank cohort includes over 375 000 adults (aged 39-73 years at baseline) recruited between 2006 and 2010, who gave blood and urine samples at baseline. Individuals in the sample classed as TRS were compared to non-TRS and non-schizophrenic individuals.

[19] "Peripheral blood and urine biomarkers are frequently measured to diagnose and evaluate chronic disease conditions. Many biochemical indicators in peripheral blood and urine have been found to be abnormal in patients with mental diseases, such as schizophrenia, major depressive disorder, autism spectrum disorder, and anxiety. A recent large observational study [Fiandaca et al 2015] demonstrated that higher concentrations of tau protein in peripheral blood were associated with cognitive degeneration in patients with Alzheimer's disease (AD). It is noteworthy that peripheral blood biomarkers hold promise as a substitute for the central nervous system in characterising psychiatric disorders, although their role has yet to be widely applied in clinical practice. Urine is also a convenient and appropriate substance for use in diagnostic or predictive tests for disease, as subtle changes in urine are accumulated in the blood and are unaffected by homeostasis mechanisms" (Cheng et al 2024 p2).

Note that "there is no objective biological measurement available for the diagnosis of TRS" (Cheng et al 2024 p5). But Cheng et al (2024) found "candidate biomarkers" (seven in male samples and three in female samples. "For example, total protein and phosphate for males, creatinine and phosphate for females" (Cheng et al 2024 p1).

The researchers concluded: "These discoveries are important because they can help doctors identify people who are more likely to develop TRS earlier, enabling them to avoid using treatments that might not work well for them" (Cheng et al 2024 p1).

- The search for biomarkers related to AD includes the ADAPT (Alzheimer's Disease Anti-inflammatory Prevention Trial) study (eg: ADAPT Research Group 2009) and the protein p-tau217 in a blood sample (Luthi 2025).

- Biomarkers offer the possibility of early diagnosis, and medication. But how to define individuals with abnormal biomarkers who are cognitively unimpaired (ie: show no overt symptoms of the disease)? One answer is to define such individuals as in a "pre-clinical" stage of the disease, or to describe them as "at risk" from developing the illness. The majority of the latter group, however, will never develop symptoms in their lifetime. Neurologist Nicolas Villain warned: "Labelling people who will never have symptoms with Alzheimer's is deleterious" (quoted in Luthi 2025). While bioethicist Timothy Daly stated: "Using risk factors to define disease will create confusion among patients, physicians and public health experts" (quoted in Luthi 2025).

- Another issue is which biomarkers to search for, particularly as the physiology of AD is not entirely known (eg: amyloid and tau and disease progression) (Luthi 2025).

Table 4.5 - Ethics of diagnosis using biomarkers, particularly for Alzheimer's Disease (AD).

4.6.6. Ultrasound

Ultrasound (high-frequency sound above 20 kilohertz) is commonly used as a means of medical imaging. Targeting the sound as in high-intensity focused ultrasound (HIFU) can destroy tumours, for example (Sukel 2023). It produces significant heating, which is the means of destroying tissue, and this is a problem if tissue damage is not the aim (Tyler et al 2018).

Harvey (1929) first showed that HIFU could alter neuronal activity in muscles in experiments with frogs

and turtles, while Fry (1958) later suppressed visual cortex activity in cats (Tyler et al 2018).

But it is low-intensity focused ultrasound (LIFU) that has gained interest as a treatment for different conditions. It has the advantage that it "can be focused through the human skull to target deep cerebral structures without affecting intervening tissues, while demonstrating a high spatial accuracy that is not available with current non-invasive neuromodulation methods such as transcranial magnetic stimulation or transcranial electrical stimulation" (Dallapiazza et al 2018 p876).

LIFU and injected micro-bubbles (containing drugs) has been found to open the blood-brain barrier to allow drug delivery to specific areas of the brain. This is ultrasound as a "blood-brain barrier opening" (BBBO) tool (Blackmore et al 2023).

Senescent cells are those in the body not growing, and they cause age-related pathologies. These cells can be rejuvenated (ie: caused to grow again) by LIFU as Kureel et al (2025) showed in cells in culture, and in mice.

Hayflick and Moorhead (1961) were the first to show that cells in culture stopped dividing (growing) after a certain number of divisions. Subsequently, studies have transplanted senescent cells into young mice and produced age-related pathologies, or removed such cells from older mice and enhanced their lifespan (Kureel et al 2025). "While cell senescence is typically considered detrimental, it should be noted that senescence has general physiological significance in preventing the propagation of damaged cells, suppressing tumour progression, in early development..., wound healing... and in tissue repair processes... Despite the benefits of senescent cells, they are linked to many age-associated maladies..., including in the lung, adipose tissue, aorta, pancreas, and osteoarthritic joints" (Kureel et al 2025 p2).

4.6.7. AI and Scans

"Focal cortical dysplasia" (FCD) is a major cause of drug-resistant focal epilepsy, and it can be detected by brain lesions observed with magnetic resonance imaging scans, and surgery recommended. Machine learning could be used to detect lesions from the scans.

Ripart et al (2025) reported the use of a neural

network in the "Multi-Centre Epilepsy Lesion Detection" (MELD) Project. The overall dataset came from 1185 participants from 23 international epilepsy surgery centres. The training dataset was 278 patients and 180 controls, while the testing dataset was 260 patients and 193 controls.

The correct detection rate overall was 67% (ie: correct detection of patients 70% (sensitivity), and of controls 60% (specificity)). A previous algorithm had an overall accuracy of 39% (Ripart et al 2025). The conclusion of Ripart et al (2025) was that AI "holds promise for early detection and improved management of focal epilepsy..." (p397).

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