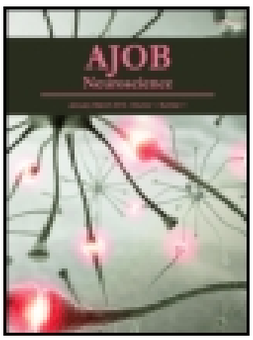

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Personality and Authenticity in Light of the Memory-Modifying Potential of Optogenetics: A Reply to Objections about Potential Therapeutic Applicability of Optogenetics

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In our article (Zawadzki and Adamczyk 2021), we analyzed threats that novel memory-modifying interventions may pose in the future. More specifically, we discussed how optogenetics' potential for reversible erasure/deactivation of memory "may impact authenticity by producing changes at different levels of personality." Our article has received many thoughtful open peer commentaries for which we would like to express our great appreciation. We have identified two main threads of objections. They are related to the potential applicability of optogenetics as a therapeutic memory modification technology (MMT) in humans—*applicability thread*, and the normative value of authenticity, that is, the assumption that preserving authenticity is valuable (either in general or in the particular approach we adopted)—*normative thread*. Both of these threads concern fundamental issues: The former deals with the scientific credibility of the case vignette on which our discussion is based, and the latter deals with the normative weight of our considerations. We think that addressing both of them can be instructive in a broader context as they reflect a more general disagreement among neuroethicists about the very purpose and method of our discipline. The *applicability thread* relates to the question of whether the role of neuroethics should be to "think ahead and act proactively" (Adamczyk and Zawadzki 2020; also see, Elsey and Kindt 2018), or whether neuroethical considerations should be necessarily tied down to empirical results that are already well established, since "thinking ahead future development of invasive brain devices 'too much' and 'too far' propels neuroethics into a speculative narrative" (Gilbert and Goddard 2014). Objections related to the *normative thread* put on the spot another basic methodological concern of neuroethics: the metaethical question of how neuroethicists should justify the normative value of the concepts they employ. Unfortunately, due to the space limitations, we can cover only one of these threads exhaustively. We decided to address the *applicability thread* concerns in this response.

It is necessary to distinguish two further categories within the *applicability thread*: objections associated with *technological obstacles*, and *the nature of memory*. The former category consists of objections related to our extrapolation that using optogenetic technology as a therapeutic MMT in humans may be possible in the future. The latter consists of objections related to our claims about how optogenetics may influence memory.

Technological obstacles noted by Gilbert, Harris, and Kidd (2021) relate to the following safety issues: "genetic modification of an individual, implanting an optrode which would induce severe trauma and risks of using the device including thermal damage to tissue." While Gilbert and colleagues have certainly identified crucial safety risks associated with the potential use of optogenetics in humans, we believe that these concerns can be alleviated to some extent in light of the latest advances in optogenetic-related technologies.

There are promising approaches that may help to reduce risks associated with the delivery of foreign genes, such as utilization of nanoparticles or carbon dots as gene carriers (Shen et al. 2020). Moreover, a viral vector, adeno-associated virus (AAV) is already being used in neural tissue to treat vision impairment and—despite several technological limitations that need to be overcome—this technique appears to be

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the frontrunner for optogenetic applications in humans (Shen et al. 2020).

Furthermore, strategies are currently under development to reduce the invasiveness of an optrode implantation and the use of the device in general. Chen et al. (2018) demonstrated that molecularly tailored upconversion nanoparticles (UCNPs) can be utilized as optogenetic actuators of transcranial near-infrared light to stimulate deep brain neurons of mammals, thereby enabling less-invasive optical neuronal activity manipulation with the promise of remote therapy. Moreover, Bedbrook et al. (2019) designed channelrhodopsin, a Gaussian process-engineered recombinant opsin (ChRgers) that allows optogenetic control over neural populations that are particularly difficult to access or distribute. Notably, ChRgers can be coupled with UCNPs to allow for minimally-invasive optogenetics in deep brain areas with systemic transgene delivery and near-infrared light for neuronal excitation. This system could offer a minimally-invasive therapeutic optogenetic tool with potential applicability in humans (Bedbrook et al. 2019).

Other strategies may offer even less-invasive approaches with the potential for therapeutic use. Recently, Rich et al. (2020) reported successful noninvasive delivery of light-emitting radio luminescent X-ray sensitive particles (RLPs) to the hippocampus of rats using magnetic resonance imaging (MRI)-guided focused ultrasound (FUS). Crucially, MRI-guided FUS can be used to deliver both RLPs and viral vectors for light-sensitive channel expression as demonstrated by Wang et al. (2017). Thus, since RLPs can be noninvasively activated with X-ray exposure, the need of any invasive procedure is negated.

Finally, it also seems that the safety concern of Gilbert and colleagues that optogenetic de/activation of modified cells would damage target brain tissue and "burn memory" can be mitigated. First, contrary to the commentators' assumption, memory de/activation does not require "continually de/activating precise optogenetically modified cells," as memory silencing can also be achieved through a single session of long-term depression (LTD) protocol (see Josselyn and Tonegawa 2020; Nabavi et al. 2014). Second, there are ways to minimize photodamage, for instance, by using shorter wavelengths or proteins that are more sensitive to light (Shen et al. 2020).

Despite the above-mentioned results, we strongly agree with Gilbert and colleagues that the number of technological obstacles to translating optogenetic techniques from animal models to humans is great. Our only point is that many novel approaches are currently being explored with a good chance of alleviating some of the concerns raised by the commentators—concerns that might have seemed insurmountable just a few years ago. Given this rapidity in the pace of technological progress, unlike Gilbert and Goddard (2014), we believe that the important mission of neuroethics should include engaging in proactive inquiries which sometimes look boldly into the future "so that a sufficient amount of relevant literature will be available to fall back on when various technologies are about to be applied in humans; in this way, ethics committees will not be forced to make ill-informed ad-hoc decisions when facing the dilemma of whether to issue approval for a specific investigation or treatment involving invasive neurostimulation technologies" (Adamczyk and Zawadzki 2020).

Relating to objections associated with *the nature of memory*, Gilbert, Harris, and Kidd (2021) argue against the premise that it may be possible in the future to have "precise control on specific memory contents in human brains." However, this premise is supported by not only a multitude of optogenetic studies in animal models (see Josselyn and Tonegawa 2020), but also, as noted by Elsey (2021), as well as Bublitz and Repantis (2021), engram theories of memory, according to which there is an enduring off-line physical and/or chemical representation of a past experience allocated to particular engram cells (see Josselyn and Tonegawa 2020).

On the other hand, as Bublitz and Repantis note, "Current [optogenetic] research concerns only specific parts of a memory such as contextual information," and since our neuroethical analysis refers to more complex autobiographical memories that are "stored in dynamic and plastic connections between cells as well as cell ensembles," it may be impossible to pinpoint them (an issue which we also examined in more detail in Adamczyk and Zawadzki 2020). However, contextual memories are also stored in dynamic and plastic connections between cells and cell ensembles, and previous optogenetic "nonengram" studies demonstrated the ability to target such memories by modifying the synaptic strength of various neural assemblies (Josselyn and Tonegawa 2020). Moreover, although the neural circuits which underlie memory change over time as memory undergoes consolidation, targeting such "relocated" or "neuronally distributed" memories could be also possible by stimulating brain regions that are indispensable for initiating the activity of the whole neural network implicated in storing and retrieving both recent and remote (autobiographical)

memories (see Adamczyk and Zawadzki 2020; Goshen et al. 2011; Sousa et al. 2019).

Another related objection is that autobiographical memories can be: 1) "branched out into many other mental states" (Lavazza 2021) and 2) "naturally protected against minor, localized disruptions due to their synergistic distribution and redundancy" (Kostick and Lázaro-Muñoz 2021), thus it may not be possible to selectively erase them. While, in general, we agree with these arguments, previous studies show that interfering with only one aspect of autobiographical memory (such as valence) may be sufficient to produce tangible changes (e.g., reduce PTSD symptoms that are intrinsically related to negative autobiographical memories) (Brunet et al. 2018). Thus, it seems likely that interfering with only selected parts of the neural circuit responsible for storing given autobiographical memory would be sufficient to disrupt that memory and produce substantial changes to the effect which that memory had for the person.

All things considered, we agree with the critics that it is unlikely that optogenetics will be used to modify memory in humans in the nearest future, and that there is a possibility that it will not work in the way supposed in the target article. However, even if this is the case, our paper adds to the current neuroethical debate by examining intricate relations between memory, personality, and authenticity which may also be useful for analyzing neuroethical consequences of other MMTs as well as various neurological disorders that impact memory (e.g., Alzheimer's). Finally, even if one does not believe that optogenetics (or optogenetic-like) technology will ever be allowed to be used as MMT in humans, our considerations can still be viewed as theoretically useful thought experiments (Bublitz and Repantis 2021; Gilbert, Harris, and Kidd 2021). Through this lens, one of the functions of our article would also be to explore the conceptual toolkit of neuroethics, that is, intuitions about the meaning and normative weight of philosophical concepts (such as authenticity). However, this last point relates to the *normative thread* which we cannot discuss here as it needs to be addressed on its own due to its complexity.

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