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Title: The Effects of Closed-Loop Brain Implants on Autonomy and Deliberation: What are the Risks of Being Kept in the Loop?

Abstract:

A new generation of implantable Brain Computer Interfaces (BCI) devices have been tested for the first time in a human clinical trial with significant success. These intelligent implants detect specific neuronal activity patterns, like an epileptic seizure, then provide information to help patients to respond to the upcoming neuronal events. By forecasting a seizure, the technology keeps patients in the decisional loop; the device gives control to patients on how to respond and decide on a therapeutic course ahead time. Being kept in the decisional loop can positively increase patients quality of life; however, doing so does not come free of ethical concerns. There is currently a lack of evidence concerning the various impacts of closed-loop system BCIs on patients' decision-making processes, especially how being in the decisional loop impacts patients' sense of autonomy. This article addresses these gaps by providing data we obtained from a first-in-human clinical trial involving patients implanted with advisory brain devices. This manuscript explores ethical issues related to the risks involved with being kept in the decisional loop.

Key Words: Advisory system, Autonomy, Brain Computer Interfaces, Closed-loop system, Decision-making processes, Decisional Vulnarebility, Deliberation, Identity, Predictive implant, Self.

Introduction:

Research involving implantable closed-loop therapeutic technologies, which both detect neurological patterns and deliver stimulation in order to avoid or diminish the effects of an unwanted neuronal event, are an important field of Brain Computer Interfaces (BCI). [1] Concretely, these implantable closed-loop BCIs have a significant role to play in medicine. Contrary to open-loop implants, which always discharge a therapeutic response (e.g. Deep Brain Stimulation (DBS) for Parkinson's disease), closed-loop implants adapt to brain activity and activate a therapeutic response accordingly. For instance, since late 2013, an electrical stimulation device capable of both detecting the onset of an epileptic seizure and responding so as to diminish the seizure effects has been distributed under the brand name Neurospace and approved for use in humans. [2] What distinguishes these particular closed-loop brain technologies is that they operate by way of automated activation processes,

independent of the patient's will. Put otherwise, an implanted patient does not control if and when a therapeutic response is to be delivered; consequently the technology *takes the patient out of the decisional loop entirely*.

This article focuses on a parallel, but operationally different technology, namely closed-loop advisory brain devices.[3 4] In contrast with the Neurospace technology, closed-loop devices do not supplant the patient's voluntary control over if and when to initiate a therapeutic response: *the implanted patient is kept in the decisional loop*.[5 6] It is assumed in the ethical literature that "if the subject is in the [decisional] loop, she retains some autonomy over decision-making".[7] This assumption needs urgent examination with empirical testing.

Indeed, there is currently a gap in our knowledge concerning how being kept in the decisional loop impacts patients' autonomy and deliberatative processes. Closed-loop devices offer a greater degree of control at the neural-circuit level, but this grasp on neuronal function raises questions about control at the psychological level of the patient.[8] To date, most research in this area has not been explored empirically and remains speculative and at a purely conceptual level of investigation.[9 10] This article addresses these gaps by providing data we obtained from a first-in-human clinical trial involving 07 patients implanted with advisory brain devices.

In each case, the predictive and advisory device works as a closed-loop system, but instead of having the implant deliver an automatic therapeutic response[11 12 13 14], it is the patient that elects which therapeutic course to take. For instance, the technology uses continuous electroencephalography recordings from patients' brain activity to detect specific neuronal activity patterns that are taken to be precursors to epileptic seizures. The technology then advises the patient that they will soon experience a seizure, allowing the patient to take precautionary steps.[15] In brief, when the brain device forecasts a seizure, it gives the implanted patient a visual or auditory signal. The patient, in turn, may elect to prepare for, or even prevent the oncoming seizure, by instigating a certain course of action (e.g. by taking anti-seizure medications). In that respect, the device maintains patients in the decisional therapeutic loop; patients retain some volitional controls. As such, this manuscript explores ethical issues related to the risks involved with being kept in the decisional loop.

1) What is it like to be kept in the decisional loop?

There is currently a lack of evidence concerning the various impacts of closed-loop system BCIs on patients' decision-making processes, especially how being in the decisional loop impacts patients' sense of autonomy.[16 17] To address the lack of relevant evidence, we conducted in-depth, semi-structured interviews[18] using open-ended questions directed at patients who had volunteered to be implanted with the first-in-human experimental advisory brain devices capable of predicting epilepsy seizure.[19] Description of the trial's details can be found here.[20] As this was a qualitative study based on first-person narrative interviews, the results are presented as excerpts.

Interviews were analysed by regrouping patients' subjective experiences into five main phenomenological clusters which reflect patients' autonomy and decision making processes: 1) Insecurities and risks attached to living with epilepsy; 2) How patients integrate device predictions into their deliberative processes leading up to their relevant decisions; 3) Patients not trusting the device; 4) Device-induced sense of control and empowerment; and, 5) Device-induced lack of confidence and sense of control. Below, these clusters are populated by patients' key answers and quotes.

Cluster 1 -Insecurities and risks attached to living with epilepsy:

> Patient 02: "The uncertainty about whether you're going to have a seizure […] you find yourself avoiding situations. I've had some rather unpleasant experiences: one when I was vacuuming the pool at home and ended up falling and bashing my head against the concrete and then falling into the pool. […] and then you avoid dangerous situations. I don't drive anymore because I have had seizures while I've been driving".
>
> Patient 03: "I kind of grew up having seizures […] since I was sixteen. I pretended that they didn't really exist for a while […] I lost a lot of my confidence and I'd stay inside a lot".
>
> Patient 07: "I see my epilepsy-I've never liked it-it's been an opposition to me and it's caused me a lot of depression, anguish and a lot of teasing. […] I believe my parents mainly centred around home because nobody knew when or where so it's a bit of a-what do you call it? I felt uncomfortable with being out in public because you didn't trust yourself-and I didn't want people to see me having a seizure because I considered them as being really ugly".

Cluster 2 -How patients integrate device's predictions into their deliberative processes leading up to their relevant decisions:

> Patient 02: "Well as I got more and more confident, I didn't question it, no. But initially when the algorithm was first put in, then I had very little confidence that it was going to be of any assistance. But then over time, I got more and more confident and so, yeah, I trusted it".
>
> Patient06**: "**I just do not want to believe [seizure] will happen.
> Interviewer: What do you mean by "I do not want to believe".
> Patient 06: When I see Kermit the frog[21], I'm in an automatic denial that it is an actual warning, I believe it is a false feelings. […].
> Interviewer: So when the device was in conjunction with your auras, did it give you an extra level of confidence?
> Paitent06: Yes.
> Interviewer: It was slowly breaking down your denial?
> Patient 06: Yes".

Patient 07: “The device took all of that insecurity away because now I’ve got to trust myself with that […] I was more capable of making good decisions-not bad decisions-because there’s been times [without device] where I’ve made bad decisions […] When the red light came on was when I took the pill, depending on the severity of my symptoms or after I took one or two”.

Cluster 3 -Patients not experiencing trust while being in the loop:

Interviewer: “[…] did you have a fit without a warning?
Patient 04: But a few times yeah, so it did beep a few times as well. So yeah.
Interviewer: So with the device did you feel more confident for instance.
Patient 04: No I wasn’t trusting it. […] I just ignore it anyway”.

Patient 06: “The device was not relevant in the sense it gave me many false warnings […] Because there was so many falses warning that you never knew what to believe at the time”.

Cluster 4 - Being in the loop induced a sense of control and empowerment:

Patient 01: “I felt more in control when I used the device. I could push on and do what I wanted to do.”

Patient 02 reported: “It gave me more confidence to do things that I wouldn’t necessarily and normally do.”

Patient 02: “It’s a natural consequence [to decide to push]. It was not imposed, no. So it was a natural consequence of the development of the algorithm”.

Patient 07: “With the device I felt like I could do anything-I can do this-I can do everything I want to do […] I can bake safely, I can shower safely-I can bath shower safely. So it gave me a new lease on life and nothing could stop me”.

Cluster 5 -Being in the loop induced lack of confidence and control:

Patient 03: “because it was always beeping and always red, it made me feel like *I had no control*. So *I didn’t have control over what I was going to do*.[…] I got really depressed”.

2) Analysis of the data

In order to understand how being in the decisional loop can affect patients' decision-making processes and sense of autonomy, [22] it is fundamental to note that individuals suffering from chronic epilepsy, as indicated in Cluster 1, live in a constant state of insecurity owing to the possibility of having unpredictable seizures. Many daily and basic decisions taken by

these patients are experienced as challenging because they are impacted by the insecurities and risks attached to living with epilepsy.

Living in a permanent state of uncertainty, it is easy to understand that all patients, pre- and post- implantation, reported being sceptical regarding whether the predictive and advisory functionalities would work. Still, when implanted individuals realised the advisory functionalities were helping—albeit with varying degrees of perceived effectiveness (see [23] for more details)—they began integrating the device predictions into their deliberative processes leading up to their relevant decisions. For instance, Patient 02 declared: “I had very little confidence that it was going to be of any assistance. But then over time, I got more and more confident and so, yeah, I trusted it”. As another instance, Patient 06 started to trust his own biological phenomenology and the device forecast because he realised that specific mental images of Kermit the Frog (auras) associated with device prediciton indicated an upcoming epileptic seizure. In the latter case, Patient 06 used the device signal when synchronized with auras as an informational basis upon which to initiate therapeutic decisions and choices.

In contrast, Cluster 3 Patients did not experience trust while being in the loop because they suffered seizures without warning and surmised that their devices were not reliable, leading them to ignore signals. For instance, Patient 04: “No I wasn’t trusting it. […] I just ignore it anyway”; or, as Patient 06 indicated: “Because there was so many false warnings that you never knew what to believe at the time”. From these reports, it seems that for patients to be comfortable in the decisional loop and to integrate the device’s predictions into their decision-making, they require a certain amount of trust in the device. It seems that the trust is built upon accurate cumulative interactions; the hypothesis being that trust took the place of what they lacked in terms of knowledge.

It is difficult to ascribe decisional outcomes to any single cause, but factoring trust into the prediction while being in the loop appears to substantially affect patients’ deliberations. In some cases, the trust induced a level of certainty which influenced their decisions. Patient 07: “With the device I felt like I could do anything-I can do this-I can do everything I want to do”. In some instances, being in the loop allowed patients to diminish decisional uncertainty by notifying them of the signs indicative of a potential upcoming seizure. In the words of Patient 07: “I was more capable of making good decisions-not bad decisions-because there’s been times [without the device] where I’ve made bad decisions”. As a result, “[w]hen the red light came on was when I took the pill, depending on the severity of my symptoms or after I took one or two”. From this perspective, it would seem that Patient 07 experienced an augmented sense of autonomy. In opposition, Patient 03 describes her experience as follow: “[the device] made me feel like I had no control. So I didn’t have control over what I was going to do.” Feelings associated with having no control would seem to indicate a pereceived loss of autonomy. As the device “was always beeping and always red”, Patient 03 experienced being in the decisional loop as a malaise, as evidenced by her self-description of feeling “really depressed”. [24 25 26]

It seems the reliability of the implanted device translated into a reason for adopting these predictions as trustworthy evidence. As evidence accumulated, most patients not experiencing false warning signals gradually stopped doubting the accuracy of the device

and instead just followed the machine's predictions and advice. The net effect of this seems to have allowed them to confidently enjoy their daily-life activities without the uncertainties of when they might become symptomatic and have a seizure. These effects directly impacted patients' sense of their own autonomy. On these accounts, being in the decisional loop seems to have enabled some patients to take their decisions beyond the pre-implanted repertoire. As Patient 2 testifies: "[the device allow me to] do things that I wouldn't necessarily and normally do" (Patient 02); or, as Patient 1 puts it, "I felt more in control when I used the device. I could push on" and "do what I wanted to do" (Patient 01).

The above data displayed in our cluster as obtained from our interviews is evidence that being in the loop can have a radical and profound influence on how patients retain some sense of autonomy over decision-making . Our analysis of the data lead us to advance the following conclusions:

1) Being in the loop may partly increase a sense of autonomy over decision-making.
2) Being in the loop may partly decrease a sense of autonomy over decision-making.
3) Being in the loop may not impact a sense of autonomy over decision-making.

Conclusions 1 and 2 teach us that, being in the loop may partly impact a patient's sense of autonomy over decision-making, which raises many ethical concerns. These ethical concerns translate into what are the risks of iatrogenic harms involved with being in the loop? For instance, Conclusion 2 is mostly linked to a malaise of losing a sense of control over decision-making. For Patient 03, being in the loop made her feel like she didn't have control over what she was going to do. In that respect, the procedure has impaired this patient's postoperative sense of autonomy, which translated into her experience of iatrogenic harms related to feelings of depression. In some contexts, the risk of having an agent lose control raises questions about how a patient can give a genuine informed consent to an intervention that may not offer the prospect of choosing to control oneself in the future. [27]

However, for Conclusion 1, although on first approximation boosting a sense of autonomy seems to confer a direct benefit, augmented sense of autonomy may also contain risk of harms which are not as explicit as it appears in Conclusion 2. How can retaining some autonomy over decision-making become harmful for a patient's decisional autonomy (even if it does not strictly speaking remove choice from the agent)? The rest of the manuscript addresses risks and ethical concerns related to Conclusion 1.

3) Being in the loop: ethical issues around retaining some autonomy over decision-making?

While patients are being kept in the decisional loop, and facing uncertainties about seizures, if the device can provide a rare glimpse of accurate information with relevant predictions, the device (over time) will become that which provides the only relevant information that is seen as trustworthy (Patient 07: "The device took all of that insecurity away because now I've got to trust myself with that […] I was more capable of making good decisions. […] When the red light came on was when I took the pill, depending on the severity of my symptoms or after I took one or two"). It appears the patients are willing to rely on device

prediction as long as interactions are phenomenally experienced as trustworthy. If we look at how decision-making is influenced by the device, then we understand that being in the loop plays a critical role in patients' deliberative psychology. The effect of this trust increases the influence of, and dependence on, the device. Most often this means that the implanted individual will act and decide with an increased sense of autonomy and control (Patient 01 explained: "I felt more in control when I used the device. I could push on and do what I wanted to do"). Here let us put further attention on the point that experiencing an augmented sense of autonomy may lead to harms.

By providing patients with greater autonomy over relevant decision-making, the experience of being in the loop also includes the choice not to act according to device prediction. For instance, by offering options that she can take up or not, the patient appears to be an autonomous contributor to the causal pathway that leads to a decision to take, or not to take, the anti-seizure medication. It would be different if the advisory functions shifted to automatic medication delivery, taking the subject out of the decisional loop entirely, leaving no choice or opportunity for the patient to autonomously contribute to therapeutic responses. By being kept in the decisional loop, not only are patients able to retain some degree of autonomy, but they also report being "more capable of making good decisions"(Patient 07). Giving control to patients over therapeutic interventions by allowing them in the decisional loop suggests that patients may appreciate what is good for them. In Patiens trust into the device indicates a better outcomes, consequently following advisory recommendation is consequently good for patients. This is precisely where an important ethical concern appears: by providing assistive guidance (for the agent to act upon or not) a closed-loop advisory device may become a device that decreases decisional autonomy (even if it does not strictly speaking remove choice from the agent).

Eran Klein et al (2016), while discussing closed-loop BCIs, suggest that "if a patient is given control over device settings, the temptation to increase stimulation settings to feel better and better may be difficult to resist". [28] Klein and colleagues' concerns about addiction with respect to closed-loop devices further support results we obtained in 2015. [29] In our preliminary data—obtained after interviewing the first patients to be implanted with advisory DBS devices—we highlighted that some implanted patients may be at risk of over-reliance on advisory devices. We argued that this translates into *decisional vulnerability* when patients are faced with forming a decision to follow the device information. [30] Decisional vulnerability occurs in a context of epistemic dependence, in particular when patients outsource their deliberative capacities to device instructions despite the absence of immediate evidence. 'Technological outsourcing' can be defined as the practice whereby people get their computers, smart phones, etc. to perform certain day-to-day tasks that *they would otherwise have to perform themselves.* [31] But here it is not the case that patients could otherwise decide for themselves: they rely entirely on the BCI device as their sole source of information to forecast their seizures.

All things being considered, if the implanted individual is not in a position to base her decision on any other relevant and reliable available evidence, then she may not have any other choice but to outsource her decision to an advisory system. This is precisely a context in which the patient may be said to be facing epistemic dependency. The concern here is that such a case of decisional vulnerability compounded by epistemic dependency puts the

patient in a precarious deliberative position. In practical terms, this makes it very hard for the patient to resist undue external influences[32] and she will not be in a position to make decisions free of the control of some confounding influences. [33] [34] By predicting upcoming neurological events, devices may have substantial epistemic influence that propels patients to initiate a particular decision.

This situation is not at all unusual. People become over-reliant on sources of information that make and keep them dependent all the time. Doing so makes them vulnerable and unable to resist certain influences. What makes this situation ethically alarming to us are the potential medical consequences: not following the instructions as provided by the BCI device increases the risk of suffering from epileptic seizures. And, the fear of experiencing such consequences may increase dosage intake (Patient 07).

We have identified this risk of decisional vulnerability and the risk of over-reliance on the device to highlight the risk of decreasing relevant patients' capacities to make freely informed choices on how to proceed with the advice received. This hypothesis is in line with our earlier observations that implanted individuals may start over-trusting, then progressively over-relying on the advisory system while being in the decisional loop. Consequently, over-relying on device information simply means that in some cases the patient will no longer be sovereign in the decisional loop. *The ethical problem with over-reliance is that the device ends up supplanting agency rather than supplementing it.*

Over-reliance on advisory implantable brain devices may entail the risk of a false sense of security for some patients. There is not yet any published research on this topic. But, to take a related example, studies have observed that devices that can continuously inform and guide an individual, such as global positioning system (GPS) devices, may lull users into a false sense of security; the effect of this is that individuals neglect other stimuli that may guide them just as well. [35] Our findings as taken from above show that patients sometimes push their limits when they trust DBS advisory devices as evidenced by the following patients' comments:

> [Patient 02]: It [the device] gave me more confidence to do things that I wouldn't necessarily and normally do.
>
> [Patient 07]: With the device I felt like I could do anything-I can do this-I can do everything I want to do.

If some patients are over-reliant on these devices, then the central concern likely is not whether over-reliance is ethically wrong, but rather whether over-reliance is justified or helpful. Over-reliance is particularly problematic when market forces might be influencing treatment. [36] For instance, if a company offers to patients neuronal drug delivery systems for free, but asks those patients to pay for medication, and suddenly increase the price of the medication—what then? Here the question would be whether over-reliance on this particular drug is necessary.

Applied to the case of epilepsy, over-reliance on DBS advisory devices may mean that an implanted patient may stop trying to look at other sources of available information to guide her responsive decision-making. In saying this we need to ask what are the other sources of information that would be relevant and how could implanted individuals confirm (or disconfirm) the reliability of such information? For instance, should individuals pay more

attention to their own subjective experiences, their instincts of a seizure about to happen? How reliable can such instincts be? The reason why patients are implanted in the first place is because they cannot reliably detect or control epileptic symptoms leading up to a seizure. Given the lack of other relevant and reliable available evidence upon which to base responsive decisions, there is a strong chance that the affected individual at risk for seizures will come to the conclusion that she *should* follow the instructions of the advisory device. In that respect, being over-reliant on the device might be justified for some patients when facing some circumstances. Adequate predictive and advisory settings might be a matter of individual preference. [37]

Conclusion:

In this article we discussed issues concerning the postoperative impact of advisory and predictive brain device on patients' sense of their autonomy as well as their deliberative processes. We tried to explore potential issues associated with being in the decisional loop. Our hypothesis is that in some circumstances, advisory devices are an indispensable feature of autonomy. [38 39] Patients get implanted with closed-loop advisory devices to obtain a larger range of choice. However, even if they are kept in the decisional loop, there could be be internal and external coercive factors, [40 41 42 43] beyond patient and device control, playing a key role in the decision making-process. Although some postoperative effects on decision-making processes are not problematic (for instance augmented deliberative autonomy allowing to go beyond daily routine), in other cases they may lead to patients experiencing distress. Establishing preparedness protocols specific to closed-loop technologies is essential and will likely prevent potential iatrogenic harms. Priority should be given to make sure prospective patients are properly informed of the potential effects of being kept in the loop. Access to information should highlight the limits of the treatment, and its potential long-term effects on the patient's sense of autonomy as well as her deliberative processes. A lack of preparedness to deal with unwanted outcomes could make patients and their families more fragile and lead to potential iatrogenic harms. Mapping these ethical concerns helps to prepare prospective patients so as to avoid some preventable negative impacts; it may also serve to detail a protocol to possibly exclude some specific cohorts of patients from being enrolled as candidates for implantation.

We concede that this article only discusses some preliminary results from a first-in-human study. Without further evidence, on the basis of our patients' testimony alone, it is difficult to generalize from our observations. More work is required to fully comprehend the ethical concerns associated with being kept in the loop, as it may share a limited number of concerns with other novel invasive brain technologies or other types of neuro-interventions. [44 45 46 47 48 49 50 51] A further important question to explore would be whether bypassing implanted individual consent by allowing a system to deliver an automated therapeutic response could be ethically acceptable in some cases?

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[11] In theory, this generation of BCI devices could be used to automate drug delivery so as to avoid unwanted outcomes. See note 12-14.

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[18] This study was conducted in accordance with Tasmanian Human Research Ethics Committee regulations. Patient Consent and Minimal Risk Ethics Application Approval, entitled "(H0013883) Implantable Seizure Advisory Brain Devices: Ethical Implications" is in compliance with the Tasmanian Human Research Ethics Committee regulations. Initial ethics approval was obtained in March 2013, and an amendment was approved on November 2014.

[19] Semi-structured interviews consisted in following an unobstructive script with a duration average of 45 minutes per patient. Open questions such as: "how was it to live with/out the device"; "how did you experienced device prediction"; etc. were asked. Following patients answers, we followed up on some key themes or concepts introduced by patients. This qualitative approach allowed us to capture first-personal perspectives that are not identified by standardised questionnaires and scales.

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