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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?

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1 **Forthcoming in: Cambridge Quarterly of Healthcare Ethics**

2

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7

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9

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

12

13

14 **Abstract:**

15

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

29

30

31

32 **Key Words:** Advisory system, Autonomy, Brain Computer Interfaces, Closed-loop system,
33 Decision-making processes, Decisional Vulnerability, Deliberation, Identity, Predictive
34 implant, Self.

35

36 **Introduction:**

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

48 independent of the patient's will. Put otherwise, an implanted patient does not control if
49 and when a therapeutic response is to be delivered; consequently the technology *takes the*
50 *patient out of the decisional loop entirely*.
51

52 This article focuses on a parallel, but operationally different technology, namely closed-loop
53 advisory brain devices.^{3 4} In contrast with the Neurospace technology, closed-loop devices
54 do not supplant the patient's voluntary control over if and when to initiate a therapeutic
55 response: *the implanted patient is kept in the decisional loop*.^{5 6} It is assumed in the ethical
56 literature that "if the subject is in the [decisional] loop, she retains some autonomy over
57 decision-making".⁷ This assumption needs urgent examination with empirical testing.
58

59 Indeed, there is currently a gap in our knowledge concerning how being kept in the
60 decisional loop impacts patients' autonomy and deliberative processes. Closed-loop
61 devices offer a greater degree of control at the neural-circuit level, but this grasp on
62 neuronal function raises questions about control at the psychological level of the patient.⁸
63 To date, most research in this area has not been explored empirically and remains
64 speculative and at a purely conceptual level of investigation.^{9 10} This article addresses these
65 gaps by providing data we obtained from a first-in-human clinical trial involving 07 patients
66 implanted with advisory brain devices.
67

68 In each case, the predictive and advisory device works as a closed-loop system, but instead
69 of having the implant deliver an automatic therapeutic response^{11 12 13 14}, it is the patient
70 that elects which therapeutic course to take. For instance, the technology uses continuous
71 electroencephalography recordings from patients' brain activity to detect specific neuronal
72 activity patterns that are taken to be precursors to epileptic seizures. The technology then
73 advises the patient that they will soon experience a seizure, allowing the patient to take
74 precautionary steps.¹⁵ In brief, when the brain device forecasts a seizure, it gives the
75 implanted patient a visual or auditory signal. The patient, in turn, may elect to prepare for,
76 or even prevent the oncoming seizure, by instigating a certain course of action (e.g. by
77 taking anti-seizure medications). In that respect, the device maintains patients in the
78 decisional therapeutic loop; patients retain some volitional controls. As such, this
79 manuscript explores ethical issues related to the risks involved with being kept in the
80 decisional loop.
81

82
83

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

85

86 There is currently a lack of evidence concerning the various impacts of closed-loop system
87 BCIs on patients' decision-making processes, especially how being in the decisional loop
88 impacts patients' sense of autonomy.^{16 17} To address the lack of relevant evidence, we
89 conducted in-depth, semi-structured interviews¹⁸ using open-ended questions directed at
90 patients who had volunteered to be implanted with the first-in-human experimental
91 advisory brain devices capable of predicting epilepsy seizure.¹⁹ Description of the trial's
92 details can be found here.²⁰ As this was a qualitative study based on first-person narrative
93 interviews, the results are presented as excerpts.
94

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

102

103

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

105

106 Patient 02: "The uncertainty about whether you're going to have a seizure [...] you
107 find yourself avoiding situations. I've had some rather unpleasant experiences: one
108 when I was vacuuming the pool at home and ended up falling and bashing my head
109 against the concrete and then falling into the pool. [...] and then you avoid
110 dangerous situations. I don't drive anymore because I have had seizures while I've
111 been driving".

112

113 Patient 03: "I kind of grew up having seizures [...] since I was sixteen. I pretended
114 that they didn't really exist for a while [...] I lost a lot of my confidence and I'd stay
115 inside a lot".

116

117 Patient 07: "I see my epilepsy-I've never liked it-it's been an opposition to me and
118 it's caused me a lot of depression, anguish and a lot of teasing. [...] I believe my
119 parents mainly centred around home because nobody knew when or where so it's a
120 bit of a-what do you call it? I felt uncomfortable with being out in public because you
121 didn't trust yourself-and I didn't want people to see me having a seizure because I
122 considered them as being really ugly".

123

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

126

127 Patient 02: "Well as I got more and more confident, I didn't question it, no. But
128 initially when the algorithm was first put in, then I had very little confidence that it
129 was going to be of any assistance. But then over time, I got more and more confident
130 and so, yeah, I trusted it".

131

132 Patient06: "I just do not want to believe [seizure] will happen.

133 Interviewer: What do you mean by "I do not want to believe".

134 Patient 06: When I see Kermit the frog²¹, I'm in an automatic denial that it is an
135 actual warning, I believe it is a false feelings. [...].

136 Interviewer: So when the device was in conjunction with your auras, did it give you
137 an extra level of confidence?

138 Patient06: Yes.

139 Interviewer: It was slowly breaking down your denial?

140 Patient 06: Yes".

141

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

147
148

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

150

151 Interviewer: "[...] did you have a fit without a warning?

152 Patient 04: But a few times yeah, so it did beep a few times as well. So yeah.

153 Interviewer: So with the device did you feel more confident for instance.

154 Patient 04: No I wasn't trusting it. [...] I just ignore it anyway".

155

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

159

160

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

162

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

165

166 Patient 02 reported: "It gave me more confidence to do things that I wouldn't
167 necessarily and normally do."

168

169 Patient 02: "It's a natural consequence [to decide to push]. It was not imposed, no.
170 So it was a natural consequence of the development of the algorithm".

171

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

175

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

177

178 Patient 03: "because it was always beeping and always red, it made me feel like *I had*
179 *no control. So I didn't have control over what I was going to do.*[...] I got really
180 depressed".

181

182

183 **2) Analysis of the data**

184

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

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

191

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

205

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

215

216 It is difficult to ascribe decisional outcomes to any single cause, but factoring trust into the
217 prediction while being in the loop appears to substantially affect patients’ deliberations. In
218 some cases, the trust induced a level of certainty which influenced their decisions. Patient
219 07: “With the device I felt like I could do anything-I can do this-I can do everything I want to
220 do”. In some instances, being in the loop allowed patients to diminish decisional uncertainty
221 by notifying them of the signs indicative of a potential upcoming seizure. In the words of
222 Patient 07: “I was more capable of making good decisions-not bad decisions-because there’s
223 been times [without the device] where I’ve made bad decisions”. As a result, “[w]hen the
224 red light came on was when I took the pill, depending on the severity of my symptoms or
225 after I took one or two”. From this perspective, it would seem that Patient 07 experienced
226 an augmented sense of autonomy. In opposition, Patient 03 describes her experience as
227 follow: “[the device] made me feel like I had no control. So I didn’t have control over what I
228 was going to do.” Feelings associated with having no control would seem to indicate a
229 perceived loss of autonomy. As the device “was always beeping and always red”, Patient
230 03 experienced being in the decisional loop as a malaise, as evidenced by her self-
231 description of feeling “really depressed”. ^{24 25 26}

232

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

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

244

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

249

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

253

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

264

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

271

272

273 **3) Being in the loop: ethical issues around retaining some autonomy over decision-** 274 **making?**

275

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

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

291

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

308

309 Eran Klein et al (2016), while discussing closed-loop BCIs, suggest that "if a patient is given
310 control over device settings, the temptation to increase stimulation settings to feel better
311 and better may be difficult to resist".²⁸ Klein and colleagues' concerns about addiction with
312 respect to closed-loop devices further support results we obtained in 2015.²⁹ In our
313 preliminary data—obtained after interviewing the first patients to be implanted with
314 advisory DBS devices—we highlighted that some implanted patients may be at risk of over-
315 reliance on advisory devices. We argued that this translates into *decisional vulnerability*
316 when patients are faced with forming a decision to follow the device information.³⁰
317 Decisional vulnerability occurs in a context of epistemic dependence, in particular when
318 patients outsource their deliberative capacities to device instructions despite the absence of
319 immediate evidence. 'Technological outsourcing' can be defined as the practice whereby
320 people get their computers, smart phones, etc. to perform certain day-to-day tasks that
321 *they would otherwise have to perform themselves*.³¹ But here it is not the case that patients
322 could otherwise decide for themselves: they rely entirely on the BCI device as their sole
323 source of information to forecast their seizures.

324

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

330 patient in a precarious deliberative position. In practical terms, this makes it very hard for
331 the patient to resist undue external influences³² and she will not be in a position to make
332 decisions free of the control of some confounding influences.^{33 34} By predicting upcoming
333 neurological events, devices may have substantial epistemic influence that propels patients
334 to initiate a particular decision.

335
336 This situation is not at all unusual. People become over-reliant on sources of information
337 that make and keep them dependent all the time. Doing so makes them vulnerable and
338 unable to resist certain influences. What makes this situation ethically alarming to us are the
339 potential medical consequences: not following the instructions as provided by the BCI
340 device increases the risk of suffering from epileptic seizures. And, the fear of experiencing
341 such consequences may increase dosage intake (Patient 07).

342
343 We have identified this risk of decisional vulnerability and the risk of over-reliance on the
344 device to highlight the risk of decreasing relevant patients' capacities to make freely
345 informed choices on how to proceed with the advice received. This hypothesis is in line with
346 our earlier observations that implanted individuals may start over-trusting, then
347 progressively over-relying on the advisory system while being in the decisional loop.
348 Consequently, over-relying on device information simply means that in some cases the
349 patient will no longer be sovereign in the decisional loop. *The ethical problem with over-*
350 *reliance is that the device ends up supplanting agency rather than supplementing it.*

351
352 Over-reliance on advisory implantable brain devices may entail the risk of a false sense of
353 security for some patients. There is not yet any published research on this topic. But, to take
354 a related example, studies have observed that devices that can continuously inform and
355 guide an individual, such as global positioning system (GPS) devices, may lull users into a
356 false sense of security; the effect of this is that individuals neglect other stimuli that may
357 guide them just as well.³⁵ Our findings as taken from above show that patients sometimes
358 push their limits when they trust DBS advisory devices as evidenced by the following
359 patients' comments:

360 [Patient 02]: It [the device] gave me more confidence to do things that I
361 wouldn't necessarily and normally do.

362 [Patient 07]: With the device I felt like I could do anything-I can do this-I can
363 do everything I want to do.

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

371
372 Applied to the case of epilepsy, over-reliance on DBS advisory devices may mean that an
373 implanted patient may stop trying to look at other sources of available information to guide
374 her responsive decision-making. In saying this we need to ask what are the other sources of
375 information that would be relevant and how could implanted individuals confirm (or
376 disconfirm) the reliability of such information? For instance, should individuals pay more

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

386
387

388 **Conclusion:**

389

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

410

411 We concede that this article only discusses some preliminary results from a first-in-human
412 study. Without further evidence, on the basis of our patients' testimony alone, it is difficult
413 to generalize from our observations. More work is required to fully comprehend the ethical
414 concerns associated with being kept in the loop, as it may share a limited number of
415 concerns with other novel invasive brain technologies or other types of neuro-interventions.
416^{44 45 46 47 48 49 50 51} A further important question to explore would be whether bypassing
417 implanted individual consent by allowing a system to deliver an automated therapeutic
418 response could be ethically acceptable in some cases?

419

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427

428

429 Notes

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² fda.com Food and Drug Administration

http://www.accessdata.fda.gov/cdrh_docs/pdf10/p100026a.pdf

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⁷ See note 5 Kellmeyer et al 2016.

⁸ Glannon W, Ineichen C 2016 Philosophical Aspects of Closed-Loop Neuroscience; In book: Closed Loop Neuroscience, pp.259-270

⁹ See Note 5 Kellmeyer et al 2016.

¹⁰ See Note 6 Goering et al 2017

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.

¹² Abc.net.au World-first epilepsy treatment delivers promising trial results in Victoria, <http://www.abc.net.au/news/2016-12-15/world-first-trial-for-new-epilepsy-producing-promising-results/8122668> , Last retrieved March 08 2017.

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¹⁴ Yue, Z., S. E. Moulton, M. Cook, S. O'Leary, and G. G. Wallace. Controlled delivery for neuro-bionic devices. *Advanced Drug Delivery Reviews*; 2013; 65(4): 559–69.

¹⁵ See note 3 Cook, M., T. J. O'Brien, S. F. Berkovic et al,.

¹⁶ See Note 5 Kellmeyer et al 2016.

¹⁷ See Note 6 Goering et al 2017.

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.

²⁰ See note 3 Cook, M., T. J. O'Brien, S. F. Berkovic et al, 2013.

²¹ Here, Kermit the frog is an aura. An aura is a physiological phenomenon experienced by some patients announcing an upcoming epileptic seizure.

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