Treatment of Brain Disorders using Closed-Loop Brain-Computer Interfaces

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Existing treatments for brain disorders are time and resource-intensive, requiring patients to continually attend therapy sessions or purchase medicine. Closed-loop brain-computer interfaces (BCIs) allow an implanted computer to monitor brain activity, recognize illness-associated patterns and impact brain activity through deep brain stimulation (DBS). This technology could improve existing treatments by replacing a lifetime of therapy or pharmaceuticals with a one-time surgery and a short calibration period. This paper discusses how BCIs could be paired with DBS to increase its responsiveness to assist patients with major depressive disorder or post-traumatic stress disorder,and how a BCI could calibrate the stimulation pattern to improve function in patients with Parkinson's disease, obsessive-compulsive disorder, and neuropathic pain. BCIs are currently limited by a lack of flexibility and the foreign-body response, but organic electronic biomimetic neurons are being developed that could overcome these issues. BCIs may also cause concerns about patient autonomy, but open-source coding and electromagnetic shielding could be used to alleviate their fears. By giving patients control over certain aspects of their treatment and requiring less clinical intervention for DBS calibration, BCIs could increase patient autonomy and improve treatment outcomes.

Keywords: Brain-computer interface, MDD, PTSD, Parkinson's, OCD, neuropathic pain

Over one in three Canadians will suffer from some form of mental or substance use disorder in their lifetime (Pearson, Janz & Ali, 2013), rivaling coronary heart disease (Lloyd-Jones, Larson, Beiser & Levy, 1999) and diabetes (Venkat Narayan, Boyle, Thompson, Sorensen, & Williamson, 2003) in incidence rates. Brain disorders have primarily been treated using medicine and psychiatric therapy, and while these methods are effective they also have major drawbacks. Although these techniques are noninvasive, they often involve lengthy regimens of expensive medication or visits to the therapist. Medicines also often come with various side-effects, while therapy sessions take time from the patient's daily life that they may wish to use elsewhere (as compared to a one-time recovery from surgery). Deep brain stimulation (DBS) has also been used to treat disorders; however only a specialist can adjust the stimulation (Volkmann, Herzog, Kopper & Deuschl, 2002). This means that it is not very responsive to changing brain states, as the patient must wait for an appointment with their specialist to adjust the stimulation.

However, brain-computer interfaces (BCI) show potential for providing treatment without extracranial side effects, constant cost or frequent appointments (Shih, Krusienski, & Wolpaw, 2012). BCIs provide communication pathways between the human brain and computer algorithms, allowing the brain and the computer to directly affect each other. Currently, there are two main types of open-loop BCIs, where information flows in only one direction between the brain and the computer. One type ('Computer to Brain') utilizes computer sensors to collect external information, which is then directed towards the relevant brain region(s) to circumvent faulty sensory organs (e.g., camera sending signals to the visual cortex to bypass a damaged retina). The other type ('Brain to Computer') observes the motor cortices of the brain, watching for motor commands that can be passed on to prosthetic or paralyzed limbs. These allow their users to mitigate disabilities such as blindness (Kotler, 2002), locked-in syndrome (Kelland, 2017) and quadriplegia (Gettler, 2012). Closed-loop BCIs differ from these open-loop BCIs in that they can both monitor and affect brain activity, allowing them to identify pathological activity and work to normalize it. While they have only been tested in mice (Widge, Dougherty & Moritz, 2014) and sheep (Afshar et al., 2013), in humans, closed-loop BCIs could allow for highly responsive brain disorder treatment without requiring long-term medication or therapeutic regimens. These closed-loop BCIs would work by analyzing brain activity using

electrocorticography (ECoG), then modulating DBS activity to treat the disorder. Therefore, closed-loop BCIs can be used to increase the effectiveness and efficiency of DBS in treating brain disorders (such as mood and sensorimotor disorders) by using brain activity to regulate treatment.

Brain Disorders

Major Depressive Disorder

Extreme cases of major depressive disorder (MDD) could be alleviated using DBS, with usage of closed-loop BCIs improving DBS responsiveness and efficiency. MDD is a mental illness characterized by persistent negative mood, impacting a person's emotional and social quality of life (American Psychiatric Association, 2013). This disorder is primarily treated using individualized regimens of antidepressants or psychotherapy, but these come with the risks of side effects, dependency and continued financial cost. These treatment methods are usually successful, but at least 30% of people with MDD are resistant to more than one antidepressant (Little, 2009), complicating and extending the treatment plan.

However, DBS inhibition of the subgenual cingulate region (SCR) has been found to help alleviate symptoms in over half of treatment-resistant MDD cases (Mayberg et al., 2005), with less than half of these patients lapsing back over the 3 years following DBS implantation (Kennedy et al., 2011). The issue with this is that DBS activity must be adjusted every few months for best results, and on its own this can only be done by visiting a specialist (Shukla, Zeilman, Fernandez, Bajwa & Mehanna, 2017). By using a DBS contact with a built-in microelectrode (University of Pittsburgh Neurological Surgery Department, n.d.), an attached BCI could continually monitor activity of the SCR and adjust DBS inhibition to keep SCR activity at an optimal level (Khan & Deng, 2017). This increased responsiveness would in turn lead to greater effectiveness, as the SCR would not become desensitized to constant DBS, but instead would only receive stimulation when it was needed. It would also lead to higher efficiency; as intermittent stimulation would deplete the battery slower than constant stimulation.

Post-Traumatic Stress Disorder

BCI-mediated amygdala DBS could be used to alleviate post-traumatic stress disorder (PTSD) symptoms. PTSD is a mental illness where after experiencing a traumatic situation, a person develops symptoms such as flashbacks of the traumatic event, a sensitivity to elements that remind them of the event, and mood problems (National Institute of Mental Health, 2016b). Depending on the nature of the event, the duration of these symptoms and their effect on daily functioning can range from slightly inconveniencing (e.g., unable to skydive for a month) to crippling (e.g., unable to be near cars ever again). Like MDD, PTSD is mainly treated using individualized treatment plans of antidepressants and psychotherapy (U.S. Department of Veterans Affairs, 2017), with similar downsides (side effects, dependency, continual cost, personal effort required for treatment).

DBS treatment of the basolateral amygdala for PTSD symptoms recently underwent its first human trial, where there was a decrease in the severity of a veteran's PTSD symptomatology as measured by a 37.8% decrease in score on the Clinician-Administered PTSD Scale (Blake et al., 1995) from baseline (Langevin et al., 2016). This and other successes in the rodent model point to DBS as being a possible major treatment method for PTSD. However, like MDD, without the controlling influence of a BCI, DBS calibration is slow and inefficient. In the case of PTSD, an additional complication to BCI usage is that current technology (which relies solely on the amygdala to identify pathological activity) may confuse PTSD-related activity with normal fear-triggering activity (e.g., watching a scary movie or going bungee-jumping). To distinguish between the two, the user could use a phone or computer to communicate with the BCI and tell it to deactivate for a certain length of time. This would temporarily diminish or turn off the DBS, allowing the user to fully experience normal fear-triggering activities. In this way, the BCI would still allow for normal amygdala functioning, while preventing pathological activity.

Obsessive-Compulsive Disorder

Obsessive-compulsive disorder (OCD) could also be treated using DBS controlled by closed-loop BCIs. OCD is a mental illness characterized by reoccurring urges, known as obsessions, which cause anxiety unless the patient performs specific behaviors, referred to as compulsions (National Institute of Mental Health, 2016a). These rituals regularly interrupt the patient's daily life, forcing them to stop whatever they are doing and deal with the nagging compulsion. Currently, this disorder is treated using medication and cognitive-behavioural therapy (Abramowitz, Taylor, & McKay, 2009). However, as mentioned previously, these methods involve extensive pharmaceutical regimens and frequent trips to a psychiatrist for treatment.

DBS has been used on patients who prove resistant to these methods, where it was found to be able to reduce

symptoms by around 30% for several years (Greenberg et al., 2006). OCD can be treated using DBS in several different brain regions, including the nucleus accumbens, the anterior limb of the internal capsule, the ventral striatum, the subthalamic nucleus, and the bed nucleus of the stria terminalis (Jancin, 2016). For patients with comorbid mood disorders, DBS of the ventral striatum has been effective in reducing OCD symptoms as well as improving mood (Holtzheimer & Mayberg, 2011). This variety of possible DBS locations implies that OCD involves multiple brain structures, meaning that individual cases may have different areas receptive to treatment. In patients with multiple DBS electrodes, the BCI could monitor brain activity and use patient feedback to learn what OCD-related brain activity looks like in each specific patient through machine learning. For instance, the patient could answer a prompt on their phone every few hours asking how active their OCD has been, and by comparing stored activity from high-OCD times and low-OCD times the device could identify the pathological signals. The DBS-BCI could then experiment with different stimulation patterns to determine which stimulation pattern is most effective for the patient (i.e., minimizes high-OCD times). If that pattern later becomes ineffective, the BCI could either start experimenting after a certain threshold of OCD activity has been reached or the user could signal the BCI to start finding a new pattern. By monitoring brain activity and allowing for easy recalibration of the stimulation pattern, a closed-loop BCI can make DBS treatment of OCD much more responsive, bringing with it the efficiency and efficacy benefits discussed in prior sections.

Parkinson's Disease

Closed-loop BCIs could be used to improve DBS functioning in patients with Parkinson's. Parkinson's is a gradual motor system disorder that causes trembling and impairs balance, movement speed, and flexibility, making many everyday tasks impossible as the symptoms worsen (National Institute of Neurological Disorders and Stroke, 2019). Current treatments of Parkinson's include medication and DBS of the subthalamic nucleus (STN) (Davie, 2008). Medication suffers from the same faults as in prior disorders, but usage of DBS in Parkinson's cases can cause side-effects as well. Although DBS does have a positive effect on motor symptoms, it can also cause or worsen commonly comorbid disorders like impulse control disorder by stimulating nearby brain reward pathways (Broen, Duits, Visse-Vandewalle, Temel & Winogrodzka, 2011), limiting its overall usefulness. However, a closed-loop BCI could monitor brain activity levels in the putamen, which is inhibited in Parkinson's (National Institutes of Health, 2016), as well as the nucleus accumbens, which is a focal point of the reward pathway (Malenka, Nestler & Hyman, 2009). By controlling multiple microelectrodes in the STN, the BCI could then find the firing pattern that maximizes putamen activity, while minimizing reward pathway stimulation. In this way, the BCI could increase DBS flexibility, efficiency and responsiveness without addictive side-effects.

Neuropathic Pain

Neuropathic pain could be treated without costly pharmaceutical regimens by using DBS paired with closed-loop BCI modulation. Neuropathic pain is the product of damage or dysfunction in the somatosensory cortex, stimulating neurons responsible for pain sensation and causing illusory pain elsewhere in the body (Treede et al., 2008). One form of this is phantom limb syndrome, where somatosensory neurons associated with an amputated limb misfire and cause perception of activity or pain in the absent limb (Elbert, 2012). Neuropathic pain is primarily treated using a variety of pain medication (Finnerup, Sindrup, & Jensen, 2010), all of which have side effects and have to be taken for the rest of the patient's life.

Alternatively, DBS has been found to be effective in treating certain kinds of neuropathic pain such as peripheral neuropathic pain (Rasche, Rinaldi, Young & Tronnier, 2006) and long-term treatment of phantom limb pain (Abreu et al., 2017). As with any of the other usages of DBS to treat brain disorders, combining it with a closed-loop BCI could make the system more reactive and more efficient. After the BCI is installed, the user could use an outside device to signal the BCI when they feel illusory pain. The BCI could then examine brain activity recorded before and during the pain. Over many occurrences, the BCI could be trained to recognize brain signals associated with the neuropathic pain, at which point it could use DBS stimulation to shut down the pathological brain activity. Increasing the responsiveness of DBS makes constant stimulation unnecessary, preserving battery life and preventing desensitization of the target tissue.

Limitations and Solutions

Physiological

While closed-loop BCIs have the potential to improve treatment plans for the aforementioned brain disorders, their current effectiveness is hampered by the lack of long-term stability or flexibility in intracranial BCI components. ECoG electrodes have been shown to last for many months with no signal loss or degradation (Chao, Nagasaka & Fujii, 2010). However intracortical electrodes such as those used in DBS are connected to the skull, occasionally leading to motion relative to the brain and separation of stimulation from the target neurons (Adewole et al., 2016). This lack of flexibility also excludes children and adolescents from treatment due to their still-growing

brains, which may cause the target neurons to move away from the DBS location over time. In addition, these fixed electrodes trigger the brain's foreign-body response, isolating the electrode within scar tissue and degrading signal stability (Tresco & Winslow, 2011).

However, the foreign-body response can be minimized if an implant is as flexible as neural tissue (University of Cambridge, 2014), and a flexible implant is also more likely to stay in place among the brain's existing structures. Simon et al. (2015) have developed organic electronic biomimetic neurons (OEBNs) that are made of flexible organic polymers, allowing them to avoid the foreign-body response if they were used instead of intracortical electrodes. OEBNs work by using enzyme-based biosensors and organic electronic ion pumps to translate chemical signals to electrical signals and back again, mimicking neuronal activity and successfully using acetylcholine to communicate with human cells (Simon et al., 2015). They could also act as a translator between chemical signals within the brain and electrical signals within a computer (Cronberg, 2015), making them ideal for usage in BCIs. Compared to standard electrodes, OEBNs carry the additional benefit of stimulating neurons through chemical means rather than just electrical. This lessens the risk of neuronal damage from repeated electrical stimulation and expands the possible usage of this technique through usage of different neurotransmitters. OEBNs controlled by closed-loop BCIs could be used to treat disorders caused by the death of specific neurons, such as orexin in narcolepsy (Mahlios, De la Herrán-Arita, & Mignot, 2013) or dopamine in Parkinson's (Bernheimer, Birkmayer, Hornykiewicz, Jellinger, & Seitelberger, 1973). Unfortunately, OEBNs are currently too large to be implanted into the brain, but researchers at the Karolinska Institutet in Sweden are working on miniaturizing them (Cronberg, 2015).

Psychological

In addition to the physical limitations of BCI, patients may be concerned that by using BCIs they are opening themselves to being controlled or deceived by other people. Such lines of thought have existed for decades, being crystallized in movies like the Matrix, and have only intensified since the 9/11 attacks in the USA (Harrington, 1996; Shrira, 2008). However, there are two main ways BCIs can overcome this potential negative reaction. First, to overcome fear of the companies producing this technology, the design and coding of the BCIs could be made open-source. This would allow the global community of patients, computer programmers and neurologists to pick it apart, multiplying the number of possible opportunities for a mind-control attempt to be exposed. By being open-source about everything involved with the device, the BCI producer would also display themselves as having nothing to hide, helping users trust them even if they themselves cannot understand the code. While having an open-source design could lead to copycat devices being developed, quality would be ensured by the stringent clinical testing process required for distribution.

Second, to avoid outside manipulation of the BCI signal, bio-friendly electromagnetic shielding could encase the main circuitry of the device (e.g., a very thin layer of titanium). For devices that interact with an outside device (such as the PTSD deactivation app discussed earlier), it may be possible to use miniaturized quantum key distribution (QKD) to ensure the connection is not tampered with. QKD uses quantum mechanics to ensure a signal sent by one device cannot be manipulated before it reaches the target device (Powell, 2016), which would allow for very high security despite open-source design. It is possible that despite efforts to secure the wireless connection between two devices that hacking will still remain a concern. However, with advancements in cryptographic methods, the risk of manipulation of the signal or devices will hopefully be minimized to a point that patients can safely use the technology.

By using these two methods, BCI development companies can help counter the dual accusations of trying to control people or letting others control people. In cases where the patient can give external commands to the BCI (e.g., patients with PTSD turning off amygdala inhibition when they want to be scared), having this ability would greatly increase the patient's participation in and feeling of control over their treatment. Increased patient participation is associated with improved treatment results over a variety of physiological and psychological diseases (Vahdat, Hamzehgardeshi, Hessam & Hamzehgardeshi, 2014), while increased feelings of control have been correlated with diminished post-operative issues, earlier discharge from hospital, decreased anxiety and overall health improvements (Auerbach, 2000). Meanwhile, patient misuse of the device could be avoided by only allowing user input to electrodes far from the reward pathways, preventing an addiction cycle. Overall, by taking steps to mitigate patient concerns regarding autonomy and by emphasizing the increased patient control BCI technology can offer, patients can be made more comfortable with the technology, resulting in better treatment outcomes and decreased patient stress.

Conclusion

Overall, closed-loop BCIs can improve treatment of multiple brain disorders across different disorder families through DBS modulation. DBS treatments can be enhanced via closed-loop BCIs, which can coordinate DBS activation with relevant brain activity to improve system responsiveness

and power efficiency. If the DBS target is close to sensitive nuclei, usage of a closed-loop BCI can help maximize treatment efficacy while minimizing side effects by monitoring relevant brain regions. In cases where multiple target locations can be stimulated for the effect, BCIs can simplify the process of trying different firing patterns between the areas to determine what is most effective for the user. The BCI could additionally be attached to a smartphone or regular computer via a quantum or otherwise-encrypted wireless signal, allowing the user to give feedback to the BCI and improving patient agency. While usage of closed-loop BCIs would require an invasive surgery and recovery from the surgery, this would be a one-time cost compared to the potentially long and expensive regimen of medication or therapy. Additionally, BCIs could handle treatment of multiple comorbid disorders through their ability to quickly adjust DBS firing patterns in response to brain activity. These potential advantages over traditional methods suggest that once the technology involved in BCIs develops to a certain point (e.g., OEBN and QKD development), there may be a sudden surge in BCI usage for treating brain disorders. This increased demand would lead to faster development of BCI technology, making them cheaper, more reliable, and easier to install and maintain. This would then lead to greater acceptance of BCIs in the public eye, which may eventually lead to them being as integrated into society as regular computers are now. By gaining an understanding of computer programming and the basic principles behind BCIs, the average person can prepare themselves for the arrival of BCIs in the doctor's office, in everyday life, and perhaps someday into their own body.

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References

Abramowitz, J. S., Taylor, S., & McKay, D. (2009). Obsessive-compulsive disorder. The Lancet, 374(9688), 491-499. doi:10.1016/S0140-6736(09)60240-3

Abreu, V., Vaz, R., Rebelo, V., Rosas, M. J., Chamadoira, C., Gillies, M. J., … Pereira, E. A. C. (2017). Thalamic deep brain stimulation for neuropathic pain: Efficacy at three years' follow-up. Neuromodulation: Technology at the Neural Interface, 20(5), 504-513. doi:10.1111/ner.12620

Adewole, D. O., Serruya, M. D., Harris, J. P., Burrell, J. C., Petrov, D., Chen, H. I., … Cullen, D. K. (2016). The evolution of neuroprosthetic interfaces. Critical Reviews in Biomedical Engineering, 44(1-2), 123-152. doi:10.1615/CritRevBiomedEng.2016017198

Afshar, P., Khambhati, A., Stanslaski, S., Carlson, D., Jensen, R., Linde, D., … Denison, T. (2013). A translational platform for prototyping closed-loop neuromodulation systems. Frontiers in Neural Circuits, 6. doi:10.3389/fncir.2012.00117

American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders (5th ed.). Arlington, VA: Author.

Auerbach, S. M. (2000). Should patients have control over their own health care? Empirical evidence and research issues. Annals of Behavioral Medicine, 22 (3), 246-259. doi:10.1007/BF02895120

Bernheimer, H., Birkmayer, W., Hornykiewicz, O., Jellinger, K., & Seitelberger, F. (1973). Brain dopamine and the syndromes of Parkinson and Huntington clinical, morphological and neurochemical correlations. Journal of the Neurological Sciences, 20(4), 415-455. doi:10.1016/0022-510X(73)90175-5

Blake, D. D., Weathers, F. W., Nagy, L. M., Kaloupek, D. G., Gusman, F. D., Charney, D. S., & Keane, T. M. (1995). The development of a clinician-administered PTSD scale. Journal of Traumatic Stress, 8(1), 75-90. doi:10.1007/BF02105408

Broen, M., Duits, A., Visser-Vandewalle, V., Temel, Y., & Winogrodzka, A. (2011). Impulse control and related disorders in Parkinson's disease patients treated with bilateral subthalamic nucleus stimulation: A review. Parkinsonism and Related Disorders, 17(6), 413-417. doi:10.1016/j.parkreldis.2011.02.013

Chao, Z. C., Nagasaka, Y., & Fujii, N. (2010). Long-term asynchronous decoding of arm motion using electrocorticographic signals in monkeys. Frontiers in Neuroengineering, 3. doi:10.3389/fneng.2010.00003

Cronberg, E. [karolinskainstitutet]. (2015, June 24). Artificial neuron mimicks function of human cells [Video file]. Retrieved from https://www.youtube.com/watch?v=NhTZnnJJP64

Davie, C. A. (2008). A review of Parkinson's disease. British Medical Bulletin, 86(1), 109-127. doi:10.1093/bmb/ldn013

Elbert, T. (2012). Pain from brain: Can we remodel neural circuitry that generates phantom limb pain

and other forms of neuropathic pain? Neuroscience Letters, 507(2), 95-96. doi:10.1016/j.neulet.2011.12.004

Finnerup, N. B., Sindrup, S. H., & Jensen, T. S. (2010). The evidence for pharmacological treatment of neuropathic pain. Pain, 150(3), 573-581. doi:10.1016/j.pain.2010.06.019

Gettler, L. (2012, December 18). Quadriplegic woman gets chocolate fix using thought-controlled robotic arm. New Atlas. Retrieved from https://newatlas.com/

Greenberg, B. D., Malone, D. A., Friehs, G. M., Rezai, A. R., Kubu, C. S., Malloy, P. F., … Rasmussen, S. A. (2006). Three-year outcomes in deep brain stimulation for highly resistant obsessive-compulsive disorder. Neuropsychopharmacology, 31, 2384-2393. doi:10.1038/sj.npp.1301165

Harrington, E. (1996). Conspiracy theories and paranoia: Notes from a mind-control conference. Skeptical Inquirer, 20(5), 35-42. Retrieved from https://skepticalinquirer.org/

Holtzheimer, P. E., & Mayberg, H. S. (2011). Deep brain stimulation for psychiatric disorders. Annual Review of Neuroscience, 34, 289-307. doi:10.1146/annurev-neuro-061010-113638

Jancin, B. (2016, December 28). What's next for deep brain stimulation in OCD? MDedge Psychiatry. Retrieved from https://www.mdedge.com/psychiatry

Kelland, K. (2017, January 31). Paralyzed patients communicate thoughts via brain-computer interface. Reuters. Retrieved from https://www.reuters.com/

Kennedy, S. H., Giacobbe, P., Rizvi, S. J., Placenza, F. M., Nishikawa, Y., Mayberg, H. S., … Lozano, A. M. (2011). Deep brain stimulation for treatment-resistant depression: Follow-up after 3 to 6 years. The American Journal of Psychiatry, 168(5), 502-510. doi:10.1176/appi.ajp.2010.10081187

Khan, M. S., & Deng, H. (2017). Design and prototyping a smart deep brain stimulator: An autonomous neuro-sensing and stimulating electrode system. IEEE Intelligent Systems, 32(5), 14-27. doi:10.1109/MIS.2017.3711648

Kotler, S. (2002, September 1). Vision quest. WIRED. Retrieved from https://www.wired.com/

Langevin, J.-P., Koek, R. J., Schwartz, H. N., Chen, J. W. Y., Sultzer, D., L., Mandelkern, M. A., … Krahl, S. E. (2016). Deep brain stimulation of the basolateral amygdala for treatment-refractory posttraumatic stress disorder. Biological Psychiatry, 79(10), e82-e84. doi:10.1016/j.biopsych.2015.09.003

Little, A. (2009). Treatment-resistant depression. American Family Physician, 80(2), 167-172. Retrived from https://www.aafp.org/journals/afp.html

Lloyd-Jones, D. M., Larson, M. G., Beiser, A., & Levy, D. (1999). Lifetime risk of developing coronary heart disease. The Lancet,353(9147), 89-92. doi:10.1016/S0140-6736(98)10279-9

Mahlios, J., De la Herrán-Arita, A. K., & Mignot, E. (2013). The autoimmune basis of narcolepsy. Current Opinion in Neurobiology, 23(5), 767-773. doi:10.1016/j.conb.2013.04.013

Malenka, R. C., Nestler, E. J., & Hyman, S. E. (2009). Molecular neuropharmacology: A foundation for clinical neuroscience (2nd ed.). A. Sydor & R. Y. Brown (Ed.). New York, NY: McGraw-Hill Medical.

Mayberg, H. S., Lozano, A. M., Voon, V., McNeely, H. E., Seminowicz, D., Hamani, C., … Kennedy, S. H. (2005). Deep brain stimulation for treatment-resistant depression. Neuron, 45(5), 651-660. doi:10.1016/j.neuron.2005.02.014

National Institutes of Health. (2016). Researchers examine how Parkinson's Disease alters brain activity over time. Retrieved from https://www.nih.gov/news-events/news-releases/researchers-examine-how-parkinsons-disease-alters-brain-activity-over-time

National Institute of Mental Health. (2016a). Obsessive-compulsive disorder. Retrieved from https://www.nimh.nih.gov/health/topics/obsessive-compulsive-disorder-ocd/index.shtml

National Institute of Mental Health. (2016b). Post-traumatic stress disorder. Retrieved from https://www.nimh.nih.gov/health/topics/post-traumatic-stress-disorder-ptsd/index.shtml

National Institute of Neurological Disorders and Stroke. (2019). Parkinson's Disease information page. Retrieved from https://www.ninds.nih.gov/Disorders/All-Disorders/Parkinsons-Disease-Information-Page

Pearson, C., Janz, T., & Ali, J. (2013). Mental and substance use disorders in Canada. (Catalogue No. 82-624-X). Retrieved from http://www.statcan.gc.ca/pub/82-624-x/2013001/article/11855-eng.pdf

Powell, D. (2016, March 3). What is quantum cryptography? Popular Science. Retrieved from https://www.popsci.com/

Rasche, D., Rinaldi, P. C., Young, R. F., & Tronnier, V. M. (2006). Deep brain stimulation for the treatment of various chronic pain syndromes. Journal of Neurosurgery, 21(6), E8. doi:10.3171/foc.2006.21.6.10

Shih, J. J., Krusienski, D. J., & Wolpaw, J. R. (2012). Brain-computer interfaces in medicine. Mayo Clinic Proceedings, 87(3), 268-279. doi:10.1016/j.mayocp.2011.12.008

Shrira, I. (2008). Paranoia and the roots of conspiracy theories. Psychology Today. Retrieved from https://www.psychologytoday.com/

Shukla, A. W., Zeilman, P., Fernandez, H., Bajwa, J. A., & Mehanna, R. (2017). DBS programming: An evolving approach for patients with Parkinson's disease. Parkinson's Disease, 2017. doi:10.1155/2017/8492619

Simon, D. T., Larsson, K. C., Nilsson, D., Burström, G., Galter, D., Berggren, M., & Richter-Dahlfors, A. (2015). An organic electronic biomimetic neuron enables auto-regulated neuromodulation. Biosensors and Bioelectronics, 71, 359-364. doi:10.1016/j.bios.2015.04.058

Treede, R.-D., Jensen, T. S., Campbell, J. N., Cruccu, G., Dostrovsky, J. O., Griffin, J. W., … Serra, J. (2008). Neuropathic pain. Neurology, 70(18), 1630-1635. doi:10.1212/01.wnl.0000282763.29778.59

Tresco, P. A., & Winslow, B. D. (2011). The challenge of integrating devices into the central nervous system. Critical Reviews in Biomedical Engineering, 39(1), 29-44. doi:10.1615/CritRevBiomedEng.v39.i1.30

University of Cambridge. (2014, February 12). Surgical implants: Implant stiffness is a major cause of foreign body reaction. ScienceDaily. Retrieved from https://www.sciencedaily.com/

University of Pittsburgh Neurological Surgery Department. (n.d.) Micro-electrode recording. Retrieved from http://www.neurosurgery.pitt.edu/centers-excellence/clinical-neurophysiology/micro-electrode-recording

U.S. Department of Veterans Affairs. (2017). Treatment of PTSD. Retrieved from https://www.ptsd.va.gov/understand_tx/index.asp

Vahdat, S., Hamzehgardeshi, L., Hessam, S., & Hamzehgardeshi, Z. (2014). Patient involvement in health care decision making: A review. Iranian Red Crescent Medical Journal, 16(1), e12454. doi:10.5812/ircmj.12454

Venkat Narayan, K. M., Boyle, J. P., Thompson, T. J., Sorensen, S. W., & Williamson, D. F. (2003). Lifetime risk for diabetes mellitus in the United States. The Journal of the American Medical Association, 290(14), 1884-1890. doi:10.1001/jama.290.14.1884

Volkmann, J., Herzog, J., Kopper, F., & Deuschl, G. (2002). Introduction to the programming of deep brain stimulators. Movement Disorders, 17, 5181-5187. doi:10.1002/mds.10162

Widge, A. S., Dougherty, D. D., & Moritz, C. T. (2014). Affective brain-computer interfaces as enabling technology for responsive psychiatric stimulation. Brain-Computer Interfaces, 1(2), 126-136. doi:10.1080/2326263X.2014.912885