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Neuroscience Intervention for A Better Life: From Molecular, Cellular, To Organ Interventions

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ABSTRACT
Neuroscience is a scientific study of the nervous system through various approaches. This review summarized intervention on molecular, cellular, and organ systems. One example of molecular and cellular interventions is stem cells. Stem cells are cells that can differentiate into other types of cells and can also produce more of the same type of stem cells. Organ system intervention is organ transplantation that medical procedure in which an organ is removed from one body and placed in the body of a recipient to replace a damaged or missing organ. In addition, there are behavioural interventions, such as mindfulness meditation and cognitive behavioural therapy. Mindfulness meditation is the mental practice that involves focusing on your experience currently. Mindfulness meditation can be in the form of breathing exercises, mental imagery, body and mind awareness, and relaxation of muscles and body while cognitive-affective training (CBT) is a particularly promising strategy for enhancing cognitive control over affective processes via modulation of these abnormally functioning neural networks. Neuroscience intervention is the act of intervening, which is usually intended for better life, such as on molecular, cellular, organ system, and behavioural interventions.

Keywords: Neuroscience Intervention, Molecular, Cellular, Organ Interventions

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INTRODUCTION

Scientific study of the nervous system is called neuroscience (or neurobiology). This is a multidisciplinary branch of biology that is a combination of anatomy, physiology, cytology, molecular biology, developmental biology, mathematical models and psychology.(1) It is become alternative approach amid discussion about the various roles of infection in various neurological diseases.(2,3)

The neuroscience intervention is an intervention in neuroscience that occurs at molecular, cellular, and organ levels.(4) One example of molecular and cellular interventions is stem cells. Stem cells are cells that can differentiate into other types of cells, and can also produce more of the same cell type. At present, many stem cell studies are intended to treat various neurological diseases.(5)

Cognitive-affective training is a very promising strategy to improve cognitive control over the affective process through modulation of neural networks that function abnormally. Some psychological interventions have been developed. There are two evidence-based psychotherapy commonly used to treat anxiety and depression namely cognitive behavioral therapy (CBT) and interpersonal psychotherapy (IPT).(6)

One example of organ intervention is transplantation. Organ transplantation is a medical procedure in which an organ is removed from one body and placed in the recipient's body to replace damaged or missing organs. This kind of transplant saves a lot of lives.(7) This review summarized neuroscience intervention on molecular, cellular, and organ systems.

LITERATURE REVIEW

Stem Cells, One Example of Molecular and Cellular Interventions

Stem cells are a collection of cells that can differentiate into other types of cells, and can also divide by renewing themselves to produce more of the same types of stem cells. In mammals, there are two types of stem cells. The first is embryonic stem cells, which are isolated from the inner cell mass of blastocysts in the early development of embryos. The second is adult stem cells, which are found in various mammalian tissues.(8)

In adult organisms, stem cells and progenitor cells act as a body repair system, which replaces adult tissue. In developing embryos, stem cells can differentiate into all special cells – ectoderm, endoderm, and mesoderm. Besides these, stem cells also maintain normal replacement of regenerative organs, such as blood, skin, or intestinal tissue.(8)

The classic definition of stem cells requires that it has two properties: (1) Self-renewal: namely the ability to maintain undifferentiated state through various cycles of cell division; (2) Potential: the capacity to differentiate into a special cell type, with the following description:

- Totipotent stem cells can differentiate into embryonic and extraembryonic cell types. These cells can build complete and feasible organisms that produced from a combination of egg and sperm cells. Cells produced by the first few divisions of fertilized eggs are also totipotent.(9)
- Pluripotent stem cells are descendants of totipotent cells and can differentiate into almost all cells, namely cells derived from one of three germ layers.(10)
- Multipotent stem cells can differentiate into several cell types, but only cells of the cell family are closely related.(11)
- Oligopotent stem cells can differentiate into only a few cell types, such as lymphoid or myeloid stem cells.(11)
- Unipotent cells can only produce one type of cell, but have the nature of self-renewal, which distinguishes it from non-stem cell cells (e.g., progenitor cells, which cannot renew themselves).(11)

Embryonic stem cells are cells of the internal mass of the blastocyst cells, which are formed before implantation in the uterus. In the embryonic development of humans, the blastocyst stage reaches 4-5 days after fertilization, which at that time consisted of 50-150 cells. Cells are pluripotent and

appear during development for all derivatives of three seed layers: ectoderm, endoderm, and mesoderm. Addition, they can develop into more than 200 types of cells of an adult's body when given enough stimulation and are needed for certain cell types. They do not contribute to extraembryonic membranes or placenta.(12)

Primitive stem cells in the fetus are often called fetal stem cells. There are two types of fetal stem cells, namely 1) fetal stem cells that are appropriate and generally obtained after an abortion. These cells are not enduring but have a high and multipotent division; 2) extra-embryonic stem cells that are generally indistinguishable from adult stem cells. These cells are obtained after birth. They are not immortal but have a high level of cell division, and are pluripotent.(13)

Adult stem cells are also known as somatic stem cells. This cell is responsible for maintaining and replacing damaged body cells. These cells are found in children and adults.(14)

There are three adult stem cell sources, namely bone marrow, which requires extraction by harvesting, drilling bones (usually the thigh bone or iliac); fat tissue taken by liposuction; and blood that requires extraction through apheresis, where blood is taken from a donor (similar to a blood donor), and passed through a machine that extracts stem cells and returns other parts of the blood to the donor.(15)

Stem cells can also be taken from cord blood after birth. Of all types of stem cells, autologous harvesting has the smallest risk. By definition, autologous cells are obtained from the body itself, just as a person can store his own blood for elective surgical procedures.(15,16)

Stem cell therapy is used in various conditions and diseases. Bone marrow transplantation is a form of stem cell therapy that has been used for several years without controversy. Stem cell therapy can relieve symptoms of the disease being treated. Decreasing these symptoms can reduce the medication taken.(17)

Stem cell therapy requires immune-suppressants because of radiation before transplantation to remove the previous cell. This is because the target of this cell therapy is the immune system. One approach to avoiding the second possibility is to use stem cells from the same patient being treated.(17)

Behavioral Interventions in Health Neuroscience

There are several chronic health problems, such as chronic pain, obesity, addiction, stress, and depression, which have received attention. This is related to the increasing frequency and affect serious health outcomes. Since they are often difficult to treat, and it is not always effective with pharmacological treatment, so this kind of behavior therapy is carried out in patients. There is experimental behavioral intervention studies that have shown health benefits. However, the mechanism is not well understood.(6)

Health neuroscience is a developing field that links nerve function and structure with physical and mental health. This study intends to find out how behavioral interventions can modulate nerve function.(6)

The key strategies for advancing the science that connects nerve processes with health are by manipulating brain activity through behavioral intervention. These interventions can manipulate brain systems that have an impact on health, helping us to draw conclusions about how changes in the brain system relate to changes in health over time. These behavioral interventions are mindfulness meditation, cognitive behavioral therapy, intervention training, and diet.(6)

Mindfulness Meditation

Mindfulness meditation is the mental practice that involves focusing on your experience (such as your own emotions, thoughts, and sensations) at this time. Mindfulness meditation can be in the form of breathing exercises, mental imagery, body and mind awareness (awareness of body and mind), and relaxation of muscles and body.(18)

Mindfulness meditation techniques are as follows:

1. Find a quiet and comfortable place.
2. Try to put aside all thoughts about the past and the future and keep focused on the present.
3. Feel your breath, focus on the air coming out when you breathe.
4. Pay attention to every thought that comes and goes, whether it is a concern, anxiety, fear, or hope.
5. When the time is almost over, sit for one or two minutes, knowing where you are. Get up gradually.(18)

Mindfulness meditation, which fosters awareness and acceptance of current experiences, has been proven in behavioral studies to reduce stress reactivity and hence can be used as an intervention to change nervous system dynamics.(19) Preliminary evidence shows that mindfulness meditation can improve functional connectivity in resting regions known to be important in executive control and top-down regulation.(20)

Mindfulness meditation studies in veterans with post-traumatic stress disorder (PTSD) have increased connectivity between the posterior cingulate cortex (PCC) and the dorsolateral prefrontal cortex (DLPFC), and this is associated with a decrease in PTSD symptoms. This shows that changes in connectivity have important implications in biological stress and PTSD.(21)

Cognitive Behavioral Therapy (CBT)

CBT is a psycho-social intervention that aims to improve mental health.(22) CBT focuses on challenges and changes destructive cognitive distortions (such as thoughts, beliefs, attitudes, and behaviors). It can increase emotional regulation and the development of personal coping strategies that target current problem solving.(23,24)

At first, CBT was intended for the treatment of depression, but its use is extended to several mental disorders, including anxiety.(25,26) CBT is very beneficial for PTSD patients. CBT intervention for 12 weeks can cause restructuring of disturbed cognitive patterns and build coping skills. In particular, PTSD patients showed an increase in the subgenual activity of the anterior cingulate cortex (sgACC), a decrease in amygdala activity, and PTSD symptoms are reduced after CBT treatment.(27)

Organ Transplantation

Organ transplantation is a medical procedure in which an organ is removed from one body and placed in the

recipient's body to replace damaged or missing organs. The organs and/or tissues that are transplanted in the body of the same person are called autografts. A recent transplant between two subjects from the same species is called allografts. Allografts can come from living sources or cadavers.(28)

The organs including the heart, kidneys, liver, lungs, pancreas, intestines, and thymus have been successfully transplanted. The tissues include bones, tendons (both called musculoskeletal grafts), cornea, skin, heart valves, nerves and blood vessels. Globally, the kidneys are commonly often transplanted organs, followed by the liver and then the heart. Corneal and musculoskeletal grafts are the most transplanted tissue; this exceeds the number of organ transplants more than ten times.(29)

Organ donors may live, brain death, or die through blood circulation. The tissue can be recovered from donors who die from circulatory deaths, and brain death - up to 24 hours after the heartbeat is stopped. Unlike organs, most tissues (except the cornea) can be stored for up to five years. Transplantation increases a number of bioethical problems, including the definition of death, when and how approval must be given to organs to be transplanted, and payments for organs for transplantation.(7)

Other ethical issues include transplant tourism (medical tourism) and the broader socio-economic context in which organ procurement or transplantation can occur. A special problem is organ trafficking. There is also an ethical problem for not giving false hope to patients.(30)

Transplant Type

Autografts are transplanting tissue to the same person. Sometimes this is done with tissue that can regenerate or tissue that is more needed elsewhere (for example, including skin grafts, venous extraction, etc.). Sometimes an autograft is performed to remove the tissue and then treat it or the person before returning it (for example, including stem cell autograft and storing blood before surgery).(31)

Allografts are organ or tissue transplants between two people who are not genetically identical from the same species. Most transplants of human tissues and organs are allografts. The recipient's immune system will identify the organ as a foreign body and try to destroy it because of genetic differences between the organ giver and the recipient, thereby causing transplant rejection.(32)

The risk of transplant rejection can be estimated by measuring the level of reactive antibodies. A subset of allografts in which organs or tissues are transplanted from donors to genetically identical recipients (such as identical twins). Isografts are distinguished from other types of transplants because although they are anatomically identical to allografts, they do not trigger an immune response.(32)

Xenograft and xenotransplantation are defined as organ or tissue transplantation from one species to another. An example is a pig heart valve transplant, which is quite common and successful. However, xenotransplantation is often a type of transplant that is very dangerous because of the increased risk of incompatibility, rejection, and diseases carried on the network.(29)

Kidney Transplant

Kidney transplants are kidney organ transplants to patients with end-stage kidney disease. Kidney transplants are usually classified as dead donors (previously known as cadavers) or live donor transplants depending on the source of donor organs.(29,33)

Indications for kidney transplantation are end-stage kidney disease, regardless of the main cause. This occurs when the glomerular filtration rate is below 15 ml/minute/1.73 m^2. Usually, this is caused by malignant hypertension, infection, diabetes mellitus, and focal segmental glomerulosclerosis; genetic causes include polycystic kidney disease, a number of inherited metabolic disorders, and autoimmune conditions, such as lupus.(29)

Diabetes is the most common cause of kidney transplants, accounting for around 25% of them in the United States. The majority of kidney transplant recipients use dialysis (peritoneal dialysis or hemodialysis) during transplantation. However, individuals with chronic kidney disease who have a living donor can undergo a pre-emptive transplant before dialysis is needed.[28]

Contraindications include cardiac and pulmonary insufficiency, as well as liver disease and some cancers. Simultaneous use of tobacco and unhealthy obesity is also one indicator that places patients at a higher risk for surgical complications.(34)

The requirements for kidney transplants vary from program to program and country to country. Many programs limit age (e.g., someone must be under a certain age to be on a waiting list) and require donor to be healthy.(29)

Significant cardiovascular disease, terminal diseases that cannot be cured, and cancer are often transplantation exclusion criteria. In addition, candidates are usually screened to determine whether they will comply with their medicines, which is important for the survival of the transplant. People with mental illness and/or ongoing drug abuse problems may be excluded.(29)

HIV at one point is considered a complete contraindication for transplantation. There is a fear that immunosuppression of a person with a reduced immune system will lead to the development of disease. However, several studies seem to suggest that immunosuppressive drugs and antiretrovirals can work synergistically to help HIV viral load/CD4 counts and prevent active rejection.(34)

DISSCUSION AND CONCLUSION

Neuroscience intervention is the act of intervening which is usually intended for better life. This intervention can be carried out on molecular, cellular and organ systems. Stem cell therapy can relieve symptoms of the disease being treated. Decreasing these symptoms can reduce the medication taken. In organ system, organ transplantation is a form of neuroscience intervention at the organ level. This kind of transplant has saved a person's life a lot.

Health neuroscience is a developing field that links nerve function and structure with physical and mental health. This study intends to find out how behavioral interventions can modulate nerve function. The behavioral interventions as a part of health neuroscience can manipulate brain systems that have an impact on health, helping us to draw

conclusions about how changes in the brain system relate to changes in health over the time. These behavioral interventions include mindfulness meditation, cognitive behavioral therapy, intervention training, and diet.

REFERENCES

1. Shulman R. Brain Imaging: What It Can (and Cannot) Tell Us About Consciousness. Oxford: Oxford University Press; 2013.
2. Uotani T, Miftahussurur M, Yamaoka Y. Effect of bacterial and host factors on Helicobacter pylori eradication therapy. Expert Opin Ther Targets. 2015;19(12):1637–50.
3. Miftahussurur M, Yamaoka Y. Helicobacter pylori virulence genes and host genetic polymorphisms as risk factors for peptic ulcer disease. Expert Rev Gastroenterol Hepatol. 2015;9(12):1535.
4. Fisher PA, Berkman ET. Designing Interventions Informed by Scientific Knowledge About Effects of Early Adversity: A Translational Neuroscience Agenda for Next Generation Addictions Research. Curr Addict reports [Internet]. 2015/09/28. 2015 Dec 1;2(4):347–53. Available from: https://pubmed.ncbi.nlm.nih.gov/26985399
5. Mahla RS. Stem Cells Applications in Regenerative Medicine and Disease Therapeutics. Int J Cell Biol [Internet]. 2016/07/19. 2016;2016:6940283. Available from: https://pubmed.ncbi.nlm.nih.gov/27516776
6. Dutcher JM, Creswell JD. Behavioral interventions in health neuroscience. Ann N Y Acad Sci. 2018;1428(1):51.
7. WHO. WHO Guiding Principles on Human Cell, Tissue and Organ Transplantation. 2010.
8. Tuch B. Stem cells--a clinical update. Aust Fam Physician. 2006;35:719–21.
9. Mitalipov S, Wolf D. Totipotency, Pluripotency and Nuclear Reprogramming. In: Martin U, editor. Engineering of Stem Cells [Internet]. Berlin, Heidelberg: Springer Berlin Heidelberg; 2009. p. 185–99. Available from: https://doi.org/10.1007/10_2008_45
10. Ulloa-Montoya F, Verfaillie CM, Hu W-S. Culture systems for pluripotent stem cells. J Biosci Bioeng [Internet]. 2005;100(1):12–27. Available from: http://www.sciencedirect.com/science/article/pii/S1389172305704230
11. Schöler HR. The Potential of Stem Cells: An Inventory. In: Humanbiotechnology as Social Challenge An Interdisciplinary Introduction to Bioethics. 1st Editio. London: Routledge Taylor & Francis Group; 2007.
12. Thomson JA, Itskovitz-Eldor J, Shapiro SS, Waknitz MA, Swiergiel JJ, Marshall VS, et al. Embryonic Stem Cell Lines Derived from Human Blastocysts. Science (80-) [Internet]. 1998 Nov 6;282(5391):1145 LP – 1147. Available from: http://science.sciencemag.org/content/282/5391/1145.abstract
13. Moore KL, Persaud TVN, Torchia M. Before We Are Born : Essentials of Embryology and Birth Defects. Philadelphia: Saunders; 2013.
14. Jiang Y, Jahagirdar BN, Reinhardt RL, Schwartz RE, Keene CD, Ortiz-Gonzalez XR, et al. Pluripotency of mesenchymal stem cells derived from adult marrow. Nature [Internet]. 2002;418(6893):41–9. Available from: https://doi.org/10.1038/nature00870
15. Coughlin RP, Oldweiler A, Mickelson DT, Moorman 3rd CT. Adipose-Derived Stem Cell Transplant Technique for Degenerative Joint Disease. Arthrosc Tech [Internet]. 2017 Oct 2;6(5):e1761–6. Available from: https://pubmed.ncbi.nlm.nih.gov/29399463
16. Hariman H. The hematopoietic stem cell transplantation in Indonesia: An unsolved dilemma. Bone Marrow Transplant [Internet]. 2008;42(SUPPL.1):S85–8. Available from: https://www.scopus.com/inward/record.uri?eid=2-s2.0-50549087554&doi=10.1038%2Fbmt.2008.125&partnerID=40&md5=c1a5d356ad7d7619a383bc4c0faaec3d
17. Hardjo M, Miyazaki M, Sakaguchi M, Masaka T, Ibrahim S, Kataoka K, et al. Suppression of carbon tetrachloride-induced liver fibrosis by transplantation of a clonal mesenchymal stem cell line derived from rat bone marrow. Cell Transplant [Internet]. 2009;18(1):89–99. Available from: https://www.scopus.com/inward/record.uri?eid=2-s2.0-66849113865&doi=10.3727%2F096368909788237140&partnerID=40&md5=aa95bad4362f16172c74d23adc97b7bd
18. Arbi D, Ambarini T. Terapi Brief Mindfulness-Based Body Scan untuk Menurunkan Stres Atlet Bola Basket Wanita Profesional. Insa J Psikol dan Kesehat Ment. 2018;3(1):1–12.
19. Lindsay EK, Young S, Smyth JM, Brown KW, Creswell JD. Acceptance lowers stress reactivity: Dismantling mindfulness training in a randomized controlled trial. Psychoneuroendocrinology [Internet]. 2018;87:63–73. Available from: http://www.sciencedirect.com/science/article/pii/S0306453017304109
20. Taren AA, Gianaros PJ, Greco CM, Lindsay EK, Fairgrieve A, Brown KW, et al. Mindfulness Meditation Training and Executive Control Network Resting State Functional Connectivity: A Randomized Controlled Trial. Psychosom Med [Internet]. 2017;79(6):674–83. Available from: https://pubmed.ncbi.nlm.nih.gov/28323668
21. King AP, Block SR, Sripada RK, Rauch S, Giardino N, Favorite T, et al. Altered Default Mode Network (DMN) Resting State Functional Connectivity Following A Mindfulness-Based Exposure Therapy For Posttraumatic Stress Disorder (Ptsd) In Combat Veterans Of Afghanistan And Iraq. Depress Anxiety [Internet]. 2016 Apr 1;33(4):289–99. Available from: https://doi.org/10.1002/da.22481
22. Field TA, Beeson ET, Jones LK. The New ABCs: A Practitioner's Guide to Neuroscience-Informed Cognitive-Behavior Therapy. J Ment Heal Couns [Internet]. 2015 Jul 1;37(3):206–20. Available from:

https://doi.org/10.17744/1040-2861-37.3.206
23. Benjamin CL, Puleo CM, Settipani CA, Brodman DM, Edmunds JM, Cummings CM, et al. History of cognitive-behavioral therapy in youth. Child Adolesc Psychiatr Clin N Am [Internet]. 2011 Apr;20(2):179–89. Available from: https://pubmed.ncbi.nlm.nih.gov/21440849
24. Soetrisno, Sulistyowati S, Respati S, Nasrudin M. Effect of Cognitive Behavioral Therapy for Serotonin Level, Depression Score and Quality of Life in Cervical Cancer Patients. Folia Medica Indones. 2016;52(3):231–4.
25. McKay D, Sookman D, Neziroglu F, Wilhelm S, Stein DJ, Kyrios M, et al. Efficacy of cognitive-behavioral therapy for obsessive–compulsive disorder. Psychiatry Res [Internet]. 2015;225(3):236–46. Available from: http://www.sciencedirect.com/science/article/pii/S0165178114009512
26. Fitri FI, Rambe AS. Correlation between hypertension and cognitive function in elderly. In: L. W, D. W, W. M, J.K. B, P.C. E, M. de J, et al., editors. Department of Neurology, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia: Institute of Physics Publishing; 2018. Available from: https://www.scopus.com/inward/record.uri?eid=2-s2.0-85045682711&doi=10.1088%2F1755-1315%2F125%2F1%2F012177&partnerID=40&md5=1c4029c0a8fef2cf456ef28732483eb5
27. Felmingham K, Kemp A, Williams L, Das P, Hughes G, Peduto A, et al. Changes in Anterior Cingulate and Amygdala After Cognitive Behavior Therapy of Posttraumatic Stress Disorder. Psychol Sci. 2007 Feb 1;18:127–9.
28. Manara AR, Murphy PG, O'Callaghan G. Donation after circulatory death. BJA Br J Anaesth [Internet]. 2012 Jan 1;108(suppl_1):i108–21. Available from: https://doi.org/10.1093/bja/aer357
29. Black CK, Termanini KM, Aguirre O, Hawksworth JS, Sosin M. Solid organ transplantation in the 21(st) century. Ann Transl Med [Internet]. 2018 Oct;6(20):409. Available from: https://pubmed.ncbi.nlm.nih.gov/30498736
30. Yosepin Simbolon N, Ablisar M. The prevention of child trafficking crimes and its legal reform. In: S.F. S, R.B.M.I. F, D. C, M. K, R. B, A.H.I. AH, editors. Graduate School, Universitas Sumatera Utara, Medan, Indonesia: EDP Sciences; 2018. Available from: https://www.scopus.com/inward/record.uri?eid=2-s2.0-85054504629&doi=10.1051%2Fe3sconf%2F20185200033&partnerID=40&md5=7d8af9fb22deddd9c1611b67403f18c9
31. Akita S, Hayashida K, Yoshimoto H, Fujioka M, Senju C, Morooka S, et al. Novel Application of Cultured Epithelial Autografts (CEA) with Expanded Mesh Skin Grafting Over an Artificial Dermis or Dermal Wound Bed Preparation. Int J Mol Sci [Internet]. 2017 Dec 25;19(1):57. Available from: https://pubmed.ncbi.nlm.nih.gov/29295606
32. Kohei N, Tanaka T, Tanabe K, Masumori N, Dvorina N, Valujskikh A, et al. Natural killer cells play a critical role in mediating inflammation and graft failure during antibody-mediated rejection of kidney allografts. Kidney Int [Internet]. 2016/04/28. 2016 Jun;89(6):1293–306. Available from: https://pubmed.ncbi.nlm.nih.gov/27165816
33. Sulania A, Sachdeva S, Jha D, Kaur G, Sachdeva R. Organ donation and transplantation: An updated overview. MAMC J Med Sci. 2016 Jan 1;2:18.
34. Charlton MR, Gane EJ, Shukla A, Dashtseren B, Duger D, Muljono DH, et al. International liver transplantation society asian consensus on the management of hepatitis c virus infection in resource limited setting-From noncirrhotic to decompensated disease and after liver transplantation. Transplantation [Internet]. 2019;103(4):733–46. Available from: https://www.scopus.com/inward/record.uri?eid=2-s2.0-85063711780&doi=10.1097%2FTP.0000000000002453&partnerID=40&md5=27a3ec05845455f9ef517f4acc83d98e