frontiers | Frontiers in Psychiatry

TYPE Editorial
PUBLISHED 12 June 2023
DOI 10.3389/fpsyt.2023.1225755

OPEN ACCESS

EDITED AND REVIEWED BY
Stefan Borgwardt,
University of Lübeck, Germany

*CORRESPONDENCE
Masaru Tanaka
✉ tanaka.masaru.1@med.u-szeged.hu
Simone Battaglia
✉ simone.battaglia@unibo.it

†These authors have contributed equally to this work

RECEIVED 19 May 2023
ACCEPTED 24 May 2023
PUBLISHED 12 June 2023

CITATION
Tanaka M, Diano M and Battaglia S (2023) Editorial: Insights into structural and functional organization of the brain: evidence from neuroimaging and non-invasive brain stimulation techniques.
Front. Psychiatry 14:1225755.
doi: 10.3389/fpsyt.2023.1225755

Editorial: Insights into structural and functional organization of the brain: evidence from neuroimaging and non-invasive brain stimulation techniques

Masaru Tanaka[1*†], Matteo Diano[2] and Simone Battaglia[3*†]

[1]ELKH-SZTE Neuroscience Research Group, Danube Neuroscience Research Laboratory, Eötvös Loránd Research Network, University of Szeged (ELKH-SZTE), Szeged, Hungary, [2]Department of Psychology, University of Turin, Turin, Italy, [3]Center for Studies and Research in Cognitive Neuroscience, Department of Psychology "Renzo Canestrari", Cesena Campus, Alma Mater Studiorum Università di Bologna, Cesena, Italy

KEYWORDS

substance-related disorders, bipolar disorder, dysmenorrhea, dyspepsia, schizophrenia, biomarkers, machine learning

Editorial on the Research Topic
Insights into structural and functional organization of the brain: evidence from neuroimaging and non-invasive brain stimulation techniques

The brain is a complex and dynamic system that underlies our behavior, emotions, and cognition (1–3). To better understand the structural and functional organization of the brain, neuroimaging and brain stimulation techniques have emerged as powerful tools (Nyatega et al.) (4–9). The development of non-invasive brain stimulation (NIBS) techniques has substantially enriched our understanding of human brain function across the last decades (10, 11). An increasing number of studies have used different NIBS protocols in various research disciplines, spanning electrophysiological applications (12), studies of human cognition (13, 14), physiological markers (15, 16) and the treatment of neurological and psychiatric disorders (17). These techniques allow researchers to investigate the brain's underlying mechanisms and neural networks in real-time, enabling new insights into the diagnosis and treatment of neuropsychiatric disorders: while neuroimaging provides correlational evidence for structure–function relationships, NIBS provide causal relevance of a given brain region for a function of interest, but also the interaction between several nodes in larger brain networks (18). Recent advances in dynamic functional connectivity have expanded our ability to probe and understand the interplay among brain regions and their responses to TMS. By detecting and analyzing communication fluctuations across the brain, this approach has been instrumental in studying complex neuropsychiatric disorders such as Frontotemporal Dementia (FTD) (19, 20) and schizophrenia (SCZ), enhancing our diagnostic capabilities and potential therapeutic interventions.

Therefore, in this Research Topic, we present a collection of articles that showcase recent advances in neuroimaging and non-invasive brain stimulation techniques and their application to the study of the brain's structural and functional organization.

Understanding the brain's structure and function is vital in the diagnosis and treatment of neuropsychiatric disorders. Advances in neuroimaging and NIBS techniques have enabled researchers to explore the underlying mechanisms of disorders such as depression, SCZ, anxiety and post-traumatic stress disorders (18, 21, 22). Identifying the neural circuits and networks involved in these disorders can lead to targeted interventions that aim to modulate brain activity and restore normal function (23). This deeper understanding has the potential to revolutionize the diagnosis and treatment of neuropsychiatric disorders, significantly improving the lives of millions of individuals worldwide.

These articles demonstrate the applications of neuroimaging in studying drug abuse, bipolar disorder (BP), dysmenorrhea, white matter lesions (WML), functional dyspepsia (FD), and SCZ. The meta-analysis of cocaine addiction shows how drug abuse affects the brain. The study on BP reveals the relationship between cerebral WML and the incidence of BP. The investigation of primary dysmenorrhea offers insights into the relationship between pain and the brain, while the exploration of differential brain responses to meal ingestion in FD patients provides a better understanding of this meal-induced syndrome. Finally, structural magnetic resonance imaging studies provide insights into the pathophysiology of SCZ.

Cocaine addiction causes significant changes in brain structure and function (24), affecting gray matter volume, white matter integrity, and neural activity, according to a meta-analysis by Dang et al. These findings suggest that drug addiction is a complex neurobiological disorder and not solely a behavioral problem. Identifying the specific brain regions and circuits impacted by cocaine addiction can help develop new treatments targeting these neural mechanisms (25). The study's implications are vital for the diagnosis and treatment of drug addiction.

Nyatega et al.'s study on BP found that individuals with the condition have altered striatal functional connectivity and structural dysconnectivity in the brain. These findings could serve as biomarkers for early detection and personalized treatment approaches for BP, advancing our understanding of neuropsychiatric disorders. The research provides insights into the structural and functional organization of the brain and has significant implications for improving the diagnosis and treatment of neuropsychiatric disorders (26, 27). In summary, this study's contributions could lead to more effective treatments and improve our understanding of BP.

Liu et al. studied the relationship between primary dysmenorrhea and brain activity changes, finding that patients with the condition have altered activity in the mesocorticolimbic pathway. This pathway is involved in pain processing and emotional regulation (28), suggesting that chronic pain conditions may be linked to changes in brain activity (29). The study's relevance to neuropsychiatric disorders is significant, as it highlights the importance of considering structural and functional changes in the brain when developing treatment plans for patients with chronic pain conditions (30). These findings provide valuable insights into the underlying mechanisms of chronic pain and may lead to more effective treatments (31).

Du et al. present a secondary analysis of data from a cross-sectional study investigating the non-linear correlation between the volume of cerebral WML and the incidence of BD. The study found that there is a positive and non-linear correlation between WML volume and BD risk, with the correlation being stronger when WML volume was <6,200 mm^3 (Du et al.). These findings provide valuable insights into the structural and functional organization of the brain in individuals with BD (32). The study's results may have important implications for the diagnosis and treatment of neuropsychiatric disorders, as they suggest that WML volume could be used as a biomarker for BD risk assessment.

Chen et al. used resting-state fMRI to investigate brain responses to meal ingestion in FD patients. They found abnormal connectivity in areas related to pain processing and emotional response networks, including the left postcentral gyrus, right precuneus, right middle frontal gyrus, anterior cingulate cortex, and right inferior frontal gyrus (Chen et al.). These findings provide insights into the structural and functional organization of the brain in FD patients and may have implications for the diagnosis and treatment of neuropsychiatric disorders involving visceral hypersensitivity and emotional dysregulation (33, 34). Overall, this study's contributions could lead to more effective treatments for patients with FD and related disorders.

Adamu et al.'s structural MRI study sheds light on the pathophysiology of SCZ, showing that individuals with the disorder have structural brain abnormalities linked to specific symptom clusters and cognitive impairments. The study also highlights the use of machine learning to identify patterns of brain structure associated with symptoms and impairments. The findings contribute to our understanding of the structural and functional organization of the brain in neuropsychiatric disorders and could improve diagnosis and treatment (35, 36). By identifying specific brain structure patterns associated with symptoms, clinicians may develop more targeted interventions for individuals with SCZ.

The articles in this Research Topic highlight the importance of continued research on the structural and functional organization of the brain and its potential impact on the diagnosis and treatment of neuropsychiatric disorders (37–41). The studies presented provide valuable insights into the complex relationship between drug abuse, BP, dysmenorrhea, WML, FD, and SCZ. These findings contribute to our understanding of the structural and functional organization of the brain in neuropsychiatric disorders and offer potential biomarkers for early detection and personalized treatment approaches (42–45). Additionally, the use of machine learning to identify brain structure patterns associated with symptoms and impairments could lead to more targeted interventions for individuals with psychiatric disorders (46–48). While the introduction of machine learning techniques, including deep learning, to the clinical field has significantly enhanced our understanding of diseases, the use of these techniques in diagnostics is often overlooked due to the "black box" phenomenon (49). This issue is especially conspicuous in the medical and psychiatric fields, where decisions regarding diagnoses and treatments bear direct and significant consequences for patients' lives. The "black

Abbreviations: BP, bipolar disorder; FD, functional dyspepsia; NIBS, non-invasive brain stimulation; FTD, Frontotemporal Dementia; SCZ, schizophrenia; WML, white matter lesions.

box" problem refers to the obscurity of the inner workings of machine learning models. Despite their impressive predictive or analytical abilities, the lack of transparency in how these models arrive at their outputs often poses a significant challenge. This has led to the emergence of a specialized subfield known as explainable machine learning (50). This branch prioritizes creating models that, alongside delivering predictions or classifications, also provide clear explanations of how they reach these conclusions. By doing so, explainable machine learning attempts to solve the "black box" problem, promoting transparency and fostering greater trust in machine learning applications within the medical and psychiatric domains (49). Overall, these studies highlight the importance of considering both structural and functional changes in the brain when developing treatment plans for patients with neuropsychiatric disorders. In conclusion, continued research in this field could ultimately lead to more effective treatments and improved outcomes for individuals with these challenging conditions.

Author contributions

MT, MD, and SB contributed to conception and design and wrote sections of the manuscript. MT wrote the first draft of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

Funding

This work was supported by #NEXTGENERATIONEU (NGEU) and funded by the Ministry of University and Research (MUR), National Recovery and Resilience Plan (NRRP), project MNESYS (PE0000006)—A Multiscale integrated approach to the study of the nervous system in health and disease (DN. 1553 11.10.2022) to SB, and by OTKA-138125-K, TUDFO/47138-1/2019-ITM, ELKH-SZTE Eötvös Loránd Research Network, and the University of Szeged to MT.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Tanaka M, Telegdy G. Involvement of adrenergic and serotonergic receptors in antidepressant-like effect of urocortin 3 in a modified forced swimming test in mice. *Brain Res Bull.* (2008) 77:301–5. doi: 10.1016/j.brainresbull.2008.08.012

2. Tanaka M, Kádár K, Tóth G, Telegdy G. Antidepressant-like effects of urocortin 3 fragments. *Brain Res Bull.* (2011) 84:414–8. doi: 10.1016/j.brainresbull.2011.01.016

3. Palotai M, Telegdy G, Tanaka M, Bagosi Z, Jászberényi M. Neuropeptide AF induces anxiety-like and antidepressant-like behavior in mice. *Behav Brain Res.* (2014) 274:264–9. doi: 10.1016/j.bbr.2014.08.007

4. Nyatega CO, Qiang L, Adamu MJ, Kawuwa HB. Gray matter, white matter and cerebrospinal fluid abnormalities in Parkinson's disease: a voxel-based morphometry study. *Front Psychiatry.* (2022) 13:1027907. doi: 10.3389/fpsyt.2022.1027907

5. Vila-Merkle H, González-Martínez A, Campos-Jiménez R, Martínez-Ricós J, Teruel-Martí V, Lloret A, et al. Sex differences in amygdalohippocampal oscillations and neuronal activation in a rodent anxiety model and in response to infralimbic deep brain stimulation. *Front Behav Neurosci.* (2023) 17:1122163. doi: 10.3389/fnbeh.2023.1122163

6. Rymaszewska J, Wieczorek T, Fila-Witecka K, Smarzewska K, Weiser A, Piotrowski P, et al. Various neuromodulation methods including deep brain stimulation of the medial forebrain bundle combined with psychopharmacotherapy of treatment-resistant depression-Case report. *Front Psychiatry.* (2023) 13:1068054. doi: 10.3389/fpsyt.2022.1068054

7. Fernández-Pajarín G, Sesar Á, Relova JL, Ares B, Jiménez I, Gelabert-González M, et al. Parkinson's disease symptoms associated with developing on-state axial symptoms early after subthalamic deep brain stimulation. *Diagnostics.* (2022) 12:1001. doi: 10.3390/diagnostics12041001

8. Jeong WH, Kim WI, Lee JW, Park HK, Song MK, Choi IS, et al. Modulation of long-term potentiation by gamma frequency transcranial alternating current stimulation in transgenic mouse models of Alzheimer's disease. *Brain Sci.* (2021) 11:1532. doi: 10.3390/brainsci11111532

9. Vila-Merkle H, González-Martínez A, Campos-Jiménez R, Martínez-Ricós J, Teruel-Martí V, Blasco-Serra A, et al. The oscillatory profile induced by the anxiogenic drug FG-7142 in the amygdala-hippocampal network is reversed by infralimbic deep brain stimulation: relevance for mood disorders. *Biomedicines.* (2021) 9:783. doi: 10.3390/biomedicines9070783

10. Du XD, Li Z, Yuan N, Yin M, Zhao XL, Lv XL, et al. Delayed improvements in visual memory task performance among chronic schizophrenia patients after high-frequency repetitive transcranial magnetic stimulation. *World J Psychiatry.* (2022) 12:1169–82. doi: 10.5498/wjp.v12.i9.1169

11. Pinto BS, Cavendish BA, da Silva PHR, Suen PJC, Marinho KAP, Valiengo LDCL, et al. The effects of transcranial direct current stimulation in obsessive-compulsive disorder symptoms: a meta-analysis and integrated electric fields modeling analysis. *Biomedicines.* (2022) 11:80. doi: 10.3390/biomedicines11010080

12. Di Gregorio F, La Porta F, Petrone V, Battaglia S, Orlandi S, Ippolito G, et al. Accuracy of EEG biomarkers in the detection of clinical outcome in disorders of consciousness after severe acquired brain injury: preliminary results of a pilot study using a machine learning approach. *Biomedicines.* (2022) 10:1897. doi: 10.3390/biomedicines10081897

13. Battaglia S, Cardellicchio P, Di Fazio C, Nazzi C, Fracasso A, Borgomaneri S. Stopping in (e)motion: reactive action inhibition when facing valence-independent emotional stimuli. *Front Behav Neurosci.* (2022) 16:998714. doi: 10.3389/fnbeh.2022.998714

14. Battaglia S, Cardellicchio P, Di Fazio C, Nazzi C, Fracasso A, Borgomaneri S. The influence of vicarious fear-learning in "infecting" reactive action inhibition. *Front Behav Neurosci.* (2022) 16:946263. doi: 10.3389/fnbeh.2022.946263

15. Battaglia S, Thayer JF. Functional interplay between central and autonomic nervous systems in human fear conditioning. *Trends Neurosci.* (2022) 45:504–6. doi: 10.1016/j.tins.2022.04.003

16. Battaglia S, Orsolini S, Borgomaneri S, Barbieri R, Diciotti S, di Pellegrino G. Characterizing cardiac autonomic dynamics of fear learning in humans [published online ahead of print, 2022 Jun 7]. *Psychophysiology.* (2022) 59:e14122. doi: 10.1111/psyp.14122

17. Battaglia S, Nazzi C, Thayer JF. Fear-induced bradycardia in mental disorders: foundations, current advances, future perspectives. *Neurosci Biobehav Rev.* (2023) 149:105163. doi: 10.1016/j.neubiorev.2023.105163

18. Borgomaneri S, Battaglia S, Sciamanna G, Tortora F, Laricchiuta D. Memories are not written in stone: re-writing fear memories by means of non-invasive brain stimulation and optogenetic manipulations. *Neurosci Biobehav Rev.* (2021) 127:334–52. doi: 10.1016/j.neubiorev.2021.04.036

19. Benussi A, Premi E, Gazzina S, Cantoni V, Cotelli MS, Giunta M, et al. Neurotransmitter imbalance dysregulates brain dynamic fluidity in frontotemporal degeneration. *Neurobiol Aging.* (2020) 94:176–84. doi: 10.1016/j.neurobiolaging.2020.05.017

20. Premi E, Calhoun VD, Diano M, Gazzina S, Cosseddu M, Alberici A, et al. The inner fluctuations of the brain in presymptomatic Frontotemporal Dementia: the chronnectome fingerprint. *Neuroimage.* (2019) 189:645–54. doi: 10.1016/j.neuroimage.2019.01.080

21. Battaglia S, Garofalo S, di Pellegrino G, Starita F. Revaluing the role of vmPFC in the acquisition of pavlovian threat conditioning in humans. *J Neurosci.* (2020) 40:8491–500. doi: 10.1523/JNEUROSCI.0304-20.2020

22. Battaglia S, Harrison BJ, Fullana MA. Does the human ventromedial prefrontal cortex support fear learning, fear extinction or both? A commentary on subregional contributions. *Mol Psychiatry.* (2022) 27:784–6. doi: 10.1038/s41380-021-01326-4

23. Liu M, Xie X, Xie J, Tian S, Du X, Feng H, et al. Early-onset Alzheimer's disease with depression as the first symptom: a case report with literature review. *Front Psychiatry.* (2023) 14:1192562. doi: 10.3389/fpsyt.2023.1192562

24. NIDA. *Chronic Cocaine Use Changes Brain Structure and Cognitive Function in Rhesus Monkeys*. National Institute on Drug Abuse (2021). Available online at: https://nida.nih.gov/news-events/nida-notes/2021/08/chronic-cocaine-use-changes-brain-structure-cognitive-function-rhesus-monkeys (accessed May 16, 2023).

25. Winger G, Woods JH, Galuska CM, Wade-Galuska T. Behavioral perspectives on the neuroscience of drug addiction. *J Exp Anal Behav.* (2005) 84:667–81. doi: 10.1901/jeab.2005.101-04

26. Mueller S, Keeser D, Reiser MF, Teipel S, Meindl T. Functional and structural MR imaging in neuropsychiatric disorders, part 2: application in schizophrenia and autism. *Am J Neuroradiol.* (2012) 33:2033–7. doi: 10.3174/ajnr.A2800

27. Drevets WC, Price JL, Furey ML. Brain structural and functional abnormalities in mood disorders: implications for neurocircuitry models of depression. *Brain Struct Funct.* (2008) 213:93–118. doi: 10.1007/s00429-008-0189-x

28. Serafini RA, Pryce KD, Zachariou V. The mesolimbic dopamine system in chronic pain and associated affective comorbidities. *Biol Psychiatry.* (2020) 87:64–73. doi: 10.1016/j.biopsych.2019.10.018

29. Yang S, Boudier-Revéret M, Choo YJ, Chang MC. Association between chronic pain and alterations in the mesolimbic dopaminergic system. *Brain Sci.* (2020) 10:701. doi: 10.3390/brainsci10100701

30. Tanaka M, Török N, Tóth F, Szabó Á, Vécsei L. Co-players in chronic pain: neuroinflammation and the tryptophan-kynurenine metabolic pathway. *Biomedicines.* (2021) 9:897. doi: 10.3390/biomedicines9080897

31. Tajti J, Szok D, Csáti A, Szabó Á, Tanaka M, Vécsei L. Exploring novel therapeutic targets in the common pathogenic factors in migraine and neuropathic pain. *Int J Mol Sci.* (2023) 24:4114. doi: 10.3390/ijms24044114

32. Frangou S. Brain structural and functional correlates of resilience to Bipolar Disorder. *Front Hum Neurosci.* (2012) 5:184. doi: 10.3389/fnhum.2011.00184

33. Rosen JM, Cocjin JT, Schurman JV, Colombo JM, Friesen CA. Visceral hypersensitivity and electromechanical dysfunction as therapeutic targets in pediatric functional dyspepsia. *World J Gastrointest Pharmacol Ther.* (2014) 5:122–38. doi: 10.4292/wjgpt.v5.i3.122

34. Marsili L, Marcucci S, LaPorta J, Chirra M, Espay AJ, Colosimo C. Paraneoplastic neurological syndromes of the central nervous system: pathophysiology, diagnosis, and treatment. *Biomedicines.* (2023) 11:1406. doi: 10.3390/biomedicines11051406

35. de Filippis R, Carbone EA, Gaetano R, Bruni A, Pugliese V, Segura-Garcia C, et al. Machine learning techniques in a structural and functional MRI diagnostic approach in schizophrenia: a systematic review. *Neuropsychiatr Dis Treat.* (2019) 15:1605–27. doi: 10.2147/NDT.S202418

36. Tanaka M, Szabó Á, Vécsei L. Integrating armchair, bench, and bedside research for behavioral neurology and neuropsychiatry: editorial. *Biomedicines.* (2022) 10:2999. doi: 10.3390/biomedicines10122999

37. Ippolito G, Bertaccini R, Tarasi L, Di Gregorio F, Trajkovic J, Battaglia S, et al. The role of alpha oscillations among the main neuropsychiatric disorders in the adult and developing human brain: evidence from the last 10 years of research. *Biomedicines.* (2022) 10:3189. doi: 10.3390/biomedicines10123189

38. Battaglia S, Di Fazio C, Vicario CM, Avenanti A. Neuropharmacological modulation of n-methyl-d-aspartate, noradrenaline and endocannabinoid receptors in fear extinction learning: synaptic transmission and plasticity. *Int J Mol Sci.* (2023) 24:5926. doi: 10.3390/ijms24065926

39. Tanaka M, Vécsei L. Editorial of special issue 'dissecting neurological and neuropsychiatric diseases: neurodegeneration and neuroprotection'. *Int J Mol Sci.* (2022) 23:6991. doi: 10.3390/ijms23136991

40. Balogh L, Tanaka M, Török N, Vécsei L, Taguchi S. Crosstalk between existential phenomenological psychotherapy and neurological sciences in mood and anxiety disorders. *Biomedicines.* (2021) 9:340. doi: 10.3390/biomedicines9040340

41. Tanaka M, Spekker E, Szabó Á, Polyák H, Vécsei L. Modelling the neurodevelopmental pathogenesis in neuropsychiatric disorders. Bioactive kynurenines and their analogues as neuroprotective agents-in celebration of 80th birthday of Professor Peter Riederer. *J Neural Transm.* (2022) 129:627–42. doi: 10.1007/s00702-022-02513-5

42. Sivananthan S, Lee L, Anderson G, Csanyi B, Williams R, Gissen P. Buffy coat score as a biomarker of treatment response in neuronal ceroid lipofuscinosis type 2. *Brain Sci.* (2023) 13:209. doi: 10.3390/brainsci13020209

43. Matera E, Cristofano G, Furente F, Marzulli L, Tarantini M, Margari L, et al. Glucose and lipid profiles predict anthropometric changes in drug-naïve adolescents starting treatment with risperidone or sertraline: a pilot study. *Biomedicines.* (2022) 11:48. doi: 10.3390/biomedicines11010048

44. Chen Z, Zhang H. A meta-analysis on the role of brain-derived neurotrophic factor in Parkinson's disease patients. *Adv Clin Exp Med.* (2023) 32:285–95. doi: 10.17219/acem/154955

45. Taranu D, Tumani H, Holbrook J, Tumani V, Uttner I, Fissler P. The TRACK-MS test battery: a very brief tool to track multiple sclerosis-related cognitive impairment. *Biomedicines.* (2022) 10:2975. doi: 10.3390/biomedicines10112975

46. Patel MJ, Khalaf A, Aizenstein HJ. Studying depression using imaging and machine learning methods. *Neuroimage Clin.* (2015) 10:115–23. doi: 10.1016/j.nicl.2015.11.003

47. Pan D, Zeng A, Yang B, Lai G, Hu B, Song X, et al. Deep learning for brain MRI confirms patterned pathological progression in Alzheimer's disease. *Adv Sci.* (2023) 10:e2204717. doi: 10.1002/advs.202204717

48. Khaliq F, Oberhauser J, Wakhloo D, Mahajani S. Decoding degeneration: the implementation of machine learning for clinical detection of neurodegenerative disorders. *Neural Regen Res.* (2023) 18:1235–42. doi: 10.4103/1673-5374.355982

49. Joyce DW, Kormilitzin A, Smith KA, Cipriani A. Explainable artificial intelligence for mental health through transparency and interpretability for understandability. *NPJ Digit Med.* (2023) 6:6. doi: 10.1038/s41746-023-00751-9

50. Lundberg SM, Nair B, Vavilala MS, Horibe M, Eisses MJ, Adams T, et al. Explainable machine-learning predictions for the prevention of hypoxaemia during surgery. *Nat Biomed Eng.* (2018) 2:749–60. doi: 10.1038/s41551-018-0304-0