gp.genomicpress.com

Genomic Psychiatry

OPEN

COMMENTARY

The salience network is functionally twice as large in depression: The first depression biomarker?

Genomic Psychiatry; https://doi.org/10.61373/gp025c.0041

Keywords: Depression, salience network, biomarker, neuroimaging, functional connectivity, brain plasticity

This commentary examines recent findings demonstrating that individuals with depression exhibit a functionally expanded salience network compared to non-depressed controls. Neuroimaging data reveals this network expansion predates symptom onset and remains stable regardless of symptom severity or treatment interventions. The authors propose this distinctive neural signature as a potential biomarker for depression risk, enabling earlier identification and intervention. They discuss three potential mechanisms underlying this expansion: compensatory network changes, genetic predisposition, and relative expansion secondary to atrophy in other brain regions. The commentary emphasizes the need to conceptualize depression as a disorder of neural connectivity rather than isolated neurotransmitter imbalances, with implications for developing targeted therapeutic approaches.

Depression is a neuropsychiatric condition defined by persistent low mood and the inability to experience pleasure, significantly impacting an individual's overall well-being. Despite depression being one of the most common contributors to the global disease burden and the leading cause of health-related disability, the neurobiological mechanisms underlying this disorder remain poorly understood from the perspective of neural network systems (1, 2). While the roles of isolated brain areas and neurotransmitters in depression have been relatively well explored, there remains a lack of understanding of the functional interactions among these systems and how these interactions evolve (1). Furthermore, the majority of research to date has focused on cross-sectional data (1). As a result, despite the burden on people's lives, the economy, and the medical resources that depression inflicts, its genesis and evolution over time at the system level remain unclear. The absence of this information prevents the understanding of depression and potential therapeutics from progressing (1). This is where the recent Nature paper, Frontostriatal Salience Network Expansion in Individuals with Depression by Lynch et al. makes a significant contribution, shedding light on the functional connectivity of neural networks in depression (1).

Lynch et al. used functional magnetic resonance imaging (fMRI) to measure communication among brain areas by analyzing the synchronous activity levels over multiple sessions over time (1, 3). Their results demonstrated that, compared to those without a history of depression, nearly every individual with a current or a history of depression illustrated a salience network, which, by synchronous activity, was almost twice as large as that of non-depressed controls (3). The salience network consists of the fronto-insular cortex, the dorsal anterior cingulate cortex, the amygdala, and the temporal poles (4). This network has been implicated in reward processing and regulating the switch between the default mode network and the frontoparietal network depending on the salience of stimuli and how the stimuli align with the internal goals of the person (3, 5).

Lynch et al. question whether the topology of the salience network varied with the severity of depression symptoms. Subsequently, they found that quick-acting antidepressant treatment (repetitive transcranial magnetic stimulation [rTMS]), frequency of depressive episodes, and the severity of their symptoms changed the topology of the salience network. Lynch et al. concluded that the increased functional size of the salience network was characteristic of individuals with depression but that it was not indicative of the time course or severity of the disease. This led them to speculate that the expansion of this network predated and stood as a potential trait biomarker for depression as opposed to single-handedly underlying or causing depression. To test this theory, they subsequently analyzed the brains of children (between the ages of 9 and young adulthood) before the onset of depressive symptoms. They discovered that children who ultimately went on to be diagnosed with depression had expanded salience networks when compared with those who were not. Collectively, these findings illustrate that the functional enlargement of the salience network is a characteristic feature of brain network organization among people predisposed to depression. Furthermore, this distinctive feature predates the onset of symptoms of depression, is stable, and is unaffected by fluctuations in depressive symptoms (1).

Lynch et al. propose two reasons for this expansion of the salience network in those with depression. First, they comment that their findings are consistent with multiple studies that indicate brain network topology distribution is a compensatory response based on use and that individuals who go on to develop depression are those who have relatively increased usage of this network (6, 7). Second, they postulate that there could be a genetic predisposition to developing an enlarged salience network in individuals who will go on to develop depression (1). Based on previous research that has consistently found significant atrophy in the brains of individuals with depression, we propose a third explanation (8). Specifically, we propose that the salience network could appear to be relatively functionally expanded as a consequence of atrophy of other brain areas that could also predate depressive symptoms (8, 9). While Lynch et al. commented that the salience network may be enlarged to compensate for the atrophied other areas where connections may not be as strong in their first reason, we propose that perhaps the salience network is functionally enlarged as a secondary consequence of normalization in other areas of the individual's atrophied brain.

It is important to note that there are many similarities between the regions implicated in atrophy in depression and the salience network, including the insular cortex, anterior cingulate cortex, and sections of the prefrontal cortex. However, the hippocampus and striatum are found to be atrophied in individuals with depression and are not found in the salience network (10). Furthermore, while some regions of the prefrontal cortex have been associated with the salience network, atrophy is found to be more widespread throughout the prefrontal cortex in individuals with depression (10). The atrophy of these regions found outside the salience network could account for the appearance of relative functional expansion of the salience network in the paper by Lynch et al.

Received: 3 March 2025. Revised: 25 March 2025 and 3 April 2025
Published online: 13 May 2025.

Regardless of the foundation of these findings, the topological difference in the salience exists, persists, and predates the onset of depressive symptoms. This suggests that a functionally enlarged salience network could be interpreted as a predictive depression biomarker. The United States National Institute of Health defines a biomarker as a measurable trait indicative of a normal process, a pathogenic one, or in response to intervention (11). Biomarkers in psychiatry remain challenging to characterize due to disorders' overlap and heterogeneous presentation (11). However, despite the heterogeneous presentation of depression, the salience network is observed to be consistently enlarged in those with depression. Those findings suggest that there is potential for identifying individuals at risk of developing the disorder.

Depression remains a poorly predicted and diagnosed disorder despite the significant burden it inflicts. By identifying those at risk of developing the disorder earlier, more strenuous proactive monitoring and preventative measures could be brought to bear, and fewer individuals would fail to receive a diagnosis and, ultimately, treatment. Symptoms of depression have life-lasting physical, professional, and social consequences, particularly with the typical onset of depression falling synchronously with significant life decisions in adolescence (12). By identifying individuals at risk before they experience the full impact of depression, we can intervene earlier, leading to lasting improvements in their quality of life. Finally, early detection has been proven to support remission in those with depressive symptoms and decrease the likelihood of progression to treatment resistance, ultimately lessening the likelihood of relapse, longer depressive episodes, and shorter periods of remission (13, 14).

Additionally, it is important to consider the strong association between adverse life events and later life psychopathology (15). Adverse life events are also associated with functional and morphological changes in brain regions found in the salience network (16). This raises the question as to whether the enlarged salience network and the increased risk of depression associated with it, found by Lynch et al., are simply an effect of these adverse events. However, while previous work has illustrated dysfunction in the salience network in a multitude of cognitive disorders associated with adverse life events, the dysfunction of the salience network presents on a spectrum of hypo and hyperactivity in varying psychiatric disorders (5). Specifically, past work demonstrates hyperactivity in the network in individuals with PTSD, a mix of hyper and hypoactivity in anxiety, and hypoactivity in anorexia nervosa (17–19). Therefore, while dysfunctional connectivity in the salience network presents in a majority of individuals with psychiatric disorders strongly associated with adverse life events, the exact dysfunctions appear to vary across multiple psychiatric presentations.

In addition to identifying individuals at risk for depression earlier, these findings hold the potential to inform the development of depression therapeutics that target the reduction in functional connectivity in the salience network. While Lynch et al. found that a larger salience network was characteristic of individuals with depression but not indicative of the time course or severity of the disease, it remains unclear if we can modulate the network's size with any therapeutics other than rTMS (as rTMS was found to have no impact), and if so, how would this impact the course of disease in individuals. There could be value in investigating the effects of other established and novel treatments for depression, including antidepressants, exercise, diet, electroconvulsive therapy, ketamine, and psychedelics, among others, as emerging studies have found that all the above have been implicated in the central nervous system plasticity (20–22). In particular, one day after psilocybin therapy, a significant reduction in the default mode network (DMN) recruitment was observed, with increased between-network integration between the DMN and salience network (23). Specifically, longitudinal studies tracking how the size of the salience network evolves with different treatment modalities could provide transformative insights into whether external stimuli can modify this network, the impact of these interventions on the network at various stages of life, and if a reduction in the size of the salience network impacts symptoms of depression. Ultimately, these insights could lead to a more substantial understanding of how external factors alter the salience network and if alterations in this network can lead to improved symptoms of depression, thereby paving the way for the development of improved personalized treatments to mitigate the continued impact of depression.

Depression is not a simple disease characterized by independently functioning brain areas or isolated neurotransmitter imbalances. Instead, by record, it is a multifaceted condition with altered brain-wide connectivity that cannot be comprehensively understood through these fragmented lenses. Furthermore, should the identified expansion in the salience network prove to be related to the likelihood of developing other psychiatric disorders, it could be used as a potential biomarker for the development of these disorders as well, improving outcomes for patients with multiple psychiatric conditions. Future advances in the treatment of depression must recognize that depression is a disease characterized by altered connectivity across the brain versus taking a (too) low-level e.g., 'reductionist' approach. Only then will we make truly incremental advances on addressing the burden of depression at the individual and societal levels.

Katerina Palacek[1], Robin Carhart-Harris, PhD[2], and Nicholas Fabiano, MD[3]

[1]University of Ottawa, Faculty of Medicine, Ottawa, ON, Canada; [2]Weill Institute for Neurosciences, University of California San Francisco, San Francisco, CA, United States; [3]University of Ottawa, Department of Psychiatry, Ottawa, ON, Canada

✉ *e-mail: nfabi026@uottawa.ca*

References

1. Lynch CJ, Elbau IG, Ng T, Ayaz A, Zhu S, Wolk D, et al. Frontostriatal salience network expansion in individuals in depression. Nature. 2024;633(8030):624–33. DOI: 10.1038/s41586-024-07805-2. PMID: 39232159; PMCID: PMC11410656
2. Liu Q, He H, Yang J, Feng X, Zhao F, Lyu J. Changes in the global burden of depression from 1990 to 2017: findings from the Global Burden of Disease study. J Psychiatr Res. 2020;126:134–40. DOI: 10.1016/j.jpsychires.2019.08.002. PMID: 31439359
3. Reardon S. Found: a brain-wiring pattern linked to depression. Nature. 2024; 633(8029):265–6. DOI: 10.1038/d41586-024-02857-w. PMID: 39232236
4. Mulders PC, van Eijndhoven PF, Beckmann CF. Chapter 7 – Identifying Large-Scale Neural Networks Using fMRI: Academic Press; 2016. p. 28.
5. Schimmelpfennig J, Topczewski J, Zajkowski W, Jankowiak-Siuda K. The role of the salience network in cognitive and affective deficits. Front Hum Neurosci. 2023;17:1133367. DOI: 10.3389/fnhum.2023.1133367. PMID: 37020493; PMCID: PMC10067884
6. Penfield W, Boldrey E. Somatic motor and sensory representation in the cerebral cortex of man as studied by electrical stimulation. Brain. 1937;60(4):389–443.
7. Yu XJ, He HJ, Zhang QW, Zhao F, Zee CS, Zhang SZ, et al. Somatotopic reorganization of hand representation in bilateral arm amputees with or without special foot movement skill. Brain Res. 2014;1546:9–17. DOI: 10.1016/j.brainres.2013.12.025. PMID: 24373804
8. Kokce A, Can MS, Karaca O, Ozcan E, Kus I. Atlas-based structural analysis of prefrontal cortex atrophy in major depressive disorder: correlations with severity and episode frequency. Psychiatry Res Neuroimaging. 2024;344:111885. DOI: 10.1016/j.pscychresns.2024.111885. PMID: 39217669
9. Elkommos S, Mula M. A systematic review of neuroimaging studies of depression in adults with epilepsy. Epilepsy Behav. 2021;115:107695. DOI: 10.1016/j.yebeh.2020.107695. PMID: 33348194
10. Zhang FF, Peng W, Sweeney JA, Jia ZY, Gong QY. Brain structure alterations in depression: psychoradiological evidence. CNS Neurosci Ther. 2018;24(11):994–1003. DOI: 10.1111/cns.12835. PMID: 29508560; PMCID: PMC6489983
11. Garcia-Gutierrez MS, Navarrete F, Sala F, Gasparyan A, Austrich-Olivares A, Manzanares J. Biomarkers in psychiatry: concept, definition, types and relevance to the clinical reality. Front Psychiatry. 2020;11:432. DOI: 10.3389/fpsyt.2020.00432. PMID: 32499729; PMCID: PMC7243207
12. Beames JR, Kikas K, Werner-Seidler A. Prevention and early intervention of depression in young people: an integrated narrative review of affective awareness and ecological Momentary Assessment. BMC Psychol. 2021;9(1):113. DOI: 10.1186/s40359-021-00614-6. PMID: 34392830; PMCID: PMC8365890
13. Halfin A. Depression: the benefits of early and appropriate treatment. Am J Manag Care. 2007;13(4 Suppl):S92–7. PMID: 18041868
14. Corey-Lisle PK, Nash R, Stang P, Swindle R.Response, partial response, and nonresponse in primary care treatment of depression. Arch Intern Med. 2004;164(11):1197–204. DOI: 10.1001/archinte.164.11.1197. PMID: 15197045
15. Felitti VJ, Anda RF, Nordenberg D, Williamson DF, Spitz AM, Edwards V, et al. Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults. The Adverse Childhood Experiences (ACE) Study. Am J Prev Med. 1998;14(4):245–58. DOI: 10.1016/s0749-3797(98)00017-8. PMID: 9635069
16. Herzog JI, Schmahl C. Adverse childhood experiences and the consequences on neurobiological, psychosocial, and somatic conditions across the lifespan. Front Psychiatry. 2018;9:420. DOI: 10.3389/fpsyt.2018.00420. PMID: 30233435; PMCID: PMC6131660
17. McFadden KL, Tregellas JR, Shott ME, Frank GK. Reduced salience and default mode network activity in women with anorexia nervosa. J Psychiatry Neurosci. 2014;39(3):178–88. DOI: 10.1503/jpn.130046. PMID: 24280181; PMCID: PMC3997603

18. Li R, Shen F, Sun X, Zou T, Li L, Wang X, et al. Dissociable salience and default mode network modulation in generalized anxiety disorder: a connectome-wide association study. Cereb Cortex. 2023;33(10):6354–65. DOI: 10.1093/cercor/bhac509. PMID: 36627243
19. Akiki TJ, Averill CL, Abdallah CG. A network-based neurobiological model of PTSD: evidence from structural and functional neuroimaging studies. Curr Psychiatry Rep. 2017;19(11):81. DOI: 10.1007/s11920-017-0840-4. PMID: 28924828; PMCID: PMC5960989
20. Fabiano N, Lane MM, Marx W. Diet and depression. CMAJ. 2024;196(35):E1205–6. DOI: 10.1503/cmaj.240440. PMID: 39433309; PMCID: PMC11498342
21. Fabiano N, Puder D, Stubbs B. The evidence is clear, exercise is not better than antidepressants or therapy: it is crucial to communicate science honestly. J Phys Act Health. 2025;22(2):161–2. DOI: 10.1123/jpah.2024-0743. PMID: 39662311
22. Wang YB, Song NN, Ding YQ, Zhang L. Neural plasticity and depression treatment. IBRO Neurosci Rep. 2023;14:160–84. DOI: 10.1016/j.ibneur.2022.09.001. PMID: 37388497; PMCID: PMC10300479
23. Daws RE, Timmermann C, Giribaldi B, Sexton JD, Wall MB, Erritzoe D, et al. Increased global integration in the brain after psilocybin therapy for depression. Nat Med. 2022;28(4):844–51. DOI: 10.1038/s41591-022-01744-z. PMID: 35411074