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Egyptian Journal of Medical Human Genetics (2024) 25:84
https://doi.org/10.1186/s43042-024-00559-6

Egyptian Journal of Medical Human Genetics

RESEARCH

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Computational analysis of the divergent neurotranscriptomic signatures of major depression and suicidality

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Abstract

Background Suicide is a leading cause of death globally. Identifying individuals at higher suicidal risk is a key to suicide prevention. Patients with comorbid psychiatric disorders, especially major depressive disorder (MDD), are known to be highly prone to suicidality. However, the behavioural manifestations of MDD and suicidality are distinct, indicating potentially unique molecular underpinnings, of which our current understanding is limited. Delineating the unique and shared molecular etiologies of MDD and suicidality would be imperative to devise effective treatment strategies for suicidal behaviour. To this end, we analysed the existing literature pertaining to transcriptomic alterations in brain samples of individuals who died from MDD or by suicide. Subsequently, biological processes associated with the differentially expressed genes (DEGs) were identified. In addition, we also examined the transcriptional regulators (TRs) potentially driving cortical gene expression changes in MDD and suicidality.

Results A set of immunological genes was found to be commonly upregulated in MDD but downregulated in suicide. Actin and cytoskeleton organization genes also had a similar trend. In addition, MDD-upregulated and suicide-downregulated genes were found to have overrepresented target sites for 40 TRs associated with epigenetic as well as polymerase-mediated regulation. Any variations in the levels of these TRs could be of behavioural consequence in MDD and suicidality.

Conclusions A clear understanding of the condition-specific neurotranscriptomic differences in MDD and suicidality would be valuable in order to delineate the biological mechanisms underlying these conditions. Importantly, it would provide insights into more effective treatment strategies for suicidality among individuals with or without MDD. However, we have yet to determine the molecular basis of suicidality in the context of MDD and as a standalone mental condition. In this regard, the present findings would be of scientific and clinical relevance and could stimulate further research.

Keywords Major depressive disorder, Suicidal behaviour, Neurotranscriptomics, Neuroimmune system, Transcriptional regulation, Cytoskeleton

Background

Suicide is a major contributor to global mortality. Suicidal deaths are predicted to increase globally, and concerted efforts are being made towards their reduction [1]. The recent inclusion of suicidality in the Diagnostic and Statistical Manual of Mental Disorders-V highlighted the need for a better understanding of the neurobiological underpinnings of suicidal behaviour [2]. Identification of at-risk individuals would be a cornerstone of suicide

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prevention. 90% of suicidal individuals are known to suffer from other psychiatric disorders. Major depressive disorder (MDD) is among the most prevalent mental illnesses, and suicide risk in MDD is reported to be 20 times greater than that among non-depressed individuals [3]. However, the symptomology and behavioural outcomes of suicidality and MDD are distinct [2], suggesting unique molecular etiologies underlying these conditions. A clear understanding of these molecular signatures would be important for a better scientific understanding as well as to develop clinically-effective therapeutic strategies personalised to treat suicidality in MDD patients and non-MDD individuals. Though imperative, the unique molecular features associated with MDD and suicidality are yet to be delineated [3, 4]. To date, there have been limited efforts to untangle the molecular processes driving the unique behavioural outcomes in MDD and suicidality. Most reports published so far, related to MDD and/or suicidality, have not differentiated the molecular signatures of the two conditions [5–9]. In this regard, the present study critically analysed the existing literature, to separate the molecular signatures of suicidality and MDD. This study provides novel insights into unique gene expression patterns potentially contributing to distinct outcomes of depressive and suicidal behaviour.

Methods and materials

Selection of research reports: inclusion and exclusion criteria

The transcriptomic studies performed using postmortem human brain samples were considered. Systematic database searches were performed on PubMed, Google Scholar, and NCBI GEO to identify the relevant studies. The search words used were suicide, major depression, human, gene expression, transcriptomics, RNA seq, and microarray. Experiments conducted on suicide victims who had MDD were not included. Only those studies reporting the transcriptomic changes within the cortical tissues in cohorts of MDD subjects who did not commit suicide, and suicide victims who did not suffer from MDD were considered for the present analysis. The details of these studies and the differentially expressed genes (DEGs) are given in Table 1 and Supplementary File 1. The gene expression data of all the identified studies were not publicly available, precluding a meta-analysis approach. Hence, the DEGs were considered as reported by the authors.

Identification of biological processes and cellular pathways associated with genes differentially expressed in suicidality and MDD

The genes reported to be up/downregulated in suicide and MDD were analysed to identify their biological roles. The genes found to be differentially expressed in opposite directions between studies were excluded from the analysis. The biological processes, molecular functions, and cellular pathways significantly associated with the DEGs were identified through Gene Ontology (GO) analysis using the Enrichr web server [10]. The analyses were performed against the respective GO databases (GO Biological Process 2021, GO Molecular Function 2021, and KEGG 2021 Human), as per the default parameters. The GO terms found to be enriched among the DEGs were manually analysed to identify any prominent patterns between suicide and MDD gene lists. Subsequently, significantly overrepresented GO terms were identified using FunSet and g:GOSt tools. FunSet clusters similar functional terms using spectral clustering and identifies a representative term for each cluster [11]. The Benjamini–Hochberg false discovery rate of 0.05 (default value) was used as the statistical cut-off value to identify overrepresented terms. The enrichment of GO terms of 'biological process' was analysed against the human database. In addition, a similar gene set enrichment analysis was also performed through the g:GOSt web server, to identify overrepresented terms associated with the gene lists, from GO 'molecular function' and 'biological process' as well as KEGG, against the human database as per the default statistical algorithm (g:SCS) and a cut-off value of 0.05 [12].

Identification of transcriptional regulators potentially driving gene expression changes in suicidality and MDD

The TRs having overrepresented binding sites in the regulatory regions of DEGs were identified using the BART web tool (v 2.0) [13], against the Human (hg38) database. The TRs with overrepresented target sites in the DEGs were identified with the Irwin-Hall p-value cut-off of

Table 1 Studies considered in the present analysis

Sr. no	Study	Comparison	DEGs		References
			Upregulated	Downregulated	
1	Dóra et al. 2022	Suicide versus controls	138	1262	[14]
2	Klempan et al. 2009	Suicide versus controls	7	5	[15]
3	Yoshino et al. 2021	MDD versus controls	440	259	[16]

0.01, as per the default parameters. The TRs identified within the different categories of genes were compared using a Venn diagram tool (bioinformatics.psb.ugent.be / webtools/Venn/).

Results

Biological functions of genes differentially expressed in cortical tissue samples of MDD patients and suicide victims

An analysis of the published reports of transcriptomic alterations associated with suicidality and MDD identified three studies which qualified for the present analysis (Table 1). These studies analysed the MDD and suicide subjects separately. The unavailability of the gene expression raw data of all three studies precluded a meta-analysis approach. Thus, the DEGs reported in the original studies were considered directly for comparative and functional analyses.

The DEGs pertaining to MDD patients and suicide victims were separately analysed to identify their biological functions. The numbers of DEGs reported under each category are given in Table 1 and Fig. 1. Two genes, *GABRG1* and *S100B*, were found to be differentially expressed in opposite directions between the two considered studies on suicide. While these genes were found to be downregulated in the suicide samples studied by Dóra et al. [14], they were upregulated in the suicide samples analysed by Klempan et al. [15]. Owing to the inconsistent expression patterns, these two genes were not considered for further analyses. Remarkably, 37 genes found to be upregulated in MDD were downregulated in suicide.

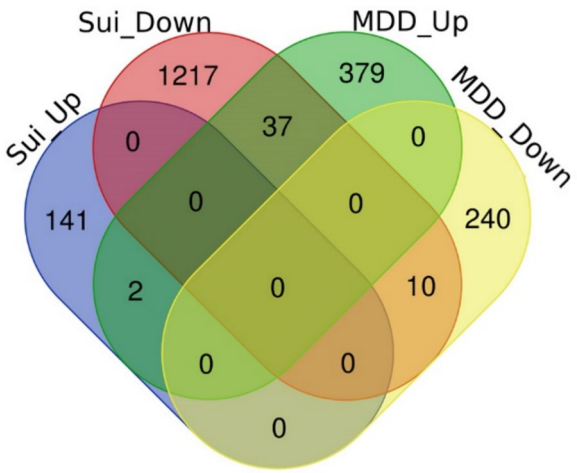

Fig. 1 Number of differentially expressed genes in the cortical samples of MDD patients and suicide victims. Sui_Up and Sui_Down: upregulated and downregulated in suicide, respectively. MDD_Up and MDD_Down: upregulated and downregulated in MDD, respectively

GO analysis of these genes showed them to be associated with immune system functioning, including Toll-like receptor signalling and cytokine functioning. Also, cytoskeleton and actin-associated genes were upregulated in MDD and downregulated in suicide. In addition, glutathione metabolism genes were downregulated in both conditions, while synaptic signalling and monoamine transport genes were upregulated in suicide. Notably, the majority of the genes downregulated in MDD were TRs. These results are summarized in Table 2, with further details given in Supplementary File 2.

Transcriptional regulators potentially influencing differential gene expression in MDD and suicide

We further analysed the TRs having overrepresented targets in the regulatory regions of DEGs, followed by a comparison of the identified TRs (Supplementary Files 3 and 4). Interestingly, 40 TRs were commonly found to have overrepresented binding sites within MDD-upregulated and suicide-downregulated genes (Supplementary Fig. 1). They were found to be associated with epigenetic regulation and also polymerase-mediated transcription. The functions of these TRs are detailed in Supplementary Table 1. Potential changes in the levels of these TRs could have major consequences in suicidality and MDD. These included the members of polycomb complex, EZH1, PCGF1, and RYBP, known to play pivotal roles in epigenetic modifications [17–19], as well as other known TRs such as TRIM25 and KLF family members.

In summary, the present study highlighted an overlapping set of immunological genes upregulated in MDD while downregulated in suicide, and a similar see-saw trend was observed among cytoskeleton and actin-related genes. Genes downregulated in MDD were largely TRs; additional analysis identified common TRs with significantly overrepresented binding sites in the regulatory regions of the genes upregulated in MDD and downregulated in suicide.

Discussion

In light of the globally increasing number of suicidal deaths, clinically effective therapy to treat suicidality would be imperative. MDD is a known, major psychiatric correlate of suicidality; however, the two conditions have remarkably distinct behavioural outcomes, whose molecular basis is yet to be understood. The present literature-based study analysed the gene expression patterns in human cortical samples. Notwithstanding the limited number of studies that qualified for the present analysis, intriguing patterns of transcriptomic alterations were observed. Potential interactions between neuroimmune pathways, cytoskeleton, and TRs could be underlying the

Table 2 An indicative list of prominent GO terms associated with DEGs

S. no	Category	GO term	Adj. p value
1	Downregulated in suicide and MDD	Glutathione transferase activity	1.048×10^{-2}
2	Downregulated in suicide	Actin binding	1.974×10^{-3}
		Cis-regulatory region sequence-specific DNA binding	6.266×10^{-3}
		Adaptive immune response based on somatic recombination of immune receptors built from immunoglobulin superfamily domains	2.524×10^{-3}
3	Upregulated in MDD	Actin cytoskeleton organization	9.723×10^{-5}
		Regulation of neutrophil degranulation	8.563×10^{-3}
		Neutrophil activation involved in immune response	1.912×10^{-2}
4	Upregulated in MDD and downregulated in suicide	Toll-like receptor binding	4.601×10^{-4}
		Immune system process	7.296×10^{-4}
		Regulation of cytokine production	1.934×10^{-2}
5	Downregulated in MDD	Sequence-specific DNA binding	1.126×10^{-4}
		DNA-binding transcription factor activity	9.921×10^{-4}
		Transcription regulator activity	1.073×10^{-2}
6	Upregulated in suicide	Synaptic signalling	2.175×10^{-5}
		Regulation of postsynaptic membrane potential	3.398×10^{-2}

pathologies of suicidality and MDD, which need to be further investigated.

Perturbation of the immune system in MDD and other psychiatric conditions is well-documented, even though a consensus is yet to be reached regarding the individual immunological parameters such as cytokine levels [3, 4]. Hyperactivity of immunological genes in the brain may induce inflammation, leading to oxidative stress and neuronal damage [20, 21]. Notably, several studies have also suggested hyperneuroinflammation in the brain tissues of suicidal individuals; however, most studies were unable to untangle the possible effects of MDD on neuroinflammation in these individuals [3, 22]. Through careful selection of the available research reports, the present analysis points towards an opposite trend of immunological gene expression in the brain tissues of individuals with MDD and suicidality, which could provide novel insights into the neurotranscriptomic changes in these conditions.

The present analysis also suggested cytoskeleton-related genes to be downregulated in suicide, while synaptic signalling genes were upregulated. Altered activity of cytoskeleton, including changes in dendritic architecture and synaptic density, is known to be associated with MDD and other psychiatric conditions [23–25]. Interestingly, dysregulation of plasma membrane-actin functioning due to decreased acetylation was suggested to be associated with suicidality in the context of depression [26]. Further, multiple psychiatric disorders including schizophrenia and autism spectrum disorders might be associated with dysregulated cytoskeleton [26]. Thus, an altered cytoskeleton could be a common hallmark associated with both MDD and suicidality.

The genes downregulated in both suicide and MDD (Supplementary File 1) included critical modulators of neural physiology. The loss-of-function variants of *CACHD1* were reported to be associated with a rare neurodevelopmental disorder and congenital abnormalities [27]. *PXMP2*, also found to be downregulated in both conditions, was reported to be a potential biomarker of depression [28]. Two other genes, *PPARA* and *TET1*, are known regulatory proteins involved in transcriptional and epigenetic regulation of brain gene expression [29, 30]. Another downregulated gene, *ACSS*, potentially regulated lipidomic composition and diversity in the brain [31]. Two genes, *RTP5* and *LY6H*, were found to be upregulated in both the conditions. However, further research is needed to understand their roles in human brain health. Thus, a modulation of transcriptional and epigenetic regulatory factors as well as lipidomic composition may be commonly associated with MDD and suicide.

In addition, several TRs were found to be remarkably downregulated in MDD, pointing towards the underlying neurotranscriptomic abnormalities. This analysis identified 40 TRs potentially driving gene expression changes in both MDD and suicidality. These TRs had overrepresented binding sites within the regulatory regions of genes upregulated in MDD as well as those downregulated in suicide. A previous study in this regard also has identified a few TRs that could be associated with suicidality in the context of other psychiatric conditions [32]. However, in contrast, the present study aimed at identifying the unique and overlapping gene expression differences in MDD and suicidality. Recent research has

started to unravel the control of gene expression through cis-regulatory regions in mental illnesses. Notably, a recent study identified regulatory elements associated with transcriptional regulation potentially driving gene expression changes in MDD and bipolar disorders [33]. Interestingly, a few members of the polycomb complex proteins were identified in this analysis. Polycomb proteins are proposed to be associated with the development of psychiatric disorders [34]. However, suicide-specific transcriptional dysregulation with and without other psychiatric disorders needs to be understood through further studies.

Limitations

Only three studies qualified for the present analysis, in which the samples from MDD patients and suicidal individuals were separately analysed. A higher number of experiments would be needed for a more powerful analysis. Also, owing to the unavailability of primary data of the selected studies in public databases, we considered the DEGs as presented by the authors of the original studies, which is another caveat of the present study. These shortcomings could be addressed through more studies in the future.

Conclusions and future perspectives

The present report highlights potential interaction between the neuroimmune system, cytoskeleton, and transcriptional regulation, underlying the distinct molecular etiologies associated with MDD patients and suicide victims (Fig. 2). Rigorous, large-scale studies would be required to further our understanding of the molecular nuances underlying suicidal behaviour in the context of MDD. Future research should also account for the contributing factors such as age and cortical development, sex of the individuals, and epigenetic influences. The present work has identified novel molecular patterns associated with MDD and suicidality. The observations presented here support the role of immune system genes in modulating the development of MDD or suicidal tendencies, thus highlighting the potential of immunomodulatory drugs in the treatment of MDD and suicidality. In future, studies and clinical trials to manage depressive and suicidal behaviour using immunomodulatory agents could be considered. Further studies separately analysing the gene expression changes in suicidal and depressive individuals would be beneficial towards better understanding of the molecular and neural underpinnings of suicidality versus MDD, which could aid in clinically effective therapeutic strategies towards reducing suicidality and better mental health.

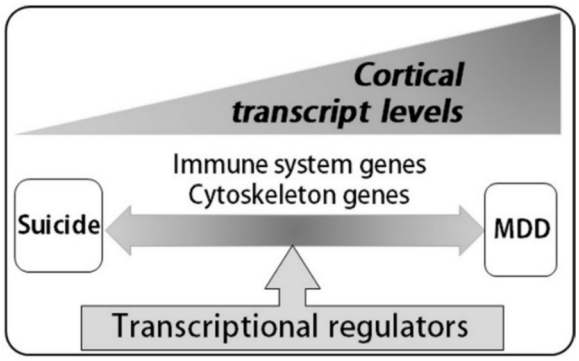

Fig. 2 Potential transcriptional signatures in cortical tissues of MDD patients and suicide victims. Contrasting trends in gene expression patterns in cortical regions could contribute to the behavioural differences in MDD and suicidality. Differential expression of immune system genes and cytoskeleton genes, potentially driven by a set of common TRs, may regulate the behavioural manifestation of MDD and suicidality. Any variations in their levels could also influence MDD and suicidality

Abbreviations

DEGs Differentially expressed genes
GO Gene ontology
MDD Major depressive disorder
TRs Transcriptional regulators

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s43042-024-00559-6.

Additional file 1.

Additional file 2.

Additional file 3: downregulated in MDD/suicide. 40 TRs were found to be common between the MDD-upregulated and suicide-downregulated categories. Table 1 Transcriptional regulators having overrepresented binding sites in the regulatory genomic regions of the genes upregulated in MDD and downregulated in suicide.)

Additional file 4.

Acknowledgements

The authors are thankful to SASTRA Deemed to be University, Thanjavur, and St Joseph's University, Bengaluru, for infrastructural facilities.

Author contributions

NMJ and SJ: conceptualization, execution, data analysis, manuscript writing, and revision; SKS: analysis of data.

Funding

Research in the laboratory of SJ is funded by Department of Science and Technology, Govt. of India (Grant No. SRG/2019/000382), and TRR Grant of SASTRA Deemed to be University.

Availability of data and materials

Not applicable.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Received: 17 July 2023 Accepted: 18 July 2024
Published online: 27 July 2024

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