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Suicide and suicide behaviors: A review of transcriptomics and multiomics studies in psychiatric disorders

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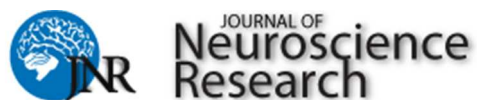
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Suicide and suicide behaviors: a comprehensive review of transcriptomics studies

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3 Suicide and suicide behaviors: a comprehensive review of transcriptomics
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5 studies
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3 Abstract (max 250 words)
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5 Aberrant gene expression can contribute to brain and nervous system dysfunction that causes
6 many psychiatric illnesses. Here, we review how transcriptomic approaches have deepened
7 our understanding of the neurobiological underpinnings of suicide and suicidal behaviors, as
8 well as how such approaches have contributed to the identification of biomarkers for these
9 disorders. We begin by providing an overview of the genetic, transcriptomic, and epigenetic
10 factors (including non-coding RNAs) implicated in suicide and their roles in the regulation of
11 gene expression. Then, we highlight the unique benefits and limitations of using either *post-*
12 *mortem* brain or peripheral tissues in transcriptomic analyses. We examine the current shift
13 from candidate-gene to genome-wide approaches in psychiatric research, which are
14 concurrently emerging with the increased consideration of the Research Domain Criteria
15 (RDoC) framework for classifying mental illnesses. Furthermore, we discuss the use of
16 transcription networks and how they can be integrated into *multi-omic* analyses. Finally, we
17 end by highlighting recent findings of peripheral markers of suicide risk identified through the
18 use of transcriptomic tools. Technological advancements and increased accessibility of these
19 technologies are drastically shaping the current research landscape. We present an overview
20 of the significant changes currently taking place to usher in a new era of psychiatric research.
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34 Significance statement (max 100 words)
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36 Genes can cause biological processes in the brain to break down. Biological and
37 environmental factors determine whether a gene is “turned on or off” and we can get a read-
38 out of which genes are turned on or off, whether or not they are transcribed, in certain disease
39 conditions. Here, we review how patterns of transcribed genes can help us understanding the
40 causes of suicide and identifying markers that predict the risk for suicide and suicidal
41 behaviors.
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3 Suicide is a major public health issue. According to the last world health statistics, close to
4
5 800,000 people die due to suicide every year, which is one person every 40 seconds and many
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7 more attempt suicide. Suicide occurs throughout the lifespan and is the second leading cause
8
9 of death among 15-29 year olds globally (World Health Organization 2016). Although suicide
10
11 is very often associated with a serious complication of major psychiatric illnesses (including
12
13 mainly mood disorders and schizophrenia), it is now considered a specific behavior with
14
15 specific vulnerability factors and pathophysiology. Moreover, while the burden of suicide is
16
17 considerable (Bolton et al. 2015), our understanding of its pathophysiology is limited and
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19 predictive biomarker development in this area is still in its infancy. To develop both a deeper
20
21 knowledge of suicide pathophysiology and to open up an avenue for the development of
22
23 predictive biomarkers of risk, transcriptomic studies of suicide behavior offer significant
24
25 opportunities. In this review, we aim to detail several conceptual and methodological
26
27 opportunities and caveats of transcriptomic studies according to the literature. Then, we will
28
29 conduct a comprehensive review of past and present results in this field.
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35 **Concepts and methodologies used to study suicide transcriptomics: opportunities and** 36 37 **caveats**

38 *From genes to epigenetics*

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41 The biological contributions to suicide and suicidal behaviors have been largely investigated
42
43 through identifying pathophysiological processes implicated in both central and peripheral
44
45 systems. Genetic association and gene expression studies aim to elucidate the molecular
46
47 mechanisms by which, genes and their regulatory roles contribute to risk factors, or biological
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49 dysfunctions lead to these complex behaviors and outcomes (Lutz et al. 2017). Suicide and
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51 suicidal behaviors have been shown to be heritable (Egeland and Sussex 1985) with twin
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53 studies suggesting significant genetic influences contributing to suicide and suicidal behaviors
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3 (Pedersen and Fiske 2010). For instance, one twin study investigating suicidal behaviors in
4 men estimated the heritability of suicide ideation and attempt to be 36% and 17%,
5 respectively (Fu et al. 2002). Accordingly, these results prompted researchers to identify
6 specific genes associated with suicide in an effort to better understand the etiology of this
7 disorder and identify potential targets for therapeutic intervention (Turecki 2014).
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14 It should be noted that individual genetic variations associated with suicide often
15 account only for a small proportion of the total phenotypic variation (small effect sizes) and
16 those with larger effect sizes tend to lack reproducibility (Perlis et al. 2010). As such, these
17 trends indicate that the risk of suicide and suicidal behaviors is likely modulated by multiple
18 genetic variations at various loci, with each contributing a small amount to the total risk of
19 disease. Subsequently, variations at multiple genetic loci have been used to produce
20 polygenic-risk-scores that have been more successfully able to predict the risk of suicidal
21 behaviors (Mullins et al. 2014)(Sokolowski et al. 2016).
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32 Although genetic variations can be used to predict suicide risk, the mechanisms by
33 which these variations disrupt regulatory processes or molecular pathways to contribute to
34 pathophysiological dysfunction belong to the field of functional genomics or transcriptomics
35 (Cooper and Shendure 2011; Pastinen 2010). Gene transcription is one functional output of
36 genetic regulation that signifies the initiation of a biological response and can be used to
37 represent the activity of a particular molecular pathway or regulatory process. Biological
38 responses that affect gene transcription can vary in timescales ranging from milliseconds, to
39 seconds, to days, or even decades with various regulatory processes contributing to varying
40 transcription kinetics (Lenstra et al. 2016). Therefore, characterizing the transcriptional
41 activity of genes associated with suicide can provide an important snapshot of the underlying
42 biology contributing to the disease state.
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3 With the development of transcriptomic technologies, data-driven genome-wide
4 analysis of gene expression has enabled the ‘unbiased’ investigation of the suicide
5 transcriptome. Microarrays were among the first technologies used to characterize whole-
6 transcriptomes and were based on the hybridization of fluorescently labeled complementary
7 DNA to hundreds of thousands of unique oligomer probes generated from a library of known
8 genomic sequences (Lowe et al. 2017). Later, the development of next-generation high-
9 throughput sequencing technologies enabled RNA-sequencing of the entire transcriptome. As
10 well, whole transcriptome sequencing allowed for the quantification of previously un-
11 annotated genes, thereby aiding novel gene discovery, which is a significant advantage over
12 microarrays (Trapnell et al. 2012). Importantly, the ability to generate whole-transcriptome
13 gene expression data has led to the development of various types of global analyses, which
14 include the identification of networks of co-expressed genes (i.e. gene which level of
15 expression is correlated) that are more likely to underlie genes with common biological
16 processes implicated in disease (Langfelder and Horvath 2008). Gene expression networks
17 may even help identify common pathways between different psychiatric diseases or between
18 different groups of patients. These gene sets and their pathways may also be easier to
19 reproduce in different studies. This could be especially useful in the study of factors unique to
20 suicidal behaviors, which are very often comorbid with other psychopathologies. Moreover,
21 the identification of gene expression networks that are highly preserved in specific tissues or
22 species can greatly facilitate the characterization of conserved biological processes, allowing
23 for translational and biomarker studies, including in different tissues (see below).
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51 *RDoC framework for mental disorder research*

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53 Interestingly, there is strong evidence supporting the association of the serotonergic system
54 with specific psychiatric behaviors or endophenotypes, such as lower serotonin metabolite
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3 levels with aggression (Brown et al. 1982) as well as serotonin transporter polymorphisms
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5 with stress susceptibility (Karg et al. 2011). These findings represent risk factors and
6
7 endophenotypes potentially common across several psychiatric diagnoses (such as
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9 schizophrenia, bipolar disorders, and personality disorders) that may help elucidate the
10
11 common mechanisms underlying specific brain functions dysregulated in psychiatric
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13 disorders. In fact, such a framework around dimensional psychological constructs relevant to
14
15 human behavior, including systems of emotion, cognition, motivation, and social behavior,
16
17 has been proposed to categorize and classify research domains in mental disorders. This
18
19 classification framework is called Research Domain Criteria (RDoC) and aims to aid
20
21 researchers to integrate molecular, genetic, neuro-circuit information and behavioral
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23 assessments to explore human brain function and behavior (Insel et al. 2010). Interestingly,
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25 potential correspondence between individual genes and specific RDoC constructs have all
26
27 been recently removed from RDoC website, with a statement, as of May 2017, indicating that
28
29 the “*current state of the field emphasizes the need for robust evidence of association,*
30
31 *generally resulting from adequately powered, genome wide studies, as opposed to candidate*
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33 *gene approaches.*” ([https://www.nimh.nih.gov/research-priorities/rdoc/update-on-genes-in-](https://www.nimh.nih.gov/research-priorities/rdoc/update-on-genes-in-the-rdoc-matrix.shtml)
34
35 [the-rdoc-matrix.shtml](https://www.nimh.nih.gov/research-priorities/rdoc/update-on-genes-in-the-rdoc-matrix.shtml)). Clearly, there appears to be a shift away from candidate gene
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37 approaches that are usually limited in scope and clinical value (Collins et al. 2012; Van der
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39 Auwera et al. 2018).

43 44 45 46 *Transcriptomic Network Approaches*

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48 The movement towards large genome-wide datasets not only allows for the discovery of
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50 associations in a more unbiased approach, but the large comprehensive sets of data allows for
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52 the study of various systems in parallel and can lead to the detection of broader molecular
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54 signatures underlying suicide (Oquendo et al. 2014). As well, the interactions between various
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3 systems can be detected. For example, significant overlap between the HPA axis and immune
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5 system has been reported in the context of social stress (Bekhbat et al. 2017) and serotonergic
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7 and dopaminergic interactions have been shown to be important in impulsive aggressive
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9 behaviors (Sen et al. 2008).

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11 One way to detect such broader signals of biological processes and interactions is
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13 through the use of transcriptomic network analyses. Transcriptomic analyses of co-expression
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15 networks can allow for the study of the molecular processes governing brain structure, circuit
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17 organization, brain function, as well as other regulatory systems including epigenetic
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19 processes and non-coding gene regulatory networks (Gaiteri et al. 2014). Genes co-expressed
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21 in a specific spatial or temporal manner are more likely to be functionally related and have
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23 been shown to be preserved across brain regions and species (Langfelder et al. 2011; Oldham
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25 et al. 2006), as well as across psychiatric categories like depression (Gaiteri and Sibille 2011).
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27 Network approaches, such as Weighted Gene Co-expression Network Analysis (WGCNA)
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29 (Langfelder and Horvath 2008), have been used to study gene co-expression in various brain
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31 regions across psychiatric and neurodegenerative diseases including schizophrenia (Chen et
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33 al. 2013) and Alzheimer's disease (Miller et al. 2008; Zhang et al. 2013). Interestingly, gene
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35 co-expression analyses have been combined with other types of data such as DNA
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37 methylation in major depression (Bustamante AC et al 2017 Psychiatry Res), miRNA, and
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39 expression quantitative trait loci (eQTL) analyses in alcohol addiction (Mamdani et al. 2015;
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41 Ponomarev et al. 2012), and GWAS in autism disorder (Voineagu et al. 2011). As well, co-
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43 expressed genes in the dorso-lateral PFC (dlPFC) have been associated with MRI measures of
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45 cognitive decline in later life (Yu et al. 2017). Other applications include characterizing co-
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47 expression networks across different brain regions in the same subjects to shed light onto the
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49 molecular processes underlying neural-circuit processes. For example, one study examining
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51 depressed subjects showed robust shifts in amygdala-cingulate gene synchrony involving
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2 hormone-type factors including insulin, interleukin-1, thyroid hormone, estradiol and
3 glucocorticoids (Gaiteri et al. 2010). Finally, studies examining drug-induced changes in
4 transcriptional networks hold the potential to unveil broader mechanisms of drug action and
5 whether they are effective at targeting the molecular networks disrupted in disease states
6 (Iskar et al. 2013). To the best of our knowledge, no previous study focused specifically on
7 gene networks associated with suicide behavior.
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11 The integration of transcriptomic data with other *omic* pillars into “Gestaltomics”
12 (such as the genome, epigenome, proteome, metabolome, phenome and microbiome) provides
13 an exciting new approach to guide a broader and multi-system understanding of specific
14 psychiatric phenotypes (Amare et al. 2017; Gutierrez Najera et al. 2017). As an example, one
15 study identified a unique co-expression network associated with cognitive performance in the
16 blood of depressed patients, and validated the expression of various genes within this network
17 at the proteomic level (Schubert et al. 2018). This analysis implicated molecular processes
18 and genes related to cell-cycle signaling, protein processing, and interferon signaling. Such a
19 multi-omic approach could facilitate biomarker discovery and can be integrated with other
20 clinical measures to better model and predict disease.
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24 Currently, several approaches, such as twin studies utilizing Structural Equation
25 Modeling, exist that are capable of integrating neurocognitive, social/psychological, and
26 biological factors (such as transcriptional networks) to model psychiatric disorders and to
27 estimate the specific contributions of genetic and environmental factors to clinical outcomes
28 (Iacono et al. 2017). As the field of psychiatric research moves forward, the use of
29 transcriptomic and other *omic* datasets will help provide a more comprehensive understanding
30 of the processes that cause psychiatric diseases and hopefully help overcome current
31 limitations in generating clinically useful tests for psychiatric diseases (Kapur et al. 2012).
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Epigenetics and non-coding RNA

Finally, an important factor contributing to gene regulation that may bridge the gap between genetic variation and transcriptomic effects in suicide, and potentially mediate the translation of social stress into biological dysfunction, is the epigenetic control of gene expression. Epigenetic mechanisms of gene regulation are heritable changes in gene function that do not involve changes in the sequence of the DNA (Dupont et al. 2009). Epigenetic mechanisms of regulation include covalent modifications of DNA, such as DNA methylation, as well as modifications of histone proteins that determine chromatin conformation, such as histone methylation and acetylation (Allis and Jenuwein 2016). Genome-wide DNA methylation studies in the suicidal brain have shown significant correlations between DNA methylation and gene expression (Labonte et al. 2013; Schneider et al. 2015).

Additionally, non-coding RNAs (ncRNAs), such as microRNAs (miRNAs) and long non-coding RNAs (lncRNAs) are increasingly recognized as important regulators of gene expression and mediators of epigenetic modifications, including in suicide and related psychiatric disorders (Lin and Turecki 2017; Serafini et al. 2014). Originating from genomic regions previously thought of as “junk DNA”, ncRNAs are becoming an essential component of transcriptomic analyses. While adding to the complexity of genetic regulation, ncRNAs represent a whole new world of processes and pathways that can help us better understand how environmental factors like social stress can have lasting effects in the human body that lead to suicide and other psychiatric disorders.

Small ncRNAs, such as miRNAs, around 22 nucleotides in length, have emerged as important negative post-transcriptional regulators of gene expression and have been implicated in the pathophysiology of various psychiatric illnesses (Geaghan and Cairns 2015). Single miRNAs may regulate many target transcripts and single transcripts may be regulated by many miRNAs (ie. multiple-to-multiple relationships) thereby allowing miRNAs to

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3 broadly regulate the expression of gene networks potentially underlying complex disease
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5 processes (Hashimoto et al. 2013).
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8 There are a few other classes of ncRNAs, which have recently emerged and may have
9
10 significant regulatory functions. Small nucleolar RNAs (snoRNAs) are able to guide the
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12 chemical modification of other RNA molecules, including ribosomal RNAs, transfer RNAs,
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14 and nuclear RNAs, leading to such processes as alternative splicing, and have been implicated
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16 in affective disorders (Lin and Turecki 2017).
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19 Another class of regulatory ncRNAs is the long ncRNAs (lncRNAs), which are greater
20
21 than 200 nucleotides in length and have low protein-coding potential. LncRNAs have been
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23 shown to be implicated in neurodevelopment, brain function and neurodegenerative diseases
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25 (Wu et al. 2013). Interestingly, there is seemingly no canonical mechanism by which
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27 lncRNAs mediate their regulatory processes (as is the case for miRNAs), but generally
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29 speaking, they are known to be able to regulate both nearby protein coding gene-targets *in cis*,
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31 through interference of transcriptional and other regulatory protein machinery, and more
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33 distal genes *in trans*, through the recruitment and targeting of protein complexes to target
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35 genomic loci (Roberts et al. 2014). LncRNAs are able to fold into complex 2D and 3D
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37 modular domains capable of binding to other genomic materials or protein machinery, thus
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39 contributing to their significant regulatory potential (Ferre et al. 2016; Novikova et al. 2012).
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46 *Transcriptomics across central and peripheral tissues*

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49 Of course, the extent to which suicidal thoughts and attempts, and their fatal realization share
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51 common or distinct underpinnings remains a difficult problem to resolve, primarily because of
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53 the tissue available for study. When it comes to psychiatry, the brain is thought to be the most
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55 direct organ involved in the pathophysiology of disease. Owing to its functions in cognition,
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3 emotional processing, and memory, the brain is poised to be the primary organ underlying the
4 symptoms and diagnostic characteristics associated with psychiatric illnesses. Thus, the use of
5 *post-mortem* brain for the study of psychiatric disease has been crucial to our understanding
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7 of suicide as well as the impact of social stress on brain dysfunction (McCullumsmith and
8 Meador-Woodruff 2011). It has allowed scientists to carry out investigations of
9 neurobiological processes of suicide in specific brain regions (Furczyk et al. 2013). With the
10 latest developments in cell type specific and single cell isolation techniques, such as
11 Fluorescence Activated Cell Sorting (FACS) and Laser-Capture Microdissection (LCM),
12 exploration of the molecular mechanisms carried out by distinct cell populations are possible
13 using *post-mortem* tissues (Hu et al. 2016; Lutz et al. 2017). Studies using these techniques
14 have only just begun to reveal distinct molecular profiles from specific cell types and
15 populations (Byne et al. 2008; Ruzicka et al. 2007), which could even be used to distinguish
16 between certain psychiatric illnesses (Arion et al. 2017). As we uncover more of the complex
17 nature of the brain, *post-mortem* brain tissues will continue to be an invaluable resource for
18 the study of the psychiatric illnesses (de Lange 2017). Some of these molecular findings can
19 then be investigated, at least in part, in living patients using brain imaging techniques
20 (Oquendo et al. 2003) or studied in animal and *in vitro* models to provide further insight into
21 the molecular mechanisms underlying brain dysfunction (McGowan et al. 2009).

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41 While *post-mortem* brain tissues offer many advantages for the study of psychiatric
42 disease, there are also unique challenges and limitations associated with their use. Since *post-*
43 *mortem* tissues provide a snapshot of the subject's state at a specific time, they are usually
44 used only in cross-sectional study designs that may not be able to confirm cause-and-effect
45 relationship and may have no predictive value. Several factors affecting tissue quality have
46 varying effects on biomolecules used for study, including DNA, RNA, proteins, and lipids
47 (Ferrer et al. 2008; Kretschmar 2009). The period of time in between the moment of death
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3 and the retrieval of brain tissue is called the post-mortem-interval (PMI) and has been shown
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5 to have varying effects on different classes of RNA and other biomolecules (Nagy et al. 2015)
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7 with longer PMI generally associating with higher RNA degradation (Birdsill et al. 2011). It
8
9 is important to note that in cases where death occurs outside of a monitored clinical setting,
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11 forensic estimates of human PMI's can be used but several factors, including environmental
12
13 temperature and cause of death, can affect rates of *post-mortem* changes used in these
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15 estimates (Sampaio-Silva et al. 2013). Fortunately, RNA integrity has been found to be a good
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17 indicator of tissue quality (Stan et al. 2006) and can be estimated with automated high-
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19 throughput technologies (Schroeder et al. 2006). As such, RNA Integrity Numbers (RIN) are
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21 reported for each sample, and also frequently controlled for in *post-mortem* brain studies,
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23 while more recently bioinformatics approaches have been developed to measure and control
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25 for RNA degradation at the level of each transcript (Wang et al. 2016). Several other factors
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27 such as mode of death (agonal conditions leading to coma and hypoxia) (Tomita et al. 2004),
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29 history of drug exposure (Karege et al. 2005), and lifetime history of disease and stress
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31 exposure (Lupien et al. 2009) can all have significant effects on gene expression and brain
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33 function. However, these factors are difficult to control for if this information is incomplete
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35 and there is not enough statistical power to do any meaningful analyses with them. Finally, in
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37 a similar vein, almost all suicide victims are suffering from at least one axis-I disorder,
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39 including major depressive disorder and/or substance use disorder (Henriksson et al. 1993).
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41 As brain tissues are rare, properly controlled and well-powered studies are difficult to carry
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43 out but crucial to disentangle the specific effects of suicide on gene expression from those
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45 arising from co-morbid psychopathologies (Zhao et al. 2015). The limited sample sizes may
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47 also pose challenges for case-control matching for factors such as age and sex, although the
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49 combination of samples from a network of brain banks may help overcome this issue
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51 (Kretzschmar 2009).
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3 It is worth noting that *post-mortem* brain is often used in studies investigating suicide
4 completion while only peripheral samples, such as blood and saliva, are used in studies of
5 other suicidal behaviors, for obvious reasons. Although most genetic association studies are
6 not hampered with such limitations (since the DNA sequence is the same across all healthy
7 cells and tissues), gene expression varies greatly across tissues (Mele et al. 2015) and is likely
8 due to different regulatory processes and mechanisms. Whether changes in the periphery
9 reflect changes in the central nervous system is an area of debate that justifiably requires
10 critical investigation (Gladkevich et al. 2004; Liew et al. 2006; Luykx et al. 2016; Rollins et
11 al. 2010; Sullivan et al. 2006; Tylee et al. 2013; van Heerden et al. 2009; Witt et al. 2013).
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23 With that being said, several candidate genes in suicide behavior are expressed in
24 blood and several studies have demonstrated that blood provides an interesting and useful
25 window to study the relationships between peripheral systems and brain processes in
26 psychiatric disorders (Belzeaux et al. 2018). Interestingly, some studies have shown that
27 social stress as well as suicide behavior can affect inflammatory gene expression in peripheral
28 immune cells. As a consequence, transcriptomics based on peripheral blood samples become
29 fully relevant to explore such hypotheses. Additionally, the use of peripheral samples could
30 provide invaluable information about brain processes that would be otherwise difficult to
31 infer. As an example, peripheral gene expression could be linked to monoamine metabolite
32 levels in the cerebral spinal fluid (CSF), which may reflect CNS metabolism (Luykx et al.
33 2016).
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50 *Gene expression patterns as biomarkers of suicide behavior*

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53 Biomarkers are considered by the American Food and Drug Administration as “a
54 characteristic that is objectively measured and evaluated as an indicator of normal biological
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3 processes, pathogenic processes, or biological responses to a therapeutic intervention”.

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5 Following this simple definition, several important properties emerge: a biomarker needs to
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7 be precisely “measured” (i.e. with high fidelity and stability), and moreover, a biomarker
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9 should be an “indicator” of disease (i.e. should be related to a specific biological process). In
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11 other words, biomarker development needs to take into account biological plausibility.
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13 Beyond the trend for hypothesis-driven research to be more impacted by error type 1 (i.e. high
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15 rate of false positive findings), high biological plausibility may lead to better reproducibility
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17 and could allow for improved therapeutic discovery and application. Lastly, a biomarker may
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19 serve different functions in the medical decision-making process. In cases of suicide
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21 prevention, clinicians could be interested in biomarkers predictive of suicide attempts or
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23 suicide death. However, the population in which such a biomarker is validated (i.e. general
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25 population vs. population with suicide behavior disorder) could largely influence its validity.
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27 Interestingly, several authors suggest that follow-up biomarkers measured longitudinally in
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29 given subjects who act as their own controls, could be more accurate than biomarkers
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31 identified through absolute differences between individuals. Thus, mediator or moderator
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33 biomarkers have been defined as biomarkers whose variation within the subject is due to a
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35 specific therapeutic intervention or life event (Belzeaux et al. 2017). We previously detailed
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37 the different technical steps that are critically important in biomarker development (Belzeaux
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39 et al. 2017). It is worth noting that no biomarker in psychiatric disorders, to this date, has been
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41 validated at each step of this process (Scarr et al. 2015). However, due to the heterogeneity of
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43 psychiatric phenotypes, and the major issue of predictive value of clinical symptoms to
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45 predict side effects, treatment response, or clinical worsening, the development of biomarkers
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47 has been an extensive field of research in mood disorders and suicide.
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54 **Understanding suicide behavior using transcriptomics**

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Suicide brain

Many biological systems are implicated in suicide and several reviews extensively discuss a number of recent findings. Generally speaking, suicide is characterized by dysregulated gene expression in stress response systems (HPA axis and Locus Coeruleus/Norepinephrine system), immune/neuroinflammatory processes, the endogenous opioid system, lipid metabolic processes, and several neurotransmitter/neuromodulator systems (serotonin, dopamine, GABA, and glutamate) (Lutz et al. 2017; Oquendo et al. 2014).

These systems have been teased apart, predominantly with candidate gene approaches that often aim to identify a single or a handful of genes underlying a Diagnostic and Statistical Manual of Mental Disorders (DSM)-defined psychiatric diagnosis. However, the DSM categorizes psychiatric disorders by emotional, cognitive, and behavioral symptoms and signs that are extremely complex (on a biological level), and thus are not likely to be characterized by dysregulation in single biological systems, let alone a few genes. In other words, the clinical classification of psychiatric disorders by complex emotional and cognitive states and behaviors likely contributes to the extreme difficulty in finding genes that cause one of the DSM's 22 broad categories of psychiatric disorders, and the ability to reproduce these results across patient groups that are often very heterogeneous (Demkow and Wolanczyk 2017).

Candidate Gene Approaches

The last few decades of biological psychiatric research have deepened our understanding of various pathophysiological processes associated with suicide. The dysregulation of the Hypothalamic-pituitary-adrenal (HPA) axis has been consistently implicated in suicide with altered levels of Corticotropin-releasing hormone (CRH) and other stress related neuropeptides in various brain regions, generally suggesting overactive HPA axis function in depression and suicide cases (Merali et al. 2006). Furthermore, increased DNA methylation

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3 and decreased mRNA expression of the glucocorticoid receptor (GR) gene, which is
4 responsible for the negative feedback regulation of HPA axis activity, has specifically been
5 found in the hippocampus of suicide completers with a history of childhood abuse (Labonte et
6 al. 2012; McGowan et al. 2009). These findings, which build on results from animal models,
7 suggest that early life social stressors may alter the expression of genes underlying the
8 regulation of HPA axis activity in the brain, thereby contributing to increased risk of suicide.
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16 However, such insight into the role of the HPA axis in suicide has yet to reconcile
17 previous studies showing the lack of consistent clinical prognostic or diagnostic value in using
18 the dexamethasone suppression test (DST), a test measuring HPA axis function, in major
19 depression (Ribeiro et al. 1993) and suicide. For example, while an early study showed DST
20 non-suppression was associated with increased risk of suicide in depressed patients
21 (Yerevanian et al. 2004), other later ones showed no such effect (Jokinen et al. 2007; Jokinen
22 et al. 2010). Clearly, the translation of these valuable, yet incremental, advances in
23 understanding the pathophysiology of suicide into significant clinical applications is still a
24 work in progress.
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36 Other candidate gene approaches to identify biomarkers of suicide have focused on the
37 *SKA2* gene, which chaperones the GR from the cytoplasm to the nucleus, and which is
38 differentially expressed with higher DNA methylation and lower mRNA expression in the
39 prefrontal cortex of suicide completers (Guintivano et al. 2014). In this study, *SKA2*
40 methylation was a statistically significant factor in additive linear models of suicide and
41 suicidal behavior across 3 independent brain gene expression cohorts and 2 blood-based gene
42 expression datasets, respectively. However, effect sizes were quite small after accounting for
43 genotypic variation, which seemed to be a much stronger factor associated with suicide and
44 related behaviors. In a subsequent study, although the *SKA2* methylation and genotype linear
45 model was statistically significant for modeling suicide attempt (but not suicide ideation), it
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3 showed poor predictive accuracy in discriminating attempters from non-attempters (Kaminsky
4 et al. 2015). Again, while the HPA axis seems to be associated with suicide at large, findings
5 at the single-gene level exhibit small effect sizes that, although statistically significant, likely
6 represent only a small piece of the puzzle, with limited clinical utility.
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11 A similar story exists for findings implicating the serotonergic system in suicide.
12 Overall findings suggest lower levels of serotonergic transmission in depressed suicide
13 completers and the up-regulation of compensatory processes (Lutz et al. 2017), such as
14 increased 5-HT neurons in the dorsal raphe (Arango et al. 2001) and increased tyrosine
15 hydroxylase mRNA and protein expression (Bach-Mizrachi et al. 2008). Furthermore, the
16 literature currently consists of reports of associations between suicidal behaviors and several
17 other genes that make up the serotonergic system, including the serotonin transporter,
18 serotonin receptors, and monoamine oxidases, although the results are variable and sometimes
19 inconsistent (Antypa et al. 2013). While abundant, the translation of these findings into
20 clinical applications has been limited. For example, a recent PET study quantifying serotonin
21 receptor 1A binding in the prefrontal cortex (PFC) showed no differences in suicide
22 attempters and non-attempters, although serotonin receptor binding in the dorsal raphe was
23 associated with lethality in attempters (Sullivan et al. 2015).
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41 *miRNAs*

42 miRNAs in the brain have been implicated in affective disorders, with some specifically
43 associated with suicidal behaviors (Serafini et al. 2014). While it has been shown that there is
44 overall down-regulation of miRNAs in the PFC of depressed suicide completers compared to
45 controls (Smalheiser et al. 2012), other studies have shown the up-regulation of specific
46 miRNAs in the PFC of depressed suicide completers compared to both controls and depressed
47 patients who died by other causes (Wang et al. 2018), suggesting suicide specific differences
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3 in miRNA dysregulation. Another study showed the up-regulation of several miRNAs
4 predicted to target several polyamine-related genes, which have been previously shown to be
5 down-regulated in the PFC of suicide completers (Lopez et al. 2014). Finally, miRNA
6 expression networks associated with suicide have been examined in the brain and may lead to
7 further characterization of more consistent miRNA-driven molecular signatures (Roy et al.
8 2017b).

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16 Inconsistencies in the characterization of miRNA dysregulations, as well as other
17 classes of molecules, may in part be attributable to heterogeneous samples grouped by broad
18 psychiatric categories such as depression and suicide. Considering the polythetic diagnostic
19 nature of many DSM psychiatric disorders, individual patients may share very few symptoms
20 and still receive the same diagnosis (as in depression where only 5/9 symptom based criteria
21 must be met) (Olbert et al. 2014). The use of more specific patient groups, perhaps stratified
22 by brain and cognitive function or behavioral symptomology (as proposed in the RDoC
23 framework), could help address this issue and develop clinical measurements that cut across
24 diagnostic categories.

35 36 37 *Other ncRNAs*

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39 LncRNAs have been studied in the context of various psychiatric disorders, including in
40 schizophrenia where the lncRNA Gomafu was found to bind to various splicing factors in the
41 brain to contribute to the alternative splicing patterns of the important schizophrenia related
42 genes *DISC1* and *ERBB4* (Barry et al. 2014). As well, lncRNAs have been found to be
43 dysregulated in the autistic brain (Ziats and Rennert 2013), and in the frontal cortex and
44 nucleus accumbens of depressed patients (Zeng et al. 2017). Only one study reported on
45 lncRNA dysregulation in the suicidal brain, with the association between one lncRNA and
46 violent suicide (Punzi et al. 2014). Another recent study identified 6 down-regulated lncRNAs
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3 in peripheral mononuclear cells that had a negative association risk in major depressive
4 disorder (Cui et al. 2017). With the discovery of these novel categories of ncRNAs, a whole
5 new window has been opened to our understanding of the regulatory mechanisms governing
6 the complex biological processes underlying psychiatric disorders. Further investigation of
7 ncRNAs will not only increase our understanding of disease etiology, but will undoubtedly
8 allow for the development of novel clinical tools and treatments.
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18 *Transcriptomic for peripheral biomarker of suicide risk*

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20 Peripheral biomarkers based on transcriptomic tools have been proposed in a few studies. One
21 research group has proposed complex convergent functional genomics strategies in various
22 cohorts, including some very small ones ($n < 10$) and with patients with heterogeneous
23 disorders, to identify biomarkers of suicide behavior (Le-Niculescu et al. 2013; Niculescu et
24 al. 2017; Niculescu et al. 2015). In one of these studies, the authors replicated the association
25 between *SATI* gene expression and suicide that was previously described (Fiori et al. 2011;
26 Le-Niculescu et al. 2013), while another one replicated associations between *SKA2* and
27 suicide behavior (Guintivano et al. 2014; Niculescu et al. 2015). Although promising,
28 associations between suicide ideation and *SATI*, *PTEN*, *MAP3K3* and *MARCKS* mRNAs have
29 not been replicated by another independent group (Mullins et al. 2014). In the same vein,
30 using hypothesis-driven strategies based on the relationship between stress and suicide
31 behavior, another study described gene expression variation of *BDNF*, *FKBP5* and *NR3C1*
32 genes and found no differences between patients with or without suicide ideation in a cross-
33 sectional study (Roy et al. 2017a).
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50 We also recently conducted a prospective study to identify biomarkers of suicide
51 behavior. We focused on *SLC6A4* mRNA (encoding the serotonin transporter), based on the
52 assumption of implicated role of the serotonin system in suicide behavior (see above).
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3 Interestingly, no previous study has focused on gene expression variation of this gene to
4 predict suicide behavior in living patients. Based on a large cohort of 148 patients with a
5 Major Depressive Episode and 100 healthy controls, we demonstrated that a lower level of
6 expression of *SLC6A4* mRNA was predictive of suicide ideation worsening during an 8-week
7 follow-up study (Consoloni et al. 2018). We also demonstrated that increased *SLC6A4* mRNA
8 across time was predictive of later suicide ideation as well as later suicide attempts. Taken
9 together, our results suggested that *SLC6A4* mRNA may constitute an interesting biomarker
10 of suicide behavior.
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20 However, it is worth noting that these few studies are not sufficiently convincing to
21 allow for a new prediction avenue based on transcriptomics. The predictive value of the most
22 promising mRNA from these studies remains modest with an area under the curve (AUC) <
23 0.75 when mRNAs are used alone (Levey et al. 2016; Niculescu et al. 2015) Although some
24 studies have used prospective and within-subject designs, future well-powered studies with
25 precise phenotypic strategies are still required.
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36 **Conclusion**

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38 Transcriptomics offers a unique perspective through which the neurobiology of suicide and
39 the impact of social stressors can be understood. Gene expression is a major output of
40 biological functions, and thus a critical substrate to study in order to understand how various
41 factors regulate the processes leading to altered brain function. Suicide and associated
42 behaviors face unique challenges in their study and careful considerations must especially be
43 taken when working with central and peripheral tissues as each has its own set of advantages
44 and caveats. While *post-mortem* brain offers a more direct window into the mechanisms
45 underlying dysfunctional processes in suicide, peripheral samples such as blood and saliva
46 offer a much more practical and clinically relevant tissue from which useful biomarkers and
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3 clinical tools based on gene expression are likely to be developed in the near future.
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5 Nevertheless, the development of clinically useful biomarkers will need to be supported by
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7 highly powered studies and confer biological plausibility. Larger network based approaches,
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9 including those integrating various *omic* domains, will likely play an important role in
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11 determining how specific transcriptomic bio-markers are related to broad molecular
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13 signatures characterizing disease as well as relevant systemic and clinical outcomes.
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15 Furthermore, research that stratifies psychiatric disorders by specific behavioral or clinical
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17 phenotypes will aid the discovery of novel disease-associated biological processes, such as
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19 regulation by miRNAs, lncRNAs, and other ncRNAs, with higher reproducibility and validity.
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21 We are currently in the midst of a major change in the scientific approaches used in
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23 psychiatric research. Shifting from candidate gene to genome-wide and network approaches
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25 as well as well from a focus on broad psychiatric disorder categories to specific
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27 endophenotypes present exciting opportunities in psychiatric research. Only time will tell how
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29 these changes will impact our understanding of psychiatric disease and personalized
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31 medicine.
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