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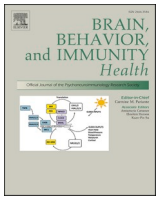

Transcriptomics and psychotherapy: An integrative review

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ABSTRACT

Gold-standard psychotherapies like cognitive-behavioral therapy (CBT) show beneficial effects, but patient responses vary, indicating a need to predict and optimize treatment efficacy. Gene expression analysis may offer insights into the interplay between psychosocial processes and biological factors that impact psychopathology and therapeutic response. This integrative review examines 17 studies that assess gene expression in the context of psychotherapy, highlighting innovative frameworks for incorporating gene expression analysis in diagnosis, predicting treatment response, and monitoring treatment progress. Current evidence points to transcriptional control pathways downstream of the hypothalamic-pituitary-adrenal (HPA)-axis and sympathetic nervous system (SNS) signaling pathways, particularly their effects on immune cells (e.g., pro-inflammatory processes and wound healing), as key areas for future research. Higher-level pathway analyses, whether theory-based or empirically driven, appear to offer the most robust framework for future studies. This review also discusses significant limitations of current literature and proposes directions for future research.

1. Introduction

In 2019, there were approximately 970 million people globally living with mental disorders, of which, 31% were living with anxiety, and 29% with depression (WHO, 2022). Currently, the success rates of gold-standard therapies for a wide range of anxiety and depressive disorders are around 50% (Pybis et al., 2017; Springer et al., 2018). Therefore, although treatments like cognitive-behavioral therapy (CBT) provide essential support for many people with mental disorders, the variability in treatment response indicates a need for improved treatment strategies. To enhance efficacy, the current guidelines from the American Psychological Association (APA) recommend personalizing psychotherapy based on a patient's psychosocial context, such as socio-economic status (American Psychological Association, 2021). Similarly, the Research Domain Criteria (RDoC) project was developed in response to the need for improved prevention and treatment efficacy in psychotherapies (Cuthbert and Insel, 2013). RDoC advocates for a dimensional perspective on mental distress, integrating behavioral and biological data, and moving beyond mere categorization of patients into discrete categories based on diagnostic criteria. Both the APA guidelines and RDoC framework point to a different outlook on psychotherapeutic processes, one that considers patients' broader psycho-social-biological context. One approach that might allow to assess this broader context is via gene expression analysis in the context of psychotherapy.

Accumulating evidence shows that our external environment (e.g., social integration vs. isolation, socio-economic status, etc.) can affect the activity of our immune system by altering the gene transcriptional activity of immune cells (Slavich et al., 2023). One example of such "social genomic" regulation is the Conserved Transcriptional Response to Adversity (CTRA), which is an immune cell gene expression profile characterized by increased inflammation and decreased anti-viral activity. In response to social stressors, fight-or-flight stress responses lead to the systemic release of adrenaline and noradrenaline. Both ligands can modulate leukocyte gene expression via adrenergic receptors that activate multiple transcription factor (TF) families such as the cyclic-AMP response binding protein (CREB), nuclear factor kappa B (NF-κB), activator protein 1 (AP-1), and GATA. Through changes to TF activity, SNS-signaling can exert significant influence over a wide array of gene expression programs, such as increasing pro-inflammatory gene expression (e.g., *IL1B*, *IL6*, *TNF*) and decreasing anti-viral type-I interferon (IFN) gene expression (e.g., *IFNA, IFNB*). Importantly, exposure to chronic stress can blunt HPA-regulated glucocorticoid signaling (Miller et al., 2008). In general, the activation of glucocorticoid receptors in leukocytes has an inhibitory effect on the same pro-inflammatory TF families that are activated by SNS signaling. Blunting of HPA-regulated gene expression inhibits this negative feedback loop and can worsen the

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pro-inflammatory impact of chronic social stressors (for extensive reviews of this topic, please see Irwin and Cole, 2011, and Cole, 2019). The CTRA pattern manifests in the context of a variety of adverse psychosocial conditions such as loneliness (Cole et al., 2015), early life adversity (Miller et al., 2009), bereavement (O'Connor et al., 2014), and chronic stress (Miller et al., 2008), while positive social experiences such as maternal warmth (Chen et al., 2011), and social connectedness (Snodgrass et al., 2022) can reduce CTRA activity (for reviews see Slavich et al., 2023; Cole, 2019). Elevated inflammatory signaling has been shown to induce depressive symptoms (Miller and Raison, 2015; Cho et al., 2019), as well as impact central nervous system (CNS) threat- and reward-related processing (Inagaki et al., 2012; Muscatell et al., 2016; Eisenberger et al., 2010).

Interestingly, maladaptive psychosocial factors are known risk factors for developing psychopathology (Bruce, 2002; Steen et al., 2022; Ridley et al., 2020; Snyder et al., 2019), and have been negatively associated with success of psychotherapy (Chen et al., 2019; Gómez et al., 2023). Yet, to date, studies investigating these psychosocial factors as predictors of psychotherapy success have yielded few consistent findings (Nilsen et al., 2013; Eilertsen and Eilertsen, 2023). These inconsistencies suggest the differential impact of psychosocial factors, potentially based on different genetic makeup alongside other potential environmental or historical risk and resilience factors. Given the role of genetic, environmental, and historical processes in regulating immune cell gene expression, blood cell transcriptomic analyses could provide a novel approach for assessing those determinants of psychopathology and psychotherapeutic response.

In this review, we explore the possibility that psychosocial risk factors can produce a measurable molecular 'fingerprint' in the immune system that could potentially affect psychopathology and treatment outcomes (see Fig. 1). As a result, gene expression analysis could potentially have utility in (i) psychopathology assessment and diagnosis, (ii) predicting response to treatment, and (iii) tracking treatment progress and outcomes.

Most previous genomic and epigenomic analyses of psychopathology and psychotherapy have employed DNA analysis (i.e., analyses of genetic polymorphisms in DNA sequence, as opposed to RNA in gene expression analysis), including candidate genes (i.e., studying a few a priori specified genes based on biological, empirical, or theoretical rationale) and genome-wide association studies (GWAS; systematically assessing the association between genetic variation and traits across the whole genome), as well as methylation studies (e.g., studying how variations in DNA methylation in a specific segment of DNA relates to traits or health conditions) (Lester and Eley, 2013; Coleman et al., 2016, 2017; Schiele et al., 2021; Rayner et al., 2019). Although these studies have provided seminal evidence, they often yield modest effect sizes due to the complex nature of gene-behavior associations. Consequently, such approaches typically require large sample sizes to detect significant effects (Coleman et al., 2016; Rayner et al., 2019), and results are not large enough in biological terms to appreciably guide clinical interventions. In this context, RNA-based gene expression studies may offer a complementary approach to the current DNA-based research toolbox. This review explores gene expression within the context of psychotherapy intervention studies, aiming to identify specific approaches to gene expression analysis that may provide greater scientific and clinical gains in the future (particularly in the areas of treatment diagnosis, treatment selection, and treatment monitoring).

Successful translation of findings from the literature reviewed below

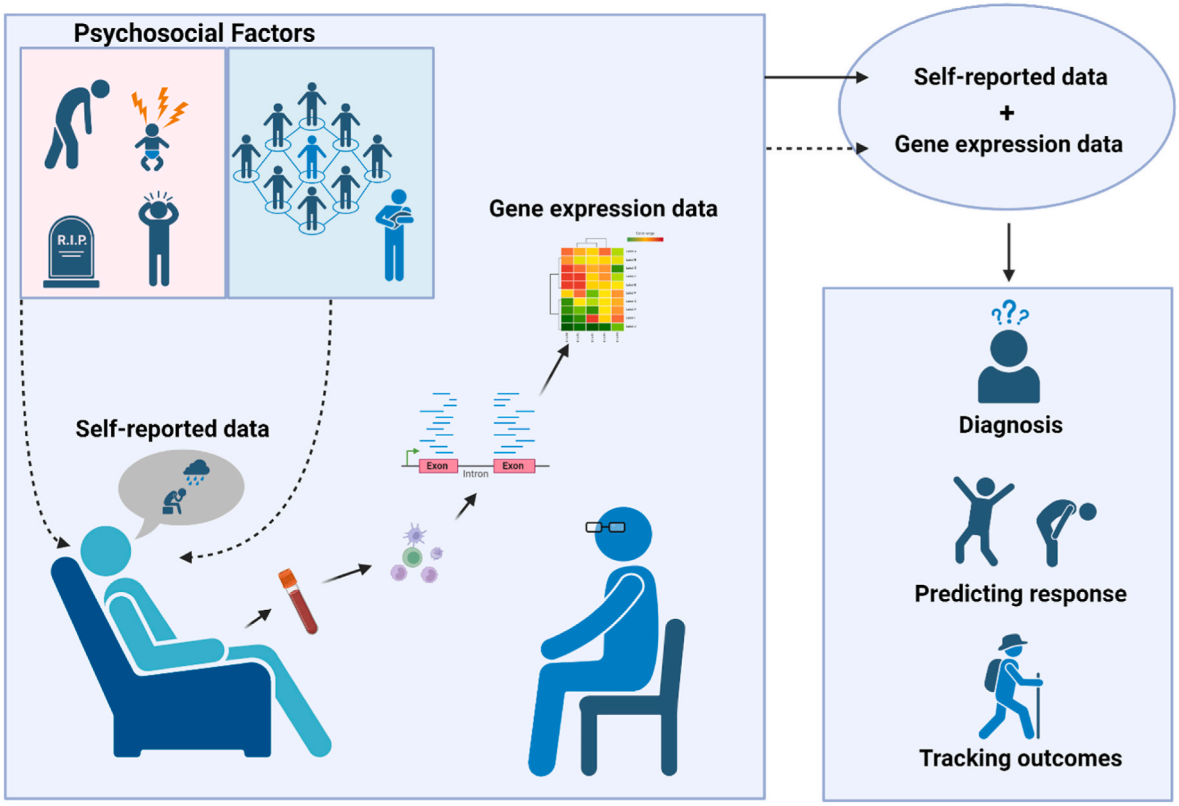

Fig. 1. Molecular 'fingerprints' of psychosocial factors and their potential utility in the psychotherapeutic process.
Psychosocial risk factors (e.g., early life adversity, bereavement, chronic stress, loneliness) and resilience factors (e.g., maternal warmth, social connectedness), impact immune cells at the molecular level (e.g., gene expression analysis). These effects can induce differential gene expression profiles ('molecular fingerprints'). In turn, this molecular level data may complement self-reported data to potentially guide aspects of the therapeutic process. Initial evidence suggests that this comprehensive psycho-molecular approach could be used to improve diagnosis accuracy, predict response to different interventions, and track treatment outcomes.

into clinical practice will require development of stable, validated algorithms which convert generically assessed genomic data as input into predicted responses to psychotherapy. Developing and validating such an algorithm faces several critical validity issues. A significant challenge is sufficient sample size for the initial training data set. Related issues involve the "large p, small n" problem, when the number of predictors (e.g., whole-genome gene expression data) is much larger than the number of observations. This may lead to overfitting and replication failures. Additionally, algorithm development, validation and testing should be carried out in independent samples (Hastie et al., 2001). While summarizing the current available evidence, we will also briefly comment on these critical validity issues.

To identify studies for inclusion in this review, we searched PubMed up until December 5th, 2023. Searches focused on human studies published in English. The following search terms were used: "gene expression" or "transcriptomics" were searched together with one of the following types of psychotherapy: Behavioral therapy, cognitive therapy, cognitive behavioral therapy, mindfulness based cognitive therapy, interpersonal psychotherapy, psychodynamic, supportive therapy, family therapy, cognitive processing, prolonged exposure, eye movement desensitization and reprocessing (EMDR; focusing on traumatic memories while experiencing bilateral stimulation, usually based on eye movements), narrative exposure therapy, contingency management therapy, emotion focused therapy, acceptance and commitment therapy, biofeedback, exposure therapy, mentalization, and psychotherapy. Additionally, reference lists of selected papers were screened. Key factors for the assessment of validity were extracted and are briefly summarized below and in Tables 1–3.

2. Assessment and diagnosis (see Table 1)

We identified 4 studies employing CBT-based interventions which provide an initial perspective on the possible utility of gene expression in differentiating between patients experiencing different levels of distress in the context of treatment.

Three studies successfully differentiated between responders and non-responders to CBT treatment based on baseline whole-blood gene expression data (Kéri et al., 2014; Levy-Gigi et al., 2013; Redei et al., 2014). Levy-Gigi et al. (2013) compared PTSD patients undergoing CBT (n = 47) to trauma-exposed individuals without PTSD (n = 31). The study assessed baseline and post-intervention gene expression levels of the *FKBP5* gene, a modulator of glucocorticoid receptor sensitivity. Lower expression levels of this gene can indicate reduced capacity to inhibit inflammation via HPA-axis signaling. The researchers found that baseline expression of the *FKBP5* gene in PTSD patients (n = 47) was lower in comparison with trauma-exposed non-PTSD participants (n = 31). A significant strength of this study is that it replicates findings from a previous non-intervention study conducted by Yehuda et al. (2009), assessing gene expression as predictor of developing PTSD following exposure to the World Trade Center Attacks (N = 35; PTSD, n = 15/35). A second study, by Kéri et al. (2014), assessed an a priori defined 10-gene construct, the Biom-10, before and after CBT in patients with a first episode of major depression disorder (MDD; n = 44) compared with a healthy control group (n = 30). The Biom-10 construct was designed to reflect affective balance, and is calculated as the sum of five "high mood"-associated genes' expression divided by five "low mood"-associated genes' expression (see Supplementary Table 1). The Biom-10 score was derived, following a rigorous process integrating findings from human peripheral blood gene expression studies, as well as animal models and post-mortem human data (Kéri et al., 2014). Higher Biom-10 scores reflect greater positive affect-related gene expression compared to negative affect-related gene expression. Baseline BioM-10 scores were negatively and significantly correlated with the magnitude of self-reported symptoms (i.e., lower Biom-10, indicating a bias towards negative affect-related gene expression, was correlated with higher self-reported depressive symptoms). Also, baseline Biom-10 scores successfully identified patients with MDD with an 84% accuracy compared with 90% accuracy for non-MDD participants. A third study by Redei et al. (2014) successfully differentiated between primary care MDD patients (n = 32) undergoing CBT and healthy controls (non-MDD, n = 32), using an a priori-defined 20-gene list (see Supplementary Table 1). This 20-gene list was also derived following a rigorous process. First the researchers identified MDD-associated genes employing animal chronic-stress models of depression assessing gene expression profiles in hippocampus and amygdala tissue to derive a blood-based gene expression panel (Andrus et al., 2012). Then, this MDD-associated blood-based gene expression panel, derived from animal models, was validated in a human study, which successfully distinguished between adolescents with early-onset MDD (n = 14) and healthy controls (n = 14) (Pajer et al., 2012).

Our review identified one randomized-controlled trial (RCT) which used an exploratory/discovery analysis to assess baseline gene expression data correlating with negative affect. Antoni et al. (2012) employed a group cognitive-based stress-management (CBSM) intervention aiming to reduce anxiety and stress in a sample of breast cancer patients randomized to intervention (n = 45) vs. active control (psychoeducation) (n = 45). In this study, peripheral blood mononuclear cells (PBMCs) gene expression analysis identified 177 genes that were differentially expressed in relation to baseline negative affect. Gene ontology analysis indicated that these genes were enriched in genes involved in pro-inflammatory processes and wound healing, potentially indicating heightened immune cell readiness to respond to injury.

Taken together, the studies above provide a framework for utilizing different approaches (i.e., candidate genes, muti-gene constructs, whole-genome gene expression profiles) for assessing baseline gene expression profiles in relation to pre-treatment psychological status. However, to the best of our knowledge, none of the findings above have yet been replicated in larger studies or independent samples. Given the poor replication rates of such small-sample "candidate gene" studies and exploratory studies, these results should be treated with caution until they are replicated in larger independent cohorts.

Considering a higher-level bioinformatics-based approach to transcriptome profiling, several additional non-intervention studies (not included in 17 intervention studies reviewed herein) show a similar pattern to that reported by Antoni et al. (2012) . These whole genome RNA profiling analyses have linked psychosocial risk factors to altered activity in transcriptional control pathways down-stream of HPA-axis and SNS signaling, as well as pathways involved in innate immunity and wound healing in the context of PTSD (Marchese et al., 2022; O'Donovan et al., 2011), chronic stress (Miller et al., 2008), low socio-economic status (SES) (Miller et al., 2009), chronic loneliness (Cole et al., 2007), and bereavement (O'Connor et al., 2014). Additionally, in a recent gene co-expression analysis study (i.e., identifying clusters of genes with correlated expression levels), a similar pattern emerged in adults with a history of childhood adversity. When these adults were exposed to stress, gene expression analysis identified two co-expressed gene modules that were enriched for genes related to pro-inflammatory processes and wound healing (Dieckmann et al., 2020). Interestingly, O'Connor et al. (2014) reported down-regulation of type I interferon responses in individuals experiencing complicated grief compared with bereaved individuals not experiencing complicated grief. This emphasizes the possible role of down-regulation of genes involved in anti-viral responses as a significant correlate of distress in the context of mental disorders.

In sum, higher level bioinformatic analysis (i.e., analyses of multi-gene "pathways" or gene sets, as opposed to individual candidate gene transcripts) seems to produce comparable results across studies and populations that implicate pro-inflammatory processes, anti-viral responses, and wound healing, which are down-stream of HPA-axis and SNS-signaling.

Table 1
Intervention studies showing gene expression profiles association with psychological distress.

Study	Distress Type	Population	Age (SD)	Intervention Type	Sample size	Analytic approach	Outcomes
Levy-Gigi et al., 2013	PTSD	Trauma exposed individuals	PTSD patients 35.9 (12) Non-PTSD controls 37 (10.4)	CBT	N = 78 PTSD patients (n = 47); Non-PTSD participants (n = 31)	A priori defined Candidate gene (*FKBP5*)	PTSD patients had lower *FKBP5* gene expression at baseline.
Kéri et al., 2014	MDD	First episode of MDD	MDD: 25.6 (4.9); Healthy controls: 25.8 (6.2)	CBT	N = 74 CBT (n = 44); Healthy Controls (n = 30)	A priori defined gene-list construct (BIOM-10)	Biom-10 scores identified depressed and non-depressed individuals
Redei et al., 2014	MDD	Primary care patients with MDD	Female/Male MDD: 48.9 (16.1)/50.3 (13.6); Controls: 48.5 (15.6)/ 53.6 (14.6)	CBT	N = 64 MDD (n = 32); Healthy controls (n = 32)	A priori defined 20-gene list	Baseline transcript abundance differed between patients and matched controls (9/20 genes). 5/20 genes were still differentially expressed between groups at Post-intervention.
Antoni et al., 2012	Anxiety and stress	Breast cancer patients	CBSM: 50.1 (7.5); Control: 49.2 (7.8)	CBSM	N = 79 CBSM (n = 45); Control (n = 34)	Exploratory discovery: Whole-genome RNA seq	Baseline negative affect was associated with 201 differentially expressed genes (>1.5 fold; including pro-inflammatory and pro-metastatic related genes).

PTSD: Post-traumatic stress disorder; MDD: Major depressive disorder; CBT: Cognitive behavioral therapy; CBSM: Cognitive behavioral stress-management.

3. Predicting response to treatment (see Table 2)

We identified 8 intervention studies assessing gene expression as a predictor of treatment efficacy. Five studies employed a CBT intervention (Coleman et al., 2017; Antoni et al., 2016; Roberts et al., 2017; Moser et al., 2022; Rodriguez et al., 2021) and the other 3 included dyadic therapy (therapy for parent and child together) (Aschbacher et al., 2022), inpatient intensive treatment for PTSD (Kumsta et al., 2023), and a citalopram treatment combined with interpersonal psychotherapy (IPT) or a brief-supportive psychotherapy (BSP) (Guilloux et al., 2015).

Two single-arm studies, both based on the same original cohort, employed CBT for anxiety (N = 102 and N = 166) and used exploratory/discovery analyses of genome-wide data to predict treatment outcome using a weighted gene co-expression network analysis (identifying clusters of highly correlated gene transcripts) and combination of genotype analysis with gene expression quantitative trait loci (eQTL) analysis (i.e., relating DNA variations to variations in gene expression (RNA)). Both studies reported no significant associations between treatment outcome and baseline peripheral blood gene expression data (Coleman et al., 2017; Roberts et al., 2017). A significant strength of these two studies is their large sample sizes compared to other gene expression psychological intervention studies. Yet, the null findings from these robustly powered studies suggest that the absolute predictive power of baseline gene expression may not be substantial enough to be clinically actionable (i.e., provide reliable distinctions in treatment outcomes for different patients). Indeed, single-arm psycho-genomic studies employing similar bioinformatic approaches usually require thousands (or more) of participants to achieve sufficient power (Kim et al., 2019; Crinion et al., 2024). In the context of psychotherapy intervention studies, obtaining such large sample sizes (n > 10,000) is a significant challenge and is likely not feasible.

Two additional single-arm studies employed a different analytical approach, focusing the statistical analysis on targets identified in previous steps or previous research. Moser et al. (2022) studied the effects of CBT on methylation and gene expression along CBT treatment course (n = 38), as well as during a first fear exposure session (n = 21; exposure protocols for treatment of PTSD include exposing patients to stimuli that trigger PTSD symptoms). Through methylation analysis, the researchers first identified the serotonin receptor 3A gene (*HTR3A*) as a candidate for further assessment. This was based on an abrupt increase in methylation of this gene following exposure training. Gene expression data for the *HTR3A* gene was then used to elucidate the functional consequences of methylation. Interestingly, *HTR3A* gene expression dynamics during fear exposure training were significantly different for remitters (n = 7) and non-remitters (n = 12). For remitters only, *HTR3A* gene expression dropped from baseline to 1 h following peak anxiety during exposure, then returning to baseline levels after 24 h. This is an example of a robust bioinformatic design utilizing whole-genome data to generate targeted hypotheses regarding specific genes. These findings, although in a small sample, suggest a mechanistic role for *HTR3A*, and serotonin-dependent signaling, in the effects of exposure-based therapy. In a different study, Aschbacher et al. (2022) a priori suggested the M1/M2 phenotype, an indicator of peripheral inflammation imbalance (assessed by gene expression profiling), to be a predictor of therapeutic outcomes following dyadic treatment for mothers and children exposed to high levels of interpersonal violence (n = 34). Their findings show that baseline M1/M2 polarization ratios in mothers predicted reduction in PTSD and depression symptoms in mothers, reduction in PTSD symptoms among children, and also differentiated between responders and non-responders (i.e., according to PTSD cut-off scores) in both mothers and children. They further suggest monocytes (which are the primary source of M1/M2 RNA transcripts in blood) as a focus for further research given their ability to cross the blood-brain-barrier and induce neuro-inflammation thus providing a neuro-immune mechanistic explanation for the observed differences in treatment response.

Two additional exploratory/discovery studies employed genome-wide co-expression analysis comparing responders vs. non-responders. In a CBT study for obsessive compulsive disorder (OCD) patients (N = 12, responders n = 6, non-responders, n = 6), an initial identification of methylation sites, followed by a genome-wide gene expression analysis, identified 197 co-expressed genes that were up-regulated in non-responders (Rodriguez et al., 2021). A second study (Kumsta et al., 2023), assessing intensive in-patient treatment for PTSD (responders, n = 32, non-responders, n = 19) identified two co-expressed gene modules that correlated with response status. Genes in those modules were involved in inflammatory processes, immune response, and positive blood coagulation (i.e., wound healing). Yet, both studies quantified predictive accuracy in the same sample used to derive the predictor (i.e., no hold-out replication or test of an a priori-specified predictor), so the robustness and general predictive accuracy of these results remain to be determined.

Another approach to gene expression analysis utilizes machine learning algorithms to identify the gene sets that are most predictive of clinical outcomes. Guilloux et al. (2015) treated adult MDD patients (n = 34) with a combination of citalopram and psychotherapy (interpersonal psychotherapy, IPT; or brief supportive psychotherapy, BSP). A whole-blood whole-genome expression analysis compared remitters (n = 19) to non-remitters (n = 10). A machine learning-based algorithm, employing a nested cross-validation approach, produced a list of 13-genes (see Supplementary Table 1), the baseline expression of which predicted remission status post-treatment (after 12 weeks) with 79% accuracy. Inputting the 13-gene list together with baseline psychometrics predicted remission status with a 97% accuracy based on only 2-genes (*IFITM3* involved in anti-viral defense, and *TIMP1* involved in immune signaling and wound healing), and one clinical feature - the QIDS (patient-reported depressive symptoms). Interestingly, the 13-gene set was additionally validated using an archival data set of MDD patients at another medical center (n = 63) treated with citalopram alone (no added psychotherapy). The 13-gene list derived from the first study predicted non-remission following 8 weeks of drug treatment with 76% accuracy (Guilloux et al., 2015). However, the relevance of the validation study to prediction of psychotherapeutic effects is not clear, especially given the small sample size of the initial "training" data set. Thus, these results should be interpreted with caution, pending replication in a larger study in the context of psychotherapy.

Across studies, it appears that the strongest prediction of clinical outcomes from baseline gene expression data comes when those baseline RNA values are augmented by additional theory- or empirically-driven insights (e.g., transcript-driven bioinformatic inferences of TF activity or cellular activation). Evidence points in particular to a potential role of transcriptional control pathways involved in pro-inflammatory process, immune response, and wound healing (implicating immune cells), as factors that might be used in prediction models of response to

Table 2
Intervention studies assessing gene expression profiles as predictors of psychotherapy response.

Study	Type of distress	Population	Age (SD)	Intervention Type	Design & Sample size	Analytic approach	Outcomes
Roberts et al., 2017	Anxiety	Adults with panic disorder or a specific phobia	39.8 (range: 19 to 68)	CBT	Single arm study N = 102	Exploratory: Weighted gene co-expression network analysis	No significant outcomes.
Coleman et al., 2017	Anxiety	Adults with panic disorder or a specific phobia	39.2 (11.4)	CBT	Single arm study BL to post-treatment: 166 BL to 6-months follow-up: 110	Exploratory: Genotype and expression data combined in eQTL analyses.	No significant outcomes
Moser et al., 2022	Panic Disorder	Adults with panic disorder with/without agoraphobia	32 (10)	CBT	Single arm study N = 21	Exploratory: Candidate gene expression, identified by genome-wide methylation analysis	In remitters, *HTR3A* gene expression dropped significantly from baseline to 1 h after peak anxiety during exposure
Aschbacher et al., 2022	PTSD & Depression	Low income mothers and children exposed to high levels of interpersonal trauma.	Mothers 31.58 (0.88) Children 4.17 (0.19)	Child-parent Psycho-therapy	Single arm study N = 34 (pairs of mothers and children)	A priori defined: Macrophage M1/M2 ratio (based on differential gene expression)	Greater baseline M1/M2 phenotype significantly predicted poorer treatment response in mothers (for both PTSD and depression symptoms), and predicted non-response. In children, greater baseline M1/M2 phenotype predicted lesser reduction in PTSD scores (trend, p = 0.054), and predicted non-response.
Rodriguez et al., 2021	OCD	Children & Adolescents	Responders 11.8 (3.1) Non-responders 13.3 (2.1)	CBT	Responders vs. non-respoders N = 12; Responders (n = 6); Non-responders (n = 6)	Exploratory: Genome-wide methylation and gene expression analysis	Two genes, *PIWIL1* and *MIR886* were enriched in CpG sites showing higher methylation in non-responders, in association with a module of 197 co-expressed genes that were up-regulated in non-responders.
Kumsta et al., 2023	PTSD	PTSD inpatients	Responders 40.38 (12.16) Non-responders 37.16 (11.58)	In-patient intensive PTSD treatment	Responders vs. non-responders N = 51; Responders (n = 32); Non-responders (n = 19)	Exploratory: Co-expression network. & Differential gene expression.	Baseline co-expression networks analysis identified two modules (32 genes; 162 genes) with Eigengenes that were correlated with response status.
Guilloux et al., 2015	MDD and anxiety	Patients with MDD	MDD 30.27 (10.31) Healthy controls: 34.01 (11.15)	IPT + Citalopram or BSP + Citalopram	Healthy controls; N = 67; MDD (n = 34; remitters, n = 19; non-remitters, n = 10); Healthy controls (n = 33)	Whole-genome gene expression analysis + machine learning identified a 13-gene list.	A list of 13-genes expressed at baseline predicted remission status post treatment (after 12 weeks) with a 79.4% accuracy. Further refinement with machine learning led to a model that predicted remission status with a 97% accuracy based on only 2-genes (*IFITM3* and *TIMP1*), and one clinical feature: patients reported depressive symptoms.

PTSD: post-traumatic stress disorder; OCD: obsessive-compulsive disorder; MDD: major depression disorder; CBT: cognitive behavioral therapy; IPT: interpersonal psychotherapy; BSP: Brief supportive psychotherapy; BL: Baseline; eQTL: expression quantitative trait loci.

psychotherapy. Notably, the increased predictive power of the prediction model used by Guilloux et al. (2015), suggests a distinct contribution of self-report measures and gene-expression data to overall outcome prediction. Nonetheless, these studies suffer from significant methodological limitations involving either small sample size, post-hoc "predictor" generation, and/or lack of replication in independent samples (all of which lead to overestimation of predictive accuracy).

4. Tracking treatment progress and outcomes (see Table 3)

Seven studies were identified in which the correlation between changes in peripheral-blood gene expression (from pre-to post-intervention) and changes in psychological distress were assessed. Additionally, one RCT was identified assessing the prognostic relevance of such gene expression effects on long-term disease outcomes (i.e., cancer survival) (Antoni et al., 2016).

Two of the 7 were RCTs employing a candidate gene approach. The first study, employed a mindfulness based cognitive therapy (MBCT) intervention with older adults with anxiety and depression (MBCT, n = 17, treatment-as-usual = 20) (Belliveau et al., 2021), and assessed the following candidate genes involved in inflammatory processes: *CRP*, *IL1B*, *CCL2*, *NR3C2*. The second study (Saxena et al., 2021) employed CBT in addition to pregabalin (Pr) to treat neuropathic pain (CBT + Pr, n = 20; Pr, n = 20), studying the following candidate genes: *IL6*, and *MTOR* (involved in inflammation and wound healing). Both studies specifically chose these genes based on the higher-level biological processes these genes reflect, and both found no association between changes in gene expression and distress. These two studies focused on a limited number of genes in their analysis. Such an approach may lack sufficient sensitivity and discovery power to identify significant associations between treatment effects and changes in gene expression from pre-to post-treatment. An additional exploratory/discovery study by Kumsta et al. (2023) compared responders and non-responders in the context of an in-patient intensive treatment for PTSD (see above) and reported 2 co-expressed modules changing from pre-to post--intervention: A "wound healing" module was down-regulated, and an "inflammatory" module was unexpectedly up-regulated in responders but not in non-responders. One potential explanation for this unexpected finding could stem from including different types of inflammation-related genes within the "inflammatory" module. For example, one gene that was up-regulated following therapy in the Kumsta study is the *PTGIR* gene. This gene can be pro-inflammatory in the context of rheumatoid arthritis but anti-inflammatory in the context of pulmonary vascular disease and atherosclerosis (Stitham et al., 2011). Thus, gene co-expression analysis can be useful in identifying general biological processes that are associated with treatment response, but inferences regarding the biological mechanisms and specific direction of these associations should be made with caution.

Four additional studies assessed a priori defined gene constructs or a candidate gene. Two studies employing a candidate gene approach utilized a CBT treatment for PTSD, comparing trauma-exposed individuals with and without PTSD. Levy-Gigi et al. (2013) (CBT, n = 20; control, n = 20) reported increases in *FKBP5* gene expression following treatment, and that increases in *FKBP5* gene expression were associated with greater reductions in PTSD symptom self-reports, as well as with increases in hippocampal volume (which was also increased by CBT). In the second study, Szabó et al. (2014) replicated the previous study findings, showing that CBT for PTSD lead to increased expression of *FKBP5* gene expression (compared with trauma-exposed non-PTSD controls (CBT, n = 20; control, n = 20). Additionally, increases in *FKBP5* gene expression were correlated with reduction in paired association learning (PAL) test scores (lower scores indicating improved hippocampal function; e.g., improved associative learning and spatial memory). The replication of these results, using a comprehensive assessment of both gene expression and hippocampus functions, provides strong support for the potential role of *FKBP5* as a mechanistic target in PTSD treatments. Yet, the small sample size merits caution in the interpretation of these results. Two additional studies employing a priori-defined gene constructs - the Biom-10 construct (see above) (Kéri et al., 2014), and a pre-defined 20-gene construct (see above) (Redei et al., 2014) - tracked treatment outcomes. Changes in Biom-10 scores negatively and significantly correlated with changes in self-reported depressive symptoms (i.e., greater increases in BioM-10 scores representing greater positive/negative ratio of affect-related gene expression, were associated with greater reduction in self-reported depressive symptoms) (Kéri et al., 2014). In the second study, at post-intervention greater correlation between genes was evident for remitters vs non-remitters (Redei et al., 2014), potentially indicating the activity of a regulatory mechanism (e.g., transcription factor).

Interestingly, a confirmatory analysis of RNA data from an RCT conducted by Antoni et al. (2016) provides a framework for tracking treatment progress at the functional genomic level, and assessing such progress in terms of long-term biological impact. Breast cancer patients were randomized to either a cognitive behavioral stress management (CBSM) intervention (n = 28) or to a psychoeducation control group (n = 23). Women in the control group showed increased CTRA gene expression at a 6–12 months follow-up, which was attenuated in the CBSM group (i.e., no change in CTRA at follow-up). Importantly, these RCT results show a significant correlation between pre-to post-treatment change in an a priori-specified multi-gene composite measure of the CTRA and long-term cancer survival following the CBSM intervention (N = 51; CBSM, n = 28; control, n = 23), such that increases in CTRA were significantly associated with reduced disease-free-survival.

As in previous sections, available evidence is significantly restricted by small sample sizes. Again, studies employing a pre-defined gene construct/candidate gene approach proved more successful, yet these also suffer from small sample sizes. With this significant limitation in mind, current evidence generally supports a role for HPA-dependent signaling (i.e., *FKBP5* gene expression), and pro-inflammatory processes in tracking treatment outcomes.

5. Discussion

This integrative review synthesizes the available data on the use of gene expression analysis to predict treatment responses and monitor treatment impact in the context of psychotherapy. The available data, from 17 intervention studies, suggest potential directions for future research aiming to (i) improve diagnosis and assessment (Kéri et al., 2014; Levy-Gigi et al., 2013; Redei et al., 2014; Antoni et al., 2012), (ii) predict treatment outcomes (Coleman et al., 2017; Roberts et al., 2017; Moser et al., 2022; Rodriguez et al., 2021; Aschbacher et al., 2022; Kumsta et al., 2023; Guilloux et al., 2015), and (iii) track treatment progress (Kéri et al., 2014; Levy-Gigi et al., 2013; Redei et al., 2014; Antoni et al., 2016; Kumsta et al., 2023; Belliveau et al., 2021; Saxena et al., 2021; Szabó et al., 2014). A clinically useful predictive tool would require establishing a stable scoring algorithm that converts generic measures of gene expression into predicted treatment outcomes, and is tested for predictive accuracy in large "validation" samples (n > 100) that are separate from the "training" sample used to develop the algorithm (and are ideally drawn from a different study context, in order to capture the effects of sampling and technical heterogeneity). As the field is still in its early stages, this review did not identify any studies that fulfilled all of these requirements (see discussion on limitations below). However, the studies assessed within this potential clinical-social-genomics prism (CSG; i.e., assessment, prediction, and tracking outcomes assisted by social genomics-derived insights) indicate that higher-level analysis (i.e., analysis of sets of gene transcripts, based on theory- and/or empirically driven bioinformatic constructs) might provide a more robust method for this endeavor. Additionally, the limited evidence currently available points to the involvement of several neuroendocrine- and immune-related transcription control pathways that may provide biologically plausible predictors, namely: (i)

pro-inflammatory processes, (ii) wound-healing pathways, (iii) immune response pathways, (iv) HPA-axis neuroendocrine signaling, and (v) SNS signaling pathways involving catecholamine neurotransmitters. Interestingly, this emerging empirical evidence is consistent with existing biological mechanism data from the broader social genomics literature (i.e., research mapping the pathways by which social and psychological processes affect gene expression and disease development) (Slavich et al., 2023).

5.1. Limitations and implications for future research

The studies above present novel analytic frameworks for gene expression analysis in the context of psychotherapy research. Yet, these frameworks can currently only be viewed as potential avenues for future research, and their clinical utility is far from being established. Below we consider in greater detail the limitations and challenges the field faces, as these provide a road map for future discoveries.

Table 3
Intervention studies assessing associations between gene expression changes and change in psychological measures.

Study	Distress Type	Population	Age (SD)	Intervention Type	Design & Sample size	Analytic approach	Outcomes
Antoni et al., 2016	Anxiety & stress	Breast cancer patients experiencing anxiety	CBSM: 48.71 (7.37) Control: 50.83 (6.84)	CBSM	RCT; N = 51; CBSM (n = 28); Control (n = 23)	A priori defined: Gene -construct (CTRA)	Greater 6-12-month CTRA increases predicted shorter 11-year disease-free-survival
Belliveau et al., 2021	Anxiety and Depression	Older adults with anxiety & depression	MBCT 67.8 (6.8) Control: 68.1 (5.9)	MBCT	RCT N = 37; MBCT (n = 17); Control, (n = 20)	A priori defined: Candidate genes *CRP*, *IL1B*, *CCL2*, *NR3C2*	No association between change in gene expression and change in psychological distress (measured by PHQ9 and GAD-7 questionnaires)
Saxena et al., 2021	Neuropathic Pain	Patients with Neuropathic Pain	CBT + Pregabalin: 54.45 (13.47) Pregabalin: 57 (11.21)	CBT	RCT N = 40; CBT + Pregabalin (n = 20); Pregabalin (n = 20)	A priori defined: Candidate genes *IL6*, *MTOR*	No association between pain score (Numeric rating scale) and change in gene expression.
Kumsta et al., 2023	PTSD	PTSD inpatients	Responders 40.38 (12.16) Non-responders 37.16 (11.58)	In-patient intensive PTSD treatment	Responders vs. non-responders N = 51; Responders (n = 32); Non-responders (n = 19)	Exploratory: Co-expression network. Differential gene expression.	The activity of 2 modules changed from pre- to post-treatment in responders but not in non-responders. These results indicate the involvement of a "wound healing" and an "Inflammatory processes" modules in treatment induced changes.
Levy-Gigi et al., 2013	PTSD	Trauma exposed individuals with or without PTSD	PTSD patients 35.9 (12) Trauma exposed controls 37 (10.4)	CBT	Healthy-control; N = 78; PTSD patient (n = 47); Non-PTSD participants (n = 31)	A priori defined: Candidate gene (*FKBP5*)	Greater increase in FKBP5 gene expression was associated with greater reductions in PTSD symptoms, as well with greater increase in hippocampal volume.
Szabó et al., 2014	PTSD	Trauma exposed individuals with or without PTSD	PTSD 42.4 (9.6) Trauma-exposed control 44 (12.8)	CBT	Healthy-control; N = 40; CBT (n = 20); Trauma-exposed non-PTSD controls (n = 20)	A priori defined: Candidate gene (*FKBP5*)	CBT led to increases in *FKBP5* gene expression in PTSD patients (n = 20), increasing gene expression from a significantly lower expression level (compared with trauma-exposed non-PTSD controls, n = 20), to an equivalent level. Changes in *FKBP5* gene expression were significantly and negatively correlated with changes in PAL (a task sensitive to hippocampal-related functions such as improved associative learning and spatial memory).
Kéri et al., 2014	MDD	First episode of MDD	MDD: 25.6 (4.9) Healthy controls: 25.8 (6.2)	CBT	Healthy-control N = 74; CBT (n = 44); Healthy Controls (n = 30)	A priori defined: Genes construct (BIOM-10)	Changes in Biom 10 scores were negatively and significantly correlated with changes in self-reported depressive symptoms
Redei et al., 2014	MDD	Primary care patients with MDD	Female/ Male MDD: 48.9 (16.1)/ 50.3 (13.6) Controls: 48.5 (15.6)/ 53.6 (14.6)	CBT	Healthy-control; N = 64; MDD (n = 32); Non-depressed controls (n = 32)	A priori defined: Gene list	At post-intervention, 3/20 genes were differentially expressed between remitters and non-remitters (n = 9 vs. n = 13). More correlation between genes was evident for remitters vs. non-remitters.

PTSD: post-traumatic stress disorder; MDD: major depression disorder; CBSM: cognitive behavioral stress management; MBCT: Mindfulness-based cognitive therapy; CBT: cognitive behavioral therapy; RCT: Randomized controlled trial; BL: Baseline.

Design, sample size and analytic approach. Only a few randomized-controlled intervention studies assessed gene expression in the context of psychotherapy research, with most studies employing a single-arm study (treatment responders vs. non-responders), or healthy controls. All included small sample sizes (12–166 participants). Additional significant constraints are the lack of independent replication studies, using the same (often small) "training" sample to develop an algorithm and quantify its "predictive" accuracy, use of limited number of genes, and "retrospective prediction" (i.e., using defined treatment responses to discover correlated genes/networks/gene sets, rather than specifying gene constructs a priori and then testing their empirical performance in predicting treatment outcomes). The above limitations, combined with using data derived from small studies with large numbers of predictors (on a genomic scale) leads to overfitting of prediction models, resulting in optimistically biased estimates of "predictive" accuracy. When a priori defined constructs/genes are used (e.g., Biom-10, *FKBP5*, CTRA), the tautology of using the same data to develop and test the predictive performance of an algorithm is mitigated, but small sample sizes, and/or lack of independent replications still hinder the precision and generality of conclusions. Together these are fairly profound methodological and statistical limitations pointing to the early stages of this domain of research.

The majority of studies above included primarily adult white women. Future studies should strive to incorporate more diverse samples. Additionally, the vast majority of the existing studies employed CBT-based interventions, mostly for PTSD, depression, or anxiety disorders. These consist the vast majority of mental disorder burden globally (WHO, 2022), and CBT is a main first-line treatment option for these disorders. Yet, future studies could benefit from comparing different treatment modalities. Different psychotherapies might work via differing psychological mechanisms (e.g., IPT via social processes, CBT via cognitive processes; DBT via enhancing emotional regulation). Targeting different psychological mechanisms could potentially induce differential effects on different brain regions and different top-down effects on immunity (e.g., via SNS, HPA, and/or vagus nerve dependent signaling). Indeed, accumulating evidence suggests that different psychotherapies may exert differential impacts on brain activity in a treatment- and psychopathology-dependent manner (for review, see Barsaglini et al., 2014). Furthermore, recent work by Ballesio et al. (2023), reported differential impacts of several psychological interventions on immune activity. Thus, different psychotherapies, which target different psychological processes, may differentially interact with neuro-immune systems. These multiple interactions are likely to be reflected in, and potentially affected by, different molecular pathways.

Similarly, different pre-specified gene sets are also likely to reflect different dynamics of neuro-immune interactions. This is emphasized in the lack of overlap between any of the 4 pre-specified gene lists reviewed above (i.e., Biom-10, CTRA, the Guilloux gene list, and the Redei gene list; please see Supplementary Table 1 with detailed gene names for each list). Each of these lists was derived based on different methodology, and thus is likely to reflect different neuro-immune processes involved in psychotherapeutic processes and pathology. Guilloux utilized the strengths of machine learning to refine a 13-gene list; Redei's process started with animal models of MDD, and then was tested in adolescents and adults with MDD; and Keri's Biom-10 list was developed based on the integration of animal models, gene expression and DNA analysis, and post-mortem studies in humans, followed by clinical testing. The CTRA gene list was specified based on fundamental immunology of inflammation and Type I IFN antiviral responses, and validated based on multiple studies across species (from fish to humans (Cole, 2019)), and has now been tested in the context of multiple different interventions (e.g., CBSM, CBT-I, meditation based-interventions). Future studies should combine and contrast these different comprehensive approaches to improve predictive accuracy. It is also likely that one approach might provide better diagnostic value, another be better utilized to predict response to interventions, while another might be more suitable to track treatment progress. It should be noted that with the exception of CTRA, the other 3 lists were tested for diagnostic accuracy and/or predicting treatment outcomes mainly in the context of MDD. Future studies should also consider testing all four approaches in the context of additional diagnoses and treatment modalities, and in different stages of treatments.

This review addresses only several of the RDoC dimensions. Yet, accumulating evidence from studies of interventions aimed at improving positive valence domain factors (e.g., social connectedness, well-being), were recently shown to impact peripheral-blood gene expression. For examples, in a seminal RCT, Nelson-Coffey et al. (2017), showed that a brief intervention in which participants (N = 159) were instructed to preform acts of kindness led to improvement in CTRA. A more recent study by the same group replicated this finding in a larger sample (N = 182) (Regan et al., 2022). Additionally, mindfulness-based interventions that were shown to improve both distress and well-being, are also known to significantly impact gene expression profiles, including CTRA (Bower and Irwin, 2016; Black et al., 2019). Thus, an interesting direction for future studies could also be to test gene expression as a predictor of response to other types of interventions, beyond those traditionally defined as psychotherapies. We recently conducted such a study, assessing individual-level inferences of TF activity to predict the psychosocial impacts of a compassion-based meditation (CM) in two separate cohorts (Ricon-Becker et al., 2024). In the first cohort, we found that inferences of CREB TF activity at baseline predicted reductions in loneliness and negative affect following CM. These results were validated in a second separate cohort in which CREB again predicted reductions in loneliness following CM, as well as an increase in satisfaction with life. These proof-of-concept results should motivate further research on TF activity as potential predictor of psychological treatment outcomes.

The studies above were all based on peripheral blood samples. In most psychotherapy interventions studies, it is not-feasible to collect samples from other compartments (with the exception of post-mortem brain tissue collection). Yet, studying tissues collected during medical procedures (e.g., biopsy, oncological surgery), could identify additional molecular profiles that may be useful in tailoring interventions or assessing effects on clinically relevant biological pathways to improve medical outcomes (e.g., analyzing molecular profiles in tumors extracted during surgery to determine impact on pro-metastatic processes (Hanalis et al., 2024)). Also, recent advances in molecular biology allow us to identify exosomes which are likely derived from brain tissue (Nasca et al., 2020). Through isolating and assessing RNA from such "brain-enriched" exosomes (Nasca et al., 2020) future gene expression studies may gain insight into central nervous system processes using a non-invasive peripheral sampling procedure.

Another complication is that blood sampling procedures varied between the studies reviewed above. Several studies used whole-blood samples, while others used isolated leukocytes or monocytes, peripheral mononuclear cells (PBMC), or dried blood spots (DBS). Each approach carries advantages (e.g., higher collection feasibility in the field for DBS; higher mechanistic accuracy for purification of specific cell types) and disadvantages (e.g., increased noise in the signal from DBS due to smaller sample volume; clinical phlebotomy required for venipuncture samples). Despite these differences, previous work has shown that gene expression results using these three approaches are highly correlated ($r = +0.85$ association between DBS and whole-blood and PBMC samples; $r = +0.92$ correlation between whole-blood samples and PBMC samples (McDade et al., 2016). As such, future studies should strive to balance feasibility, costs, and theoretical considerations when choosing which method to employ.

Practical limitations. The future integration of functional genomics into the field of psychotherapy, on a large scale, will require overcoming several practical challenges. We believe that considering these challenges in future clinical-translational studies will facilitate the successful integration of genomics into psychotherapy. For instance, the need for

licensed phlebotomists or other clinical professionals to collect blood samples can be addressed by using dried-blood spot samples. This method, in which patients can collect samples themselves, and does not require storage or specialized shipping in low temperatures, offers a promising solution to this issue. In terms of technological infrastructure, current commercial labs operating in the field of oncology have been perfecting the process of sequencing, analysis, and delivery of results to clinicians. Early-stage collaborations between academia and industry might improve the assimilation of psychotherapeutic gene expression assessments in the existing infrastructure. This may speed up the required training of lab personnel and could potentially guide the development of specific gene expression panels tailored to mental health requirements. Last, cost might be considered another limitation. With that, the exponential reduction in the price of RNA sequencing, down to a few hundred US dollars in recent years, can potentially allow multiple gene expression assessments from baseline through the end of treatment. Yet, current psychotherapeutic schedule is usually based on weekly sessions. To effectively support diagnosis and treatment selection, gene expression profiling should not take longer than 1–2 weeks at each time point. With current technologies favoring batch analyses (of few dozens to a few hundreds of samples per panel), timely generation of insights which will support psychotherapeutic decisions might depend on large volumes of patients assessed at the same time. Other limitations might also include patients' reluctance to share genomic data, the need to train clinicians and lab technicians in social genomics approaches and interpretations, and providing robust high quality data to justify coverage of such testing on large scale by health organizations and insurance companies. Communicating with these different stakeholders already at this early stage of research might be critical if this research is to beneficially impact patients in the future.

5.2. Conclusions

Peripheral-blood gene expression analysis provides a conceptually novel and promising approach for personalizing psychotherapy (e.g., predicting response to various alternative treatments) and monitoring the impact of psychotherapy on psychobiological processes. Although this field is in its infancy, current evidence suggests that focusing on biologically plausible a priori-defined gene constructs (e.g., measuring inflammation, immune response patterns, and neural or endocrine activity) represents a particularly promising approach. However, current tools derived from genome-wide discovery in small samples without any evidence of replication in independent samples are unlikely to be useful in guiding clinical practice due to critical statistical issues. Considering the logistics involved in managing the required large scale clinical intervention studies, a potential path forward may require large collaborations between researchers and clinicians, large scale secondary analysis studies, and perhaps more accessible methods of blood collection (e.g., dried-blood spots). There is a great need for studies of larger and more representative samples, multiple psychotherapeutic interventions in parallel, and well-defined pre-specified analytic protocols for converting gene expression data into clinically useful predictions of treatment response and therapeutic impact.

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Data availability statement

All data pertaining this review is available within text or in supplementary files.

CRediT authorship contribution statement

Itay Ricon-Becker: Writing – review & editing, Writing – original draft, Visualization, Methodology, Data curation, Conceptualization. **Steve W. Cole:** Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology, Conceptualization.

Declaration of competing 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 competing interests.

Data availability

No data was used for the research described in the article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbih.2024.100867.

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