

TRANSLATIONAL NEUROSCIENCE: LEVERS AND BARRIERS

Levers and barriers to success in the use of translational neuroscience for the prevention and treatment of mental health and promotion of well-being across the lifespan

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Abstract

Neuroscientific tools and approaches such as neuroimaging, measures of neuroendocrine and psychoneuroimmune activity, and peripheral physiology are increasingly used in clinical science and health psychology research. We define *translational neuroscience* (TN) as a systematic, theory driven approach that aims to develop and leverage basic and clinical neuroscientific knowledge to aid the development and optimization of clinical and public health interventions. There is considerable potential across basic and clinical science fields for this approach to provide insights into mental and physical health pathology that had previously been inaccessible. For example, TN might hold the potential to enhance diagnostic specificity, better recognize increased vulnerability in at-risk populations, and augment intervention efficacy. Despite this potential, there has been limited consideration of the advantages and limitations of such an approach. In this paper, we articulate extant challenges in defining TN, and propose a unifying conceptualization. We illustrate how TN can inform the application of neuroscientific tools to realistically guide clinical research and inform intervention design. We outline specific leverage points of the TN approach and barriers to progress. Ten principles of TN are presented to guide and shape the emerging field. We close by articulating ongoing issues facing TN research.

Keywords: translational neuroscience, neuroimaging, psychoneuroimmune, physiology

General Scientific Summary: We present an overview of translational neuroscience (TN) as a systematic and theory-driven approach with promise to develop and leverage basic and clinical neuroscientific knowledge to aid the development and optimization of clinical and public health interventions. In this paper, we outline specific leverage points of the TN approach and barriers to progress. Finally, ten principles of TN (with corresponding examples) are presented to guide and shape the emerging field. We close by articulating outstanding issues facing TN research.

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Basic psychological and clinical intervention science have historically operated on somewhat independent tracks. These tracks must meet to address pressing gaps in the field (Allen & Dahl, 2015; Fisher & Berkman, 2015; Roos, Horn, Berkman, Pears, & Fisher, 2018). Researchers have made progress in delineating the basic neurobiological mechanisms underlying mental and physical health outcomes (e.g., depression, obesity), and advances have been made in using basic psychological processes to improve therapeutic outcomes (e.g., cognitive principles with cognitive behavioral therapy [CBT]). However, despite promising translational efforts to directly alter brain function (e.g., deep brain stimulation and depression; Mayberg et al., 2005), we have yet to witness targeted and readily scalable psychosocial programs that were designed with an advancing understanding of neurobiological mechanisms (Shonkoff et al., 2012). Translational neuroscience (TN) is a systematic research approach for using basic and clinical neuroscientific knowledge to aid the design and optimization of clinical and public health interventions (Fisher & Berkman, 2015). Here, we describe TN as it has been used in developmental and clinical psychology, affective and social neuroscience, and prevention and intervention science, with a focus on demonstrating how TN can inform scalable, non-invasive intervention strategies. Our purpose is to describe the specific ways TN can be useful in advancing this agenda and its current limitations.

In the section that follows, we present two key issues in which TN may be useful in advancing the field, accompanied by examples. We then propose ten guiding TN principles imperative to future work in the field. Next, we highlight five “Levers”, or strengths inherent in a

TN approach, and five “Barriers” to be addressed. We conclude with a synopsis and future directions.

TN to Address Variability and Individual Differences.

Heterogeneity is a pervasive problem in clinical psychological research. This is true in terms of variation in responses to environmental influences and in the definition and measurement of psychopathology.

Heterogeneity in response to environmental influences.

Clinical science has accumulated a strong evidence base about the psychosocial factors that predispose individuals to mental and physical health disorders (Bruce, 2002; Donovan, 2004). For example, early adversity predicts poor outcomes across the lifespan (Albott, Forbes, & Anker, 2018; Felitti et al., 1998; Shonkoff et al., 2012). However, prospective prediction of illness is complicated by significant multi-finality (i.e., early adversity predicts a wide range of outcomes; Albott et al., 2018) and heterogeneity (i.e., many children are resilient to the impact of adversity; Masten, 2001). A full account of the biological pathways linking early adversity to later outcomes, and individual differences that might predispose individuals toward one outcome versus another, is not yet available.

As such, there has been a significant push to identify biomarkers that signal high risk for pathology (Jaffee, 2018). Valid biomarkers could identify risk before behavioral indicators emerge, particularly in developmental periods (e.g., birth to three) when behavioral measures are less reliable (Bauer, Wiebe, Carver, Waters, & Nelson, 2003) and significant heterogeneity exists (e.g., in early presentation of autism spectrum disorder (ASD); Pelphrey, Shultz, Hudac, & Vander Wyk, 2011). Neurobiological processes can help elucidate behavioral phenotypes by

providing greater specificity about underlying mechanisms. For example, adversity-exposed children, who often exhibit early signs of oppositional defiant symptomatology, have been observed to have a neural deficit in processing corrective feedback as indexed with electroencephalography (Bruce, McDermott, Fisher, & Fox, 2009, Roos, Pears, Bruce, Kim, & Fisher, 2015, McDermott et al., 2018), and this index has been linked to impulsivity (Roos et al., 2015). One implication is that adversity-exposed children may not be purposely defiant, but rather possess a deficiency in neural processes contributing to blunted receptiveness to external feedback, which may underlie important behavioral phenotypes.

Biomarkers are not the only way to identify risk. There are instances where lower cost, non-invasive methods (e.g., surveys, eye-tracking) perform well on their own. We advocate a transdisciplinary approach to TN wherein the goal is to determine an individual's comprehensive risk profile across domains and in which biomarkers complement behavioral assessments. How well neurobiological markers can enhance behavioral assessments for early detection of risk is an open question.

Heterogeneity in psychopathology measurement.

There is substantial diagnostic overlap as well as heterogeneity within individual disorder presentations. Heterogeneity in presentation is ubiquitous, with upwards of 1000 unique possible symptom profiles for major depressive disorder (MDD) alone (Fried & Nesse, 2015). Neurobiological phenotypes have also not linked robustly onto clinical diagnostic categories, as indicated by the low replicability of candidate gene studies for MDD (Bosker et al., 2011). Diagnostic heterogeneity hinders our ability to accurately examine neurobiological underpinnings and is an obstacle to successfully translating neuroscientific findings to inform treatment. The National Institute of Mental Health (NIMH) released the Research Domain

Criteria (RDoC) project in recognition of this problem (Insel et al., 2010). The goals of the TN approach are complementary to those of RDoC, but we view TN as superceding the RDoC by presenting a means of conducting integrative research rather than organizing knowledge from separate domains.

TN Example: Leveraging Psychoneuroimmunology to Enhance Etiology and Diagnostic Specificity of MDD.

Early life adversity is a potent risk factor for the development of MDD (Heim & Nemeroff, 2001; Horesh, Klomek, & Apter, 2008). However, not everyone with a history of early adversity exposure develops MDD, indicating moderators of this relationship (Wingo et al., 2010). Immune functioning is one candidate pathway implicated in both early life adversity (Baumeister, Akhtar, Ciufolini, Pariante, & Mondelli, 2016) and MDD (Dantzer, O'Connor, Freund, Johnson, & Kelley, 2008). In a prospective study, children exposed to early adversity have elevated risk for both depression and high inflammation in adulthood (Danese et al., 2009). In a community sample, levels of inflammation in 9 year olds predicted both depression and psychosis at age 18, even after adjustment for several covariates (Khandaker, Pearson, Zammit, Lewis, & Jones, 2014).

Tools from psychoneuroimmunology can enhance diagnostic specificity by identifying transdiagnostic symptom clusters. For example, inflammation has been associated with MDD (Howren, Lamkin, & Suls, 2009), albeit somewhat inconsistently (Horn et al., 2018). Researchers have begun to test the notion of an “inflammatory subtype” of depression whereby specific (sub)sets of symptoms are more robustly associated with hyperinflammation than others. Emerging evidence supports that inflammation may be most linked to somatic symptoms of depression, such as fatigue, sleep disturbance, and appetite changes (Bai, Chiou, Su, Li, & Chen,

2014; Jokela, Virtanen, Batty, & Kivimäki, 2016; White, Kivimäki, Jokela, & Batty, 2017).

Differentiating the neurobiological underpinnings of symptom profiles in this way can help clarify the etiology and diagnosis of disorders such as MDD.

A next step is to identify transdiagnostic neurobiological systems implicated across adverse outcomes such as those related to threat and reward brain systems (Nelson et al., 2013), anhedonia (Christensen, Bisgaard, & Wiborg, 2011), insomnia (Gehrman et al., 2018), and addiction (Kwako, Bickel, & Goldman, 2018). These are promising targets for research because they might function as intermediary links between clinical disorders and associated propensities and past experiences.

TN for Indices of Treatment Response.

Another promising direction is the use of neuroscientific markers to predict treatment response (Fishbein & Dariotis, 2017). For instance, despite significant movement in delineating neurobiological mechanisms associated with MDD (Otte et al., 2016), the majority of patients are still treated first with antidepressants that work only for a minority of individuals, whose underlying mechanisms are poorly understood, and which only slightly outperform placebo (Cipriani et al., 2018). Clinical science is moving past the “one-size-fits-all” mentality toward one that accounts for individual difference moderators of treatment efficacy.

Neuroscientific measures might also afford theory-driven hypotheses about *who* is likely to respond (i.e., does this neuroscientific index predict who will respond?) and *how* certain therapeutic strategies are working (i.e., does a neuroscientific index change pre/post treatment?). This information can inform individualized approaches to treatment planning and provide guidance on optimizing treatment designs. Treatment response might be apparent more quickly

on neuroscientific indices than on behavioral measures when the former measure processes are closer to the underlying targets of change.

Example: Moderators of Treatment Response with rs-fcMRI

Resting-state functional connectivity (rs-fcMRI) is a neuroscientific method with significant potential to predict and detect moderators of treatment response. Rs-fcMRI measures correlations in spontaneous neural activity when participants are not engaged in an explicit task, believed to reflect more trait-like, “intrinsic” brain networks. A systematic review found increased connectivity between frontal and limbic brain regions predicted response to antidepressant treatment, potentially indicating better functioning of inhibitory control in circuits that process emotions (Dichter, Gibbs, & Smoski, 2015). The clinical translatability of this line of work can be enhanced by going beyond associations with treatment response to identify measures that prospectively predict treatment response. Recent work has used predictive models to take this next step. For example, a single-subject pre-treatment fMRI study identified brain activation that predicted response to CBT treatment response for individuals with generalized anxiety or panic disorder. The neuroimaging measures out-performed clinical or demographic variables in predicting individual patient treatment response (Ball, Stein, Ramsawh, Campbell-Sills & Paulus, 2014). This approach could predict who is more likely to respond to therapeutic approaches and help to delineate how a treatment might work.

These examples illustrate only some of the ways that the TN approach might inform clinical science. Creative researchers will undoubtedly identify more strategies for deploying the TN approach as the field accelerates. As they do so, a careful analysis of not only the strengths but also the limitations of TN will be critical. A skeptical view is that the attention that TN has received outstrips the advances it has brought to clinical science. The field has yet to develop

a systematic approach to articulate how neuroscience tools can tangibly and realistically inform, guide, and be integrated into clinical research, nor rigorously mapped out the barriers to progress. Despite the rapid accumulation of knowledge about the neural alterations associated with mental illness, there is little concrete evidence that this knowledge has facilitated improved treatments.

TN Principles, Leverage Points, and Barriers

We have identified ten principles of TN as a systematic framework to guide future work in the field toward a resolution of these challenges. These principles are intended to enable TN research to efficiently and realistically inform and improve clinical science interventions. Each principle is paired with an example to illustrate these principles in practice. We describe the principles below in terms of how they pertain to TN specifically; however, we also acknowledge the principles may be more broadly applicable to other domains of psychology.

Alongside the principles and examples, we integrate discussion of five leverage points (“Levers”) and five barriers of TN (“Barriers”) (see Table 1). The leverage points highlight strengths of the TN approach that can fuel progress in basic and clinical sciences and inform public policy. Specifically, neuroscientific knowledge can improve each step of the translational process from identification of neurobiological mechanistic pathways (Lever 1) to treatment development and optimization (Lever 2) to addressing public policy (Lever 3). TN also can help spur new basic neuroscience advances, including establishing a bridge between superficially dissimilar topics (Lever 4) and discriminating between superficially similar processes (Lever 5).

However, there are also significant barriers for the field of TN. Notably, these barriers are potentially germane to many methodologies, but are particularly salient for TN. These include

the “So What?” (Barrier 1) and “Now What?” (Barrier 2) problems, which highlight the lack of relevant progress in the clinical applicability of TN. These barriers arise when a novel “biomarker” differentiates between subgroups but is not clearly implicated as a causal factor (“So What?”), or a neurological pathway offers no path to intervention (“Now What?”). Scalability (Barrier 3) and costliness (Barrier 4) are additional significant obstacles for TN to achieve meaningful, real-world impacts. A related barrier is the need for a diverse set of skills required for the entire translational process (Barrier 5). Overcoming these barriers requires a combination of high-quality data and methods, collaboration among scientists across the translational spectrum, changes in the funding model to support rapid-scale, iterative clinical trials, and new ways of training the next generation of translational neuroscientists who will be well versed in clinical science and practice, neurobiology and neuroscientific research tools, and transdisciplinary collaboration.

- 1. Identify environmentally malleable neurobiological functions, circuits, and systems that underlie behavioral risk and resilience.*

Identifying *malleable* neurobiological pathways is critical for preventative and intervention efforts. The relationship between neurobiological and environmental processes is reciprocal and dynamic (Fishbein, 2000). Environmental conditions such as early adversity, poverty, parenting, and neighborhood conditions can influence neurobiological development and functioning across the lifespan. Neurobiological functioning is also malleable and sensitive to environmental influences. Translational neuroscience must identify relevant and malleable environmental, psychosocial, and neurobiological systems spanning across genetic, epigenetic,

peripheral (e.g., neuroendocrine, immune) and brain functioning, to inform the development of prevention and intervention efforts.

Example:

As discussed previously, the immune system is an environmentally malleable neurobiological system and thus highly germane to TN. Several environmental factors can influence inflammation, such as parenting (Byrne et al., 2017), neighborhood violence (Janusek, Tell, Gaylord-Harden, & Mathews, 2017), early adversity (Miller & Cole, 2012), and physical activity (Ford, 2002), and some are easier to target with intervention than others (see Barrier 2). Moreover, inflammatory mechanisms may be malleable by treatments, such as CBT (Lopresti, 2017), antidepressant medication (Strawbridge et al., 2015), and a family-oriented psychosocial intervention (Miller, Brody, Yu, & Chen, 2014).

Inflammation has also been shown to underlie specific behavioral indices of risk and resilience. For example, inflammatory markers may relate to cognitive vulnerabilities, such as rumination, in adolescents (Moriarty et al., 2018). Rumination is a behavioral risk factor implicated as a target to improve cognitive behavioral treatments (Watkins, 2009). In a longitudinal study with adolescents, Moriarty et al. (2018) found that the inflammatory cytokine interleukin-6 (IL-6) mediated the association between baseline anxiety symptoms and later-onset depressive symptoms, such that as rumination increased, anxiety symptoms predicted greater inflammation and depressive symptoms. This study illustrates Lever 1 by elucidating how inflammation may be a neurobiological mechanism underlying rumination. This research may help to distinguish between processes that appear similar (i.e., if inflammation is associated with rumination above and beyond other cognitive symptoms) (Lever 5).

2. *Focus on central neurobiological processes broadly implicated in well-being and maladjustment.*

A multilevel focus on neurobiological systems implicated across well-being and maladjustment is necessary for translating neuroscientific knowledge into clinical applicability. Central nervous system processes play a critical role in psychological functioning and coordinating peripheral processes (e.g., the hypothalamic-pituitary-adrenal (HPA) axis is associated with several disorders; Tsigos & Chrousos, 2002). The dynamic and interactive pathways between peripheral systems (e.g., co-regulation of HPA-axis and immune system; Kuhlman, Chiang, Horn, & Bower, 2017) are also significant. A comprehensive account requires examination of common transdiagnostic processes at multiple levels, including broad central level (e.g., functional connectivity of neural regions), focal brain region levels (e.g., areas involved in reward processing and sensitivity), at the peripheral biological level (e.g., inflammation), and even at the cellular level (e.g., mitochondria).

Example: Reward processing and sensitivity is an example of a core transdiagnostic process implicated in a range of psychiatric disorders (Nusslock & Alloy, 2017). Reward processing has been implicated as a mechanism underlying important transdiagnostic symptoms, such as anhedonia (Corral-Frías et al., 2015; Treadway & Zald, 2013). Both the activation of reward-related brain structures and their pattern of connectivity with other regions and peripheral systems has been identified as a target for treatments across a broad range of maladaptive behavior and outcomes including alcohol addiction (Becker et al., 2018), smoking (Cinciripini et al., 2017), depression (Allen et al., 2018), and binge eating (Balodis et al., 2014).

Reduced reward responsivity is linked to dissociable patterns of connectivity between the nucleus accumbens (NA), the default mode network and the cingulo-opercular network (Sharma et al., 2017) in adults with mood and/or psychotic disorders. This study highlights the principle by examining a central process and its relation to mental health outcomes and Lever 4 by establishing a bridge between superficially dissimilar topics (mood and psychotic-based disorders).

3. Employ developmentally sensitive, neurobiologically-informed intervention strategies.

Developmental processes are crucial to the onset and maintenance of psychological disorders and to designing effective prevention and intervention programs. Infancy (Kieling et al., 2011) and adolescence (Allen & Dahl, 2015) are particularly critical periods of interest. Yet, developmental research often does not inform intervention strategies. Gold-standard interventions designed for and tested originally with an adult population (e.g., CBT) are often adapted for younger populations (e.g., Cohen, Mannarino, Berliner, & Deblinger, 2000) with less consideration of the relevant developmental processes. Neuroscientific insights can inform developmentally-sensitive treatments (Cicchetti & Toth, 2009).

Example:

Infancy is a highly sensitive period characterized by dynamic brain growth associated with hormonal changes, synaptic pruning, and metabolic shifts (Gee & Casey, 2015). Attachment patterns form in early life and these have strong implications for children's health and development (Meins, Bureau, & Fernyhough, 2018). A secure, reciprocal, and warm attachment

between child and caregiver during infancy is a moderator of developmental processes and psychological well-being (Mikulincer & Shaver, 2007).

The Attachment and Biobehavioral Catch-up (ABC) intervention illustrates how an intervention can be tailored to a developmental period. ABC was developed for foster infants and infants living with potentially neglecting parents (Dozier, Roben, Caron, Hoye, & Bernard, 2018). In building the program, the developers of ABC leveraged knowledge from developmental psychology about the sensitive nature of infancy; public policy regarding elevated rates of neglect with foster care and child welfare involved children (Lever 3); attachment theory with respect to the links between neglect and disorganized attachment styles; and neurobiology about the impact of neglect on neuroendocrine dysfunction (Dozier et al., 2018). Several studies have demonstrated the efficacy of the ABC program compared to a control intervention on child and caregiver outcomes (Dozier et al., 2018).

4. Prioritize those neurobiological models that parsimoniously add explanatory power to behavioral theories and evidence and to inform intervention.

In addition to knowledge about developmental periods, neuroscientific knowledge can also inform prevention and intervention design (Shonkoff & Fisher, 2013). For example, prolonged and/or disrupted activation of stress response systems impact neurobiological and neural development (Lupien, McEwen, Gunnar, & Heim, 2009). The specificity provided by such studies can sharpen the hypotheses and assessment strategies in testing the hypothesized mechanisms underlying intervention effects (Shonkoff & Fisher, 2013). Neurobiological measures are not without their costs (see Barrier 4), but a clear theoretical rationale can justify

their inclusion in intervention trials. The more precision with which an intervention target is described, the more compelling such rationales become.

Example: The Filming Interactions to Nurture Development (FIND) video coaching program is a brief video coaching program developed for parents and caregivers with infants and young children (Fisher, Frenkel, Noll, Berry, & Yockelson, 2016). The FIND intervention draws on knowledge about the neurobiological effects of early adversity, particularly its disruptive effects on the stress, immune, and metabolic systems (Lupien et al., 2009; Maccari, Krugers, Morley-Fletcher, Szyf, & Brunton, 2014). The FIND targets specifically the interactions between caregivers and children when children's brain circuitry is most sensitive to alter emerging language, socioemotional, cognitive, and self-regulatory capacities (Lever 1) (Fisher et al., 2016). The FIND program also leverages technology (i.e., video editing) to maximize scalability (Barrier 3); the program is under evaluation worldwide.

5. Use intervention trials to test theories that connect causes to outcomes via underlying neurobiological mediators.

A TN approach draws on neuroscientific knowledge to examine neurobiological mediators of intervention outcomes. Researchers can advance the knowledge of neurobiological pathways implicated in health outcomes and begin to delineate *how* certain treatments work and *for whom* they are most effective (Lever 2). This requires pinpointing the neural and/or biological targets that correspond to the mechanisms of the intervention action. Neurobiological moderators may indicate relevant individual differences that enable the development of increasingly refined hypotheses, a nuanced understanding of how and for whom an intervention is working, and can help increase intervention efficacy (Fisher & Berkman, 2015).

Example: Multidimensional Treatment Foster Care for Preschoolers (MTFC-P) is an intervention for preschool-aged foster care children with a history of maltreatment (Fisher, Burraston, & Pears, 2005; Fisher, Ellis, & Chamberlain, 1999). The theory behind MTFC-P is that neglect exerted its effects via chronic stress and HPA-axis dysfunction as indicated by a blunted diurnal cortisol slope. A mechanistic efficacy trial tested not only the intervention's effects on outcomes but also whether it would normalize children's diurnal cortisol slopes (Fisher, Stoolmiller, Gunnar, & Burraston, 2007). Foster children in the MTFC-P group showed more typical diurnal cortisol slopes comparable to a community control group (Fisher et al., 2007), while foster care children receiving routine services demonstrated a blunted morning-to-evening cortisol slope. Additionally, foster parents in the routine services group but not the other groups had elevated levels of caregiver stress that was associated with atypical cortisol activity in children (Fisher & Stoolmiller, 2008). This line of work illustrates how TN can test not only the efficacy of an intervention but also its hypothesized neurobiological mechanisms (Lever 2).

6. *Include rigorous measurement of potentially moderating contextual factors (e.g., poverty, neighborhood, culture) that confer risk or resiliency.*

Contextual environmental factors are related to maladjustment and well-being and also to neurobiological underpinnings of health and resilience (Rutten et al., 2013). A comprehensive understanding of risk requires uncovering the interactive and additive impacts of contextual factors in relation to neurobiological pathways and psychosocial development. For example, race and ethnicity are often regarded as “nuisance” variables or obstacles garnering little attention beyond their perfunctory role in statistical control and analysis (Bemal, Cumba-Avilés, & Rodriguez-Quintana, 2014; Hall, Yip, & Zárata, 2016). However, there is a rapidly growing field that has examined how challenges unique to ethnic minority groups (e.g., racial discrimination)

not only confer risk for poor health outcomes, but are clearly linked to stress neurobiology, including impacts on neural and hormonal pathways (Berger & Sarnyai, 2015).

Example: Contextual knowledge about ethnic differences in sleep quality and immune functioning informed a recent study testing the idea that sleep disturbances in the postpartum period might confer risk for mood symptoms in African American and white women (Christian, Kowalsky, Mitchell, & Porter, 2018). The study showed that poor sleep and stress predicted greater stimulated cytokine production, but only in African American women. A thorough understanding of mechanisms underlying racial differences in immunological disruption and depression will be essential to delineating the etiology of depression and informing novel treatment strategies.

7. *Apply precision interventions that are tailored to individuals based on biobehavioral characteristics, and grounded in robust neuroscience.*

A long-term aim of clinical science is to provide precision treatment by integrating person-level data to inform the selection of treatment (Prendes-Alvarez & Nemeroff, 2018). A single biomarker is unlikely to predict a diagnosis or treatment, but a panel of independent biomarkers, including genetic and epigenetic factors and biomarkers of neuroendocrine, immune, and metabolic function, might have greater predictive validity. Along with clinical presentation and environmental factors (e.g., culture ; Matheson, Bombay, & Anisman, 2018), a set of valid, reliable biomarkers might help optimize existing treatments, design new interventions for treatment-resistant or complex presentations, and predict *who* is most likely to response to an intervention. A challenge lies in establishing reliable and valid individual difference measures of intervention efficacy, requiring substantial measurement expertise (Barrier 5). There is scant

empirical attention to the basic psychometric features, such as reliability and validity of neurobiological and neural measures (DuBois & Adolphs, 2016), and reliability is often found to be low when examined, such as with fMRI (Bennett & Miller, 2010; Herting et al., 2018). The scarcity of psychometric data for many measures is an outstanding obstacle for TN, which cannot be useful without reliable measures.

Example: The drug sirukumab modulates the immune response by acting against IL-6 and reduces depressive symptoms in patients with rheumatoid arthritis (Sun et al., 2017) and is a candidate adjunctive treatment for MDD. An RCT is underway with depressed patients on monoaminergic antidepressants testing a precise hypothesis grounded in neuroscientific theory. The model predicts that the medication would work only for depressed individuals with elevated inflammation; therefore, only participants with elevated systemic inflammation are eligible (NCT02473289) (Lever 2). Translating neuroscientific knowledge about inflammation and depression to test a new treatment is also an example of overcoming the “So What” and “Now What?” barriers (Barriers 1 and 2).

8. *Emphasize applications of neuroscience to interpersonal processes rather than solely individual processes.*

Interpersonal processes are intrinsic to nearly all health outcomes. Social neuroscience research uncovering the ways that “social emotion regulation” is different from other forms of self-regulation can indicate ways to facilitate emotion regulation in relationships (Levers 4 and 5) (Reeck, Ames, & Ochsner, 2016). Co-regulation is central to a range of close relationships (e.g., parenting, romantic relationships). For example, parenting quality is related to children’s emotion regulation (e.g., Chang, Schwartz, Dodge, & McBride-Chang, 2003) and the family environment is a key contextual factor (see Principle 6) in the development of emotion regulation

capabilities (Morris, Silk, Steinberg, Myers, & Robinson, 2007). Further, the neurobiology of caregiving is an essential component of child development and outcomes (Abraham & Feldman, 2018). Future directions are to understand the neurobiological underpinnings of these interpersonal processes and examine co-regulation of neurobiological processes in dyads (e.g., parent-child, couples).

Example: Parental executive function (EF) is critical to children's EF development (Cipriano-Essel, Skowron, Stifter, & Teti, 2013). For instance, a recent study found that maternal working memory capacity is positively related to preschool-aged children's inhibitory control, suggesting that maternal influences play a significant role in the development of children's EF in high-risk families (Kim et al., 2017). This study illustrates Principle 6 by accounting for the relation of EF to socioeconomic diversity, an important contextual factor, and Lever 4 by establishing a bridge between processes that may appear unrelated (i.e., maternal working memory and children's inhibitory control).

9. *Elucidate linkages between mental health and physical systems (e.g., autonomic, neuroendocrine, immune, metabolic, gut microbiome).*

The origins of many adulthood physical and psychological disorders have roots in early development and neurobiological disruptions (Shonkoff, Boyce, & McEwen, 2009). Cumulative damage (i.e., allostatic load; Juster, McEwen, & Lupien, 2010) and biological embedding of adversity within sensitive windows (Miller, Chen, & Parker, 2011) can influence health trajectories. Children exposed to early adversity are vulnerable to mental *and* physical health illnesses (Johnson & Schoeni, 2011), suggesting the need to examine mechanistic pathways that confer risk for a range of health outcomes (Nusslock & Miller, 2016). TN can examine the

shared neurobiological processes across physical and mental health outcomes as a way to increase scientific understanding of the etiology and developmental trajectory of pathology. This approach also helps to connect unknown disease-relevant processes (e.g., asthma and psychological health; Goldbeck, Koffmane, Lecheler, Thiessen, & Fegert, 2007) by emphasizing common neurobiological pathways (e.g., immune functioning; Chen, Fisher, Bacharier, & Strunk, 2003).

Example: Physical and mental health share several mechanistic pathways (Scott et al., 2016). For example, there is a high prevalence of gastrointestinal (GI) disorders and symptoms observed in children with ASD (McElhanon, McCracken, Karpen, & Sharp, 2014), with increasing attention being paid to potential shared neurobiological underpinnings (e.g., immunometabolic pathways, the gut microbiome). A novel study contrasted children with ASD with and without GI symptoms with typically developing children with and without GI symptoms. Findings indicated that children with ASD and GI symptomatology produced increased levels of mucosa-relevant inflammatory cytokines to an inflammatory stimulation challenge in contrast to children with ASD but no GI symptoms. Further, the researchers found family-level differences in gut microbiome composition between ASD and typically developing children with GI symptoms (Rose et al., 2018). Such results have several implications, such as addressing heterogeneity in ASD symptom profiles (e.g., why not all children with ASD have comorbid GI problems) and advancing new treatment possibilities. This example also highlights Lever 4 by drawing a connection between unknown disease-relevant processes (e.g., GI and ASD symptomatology).

10. Select neurobiological methodologies and measures based on their suitability to the hypotheses being tested.

Translational neuroscience encourages a thoughtful selection of methods with respect to the focal hypothesis. Simply put, the theoretical models should drive the selection of the measurement tools. Assessing the theoretical model beforehand enables selecting valid, reliable measures of relevant systems that are sensitive to change and can detect individual differences (Lever 2). Especially careful consideration is warranted within certain methodologies, such as neuroimaging (Barriers 3 and 4) (Pfeifer, Allen, Byrne, & Mills, 2018).

Example: A study of neural responses to peer emotional expressions in adolescent girls leveraged prior knowledge to make reasoned, a priori decisions about the optimal neuroimaging paradigm (Flannery, Giuliani, Flournoy, & Pfeifer, 2017). The study tested a neurodevelopmental model stating that adolescent risk-taking results from an imbalance in the maturation of networks related to self-regulation versus affect and reward. Prior research relied on static, adult face stimuli, which are particularly inappropriate given the increased salience of peers during adolescence. So, in this case, the researchers enhanced the relevance of the stimuli by using videos of children and adolescents making a range of emotional expressions. Doing so revealed very different age-based trajectories than those predicted by previous models, suggesting possible salience effects in previous work (Flannery et al., 2017). Theory-driven decision making can also combat problems associated with costliness (Barrier 4) and participant burden (Barrier 3).

Conclusions

We highlighted areas where progress in TN has been made and where growth is needed. We see several directions for TN in the coming years. Elucidating the neurobiological mechanisms of psychological processes with ever-increasing precision (Lever 1) will be critical, whether they be individual (e.g., rumination) or interpersonal processes (e.g., dyadic coregulation and EF). A larger task, which requires additional high-quality evidence, is to identify connections between seemingly dissimilar topics as well as establishing dissociations between processes that are believed to be similar (Levers 4 and 5). A downstream goal is to then apply that accumulated knowledge to prevention and intervention evaluation (Lever 2). However, as highlighted in Barrier 1, this has yet to widely occur. Interventions such as ABC and FIND are promising examples of overcoming this barrier.

The TN approach also embraces transdiagnostic constructs broadly implicated in health. Delineating the neurobiological mechanisms of symptomatology spanning physical and mental health is critical to advancing scientific knowledge of the etiology and trajectory disease. The field can formulate integrated theoretical models crossing behavioral, psychological, and neurobiological levels only once this knowledge is obtained, and then test the models in translational interventions (Lever 2). The existential questions presented in Barriers 1 and 2 (“So What?” and “Now What?”) can be answered only when the field can design, evaluate, and implement psychosocial interventions that precisely alter neurobiological function and demonstrate that their effects are mediated by the specified neurobiological mechanisms. That is admittedly a lofty goal and significant challenges persist (Barriers 3-5). Ultimately, TN is a collaborative, transdisciplinary field whose scope is deliberately ambitious to be commensurate with the magnitude of the goal of transforming the scientific approach to alleviating the burden of mental illness.

Table 1
Five Levers of TN

Five Barriers of TN

<p>1. Elucidate underlying neural and neurobiological mechanisms of behavior and health</p> <p><i>Moving “down” from behavior to biological level of analysis to facilitate creative insights and inform treatment design.</i></p> <p>2. Understand individual differences in treatment response and outcomes at a neurobiological level to increase precision of targets</p> <p><i>Identifying neurobiological moderators of treatment by identifying points of interface between individual processes and treatment mechanisms.</i></p> <p>3. Catalogue effects of context or disorder on neurobiological processes</p> <p><i>Insights about biological foundations of illness can inform public discourse and policy.</i></p> <p>4. Compare neurobiological systems to make connections between unknown disease-relevant processes</p> <p><i>Identify overlap in neurobiological processes to establish a bridge between superficially dissimilar topics and spur new advances.</i></p>	<p>1. The “So What?” problem</p> <p><i>Successfully pinpointing neurobiological mechanisms of disease-relevant processes has yet to inform treatment now.</i> Overcome: Higher quality neuroscientific data and greater acknowledgement within the field of limitations of inferences based on brain and biological-level data</p> <p>2. The “Now What?” Problem</p> <p><i>There is a limited quantity of tools available to directly intervene on a system once it is known to be causally involved in the disease.</i> Overcome: A more nuanced mapping between neural, biological, and mental processes is necessary as well as rigorous examination of biomarkers within intervention trials.</p> <p>3. Scalability</p> <p><i>Complex neuroscientific tools are difficult to scale in community settings (e.g., primary care, school)</i> Overcome: Transdisciplinary teams of neuroscientists, interventionist, implementation scientists, and community partners at all stages of TN.</p> <p>4. Costliness</p> <p><i>Neuroscientific tools (e.g., neuroimaging) are costly in terms of money and time.</i> Overcome: Develop new funding models to allow for more rapid progress in the translational cycle</p> <p>5. Need for Diverse Skills</p> <p><i>A single researcher cannot possess the set of skills necessary to fully implement TN.</i></p>
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5. Compare neurobiological systems to discriminate between processes that appear similar

Identify unique neurobiological profiles to refine scientific concepts to present new pathways for targeted interventions.

***Overcome:** Collaboration and the revision of prevailing models of training to support transdisciplinary work.*

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