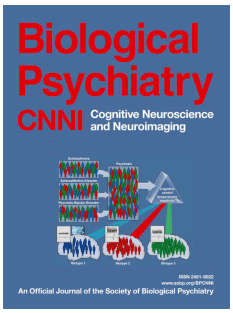

Can Translational Social Neuroscience Research offer Insights to Mitigate Structural Racism in America?

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ABSTRACT

Social isolation and conflict due to structural racism may result in human suffering and loneliness across the lifespan. Given the rising prevalence of these problems in America, combined with disruptions experienced during the COVID-19 pandemic, the neurobiology of affiliative behaviors may offer practical solutions to the pressing challenges associated with structural racism. Controlled experiments across species demonstrate that social connections are critical to survival, although strengthening individual resilience is insufficient to address the magnitude and impact of structural racism. In contrast, the multi-level construct of social resilience, defined by the power of groups to cultivate, engage in, and sustain positive relationships that endure and recuperate from social adversities, offers unique insights that may have greater impact, reach, and durability than individual-level interventions. Here, we review the putative social resilience-enhancing interventions and, when available, their biological mediators, with the hope to stimulate discovery of novel approaches to mitigate structural racism. We will first explore the social neuroscience principles underlying psychotherapy and other psychiatric interventions. Then, we will explore translational efforts across species to tailor treatments that increase social resilience, with context and cultural sensitivity in mind. Finally, we will conclude with some practical future directions for understudied areas that may be essential for progress in biological psychiatry, including ethical ways to increase representation in research and developing social paradigms that inform dynamics toward or away from socially resilient outcomes.

"When "I" is replaced by "we" even illness becomes wellness." – Malcolm X

INTRODUCTION

Social isolation and conflict associated with structural racism in the United States (US), have had devastating personal, societal, and economic consequences. Meaningful interventions for consequent mood problems ranging from loneliness to mood and anxiety disorders have long been stifled by stigma, lack of access to mental health care, clinician shortages, and partially effective treatment options. The pandemic compounded longstanding challenges and exposed the mental health co-pandemic afflicting many (1) but especially the minoritized, that may have reverberating effects on other high morbidity health conditions, such as cardiovascular disease and diabetes. Measures like recovery, relapse prevention, or encouraging individual resilience fall short of adequately addressing the magnitude and rising prevalence of deaths due to suicide or by alcohol or drug poisoning (2). This is particularly problematic in the US where the opioid crisis is intimately linked to structural inequities in access to mental health treatment, exemplifying the shortfall in treatment resources (3).

During pandemic-related lockdowns, digitally accessible treatment options became a pivotal solution to increase access. An overnight upsurge in digital health technology and innovation made admirable strides to address unmet clinical needs. Tele-mental health has demonstrably improved access (4). However, for those with significant social aversion to in-person clinical contact due to an underlying psychiatric condition (e.g. social anxiety or autism) or mistrust resulting from longstanding inequities, gaps in knowledge and implementation remain due to incomplete exploration of phenomenological, ethical, and cross-cultural factors that influence uptake (5). Knowledge of mechanisms underlying treatment responses to telepsychiatry is limited, principally from a lack of rigorous comparative effectiveness to usual

care, yet such comparisons are critical for treatment refinement, personalization, and health care policy implementation. For individuals who have health disparities due to race, socioeconomic status, age, or geographic distance (6), a new disparity called the "digital divide" has emerged (7,8). Thus, while for some, digital social connections have become a timely lifeline during the pandemic-mandated physical/social distancing, for others, those benefits remain to be seen.

The biological drive for social connection to mitigate structural racism has deep evolutionary roots (9). Human beings, like other mammals, huddle in groups for safety, comfort, entertainment, reassurance, and help, especially when facing stress or adversity. Some researchers have conceptualized psychiatric disorders as disorders of social interaction (10–12), providing a social neuroscience framework for understanding the etiology and impact of deficits in social cognition for the development of psychopathology, transdiagnostically (13). Work by these scholars and others highlight how interventions focused on increasing social belonging can effectively decrease anxiety, stress, and depression (14), and explore whether belonging itself should be a primary outcome. Pandemic-related isolation disrupted this basic need for social contact. For some with complex health problems and older individuals who are most vulnerable to infection, social isolation has contributed to new onset and worsening depression, feelings of despair, and escalating cognitive decline (15). Among some adolescents, during distance learning and restricted contact, cyberbullying has become a maladaptive strategy intended to meet others, to overcome loneliness or boredom (16). The long-term consequences of the pandemic have yet to fully unfold.

To make sense of these evolving social behaviors in the context of structural racism, we will first describe some relevant inter-related constructs in **Table 1** below.

Table 1. Key social neuroscience terms used in this review.

Key Term	Definition in Context and References
Social resilience	A multivariate construct that includes abilities of groups to cultivate, engage in, and sustain positive relationships to endure and recuperate from social isolation, conflict, or adversity, with structural racism being an exemplar.
Affiliative behaviors	Actions or behaviors that are likely to be perceived as pleasing and appealing (e.g., smiling, head nodding, waving, clapping). They facilitate species survival through human connection and affirmation.
Prosocial behaviors	These behaviors go beyond affiliative behaviors, and involve voluntary behaviors to benefit others, as characterized by acts of kindness, empathy, compassion, and helping behaviors.
Social Cognition	The means by which individuals process, remember, and utilize information in social contexts to explain or predict their own behavior or the behavior of others.
Ambient belonging	The feeling of comfort in a space where one is accepted, valued, and included. Ambient belonging is derived from tangible and intangible cues about belonging in the physical environment (17).
Stereotype threat	The experience in which people are or feel themselves to be at risk of confirming a negative stereotype about their social group (18).
Social belonging	A sense of relatedness to others associated with positive, lasting, and significant interpersonal relationships. Factors that characterize social belonging include social feedback, validation, or shared experiences.
Loneliness	A perceptual state in which one's social needs are not met by the quantity or quality of one's social relationships. It is the consequent distress that results from discrepancies between ideal and perceived relationships, with increasing motivation to seek social contact. It is unpleasant, subjective, and distinct from anxiety or depression, which may all accompany isolation (19).
Social homeostasis	The ability to detect the quantity and quality of social contact, compare it to an established set-point, and adjust effort expended to seek optimal social contact using an effector system (20). This may be a translational model of adaptation to chronic isolation.

The cultivation of affiliative and prosocial behaviors to promote social resilience depends on interrelated factors such as social cognition or a perception of ambient belonging, which are in turn influenced by the nature of material (17), structural, or interpersonal (21) interactions. Racism exacerbates stereotype threat, which affects stigmatized minority groups (22). Negative stereotypes can undermine an individual's sense of belonging and drive conflict (fight, defensive

aggression (23)), or avoidance (flight). Conflict and avoidance not only weaken individual resilience in the face of threat, but also diminish social resilience (24).

The neurobiological basis of affiliative behaviors depends on oxytocin, the affiliative brain comprised of interconnected pre-optic, limbic, striatal, and prefrontal networks that subserve the formation and maintenance of close relationships, and the coordination of biological and behavioral signals transmitted during social contact (25). Whereas oxytocin-mediated release of serotonin from the dorsal raphe into the nucleus accumbens may result in prosocial behaviors (26), amygdala-orbitofrontal and cingulate circuits have been implicated in aggressive behaviors (27). The anterior insula joins the amygdala in conditioning biased responses to White versus Black faces (28). Further, during threat conditioning, sensory inputs from thalamo-cortico-amygdalar pathways or direct thalamus-to-amygdala connectivity patterns are observable (29). These neural circuits may be putative targets for intervention. Regulation of subcortically driven fight or flight responses may depend on high order cognitive mechanisms such as inhibitory control or cognitive flexibility (30) or other biological substrates of cooperation (31). In this context, prosocial behaviors are conceptualized as markers of resilience that powerfully motivate an individual to belong (32).

Here, we first provide an overview of clinical and preclinical interventions that examine the adaptive nature of interpersonal connections (social resilience) that may mitigate structural racism as described in psychiatric research and, when available, their biological mediators. Next, we discuss the social neuroscience principles underlying placebo and active intervention responses, and the social behaviors, context, and culture that moderate these responses. Finally, we seek to fill gaps in current knowledge to develop a research agenda that could inform policies based on interventions to enhance social resilience. Critically, we ask whether and how

advancing knowledge about the science underlying affiliative behaviors could mitigate structural racism in the US. We hypothesize that, compared to interventions promoting individual resilience, interventions that target social resilience will have a greater impact on population-level mental health outcomes, which should inform policies and practices to reduce the negative effects of structural racism and related adverse experiences.

METHODS

To map experimental studies involving affiliative or prosocial behaviors that intervene on aberrant social function broadly and in the context of structural racism, this scoping review used the following search terms in Google Scholar and PubMed databases based on English language literature derived from peer-reviewed journals: ("affiliati*" OR "prosocial" AND "behavior*"; "social isolation"; "belong*," "aggress*, OR structural racism, AND "clinical trial," OR "psychosocial" AND "intervention"; "social resilience;" OR "equity;"). These search terms individually and in combination yielded 6582 titles that were further screened for relevance to structural racism. 140 references from empirical studies and review articles were read. Twenty exemplar studies were included if the authors used an experimental design and explicitly improved quantity and quality of relationships to address structural racism in the US, or manipulated settings to understand the interactions among affiliative (e.g., smiling, waving) or prosocial behaviors (e.g., empathy, compassion, helping), *and* if social resilience or social wellbeing were among possible outcomes. Wherever available, the most current thinking was referenced, yielding 120 referenced citations. Related search terms were extracted from a diverse array of disciplines, from psychiatry specifically to medicine broadly, (social) neuroscience, psychology, nursing, social work, sociology, and public health. Finally, papers were examined

to evaluate the unique circumstances pertaining to contemporary US debates, with appreciation that other countries may experience different types of race relations and that the mechanisms posited in this paper may be relevant to improving race relations everywhere, keeping in mind contextual considerations.

RESULTS

Social belonging interventions that mitigate stereotype threat

Social belonging can mitigate stereotype threat by increasing confidence in the ability to have positive and secure relationships with others. In contrast, doubts or uncertainty about social belonging can undermine a number of cognitive functions and performance, as classically illustrated by women representation in mathematics (33). Critically, social belonging to mitigate stereotype threat can lessen inequalities in achievement. It can also be trained, as illustrated by a social belonging intervention given to Black college freshman to help them adapt to socially threatening experiences, cultivate positive relationships, and receive mentoring, leading to immediate (34) and long-term (35) positive academic and health outcomes. Indeed, social belonging has been shown to mediate wellbeing (36), but a key challenge associated with prescribing social interactions is that it must meet the needs of individuals who are *disinclined* to join a group. In this context, group interventions might cause unintended harm to health and wellbeing (37), where the dose-response relationship between the number of social interactions and wellbeing may not be linear (38).

Scaling interventions from the individual to the societal

Individual versus group level outcomes from social interventions may be challenging to delineate or define depending on the social construct being targeted. In contrast to stereotype

threat, the nature of threat in relationships is qualitatively different for *loneliness*. Consequently, out of four proposed strategies to intervene on loneliness (improve social skills, enhance social support, increase opportunities for social contact, and address maladaptive social cognition (39)), those most successful seem to target maladaptive social cognition, which is consistent with theories regarding why loneliness emerges in the first place (58). Ambient belonging exemplifies bidirectional interactions between individual and group social experiences. For example, living in a neighborhood with an infrastructure in place to provide support at the community-level corresponds with reduced ensuing rates of adult-onset major depressive disorder (40). Central to global health equity debates is the question of whether interventions should prioritize targeting the individual or groups, but research suggests we need both. In a multi-level study testing the sociometer theory that self-esteem is a measure of interpersonal relationships, countries that succeeded in promoting many and high quality (e.g. friend, family, or romantic) relationships with regular contact led to higher levels of self-esteem across many individuals, even after controlling for individualism, gross domestic product, happiness, and neuroticism (41). Thus, nurturing relationships across individuals *and* societies leads to improved global wellbeing, as described in Anthony Biglan's monograph "*The Nurture Effect*" (42).

First-line psychosocial interventions for social isolation, conflict, and mood disorders involve modalities such as psychoeducation about symptoms and disorders, exposure-based cognitive behavioral therapy to gradually increase social contact, and even psychoanalysis to understand the roots of attachment and its disruption. Despite a wide array of evidence-based treatment modalities that are tailored to an individual's chief complaint, a shared assumption of such psychotherapeutic interventions is that, in addition to promoting introspection, they increase

social contact (i.e., with a therapist or a clinician), which is in itself therapeutic. Clinical contact is even better when a clinician transmits competency and warmth during that interaction (43). Above and beyond this simple contact or psychoeducation, patients randomized to receive skills that promote social connections, like effective communication and problem solving in a family setting, have delayed recurrence of depressive episodes (44) and increased post-treatment medial frontal connectivity (45), which is specifically associated with prosociality (46). By integrating neuroimaging into randomized controlled clinical trials, which may provide strong inferences while detecting relevant mediators (47), we can explore the specific neuroplastic effects of psychosocial interventions with the hope to identify increasingly targeted interventions with large treatment effect sizes and robust long-term improvements toward resilient outcomes. Nevertheless, cultivating individual resilience is necessary but insufficient to cultivate social resilience.

Social interventions that mitigate racism

Recently published experimental designs describe individual, family, or social resilience interventions leading to either promotion of affiliative/prosocial behaviors or mitigation of social conflict, aggression, or negative effects of racism. For example, in Black families randomized to a family-based prevention program versus a control condition, enhanced protective parenting buffered the impact of racial discrimination on depressive symptom changes (48). An after-school program implemented by middle school teachers trained students on promotive behaviors aimed to make enduring positive changes within the context of racism. Using a modified randomized controlled design, the program enhanced prosocial behaviors by empowering minoritized students, resulting in reduced aggressive behaviors a year later (49). White college students randomly assigned to view a video documenting the pervasiveness of institutional

racism and White privilege in the US over a neutral control condition showed increased post-test racial awareness (i.e., decrease in racial color-blindness), White empathy, and White guilt (50). A mixed-methods quasi-experimental study in 6 primary schools improved prosocial skills in students and inter-racial climate among teachers after they received training to promote effective bystander responses to racism and racial discrimination (51). White female teachers received a brief empathy-inducing intervention that decreased their implicit bias toward Black individuals (52). A one-time dose of intranasal oxytocin versus placebo administered to White Brazilian males enhanced social salience resulting in improved accuracy in behavioral responses to threat stimuli (53). These studies illustrate the diverse landscape of social interventions, targets, mediators, and outcomes that may be useful to understand and intervene on structural racism. However, they also represent opportunities to study neuroendocrine, neurophysiological, or neuroimaging biomarkers that can reveal biological mechanisms underlying the observed social, collective, or individual effects of the interventions tested. Learnings from social neuroscience experimental studies may close key knowledge gaps or identify important biomarkers for inclusion in designing future studies.

Learning from social neuroscience experiments in other species

Knowledge from social neuroscience experiments across species can guide research that refines existing interventions for aberrant social behaviors by identifying novel targets and circuits. For example, experiments in corticotropin-releasing factor (54), oxytocinergic (55), genetic (56), and metabolic (57) systems provide instructive insights about the deleterious biopsychosocial effects of social dysfunction, and the importance of context in how our brains shape and are shaped by the social world. A proxy to human loneliness (58) is the experimental induction of acute social isolation in rodents, which results in aggression, anxiety, hyperactivity,

and impaired social behaviors and memory. Acute social isolation can also induce midbrain craving response patterns that are similar to those observed during states of hunger (59). In contrast, chronic isolation, such as observed during the pandemic, may be explained by a model of social homeostasis (20), which, as above, is defined by the ability of individuals to detect the quantity and quality of social contact, compare it to a known set-point, and adjust effort expended to seek optimal social contact expressed using an effector system. Direct and indirect assessment of loneliness can also lead to differences in sexual dimorphism in the prevalence of loneliness (60).

Motivation to *seek* social contact is mediated by the mesolimbic dopamine system, with some variations across species (61). Affiliative approach and aversive avoidance are also modulated by stress. For example, rhesus macaques show affiliative social traits across the life cycle, starting with mother-child mutual gazing and progressing to social play, which are all linked to lower long-term glucocorticoid production (62). Social defeat stress models vulnerability and resilience to stress that manifests through patterns of social engagement and withdrawal. Long-term neural and behavioral plasticity in response to these chronic and aversive social experiences are mediated by brain-derived neurotrophic factor (63), but milder forms of chronic stress using unpredictable stimuli are modulated by dopamine signaling (64). Multisystem effects have been demonstrated after exposure to social defeat, in which vulnerable rodents have more anxiety, hippocampal volume reductions, and elevated systemic interleukin-6 levels compared to resilient ones (65). Thus, social defeat models provide context-sensitive mechanisms to explain adaptive and maladaptive responses to social stress and have been used to understand the etiology of mood and psychotic disorders.

Models of lifelong monogamous pair bonding in prairie voles provide an alternative conceptual framework for understanding social dynamics and homeostasis, mediated via neuromodulatory signaling within the nucleus accumbens (66), and involve complex oxytocin, dopamine, and opioid interactions to form and maintain pair bonds over time (67). This model also highlights how vasopressin regulates social behaviors through signaling in key brain regions (68). These studies, and the complimentary regulation of social behaviors by oxytocin and vasopressin (69), have implications for translation to novel therapeutic strategies to target disorders that are associated with qualitatively divergent social deficits, such as the social anhedonia experienced in major depressive disorder versus the social cognition deficits observed in autism spectrum disorders. However, studies have shown mixed efficacy in animals versus humans to provide a unifying theory that would facilitate translation. To illustrate, in a mouse model of autism, oxytocin response and social novelty behaviors were rescued by a specific and brain-penetrant inhibitor of MAP kinase (70). However, when children and adolescents with autism spectrum disorder were randomized to intranasal oxytocin versus placebo, there were no significant between-group differences in the change from baseline on measures of social or cognitive functioning over 24 weeks (71). A lack of forward translation from preclinical to clinical studies may be due to several factors that merit examination but may be partially rooted in the lack of complete phenotypic homology across species. Further, translating complex social constructs may not be easily modeled across species using existing experimental paradigms.

DISCUSSION

Although each of the above studies contributes uniquely toward the broader social impact of promoting social resilience to mitigate structural racism, there are several research design

considerations in these clinical trials and lessons from preclinical studies that may inform future research. Indeed, mixed-method qualitative and quantitative methods may facilitate frontiers in understanding and innovating in diversity science (72). We now consider other methodological opportunities based on gaps that have previously contributed to the perpetuation of structural racism in biological psychiatry research. These gaps represent potential opportunities for redesigning preclinical and clinical research through the lens of social neuroscience and informed by diversity, equity, and inclusivity principles.

Understanding the affiliative power of placebo

A positive contact phenomenon is observed clinically across many areas, where simple contact with a friendly healthcare team member may be intrinsically pleasurable, and lead to clinical improvement (73). This biopsychological phenomenon, called a *placebo effect*, occurs as a product of an individual's intrinsic response to a placebo, to produce a tangible and positive neurobiological event that induces a change or perception of a change in symptoms. In contrast, a *placebo response* is the quantified improvement of an outcome variable in a clinical trial after an individual receives a sham (inactive) intervention. Like the social neuroscience concepts described above, the placebo response is rooted in a combination of intrinsic and socially defined constructs, such as the placebo effect, expectancy, trust, geography, culture, and demographics (**Figure 1**).

Understanding and experimentally varying these individual and social factors that contribute to the placebo response can provide fundamental insights about how the brain works and about mind-body interactions (74). For example, learning models of constructs such as mindset (75), or expectancy during error detection and reward prediction error signaling are localized to prefrontal regions such as the anterior cingulate cortex, through μ-opioid receptor-

mediated neurotransmission (76). These models describe potential targets for individual level intervention. Social influences conveyed through how a commercial product is labeled may moderate physiological, functional, and psychological responses to a placebo (77). In addition, interventions can take into account ethnic matching of professionals to patients, involve cultural adaptation, or empower patients with agency in decisions at branch points that may enhance the therapeutic relationship (78). Some key questions emerge from this literature. How can this knowledge be leveraged to design trials that improve individual versus social resilience? What would be the scientific and societal consequences of matching on the ethnicity, gender, or sexuality of a participant and/or interventionalist? Who would conduct the trial for intersectionally diverse prospective participants? These questions merit consideration in efforts to test novel therapeutics that have the potential for broader reach and greater overall impact.

Finally, the placebo response involves complex mental events such as trust and expectancy, but also beliefs and hope. It can be conceptualized as a means to assess the superiority of a therapy to placebo (trialist's view), or as a summation of all biopsychological influences that change the time course of a symptom in relation to an intervention (neuroscientist's view) (79). Indeed, neuroscience and trialist viewpoints on how treatment response is defined each have merits.

Understanding why representation matters while avoiding bounded justice

Clinical trials may sometimes fail due to inclusion of individuals who may be highly susceptible to showing a placebo response. Even in the context of a positive trial outcome, there may be other participant characteristics or trial complications that limit the generalizability of results to affected or broader populations. This, in part, has to do with efforts to select a sample that is representative of those being targeted for intervention. Unfortunately, many clinical trials

in psychiatry have generated data in subsets of the population which may be biased on certain demographic characteristics. Race is a key area of concern because most available psychiatric treatments have not been studied in underrepresented populations, resulting in limited knowledge about how available evidence-based interventions can benefit, show no response, or even harm their health (80,81). Participatory hesitancy may be rooted in a fundamental mistrust of doctors, or due to inherent barriers to medicine evolving towards engaging in the practice of anti-racism (82,83) and avoiding bounded justice (84). For example, Black youth (85) and Black pregnant mothers (86) experience significant levels of chronic stress. Although these studies cannot delineate whether chronic stress was attributed to biological differences in race or exposure to racism, they highlight the importance of developing interventions that can target these complex and embedded factors. The experience and expression of suffering varies individually and across groups, as does their attribution, and can influence help-seeking and care pathways. These same factors may contribute to shaping feelings of social belonging. Further, trusting or not trusting a doctor or believing or not believing in a therapy may trigger a cascade of neurophysiological events that, in turn, may change the experience of a symptom or the clinical course of a disease (87).

Building trust and cultural competency

Mistrust is a natural consequence resulting from the mistreatment of Black Americans, given the discredited legacy of race and racism in medicine (88). This may partially explain vaccine trials for COVID-19 struggling to recruit from the Black community (89). There is a disconnect between vaccine hesitancy and wider trust related to matters of personal health. This is compounded by a dearth of research on trust in diverse groups and specifically in low and middle-income settings (90). Virtually no studies have examined how trust levels change over

time or how resilience to trust-compromised information can be built into a trustworthy health system. Black and Hispanic patients in the US seem to prefer office or emergency department visits over telehealth visits compared to Whites or Asians (91).

Neuroanthropology, which integrates the social and cultural neurosciences, confirms the brain's sensitivity to culture, which can shape preexisting patterns of neural activity and influence brain function, structural plasticity, and cognitive function implicitly and explicitly (92). The prefrontal cortex is a principal consumer of culturally-influenced information, establishing relations among things, events, and corresponding regional networks. Although a broad target for neuromodulation, the specific ways in which the prefrontal cortex regulates social and emotional processes in culturally variable ways provides a strong imperative to design experiments that explore the influence of cultural competency (93).

As we move towards better understanding the unique needs of our patients in context of their histories and cultures, trial designs should sample the full breadth of race, ethnicity, culture, and socioeconomic diversity. Racism has social, historical, economic, political, and communal roots, and it has biological consequences in terms of poorer health outcomes, adverse experiences of care (94), and epigenetic imprinting across generations of stress exposure (95). Acknowledging how this history impacts research recruitment and the limited generalizability of evidence generation is a fundamental prerequisite to supporting more representation in clinical trials and building trust.

More gaps in knowledge

Much remains unknown about how interventions lead to social resilience and in whom. It is critical to determine how generalizable efficacy and safety of existing treatments are to subpopulations not represented in psychiatric clinical trials. Comparative effectiveness trials

have not been extensively conducted in psychiatry but remain essential for developing personalized treatments. When studies are insufficiently powered to enable sensitivity or moderation analyses, they might also generate spurious results. In large datasets, sensitivity analyses may address gaps in knowledge about outcome in underrepresented individuals. Further, it is unclear how existing interventions largely based on Western cultural practices and primary outcomes might perform in different cultural contexts. There are also challenges in measurement due to nuances in language, culture, race, socioeconomic status, and other factors, which without context, might introduce biases that do not accurately reflect the data.

We might make progress with humility by focusing on the needs of individuals or groups while considering the overall goals of discovery (i.e., whether to promote individual or social resilience). If social belonging experiments are to inform systems of care, there must be correct goal alignment for programs that address access to care and use tools from implementation science, pragmatic, participatory, and comparative effectiveness trials that can empirically test their effects.

TRANSFORMING BIOLOGICAL PSYCHIATRY RESEARCH INTO THE FUTURE

Transformative research in biological psychiatry should strive to ethically bridge multiple valleys of death between innovation and intervention, research and clinical care, theory and practice. Starting with a baseline that the art in psychiatric practice involves trial and error, the path toward precision psychiatry will likely involve the same iterative approach and collaborative efforts as celebrated in the scientific method (96). The social neuroscience underlying prosocial behaviors is a constructive affirmation of common and shared goals across diverse stakeholders to promote nurturance and reduce the negative consequences from structural racism. Indeed, paradigm shifts also represent unique black swan opportunities for innovation.

For example, reimagining clinical trial designs to evaluate mechanisms that drive adaptation, leverage the placebo response, or extend reach of evidence-based treatments to an unprecedented number of individuals might be solutions that have been accessible to us all along. Using these available tools, we can compare in-person and digitally-delivered psychosocial interventions for several stress-related conditions and integrate our understanding of mechanisms using multimodal neurobiological assessments and advanced computational analyses, while also working to overcome barriers in access to effective care for underrepresented groups with substantial unmet needs.

Thus, transforming mental health care may require immediate paradigm and priority shifts in science and in health care delivery. Using a model inspired by the NIH "All of Us" Precision Medicine Initiative (97), digital therapeutics and novel social paradigms may revolutionize the global landscape of mental health by being accessible, cost-effective, and convenient (98,99). However, we need more evidence to guide how these interventions address privacy and quality control (100,101). Similarly, translational paradigms that can interrogate social dynamics during play or bonding rather than during stress induction may lead to discovering novel biomarkers of social resilience, but we need more evidence that they can be effectively targeted and engaged during intervention. In group- rather than individual-level experimental designs, advances may be possible through discovering interactive components of social play (102), learning, and reward systems (103) that subserve trans-species affiliative behaviors and cooperation.

At a system level, social resilience may be encouraged across primary, secondary, and tertiary prevention strategies. For example, digital therapeutic strategies can efficiently deploy large-scale primary prevention strategies like education directly into people's homes (104).

Increasing accessibility of on-demand resources, and empowering patients to learn and practice skills at their own pace may avail health care systems to more effectively triage deployment of secondary and tertiary interventions for those at high risk or already living with a psychiatric disorder (105,106). Equitable, safe, accessible, and effective digital alternatives to standard mental health treatments could provide a model *first line of defense* more effectively triaging resource allocation. This approach may also reduce high economic costs and wait times that come with accessing clinically-validated treatment, especially for hesitant individuals and groups (107,108).

Clinical trials can democratize investigation through model community-network participatory designs to reach people across race, ethnicity, socioeconomic status, and life course. Participatory trial designs may prove useful to translate interventions into real-world settings. However, such designs should take care to maintain respect for autonomy, choice, and agency, through continuous and meaningful informed consent, to mitigate confusing the goals of clinical care versus research (109). Reducing therapeutic misconception and building trust is especially important in the digital mental health revolution, where interventions, if delivered well, may be less stigmatizing by design, or lead to high rates of engagement and self-disclosure (110–114). Perceived benefits include personalized interactive content, information collection through measurement, patient centricity by honoring self-report, and providing remote patient monitoring options for clinicians. However, to understand which treatments are best suited for which groups and under what conditions requires design and implementation strategies that have not been traditionally considered in psychiatric clinical trials (115).

The field of psychiatry can evolve how clinical trials are designed by integrating mechanistic discovery and clarifying how, when, and in which populations interventions work

best (116). This may involve bridging traditional approaches of testing efficacy and safety with real-world, pragmatic and adaptive trial designs that optimize utility and usability. To ensure that the goals of science are clearly delineated from the goals of clinical care, continuous informed consent may help (117). To achieve diverse sampling, transparency and trust may be built through learning systems, in partnership with regulatory oversight (118). To evolve trial designs originally developed for pharmacological treatments to be interoperable with digital therapeutic trials, requires engagement among multiple stakeholders (119). Finally, capitalizing on placebo delivery through digital means to remove unintended biases that might originate from contact with a human experimenter, clinician, or clinical setting, and using randomization and allocation concealment may facilitate powerful causal inference. Engaging in available research design strategies through the transformative lens of social neuroscience may increase both the robustness and relevance of interventional research (120). Of course, any success in translation begins by reflecting on gaps in current knowledge that remain unfilled.

CONCLUSION

In this scoping review, intervention studies involving affiliative and prosocial behaviors demonstrated improvement in resilience or wellbeing of individuals who experienced stereotype threat. Behavioral neuroscience has provided strong evidence that the nurturance of affiliative behaviors can have positive impacts on the wellbeing of individuals and societies. There is a lack of unifying outcomes and trials conducted in limited subpopulations to be able to infer whether social resilience is a superior target over individual resilience and in whom. Nevertheless, evidence generation including future comparative effectiveness trials with diversity, equity, and inclusivity principles embedded may inform policy and practice priorities.

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FIGURE 1: Factors that may contribute to a placebo effect and a treatment effect