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Translating the Neuroscience of Adverse Childhood Experiences to Inform Policy and Foster Population Level Resilience

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Abstract

Imaging methods have elucidated several neurobiological correlates of traumatic and adverse experiences in childhood. This knowledge base may foster the development of programs and policies that aim to build resilience and adaptation in children and youth facing adversity. Translation of this research requires both effective and accurate communication of the science. This review begins with a discussion of integrating the language used to describe and identify childhood adversity and their outcomes to clarify the translation of neurodevelopmental findings. An integrative term, Traumatic and Adverse Childhood Experiences (TRACEs+) is proposed, alongside a revised ACEs pyramid which emphasizes that a diversity of adverse experiences may lead to a common outcome and that a diversity of outcomes may result from a common adverse experience. This paper then highlights the emerging neurodevelopmental knowledge surrounding the effect of TRACEs+ on youth with an emphasis on the knowns and unknowns about neural connectivity in youth samples. How neuroscience findings may lead directly or indirectly to specific techniques or targets for intervention and the reciprocal nature of these relationships is addressed. Potential implications of the neuroscience for policy and intervention at multiple levels are illustrated using existing policy programs that may be informed by (and inform) neuroscience. The need for transdisciplinary models to continue to move the science to action closes the paper.

Key Words: Traumatic, Adverse Childhood Experiences; Neuroscience, Translation

Public Significance Statement: Neuroimaging methods have elucidated several neurobiological correlates of various traumatic and adverse childhood experiences during development. This knowledge base can serve as an anchor for the development of programs and policies that aim to build resilience and adaptation in youth facing adversity. Translation of these research requires both effective communication and accurate communication of these discoveries.

Translating the Neuroscience of Traumatic and Adverse Childhood Experiences to Inform Policy and Foster Population Level Resilience

Scientists, clinicians, and policy-makers now broadly accept that childhood exposure to adverse or traumatic events (also termed extreme, severe, toxic, or chronic stress) may have effects on the developing brain (Asmundson & Afifi, 2019; Carrión & Weems, 2017; Sheridan & McLaughlin, 2020). The public awareness and policy impact of the science in this area has been fostered by framing the discourse through the concept of Adverse Childhood Experiences (ACEs)(see e.g., Larkin et al., 2014). Indeed, the ACEs concept and research suggesting effects on brain development has been instrumental in motivating school officials, policy makers, and the public to acknowledge the potential negative impact of such experiences (Purewal et al., 2016; Srivastav et al., 2020). Developmental neuroscience can also serve as anchors from which to set goals relating to novel, effective, and empirically-driven programs that aim at building resilience and adaptation in youth (Murphey & Sacks, 2019). By accurately informing policy makers, the fields of psychology and allied brain sciences have an opportunity to create interventions "writ large" for youth who have experienced ACEs and ideally for the prevention of ACEs themselves.

Translation of research findings into well-disseminated, evidence-based interventions requires both effective communication *and* accurate communication of the discoveries (Farah, 2018; Thomas et al., 2019). A unifying language of adversity for effective and accurate communication across disciplines and stakeholders is needed. This discourse must also recognize potential differences in the effects different types of adversity may have on the individual. To that end, this paper begins with a discussion of more formally integrating the concepts of severe or traumatic stress and ACEs but also the need to wed the concepts of both 1) risk and resilience and 2) the concepts of equifinality (i.e., multiple different risks can lead to the same outcome, e.g., a genetic risk, poverty, and traumatic stress may each lead to the same negative outcomes) and multifinality (i.e., a particular risk may have diverse outcomes; e.g., exposure to a traumatic stressor does not inevitably lead to early death) (Cicchetti & Rogosch, 1996) into ACEs discourse. Next, examples from the emerging network neuroscience perspective on the effect of ACEs in childhood development are presented to highlight what is known and unknown about effects in pediatric samples. The need for a common language that recognizes the potential for differential effects of various adverse experiences is illustrated.

The review then turns toward how the neuroscience has, has not, and may yet lead to individual and community interventions that can become sustainable through existing or new policy (i.e., translating the neuroscience into action). Examples of specific techniques that aim to build resilience and adaptation in youth by directly targeting (and/or protecting) biological systems altered or at-risk in the aftermath of adversity and intervention outcomes are reviewed. Next, broad based programs supported by policy that address the consequences of ACEs, or aim to build resilience, as well as those that attempt to reduce prevalence of these experiences are discussed as avenues for identifying targets of intervention or implementing specific techniques derived from neuroscience. The potential for neuroscience research to be guided by these policies is also noted. Models for effective translation and potential issues in translating “the science” into effective action close the paper.

Effective Communication and the Need for an Accurate Discourse

By bringing attention to the importance of childhood trauma and severe stress the ACEs concept has pushed the discourse on adversity-affected youth from scientific journals to community conversations to houses of legislature. Indeed, it is not unreasonable to attribute the broad ‘push’ towards translating an understanding of the neurological consequences of ACEs in child development to transformative organizational and government policy (Bethell et al., 2014).

While translation of scientific findings can be an effective method of instantiating change, accurate communication of these discoveries is also critical (White, Edwards, Gillies, & Wastell, 2019). Certainly, the ACEs assessment has been successfully used in adult samples to examine brain differences amongst those with greater or fewer ACEs (e.g., Cohen et al., 2006). However, the extant data on neurodevelopmental effects in pediatric samples has not typically focused on ACEs per se, but instead has tended to focus on exposure to “traumatic stressors” and/or childhood maltreatment (Weems et al., 2019).

We suggest integrating the concepts of severe or traumatic stressors and ACEs in a way that recognizes the potential differential effects that various stress or adverse events will have on youth - but also recognizes that ACEs are associated with both risk and resilience, equifinality and multifinality. An example drawback to the current nomenclature is the widespread acknowledgement that the original ACEs list is limited in number and scope of potentially adverse experiences (Cronholm et al., 2015). Conversely, authors have noted that definitions of ACEs actually offer limited empirical evidence or assessment potential and thus to over-claiming the effects of ACEs (White et al., 2019).

Table 1 lists the original ACEs, the expansion of the list (Cronholm et al., 2015) and integrates work from pediatric samples (Burke, Hellman, Scott, Weems, & Carrión, 2011; Taylor & Weems, 2009). The table denotes which items are considered traumatic according to the Diagnostic and Statistical Manual of Mental Disorder (DSM-5, APA, 2013) criteria. The DSM-5 defines a traumatic stressor as a direct, witnessed, or indirect (to a loved one) exposure to actual or threatened death, serious injury, or sexual violence. As shown in Table 1, by definition, not all ACEs are traumatic. For example, having a caregiver with a substance use disorder or schizophrenia is likely to be extremely stressful for the entire family, but not necessarily traumatic per se. Moreover, not all “traumas” are included in either the traditional or expanded

ACEs lists. Experiences such as a natural disaster, war, or a car accident may be traumatic but are not included in common lists of ACEs.

Table 1 also provides findings from Taylor and Weems (2009) who examined children's subjective reports about the severity of various traumatic experiences. Taylor and Weems (2009) used an open response query, "Many kids go through things that are very upsetting or frightening. We would like to know about them and how you felt about it. They might have happened recently, or they might have happened a long time ago. Can you tell us if anything happened to you that was very scary or frightening?" The sample included ethnically diverse children and teens aged 6 to 17 (mean age of 11.15 years; SD = 3.39. Multi-rater coding of the responses revealed that the events described generally fell into seventeen categories: 1) witnessing family violence, 2) witnessing non-family violence, 3) witnessing entertainment violence, 4) separation and loss from family members, 5) separation and loss non-family, 6) physical abuse by a family member, 7) physical neglect by a family member, 8) physical trauma, 9) sexual abuse by a family member, 10) sexual assault, 11) emotional abuse by a family member, 12) emotional abuse non-family, 13) emotional trauma, 14) motor vehicle accidents, 15) natural disasters, 16) explosions/war, and 17) unclassified (reported items that were "non-events" such as psychological states).

Findings in Taylor and Weems (2009) also revealed that the perception and interpretation of the experiences reported were significantly associated with emotional difficulties. Indeed, research strongly supports the notion that individual differences matter in traumatic stress (e.g., Compas et al., 1996; La Greca et al., 1996), suggesting that posttraumatic adjustment (both risk and resilience factors) is not simply dependent on the type of event experienced, but rather *how* it was experienced. Ultimately, clinicians and scientists alike must be cognizant of the fact that in traumatic stress, both the objective facts of the event as well as the subjective experience are relevant to the aftermath.

ACEs, traumatic stress, toxic stress, posttraumatic stress, and myriad other terms all attempt to define the experience of the individual, yet the multiplicity in this nomenclature may dilute the messaging. Given its widespread recognition, it may be useful to retain the acronym “ACEs”, while adding “traumatic” centrally to the conversation and acknowledging the importance of additional (+) risk and protective factors. Thus, we suggest the full phrase to be Traumatic and Adverse Childhood Experiences *plus* relevant risk and protective factors (TRACEs+). For the remainder of this article we refer to “ACEs” when noting specific research using the original or expanded ACEs retrospective/chart review assessment. We use TRACEs+ to refer to the broader literature linking trauma and adverse experiences to brain development.

In addition to integrating terminology, there is a need to integrate the fact that a wide diversity of outcomes may follow after TRACEs+ and that resilience may be fostered by effective intervention and policy. Figure 1 presents a revised ACEs pyramid that adds a resilience pinnacle. As depicted, there is not one inevitable outcome, but multiple potential outcomes of TRACEs+ (multifinality). Consequently, there are multiple levels of interventions possible to help place individuals on a path of resilience. The addition of the resilience pinnacle emphasizes that the integration of elements in the base of the pyramid does not necessarily lead to inevitable outcomes. For example, pre-existing factors may confer specific vulnerabilities, or augment certain strengths that may worsen *or* mitigate the effects of exposure, respectively.

A life path leading to pathology or resilience is not absolute or all encompassing. Individuals may be resilient in certain aspects of their lives, but not others. In this way, Figure 1 also highlights the interaction between levels/severity of TRACEs+ and historical, pre-existing, and contextual factors. The figure builds from previous illustrations and acknowledges the potential for racial/ethnic and generational trauma for oppressed groups in both the experience of TRACEs+ and in the context within which adversity is experienced. Better understanding of TRACEs+ and tailored interventions across ethnicities, nationalities, and cultures is needed. For this figure we have added arrows denoting the potential for interventions (see Marie-Mitchell & Kostolansky, 2019) to move individuals toward resilience.

A neurodevelopmental layer has been inherent in previous conceptualizations of the ACEs pyramid (https://www.cdc.gov/violenceprevention/childabuseandneglect/acestudy/ace-graphics.html). In reality, the research which this compelling aspect of the figure is based upon is from largely retrospective assessment of "ACEs". While important for establishing a potential association, such methods are limited by memory and do not rule out all of the history an individual has experienced in the interim, including current life trauma, that may account for differential brain effects. As noted, the empirical literature on neurological effects on youth samples has tended to focus exclusively on exposure to traumatic stressors or childhood maltreatment (Weems et al., 2019). Some form of the TRACEs+ concept integrates this literature more accurately. Figure 1 also has examples from neuroscience and how these may effect linkages at other levels of the pyramid. More on this below.

What Does the Science Actually Say About TRACEs+ on the Developing Brain?

As noted, neuroscientific research has facilitated broader acceptance of the importance of addressing TRACEs+ by demonstrating the biological impacts of early life stress on brain and body. In the traditional tripartite model of adversity-related changes in the brain, the ventromedial prefrontal cortex (vmPFC) inadequately down-regulates an amygdala that has become hyper-responsive to threatening cues, resulting in chronic hyperarousal (Rauch et al., 2006). High levels of stress also impair hippocampal activity, distorting recall of trauma memories, and interfering with extinction of learned fear responses (Milad et al., 2009). Though this conceptual model has provided fruitful insights into adversity-related effects on the brain, neuroscientists have begun to acknowledge its limitations (Akiki et al., 2017). The heterogeneity of mental illness, coupled with the vast complexity of the human brain, make it unlikely that dysfunction in psychological or cognitive processes may be directly mapped to any one individual region (Menon, 2011).

Instead, neuroscientists are finding that pathology-linked systems such as emotion regulation tend to derive from coordinated activation of multiple, regionally disparate areas of the brain (Cisler et al., 2013; Menon, 2011; Whitfield-Gabrieli & Ford, 2012). This 'network' neuroscience approach expands on research into the functional role of many of the same brain regions (e.g., insula, amygdala, hippocampus), but examines how these components perform in concert rather than in isolation. This work investigates not only the functional coactivation of these structures, but the integrity of the white matter 'wiring' along which they transmit information. Research has begun exploring the role of adversity, in shaping the development of these various network systems (Herringa, 2017).

Network Neuroscience

In network models, individual regions such as the amygdala or hippocampus are considered 'nodes' serving as waystations for information as it passes throughout the brain. Each node contributes by adding, subtracting, or altering an aspect of this information. Connectivity between nodes may be assessed in terms of functional and structural terms, the former describing temporal correlation between node activation, and the latter referring to the integrity of interlinking white-matter tracts. This model can be aptly analogized to a mass transit system, where trains carrying passengers between stations correspond to electrochemical signals carrying information between brain regions. At each station, passengers on the train are likely to change, much as each node in a neurological network is likely to alter the passing information. Travel between any two stations (i.e., functional connectivity) is likely to vary as a function of each station's (node's) operations as well as the quality of the connecting tracts (structural connectivity).

Much like a transportation engineer, a 'network'-focused neuroscientist considers not only the individual nodes and their connections, but also the flow of information through the broader network under various ecological pressures. Certainly, some brain regions may play an outsized role in processing certain types of information. For example, the amygdala may be a 'hub' node during threat-related processing, much as a station near the ballpark might be heavily trafficked by fans traveling to a game. The functional brain networks that may play a role in TRACEs + include: the salience network of brain regions thought to be involved in detecting behaviorally relevant stimuli; central executive network linked regions associated with executive cognitive functions of emotion regulation, decision making, and attention; and default mode network of regions that are active during wakeful rest (Akiki et al., 2017; Menon, 2011).

Understanding the nuances of the networked brain therefore necessitates quantifying structural connectivity in various pathways throughout the brain, functional connectivity when processing various types of information, and how the two integrate to affect the dynamics of networked brain systems. While a foundational (though still developing) knowledgebase exists to describe these concepts in typically developing youth, complementary work exploring differences in adversity exposed youth is just now emerging, despite continued recognition of the enormous translational potential of network neuroscience for this population. Next is provided an exemplar area of network neuroscience research – the default mode network. We use this and other networks to describe its potential role in concert with other brain networks in the etiology and treatment of psychopathology in adversity-exposed youth.

The Default-Mode Network: Neuroscientists frequently describe research conducted with the brain in a 'resting state', yet, the term itself is a misnomer – the living brain is never truly at rest. In fact, several regions of the brain are known to show *greater* activity during periods of minimal stimulation (e.g., eyes closed) and comparatively *less* activity during cognitive engagement (Greicius et al., 2003). The synchrony in the activation of these structures, which include areas of the posterior cingulate cortex, medial temporal lobe, and ventromedial prefrontal cortex, has led to their inclusion in a 'default mode network' (DMN) thought to underlie self-referential thought processes such as daydreaming which may become active 'by default' when external cognitive demands are low. This may involve the interpretation of social information, retrieval of reference memories, or emergence of spontaneous thoughts. Clinicians will recognize each as a common target of trauma-focused interventions. Trauma-exposed youth exhibit biased interpretation of social stimuli (Shackman et al., 2007), impaired or altered retrieval of autobiographical memories (McCrory et al., 2017; Weems et al., 2014), and often experience unexpected distress from spontaneous thoughts about past traumas (Hoffmann et al., 2018).

These and similar cognitive changes may be linked to adversity-linked alterations in the organization and efficiency of the default mode network. Research with trauma-exposed adults has generally found reduced functional connectivity between nodes in the DMN, with inverse correlations to the severity of PTSD symptoms (see Weems et al., 2019). Moreover, these alterations appear at least partially rooted in a loss of neural integrity (Greicius et al., 2009; Lei et al., 2015; though see Akiki et al., 2018). Yet, while an understanding of these effects in adversity-exposed adults is beginning to take form, there is a paucity of corresponding research with youth (Herringa, 2017). Moreover, the few studies that do exist suggest remarkable differences in DMN connectivity. Patriat et al. (2016) contrasted DMN connectivity across groups of age and sex-matched youth with posttraumatic stress disorder (PTSD) and healthy controls, finding that in contrast to the adult literature, adversity-exposed youth demonstrated *increased* connectivity. Cisler et al. (2013) reported similar findings in a study of adolescent girls exposed to assaultive violence.

Interpretation of these initial findings may benefit from a consideration of developmental timing. Children experience age-related changes in metacognitive ability, particularly with regard to awareness of cognitive-emotional control. Adversity-exposed youth may be more likely to engage metacognitive abilities rooted in the default mode network to control thoughts, or actively regulate emotion. Thus, the increased connectivity among adversity-exposed youth may reflect a greater reliance on this system to regulate negative emotion and memory. Interestingly, this increased DMN connectivity mirrors findings among youth with mental illnesses well-known to involve dysfunction in self-referential thought processes (e.g., anxiety, depression). It may be that youth who experience adversity are at greater risk of 'mentalizing' distress, particularly as new cognitive systems come online that encourage abstract and existential thought. More generally, these findings align well with clinical research demonstrating distinct developmental differences in adversity-related symptomatology (Russell et al., 2017). Additional research linking changes in the default mode network to change in the severity and duration of specific psychopathology symptoms will be needed to clarify these effects. For example, future studies may test whether current treatments, such as trauma-focused cognitive behavioral therapy (TF-CBT), help trauma-exposed youth to optimize their default-mode network, instead engaging DMN nodes with regulatory networks like the central executive network to more effectively cope with trauma reminders, cognitive distortions, and build distress tolerance.

Significant Gaps Remain

Formally integrating the language of trauma and adversity is important for accurate dissemination of the neuroscience findings. Table 1 indicates whether samples have explicitly experienced the listed TRACEs and so have at least been directly linked to structural or functional differences in brain connectivity in youth samples. To illustrate, Weems et al. (2019) summarized seven diffusion tensor imaging (DTI) which examine white matter tracts and 15 functional MRI (fMRI) studies examining functional connectivity in youth under age 18. While none of these studies employed a traditional ACEs assessment all fit under the TRACEs+ conceptualization. For example, among the studies that examined structural connectivity, a picture of reduced structural connectivity between limbic system structures (e.g., hippocampus, amygdala) and regions of the frontal cortex emerges—areas linked by a white matter tract known as the uncinate fasciculus. Here the samples included early deprivation; natural disasters; witnessed death; witnessed serious injury; physical abuse; domestic violence; neglect; and abandonment. Among the functional connectivity studies in pediatric samples, as in the structural studies, a picture of differential connectivity between limbic structures and frontal cortex regions emerges. Here the samples had experienced accidents; domestic violence; emotional abuse; early deprivation; neglect; natural disasters; physical abuse; sexual abuse; traumatic grief; verbal abuse; witnessing death; witnessing serious injury; or witnessed violence. The relative consistency of findings does not mean however that all the TRACEs so far examined are the same; there may indeed be different effects of different types of experiences.

As another example, Kribakaran and colleagues (2020) conducted a meta-analysis and showed that pediatric PTSD is associated with relatively smaller volumes in a number of regions including total cerebral volume and gray matter as well as temporal lobe (total, right, left), total cerebellar vermis, and hippocampal (total, right, left) volumes. The TRACEs+ formally and accurately integrates this meta-analysis on PTSD into the broader discussion of ACEs. This is important because the specific links to the brain effects using traditional ACEs assessment is retrospective (or chart reviews) in nature (e.g., Cohen et al., 2006; see Sheridan & McLaughlin, 2020). Such studies are limited in establishing even temporal effects. Thus, while the link between brain volumes and pediatric traumatic stress is now well-established, we do not know how much of this correlation stems from preexisting differences (e.g., poverty or other socioeconomic context effects that place youth and greater risk for experiencing trauma or developing interfering PTSD symptoms after traumatic stress). Prospective longitudinal and intervention studies are critical for disentangling the confounding effects of poverty from TRACEs+. Then again food insecurity and poor nutrition are certainly adversities that should be prevented - hence the need to keep the concept of equifinality in mind.

Despite increasing knowledge of normative developmental trends in regional brain development, a truly developmental whole brain network approach to the neurobiological effects of traumatic stress has not been the norm (Weems, 2017; Weems et al., 2019). Such an approach recognizes the parts in the context of the larger system by acknowledging the myriad links between global and regional brain changes, and specific symptoms in the context of TRACEs+. Thus, another gap remaining in the neuroscience research revolves around how exactly early adversity alters the developmental trajectory of brain and symptom networks to yield risk and resilience for psychopathology. For example, what are the sensitive periods of TRACEs+ effects on these networks, and what are the sensitive periods for maximal intervention effectiveness? Which early neurodevelopmental patterns are capable of differentiating resilient and vulnerable youth? While questions remain, the time is ripe for translating the neuroscience to more actions.

Translating the Neuroscience to Action

The arrows in Figure 1 highlight the potential of community and school-based intervention to guide youth who have experienced TRACEs+ towards the resilience side of the pyramid (see Marie-Mitchell & Kostolansky, 2019) as well as broader policy to prevent exposure. The *promise* of neuroscience - to optimally inform broad interventions via policy and its' implementation - is compelling. For example, the field of educational neuroscience has emerged and seeks to translate research findings on neural mechanisms of learning to educational practice (Farah, 2018; Thomas et al., 2019). However, writers and theorists in these areas alternately warn against moving too fast by engaging in blind acceptance of tenuous connections between brain and social behavior, yet also of neglecting the potential benefits: "Neuroscience is adopted largely uncritically in social policy in relation to child welfare and child protection," Beddoe & Joy, 2017, p. 65). In developing translational models it is also important to underscore that there are likely both direct and indirect practice and policy ramifications (Thomas et al., 2019) and that the full effect and clear implications of the neurodevelopmental research on TRACEs+ are yet to be realized.

Reviews of the neuroscience translation literature suggest that the neuroscience contribution to policy has been largely successful in what Shonkoff and Levitt (2010) termed the "why". That is, making the case for why we should intervene in the lives of children who are at risk for or who have experienced TRACEs+. For example, ten years ago their commentary on translating neuroscience voiced concern that "the value of that relationship [between neuroscience and policy] is approaching a plateau that demands thoughtful examination. In practical terms, the long-term utility of neuroscience for informing public investment in young children requires a fundamental reorientation from the current focus on answering the relatively easier ''why'' question to actively confronting the more challenging ''what'' and ''how'' inquiries," (Shonkoff & Levitt, 2010; p. 689). Figure 2, Panel A, illustrates several considerations to map the direct and indirect influence of neurodevelopmental research on TRACEs+ intervention and policy. As already noted, neuroscience has broadly informed 'why', but has the potential to address also "what" the targets for intervention may be, and also the "how" these interventions may operate (i.e., specific techniques).

The translation may be very direct such as the work in noninvasive deep brain stimulation for refractory PTSD (Koek, Roach, Athanasiou, van't Wout-Frank, & Philip, 2019) or indirect (e.g., cognitive and behavioral techniques consistent with neuroscientific understanding). Figure 2, Panel A, also illustrates the nested translation of 'why', 'what', and 'how' within different contexts, from broad effects with national guidelines, programs and laws to more local implications or simply specific effects on therapeutic practice with individuals or groups in schools or clinic settings. The translation of the 'why', 'what', and 'how' can also be nested within existing, emerging, or proposed policy. How neuroscience findings can move beyond <u>why and</u> toward ideas for <u>what</u> to target and <u>how</u> to do it, and how neuroscience can lead directly to specific intervention techniques (how) and targets (what) and the reciprocal nature of these relationships is addressed next.

Neuroscience-Informed Intervention and Intervention Informed Neuroscience

As noted, some of the changes in functional connections among brain regions map onto the network model symptom associations. Figure 1 illustrates one neurodevelopmental path highlighted in previous reviews (Weems et al., 2019), with an overactive salience network and hyperarousal leading to emotional numbing and risky and self-injurious behaviors over time. The network model fits with diverse outcomes whereby a cascade of symptom associations emerge over time, leading to one set of symptoms for some youth (such behaviors then being "central" to the outcome network for those youth), and another set for others, similar to the concept of multifinality, in that there are multiple outcomes even within the criteria for PTSD (Cicchetti & Rogosch, 1996). For example, in terms of self-injurious behaviors/symptoms, within a neurobiological network some brain structural or functional regions or connections may be more critical to the etiology of a risky behavior outcome following trauma. The general idea is that some brain regions or regional connections may influence certain stress responses, and differences in their functional or structural connectivity may then represent a critical influence over risk or resilience to experiencing certain PTSD symptoms, explain certain symptom associations, or help explain symptom connection with other outcomes (Weems et al., 2019).

The linkages among self-harming, emotional numbing, as well as hyperarousal (from Figure 1) and their common neurological associations illustrate this idea. The clinical or therapeutic implications of this may mean that treating each symptom as if they were of the same importance, or only targeting those symptoms causing the most immediate distress, may not be the most effective approaches to treatment. In fact, clinical approaches may need to initially target symptoms with a high degree of centrality, or those symptoms that are most likely to have an effect on other symptoms (Russell et al., 2017). Theoretically, a cascade of symptoms following trauma may begin with uncontrollable hyperarousal leading to, for example, self-harming in order to control inefficient executive control of physiological arousal.

The identification of structural and functional neuromarkers of traumatic stress and its accretion leads to a) increased knowledge on targets of intervention, b) anchors for evaluation of treatment outcome, and c) informed development of new interventions. Key brain regions and neural networks involved with memory processing, emotion regulation and executive function have been implicated in the pathophysiology of trauma. While less is known about the bidirectional influence of resilience and adaptation on the functional maintenance of these networks, Figure 1 illustrates the idea that interventions fostering optimal executive network functioning may further help foster emotion regulation and delayed gratification, thus leading to increasing probability of resilient outcomes for those with TRACEs+. The importance of the bi-directional relationship, where neuroscience tells what the effects of intervention strategies are on the brain, is another intersection of TRACEs+ informing neuroscience.

As an example, Garrett and colleagues conducted fMRI in 20 adolescents with posttraumatic symptoms and 20 age and sex-matched healthy controls before and after a 5-month period. Trauma-Focused Cognitive Behavioral Therapy (TF-CBT) was provided to the clinical group. Improvement of symptoms in the clinical group was associated with decreasing activation in the posterior cingulate, mid-cingulate, and hippocampus (suggesting decreased DMN engagement). Dissociation, in particular was related to decreasing activation within the amygdala. This study demonstrates the neuroplasticity of key regions controlling emotion regulation and cognitive processing, highlighting the importance of early intervention (Garrett et al., 2019). In addition, the executive network findings in posttraumatic stress (for a review see Carrión & Weems, 2017) are potential targets for treatment outcome work in youth.

Accumulated knowledge identifying regions involved in emotion regulation (e.g. amygdala activation after exposure to a trigger or cue) and executive function (e.g., updating and changing mental states) can help lead efforts to develop interventions that target these core domains. Cue-Centered Therapy is an example. In this hybrid intervention, evidence-based interventions are ordered and delivered within a self-efficacy approach that has shown to improve these functions (Carrion et al., 2013). With precision we may one day be able to develop algorithms that match a specific person to a specific type of treatment. Other interventions may target networks involved in the fight-or-flight response, for example.

Analogous to brain network approaches, the promise of symptom network analysis to inform assessment and intervention is that central symptoms might be targets of intervention or targets for early identification of risk as well as for understanding the mechanisms involved. The basic idea is that central symptoms are primary in what might be thought of as a cascade of symptom associations following trauma which lead to more symptoms, other problems, and functional impairment. Prioritizing symptoms that are central to the network and related to known process in treatment may theoretically produce downstream effects on other symptoms without directly targeting those symptoms. Such a view is tempered by the fact that the centrality of specific symptoms seems to vary considerably across samples. Additional research may elucidate sample-specific central symptoms, with certain types of trauma exposure proving more likely than others to have certain symptoms as central. This work may lead to the development of knowledge concerning the downstream effects of specific symptoms. For example, theory and research suggests that early-onset hyperarousal is highly predictive of later symptoms such as emotional numbing and has been linked to poor outcomes (Litz et al., 1997; Schell et al., 2004; Weems et al., 2003). Targeting hyperarousal early on, or more importantly the cognitive flexibility of knowing when to taper this response, may help prevent the development of emotional numbing; such an approach can be person- or profile-specific.

Studies examining the down-stream effects of interventions that target the amelioration of one main symptom or symptom set would help support this hypothesis linking network effects to specific intervention targets. For example, findings in Weems et al. (2015) points to the potential of focusing on reducing and controlling arousal generally on reducing posttraumatic stress symptoms in a post-disaster environment. Youth completed a primarily behavioral and exposure-based intervention focusing on relaxation training, emotion regulation, and gradual exposure to anxiety-provoking test-related stimuli (i.e., techniques targeted hyperarousal symptoms by aiming to improve executive network control of the salience network, and strengthening executive-default mode network communication via relaxation training. Findings suggest an effect of the intervention on test anxiety levels with evidence of positive secondary effects on posttraumatic stress symptoms over the follow up periods of one to two years.

Summary: Network neuroscience may be useful in leading to specific intervention techniques and target foci for those exposed to traumatic stress, particularly those experiencing negative outcomes (i.e., those already in the disease and social problems layer of the pyramid pinnacle (see Figure 1). As others have suggested the clearest application of neuroscience to policy is the development of brain structure and function as "biomarkers" (see e.g., Pavlakis et al., 2015). These targeted or specific intervention techniques may help individuals move to the resilience pinnacle after experiencing TRACEs+ by preventing the development of more serious problems. Importantly, intervention research using imaging techniques demonstrates the neuroplasticity of key regions controlling emotion regulation and cognitive processing, highlighting the importance of early intervention (Garrett et al., 2019; Heyn & Herringa, 2019) and the potential to prevent later life difficulties early on via community and school based prevention and intervention programs (see Figure 1).

Neuroscience-Informed Policy and Policy Informed Neuroscience

As noted, the neuroscience contribution to policy has been largely successful in the "why" - making the case for intervening in the lives of children at risk for or who have experienced TRACEs+. In the following we next attempt to illustrate how neuroscience findings can move beyond suggesting to policy makers *why* we should act (i.e., because children's brains are on the line), and toward ideas for *what* to do and *how* to do it through broad-based policy. The following examples show the intersection of the various considerations noted in Figure 2, Panel A. One compelling example of the "why" motivating action are Home Visiting Programs. Home visiting programs are an empirically supported method that can help avoid exposure to TRACEs+ and also aid in early identification. For example, Durham Connects is a manualized program that assesses family needs and connects parents with community resources. Randomized trials show that involvement in these home visiting programs lead to reductions in emergency care use and are cost effective (e.g., Dodge et al., 2014). They show that for every $1 spent on Durham Connects' initiative to arrange in-home nurse visits for newborns, $3 were saved in health care costs and the effects held true for all subgroups studied (Dodge et al., 2013). Such findings have led the U.S. Department of Health and Human Services to develop and administer the Maternal, Infant, and Early Childhood Home Visiting (MIECHV) Program in partnership with the Administration for Children and Families. This program is allocated $400 million per year through fiscal year (FY) 2022, and in 2018 served approximately 150,000 parents and children.

States that receive funding through MIECHV tailor the program to serve the specific needs of their communities, identify target populations, and select home visit service delivery models that best meet state and local needs. For example, in Iowa, MIECHV supports the Iowa Home Visiting Program, which provides voluntary, evidence-based home visiting programs for at-risk pregnant women and families from birth through kindergarten entry. This program serves high risk families (25.4% of households reported a history of substance abuse) and has helped 94.6% of enrolled caregivers receive screening for Intimate Partner Violence (IPV) within 6 months of enrollment. Similarly, MIECHV in Wisconsin, serves at risk women with 32.3% of participating households reported a history of child abuse or maltreatment, and 87.0% of caregivers enrolled in home visiting were screened for IPV within 6 months of enrollment.

Home visiting programs have the potential to prevent TRACEs+ (Dodge et al., 2014) and is an example of effective empirical science leading to significant federal policy and funding. The MEICHV programs may also benefit from the “what” and “how” knowledge gained from neurodevelopmental research on TRACEs+. Again using an example noted above, the default mode network is related to self-referential thought processes including the interpretation of social information, retrieval of reference memories, or emergence of spontaneous thoughts with TRACEs+ exhibiting biased interpretation of social stimuli (Shackman et al., 2007) impaired or altered retrieval of autobiographical memories (McCrory et al., 2017) and unexpected distress from spontaneous thoughts about past traumas (Hoffmann et al., 2018). Early access to parenting programs that train positive self-soothing; may engender the development of self-regulatory skills reflecting top-down executive control of the default-mode network. Parenting interventions targeting attachment and positive parent child interventions integrated onto home visiting services have been suggested as one public policy avenue (see Morris et al., 2017). Figure 2, Panel B illustrates the intersection between the various considerations laid out in Panel A to show how this broad national policy with existing funding (i.e., MEICHV) where neuroscience may suggest specific targets and techniques derived directly or indirectly from neurodevelopmental data. Importantly, the influence can run in either direction with the policies helping to direct next steps in neuroscience research (e.g., how do practices affect the brain?)

Policy has been directly motivated by the "why" of the neuroscience, but may be further improved via suggestions on *what* and *how* implied by neuroscience. For example, in 2018the Iowa legislature passed a bill (Senate File 2113, Iowa Code § 279.70 and IAC 281—14.4) requiring protocols and school employee training relating to identification of ACEs and strategies to mitigate toxic stress responses. This legislation was fostered by grassroots community organization (Iowa ACEs 360; www.iowaaces360.org) that built a policy proposal from the ACEs concepts. The group disseminates research, tools, and provides a statewide network to empower individuals, organizations and communities to act. The group works as a coalition to advocate for system changes to address ACEs and helped get the legislation passed. The requirements of the law apply to all public school districts in Iowa and require annual training and must be provided annually. School districts have the authority to select the evidence-based, evidence-supported training that best meets the needs of their district.

Fostering the selection process could be a critical avenue for integrating neuroscience into the "what" and "how". For example, in partnership with Iowa ACEs 360, Iowa AEA Online

Learning (www.aealearningonline.org) launched a web-based learning module on ACEs, toxic stress, and education responses in the first year of the training requirement. Within the first 6 months, more than 15,000 Iowa educators accessed the module. In the second year of the training requirement, 1-2 more advanced modules will be launched to support continued learning. In addition, Iowa ACEs 360 trained more than 100 education and community professionals to deliver learning content to fulfill the training requirement (Iowa ACEs, 360, www.iowaaces360.org). Future training models might focus on strengthening executive network and its communication with default mode and salience networks that also foster learning success (see Thomas et al., 2019). Partnerships with school and education-anchored organizations are a way in which neuroscientists can interact in school programming. For example, Stanford University's Early Life Stress and Resilience Program partnered with Pure Edge, Inc., an organization that advocates for health and wellness for educators and the youth they serve, to implement a yoga and mindfulness curriculum in a schools district at high risk for TRACES + (http://med.stanford.edu/elspap/our-research.html#health-and-wellness). Program evaluation will examine neurological function, relationships, emotion regulation, executive function and cognitive flexibility.

A Transdisciplinary Model and Continuing to Move Science to Effective Action

There is a need for "transdisciplinary" research programs to move the neuroscience to sustainable action. Interdisciplinary research emphasizes the integration of perspectives, concepts, and methods from different disciplines. Transdisciplinary work seeks to extend these approaches to generate new frameworks, and methods that "transcend" the disciplinary bounds. This also involves direct collaborations and involvement of non-academic partners in research to ensure that the concepts and methods have utility in real-world settings and that the research agenda is driven by real world needs to create better approaches (Pohl, 2011). The Iowa State

University Transdisciplinary Research Network (UTuRN) is aiming to build such collaboration. The model in UTuRN aims to empower communities by developing transdisciplinary partnerships between researchers and community stakeholders, employing team-based science, and engaging scholarship resources to leverage the skills, experiences, and expertise of individuals from various sectors (e.g., university, community, schools, and government) and disciplines (e.g., human development, food science, kinesiology, engineering).

An example of transdisciplinary partnership approaches is in a relatively neglected avenue for translating neuroscience to policy – the area of paternity establishment and child support recovery. Data suggests that child support reduces the risk of child maltreatment (Cancian et al., 2013), fathers who establish paternity are more likely to support their children financially, and children who receive regular child support from their fathers experience fewer internalizing and externalizing behavioral problems coupled with greater academic achievement (Bronte-Tinkew et al., 2008; Cabrera et al., 2007; Carlson & Magnuson, 2011). Child support recovery bureaus within state Departments of Human Services (DHS) are responsible for administering and monitoring child support payments and reaching federal benchmarks on paternity establishment for unwed mothers. These programs have evolved to provide broad aid to schools, parents, and families to ensure safe and supported children (Weems et al., in press).

School-based programming designed to address teen pregnancy is a strategic opportunity for neuroscience intersect with education programming for youth on paternity establishment and child support issues. For example, Parenting: It's a Life (PIAL; Bartel et al., 2018) is a school-based curriculum that includes several components common to teen life skills programming such as responsible decision-making, healthy romantic relationships, addressing peer pressure, and importantly adds unique modules related to resiliency after adversity. As part of a statewide effort to educate youth, the Iowa Attorney General's Office partnered with the Iowa DHS and

Iowa State University's Child Welfare Research and Training Project (CWRTP) to develop and provide this programming to middle and high schools. CWRTP mobilizes expert knowledge and state of the art practices, employs UTuRN resources with applied research, direct programming, and data analysis (see Weems et al., in press). The programs offer an opportunity to directly deliver neuroscience informed skills to prevent and ameliorate the effects of TRACEs+ in direct partnership with government agencies, community schools and scientists working together.

Conclusion

Translation of research findings requires effective and accurate communication of the discoveries. A unifying term (TRACEs+) and conceptualization which integrates the concepts of traumatic stress and ACEs, risk and resilience and equifinality and multifinality is proposed. A revised pyramid illustrated these ideas. The extant empirical literature suggests a neurodevelopmental network approach to the effects of TRACEs+. However, while a link between brain volumes, brain function and pediatric traumatic stress is now well-established, we do not know how much of this correlation stems from preexisting differences (e.g., poverty or other socioeconomic context effects that place youth and greater risk for experiencing trauma or developing interfering PTSD symptoms after traumatic stress). Prospective longitudinal and intervention studies are critical for disentangling confounding effects from TRACEs+. The review shows how neuroscience has, has not, and may yet lead to new individual and community interventions that can become sustainable through existing or new policy. The potential for neuroscience research to be guided by these interventions and policies is also noted. Indeed, it will be intervention studies which establish causal effects on brain development. The field will benefit from going beyond interdisciplinary research toward transdisciplinary science models for the translation of neuroscience into effective action.

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Table 1. *Traumatic Stress, Traditional, and Expanded ACEs (TRACES+).*

ACEs [1]	**Youth Identified[2]**	**Traumatic[3]**	**Structural or Functional Connectivity Study[4]**
Physical abuse	Yes	Yes	Yes
Sexual abuse	Yes	Yes	Yes
Emotional abuse	Yes	No	Yes
Mentally ill household member	Yes	No	No
Witnessed domestic violence	Yes	Probable	Yes
Substance using household member	Yes	No	No
Incarcerated household member	Yes	No	No
One or no parents	Yes	No	No
Emotional neglect	Yes	No	No
Physical neglect	Yes	Yes	Yes
Expanded ACEs			
Witnessed violence	Yes	Yes	Yes
Subjective feeling of discrimination	No	No	No
Unsafe neighborhood	Yes	No	No
Experienced bullying	Yes	No	No
Lived in foster care	Yes	No	No
Additional Categories: Taylor & Weems			
Motor vehicle/other accidents	-	Probable	Yes
Natural disasters	-	Yes	Yes
Explosions/war	-	Yes	No
Entertainment violence	-	No	No
Separation/loss family/non-family	-	Probable	Yes

Notes: (1) Cronholm et al., (2015) (2) Taylor and Weems (2009) (3) APA (2015), (4) Weems et al., (2019).

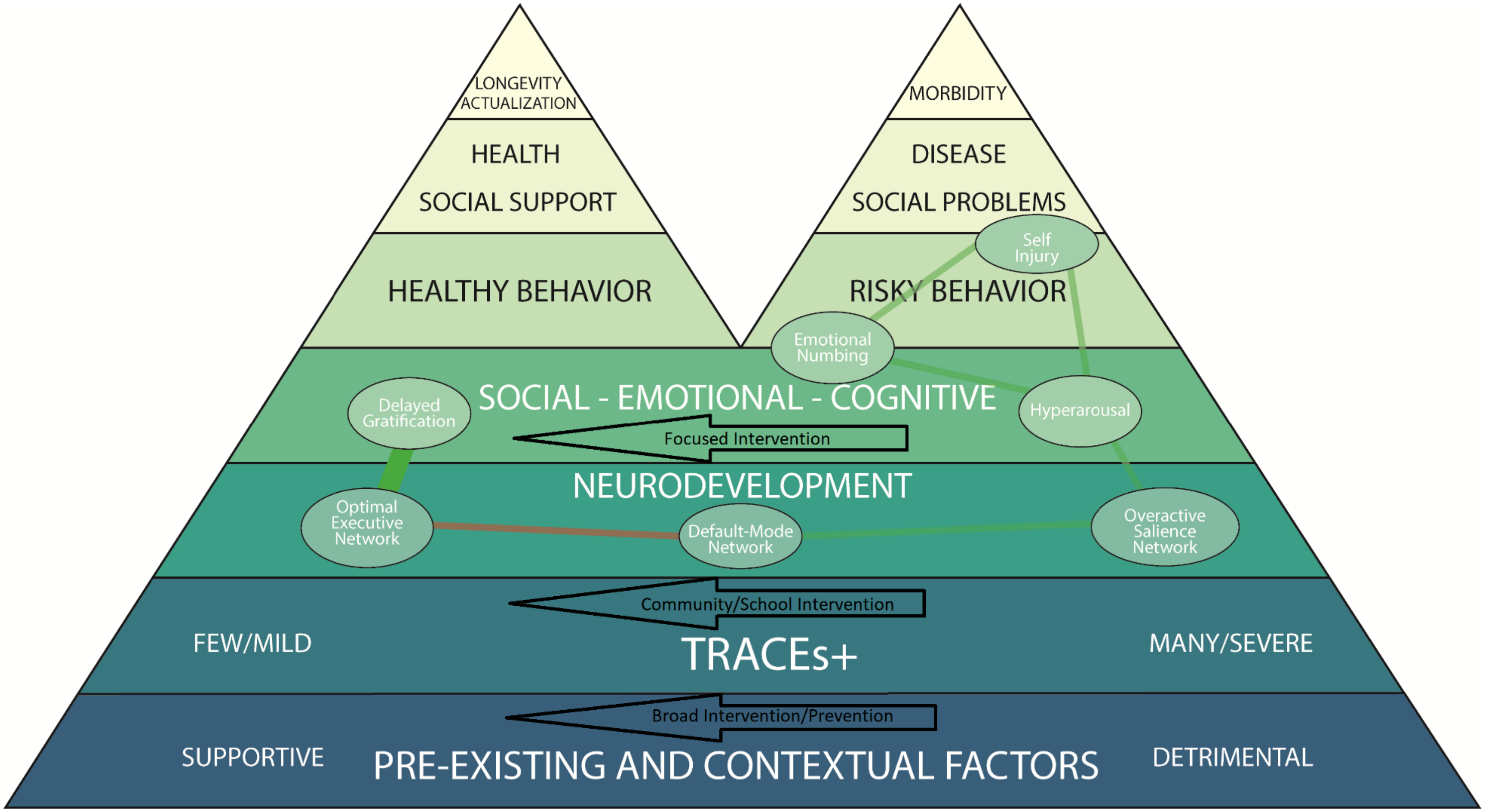

Figure 1. ***A Revised TRACEs+ Pyramid with Resilience Pinnacle.*** The figure highlights that there is not one inevitable outcome but multiple outcomes that may follow from adverse or traumatic experience and that there are multiple levels of interventions possible to help place individuals on a path of resilience. A neurodevelopmental perspective - inherent in previous conceptualizations- in this figure illustrates one neurodevelopmental path highlighted in our review with overactive salience network and hyperarousal leading to emotional numbing and risky and self-injurious behaviors over time. The figure also highlights there are levels/severity of TRACEs+ experienced and the experience is under laid with historical, pre-existing, and contextual factors.

A

Context	Policy	Why	What	How
Broad	*Well Established*	*Direct*	*Direct*	*Direct*
National/International	Existing Funded	Known Direct Effect on Neurodevelopment	Target Derived Directly from Neuroscience	Technique Derived Directly from Neuroscience
Community/School	Proposed	Effect on Neurodevelopment Related Constructs	Target Consistent with Neuroscience	Technique Consistent with Neuroscience
Individual	*New Emerging*	*Indirect*	*Indirect*	*Indirect*

B

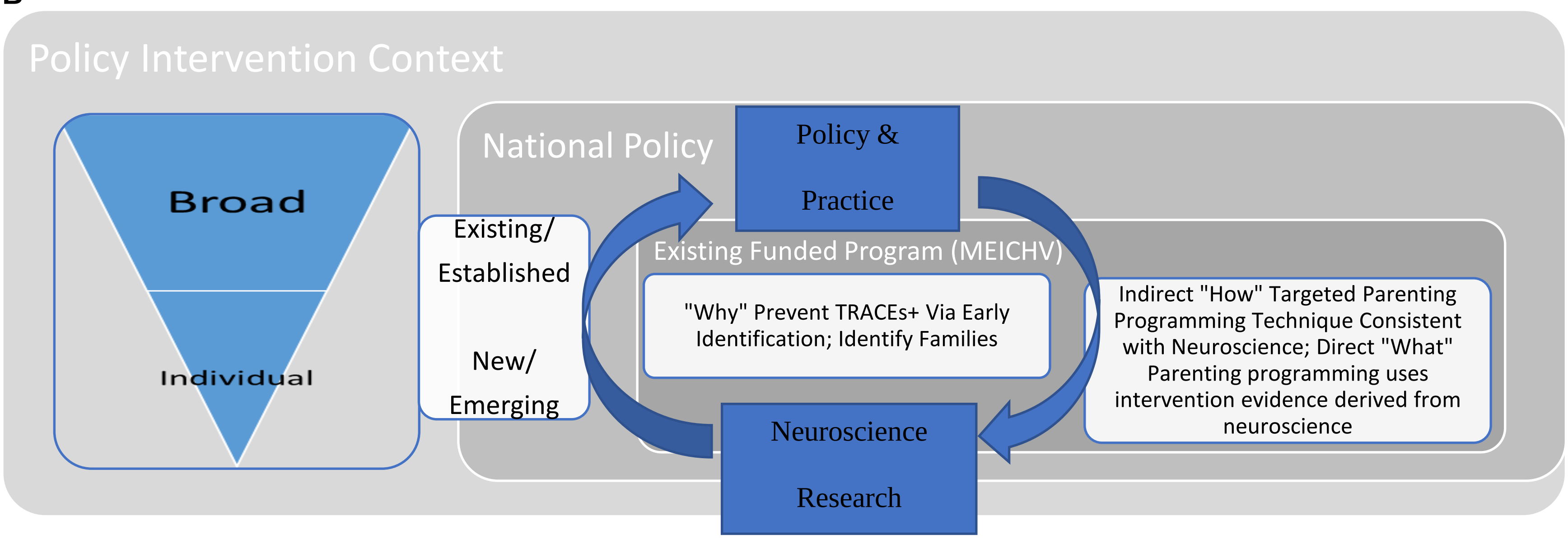

Figure 2. ***Considerations for TRACEs+ Neurodevelopmental Science Impacts on Intervention and Policy***. Panel A - context and policy considerations for direct and indirect intersections for neurodevelopmental science impacts on intervention and policy. Panel B - An example of a Broad National Policy with Existing funding that has already been implemented to for the Why question but where neuroscience may suggest specific targets and techniques derived directly or indirectly from neurodevelopmental data.