Supporting Adolescents through Mental Illness and Adversity Using Neuroscience

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*Acknowledgements***.** There seems to be a huge divide between the knowledge we hold in academia and knowledge outside of it, like some invisible wall is preventing the knowledge from escaping. I am grateful to the program "Sharing UW-Madison Postdoctoral Scholarly Research with Non-Science Audiences" for breaking down that invisible wall and providing me with an opportunity to share scientific advances with a wider audience. This program, sponsored by the Wisconsin Initiative for Science Literacy (WISL), was made possible by the dedication of the WISL staff, specifically Cayce Osborne, Elizabeth Reynolds and Professor Bassam Shakhashiri. The work I will describe was conducted in the (now defunct) BRAVE Research Collaborative, where we aim to support youth exposed to adversity with mental health challenges using neuroscience. This work would not be possible without the involvement of the adolescents and their guardians who agreed to volunteer their time and share their stories.

The burden.

The morning alarms rings and it's time to get ready for work. But it's hard to get out of bed. Maybe the day ahead causes so much stress that you want to avoid thinking about it. Maybe you completely lack the energy, having tossed and turned all night, struggling to fall asleep. Maybe you're stuck in your head, uncontrollable anxieties revolving in your mind, growing into fears, paralyzing you. The threat of being reprimanded, receiving a reduced paycheck, or even being fired doesn't motivate you as much as it should. Perhaps you make it to work on time. You have, after all, been living this cycle for months. But things seem to have been getting harder and harder to keep under control. It feels like it's just a matter of time before it all falls apart. You're too busy surviving to notice that it already has.

It's highly likely that you or someone you know can relate to this situation. Struggling with anxiety or depression is, unfortunately, a common experience. The COVID-19 pandemic certainly didn't help. It's estimated that roughly 1 in 5 adults currently live with a mental illness in the USA; the number is higher when you consider people who only experienced an episode for a temporary period in their life. To make matters worse, traumatic and adverse childhood experiences worsen mental illness by making symptoms more severe and disorders more treatment-resistant. Adverse childhood experiences encompass a wide variety of situations, including child abuse and neglect, living in a family with domestic violence, experiencing discrimination and poverty, or living in a community with frequent violence. More than half of adults with a mental illness report experiencing moderate-to-severe childhood maltreatment.

The situation for youth is not any better. Over the past couple of decades, the prevalence of mental disorders in adolescents has risen around the globe. In the USA, two out of three youth report having experienced a traumatic event by the age of 16. In a time when teenagers are learning how to navigate life and build essential life skills, mental illness throws a wrench into that progress - and adversity exacerbates effects. The domino-effect of this interrupted process causes long-lasting consequences well into adulthood. It's imperative that we improve our mental health interventions to provide youth with the best foundation possible to live a good life.

Youth are not Small Adults

Before the 17th century, children were often believed to be small adults – fully formed and functioning, only different from adults in their lack of life experience and skills. You can see an example of this in medieval art, like *Madonna with Child and Two Angels* (Figure 1), where realism was set aside in favor of representing babies and children as little men. Today, scientists and doctors know with certainty that youth are not "small adults". Advancements across multiple fields have described the development of brain and behavior from infancy to young adulthood, explaining how these changes are related to differences in perceptions, interpretations, and reactions to the world around us. Babies interact with the world differently from toddlers, who in turn respond differently from teenagers, who interact differently than adults. So why are adolescents getting the exact same mental health interventions as adults?

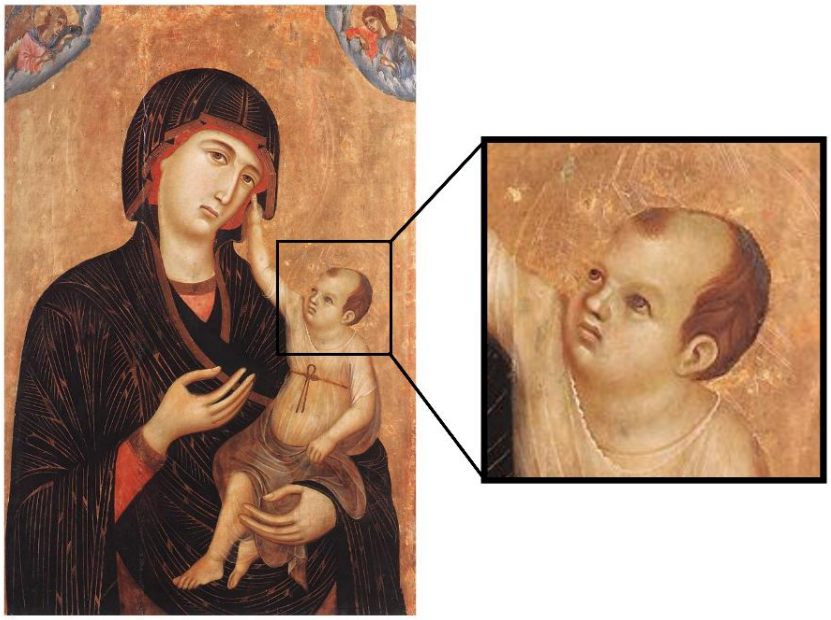

Figure 1. *Madonna with Child and Two Angels*, painted by Duccio di Buoninsegna, 1283-84. Notice the balding head on the baby. Original image taken from Web Gallery of Art. Source: https://www.wga.hu/html_m/d/duccio/various/2crevole.html

It's tempting to treat adolescents as adults. And to some degree, it's not wrong to do so. Teenagers are much more similar to adults than toddlers are to adults, for one. Adolescents have the capability to reason and make decisions like adults do, and are able to take on adult responsibilities. Biologically, their brain networks are often adult-like in function, where the brain needs just a little more experience to become more effective and efficient. In the case of mental health, adult therapies work well enough that they are applied to youth with general success. But in the end, adolescents are going through unique experiences and developmental stages that adults have already passed. We can support teens much better if we tailor our interventions to where they, and their brains, are in life.

What's so special about adolescence?

It turns out that adolescence marks a critical crossroad between brain maturation and mental illness. Adolescence is usually defined as starting at puberty (around age 10) and ending at the cultural definition of adulthood, 18 years old. Most people start presenting symptoms and get diagnosed with a mental illness during adolescence. This is happening at a time when the last major brain region to mature, the frontal lobe (Figure 2), is going through a burst of development.

Contrary to what you would expect, maturation of the frontal lobe during this time period is reflected by brain volume *decreasing*. This decrease happens because connections between the frontal lobe and the rest of the brain are being pruned. It's similar to what gardeners do to their plants, where they remove unhealthy or useless branches so that plant growth is focused on regions that need it. In the case of brain maturation, pruning improves the efficiency of communication between regions by using experience to remove redundant or unused connections. The increase in efficiency makes it easier and faster to use the functions of the frontal lobe, as you have less competing information interfering from other places.

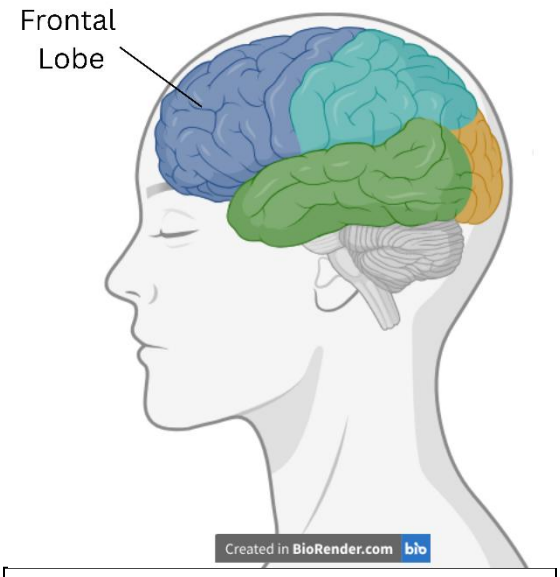

Figure 2. The four lobes of the brain. Dark blue, frontal lobe; Light blue, parietal lobe; Green, temporal lobe; Yellow, occipital lobe. Created in https://BioRender.com.

The choice of which connections to prune is driven by life experiences, allowing us to adapt to the environment that we are in. Because the brain is still undergoing significant development during adolescence, the brain is more malleable and influenced by external forces. This includes both positive and negative influences. The brain is more impacted by negative experiences like traumatic events, setting off an altered developmental trajectory aimed to help with survival. But the brain is also more easily molded by therapeutic interventions. This makes interventions during adolescence particularly powerful. We have a window of time when the brain regions that

are still developing are more responsive to interventions, and we have the opportunity to shape the function of those brain regions.

The main region developing during adolescence is the frontal lobe, particularly the prefrontal cortex. The prefrontal cortex is involved in complex skills like abstract reasoning, sustained focus, long-term planning, and inhibiting inappropriate behaviors. It's also involved in regulating mood and emotions.

Remember when you were a teenager? The rapidly fluctuating moods, how much social rejection hurt, the increased risk taking that you or your peers would engage in? That's pretty typical of adolescents. Compared to children and adults, adolescents tend to have stronger reactions to emotional events, and at least early in adolescence those emotions have a strong influence on the prefrontal cortex's function. With time and practice, they develop the skills to better regulate emotional responses. Improved emotion regulation is in turn linked to the prefrontal cortex's ability to inhibit regions that generate emotions.

In this way, emotional reactivity and emotion regulation are two sides of the same coin. The better you are at regulating your emotions, the less emotionally reactive you are likely to be.

Emotion (dys)regulation and Internalizing Disorders

Problems with emotion regulation (AKA emotion dysregulation) is characteristic of multiple mental illnesses, but is more so a major symptom in internalizing disorders such as depression and anxiety. Understanding emotion dysregulation is important because successful therapies in youth happen by improving emotion regulation skills. We tend to think of emotion dysregulation as the increased emotional response to negative events and trouble getting those feelings under control. In the case of anxiety and depression, people will often focus all their attention on one bad experience and have trouble moving on. However, another characteristic of internalizing disorders is perceiving neutral things as being negative. For example, interpreting a lukewarm response or a lack of smiling as proof that someone is upset. This aspect of being more emotionally reactive to neutral events means that not only do people with internalizing disorders have trouble regulating emotions generally, but they have negative experiences more often because they also perceive neutral events as being negative.

Experiencing high levels of adversity worsens the severity of these symptoms in people who have internalizing disorders, and this includes emotion dysregulation. Our treatments are not as effective for them, shown by the higher rate of treatment resistance in this population. It seems that something about the brain adapting to adversity changes the course of development, so that short term gains needed to survive a threatening environment may become detrimental in the long run. The fact that the brain develops differently probably plays a key role in why youth with high adversity don't respond as well to current treatments. If the cause of the symptoms differs between youth with and without adversity exposure, then identifying that difference can help us personalize treatments and ultimately improve treatment outcomes.

The Problem.

If we take all this evidence discussed so far – a period of brain development and emotion regulation skills during adolescence, emotion dysregulation being characteristic of internalizing disorders, and successful interventions being related to improved emotion regulation -- a picture starts to form. It seems that in youth struggling with mental illness, something about the development of the frontal lobe is being altered and decreasing their ability to regulate emotions. We could even go so far as to guess that this altered development of the frontal lobe is what is causing the onset of mental illness.

The science up to this point seems pretty straight forward, but there are a lot of pieces still missing. How exactly is the frontal lobe developing differently during emotion regulation? The frontal lobe is huge, taking up almost 40% of space from the four lobes (Figure 2). It is responsible for so many different functions, which are localized to different subregions within the frontal lobe. Which specific regions are impacted by internalizing disorders?

These questions don't even consider how experiencing trauma and adversity fits into the picture! Very little research has tried to identify the brain differences between adolescent patients with and without experiences of adversity. Is it that youth with adversity simply have more severe alterations of the same mechanism, or is something different happening that is unique to adversity?

Our Approach to the Problem

My work at the BRAVE Research Collaborative set out to answer these questions. The project tackling these questions is officially titled "Normative and atypical trajectories of cognitive-emotional development in adolescence". The project was funded by the National Institute of Mental Health (grant number R01MH115910) and led by my supervisor, pediatric psychiatrist and neuroscientist Dr. Ryan J. Herringa.

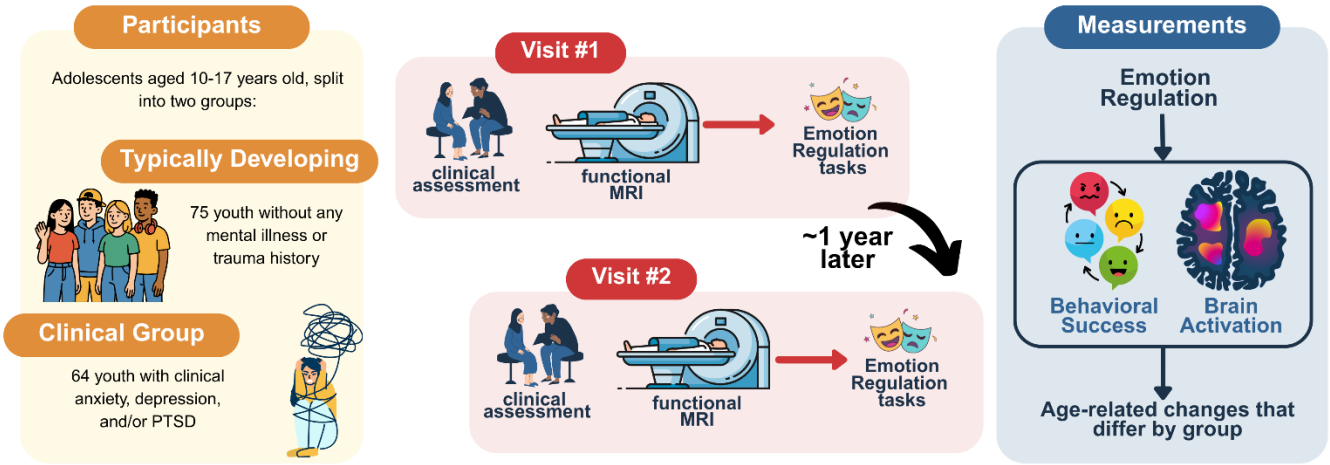

Figure 3. Overview of the project methods.

Here's how the project worked (Figure 3). Adolescents aged 10 to 17 years old were recruited from the local Madison, WI community. After a clinical assessment, youth were sorted into two groups. The clinical group consisted of 64 youth with a current diagnosis of internalizing disorder, including but not limited to generalized anxiety disorder, major depressive disorder, and PTSD. The other group consisted of 75 typically developing youth who had no history or current diagnosis of mental illness or significant trauma exposure. To understand how adversity exposure fits into the picture, youth were given a questionnaire to self-report how impacted they were by a variety of different types of stressful experiences.

To assess brain development, the adolescents underwent functional magnetic resonance imaging (fMRI) at the University of Wisconsin - Madison. Broadly speaking, fMRI can identify which brain regions are activated during a task by tracking changes in oxygenation in the blood. Brain cells need oxygen to function, which is delivered via blood. When a brain region becomes more active it requires more oxygen than usual, causing a temporary increase in blood flow to meet demand. An increase in blood equals an increase in oxygen, which fMRI can pick up on.

While undergoing fMRI, adolescents completed emotion regulation tasks, allowing us to identify which brain regions in the frontal lobe were engaged. The participants then returned approximately one year later and repeated the tasks in the fMRI. This allowed us to track changes in brain development within each individual. Because we recruited youth between the ages of 10-17, we ended up with the full spectrum of adolescence across which we could track the development of emotion regulation.

Using the brain activation data collected during emotion regulation, I compared the differences between the two groups in how their frontal lobe developed. Because the frontal lobe is so large, we used an atlas to split the frontal lobe into subregions. With this, I first identified the subregions that differed in their developmental trajectories between typically developing youth and the clinical group. When a region was identified, I then focused in on just the clinical group to see if and how adversity is impacting the development.

Our hypotheses were as follows:

1. Regions in the prefrontal cortex will be involved when youth were instructed to regulate their emotions. These regions will be less active in the clinical group, reflecting a difficulty in controlling emotions.
    a. At the same time, clinical youth will show greater activity in regions associated with emotional reactivity, indicating that the prefrontal cortex is having difficulties inhibiting them.
2. The difficulties outlined in hypothesis (1) will be present for both negative and neutral stimuli, reflecting how clinical youth perceive neutral stimuli as more negative.
3. The differences between youth with and without internalizing disorders should become greater with age, as increasing emotion regulation ability mirroring the development of the frontal lobe in the typically developing group outpaces that of the clinical group.

The Results.

Contrary to our hypothesis that we would see activity in regions in the prefrontal cortex, we instead found differences in development in a brain region called the insula (Figure 3A). You can see this region if you peel back the prefrontal cortex to look right underneath it. The insula is involved in many functions, but it plays a role in emotional reactivity. Because of this, alterations in insula function are commonly identified in adults with psychiatric disorders, and has even been used as a target for treatment. Our results are expanding this field by showing that the insula develops differently in youth with and without internalizing disorders.

How the insula development across groups is shown in Figure 4B and C. Typically developing youth showed decreasing insula activity with age (Figure 4B), which we interpret as decreasing emotional reactivity. Remember from earlier that the frontal lobe develops during adolescence by increasing the efficiency of communication with other areas of the brain? We think that the decreasing insula activity reflects the increasing efficiency of communication between the insula and prefrontal cortex. As the prefrontal cortex improves the efficiency of communication, the better it is able to respond to and manage the insula. It is interesting to note that the decreasing activity in the insula happened faster to neutral stimuli compared to negative stimuli, indicating that the insula was better able to discriminate between negative and neutral stimuli as youth age. What we can conclude is that during typical development, the insula decreases its emotional reactivity and increases its ability to discriminate between negative and neutral events.

If we compare the clinical group (Figure 4C) to the typically developing group, there are two things that stand out. First, insula activity doesn't change with age in youth with internalizing disorders, it just remains a flat line. Second, there is no difference in activity between negative and neutral stimuli. It seems like the connections between the prefrontal cortex and the insula are not becoming more efficient, limiting how much the prefrontal cortex can inhibit insula activity. This may be linked to greater emotional reactivity in the clinical group. Not only that, but the insula reacts the same way to negative and neutral stimuli. The difficulty of the insula in discriminating between negative and neutral events could be part of the reason that youth with internalizing disorders perceive neutral stimuli as being negative. From this we can conclude that in youth with internalizing disorders, the insula cannot discriminate between negative and neutral stimuli. This, combined with the lack of change, leads to greater emotional reactivity to a greater number of events that they encounter in life.

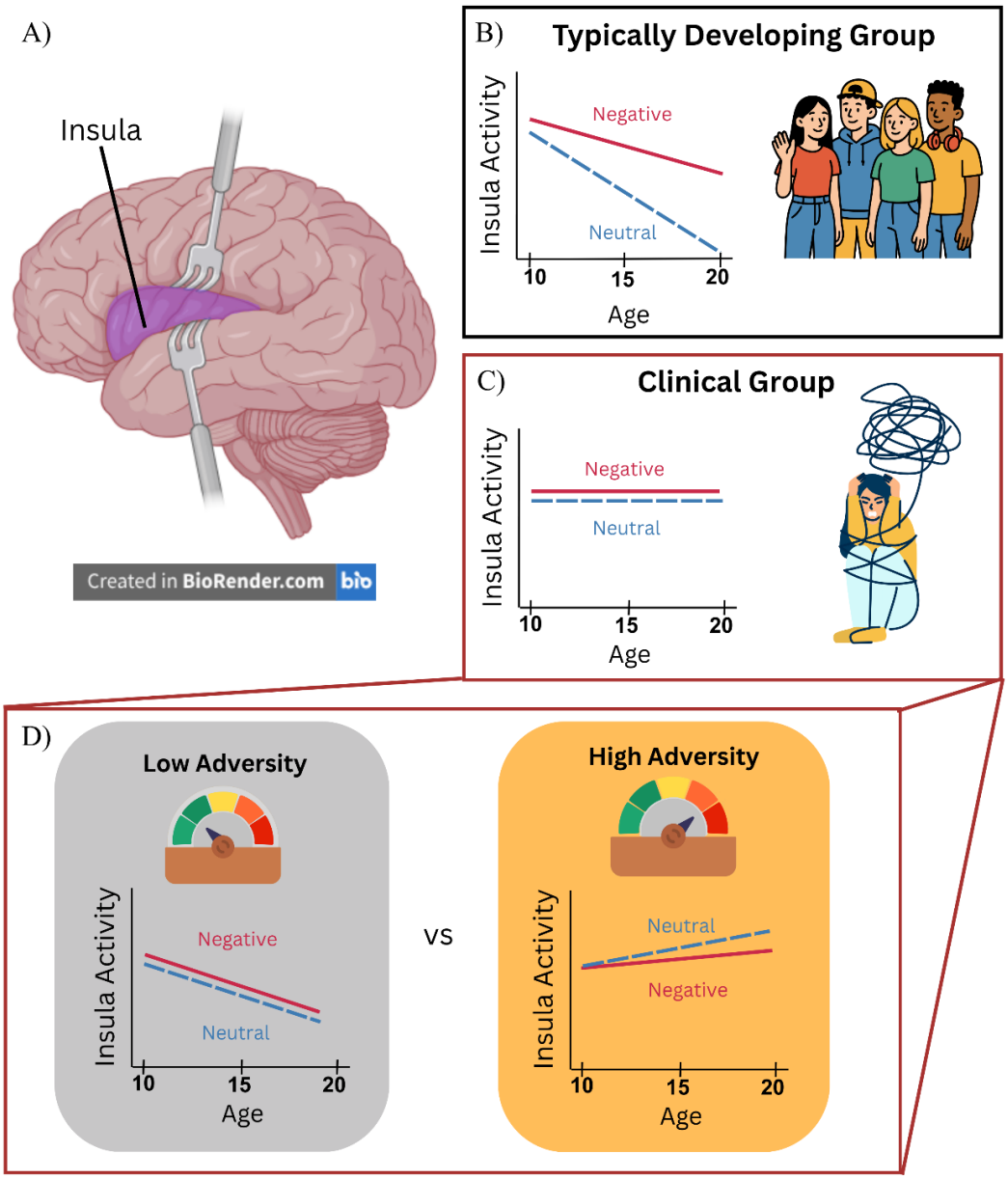

Figure 4. Results. A) Location of the insula, underneath the surface of the frontal lobe. Created in https://BioRender.com. B) Trajectory of insula development across adolescence for negative and neutral stimuli during emotion regulation in typically developing youth. C) Same as B, but in the clinical group. D) Same as B, but comparing youth with low and high adversity in the clinical group.

However, the exact way the insula develops in youth with internalizing disorders differs depending on how much adversity was experienced (Figure 4D). Clinical youth with low adversity exposure were more similar to the typically developing group than high adversity youth. Specifically, low adversity youth still showed decreasing insula activity with age, there was just no difference between negative and neutral stimuli. In contrast, high adversity youth showed increasing insula activity with age, and this increase was greater for neutral relative to negative stimuli. This is the exact opposite trajectory than what we see in typically developing youth!

From this we can speculate that in low adversity youth, the insula-prefrontal cortex connectivity is improving with age, albeit at a slower rate than typically developing youth. The bigger difference is seen in the lack of ability to discriminate between negative and neutral events. For high adversity youth, the prefrontal cortex is not able to inhibit the insula leading to increased emotional reactivity. In addition, over time the insula finds neutral events to be more threatening than negative stimuli. So, while these youth shared the commonality of having psychiatric disorders characterized by increased emotional reactivity and decreased discrimination between neutral and negative events, the brain development underlying these symptoms differs depending on the severity of adversity exposure.

Why it matters.

In the clinic, youth with a history of high adversity are much more likely to be treatment resistant. This is likely due to the differences in brain development, as we have shown here. For high adversity youth, an increasing response to both neutral and negative events is probably adaptive, helping them to identify threats and avoid them more quickly.

Take this example of a youth who is abused by their guardian. This youth would have learned that a door slamming shut and stomping feet means that the guardian is angry. When a guardian is angry, the likelihood that abuse will be directed towards the youth gets much higher. By detecting that this otherwise neutral action is predicting possible danger, the youth can prepare early and do their best to avoid the guardian. However, these initially adaptive perceptions can become detrimental in the long term when applied to contexts outside the home. Continuing the example of our abused youth, the behaviors that keep them safe at home can instead isolate them from peers at school or other activities. If the youth thinks that anyone who stomps and slams doors is a danger to them, they will be less likely to interact with those people. They could also react more defensively and strain relationships with their peers that innocently slam a door shut when entering the classroom. Over time, the youth will find that the circle of people they feel safe around and places they feel comfortable being in becomes smaller and smaller. Without proper social support, the youth risks isolating themselves and further worsening their mental health.

The good news is, we can take the information from our study as a starting point to help develop treatments that will be effective in high adversity youth with internalizing disorders. Because the brains of high and low adversity youth show opposing developmental trajectories, it doesn't make sense to use the same intervention. For example, low-adversity youth with internalizing disorders have similar brain development as youth without psychiatric disorders. For them, it makes sense for treatments to try and correct the brain development to look more like typically developing youth, and we can do that by strengthening the pre-existing connection between the prefrontal cortex and insula. However, applying this approach to high-adversity youth would be much more difficult, since that prefrontal-insula connection doesn't seem to be there.

Instead of trying to make high-adversity brains look like those of typically developing youth, it is probably more effective to make it look like the brains of resilient youth with adversity exposure. Many people come out resilient after experiencing childhood adversity, even though they too show differences in how their brains perceive the world. They have developed compensatory mechanisms that make sure their survival strategies do not become detrimental later in life. Future research can look at resilient youth who have experienced high adversity and determine what their brains look like. With this information, treatments can aim to align brain activity of the youth with internalizing disorder with that of a resilient youth who experienced similarly high levels of adversity. As our understanding of childhood adversity, the brain, and psychiatric disorders continues to unfold, the better we can serve our youth and help them build a foundation that will last a lifetime.

It takes a village to raise a child.

I think most people can agree that children deserve the chance to live up to their full potential. We don't just have to leave it to the clinicians – all of us can support youth, no matter what our role in the community is. As we increase our understanding of how the adolescent brain perceives the world, the more patient we can be with them when they struggle with their emotions, and the better we can guide them in how to regulate their emotions.

Ultimately, the best way to decrease both psychiatric disorders and their severity is to prevent chronic adverse experiences from occurring in the first place. Childhood maltreatment is the number one preventable risk factor for psychiatric disorders. Communities should come together to support families and teachers, providing material resources along with education to reduce instances of abuse and neglect. Evidence-based government policies can further ensure that infrastructure is in place so that no one falls between the cracks.

If you or someone you know has experienced chronic adversity growing up with little to no social support, know this: it was not your fault, and you did what you could to survive an uncontrollable environment. It's okay to struggle, even as an adult. For all of us, we can make the simple choice to be empathetic to the youth in our lives. They may be emotional, and make risky choices, and even ignore advice. But having the support of an adult who listens, who cares, and can be a role model for another way of living, can be the difference between resilience and vulnerability. It takes a village to raise a child, so let's make it a friendly one.