Seminar Series 9: Lecture 5

How the effects of traumatic stress are transmitted to the next generation

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Overview

Our understanding of the effects of extreme adversity has evolved a great deal over the last several decades. Early studies emphasised that the effects of stress were temporary and could be restored to pre-stress conditions by removing the stressor. It is now clear that although some effects of stress are transient, many persist for years and decades, and some are even transmitted to the next generation. The biological underpinnings of these effects have only been discovered recently, but allow for a more precise description of the effects of adversity, including, most importantly, the subjective feeling of survivors that extremely adverse events are transformative. In this talk Professor Yehuda describes the journey of her team and insights gained from decade-long studies of adult children of Holocaust survivors, and more recent studies of babies born in the immediate aftermath of 9/11. Her work involves both epigenetic studies and observations from her clinical practice. She has described these as “different instruments playing the same melodies” which together bring a rich perspective to this subject.

Introduction

Looking at a series of photographs of people who have just experienced trauma of some kind we are all able to recognise the emotions of fear, shock and grief which are the immediate responses to catastrophic events. Hormonal and other immediate biological changes in response to trauma such as this can also be identified scientifically. These responses are universal but are relatively short-lived. As time passes, facial clues may disappear and any biological changes become harder to detect.

Research in this field has, in the main, focused on these immediate responses. However, trauma can also be enduring and transformative. This insight has led to the concept, and developing field of study, around Post-Traumatic Stress Disorder (PTSD).

PTSD represents a failure to recover from the immediate effects of trauma. The symptoms include unwanted memories, nightmares, avoidance and hyper-vigilance. Not everyone exposed to trauma develops PTSD, in fact the majority do not. This is the challenge for the field – how do we understand these differences? Science has more trouble understanding individual differences to an event. In those who do develop PTSD the effects can be long lasting and these effects can be transmitted to the next generation. People with PTSD say that they are "transformed" by the experience. But what might this transformative effect mean for the first and second generations?

A 20 year Journey

Twenty years ago Prof Yehuda started to work in this field, with little idea of how it would evolve. The work started originally with combat veterans and then moved on to Holocaust survivors and their adult children. It was found that many people hadn't gone for treatment, so a specific clinic for trauma survivors was set up. For every one Holocaust survivor that got in touch, there were three or four of their children who rang the clinic saying that they were are also victims, and needed treatment too.

Working with the children of Holocaust survivors, it was clear that the same issues kept coming up. Many of these people have used the arts to portray the impact that the Holocaust has had on them personally. These portrayals are consistent with the clinical material that prompts people to seek treatment. A question Prof Yehuda sought the answer to was do the experiences we see portrayed in art and in the consultation room have a biological basis? The team were particularly intrigued by the finding that adult children of Holocaust survivors still define themselves in relation to their parents in a way which is unusual for people of that age.

Looking at the literature revealed many articles intent on dispelling the "myth" of damage to the next generation. People want the story to be that survivors are resilient and their off-spring successful against all the odds. There is a political element to working in this field, and issues such as victimisation and how you label survivors need to be treated with care and sensitivity.

Scientific enquiry presented an opportunity to investigate whether there is an effect on the second generation of survivors and provide objective data. Looking at Holocaust survivors might just bring to light new findings that would have wider-reaching and global significance. Starting conservatively, some simple questions were asked:

- Do offspring have more mental health problems than their peers?
- Are the problems similar to those of Holocaust survivors?
- Are the biological markers in offspring similar to those in Holocaust survivors?

There was also speculation about how the data might be interpreted:

- Is learnt behaviour displayed?
- Are there parental deficits, such as in child rearing?
- Is there any vicarious or imagined trauma?
- Is there biological transmission of vulnerability? For example:
    - Is there a genetic predisposition in both parents and children?
    - Is the response in the offspring a consequence of a change in the parent that occurred in response to the Holocaust?

This last possibility would be true intergenerational transmission. It is possible that the change might not even be present in the parent. There are many examples of this, including the work of Jonathan Seckle[1] who has shown that starvation in pregnancy can

lead to obesity in adult children. This is the field we now know as epigenetics[a]. What we are seeing was not in the original structure of the gene, but rather that something has happened to that gene to make it function in a different way.

Twenty years ago the field did not have a name, and Prof Yehuda did not have a grant. Not knowing even how to formulate the question, she started to do it in the best way she could. Their very first question was: “Is there a greater prevalence of mental illness in adult offspring of Holocaust survivors?”. What was found were very clear differences in the lifetime prevalence of a range of psychiatric disorders between children of Holocaust survivors and a control group of Jewish people of similar age. They were reacting differently to events in their own lives.

Prof Yehuda explained that there are various explanations and ‘risk factors’ for why some people experience PTSD and others don’t. These include:

- Trauma dose
- Trauma type or severity
- Interpretation of trauma – what you think about the event and your response (cognitive appraisal)

Subjective interpretation appears to be an important element and explains the differences in prevalence according to trauma type. For example rape results in much higher levels of PTSD than natural disaster. This is not because rape is more severe than a natural disaster but the trauma seems to be related to its interpretation and feelings such as shame and guilt. Prior attitudes and experiences are major contributors to this subjective interpretation. Even early on following a traumatic experience people differ in their appraisal of it. This was clearly seen after 9/11. So this leads to a question: where do these prior attitudes originate?

Most people will be familiar with the ‘fight or flight’ response. Stimulation of cortisol production is both the response to stress and its containment. Cortisol initiates the response but after a few hours works to return the hormones to a more normal level and return the body to homeostasis. Initial hormonal responses are ultimately modulated by what we think. This leads to a question: can individuals control the magnitude of the stress response? We can influence our response to stress by our thoughts. Trying to calm down after a traumatic event is actually very good advice. Some thoughts decrease distress and in particular the amount of adrenaline released whereas other thoughts increase distress. This is important as adrenaline is involved with the creation of memories of the event and contributes to the development of intrusive memories at a later date. So what explains these differences in thoughts?

What was discovered was that there was no difference in the actual exposure to trauma in the adult children of Holocaust survivors compared to a control group. However, there was significantly more PTSD in the offspring of Holocaust survivors. Looking further, it was found that the offspring of parents who had experienced PTSD were most likely to have PTSD themselves. This was different from anxiety and depression where simply having a parent who was a Holocaust survivor was enough to have a higher incidence whether or not the parent displayed similar symptoms.

This led to further exploration of the biological differences in this group. The team had already observed that cortisol levels are lower in veterans and first generation Holocaust survivors with PTSD. They wondered if having lower cortisol was a risk factor

[a] Epigenetics is the study of heritable changes in gene expression or cellular phenotype caused by mechanisms other than changes in the underlying DNA sequence

for PTSD. Cortisol is released in response to a threat and also has an important role in inhibiting the fight or flight response and restoring most body reactions back to pre-stress levels. If the cortisol level is low this does not happen, and adrenaline levels remain high with resulting increased distress. Prof Yehuda and her team found that cortisol levels were low in offspring of parents who had PTSD whether or not they had PTSD themselves. In other words this group of people are at risk of developing PTSD if exposed to stressful situations.

What was found over time was that lower cortisol is an indication of greater dis-regulation of the stress system. Particularly focusing on the role of glucocorticoid receptors[b], it was found that these receptors are more sensitive in people with PTSD. There was also evidence that the brain is involved. Through study of circadian rhythms, it was found that there were alterations in the metabolism of cortisol in people with PTSD. What was striking was that these differences were distinct from the differences normally associated with stress. Stress and major depression are typically associated with high cortisol levels. The amount of cortisol circulating is not an accurate reflection of its biological activity, as it must bind to receptors to have an effect. In major depression there is a lot of circulating cortisol but fewer receptors, so it has less of a biological effect. In PTSD there are lots of receptors and they are more biologically sensitive but there is only a low level of circulating cortisol. This was already known for PTSD but now it was being seen in the offspring of people with PTSD, whether or not the offspring had PTSD themselves. The team repeatedly observed a relationship between cortisol in the offspring and PTSD symptoms in their parents as rated by the offspring.

Why did the offspring of people with PTSD have lower cortisol levels? Investigation using the Childhood Trauma Questionnaire led to the finding that offspring who developed PTSD had had more emotional abuse and neglect as children. But this was not the answer.

A further study was done of pregnant women who were evacuated from the World Trade Center as a result of the 9/11 attack. Pregnant mothers who developed PTSD had lower cortisol levels, and so did their infants at seven months old. This was clearly nothing to do with years of emotional abuse. At two years old these infants showed more distress following exposure to a novel stimuli; a similar pattern to the trait anxiety seen in adult offspring of Holocaust survivors with PTSD. There was also a significant effect of the particular trimester the pregnant mother happened to be in, with the low cortisol levels only observed in mothers in the second or third trimester of pregnancy. So could low cortisol in offspring originate from *in utero* effects?

Dr Seckle[1] from Edinburgh has shown that babies born to mothers under stress show changes to the activity of an enzyme known as 11β-HSD-2. This enzyme converts active cortisol into its inactive metabolite cortisone. It is found in the placenta and protects the foetus from the effects of maternal glucocorticoids. It develops around the second trimester. Changes to this enzyme could potentially be responsible for lower glucocorticoid production and lower biological responsiveness. One idea is that this change is ideal for conditions of starvation but can result in obesity and metabolic syndrome if food is in abundance. Up to this point an *in utero* effect had not been

[b] Glucocorticoids – are a class of steroid hormones that bind to the glucocorticoid receptor, which is present in almost every animal cell. The name glucocorticoid (glucose + cortex + steroid) derives from their role in the regulation of the metabolism of glucose, their synthesis in the adrenal cortex, and their steroidal structure. Glucocorticoids are part of the feedback mechanism in the immune system that turns immune activity (inflammation) down.

considered. Returning to the data, the same changes were found in the offspring of Holocaust survivors. The effect was strongest in those who had been children in the Holocaust. They also found that PTSD in the offspring is greater in association with maternal PTSD, as are the lower levels of cortisol. This is not the same with depression and anxiety which they found was associated with any parental exposure to the Holocaust, not specifically with maternal PTSD. This maternal effect was very surprising. The same effect could also be seen when the circadian rhythm work was revisited and other methods used.

There was clearly a maternal association. This does not mean however, that it is all *in utero*. A number of people have also shown important postnatal effects that influence stress responses in the offspring. For example Meaney[2] has shown in rats that a lot of licking and grooming by the mother can change cortisol levels. This excessive grooming may in fact be 'smothering' rather than 'good mothering'. Similar over-protective and hovering behaviour is displayed by many Holocaust survivors. A relationship has also been shown between cortisol levels and maternal over-protection but no such relationship is seen with paternal over-protection. This raises the question as to whether fathers are unimportant to intergenerational transmission. Fathers and mothers appear to make different contributions, with fathers passing changes through germ cells whereas mothers pass these changes *in utero*. Both sexes may pass changes through behaviour.

These observations led the team to consider whether epigenetic changes could be involved. Epigenetics describes changes that can occur to the genome that changes the way the gene functions, or is *expressed*. DNA can either replicate itself or be transcribed into RNA. Very small changes to the chromosome environment can occur by the addition of methyl groups (the process of methylation). These small changes can have large consequences, as they can change the expression of the gene, for example by causing the gene to be mis-read or the RNA synthesis to be altered or stopped altogether. This means that the function of the gene may be altered. This can be an adaptive process not necessarily a mal-adaptive one. For example changes that happen as a result of parental starvation may in fact be preparing the foetus to tolerate similar conditions when it is born. However if food is in fact abundant the result of the changes could be obesity and metabolic syndrome.

There is a specific gene involved in the functioning of the glucocorticoid receptor (GR). The team hypothesised that decreased methylation of a specific area of this gene would result in increased glucocorticoid receptor sensitivity and be associated with PTSD and PTSD risk. Prof Yehuda's work has shown that this is indeed the case for the offspring of Holocaust survivors, and is associated with maternal but not paternal PTSD. In addition, this is also the case more generally for PTSD, for example in war veterans. These biological markers are associated with subjective reporting by individuals of having psychiatric scars from a traumatic experience.

The team also looked at 'FK506 binding protein' a protein officially involved in glucocorticoid receptor feedback sensitivity. They discovered that there was no difference in this protein in Holocaust survivors themselves, but that levels of the protein were lower in the survivor's offspring, particularly where the mothers had PTSD.

Implications of this work

A number of implications can be drawn from Prof Yehuda's work including:

- The effects of trauma can be passed to the next generation

- These are probably meant to prepare the next generation for coping with adversity
- Some of these changes may begin *in utero*
- Some continue in the early postnatal period
- Developmentally programmed changes allow a more flexible response, but may be a mismatch for the offspring's actual environment.

It appears that pregnancy and the early postnatal periods may be highly critical. Some of the biological effects may be mediated by disrupted parental behaviours related to the parents' own traumatic experiences.

Alongside the biological changes a number of different behaviour patterns can be seen in Holocaust survivors. A film in the Holocaust survivor museum in Israel depicts a mother describing how she didn't want to have children because of her own experiences. When she became pregnant she first tried to self-terminate, but a child was born and the mother took years to come to terms with this. Many other examples have been observed in clinical practice through discussion with survivors and their offspring such as, when a child playfully runs away from a parent, the parent may grasp tighter rather than letting the child go. Fear of loss may make a parent reluctant to love fully, which the child will not understand and this may in turn make it difficult for the child to express love in the future.

Prof Yehuda suggested that their work is illustrating one possible mechanism for the biological changes associated with such behaviours. *In utero* and during the early postnatal period the stress response system is organising and appears to be affected by the parent and their environment. A question that remains though is how long is this critical period? It will probably be different for every gene. There is no reason to suppose that other genes will not be affected as well. This is very early days for this discipline of epigenetics.

An important message is that epigenetic effects are enduring, but they may also be *reversible*. Current research being carried out by Prof Yehuda shows biological changes before and after psychotherapy. This is important as it gives people hope that, when they are ready to change, change is possible. If the environment can affect the genes and produce symptoms in one direction, then it is likely that a different environment can also have a similar affect in the opposite direction.

References

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