Transcription of Professor Liz Gould's lecture:
Tuesday 22 April 2008

Ladies and gentlemen welcome to the Piping Centre and to this latest in the series of seminars arranged by the Glasgow Centre for Population Health. Tonight we are really fortunate to have Professor Elizabeth Gould from Princeton University in New Jersey. Elizabeth is a New Yorker although fine Scottish ancestry, her great grandmother was from Glasgow and her dad plays the bagpipes so we will adopt her for the time she is here. She studied psychology in New York and then did her PhD at UCLA in California, worked more recently with Professor Bruce McEwen and many of you here I know will have been at Bruce McEwen's lecture a couple of years ago in this series and that fascinating bit of work has really inspired quite a lot of research since. Now tonight Elizabeth is going to talk through this title Positive and negative stress altered brain structure and I recall when I was a medical student being told that when you were born you had all the brain cells you were ever going to get, once you were born it was all down hill from then on, and we use to speculate, in the beer bar at the university how many brain cells we would knock off per pint of McEwen's 80 shilling we drank. You .count up the number of brain cells you had destroyed by the end of the evening. It's quite clear that that idea of a static brain just doesn't apply any more. That the brain as we saw from Bruce, changes its shape and its structure and we are going to hear much more about that tonight.

Over to you Elizabeth.

Professor Elizabeth Gould

Thanks very much for that kind introduction and for the invitation to speak today and thanks to everyone here for coming along to hear what I have to say. I don't have my pointer so will use my finger, I don't have a long enough arm, but I'll try to give you an indication of where I want you to look on the slides as we go through. The title of my talk is Positive and negative stress alter brain structure and I will be talking about different types of experiences which activates stress hormone systems and how they impact the adult brain and then I'd like to give you some clues about how experiences that occur during post natal life, during early life, set the stage for a response to those types of experiences later on.

Over all, the message is good. There is a down side to what stress does to the brain, but really what we've seen over the past 15 years or so in studying structural plasticity in the adult human brain is that the adult brain is very resilient, even in cases were negative developmental influences alter the brain. If the environment is changed in adulthood you can see a lot of reversal of those negative effects. So overall I would say that the take home message is positive, how to implement that in a positive environment is a much more complicated story. Now most of what I'm going to be talking about today comes from work on experimental animals because the types of measures that we're interested in making can't be done, I'm not invasive with it yet, we have a lot of hope with imaging studies as they gain in resolution, these kinds of questions can be answered directly in humans, but for the time being we've been doing our work on experimental animals. We have a lot of reason to believe that much of what we see in experimental animals is generalisable to humans, largely due to the fact that we have seen many of these phenomenal over and over again in different mammalian species, including in several species of non human primates.

Okay, so that's just sort of a way of background. I'm going to be talking not just about adult neurogenesis with the production of new neurons, but also about other kinds of structural change. So the modification of the dendritic tree and also the memories of connections between the lines, and I'll give you more details about that when we are ready and so we begin by giving you a little bit of background about structural plasticity in the adult mammalian brain and then I'd like to get into how it experience modulates brain structure in adulthood and give you the positive and negative side effect story because many experiences which activate stress hormone systems are actually considered to rewarding. I'll give you some very

obvious examples of them, it's formed in the laboratory and then talk you a bit about how development can shape brain structure and how that impacts on the adult response.

So this first slide shows three panels taken from a confocal laser scanning microscope of fluorescent brain images and this is just to give you an idea of the kind of things that we look at and the types and the types of structural change that we know occur in adulthood. On the left hand side that's a neuron a parabolal neuron in the neocortex and stained with fluorescent dye and we know that in many different circumstances the dendritic tree, which is these extensive processes that extend out of the cell body that receives a majority of synaptic input from other neurons that the dendritic tree can change it's shape and size in response to the experience. One of the dendritic segments is enlarged in this middle panel and you can see these protuberances along it Those are called dendritic spines, those are primary sights of excitatory input of synapses and we know that the size, number and shape of dendritic spines can be modulated by experience And then finally, on the right hand side there are examples of neurons that were generated in the adult brain. I'm going to be focusing most, but not all of, my talk on that process of adult neurogenesis and the new neurons in this panel shown with this green fluorescent dye - those are located in the hippocampus which is the brain region I'll be focusing extensively on today.

This is another example of some microscopic images showing new neurons in the adult hippocampuses taken from a rat. In this case the new neurons are shown in red. You can see the sort of speckle staining of fluorescent red on the top panel. Those are from a relatively large collection of cells that were produced in adulthood and down below you can see the green stains shows that some of those cells have differentiated into neurons. There is a lot of good evidence, and I'll summarise a bit of it, that some of the cells that are generated in the adult hippocampus do become functional neurons, but the majority of them don't.

First I'd like to establish the basis of my claim that this is a phenomenon that's relevant to humans. So the earliest papers that provided evidence for adult neurogenesis in the hippocampus of mammals were published in the 1960's and these were studies that were done by a neurobiologist named Joseph Altman and his colleagues and he demonstrated adult neurogensis in hippocampuses and other brain regions in the rat. Subsequently this was shown by many other investigators after a period of several decades, in the mouse as well as replicating the rat and this was work that I did with in collaboration with Bruce McEwen in early 1990s. So we had essentially rediscovered this work that had been published many decades ago, but not recognised by the neuroscience community probably for a large number of reasons that we can talk about later in the question and answer period for anyone really interested in that.

By the early 1990's we were pretty convinced that there was adult neurogenesis in the hippocampus of rodents, but the question remained whether this was a phenomenon that we might see in more complex animals. So in collaboration with Everard Hughes and Bruce McEwen we looked at the tree shrew and indeed found a substantial amount of adult neurogenesis there.. That's a tree shrew over on the right hand side. Then we moved into the study of non human primates and we looked at a new world monkey, the marmoset which is shown here on the lower right hand panel and saw the same phenomena, a large number of neurons generated in the hippocampus in adulthood. Finally we looked at macaque monkeys, which are old world monkeys relatively closely related to humans and saw the same phenomena.

One study since that time done by Frank Gage and Peter Ericson has demonstrated that there is adult neurogenesis in the hippocampus of humans and this was work that was done on cancer patients that were treated in a way that the neurons could be marked like I've shown you with those previous microscopic images. It was a method that was used to label the proliferating index of their tumours which were not in the brain and thereafter the individuals died their brains were donated to research and it was established that there was adult neurogenesis in the hippocampus. So we have very limited data about humans so far and we're not certain whether adult neurogenesis occurs in all humans so there's a very big question mark there. But we know that at least for the majority of old, even sick and dying individuals have substantial adult neurogenesis.

We know that there is evidence for new neurons in the hippocampus, not just because we see that they're produced in adulthood and they look like new neurons, but we also know that they receive synopsis on cell body's and dendrites, they also extend dendrites and axons into target regions. We know that they generate action potentials and they express their own specific proteins and this is another example of a collection of neurons that were generated in the adult hippocampus. This time the stain tells us that the cell is new. It is shown in green and the red stain shows that the cell has differentiated into a neuron and has grown dendritic processes. So the evidence now is very strong and not just for rodents but also for primates.

We asked the question how many new neurons are produced in an adult and I think this is a very important question for establishing functional significance because if it's just a few cells it's less likely that those cells would have any impact. It turns out that there is a substantial amount of adult neurogenesis in the hippocampus and I'll give you some really detailed quantative information from the rodent in a moment. But first, because we are very interested in how this was relevant to humans, I'm going to start the quantative picture by talking about marmosets. These are, as I said, new world monkeys and they're more closely related to humans, of course, than rodents are. Then I'm going to tell you how the human data, which is limited but quantitative, maps onto this picture and then give you an idea about the rodent as well. I can give you the take home message of this little part right now. It is that there doesn't seem to be a big difference in the numbers of new neurons that are produced across mammalian species. Increasing complexity, brain anatomy and function doesn't seem to be necessarily linked to a decline in structural plasticity.

This is work that a post doctoral fellow in my lab that Ben Leuner did. She looked at marmosets at different ages and what she found was that the numbers of new neurons produced in the hippocampus declined steadily with advancing age. This is something that wasn't too surprising to us because it had already been shown in rodents. But you can see that this decline begins around mid life and that also seems to be about the time when you can first detect cognitive impairments. I was sad to read this actually because most of us, I think, are under the impression that cognitive impairment is something that shows up when you reach elderly status, but it starts much earlier. In fact we can pick it up in humans in their thirties and when a marmoset is essentially in mid life, early 30s to 50s you see the big decrease in adult neurogenesis, and by the time the marmoset is considered to be aged the numbers are much, much lower than in the young adult.

What's going on with the humans? As I told you the only strong validated data we have for humans comes from this cancer study where the patients were all relatively old and very sick. So it's actually pretty remarkable that any adult neurogenesis was detectable in these individuals because, as I'll tell you in a moment, adult neurogenesis is very much suppressed by negative stress and obviously suffering from an illness is very stressful. Yet if you look at those data and knock them on to this marmoset study you see that the human has at least as many, if not more, than what we see in the marmoset and this little asterisk shows this one data point from the Ericson and Gage paper looking at a 72 year old individual who was dying of cancer. We picked that data point to put on here because that is the one that's most closely linked to the paradigm that we used for the marmoset. If anyone wants details of that then I will be happy to give it you. So you see there's a substantial amount, even in the age human. Because we've seen this in many species, rats, mice, tree shrews, dogs and marmosets, this declining with advance age in adult neurogenesis, it's reasonable to suspect that the young adult human would have many, many more new neurons than this aged sick and dying human. If we look at what the rat is generating in terms of new neurons in the hippocampus around the same age, it's very similar to the human. With the caveat that we have limited data on the human, the data that we do have, suggests that it's important to note that it doesn't appear to be a decline in humans, certainly not in primates overall in the rate of adult neurogenesis.

So now we can ask the question in species that have even more quantitative data on how many new neurons are produced in adulthood and we're talking just about the hippocampus here and Cameron & McKay did a very elegant study in young adult rats and they quantify the total numbers of neurons produced every day. They found that it's more than 9000 new neurons that are produced every day and given the fact that the type of neurons generated in

the adult rat is about 1½ to 2 million, this represents a significant proportion of the neurons that they have generated in adulthood. It extrapolates to about a quarter of a million per month and again there's a decline with advanced age, in the young adult it's a really substantial cohort of cells that are added every day. So some of you may be wondering how is it possible for the adult brain to make all these new neurons and for this brain region not to get too big for the rest of the brain to fit the skull. It turns out that there is a lot of depth, skull depth, in this area with a significant amount of turnover and the turnover of the cells is modulated by experience and I'll give you some examples of that in a moment. So the neurons are not produced by these high rates and all of them integrate permanently into existing neuro circuitry, it's only a percentage of them that get through and there seems to be a continual turnover. Production of new neurons means the death of some of our cells.

I want to talk now specifically about the hippocampus and how experience modulates, not just the incorporation of the neurons into this brain structure, but also how experience modulates the dendritic architecture and the dendric response of the pre-existing neurons. So we know a lot about the hippocampus relative to many other brain regions. It's been extensively studied specifically because of its role in and certain types of learning and memory. It also has some lesser known functions in anxiety regulation and also in feed back of the stress response and so we are very interested in understanding how these structural changes that occur in normal circumstances in the hippocampus contribute to the learning and memory as well as the anxiety that stress regulation functions of the hippocampus and that's been a major focus that we're working on that.

We know that many different types of experience can modulate adult neurogenesis as well as modulate dendritic architecture and this is just a partial list of some of these identified experiences that we know have a big impact on adult neurogenesis. I'm going to focus most of my talk today on stress and two very related experiences, related to stress, social dominance and physical exercise. We don't tend to think of physical exercise as stressful but it turns out that it has profound effect on the hypothalamic pituitary adrenal axis, which is the major stress warning system.

We also know that environmental complexity, learning and parenting have a major impact on adult neurogenesis and dendritic architecture in adulthood and a lot of our work is focussed on and I'm going to touch very briefly on environmental complexity as it pertains to the reversal of stress attacks.

For the end of my talk, we've done a lot of work on these other types of experiences, so I'll encourage anyone who is interested to ask me about that later on. So we all know that there are individual differences in response to stress and this is true not just in humans, but also in experimental animals. Some individuals respond to stress by developing psychopathology, depression or anxiety disorders. Others respond to aversive stressors with resilience and still others thrive on what the majority of people consider to be stressful experiences, they actually seek them out, they find it to be rewarding. Individual differences really are a hallmark of human experience in response to stress and we do see some of that in experimental animal populations as well, but we can block out individual differences in response to stress by selecting different types of stressors and modulating the context in which they're applied, as well.

So what determines individual responses to stress? There are many different factors that determine whether one person has a positive or negative response to potentially the same experience. Obviously psychological variables come into play whether this stressor is controlled or predictable those seem to lessen the negative impact of stressors. The emotional balance of the stressor is also very important whether or not the individual finds the experience to be aversive or rewarding and a really good example of this, I think, in humans is physical exercise. So I'll talk about this in a moment when I discuss what we know from work with experimental animals. We know that rodents love to run in wheels. It's a universally motivating experience. You give a rat or a mouse a running wheel; they'll run for several kilometres a night unless they are at death's door. That's not true for humans, in fact many humans in my country we wouldn't have the obesity epidemic if that was the case, but many humans find physical exercise to be aversive. So I think this is a really key point and

we're trying to tap into this in the laboratory. Whether or not the experience, independent of how it elevates stress hormone systems, whether or not the experience is viewed as rewarding versus aversive, this seems to have a major determinant of whether the effects of that experience were positive or negative.

Next we noted the social context can module the outcome in terms of stress effects on structural toxicity. In the social context is positive, even a stressful experience can have a positive effect on brain growth and if the social context is negative like in cases of subordination or isolation stress another stressor is applied to that, the effects are mostly negative and I'll give you some examples of that. Of course, developmental history seems to play a big part in whether or not a response to a stressful experience is positive or negative in terms of its long term outcome.

So I want to give you a brief overview of the kinds of experiences that we studied in the laboratory because we need operationalise stress when we study this in experimental animals and when we do so we have to pick well controlled stressors that we know something about the physiological effects and this is just a partial list of some of the commonly used types of experiences that are examined in the field. On the left hand side I've put the list of negative stressors and we define negative stresses experiences that are punishing or aversive. If the animals are given the opportunity they will try to escape from that. They will show freezing or immobilisation behaviours. They will induce fear and if they're given the opportunity they will escape. That list included social subordination, physical pain, restraint and predator odours exposure in the case of rodents. On the right hand side we have a list of positive stressors which are considered to be rewarding and motivating and again these describe experiments to animals, sexual behaviour seems to be universally rewarding to experimental animals as is eating and running and, you know, they're listed here and characterised as stressors because of the fact that they activate they hypothalamic pituitary adrenal axis which is a major stress hormonal system which leads to the increasing hypo-corticoids hormones in the blood stream.

Some of you may be a little surprised that the positive experiences that are listed on the positive side actually are stress related in terms of hormone response would be results are really quite dramatic and I'll give you some examples in men's sexual behaviour causes an increase in glucocorticoid levels which far exceeds what we see when an animal's exposed to subordination stress and that's fairly counter intuitive, but very interesting because it suggests that the brain is somehow buffering negative thoughts of how high levels of glucocorticoids when the stress is rewarding.

I'm going to focus for a moment on the negative side of the story and then you will be given more of the positive information because that's from our newest data and I think it also raises some really interesting questions.

This is work I started back when I was working with Bruce McEwen at the Rockefeller University and continued in my laboratory at Princeton's till the present day. We've been looking at the influence of aversive stressors on adult neurogenesis in the dentate gyrus (a part of the hippocampus) that we see in most of the adult neurogenesis. You've seen now that there is a very long list of such stressors; this is just a partial list of the numbers of different kinds of stressor that inhibit adult neurogenesis. This can be seen when the stress is acute as well as when the stress is chronic and this partial list includes predator odour; subordination; restraint stress; electric shock and sleep deprivation. They all decrease the numbers of new neurons produced in the hippocampus. This is just an example of one data set this was work done by Pat Tanapat, a grad student in the lab and she showed that when rats are exposed to the main component of fox faeces there is a natural stress response that increases the levels of glucocortocoid. The graph on the left hand side shows the amount of cortecosteroid in the blood of these animals. Glucocorticoid is the main hypo-corticoid stress hormone in rodents. And you see it increases when the animal is exposed to this predator odour and on the right hand side she has graphed the numbers of new neurons in the hippocampus and there is an increase in glucocorticoids and a decrease in neurogenesis. She did subsequent studies to link these two by cramping the levels of stress hormones in animals that were exposed to the predator odour and she completely eliminated the neurogenesis of that. So there is good news that these two findings are of positive linking.

The elevation of glucocorticoids is what is responsible for slowing the neuron growth. Again, similar effects have been observed with other aversive stressors and other species. We've seen suppression of neurogenesis in response to aversive stress in rats, mice, tree shrews and marmosets thus far. It's also been known in mere cats. Gives good reason to believe this would occur in humans as well. Interesting to study this phenomenon stress effects on neurogenesis in a more naturalistic environment and we are also very curious to evaluate dominance hierarchies because of our interest in subordination stress. So we adopted a paradigm that was first developed by the Blanchets at the University of Hawaii and this paradigm called the Visible Burrow System and this is a schematic diagram of the Visible Burrow System and you're sort of looking down on the top, it's just a very large enclosure and two sides of this contain tunnels and chambers for the rodents to run, sleep and hide and there's an open field area where the animals have to come and regain access to food and water and this is a very useful paradigm because when we put experimental animals in groups into this setting they form very potent dominance hierarchies. Rodent animals register as the dominant, it's the more oppressive animal and the other animals become subordinate and, in most cases, with most groups of rats which is the species we looked at here, the dominance hierarchy becomes relatively stable after the third night. So I want to give you an example of some of the behaviours that we witnessed what characterised this because it really is quite obvious which animal is the dominant. I've a little video tape here and you will see these animals have different marking spray painted on their back; they are albino animals so they're usually just white, but in order to quantify their behaviour we spray painted marking on their backs.

So the dominant in this cohort has the most dark painted on his back. You see he's boxing with the other rats in the field and chasing them out, generally harassing them all night long. This is work that Yevgenia Kozorovitskiy a grad student carried out. She was curious to see whether the dominance may have more new neurons than the subordinates and we had projected originally that the subordinates would make fewer than the dominants, but the dominants would be like controls because we predicted that the subordinates would be stressed. It turned out that she saw something not altogether give than what was predicted, but not exactly what we expected.

She found the predominance produced more new neurons than the subordinates, but that the subordinates did not produce fewer neurons than the controlled animals. This is a graph showing the numbers of new neurons in the hippocampus and the three different bars represent the change control animals, the animals that were not living in a dominance hierarchy, that's the cross hatch bar, or the dominant animals, that's the black bar, and the subordinate animals, which is the white bar, and you can see that the dominant animals make more new neurons that either of the other two groups. This is after just 3 nights of living in a dominance hierarchy, living as a dominant.

Now remember these animals were not living in dominance hierarchy before the start of the experiment and we have good reason to believe that this is the difference in adult neurogenesis that was induced by this social context. When the animals where put into the visible burrow system and some of them emerged with dominance they began to make more new neurons than they had previously. The reason we think this is the case is because if you examine the variance between the white and the black bar it's really tremendous relative to what we typically seen in the cage controls. So it looks like having these varied experiences, even in the same setting, really brings out individual differences in brain growth and we are looking at a very complex setting in the visible burrow systems we were very interested in sort of teasing apart the variable in order to identify what was responsible for elevating neurogenesis and the dominance and one of the things that we noticed was that the dominant animals have more access to the females so they actually mate more frequently than the subordinate animals do because the subordinate animals spend most of their time burrowing away from the dominance, hiding or trying to get food and water without getting beat up.

So what we did next was we tested in adults that were not living in the visible burrow systems specifically the influence of sexual experience on brain growth and this was work that Erica Glasper a post doc in the lab did. So she looked at the amount of neurogenesis in the hippocampus and she also looked at the level of circulating glucocorticoids, just like what I

showed you with the predator overexposure experiment, but this time it's a different kind of stressor and if you look on the right hand side this is the levels of glucocorticoids, there's a huge increase with sexual experience, the yellow bar is the animals who have had a sexual experience, the grey bar are the naïve animals. This is really a loping increasing in glucocorticoids; it's more than twice what we see in a time matched exposure to in aggressive male in a subordinate encounter. Obviously this is a positive experience of these animals because they will develop a place preference for location of a sexually receptive female and it will also learn to press a bar very readily in order to gain access to a female and obviously it will find it very rewarding.

On the left hand side we see that surprisingly there is an increase in neurogenesis despite the fact that glucocorticoid levels are so high and this was really a surprising result to us because we had seen over and over again that elevated glucocorticoids were associated with the suppression of the neuron growth and we're presently trying to identify the factors that are responsible for this, but clearly it's an indication that when stress hormone systems are activated in a more context of a rewarding experience, the brain is buffered against the negative effects of glucocorticoids. We think that one possible factor that buffers the brain, causing an increase in neuron growth instead of decrease, are endogenous opiates which are elevated under almost all rewarding case conditions and that's one of the things we are looking at in the lab, but we don't have data on that yet.

Another universally rewarding behaviour for rodents is running and I told you a bit about this before when I was introducing the concept of individual differences. We know that healthy rats will run several kilometres a night if they're given access to a running wheel, they'll develop a place preference for a running wheel and they'll readily learn to bar press for access to a running wheel.

We also know that running activates the hypothalamic pituitary adrenal axis which allows for increasing in the glucocorticoids and it also, just like what we've observed with sexual experience, enhances adult neurogenesis, but there's a caveat here and it's something that really needs to noted in rats that run only in adult neurogenesis when it occurs they're in a positive social context. When animals are running in a negative social context, at least in the short term, it has a negative effect on neurogenesis. I'll tell you a bit about that in the next few slides.

This is work that Alexis Stranahan, a grad student at Princeton did. She asked the question whether social housing affects the responsible positive stressor and in this case the positive stressor was running, so she has down on one side individuals who were in groups and she gave some of them access to a running wheel and some of them were sedentary and what she found was that there were elevations in glucocorticoid levels with running whether the animals were housed individually or in groups, there was activation of the hypothalamic pituitary adrenal axis in both cases and this particular experiment on the left hand side of the glucocorticoid values and you can see that the group housed animals have an even higher level of glucocorticoids than the individually housed animals when they are running, although that's not a statistically significant factor, they certainly don't have the reverse.

If you look at the graph on the right hand side, this is the numbers of new neurons in the hippocampus, and if you look at the group housed animals, those are the bars on the right hand side of the right handed graph the runners make more new neurons, the black bar is higher than the white bar when they're housed in group and the opposite effect is observed in the individually housed animals. When the individually housed animals graph is actually suppression of adult neurogenesis, just like what we see when we expose animals to predator odour, a cold swim or restrained stress or subordination. So there is obviously something about social housing that's again buffering the brain from negative influence of glucocorticoids. So it turns out that although this first experiment that we did here on the left hand side demonstrated that individually housed and group housed runners both had an increase in glucocorticoids and we look at many different time points of stress hormone levels, the effects were much more complicated than that. So, that graph that was shown in the previous slide is an upper left hand side of this panel. There's a baseline glucocorticoid levels and control animals and runners has individually and in groups.

If we look at different time points when glucocorticoid levels are naturally lower because there's a diurnal rhythm to these hormones. What we seen was that the grouped out animals actually had a lower level glucocorticoids at that time and that's put on the graph on upper right hand panel, but what's most interesting, I think, is when we look at baseline stress in recovery levels of glucocorticoids. We took sedentary animals and animals that have been running for several weeks and we restrained them and measured glucocorticoids in a baseline condition after the stress and after they had recovered from the stressor and we saw that the group housed runners did not mount a stress response. So they were actually buffered at the level of hypothalamic pituitary adrenal axis from having increasing glucocorticoids and you can see that in the bottom graph on the right hand side. All of the other groups showed with stress at increasing glucocorticoids so each little cluster of 3, the black bar, represents the stress level and you can see the at the right hand group, which is the group who has runners, they don't have an increased in glucocorticoids in response to stress. So there is something that's different about the stress hormones for some of these animals that, you know, at least in part, is contributing to their ability to undergo brain growth in response to an increasing glucocorticoids as opposed to a suppression of neurogenesis.

Alexis has gone onto investigate whether glucocortocoids were responsible for these random effects on neurogenesis and she did this by taking adrenal glands and planting the levels of glucocorticoids that the animals didn't have in increased or decreasing glucocortocoid levels at different time periods in diurnal rhythm. In so doing she was able to prevent the decrease in neurogenesis in the individually housed runners, so she was able to prevent the negative effect, but she was not able to alter the positive effect of running on neurogenesis and this suggested that there are other factors that are potentially involved in this, but something about running in a group enables them to provide some kind of a factor that enables the animal to produce more new neurons and to sort of bypass the negative effects of glucocorticoids. And again here, we think a good candidate might be opiates, which are known to be increased in the brain in response to running and their sum-up is that opiates, that blocking opiate receptors might actually inhibit neurogenesis, but again that's very preliminary.

So here I think the really take home message and the interesting point about this set of studies that Dr Stranahan gave was that you can expose animals to what appears to be exactly the same experience and depending upon the social context, you can get a completely different brain interpretation of that response. Some of the animals that were living alone will have the opposite effect, a negative effect of running, on a neurogenesis, whereas the animals that were living in groups there was a positive effect on neurogensis and probably there are pertinent examples that we could think of in human situations where social context was very much affect ones ability to cope with the negative stresses.

I'm going to give you the broader picture as well. Running doesn't just alter neurogenesis, it effects dendritic architecture and Dentritic spine density, remember I told you those with extensions of the dendritic segments that were the primary synapses, connections between those so we look at populations of nerves that are not produced in adulthood and found that in every case of neurons in the hippocampus circuitry, running produced an increase in Dentritic spine density or an increase in the numbers of connections between neurons. There is a lot of brain growth going on. It's not just the addition of new neurons and having the running in a positive social context obviously produces a greater beneficial effect.

So we know that running alters hippocampal function, there are many, many studies that have shown this, this data is just a partial list. Running alters, it actually enhances learning and memory functions, it also decreases anxiety in animals and many people are using running in the laboratory in rodent studies as a model of antidepressant action. And there certainly is some evidence, although it's not as clear cut, in humans that physical activity can now elevate mood. So we're very interested in understanding how these changes that occur in hippocampus structure in response to running and the other experiences that we've looked at, contribute to changes in hippocampal function which is also a major focus of my lab now is to try and find ways to pull off these structural changes to see whether the experience driven changes in the hippocampal function can re-alter it and we don't have the answer to that

question, it's actually a very broad question, but there's a lot of evidence that suggests that increases in the number of new neurons as well as increases in the number of dendritic spine are associated with improved performance of these experimental animals.

So I'm going to switch here for the last part of my talk and discuss how early life experience might impact on the brain's ability to respond to stress in adulthood. This was work done by Christian Mirescu a graduate student in the lab using the maternal separation paradigm which was so well characterised by Gabriel Bean and Michael Meaney and what it entails was actually taking rat pups away from the mother every day for 3 hours for the first 2 weeks of life and this alters the hypothalamic pituitary adrenal axis and you know, like sort of broad effect and lasting effect on certain behaviours. There is this very interesting model of early life stress.

What Christian was interested in looking at is whether early life experience, in so far as it disregulates the hypothalamic pituitary adrenal axis so that it would have a significant effect on adult neurogenesis. So he looked at animals that were undisturbed, the control animals, and he compared them to animals that were handled every day, but returned immediately to the mothers, (that's the grey bar [on the slide]) and then he looked at animals that were as I just described were moved from the mother every day for a significant amount of time for a 2 week period and then returned back every day after the maternal separation period was over. What he found was that the animals that were subjected to maternal separation when they grow up to be adults they made fewer new neurons in the hippocampus.

This is a graph which again shows the numbers of new neurons in the hippocampus and in both sets of three bars you can see that the white bar, which represents the maternal separated animals, they made few more neurons than produced in the hippocampus of the those animals in comparison to the other two groups. Remember these are adult animals that were subjected to the maternal separation. So this is a persistent effect after the first two post natal weeks of life are over the animals were not disturbed any longer and then the numbers of new neurons were examined in adulthood. So this early post natal experience has a lasting effect on the structural toxicity in adulthood. So one of the things that Christian was interested in looking at is whether or not the animals that made fewer new neurons to begin with had what we would characterise as the normal stress response in terms of suppression of the adult neurogenesis in response to universal stressors.

So he exposed these animals, these maternally deprived animals, to a predator odour in adulthood, remember that I told you at the beginning of my talk that predator odour exposure suppressive adult neurogenesis. So the returned, the deprived animals when they became adults and subjected them to that same stressor and he found that the maternally deprived animals had what appeared to be a normal glucocorticoid response, that's shown on the right hand graph, those with levels of glucocorticoids in controlled animals and handled animals and he returned the separated animals, the black bar in all case is the control condition and the white bar represents exposure to predator odour.

All three groups had a similar stress response and yet the effects on neurogenesis were really quite different. The controlled and handled animals showed the characteristics suppression of neurogenesis in response to predator odour exposure, but the maternally separated animals showed no significant decrease, perhaps because their baseline was so low to begin with they were not, what we would characterise as normal response of adult neurogenesis to an aggressive stressor. You can see those data on the left hand side, in particular, can I turn your attention to the two clusters of bars to the right hand to a pair of black and white bars, you can see there are no significant differences between those two and this is the maternally separated animals, based on level of adult neurogenesis suppressed, but no further decrease with the stress in adulthood. All that can be reversed when glucocorticoid levels are lower.

So even though these animals seem to have normal levels of glucocorticoids, there's something about the hypothalamic pituitary adrenal axis that's disregulating perhaps more of the hormone is getting into the brain they might have different models of glucocorticoid receptors, whatever it is they will increase sensitivity to glucocorticoids which makes them have a reduction in neurogenesis even in the baselines, for the baseline animal. The

unstressed animal looks like a stressed animal. So this seems to be sort of bad news in general and it looks like these effects are permanent because we looked at animals that that were fully adult after this early life experience and found that there was a suppression of adult neurogenesis until these animals were in mid life. But what we were interested in seeing was whether experiences that were known to have a positive effect on neurogenesis whether they were capable of reversing these negative influences that were made earlier in development.

So we took animals that were subjected to maternal deprivation paradigm during early life and housed them in enriched environments in adulthood. This is an example of one of the enriched environment that was used, it looks very similar to the visible burrow system, but in this case we did not set up a set of axis so that there were dominant and subordinate animals, we had animals only in same sex groups so there was no competition for mating, we also made food and water readily available to the animals. We gave them access to many interesting objects to explore and hide throughout the enriched environments so that they would engage in natural foraging like behaviours.

We know from other studies that living in enriched environments stimulates adult neurogenesis in the hippocampus. We were curious to see whether or not this would have the same effect on adult neurogenesis in maternally separated animals or whether maternally separated animals were just more structurally rigid in both ends of the continuum. So they failed to show a suppression with stress, and perhaps they would fail to show a positive effect with enriched environment. So that was the experiment that was done and we found that indeed the suppression of adult neurogenesis that occurs with maternal separation could be reversed by housing animals in enriched environment conditions in adulthood. So this graph shows the numbers of new neurons on the left hand side these are the controlled animals and the black bar represents animals that do not live in enriched environment, the white bar represents animals that have lived in enriched environment. I'll turn your attention to the bars on the right hand side and that's from maternal separation, the black bar is the control and non enriched condition, you see they have a suppression on the adult neurogenesis relative to controls on the left hand side.

But living in an enriched environment restored that back to the normal level. So these are very encouraging indeed because it suggests that even in cases where the developmental circumstances are negative and stress hormone systems are disregulated that the brain seems to be resilient enough in its output to respond in a positive way to a positive experience. We don't know the extent of this resilience, we have yet looked at very long time points, but were other types of positive experiences, but they we're certainly interested in doing that and even more importantly what we'd like to do is identify the mechanisms that underlines these effects because I think if we can identify those exact mechanisms, it's the factors that can stimulate neurogenesis in animals rats then developing the conditions that suppress neurogenesis then we can find other ways to stimulate brain growth. It's interesting and I think relevant in terms of the real world to look at experiences, but, as I suggested earlier on in my talk, one persons experience is in response to what we think is the same experience compared to another persons experience varies dramatically. So understanding the mechanisms that promote new neuron growth I think will be a real key to applying the same medicine and figuring out how it can be used in order to improve brain function.

So I'm going to conclude now and tell you what I hope are the key points that I got across today. First the adult brain is structurally plastic and I only gave you the tip of the iceberg, there are huge literatures on this now. We know that there is a vast array of structural changes that occur and I mean these changes don't occur just in response to damage, they occur under normal circumstances in response to hormone fluctuations as well as in response to experience. We know that the social context can determine any kind of neuro response to stress and we've expanded this general idea to looking at the effects of stress on structural toxicity and, in fact, social context is so powerful that it can actually reverse the effects of stress on brain plasticity. And finally, developmental experience can alter the response of the brain to aversive stress and some of these effects appear to be reversible by putting animals in more positive environments later on in life. I'll end now there by thanking the people in my lab, past and present, without whom this work would not have been at all possible, Ben

Leuner, Erica Glasper, both pot grads in the lab now do the work on marmosets as well as the sexual experience study, Alexis Stranahan who did all the work on running, Christian Mirescu did the work on maternal separation and Yeugenia Kozorovitskiy the dominance hierarchy work and the other individuals are equally important working a variety of the projects that I mentioned throughout.

So thanks very much for your attention and I'm happy to answer any questions you may have. *(Applause)*

Thank you very much for an absolutely fascinating and really very heartening I think exposition of a very complicated subject. I guess we'd just like to finish off by making comment. You've said very clearly that it's difficult to extrapolate from rat models to the kind of circumstances that many of us here are dealing with in terms of improving health and improving society more than likely and what I think you have shown us tonight is that it is even more complex than we thought. When I think of the Black Report which came out in 1980 there was a general assumption made that well if the poor are less healthy all you have to do is make them rich and they will become healthy and then it wasn't quite straightforward as that and housing developments didn't continue to, you know, and hence we've coined the term in Glasgow that everything matters, that all matters, you've got to do all of these things. But I think you've shown us tonight that you've got to all of these things for some of the people and some of the things you shouldn't do and it's down to, a lot of it's about individual response and what I certainly believe is we can't have blanket policies. Blanket policies can damage individuals, you know you might initiate a policy for the very best of reasons, but within people affected by those policies some of them will be damaged and, therefore, we need to tackle inequalities very much on a person by person basis. But we knew that already. But I think some of the comments that have been used tonight throughout your talk, stunning terrific, fascinating and eloquent, you know, I think there's no question that we've heard a really phenomenal exposition of an incredibly competent and variant mind.

Thank was an absolutely fantastic talk Liz. *(Applause)*