SUMMARY PAPER 4

'Positive and negative stress alter brain structure'

Prof Elizabeth Gould,
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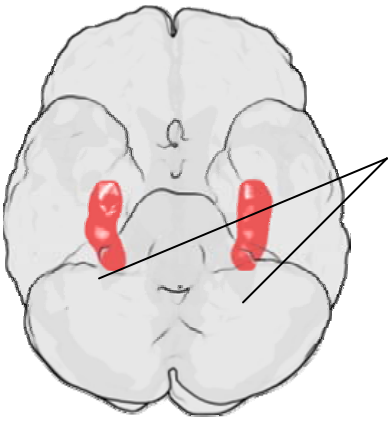
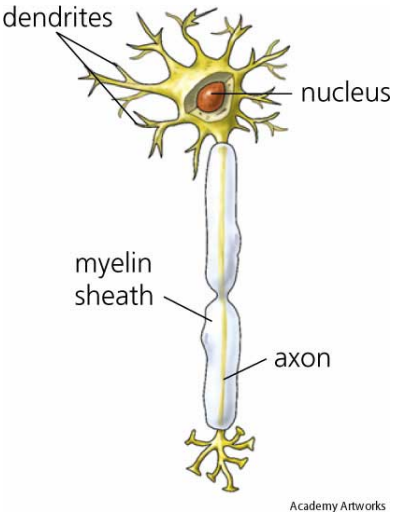
Overview:
Citing animal laboratory studies, Prof Gould showed that the adult brain structure is changeable in response to positive and negative stressors. She showed this to be the case for the number and function of new neurons and the complexity of connections between neurons. This is modulated by social context and early life experience and can be reversed.

Key ideas:
Prof Gould used a number of key terms in relation to the brain.

- **Structural plasticity:** the idea that the main structures of the brain, especially the hippocampus, are changeable and not rigid or only able to decline over time.
- **Dentate gyrus**: one of two gyri composing the hippocampus, an important area of the brain. It has memory, spatial orientation, learning and emotional functions.
- **Hippocampus:** a complex folded part of the brain (illustrated) whose function includes the mediation of memories navigation, spatial orientation, learning, stress and anxiety. The figure shows the underside (ventral view) as if the brain were a semi-transparent human brain, with the front of the brain at the top. The red areas show the approximate location of the hippocampus in the temporal lobes of the human brain. The hippocampus is entirely covered by the ventral temporal cortex (i.e. the hippocampus is **inside** the transparent brain).



- **Dendrites**, **dendritic tree**: the branching process of a neuron that conducts impulses toward the cell. A single nerve may possess many dendrites.



- **Axon:** the appendage of the neuron which transmits impulses away from the cell body.
- **Neuron:** a specialised, impulse-conducting cell that is the functional unit of the nervous system, consisting of the cell body and its processes, the axon and dendrites.
- **Neurogenesis:** the making, development and growth of neurons in the brain.
- **Synapses:** a region where nerve impulses are transmitted and received, encompassing the axon terminal of a neuron that releases neurotransmitters in response to an impulse; an extremely small gap across which the neurotransmitters travel; and the adjacent membrane of an axon, dendrite, or muscle or gland cell with the appropriate receptor molecules for picking up the neurotransmitters.

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- **Valence:** the degree of attraction or aversion that an individual feels toward a specific object or event.
- **Hypothalamic Pituitary Adrenal axis (HPA axis):** the interaction between that portion of the brain which lies beneath the thalamus and secretes substances which control metabolism by exerting an influence on pituitary gland function, such as the distribution of stress hormones like glucocorticoids.
- **Endocrine:** Pertaining to internal secretions; hormonal.

[Please note that slide numbers below relate to the accompanying slideshow which Prof Gould used during her talk.]

Summary

Prof Gould began by showing us three images which summarise what she intended to cover in the lecture (slide 1). On the left was a dendritic tree associated with synaptic responses of neurons which can change in shape and size according to stimuli. The middle pane showed one dendritic spine with a large number of synaptic connections which could be modulated by experience and the third showed some new neurons generated in the hippocampus of an adult mammalian brain. She then put up two laser microscopic images of new neurons which showed evidence of having been assimilated as functioning cells in the nervous system (slide 2).

<u>Evidence for neurogenesis</u>

Prof Gould went on to outline the evidence for effective adult neurogenesis in the hippocampus of laboratory mammals (slide 3). She listed four main sources of evidence (slide 4):

- Synapses on cell bodies and dendrites, which change with positive and negative stress.
- Extended dendrites and axons associated with desirable activities and circumstances.
- The generation of action potentials among neurons.
- Express neuronal-specific proteins.

She also suggested that about 250,000 neurons per month were observed to generate in the brains of young adult rats (slide 6). This is associated with a significant turnover of cells in a total of 1.5 to 2 million neurons. A single quantitative study of a 72 year-old cancer patient also showed significant neurogenesis – surprising in such stressful conditions. This indicated that there is no big difference across mammalian species in the ability to generate new neurons. Other structural changes such as the extension of the dendritic tree and synapses also suggest further that these changes are not simply quantitative but point to improved functioning.

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Differences in the response of individuals to stress

Having established the existence of changing brain structure, Prof Gould observed that individuals respond differently to the same stresses and went on ask what determines individual response to stress. She showed that experience modulates adult neurogenesis in various areas of life and concentrated on laboratory evidence on the effect of stress, social dominance and physical exercise (slides 7, 8 and 9).

She suggested that four factors could be shown to determine individual response to stress:

- Psychological variables – controllability, predictability
- Emotional valence of the stressor
- Social context
- Developmental history.

To investigate the effect of these, Prof Gould and various colleagues used a range of positive and negative stressors under laboratory conditions and found that negative stressors inhibit adult neurogenesis in the dentate gyrus (slides 10, 11 and 12). Stress hormone levels in the bloodstream increased, but adult neurogenesis was inhibited (slide 13). Subsequent research using a visible burrow system (slide 14) showed that dominant rats generate more new neurons than subordinates or controls (slide 15) suggesting that positive stress, while it released the same hormones as negative stress, somehow stimulates neurogenesis.

Using a positive stressor (sexual experience) in subsequent tests showed that this enhanced adult neurogenesis despite elevated stress hormones (slide 16). Prof Gould also showed that running on a wheel, which rats universally like, activates the HPA axis and enhances adult neurogenesis (slide 17).

Taking this argument further she showed that rats running on wheels in social situations show more positive stress responses than controls or running in individual circumstances (slide 18). Subsequent experiments showed that rats running on wheels in positive social situations were protected from the stress response compared with individual runners and sedentary rats (slide 19). The raised the question of whether the glucocorticoid hormone response to stress was responsible for the difference. By controlling glucocorticoids in further tests, it was possible to decrease the negative effects on individual runners, but not the positive effects on group runners, who after a few weeks of running, seemed protected from the stress response. This suggested an independent effect of social situation (slide 20).

In addition to neurogenesis, running also enhances dendritic spine density and complexity across a range of different neuron types (slide 21) suggesting dynamic brain development, improving ability to learn and reducing anxiety (slide 22).

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Early life experience and adult response to stress

In the final part of her lecture Prof Gould turned to questions relating early life experience to the ability to generate neurons in adult life (slides 23 to 26). She showed that mammals which had experienced maternal separation in early life showed inhibited ability to generate neurons in adult life. They were then placed in enriched and pleasant living environments. Living in an enriched environment reversed the effect of maternal separation on adult neurogenesis, indicating that social conditions are a powerful modulator of stress response (slide 27).

In concluding Prof Gould reiterated that:

- the adult brain is structurally plastic and responds to positive and negative stress;
- social context can determine the endocrine and neural response to stress; and
- developmental experience can alter the response of the brain to stress – at least some of these effects are reversible.