

ADULT NEUROGENESIS AND DEPRESSION: AN INTRODUCTION

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SUMMARY

The following essay provides a summary of a seminar given on the sixth of November, 2010 at the combined annual congress, held at Brussels of the Centro Studi Psichiatrici Vrije Universiteit Brussel, Université Catholique de Louvain & the Bedfordshire Centre for Mental Health Research. The talk aimed to present a brief taster, assuming no prior knowledge, of adult neurogenesis, the formation of new nerve cells, in relation to the aetiology and treatment of depression.

The talk begins with an introduction to the principles of adult neurogenesis: from initial investigations by Ramon y Cajal in the 19th century, resulting in a "static brain hypothesis", to their subsequent challenge almost one hundred years later. The potential functional implications emerging, especially in relation to depression, are explored. The fascinating effects of corticosteroids and antidepressants are used as examples to explore the possible roles of neurogenesis that have led some to propose a neurogenic theory of depression. Arguments against this theory are then presented. Finally, a consideration of future opinion: could neurogenesis be less important in the aetiology of depression, but involved in its treatment - a property of antidepressant action rather than a central final aetiological pathway.

In this young branch of neuroscience controversy abounds: our understanding of the process itself, its relations and most importantly its implications are all in their infancy. This has allowed for some of the most interesting debate of recent years as to the neurological basis and treatment of affective disorders.

Key words: neurogenesis - depression

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Introduction

Perhaps one of the central goals of contemporary psychiatry is to characterise the aetiology of the depressive disorders. Although much progress has been made in recent years, perhaps one of the largest leaps in our understanding occurred long before science was conceived as a discipline, let alone welcomed into the world of medicine. Galen, the surgeon, believed melancholia to be caused by an excess of black bile (Herbert 2007). This is more significant than it sounds - even at this early stage we can see the evolving belief that a disease of the mind could be due to an error of underlying anatomy.

"a privation or infection of the middle cell of the head"

Galen, referenced in an anatomy of melancholy (Burton 1621)

Monoamine hypothesis - reverse engineering

However, for a millenium this was to remain a fruitless avenue of exploration and it was not until useful pharmacotherapies for depression emerged that testable, scientific theories of depression began to form. This led to the unusual state of affairs where the treatments for the disease are the central path to understanding its mechanism, rather than the converse of a treatment developed through our understanding of aetiology. With this "reverse engineering" of pharmacology contemporary, testable, theories of depression have been evolving over the last 50 years.

The objectively measurable actions of antidepressants have been of interest in this way, notably the

enhanced monoamine levels (mainly serotonin 5HT and noradrenaline NA) that most induce. This led to the monoamine hypothesis: many antidepressants increase monoamine levels ergo depression was a syndrome due to the lack of monoamines. The fact that the timescale of this increase (almost instant) was incongruent with the clinical timescale of the treatment (usually over weeks rather than hours) was an early and enduring criticism of the theory.

This represents an apposite example of the limitations of this reverse engineered approach - we only see part of the picture if we only look back from an effective treatment towards an aetiology and it is all too easy to spend time exploring a branch from the aetiological process, rather than a continuation of it. The crux of this presentation, adult neurogenesis (the formation of new nerve cells), could be said to stand in a similar position, a discovery whose significance in relation to depression has resulted from noting the effects of antidepressants, rather than the process of developing the disease.

With this in mind, let us explore the concept of adult neurogenesis from its very beginnings.

"Once the development was ended, the founts of growth and regeneration of the axons and dendrites dried up irrevocably. In the adult centres, the nerves are something fixed, ended and immutable. Everything may die; nothing may be regenerated. It is for the science of the future to change, if possible, this harsh decree."

Ramon y Cajal 1890
(Colucci-D'Amato et al. 2006)

Ramon y Cajal

A single irrefutable dogma has lain at the heart of neuroscience for almost a century and to this day it can be found in introductory chapters of textbooks and has found its way into lay culture too: save the initial embryological development, no new nerve cells ever appear in the brain.

Cajal's "decree" elegantly summarises all he and his contemporaries believed.

This "static adult brain" hypothesis of Cajal was based on good histological technique: neurons cannot be seen to display any mitotic figures; however, do neurons need to divide at all to produce new neurons?

Strictly, mitosis is not at all necessary for the production of new nerve cells: undifferentiated cells could supply new neurons by periodically embarking on a neural differentiation path (Christie et al. 2006). This is believed to be the case: new neurons are formed from self replicating progenitor cells, rather than other nerve cells: mature neurons are post mitotic cells and do not divide themselves (Elder et al. 2006). These neural stem are found in few areas of the brain - notably for psychiatric studies in the Sub Granular Zone (SGZ). Thus explaining the lack of mitotic figures observed by Ramon y Cajal (Bryans, as referred to by (Gross 2000): neurons indeed do not divide, but stem cells do.

Initial implications for depression

This process of neurogenesis has been observed to occur in brains at two major sites: the SVZ (the subgranular zone) and the dentate gyrus of the hippocampus which has generated interest (and much controversy) in relation to depression. Over the last decade, many factors have been identified which appear to alter adult neurogenesis at this site, with some of these sparking particular interest in relation to depression.

The hypothalamic- pituitary axis is one such factor: elevated cortisol (corticosterone) levels have been seen to reduce rates of adults neurogenesis (Cameron et al. 1994) while in addition exogenously removing the diurnal glucocorticoid oscillation by clamping levels reduced rates of proliferation at the dentate gyrus (Wong et al. 2005). These observations are interesting in that they mirror the flattened cortisol rhythms seen in depressed patients.

One of the most notable publications in this area is that of Santarelli et al. (2003) where, in a mouse model using novelty suppressed feeding paradigms, the process of adult neurogenesis appeared to be essential in the behavioural effects of antidepressants (Table 1).

The work of Santarelli, suggesting that without neurogenesis, fluoxetine had no anti-depressant effect added credence to the previously proposed "neurogenic" theory of depression. Based on the accumulating collection of factors such as corticosteroids (Cameron et al. 1994) and other apparently active in regulating proliferation in the dentate gyrus (such as exercise and

ECT treatment) & their corollary relation to depressive symptoms some had proposed a novel thesis: that adult neurogenesis at the dentate gyrus is a final common pathway in the development of depression.

Table 1. Effects of antidepressants (Santarelli et al. 2003)

Experiment	Behaviour	Hippocampal Neurogenesis
Stress Alone	Depressed	Decreased
Stress Plus Flu	Normal	Normal
Stress + x-ray + Flu	Depressed	(decreased by the x-rays)

"We hypothesize that the waning and waxing of neurogenesis in the hippocampal formation are important causal factors, respectively, in the precipitation of, and recovery from, episodes of clinical depression."

Jacobs et al. 2000

Implications for neurogenic theory of depression

Here we have a further attractive theory on the aetiology of depression - a new final common pathway for the multitude of exogenous and endogenous factors implicated in the clinical entity of depression to act through. This theory, although giving solutions to some of the problems of its predecessors still leaves much wanting - a panacea it is not.

Indeed, the interesting findings of Santarelli et al. have indeed been criticised - with Henn et al. 2004) questioning their model of depression (a novelty suppressed feeding paradigm) which has been used in assessing anxiety rather than depression - thus highlighting both a specific deficiency and a general obstacle: the lack of a reliable animal model of depression. When Airan and Meltzer et al. 2007) investigated the effects of antidepressants on neurogenesis and depressive behaviour, it was found that irradiation did prevent the behavioural actions of fluoxetine, there was no effect on the behaviour of their mouse model on a forced swim test directly contradicting Santarelli.

A neurogenic theory of behavioural effects of antidepressants

With the consideration of these points taken into account, the final common pathway of adult neurogenesis in the aetiology of depression appears to be a little less plausible - more a novel and fascinating piece of the puzzle than its solution. It would appear that we have found neurogenesis to be essential to the behavioural effects of certain antidepressants - for example the anxiolytic effects of fluoxetine (Airan et al. 2007) and less essential to the development of the condition - in animal models as Airan showed irradiation, not to induce depressive features in an animal model, but to ablate the function of fluoxetine.

Limitations to current knowledge

Despite the fascinating possibilities proposed by this aetiological theory of depressive disease, the major hurdle to an integrative and ultimately useful thesis have still to be overcome. As yet, no comprehensive animal model exists for the syndrome of depression and while human studies may provide useful information on treatment efficacy the inability to selectively examine brain tissue will of course limit a full elaboration of human neurology. Although one post mortem study has been carried out and shows the presence of neurogenesis in adult human brains (Eriksson 1998) albeit at a lower rate, it adds little to our understanding of depression.

Progress may have been made in our understanding of this most mysterious of maladies, but there is still some work to be done before an effective pharmacotherapy is developed from this knowledge. Indeed future drug development will be the test of relevance: is this an interesting Galenic leap in our conceptualisation of depression, a grand refutation of a Raimon y Cajal, or something much more useful: a practical addition and move towards a therapeutically useful understanding of the depressive disorders. Indeed, it is still for the science of the future to determine the significance of this challenge to Cajal's decree.

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Thanks

Dr. M Agius for the opportunity to represent this talk to a wider audience & editing this article.

Prof. Herbert & Dr. Pinnock, Department of physiology, development and neuroscience, supervisors of my undergraduate dissertation & research project on this subject.

Dr. A.V.L Davis for proofreading the article

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