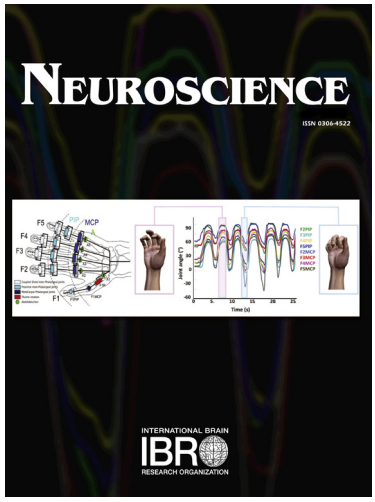
Accepted Manuscript



Commentary

Stressing the seminal role of paternal experience in transgenerational 'epigenopathy' affecting offspring health and disease susceptibility

Anthony J. Hannan

PII: S0306-4522(18)30496-2
DOI: https://doi.org/10.1016/j.neuroscience.2018.07.021
Reference: NSC 18560

To appear in: *Neuroscience*

Received Date: 4 July 2018
Accepted Date: 8 July 2018

Please cite this article as: A.J. Hannan, Stressing the seminal role of paternal experience in transgenerational 'epigenopathy' affecting offspring health and disease susceptibility, *Neuroscience* (2018), doi: https://doi.org/10.1016/j.neuroscience.2018.07.021

Stressing the seminal role of paternal experience in transgenerational 'epigenopathy' affecting offspring health and disease susceptibility

Anthony J. Hannan[1,2,*]

1. Florey Institute of Neuroscience and Mental Health, University of Melbourne, Parkville, Victoria, Australia
2. Department of Anatomy and Neuroscience, University of Melbourne, Parkville, Victoria, Australia

*Correspondence: Prof. Anthony J. Hannan, Florey Institute of Neuroscience and Mental Health, Melbourne Brain Centre, University of Melbourne, Parkville, VIC 3010, Australia;
E-mail address: anthony.hannan@florey.edu.au

Key words: envirome, epigenetic inheritance, epigenopathy, intergenerational epigenetics, epigenome, stress

The past decade has witnessed a revolution in our conception of the transgenerational impacts of paternal experience on offspring phenotypes, including various aspects of development, physiology, metabolism and endocrinology (reviewed by Bale, 2015; Bohacek and Mansuy, 2015; Yeshurun and Hannan, 2018). Some of the most striking effects observed involve experimental manipulations of male rodents, in which increased exposure to stress, or administration of stress hormone, prior to mating with control females, leads to altered behaviour of offspring, as well as a variety of cellular and molecular modifications (Franklin et al., 2010; Dietz et al., 2011; Morgan and Bale, 2011; Rodgers et al., 2013, 2015; Gapp et al., 2014a, 2014b, 2016; Bohacek et al., 2015; Short et al., 2016; Razoux et al., 2017; reviewed by Pang et al., 2017). Furthermore, other paternal exposures and environmental factors such as diet, exercise and environmental enrichment have been found to alter offspring phenotypes (e.g. Ng et al., 2010; Carone et al., 2010; Short et al., 2017; Yeshurun et al., 2017). However, we still have much to learn with respect to the way in which the male 'envirome' (McOmish et al, 2014) can affect the sperm epigenome. Furthermore, we have only have a rudimentary understanding of the associated epigenetic mechanisms, and the full extent to which transgenerational inheritance of acquired traits impacts on health and disease.

In this issue of *Neuroscience*, a new article (Harker et al., 2018) adds a piece to this puzzle of paternally mediated transgenerational epigenetic inheritance. The study involved exposure of male rats to chronic stress (daily for 4 weeks), followed by mating with control females and analysis of offspring for specific brain and behavioural correlates. Whilst paternal stress in rodents has been previously shown to impact on offspring behaviour in a sexually dimorphic manner, the most novel aspect of the present study is the demonstration that paternal stress alters the morphology of pyramidal neurons in the prefrontal cortex and hippocampus of adult offspring (Harker et al., 2018). This followed on from the prior work of these investigator, showing that the offspring of fathers exposed to chronic stress exhibited changes in global DNA methylation and neuronal morphology in brain tissues at three weeks of age (Mychasiuk et al., 2013; Harker et al., 2015). One limitation of these studies was that they only addressed the intergenerational (paternal F0 to F1 offspring) transmission of the effects of stress. Other rodent studies have demonstrated transgenerational (through to F2 and in some cases beyond) transmission from F0 paternal exposures, and have also explored specific epigenetic mechanisms. Whilst these investigators (Harker et al., 2018) did not examine the sperm epigenome, previous studies indicate that such intergenerational effects of paternal stress are mediated by selective epigenetic modifications, including small noncoding RNAs (reviewed by Pang et al., 2017).