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Review article

Social regulation of adult neurogenesis: A comparative approach

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ABSTRACT

The social environment sculpts the mammalian brain throughout life. Adult neurogenesis, the birth of new neurons in the mature brain, can be up- or down-regulated by various social manipulations. These include social isolation, social conflict, social status, socio-sexual interactions, and parent/offspring interactions. However, socially-mediated changes in neuron production are often species-, sex-, and/or region-specific. In order to reconcile the variability of social effects on neurogenesis, we need to consider species-specific social adaptations and other contextual variables (e.g. age, social status, reproductive status, etc.) that shift the valence of social stimuli. Using a comparative approach to understand how adult-generated neurons in turn influence social behaviors will shed light on how adult neurogenesis contributes to survival and reproduction in diverse species.

1. Introduction

In the approximately 50 year period during which adult neurogenesis – the birth of new neurons in the mature central nervous system – has been studied, beginning with the seminal work by Joseph Altman in the 1960s (e.g., Altman and Das, 1965, 1966; Altman, 1969), roughly half of the relevant scientific reports have been published in the past five years. This surge in interest arises from an inherent fascination with the contributions of adult neural plasticity to behavior processes (e.g., learning and memory), as well as a growing appreciation for the potential therapeutic opportunities for neurogenesis in diverse neurological and psychiatric conditions. Research to date has primarily focused on adult neurogenesis as a dependent variable, asking what intrinsic or extrinsic factors affect rates of adult neurogenesis (or the various subcomponents of the phenomenon including cell proliferation, cell survival, phenotypic differentiation, or migration) in various brain regions. Thus, the field, while growing, has been heavily biased towards a proximate, mechanistic approach. But what of a more ultimate, functional approach? What are the effects on behavior when we alter endogenous levels of neuron production? Largely due to technological limitations, considerably less research to date has employed adult neurogenesis as an *independent* variable.

One example of this emphasis on mechanism is the study of the endocrine control of adult neurogenesis. There is tremendous value in understanding which hormones increase and decrease neurogenesis, to be sure, but this is also an excellent opportunity to ask more functional questions by considering the larger context of the organism as a whole, particularly for the endocrine players in the hypothalamic–pituitary–gonadal (HPG) axis and the hypothalamic–pituitary–adrenal (HPA) axis. Estrogens, androgens, and glucocorticoids all have significant effects on adult neurogenesis (reviewed in Galea et al., 2013). These hormones are highly conserved in mammals, do not typically operate in isolation, and are inextricably linked to the social environment of an organism, both influencing the expression of, and being altered by, socio-sexual behaviors. Thus, it is somewhat surprising that the social environment has received comparatively little attention as a mediator of adult neurogenesis and social behavior as a dependent variable has received even less.

One likely reason why social factors have received less attention in the study of neurogenesis is because of the complexity of social interactions. Indeed, these interactions are nuanced, complicated by the very fact that organisms are influencing each other, making

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it difficult to control variability if using a social interaction as an independent variable. Is stimulus animal A really providing the same stimulus as animal B? This is obviously further complicated as social groups increase in size. No matter how much one experimentally controls for size, sex, age, number of conspecifics, and even social phenotype, you cannot control for what exactly happens between two or more individuals. One way of partially addressing this is, of course, the use of inbred laboratory rodents, which lack the genetic variability seen in natural animal populations. Even so, these animals still show individual differences in social behaviors and can often be categorized into distinct social phenotypes (e.g. maternal behavior; reviewed in Champagne, 2011). Similar to the hesitation of including female subjects in research because of hormonal cycling – and the misconception that this introduces too much variability (Prendergast et al., 2014) – there might be resistance to studying animals in social groups. But because most animals are social to some extent, certainly when it comes to reproduction, understanding how the social environment sculpts the brain and, in turn, how social behaviors are influenced by neural plasticity, is critical for understanding the ultimate significance of adult neurogenesis (Gheusi et al., 2009).

An additional challenge when studying the relationship between social factors and neurogenesis is the diversity of social manipulations and how they may, or may not, relate to each other across experiments. What you are actually studying can be much more opaque than a particular dose of a particular drug. For example, opposite-sex interactions (e.g., reproduction) are often considered to be "positive" or rewarding while same-sex interactions (e.g., competition or aggression) are more "negative" or stressful. Similarly, social contact or enrichment is considered positive while social isolation is stressful. Whether these classifications are correct depends on the age, sex, experience, and social status of the animals involved. The valence of social stimuli is highly plastic across context within species (e.g., Bell et al., 2013), meaning we must be cautious when making generalizations about social variables. This is particularly salient for the study of neurogenesis, a process that is sensitive to variables indirectly related to social interactions (e.g., physical activity and environmental complexity; reviewed in Olson et al., 2006). The use of creative experimental design and adequate control groups can help in this regard. For example, by housing animals in alternating environments, each differing on some variable that influences neurogenesis (e.g., environmental complexity, running activity, social complexity), Gregoire et al. (2014) attempted to tease apart the complex variables contributing to environmental enrichment-induced increases in neurogenesis using adult male mice, concluding that social interactions have relatively mild yet significant effects on neurogenesis by increasing neuroblasts in the dentate gyrus (DG).

Adding yet another level of complexity to the story are species-specific social adaptations. When comparing across species, even between laboratory rats and mice, we are rarely comparing apples to apples. So, what are we really studying? What is baseline? Did the species under investigation evolve to live in small or large social groups? Of mixed age and sex? It is very likely that laboratory housing does not mirror natural conditions. For example, laboratory rats (*Rattus norvegicus*) and mice (*Mus musculus*) are both highly social species in the wild (reviewed in Balcombe, 2010). Standard laboratory housing typically fails to provide the complex social groups in which they evolved and, as a result, various social behaviors are altered between domesticated rats and mice and their wildtype counterparts (e.g., social play: Himmler et al., 2013; social dominance: Boreman and Price, 1972). Even more extreme, species can exhibit intraspecific variation in social systems (e.g., monogamy versus polygamy) depending on context, which is closely linked to circulating HPG and HPA hormones (Lott, 1986). Collectively, this means that different social manipulations will mean different things to different species at different times. For example, social isolation might be stressful in some contexts but a release from stress in others. Fortunately, comparing closely related species of voles or mole-rats where some members within the family are gregarious and others are not provides a very rich opportunity to study the neural and endocrine mechanisms underlying mammalian social behavior (e.g., Kalamatianos et al., 2010; Ross et al., 2009). Indeed, it is this comparative approach that will shed light on general principles of neurogenesis (Amrein et al., 2008), but the existing literature also needs to be viewed through this lens (Fig. 1).

The use of exogenous markers of cell division, most commonly 5-bromo-2′-deoxyuridine (BrdU), is a powerful way to pinpoint the time of cell birth, revealing much about factors that influence cell proliferation and survival. However, there is huge experimental variation in how various thymidine analogs are used, including dose, number of injections, and timing of administration relative to experimental stimulus, all of which influence the labeling of dividing cells and, undoubtedly, interpretation of data (Leuner et al., 2009). This variability can be partially addressed by the use of endogenous markers (e.g., Ki67 or doublecortin, DCX) though variability still exists in antibody binding, particularly

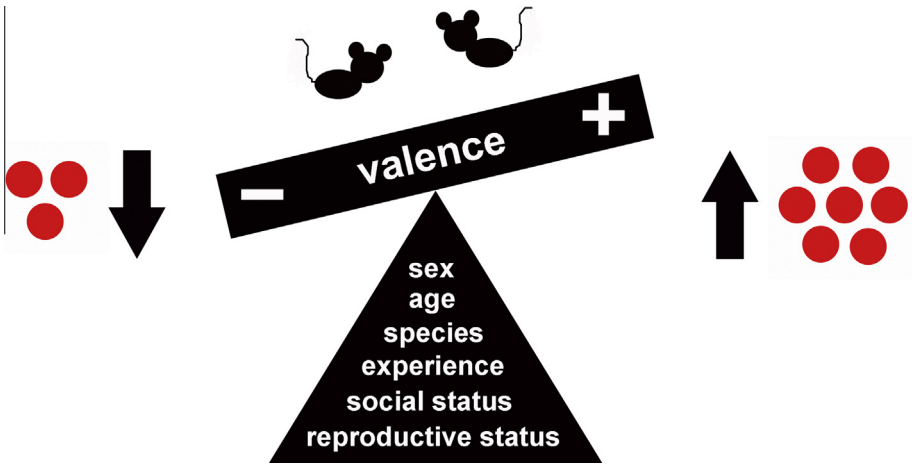

Fig. 1. Social interactions influence adult neurogenesis in diverse mammalian species. Factors including sex, age, species-specific social adaptations, social experience, social status, and reproductive status contribute to the valence of a given social manipulation. In general, "negative" social interactions inhibit neurogenic processes (cell proliferation, survival, and/or differentiation) while "positive" social interactions enhance neurogenesis.