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Of Mice and Men

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DOI: 10.1523/ENEURO.0280-17.2017

Received: 9 August 2017

Accepted: 17 August 2017

Published: 31 August 2017

Author Contributions: M.S. Performed Research and Wrote the paper; M.A.W.o.M. Wrote the paper.

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Cite as: eNeuro 2017; 10.1523/ENEURO.0280-17.2017

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Of Mice and Men: Empirical Support for the Population-Based Social Epistasis Amplification Model (A Comment on Kalbassi et al., 2017)

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Significance Statement:

This commentary article offers new perspective on recent research investigating the behavioral and social ecological effects of a mutation related to autism spectrum disorders in mice. The authors explain the consistency of this research on mice with predictions advanced by a theory of the role of interorganismal gene-gene interactions (social epistasis) in social species including humans, known as the social epistasis amplification model. The potential significance of the mouse research for understanding contemporary human behavioral trends is explored.

Kalbassi et al. (2017) examined whether and how mice carrying a behavior-altering mutation change their social ecologies. Specifically, the authors investigated the effect of deletion of the gene *Nlgn3*, which is related to autism spectrum disorders, on the phenotypes of both "*Nlgn3* knockout mice" and their "wild-type littermates" (i.e. mice without the deletion of *Nlgn3*) with which they were raised (p. 1). The authors determined that litters containing male mice both with ($Nlgn3^{y/-}$) and without ($Nlgn3^{y/+}$) deletion of *Nlgn3* were substantially different from litters containing only $Nlgn3^{y/+}$ mice (the authors also examined litters containing only $Nlgn3^{y/-}$ mice and various litters of female mice, but this comment does not focus on these cases). Among the more striking findings are that the genotypically mixed compared to homogeneous litters lacked "a structured social hierarchy" (p. 9) and had lower levels of testosterone (in both $Nlgn3^{y/-}$ and $Nlgn3^{y/+}$ mice); additionally, $Nlgn3^{y/+}$ mice from genotypically homogeneous litters showed more interest in "social" as opposed to "non-social cues" (p. 9) than $Nlgn3^{y/+}$ mice from genotypically mixed litters (the latter did not show a preference for one type of cue over the other, "showing an absence of interest for social cues" [p. 9]). However, "re-expression of *Nlgn3* in parvalbumin-

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expressing interneurons in *Nlgn3*$^{y/-}$ mice rescues their social submission phenotype and the corresponding effect on the wild-type littermates" (p. 2). The authors infer that their findings, taken collectively, indicate not only an effect of deletion of *Nlgn3* on the phenotypes of mice carrying the mutation, but also on *Nlgn3*$^{y/+}$ mice with which the carriers are raised. (Kalbassi et al. [2017] also note that it appears not only that *Nlgn3*$^{y/-}$ mice affect the phenotypes of *Nlgn3*$^{y/+}$ mice, but that the latter affect the phenotypes of the former.)

These results should be considered in the context of the broader body of theoretical and empirical work with which they are consistent. Most saliently, a paper published earlier this year integrated a great deal of research on social epistasis, i.e. interorganismal gene-gene interactions, and mutation load in humans, mice, and other organisms to develop the novel thesis that the fitness costs of the accumulation of certain kinds of deleterious mutations under conditions of relaxed negative selection in humans are externalized onto non-carrier individuals and thereby amplified via the damage that these mutations do to populations' "group-level extended phenotype[s]" (Woodley of Menie, Sarraf, Pestow & Fernandes, 2017). This theory, which was termed the *social epistasis amplification model*, is based partly on the biological literature concerning eusocial insects, in which the term "social epistasis" was coined (Linksvayer, 2007). Research on such insects has found that the adaptively optimal development of members of different castes in insect societies depends on certain inter-caste genotypic interactions, or social epistases. Thus both the individual- and group-level fitness of eusocial insects, insofar as both are contingent on (inter- and intra-) caste structure and cooperation, depend upon the existence of particular social distributions of genotypes and epistatic interactions among them. This fact suggests the possibility that, as a general rule, social species, including humans, require certain

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patterns of interorganismal genetic interaction to achieve and maintain adaptive optima at the individual and group levels.

In the same way that the *Nlgn3*$^{y/-}$ mice damaged their immediate community ecology, e.g. by inhibiting the development of normal social hierarchies and driving down the testosterone levels of their *wild-type* litter-mates, it is possible that the carriers of behavior-altering mutations in contemporary human populations reduce the fitness of their non-carrier counterparts and depress group-level fitness overall in a similar fashion. The mutations characterized by Kalbassi et al. (2017) were hypothesized to exist in Woodley of Menie et al. (2017), where they were described with the term *spiteful mutations.* Such mutations degrade the fitness of their carriers, but also incur opportunity costs on the fitness of conspecifics with whom they enter into social epistatic transaction, e.g. by imposing sociocultural conditions that disincentivize procreation (note, Kalbassi et al. [2017] found that the "courtship behavior" [p. 9] of *Nlgn3*$^{y/+}$ mice was not suppressed by exposure to *Nlgn3*$^{y/-}$ mice, indicating that deletion of *Nlgn3* reduces fitness, to the extent that it does, mostly via interference with social dominance behavior). Woodley of Menie et al. (2017) ran population-based models to explore the effects of spiteful mutations, which found that under relaxed negative selection, these mutations reach fixation because population growth offsets their individual-level fitness costs. But once a critical prevalence of mutations is present, their negative impact on the fitness of non-carriers causes rapid population decline. With negative selection against the carriers of these spiteful mutations restored, population growth continues until a stable equilibrium is established. Thus Kalbassi et al. (2017) found, as Woodley of Menie et al.'s (2017) model predicts, that restoration of adaptive behavior occurred in mouse

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97 communities when *Nlgn3* was re-expressed in *Nlgn3*$^{y/-}$ mice (this restoration simulates the
98 effects of negative selection as reflected in Woodley of Menie et al.'s [2017] model).
99
100 Further, there is much empirical evidence that some human populations are experiencing
101 increasing loads of behavior-altering, and fitness-reducing, mutations. In Western populations,
102 the prevalence of a number of mental disorders associated with advanced paternal age (because
103 older fathers bequeath more mutations to their offspring than younger ones [Rahbari et al.,
104 2016]), most notably unipolar depression (Laursen et al., 2007) and autism (Kong et al., 2012),
105 has substantially increased from the 20th to 21st centuries (Twenge et al., 2010; Demeneix, 2017,
106 p. 97). Furthermore, schizophrenia, another disorder associated with paternally acquired *de novo*
107 mutations (Malaspina, 2002), may have been extremely rare prior to AD 1800 (Hare, 1988), but
108 became more common thereafter, possibly because 19th century industrialization lowered the
109 fitness costs associated with the disease. These secular trends, and others suggesting a rising rate
110 of sub-clinical behavioral abnormalities also (e.g. Greenfeld, 2013, pp. 621-622), could indicate
111 a growing prevalence of spiteful mutations in these populations. Additionally, Kalbassi et al.'s
112 (2017) linking of the presence of *Nlgn3*$^{y/-}$ mice to testosterone decline across the board in their
113 communities yields a compelling potential explanation for the observation of significantly
114 declining testosterone levels in Western males (Travison et al., 2007) and, perhaps resultantly,
115 diminished sperm quality, which has been falling precipitously for at least the past few decades
116 (Levine et al., 2017). Certain cultural changes, such as secularization, have also been connected
117 to fertility decline at the group and individual levels (Meisenberg, 2011), and there is also
118 evidence that irreligiosity is associated with behavioral and physical abnormalities indicative of
119 higher relative burdens of deleterious mutations (E.C. Dutton, personal communication).

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120 Religion is a group-level adaptation in humans (Wilson, 2002), as is social hierarchy in mice
121 (van den Berg, Lamballais & Kushner, 2015). Thus the carriers of spiteful mutations may disrupt
122 the patterns of social epistasis that sustain religiosity and other group-level adaptations, and
123 consequently lower fitness.
124
125 Woodley of Menie et al. (2017) predicted that results similar to Kalbassi et al.'s (2017) would be
126 found in mice subjected to the proper experimental design. Kalbassi et al. (2017) are to be
127 commended for devising a better procedure than that contained in the provisional experiment
128 offered by Woodley of Menie et al. (2017) — which was based on a variant of the "mouse
129 utopia" experiments of Calhoun (1973) — wherein two mice colonies were to be bred under
130 cornucopian conditions. The colony serving as a control would be an effective replication of
131 Calhoun's own "mouse utopia," where, like Calhoun's colony, the mouse population would
132 presumably cycle through to collapse. However, the experimental colony would be treated with
133 *CRISPR* (a gene-editing technology) to remove deleterious mutations. If the experimental colony
134 could be indefinitely sustained and avoid the population collapse of the control colony, this
135 would strongly evidence that deleterious mutation accumulation, permitted by conditions of
136 minimized morbidity and mortality, is the cause of the control colony's breakdown. Since
137 Kalbassi et al. (2017) observed that adaptive behavior was restored in communities with both
138 $Nlgn3^{y/-}$ and $Nlgn3^{y/+}$, and that restoration occurred in both types of mice, when *Nlgn3* was re-
139 expressed in $Nlgn3^{y/-}$ mice, they have effectively demonstrated what Woodley of Menie et al.'s
140 (2017) proposed experiment was predicted to show.
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Finally, an interesting extension of the experiments of Kalbassi et al. (2017) would be to set up competition over limited resources (such as restricted access to food, territory, etc.) between differentially tagged groups of male mice (one group genotypically heterogeneous [containing *Nlgn3*$^{y/+}$ and *Nlgn3*$^{y/-}$ mice] and the other homogeneous [containing only *Nlgn3*$^{y/+}$ mice]). Given the suppressing effect of the presence of *Nlgn3*$^{y/-}$ mice on the testosterone levels of their *wild-type* littermates, and given the hierarchy avoidant behaviors that result, it is predicted that the homogeneous colony should outcompete the heterogeneous one indicating greater group-level fitness. Competing differentially tagged groups of mice that are composed only of *Nlgn3*$^{y/+}$ mice could serve as a control for such an experiment, as the outcome of the latter competition in terms of which group gains the upper-hand should be due to contingent factors and would therefore essentially be random.

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References

Calhoun JB (1973) Death squared: the explosive growth and demise of a mouse population. Proc R Soc Med 66: 80-88.

Demeneix B (2017) Toxic cocktail: how chemical pollution is poisoning our brains. New York, NY: Oxford University Press.

Greenfeld L (2013) Mind, modernity, madness: the impact of culture on human experience. Cambridge, MA: Harvard University Press.

Hare E (1988) Schizophrenia as a recent disease. Br J Psychiatry 153: 521-531.

Kalbassi S, Bachmann SO, Cross E, Roberton VH, Baudouin SJ (2017) Male and female mice lacking Neuroligin-3 modify the behavior of their wild-type littermates. eNeuro 4: 1-14.

Kong A, Figge ML, Masson G, Besenbacher S, Sulem P, Magnusson G, Stefansson K (2012) Rate of *de novo* mutations and the importance of father's age to disease risk. *Nature* 488: 471-475.

Laursen TM, Munk-Olsen T, Nordentoft M, Mortensen PB (2007) A comparison of selected risk factors for unipolar depressive disorder, bipolar affective disorder, schizoaffective disorder, and schizophrenia from a Danish population-based cohort. J Clin Psychiatry 68: 1673-1681.

eNeuro Accepted Manuscript

Levine H, Jørgensen N, Martino-Andrade A, Mendiola J, Weksler-Derri D, Mindlis I, Pinotti R, Swan SH (2017) Temporal trends in sperm count: a systematic review and meta-regression analysis. Hum Reprod Update: 1-14.

Linksvayer T A (2007) Ant species differences determined by epistasis between brood and worker genomes. PloS One 2: e994.

Malaspina D, Corcoran C, Fahim C, Berman A, Harkavy-Friedman J, Yale S, Goetz D, Goetz R, Harlap S, Gorman J (2002) Paternal age and sporadic schizophrenia: evidence for *de novo* mutations. Am J Med Genet 114: 299-303.

Meisenberg G (2011) Secularization and desecularization in our time. J Soc Polit Econ St 36: 318-359.

Rahbari R, Wuster A, Lindsay SJ, Hurles ME (2016) Timing, rates and spectra of human germline mutation. Nat Genet 48: 126-133.

Travison TG, Araujo AB, O'Donnell AB, Kupelian V, McKinlay JB (2007) A population-level decline in serum testosterone level in American men. J Clin Endocrinol Metab 92: 196-202.

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209 Twenge JM, Gentile B, Dewall CN, Ma D, Lacefield K, Schurtz, DR (2010) Birth cohort
210 increases in psychopathology among young Americans, 1938-2007: a crosstemporal meta-
211 analysis of the MMPI. Clin Psychol Rev 30: 145-154.
212
213 van den Berg WE, Lamballais S, Kushner SA (2015) Sex-specific mechanism of social hierarchy
214 in mice. Neuropsychopharmacology 40: 1364-1372.
215
216 Wilson DS (2002) Darwin's cathedral: evolution, religion, and the nature of society. Chicago,
217 IL: University of Chicago Press.
218
219 Woodley of Menie MA, Sarraf MA, Pestow RN, Fernandes HBF (2017) Social epistasis
220 amplifies the fitness costs of deleterious mutations, engendering rapid fitness decline among
221 modernized populations. Evol Psychol Sci 3: 181-191.
222