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Research report

The imposition of, but not the propensity for, social subordination impairs exploratory behaviors and general cognitive abilities

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ABSTRACT

Imposed social subordination, such as that which accompanies physical defeat or alienation, has been associated with impaired cognitive function in both human and non-human animals. Here we examined whether domain-specific and/or domain-general learning abilities (c.f. general intelligence) are differentially influenced by the imposition of social subordination. Furthermore, we assessed whether the impact of subordination on cognitive abilities was the result of *imposed* subordination per se, or if it reflected deficits intrinsically expressed in subjects that are *predisposed* to subordination. Subordinate and dominant behaviors were assessed in two groups of CD-1 male mice. In one group (Imposed Stratification), social stratification was imposed (through persistent physical defeat in a colonized setting) prior to the determination of cognitive abilities, while in the second group (Innate Stratification), an assessment of social stratification was made *after* cognitive abilities had been quantified. Domain-specific learning abilities were measured as performance on individual learning tasks (odor discrimination, fear conditioning, spatial maze learning, passive avoidance, and egocentric navigation) while domain-general learning abilities were determined by subjects' aggregate performance across the battery of learning tasks. We observed that the imposition of subordination prior to cognitive testing decreased exploratory tendencies, moderately impaired performance on individual learning tasks, and severely impaired general cognitive performance. However, similar impairments were not observed in subjects with a predisposition toward a subordinate phenotype (but which had not experienced physical defeat at the time of cognitive testing). Mere colonization, regardless of outcome (i.e., stratification), was associated with an increase in stress-induced serum corticosterone (CORT) levels, and thus CORT elevations were not themselves adequate to explain the effects of imposed stratification on cognitive abilities. These findings indicate that absent the imposition of subordination, individuals with subordinate tendencies do not express learning impairments. This observation could have important ramifications for individuals in environments where social stratification is prevalent (e.g., schools or workplace settings).

1. Introduction

Stress has been shown to be a potent modulator of the ability to learn and to express memories. However, the direction, degree, and duration of stress effects on cognitive abilities depends greatly on the characteristics of the stressor, the type of learning being assessed, and the social structure of an organism's environment [for reviews, see: 1–7]. The variability in reported stress effects on learning highlights the need to focus on stressors that are both ethologically relevant and conserved across both human and non-human animal species. Numerous mammalian species, including humans, live in complex social groups and are subject to intense and often unpredictable stress as a result of social interactions. As such, a relatively new area of study has emerged with the goal of investigating the learning effects induced by stressors that are primarily social in nature. One line of inquiry has focused on biobehavioral and learning challenges that arise consequent to social subordination.

In humans, subordination resulting from alienation or social defeat (e.g., bullying) has been shown to exert a negative influence on cognitive performance [8–15]. While these results are intriguing, human studies of social stress effects are limited. In the laboratory, researchers employ stressors that may be mild in comparison to the stress of actual life events. As such, the results from these studies may not fully demonstrate the impact of subordination on learning performance. Studies that examine natural instances of subordination stress in humans are similarly difficult to integrate within the larger phenomenon. For example, these

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studies often rely on self-reports or personal perceptions of subordination, which may not accurately reflect actual events. Further, prior history with aggression, environmental factors, and importantly, individual predispositions, may interact with instances of social subordination and may complicate the interpretation of effects on cognitive abilities and emotionality. Lastly, due to ethical constraints, it is difficult to probe the mechanisms that underlie changes in cognition in human participants. Studies of laboratory animals provide researchers with a greater degree of controllability over stressors and thus allow for a more detailed examination of the physiological substrates that may underlie alterations in cognition.

Animal studies examining the relationship between subordination and cognitive function have produced mixed results [16–21,23–28,30]. Commonly, two types of social subordination have been examined, i.e., imposed subordination or the innate predisposition toward subordination [16–21,23–28,30]. Imposed subordination refers to subordination (e.g., antagonistic encounters with conspecifics) that is inflicted upon the animals *prior* to assessment of cognitive function. In contrast, innate subordination (i.e., a natural predisposition toward subordination) is assessed *after* the assessment of cognitive abilities.

Imposed subordination has typically been observed to negatively impact learning abilities across several different measures [e.g., Spatial learning in a water maze or radial arm maze: 16, 21–25; reinforced alternation: 17; reference and working memory: 18–20]. Despite these observations, in many instances, imposed subordination has had no apparent effect on learning abilities [21,23–29].

In contrast to studies of imposed subordination, studies of innate subordination have been far fewer in number. Yet, like those examining imposed subordination, these studies have also provided mixed results [25,30]. One potential reason for these discrepant results is the variability in methodologies. However, it is also possible that certain forms of learning and memory are sensitive to social subordination while others are spared. Regardless of the source of the discrepancies, the mixed findings from these animal studies underscore the need for a more thorough examination of whether differences in learning abilities due to social subordination represent an innate predisposition toward subordination (of animals of lower cognitive abilities) or whether subordination-induced learning deficits arise in response to imposed subordination.

Studies of innate and imposed subordination to date have focused exclusively on domain-specific learning abilities (e.g., spatial learning). Yet, it has been established that both domain-specific (e.g., spatial abilities) as well as domain-general (general intelligence) factors influence cognition [31]. In humans, general intelligence or "*g*" has been called the "single most dominant cognitive trait ever discovered" [32], and the single factor that underlies *g* is purported to influence all domain-specific learning abilities. Like humans, CD-1 outbred mice express individual differences in their "general" cognitive abilities such that performance across tasks in a battery of diverse learning tests is positively correlated. Through the application of principal components analysis, a general learning factor can be identified that accounts for 25–48% of the variance in the performance of individual mice. This general learning factor in mice has been argued to be structurally and psychometrically analogous to general intelligence in humans [33–37].

To date, no animal studies have attempted to examine the relationship between social subordination and general learning abilities. Thus, one of the goals of the current experiment was to determine whether an individual subjects' domain-specific and/or domain-general learning abilities are altered by the imposition of social subordination (in a colony setting) in a manner similar to that seen in previous studies. Additionally, if cognitive differences do exist in animals that undergo subordination, we would determine whether they reflect the *imposition of subordination* or if they represent a disposition toward poor learning in animals that are *innately disposed to subordination*.

Domain-specific learning abilities were assessed on individual learning tasks while domain-general learning abilities were measured as the aggregate performance across a battery of learning tasks. Stress-induced levels of the adrenal hormone, corticosterone (CORT) were also measured since prior work has shown a differential activation of the HPA axis in subordinate and dominant subjects in response to stress [rats: 38,39; mice: 40–44; non-human primates 44–49; humans: 50,51]. Specifically, it is has been suggested that upregulation of HPA activity, such as that seen in highly stressed animals, may lead to HPA dysregulation and a dysfunctional response to subsequent stress exposure. Further, CORT has been implicated as a possible modulator of cognitive function [for review see: 1–7] thereby making any observation of differences in its expression of particular interest. Behavioral measures of stress/anxiety also vary in subordinate animals versus dominant subjects [52–63]. Consequently, we assessed performance in the elevated plus maze [EPM], open field [OF] and light/dark discrimination tasks. Lastly, subjects that were stratified prior to cognitive assessments underwent testing in a battery of motor tests to ensure that any deficits in learning performance that are detected are not the result of motor impairment.

2. Materials and methods

2.1. Animals and housing

Forty-eight outbred, male, non-sibling CD-1 mice (Harlan Sprague Dawley Inc., Indianapolis, IN) weighed 25–30 g and were 40–45 days of age upon arrival in our laboratory. Since animals were obtained pre-pubescence, it is generally accepted that they would not had yet stratified into social hierarchies. Subjects were non-littermates, since previous work has revealed that aggressive behaviors are more readily expressed among rodents that are unrelated [64]. Upon arrival and prior to the start of the testing, all subjects were housed individually and maintained on ad libitum food and water (unless noted otherwise) in a temperature-controlled vivarium on a 12-h light/dark cycle. They were allowed to acclimate to the vivarium and were handled (removed from the home cage and held by the experimenter for 90 s/day) for three weeks prior to behavioral testing (which began at approximately 68 days of age).

2.2. Colonization procedure

Subjects were randomly assigned to one of two colonization conditions (imposed [IMP], $n = 24$, or innate [INN], $n = 24$]. Subjects in the imposed (IMP) group were housed in groups of three (i.e., triads) from 67–81 days of age. This imposed group colonization took place *prior* to testing in the learning battery so that the effects of social stratification on learning performance could be assessed. Subjects in the innate (INN) group were colonized (at 163 days of age) in triads *after* completion of testing in the learning battery (at 150 days of age) so that the relationship between innate tendencies toward subordination/dominance and learning performance could be examined and compared with any relationships between these factors that exists as a result of the imposition of subordinance or dominance (i.e., imposed group performance) prior to tests of learning. In both conditions, animals in each triad were matched for body weight (to within ± 1.2 g).

At the start of the colonization procedure, subjects were transported in their home cages to an isolated testing room (300 lx). To examine social interactions, three subjects were placed simultaneously in a neutral area, i.e., a novel standard shoebox cage lined with wood shavings. Behavior was observed in three evenly spaced 10-min sessions during the light cycle (07:00–19:00) and three 10-min sessions during the dark cycle (19:00–7:00). Between observations that occurred during the light cycle and those during the dark cycle, subjects were returned to their home cages. Subjects remained housed in triads until the termination of the colonization period (14 days). Rather than the two weeks of colonization incurred by the IMP subjects (where it was the intention to *induce* subordination prior to testing in the cognitive battery), subjects in the INN group (where it was the intention to assess subordination *after* cognitive abilities had been determined) were colonized for only16 h (after the completion of cognitive testing). This was done as it was determined from observations of group IMP that stratification of the colonized animals was complete after only 16 h of interaction. Thus after 16 h, social stratification could be accurately estimated, and exposing animals in Group INN to additional unnecessary aggression was deemed unwarranted. Timelines of the experimental procedures for the IMP and the INN groups are provided in Fig. 1. All behavioral interactions were recorded for offline measurement as detailed below.