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BEHAVIORAL AND NEUROENDOCRINE PLASTICITY IN THE FORM OF WINNER AND LOSER EFFECTS

Nathaniel S Rieger, Matthew J. Fuxjager, Brian C. Trainor, Xin Zhao, and Catherine A. Marler

Introduction

The social lives of animals are complex. Individuals living in large populations must not only navigate a variety of affiliative relationships but also a wide range of adversarial ones (Oliveira, 2009). Furthermore, one's social landscape is always in flux, changing in response to time of year, population density, and other stochastic environmental perturbations. Accordingly, behavioral and physiological/neural mechanisms that support social agility and flexibility should evolve to allow individuals to fine-tune their behavior. One way that research has focused on this framework is by studying two related phenomena that epitomize behavioral and physiological plasticity: the winner effect and the loser effect.

The winner effect is defined as an ability to win fights following the acquisition of prior social victories, whereas the loser effect is defined as an increased propensity to lose fights following prior social defeat. Both behavioral processes are psychological in nature, and thus each potentially can occur independently of intrinsic fighting ability (Hsu & Wolf, 1999). Indeed, in an important synthesis of the winner and loser effect literature, Hsu, Early and Wolf (2006) point out that individuals form a winner effect because they have a greater willingness to engage in a fight rather than by necessarily changing intrinsic ability to become faster or stronger. The same is thought to occur for the loser effect: individuals become more likely to lose because they perceive themselves as losers, as opposed to somehow becoming intrinsically slower or weaker.

Winner and loser effects are found in a wide variety of taxa, including mammals (Huhman et al., 2003; Oyegbile and Marler, 2005), reptiles (Schuett, 1997), birds (Apfelbeck, Stegherr, & Goymann, 2011; Drummond & Canales, 1998; Popp, 1988), fish (Bakker, Feuthdebruijn, & Sevenster, 1989; Bakker & Sevenster, 1983; Beacham, 1988; Beaugrand, Goulet, & Payette, 1991; Chase, Tovey, Spangler-Martin, & Manfredonia, 2002), and invertebrates (Bergman et al., 2003; Hoefler, 2002; Whitehouse, 1997). Some work even suggests that humans form winner and loser effects (Yee, Bailenson, & Duchenaut, 2009), while other studies have considered how these effects can ripple out and have broader effects on social behavior (Coates, Gurnell, & Sarnyai, 2010). Additionally, meta-analyses of these two phenomena point out that they need not occur together – some species might show a loser effect, but not a winner effect (Hsu et al., 2006;

Mesterton-Gibbons, 1999). This suggests that while these processes are conceptually related, they are not necessarily opposite sides of the same coin. Such insight likely has implications for the physiological and neurobiological mechanisms that underlie both effects (see below). Regardless of these considerations, the taxonomic breadth in which we see evidence of robust winner and loser effects implies that these phenomena are not isolated traits that co-evolve with select aspects of social biology but instead occur in a diverse array of species that employ numerous social traits. In this way, we suspect that the winner and loser effect are relatively important behavioral mechanisms that likely help individuals contend with their environment.

However, little is actually known about the functional significance of the winner and loser effects. Few studies measure such phenomenon in free-living animals, where their direct or indirect impact on reproductive success can be measured (Rutte, Taborsky, & Brinkhof, 2006). This shortcoming means that the adaptive value of either the winner or loser effect is unclear; nonetheless, the prevailing thought is that these two events help individuals make appropriate decisions about when to engage in aggressive interactions and when to avoid them. Some of the studies highlighted below support this point of view, showing that the winner effect develops only when individuals accrue victories while defending their own territories (as reflected by the residency effect in the laboratory) (Fuxjager & Marler, 2010; Fuxjager, Mast, Becker, & Marler, 2009). In other words, the familiarity or contextual saliency of the immediate social environment might serve as a "switch" to potentiate changes in one's psychological state that occur after winning a fight, and that can lead to future aggression, agonistic persistence, and territorial vigilance. Such effects are likely adaptive because they help individuals acquire resources and reproductive opportunities. Other studies echo this finding by showing that the winner effect forms in species where the breeding environment is characterized by frequent agonism, such that only winners acquire mates (Oliveira, Silva, & Canario, 2009).

Winner and loser effects can provide other functionally important evolutionary benefits, in addition to territorial ability. For example, studies in the green swordtail fish, *Xiphophorus helleri*, show that randomly selected individuals given social victories are more likely to become the dominant individual within a linear social hierarchy (Dugatkin & Druen, 2004). The opposite is true for randomly chosen individuals who are given losing experiences, in that these individuals are more likely to emerge as low-ranking individuals. This work therefore suggests that winner and loser effects play an important role in the emergence of hierarchies that, in turn, maintain social stability within a population.

Another notable study with respect to the evolutionary significance of the loser effect is documented in crickets (Hofmann & Stevenson, 2000). When males fight, they perform a stereotyped sequence of escalating events, which end with wrestling. Either opponent can retreat at any phase of this escalation, and the one who does (the loser) displays a strong tendency to avoid further conflicts. However, this loser effect completely disappears once the loser begins to fly. Even more intriguing is that this effect does not occur when the cricket is tumbled around in a tube – it must fly to remove the loser effect. This can be traced back to the effects of a thoracic central pattern generator that controls flying in this species; once it is activated, it appears to reset the brain for aggression. These data therefore suggest that the loser effect of a cricket is purely place and time dependent, in that the phenomenon is easily erased once a losing individual relocates and has to re-establish residency. In nature, this effect likely helps individuals avoid costs associated with contests in which loss is inevitable, but still provides flexibility to allow crickets to "turn on" aggression when those costs are not severe.

With these considerations about the nature of winner and loser effects in mind, we can begin to ask how each is manifested at the physiological and neurobiological level. Indeed, for each to unfold and develop, changes in the brain must somehow underlie one's ability to "reconsider" the costs associated with aggression. Below we review these mechanisms.

Winner and loser effects in California mice

The monogamous and territorial California mouse (*Peromyscus californicus*) is developing into a unique model by which to understand winner and loser effects (Oyegbile & Marler, 2005; Fuxjager et al., 2009; Fuxjager & Marler, 2010). Both males and females strongly defend exclusive territories (Ribble, 1992), and both exhibit high levels of aggression towards the same and opposite sexes (Davis & Marler, 2003; Oyegbile & Marler, 2005; Fuxjager, Zhao, Rieger, & Marler, 2017; Rieger & Marler, 2018). Upon pair bonding, males and females share and defend a territory (Ribble, 1992), and whether an individual is in the home territory (resident) or a novel territory plays a particularly important role in physical aggression and the formation of the winner effect. Importantly, changes due to winning occur at both the behavioral and neural levels and are dependent on the interaction of residency, experience and hormones. The less researched loser effect in California mice has been studied through the lens of social defeat that acts as a stressor following repeated defeat experiences. As in the winner effect, socially defeated California mice show distinct changes at the behavioral and neural levels, with changes based on hormones and experience. The effect of residency may also play a role in social defeat with residency and status acting to create resilience against losing (Morrison et al., 2014; Morrison, Curry, & Cooper, 2012), but this has yet to be studied in California mice. California mice therefore have an integration of behavioral, neural, and hormonal processes that help to form and maintain the winner and loser effects, making them an important species through which to parse out the effects of each of these inputs.

Importantly, the differences discussed above relating to behavioral changes in both the winner and loser effect are mirrored by hormonal and neural changes that occur as a result of winning or losing fights. Internal changes occur during a fight that can rapidly influence current behavior and/or buttress future behavior, and hormonal changes are one category of mechanism through which this can occur. These hormonal changes may be important both for a permissive role in adopting a behavioral change relevant to a current social interaction, as well as modifying or stimulating neural mechanisms for maintaining long-term changes. Thus far, however, winner and loser effects do not appear to be controlled by the same behavioral and neuroendocrine mechanisms, and this is explored in detail below. Furthermore, aspects of the reward system may play a vital role in the formation and maintenance of these phenomena.

Winner effect

Behavioral mechanisms of the winner effect

The experience of winning fights is central to the formation of the winner effect (Hsu et al., 2006). The more fights an individual male California mouse wins, the more likely that individual is to win subsequent encounters against same sex conspecifics. While aggression has been studied in female California mice, the winner effect has yet to be studied. Specifically, laboratory studies have shown that winning three training fights leads to a robust winner effect being expressed in a subsequent fourth test fight (Fuxjager & Marler, 2010; Oyegbile & Marler, 2005). Subsequent aggressive encounters following a fight are marked by quicker attack latencies and greater overall aggression shown towards intruders (Trainor, Bird & Marler, 2004). Winners are also more likely to seek out aggression in the future, indicating an increased motivation to fight (Fuxjager & Marler, 2009; Fuxjager, Forbes-Lorman, et al., 2010; Hsu et al., 2006). This leads males to become more efficient at winning during fights as denoted by the winner index, a measure of the number of attack behaviors and submission behaviors completed by an individual during a fight.

The full formation of the winner effect also requires residency, a so-called home field advantage. In order to form the full winner effect, mice need both winning experience and for those experiences to happen in their home cage (Fuxjager et al., 2009). Individuals who gained their winning experiences in a novel cage showed no differences in fighting ability from inexperienced resident mice. This indicates that winning alone is not sufficient for the full formation of the winner effect. We therefore speculate that individuals are assessing their physical environment and perhaps weighing the costs and benefits associated with defending a site in a particular environment, such as an established territory that is both familiar and contains necessary resources. Studies of the closely related but polygamous and non-territorial white-footed mouse (*Peromyscus leucopus*) show that resource abundance can also affect contest outcome, with individuals who hold greater resources such as food winning more often (Fuxjager, Montgomery, Becker, & Marler, 2010) However, resource abundance shows no interaction with residency. As such, it is likely that the effect of resource abundance and the effect of experience on winning is controlled, at least in part, by different neural mechanisms. This indicates that the interaction of residency specifically with experience leads to the full formation of the winner effect and not other environmental factors (Fuxjager, Forbes-Lorman, et al., 2010; Fuxjager, Montgomery, et al., 2010; Fuxjager, Oyegbile, & Marler, 2011). This strongly ties the winner effect with residency and territoriality and indicates that the winner effect may act as a way to reinforce aggression to help maintain territories in the face of challenges.

The above described winner effect research has not incorporated the role of vocalizations and how these could be involved in the formation and maintenance of the winner effect, including the ability to communicate willingness to escalate in an aggression encounter. While we have not specifically studied the accrued effects of multiple encounters on vocalizations, we have examined vocalizations within single aggressive social interactions. California mice produce ultrasonic vocalizations (USV) in a variety of social contexts. One vocalization that shows sexual dimorphism and functions during aggression during laboratory territorial defense is the sustained vocalization (SV: previously referred to as syllable vocalizations; Kalcounis-Rueppell, Metheny, & Vonhoff, 2006; Rieger & Marler, 2018). SVs are long, low-bandwidth calls at a frequency of ~22 kHz; these vocalizations can vary in terms of total number of calls (previously referred to as syllables; Kalcounis-Rueppell, Pultorak, & Marler, 2018), duration, and calls per bout (previously referred to as syllables per phrase). Total SV calls produced by residents prior to the onset of physical aggression increased in males compared to females and predicted resident defensive behavior (Rieger & Marler, 2018). Resident SV calls therefore may act as a signal to intruders, possibly of motivation to fight that in turn alters intruder behavior. Moreover, during the transition from pre-fight to fighting, SVs are shortened. The degree of shortening of SVs predicts total offensive aggression by residents, thus corresponding with an escalation in physical aggression. Finally, along with shortening duration of calls, the number of calls per bout also decreases from pre-fight to fighting. We therefore see that the production of vocalizations prior to an aggressive encounter is increased in residents, and likely plays a role in territoriality (Rieger & Marler, 2018). An important future direction would be to study vocal signals in the context of the winner effect. For example, shortened SV duration could be used by prior winners to enhance the signals they send to intruders to convey motivation to fight or fighting quality.

AuQ2

We have alluded to residency as being critical for the development of the winner effect. A fundamental component of residency is that it is a preferred location such as a territory that needs to be defended. We hypothesize that the formation of conditioned place preferences (CPPs) may contribute to both the development of residency and increased aggression in that location. The conditioned place preference paradigm is classically used to examine the rewarding or addicting properties of a drug as a mechanism for conditioning an individual to a specific location (Tzschentke, 2007). Several lines of evidence suggest that attacking or experiencing victory can be rewarding and facilitate the association between the rewarding properties with the environmental cues (Fish, DeBold, & Miczek, 2005; Fish, Joseph, & Miczek, 2002). For example, in a T-shaped maze, focal male mice can learn to discriminate between the side that contains a submissive male from another strain versus the control side (Tellegen & Horn, 1972; Tellegen, Horn, & Legrand, 1969) and can run faster to the side conditioned with the submissive male for the opportunity to defeat the submissive mouse (Legrand, 1970). Martínez, Guillén-Salazar, Salvador, and Simón (1995) further found that mice can acquire a CPP for the initially less-preferred compartment wherein they defeated the submissive mouse. A similar effect was also observed in green anole lizards (*Anolis carolinensis*) that prefer an environment in which they exhibited aggressive behavior toward the reflection of themselves in a mirror (versus the nonreflective back of the mirror; Farrell & Wilczynski, 2006). From an evolutionary perspective, the development of the CPP may reflect an animal's natural capacity of associating aggressive and/or winning experience with a particular location. We speculate that the formation of CPPs could naturally contribute to the establishment or the consolidation of the residency effect (Fuxjager & Marler, 2009).

Neural and hormonal mechanisms of the winner effect

Testosterone

Winning encounters produces a significant change in androgens in individuals across species and taxa (Elekonich & Wingfield, 2000; Hau, Wikelski, Soma, & Wingfield, 2000; Jasnow, Huhman, Bartness, & Demas, 2000; Sperry, Wacker, & Wingfield, 2010; Trainor & Marler, 2001; Wingfield, Hegner, Dufty, & Ball, 1990). Most notably, individual male California mice that win fights in their home cage display increased testosterone levels 45 minutes following their winning experience, referred to as a testosterone-pulse (Oyegbile & Marler, 2005; Marler, Oyegbile, Plavicki, & Trainor, 2005). If an individual does not win, or wins in an unfamiliar environment, these testosterone-pulses do not occur (Fuxjager & Marler, 2010), illustrating that experience, environment, and hormonal mechanisms are required for the full formation of a winner effect. Moreover, testosterone-pulses are required to see an increase in aggressive behaviors in later fights following winning experiences. Castrated males that received testosterone implants to maintain baseline levels of testosterone but received post-victory saline showed no changes in future aggressive behavior. In addition, animals that received aromatase inhibitors, which prevent the conversion of testosterone to estrogen, still display increased aggression in later fights, suggesting that this experience dependent system is also androgen dependent (Trainor et al., 2004).

Interestingly, in the non-territorial and polygamous white-footed mouse, winning experiences do not alter testosterone. This species difference in post-victory hormone changes accounts for the formation of the winner effect in California mice but not white-footed mice (Oyegbile & Marler, 2006, Fuxjager & Marler, 2010). However, exogenous post-victory testosterone-pulses in white-footed mice induces a winner effect, thereby eliminating species differences in winner effect formation (Fuxjager, Oyegbile, & Marler, 2011). This provides evidence that pulsatile

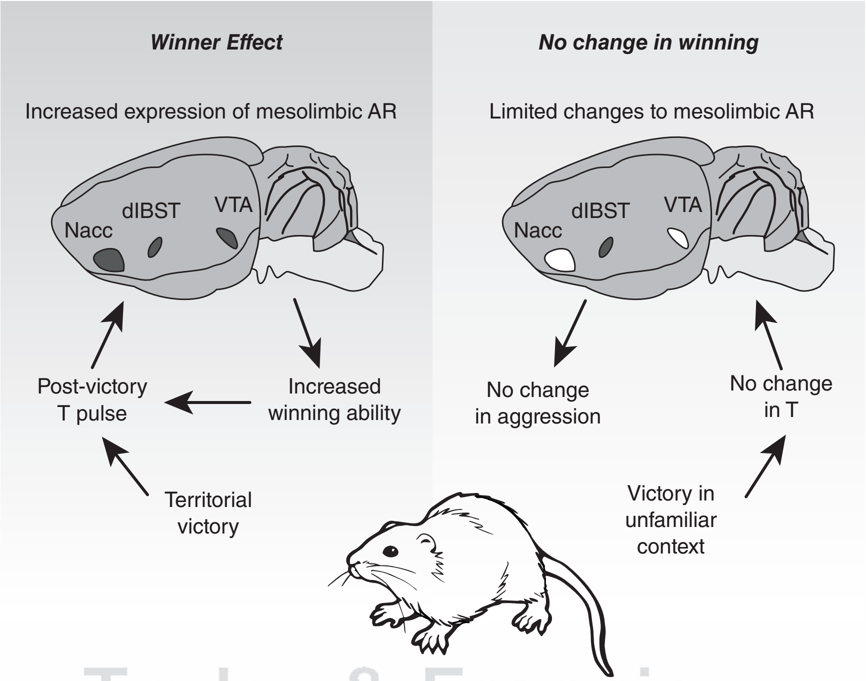

Figure 5.1 Inputs required for the winner effect in California mice. The winner effect in California mice requires multiple inputs in order to be fully realized. First, victory in an aggressive encounter must occur in a home territory. This leads to a pulse of testosterone that, in turn, increases expression of mesolimbic androgen receptors in the nucleus accumbens, dorsolateral bed nucleus of the stria terminalus, and ventral tegmental area. These changes taken together lead to increased likelihood of winning future fights. If victories occur in a novel territory, a testosterone-pulse does not occur and mesolimbic androgen receptors remain mostly unchanged.

testosterone cements the winning experience and creates the neural and psychological changes necessary for the winner effect to take hold. As such, one key to the formation of the winner effect may be the release or response to post-victory testosterone.

Testosterone-pulses following winning experiences lead to changes in androgen receptor patterns across the brain. In the bed nucleus of the stria terminalis (BNST) androgen receptors are increased following victories either in the home cage or a novel cage (Fuxjager, Forbes-Lorman, et al., 2010). This indicates that the BNST is related to aggression and winning in general but not necessarily to territoriality. Androgen receptors in the nucleus accumbens (NAc) and the ventral tegmental area (VTA) increase following wins that occur in the home territory only (Fuxjager, Forbes-Lorman, et al., 2010), indicating that these brain areas are likely vital to forming the winner effect in the context of residency. Changes in progesterone receptors following aggression in male California mice were not seen, suggesting that progesterone receptors do not play a role in the formation of the winner effect in males. We speculate that, because the NAc and VTA are tied to functions in reward and reinforcement, increased androgen receptors in these two areas may act to increase the intrinsic reward of fighting, thus increasing the motivation to fight in the future following winning experiences.

We also speculate that on a behavioral level, victory-induced testosterone-pulses contribute to residency via CPPs. On a hormonal level, testosterone has rewarding effects and can produce

CPPs to the environment where the testosterone-pulses are experienced. Early studies have reported that hormone replacement therapy for hypogonadal men has been associated with enhancement of mood (Davidson, Camargo & Smith, 1979; Stuenkel, Dudley, & Yen, 1991), and rises in plasma testosterone are positively correlated with self-reports of elation in male athletes (Booth, Shelley, Mazur, Tharp, & Kittok, 1989) as well as following a decisive victory in humans (Mehta, Snyder, Knight, & Lassetter, 2015). Animal studies further provide empirical evidence revealing the rewarding effects of T. For instance, anabolic androgenic steroids can be voluntarily consumed through oral (Wood, 2002), intravenous (Wood, Johnson, Chu, Shad, & Self, 2004), and intracerebroventricular (ICV) self-administration (DiMeo & Wood, 2004; DiMeo & Wood, 2006; Triemstra et al., 2008; Wood et al., 2004) in hamsters (*Mesocricetus auratus*). In addition, the CPP can be produced via subcutaneous (Alexander, Packard, & Hines, 1994) (De Beun, Jansen, Slangen, & van de Poll, 1992), intra-nucleus accumbens (Packard, Cornell, & Alexander, 1997), and intra-medial preoptic area injections of testosterone (King, Packard, & Alexander, 1999).

In male California mice, testosterone-induced CPP is dependent on the environment and pair-bonding experience (Zhao & Marler, 2014a; Zhao & Marler, 2016). Specifically, sexually naïve male California mice can only form testosterone-induced CPP to an unfamiliar environment, not the home environment. From the perspective of ecology, before forming pair bonds most sexually naive males are usually motivated to disperse up to 80 meters and establish ownership of a territory (Ribble, 1992). Therefore, the testosterone-induced CPPs observed in sexually naïve males may reinforce the allocation of time towards exploration of a less familiar environment (Hawley et al., 2013) and/or help to initiate territoriality. In contrast to the sexually naïve mice, pair-bonded males can only form testosterone-induced CPP to home, but not an unfamiliar environment (Zhao & Marler, 2016). For monogamous species, the pair bond is a marker for an important life history stage and affects several social behaviors (Gobrogge, Liu, Jia, & Wang, 2007; Insel, Preston, & Winslow, 1995; Pultorak, Fuxjager, Kalcounnis-Rueppell, & Marler, 2015; Becker, Petruno, & Marler, 2012). The testosterone-induced CPP to the home may reflect its natural function in maintaining or strengthening residency.

This also stands in line with the need to form the winner effect in paired males (Fuxjager, Forbes-Lorman, et al., 2010; Fuxjager & Marler, 2010; Fuxjager et al., 2009). Pair-bonded males have already established their own territories, where the interactions with the partner and familiarity with the environment may increase the salience of the territory. Through the location preferences, testosterone may further promote site-specific aggressive motivation that, along with the winning experience, results in increased expression of the winner effects. We speculate that the winner effect will further contribute to behaviors such as territorial defense and possibly mate-guarding behavior, which could eventually increase the individual fitness when expressed under appropriate conditions. In comparison, the absence of cues associated with residency and the female mate may make the unfamiliar environment less salient and inhibit male responses to the rewarding properties of testosterone and the formation of the winner effects.

Progesterone

Progesterone levels change following aggression that contributes to winning experiences. In females a progesterone challenge exists, wherein levels of progesterone exhibit a transient decrease after interacting with an intruder. Progesterone generally decreases aggression, and by decreasing the progesterone/testosterone ratio in females, aggression may be increased in future encounters (Davis & Marler, 2003). In males, progesterone also decreases following aggressive encounters (Davis & Marler, unpublished data) and likely also acts to help increase aggression. Despite this work on how progesterone contributes to aggression (an important component of winning experience) its role in winning is yet to be elucidated.

Vasopressin

Vasopressin, which acts as a central neuropeptide and has a role in aggression across species, has been shown to play a role in aggression and territoriality (Albers, 2012; Caldwell & Albers, 2004; Ferris, Albers, Wesolowski, Goldman, & Luman, 1984; Ferris, Meenan, Axelson, & Albers, 1986). Administration of a vasopressin antagonist lengthened attack latencies in fights that occurred in the home cage of California mice but not in neutral cages or in white-footed mouse fights (Bester-Meredith, Martin, & Marler, 2005). Along with this, California mice cross-fostered with white-footed mice show decreased levels of aggression compared to those raised by California mice. These cross-fostered California mice also show less vasopressin immunoreactive staining in the BNST, the supraoptic nucleus (SON), and the medial amygdala (MeA). Vasopressin has also been shown to play an important role in aggression in other species including Syrian hamsters. Administration of vasopressin to the anterior hypothalamus increases offensive aggression (Ferris et al., 1984). Following repeated victories, dominant hamsters show greater vasopressin V1aR receptor binding in the ventromedial hypothalamus than their defeated counterparts. These changes indicate that vasopressin plays an important role in the expression of aggression and may also play an important role in the formation of the winner effect which is yet to be fully understood. Future research should focus on the role of both vasopressin and oxytocin on aggression and the winner effect.

Dopamine

The winner effect is also driven by reward pathways, as is demonstrated through the role of dopamine in the formation of the winner effect. Dopamine activity has been implicated in a wide array of social behaviors, including dominance and aggression (Miczek, Fish, de Bold, & Almeida, 2002; Miller & Beninger, 1991; Winberg & Nilsson, 1992). The upregulation of gene expression of various dopamine-related proteins in the VTA has been demonstrated in male mice that won 20 encounters in succession (Bondar, Boyarskikh, Kovalenko, Filipenko, & Kudryavtseva, 2009). In male Syrian hamsters (*Mesocricetus auratus*), winning all 14 consecutive agonistic encounters results in increased TH-immunoreactivity (precursor of dopamine) in the lateral septum, BNST and the NAc shell, all brain areas associated with reward-like functions. Pharmacological antagonism of dopamine receptors in loci of the social brain network diminishes the seeking of the opportunity to fight as well as the intensity of aggressive behaviors (Couppis & Kennedy, 2008; Schwartzer & Melloni Jr, 2010). Within California mice specifically, dopamine is essential for the formation of the winner effect. The peripheral administration of D1- and D2-like receptor antagonists following a victory prevents the formation of the winner effect (Becker & Marler, 2015). Moreover, DA receptor antagonists reduce the amount of aggression that occurs during a fight with a competitive opponent (Becker & Marler, 2015). Taken together, these results indicate that dopamine activity following the experience of winning is vital to the formation of the winner effect.

As discussed above, the testosterone-induced CPP may contribute to the establishment or maintenance of the residency. It has been demonstrated that the testosterone-induced CPP can be blocked by peripheral or intra-accumbens injection of dopamine receptor antagonist, a-flupenthixol, suggesting the rewarding effects of testosterone are mediated through the dopamine system (Packard, Schroeder, & Alexander, 1998) and both dopamine D1 and D2 receptor subtypes are involved in the acquisition of testosterone-induced CPPs (Schroeder & Packard, 2000). All of these results suggest that the actions of dopamine contribute to the mechanisms underlying an animal's motivation to engage aggressively and win after previous winning behaviors.

Loser effect/social defeat

BEHAVIORAL MECHANISMS

Whereas winner effects facilitate aggression and promote engagement in future contests, loser effects are usually associated with behavioral strategies that reduce the possibility of aggressive conflict. Although the effects of losing per se have not been studied in California mice in the same level of detail that winning has (e.g., effects on the probability of winning an aggressive contest), research examining the effects of social defeat on behavior can provide insights into the behavioral and neurobiological changes that occur with adverse social experiences. Furthermore, since both male and female California mice exhibit aggressive behavior, the effects of social defeat has been studied in both males and females. Just as individual winning experiences produce unique neuroendocrine profiles in males (Marler et al., 2005; Zhao & Marler, 2014b) and females (Davis & Marler, 2003; Duque-Wilckens & Trainor, 2017), the experience of losing social encounters can also produce distinct behavioral and neuroendocrine responses in males and females (Steinman & Trainor, 2017; Trainor et al., 2011).

Male California mice exposed to three short bouts of defeat with aggressive, sexually experienced males develop an intriguing behavioral phenotype. First, defeated males confronted with an intruder in the home cage show increased fear behaviors such as freezing and decreased social approach behavior such as anogenital and social sniffing (Steinman et al., 2015, Trainor et al., 2011). These behavioral responses correspond well with other studies in hamsters (Jasnow, Davis, & Huhman, 2004) and mice (Kudryavtseva, Bakshtanovskaya, & Koryankina, 1991) that observe increases in submissive behavior after losing social interactions. Curiously, defeat does not reduce aggression in male California mice, although this might be dependent on testing conditions, including cage size (Steinman et al., 2015). The cage size for these studies is relatively small and may not provide sufficient opportunities for the resident to avoid an intruder. However, it seems likely that different neuroendocrine mechanisms drive aggression in males that have experienced defeat stress versus males that have not (Watt, Burke, Renner, & Forster, 2009). Aggression in males who have experienced defeat stress is not accompanied by anogenital sniffing, which provides important olfactory stimulation to offensive aggression circuits, and as such, assessment of the intruder is less likely to have occurred.

Whereas defeated males avoid social cues in the home cage, in a novel environment stressed males exhibit levels of social approach that are no different from unstressed males. While this degree of social approach following defeat stress is sometimes referred to as an "unsusceptible" (Krishnan et al., 2007) or "resilient" (Elliott, Ezra-Nevo, Regev, Neufeld-Cohen, & Chen, 2010) phenotype, these terms are probably not accurate descriptors for male California mice because their behavioral profiles differ based on residency status (Steinman et al., 2015, Fuxjager et al., 2011). Currently, it is unclear why social approach is not reduced by social defeat in a novel environment. One possibility mentioned earlier is that novel environments can remove the loser effect (Hsu et al., 2006). Intriguingly, forgetting or the extinction of a memory is an active neurobiological process that relies in part on the frontal cortex (Milad & Quirk, 2002). The ability to maintain social approach in novel environments could be a critical strategy for forgetting losing experiences and setting up a new territory. In a field setting, it is likely that young male California mice will be more likely to lose in social encounters with older, more experienced males. Similar to the winner effect (discussed above), exhibiting stronger submissive responses in familiar environments may be an effective strategy for avoiding territorial animals while social approach is likely an essential step towards establishing a new territory.

While defeated males have high levels of social approach in novel environments, defeated female California mice exhibit reduced social approach (Greenberg et al., 2014; Trainor et al., 2013) that is typically observed in social defeat models in other species. This response is typically interpreted as a loss of social reward because it frequently coincides with other changes in reward sensitivity such as reduced preferences for sucrose (Krishnan et al., 2007). Intriguingly, while females who have experienced defeat stress do not approach unfamiliar females, they remain vigilant as characterized by orientation towards a cage containing an unfamiliar female but not an empty cage, a behavior that is not seen in males. Whether this also occurs in a familiar environment in males or females is yet to be tested.

For vocalizations, it is unknown whether calls specific to losing exist, but we have identified sex differences in ultrasonic vocalizations associated with defensive aggression, a set of behaviors we would expect to be associated with losing. Barks, short high amplitude bursts of 18–22 kHz that begin and end in the audible range, are a hallmark of aggressive behavior and produced more by females than males. These bark calls correlate highly with defensive aggression and occur almost exclusively following the onset of physical aggression (Rieger & Marler, 2018) and may function in a manner similar to rat 22 kHz calls to prevent future aggression by residents by displaying the negative affect of the caller (Riede, 2013). We predict that with repeated losing experiences, California mouse barks become a more prevalent call type by which individuals look to mitigate the amount of aggression shown against them by residents. Such barks may provide an intriguing new area of research by which to understand aggressive behaviors, particularly from the perspective of the formation of loser effects.

Hormonal and neural mechanisms of the loser effect

Testosterone

While testosterone is vital to the formation of the winner effect, to this point there is little evidence that the loser effect and social defeat in California mice are driven by androgens or androgen receptors (Trainor et al., 2013). For example, while social defeat produces social withdrawal in females but not males, gonadectomy has no effect on social withdrawal following defeat stress (Trainor et al., 2013), indicating that circulating gonadal hormones do not play a major role in social withdrawal.

Progesterone

To this point the role of progesterone in the loser effect is unknown. Across the estrous cycle in female rats, proestrous females show an increase in hippocampal progesterone (Frye & Walf, 2004; Frye, Petralia, & Rhodes, 2000). Moreover, this increase in progesterone is correlated with anxiolytic behavior, including greater exploration during open field tests (Frye and Walf, 2004; Frye et al., 2000). The administration of progesterone to ovariectomized rats is also shown to reduce anxiety across a variety of behavioral tasks. As such, progesterone may play a role in reducing stress following social defeat, though this has yet to be tested.

Arginine vasopressin

Social defeat reduces the number of vasopressin positive cells in the PVN, SON and posterior BNST (Steinman et al., 2015). Decreases in immunoreactivity in the PVN coincide with decreased vasopressin mRNA as measured with real-time PCR. Decreases in vasopressin gene expression and immunoreactivity may be mediated by glucocorticoids, as glucocorticoids can reduce vasopressin transcription and immunoreactivity in the PVN (Davis et al., 1986). Male California mice that lost aggressive encounters have elevated corticosterone levels both in the active (dark) and inactive (light) phases (Trainor et al., 2011), a change not seen following winning experiences (Marler et al., 2005). While strong effects of losing were observed on vasopressin immunoreactivity, no effects of losing were observed on vasopressin V1a receptor (V1aR) binding across several nuclei known to modulate aggression such as the bed nucleus of the stria terminalis (BNST) and lateral septum (Duque-Wilckens et al., 2016). However, V1aR has important effects on aggression and social behavior. Infusion of vasopressin V1aR antagonists into the lateral ventricle reduces aggression in a familiar environment (Bester-Meredith et al., 2005). Thus, a decrease in vasopressin synthesis is consistent with the loss of normal patterns of aggressive behavior observed in stressed males. However, the specific sites of V1aR regulation on aggression have not yet been identified in California mice. However, in hamsters (Albers et al., 2006) and prairie voles (Gobrogge et al., 2007) activation of V1aR in the anterior hypothalamus increases male aggression in a resident intruder test. Interestingly, V1aR antagonist infused in to the medioventral BNST decreases social approach behavior in male California mice (Duque-Wilckens et al., 2016). Consistent with this, selective deletion of V1aR has also been found to reduce social interaction behavior in mice (Egashira et al., 2007). Thus, while losing does not appear to affect the expression of V1aR, decreases in vasopressin likely lead to decreased V1aR activity that could contribute to loser effects in males by decreasing both social approach (via the BNST) and aggressive behavior (possibly via the anterior hypothalamus). In female California mice, social defeat may work through oxytocin instead of vasopressin; social defeat had no effects on vasopressin immunoreactivity (ref) but can increase oxytocin immunoreactivity as well as the reactivity of oxytocin neurons in social contexts (Steinman et al., 2016).

Dopamine

Social defeat induces long-lasting increases in the activity of dopamine neurons within the VTA that project to the NAc (Trainor, 2011). This pathway is an essential component of neural circuits controlling motivation and is known to be dysregulated in psychiatric disorders such as depression (Russo & Nestler, 2013). As such, the effects of social stress on the VTA-NAc circuit have been heavily studied. While the impact of these neuroadaptations on winner and loser effects have not been directly tested, several lines of evidence indicate that hyperactivity in VTA dopamine neurons may profoundly affect how experience modulates aggressive behavior. Multiple studies in male rats (Anstrom, Miczek & Budygin, 2009) and mice (Krishnan et al., 2007; Razzoli, Andreoli, Michielin, Quarta, & Sokal, 2011) show that social defeat induces burst firing in VTA dopamine neurons. In vivo recordings show that burst firing of VTA dopamine neurons occurs in response to salient cues (Brischoux, Chakraborty, Brierly, & Ungless, 2009; Schultz, Dayan, & Montague, 1997). Although the exact function of this burst firing is still debated (Berridge, 2012; Schultz, 2016; Wise, 2006), it seems clear that disruption of this process (e.g. burst firing in the absence of salient cues) would interfere with normal motivational processes. Indeed, when optogenetic stimulation was used to normalize the activity of VTA neurons projecting to the NAc, normal social approach behavior was restored in male mice exposed to defeat stress (Chaudhury et al., 2013).

Beyond firing rate within the VTA-NAc pathway, the total dopamine context in the brain is also vital to social defeat and the loser effect. Analyses of total dopamine content illustrate that male California mice exposed to social defeat had higher levels of dopamine in the NAc than control males (Campi, Greenberg, Kapoor, Ziegler, & Trainor, 2014). Higher levels of dopamine could be driven by increased dopamine synthesis and release or simply a decrease in dopamine release. Counter intuitively, higher levels of the dopamine metabolites DOPAC and homovanilic acid (HVA) in defeated males suggest that defeat increases dopamine release. Curiously, infusion of dopamine D1 receptor agonist into the NAc that decreased social motivation in females had no effect in males (Campi et al., 2014). However, the effects of D1 receptor manipulations within the NAc have not been studied in a resident intruder test and this may reveal a context dependent role of dopamine related to territoriality. As discussed previously, both D1 and D2 receptors have important effects on the winner effect. Considering that both the NAc and VTA become more sensitive to androgens with winning experience, it seems likely that defeat-induced changes in dopamine signaling within the NAc would have important effects on this process. Female California mice exposed to social defeat also exhibit increased dopamine, DOPAC, and HVA levels within the NAc. Furthermore, D1 agonists infused in to the NAc are sufficient to reduce social motivation while D1 antagonist infusion can restore social motivation in defeated females. Again, further study is needed to determine whether changes in dopaminergic signaling would affect winning or losing in female California mice.

Conclusion

In the winner effect, both intrinsic and environmental factors interact to produce long-term behavioral and neural differences. The confluence of winning fights, residency, and increased post-encounter testosterone lead to an increased ability to win future fights. Moreover, these changes may apply more broadly than just altering the probability of winning or losing future encounters. These changes, especially relating to testosterone and residency, likely play a major role in territoriality as well as reward systems. As such, our understanding of the winner effect may lead to a broader understanding of the underlying processes of environmental stimuli and reward and how these are linked with the predictability of the environment. The responses of individuals to winning and losing experiences is intriguing because it allows us to understand the plasticity of behavioral interactions that allow individuals to adjust their behavior to adapt to both their current and future social interactions.

As knowledge about the loser effect accumulates, we can examine the similarities and differences through which these pathways change behavior and illuminate mechanisms underlying sex differences in behavior. The location of past and current experiences plays such an important role in the formation of the winner effect that it is likely to influence responses to social defeat and the loser effect as described earlier. A critical question is whether the winner effect can provide a buffer or counteract past exposure to losing or defeat stress and, if so, what the genetic and molecular underpinnings are for these interactions between complex behaviors that express such plasticity. More specifically, it would be extremely valuable to understand why male California mice exhibit such resilience in the face of social defeat. As research continues in understanding the neural mechanisms of the winner and loser effects, the hippocampus may prove to be an important additional brain area to target because of the importance of spatial location and memory for such long-lasting effects.

It is also important to note that the major results relating to the winner effect and social defeat presented in this chapter have been successfully replicated in multiple experiments using different approaches. In general, throughout these studies, sufficient sample sizes for animal studies were used (no less than *n* = 10 per group). These sample sizes are typically used for laboratory animal studies because the environments of the animals are controlled from birth, greatly reducing variability and helping to increase statistical power leading us to be highly confident in these results.

A behavioral component that has been lacking in many of these studies that would better mimic natural conditions is to provide animals routes through which they can escape or retreat from aversive stimuli. We expect highly social species to integrate information around them, assess their internal states, and to make decisions about how to make the most of social situations that they cannot escape. However, although research is lacking in this area, we would also expect individuals to employ decisions to escape those social situations when possible. Overall, while extensive behavioral plasticity has been found in the development of winner and loser effects, the plasticity is likely to be much greater as we expand the choices that individuals can make to exert more control over their environment.

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