Approach/avoidance conflict training reveals distinct behavioral phenotypes for conflict resolution.

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We recently introduced an approach/avoidance conflict task in which rats must choose between stepping onto a nearby platform to avoid a 2s shock predicted by a 30s tone, or pressing a lever for sucrose pellets (Bravo-Rivera et. al., GRC amygdala, 2017). Unlike our previous avoidance task where rats could obtain food between the shock-associated tones, here food was only available during a 30s light, which was co-presented with the tone. When presented with this light-tone conflict, 26% (19/70) of male rats spent all the tone on the platform and did not press for food (avoidance-preferring subgroup), 30% (21/70) engaged in excessive food-seeking showing little to no avoidance (food-preferring subgroup), and 44% (30/70) were able to accommodate both food seeking and avoidance by shifting their avoidance later in the tone (timer subgroup). Female rats showed similar percentages. We used the neural activity marker c-fos to assess activity profiles for each subgroup. The food-preferring subgroup showed decreased prefrontal c-fos density compared to the other two groups. This agrees with previous work showing a correlation between low prefrontal activity and increased reward sensitivity, impulsivity, and low anxiety levels (Rivalan et. al., 2010). Decreased PFC activity has also been correlated with decreased social interactions in rats (Hamilton et.al., 2010). Consistent with this, rats in the food-preferring subgroup showed decreased anxiety in the EPM ($F_{2,41}=7.65$, $p=0.002$) and impaired social interactions ($F_{2,40}=5.50$, $p=0.007$) relative to the other subgroups. Interestingly, the timer subgroup showed the highest PFC/Amygdala ratio of cFos density, consistent with prefrontal control of both foraging and avoidance. Next, we examined the factor of age. Developmental studies show that prefrontal pruning and myelination continues through P240 (Sturrock, R.R., 1980). Consistent with this, the food-preferring phenotype was less prevalent in older rats (5%, P180-P200, n=59) compared to younger rats (30%, P125-P140, n=70) (Chi sq= 15.77, $P<0.001$). This is consistent with a shift in older rats from ventrostriatal- to prefrontal-based decision making (Worthy et. al., 2012, Kolb et. al., 2012). Taken together, the approach of focusing on naturally occurring differences in approach/avoidance conflict, along with age and social factors, may provide insight into the circuitry of conflict resolution and its potential dysfunction in anxiety and addiction.

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Interrogating the projections of rostral prelimbic cortex that drive active avoidance.

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Active avoidance has recently garnered much interest; however, little is known about the neural circuits that drive avoidance. Using an avoidance task in which a rat can avoid a tone-signaled footshock by stepping onto a nearby platform (Bravo-Rivera, et al., 2014), we observed that pharmacological inactivation of the prelimbic prefrontal cortex (PL) delayed avoidance (Diehl et al., eLife, in press). Additionally, excitatory responses in rostral PL neurons (rPL) were correlated with platform entry. PL projections that drive avoidance remain largely unknown. Here, we assessed the role of rPL projections to ventral striatum (VS) or basolateral amygdala (BLA), two known targets of rPL (Sesack et al., 1989; Vertes, 2004), by either photoactivating with Channelrhodopsin (ChR2; 15-20Hz, 30 sec,) or photosilencing PL terminals with Halorhodopsin (Halo; 30 sec). Photoactivation of rPL-VS projections impaired the expression of avoidance (ChR2: 42.7% time on platform (n=11), eYFP-control: 77.6% (n=9), p=0.033). Photosilencing PL-BLA projections showed a trend toward impaired avoidance expression (Halo: 16% time on platform (n=5), eYFP-control: 26% (n=5), p=0.074). Moreover, photoactivation of rPL-BLA projections reinstated avoidance following extinction (ChR2: 25% time on platform (n=3), eYFP-control: 3% (n=3), p=0.005). These findings suggest that rPL projections to VS and BLA have opposing effects on avoidance and are consistent with recent cFos findings that avoidance retrieval activates PL-BLA projections but not PL-VS projections (Martinez-Rivera et al., Psychopharm., submitted). Additional experiments will determine whether photoactivating PL-BLA or silencing PL-VS projections impair or promote platform-mediated avoidance, respectively. Together, these findings suggest that distinct rPL projections exert bidirectional control over avoidance behavior.

The role of orbital/insular outputs in a rodent model of persistent avoidance

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Avoidance compulsions are commonly treated with exposure-with-response-prevention (ERP) therapy, in which patients are prevented from carrying out avoidant actions in response to triggers. To model excessive avoidance and ERP in rodents, we used a platform-mediated avoidance task in which rats learn to avoid a tone-signaled shock by stepping onto a nearby platform. This is followed by extinction with response prevention (Ext-RP) training, where the tone-shock association is extinguished over four days while access to the platform is blocked with a barrier (Rodriguez-Romaguera, et al., 2016). The barrier is then removed to test the transfer of extinction learning to avoidance behavior. We previously reported that pharmacological inactivation of the lateral orbitofrontal/agranular insular area (LO/AI) during the post Ext-RP test induced persistent avoidance in rats that would have otherwise not avoided (Rodriguez-Romaguera, et al., 2016). This suggests that projections of LO/AI are needed for the transfer of extinction to avoidance, but the targets of these projections are not known. To address this, we photo-inhibited LO/AI terminals in prelimbic cortex (PL), ventral striatum (VS), or basolateral amygdala (BLA) with halorhodopsin. Photo-inhibiting LO/AI-PL projections had no effect on the expression of avoidance, but induced persistent avoidance during the post-Ext-RP test ($F_{(1,14)} = 6.02$, $p= 0.03$), an effect that was maintained seven days later ($F_{(1,4)} = 13.20$, $p= 0.02$). There was no immediate effect of photo-inhibiting LO/AI projections to VS or BLA on avoidance, however seven days later, the LO/AI-BLA rats showed persistent avoidance without any additional laser exposure ($F_{(1,24)} = 6.85$, $p= 0.01$). Together, our findings suggest that activity in the projection from LO/AI to PL facilitates the execution of the appropriate avoidance decision at test, and induces plasticity in PL and BLA to maintain low levels of avoidance. Given that excessive harm-avoidant compulsions in OCD are associated with poor decision-making (Pushkarskaya et al., 2015), hypoactivity in the human homologue to rat LO/AI (vlPFC?) may promote these maladaptive behaviors.