

The reliance on inflexible versus flexible spatial learning strategies predisposes towards habitual but not compulsive behaviours in rats



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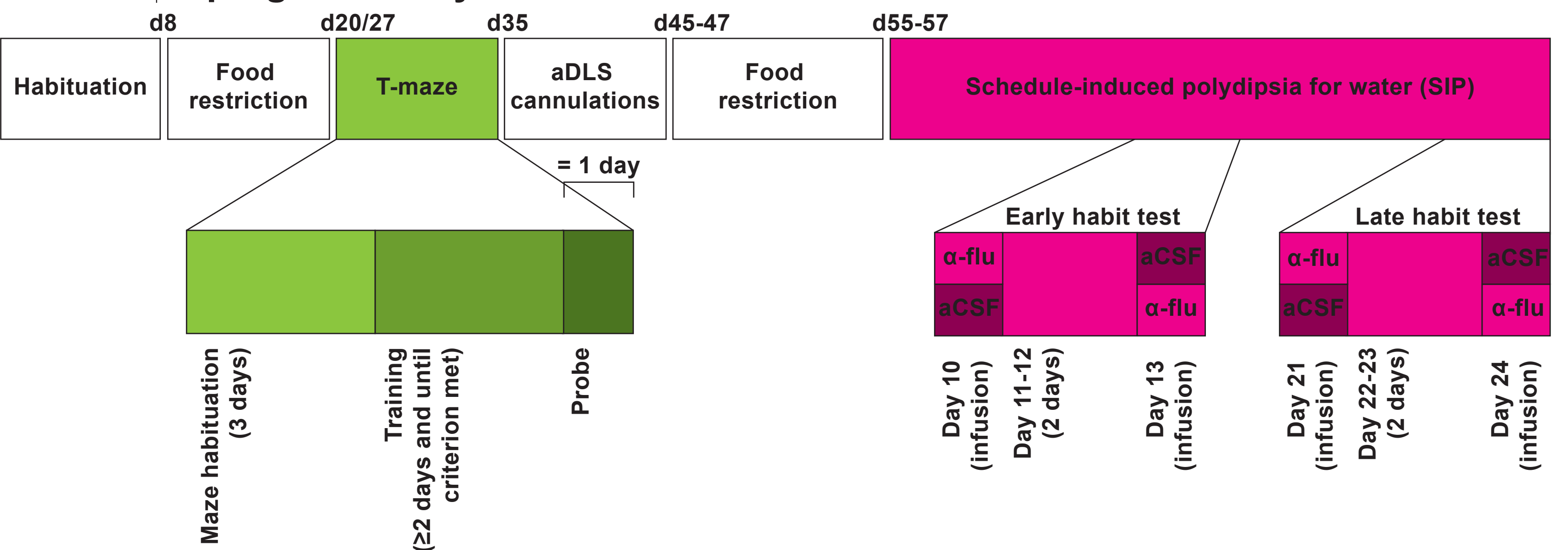
Rosetrees
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Introduction

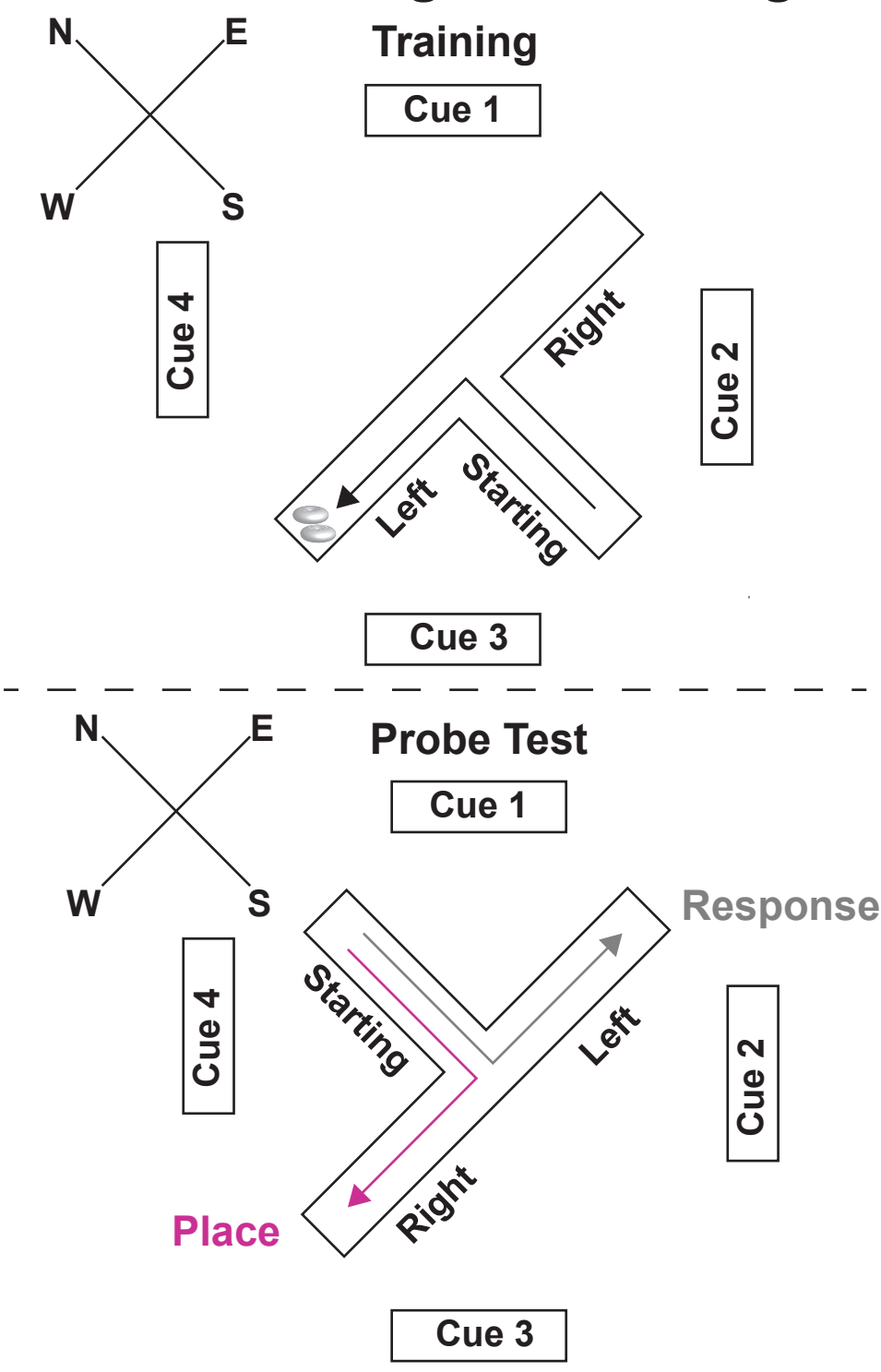
- Compulsive behaviours, those behaviours that are excessive and persist despite the negative consequences they produce¹, hallmark compulsive disorders such as substance use disorder (SUD) and obsessive-compulsive disorder (OCD)².
 - According to the maladaptive habit theory of compulsions, the development of compulsive behaviours stems from the loss of control over stimulus-response (S-R) habitual as opposed to action-outcome (A-O) goal-directed control over instrumental behaviour³⁻⁶.
 - In some compulsive disorders, such as SUD and OCD, control can be lost over behaviours initially acquired as stress coping mechanisms, resulting in their compulsive expression in vulnerable individuals^{7,8}.
 - This can be operationalised in preclinical studies by exposing hungry rats to intermittent deliveries of small amounts of food, under which conditions the majority develop a non-regulatory drinking response, called schedule-induced polydipsia (SIP)^{9,10}, that likely represents a stress coping response acquired and maintained under negative reinforcement^{11,12}.
 - A small fraction of individuals develops an excessive level of SIP, called hyperdipsia, where the negative consequences of non-regulatory drinking in hungry animals is magnified without additional stress coping benefit^{12,13}. Hyperdipsia models a compulsive stress coping behaviour.
- In accordance with the maladaptive habit theory of compulsions, SIP in hyperdipsic individuals comes under S-R habitual control once well-established, as determined by its sensitivity to inactivation of the neural substrate of habits in rats, i.e., dopamine-dependent mechanisms within the anterior dorsolateral striatum (aDLS)¹².
- Preclinical investigation of vulnerability to develop compulsive behaviours using behavioural traits has advanced our understanding of individual vulnerability to compulsive disorders, with traits that predispose towards developing compulsive behaviours in rodent models later shown to be endophenotypes for compulsive disorders^{14,15}.
 - However, only a small fraction of the behavioural trait-associated vulnerability to develop compulsive behaviours is understood.
 - Using the SIP model, we asked whether the individual tendency to rely on inflexible, dorsal striatum-dependent response as opposed to flexible, hippocampus-dependent place learning strategies for spatial navigation increases vulnerability to develop compulsive behaviours^{16,17}.
 - Our hypothesis was motivated by evidence suggesting that response navigation and habits rely on similar underlying neural circuits^{18,19}. A greater tendency to rely on response navigation strategies might consequently predispose towards developing compulsive behaviours through an increased propensity to develop habits, an important step in the development of compulsions according to the maladaptive habit theory

Methods

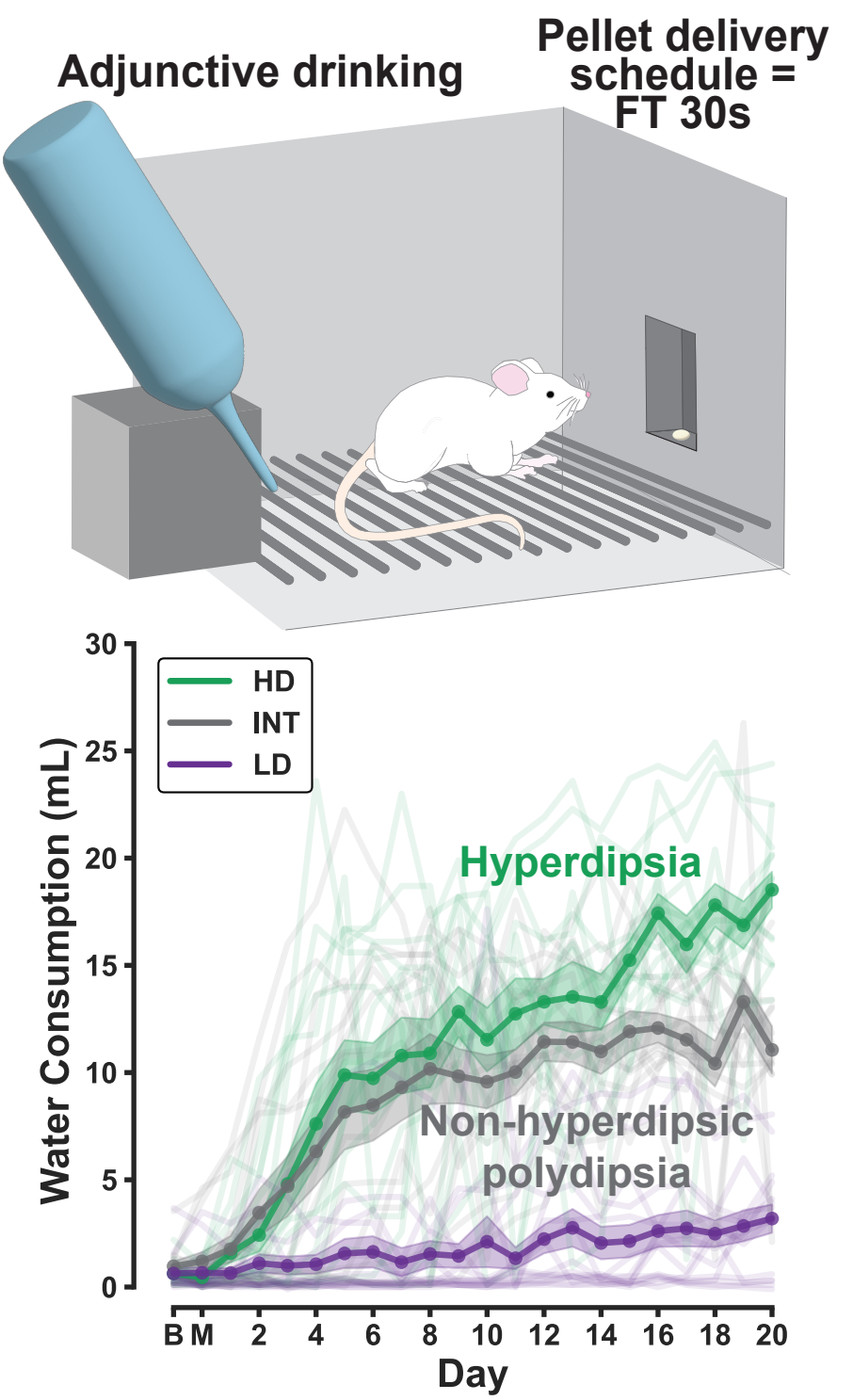
24 ♂ 24 ♀ Sprague-Dawley rats



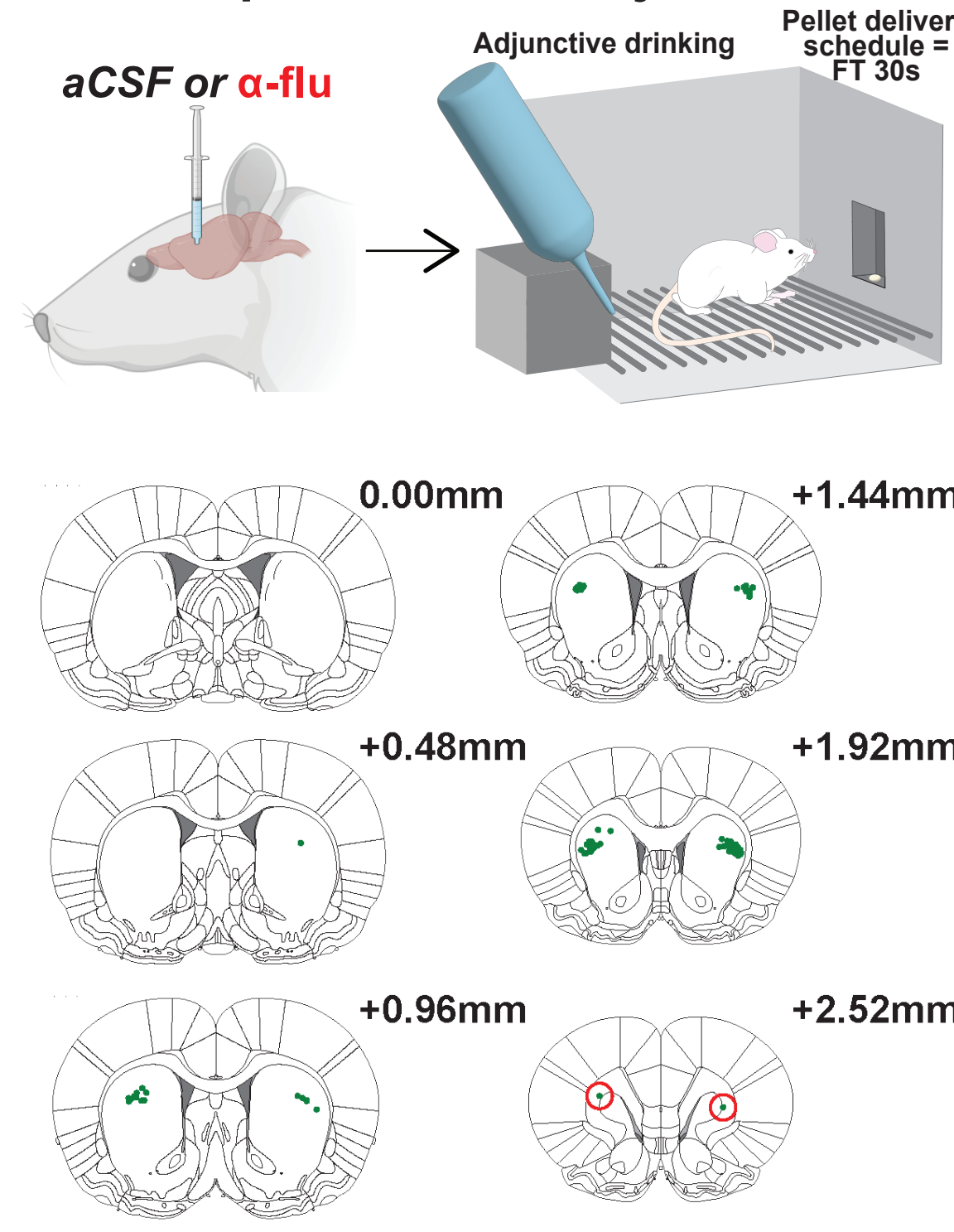
T-maze
The trait relative reliance on flexible versus inflexible navigation strategies



SIP
Acquisition and compulsive expression of stress coping behaviours

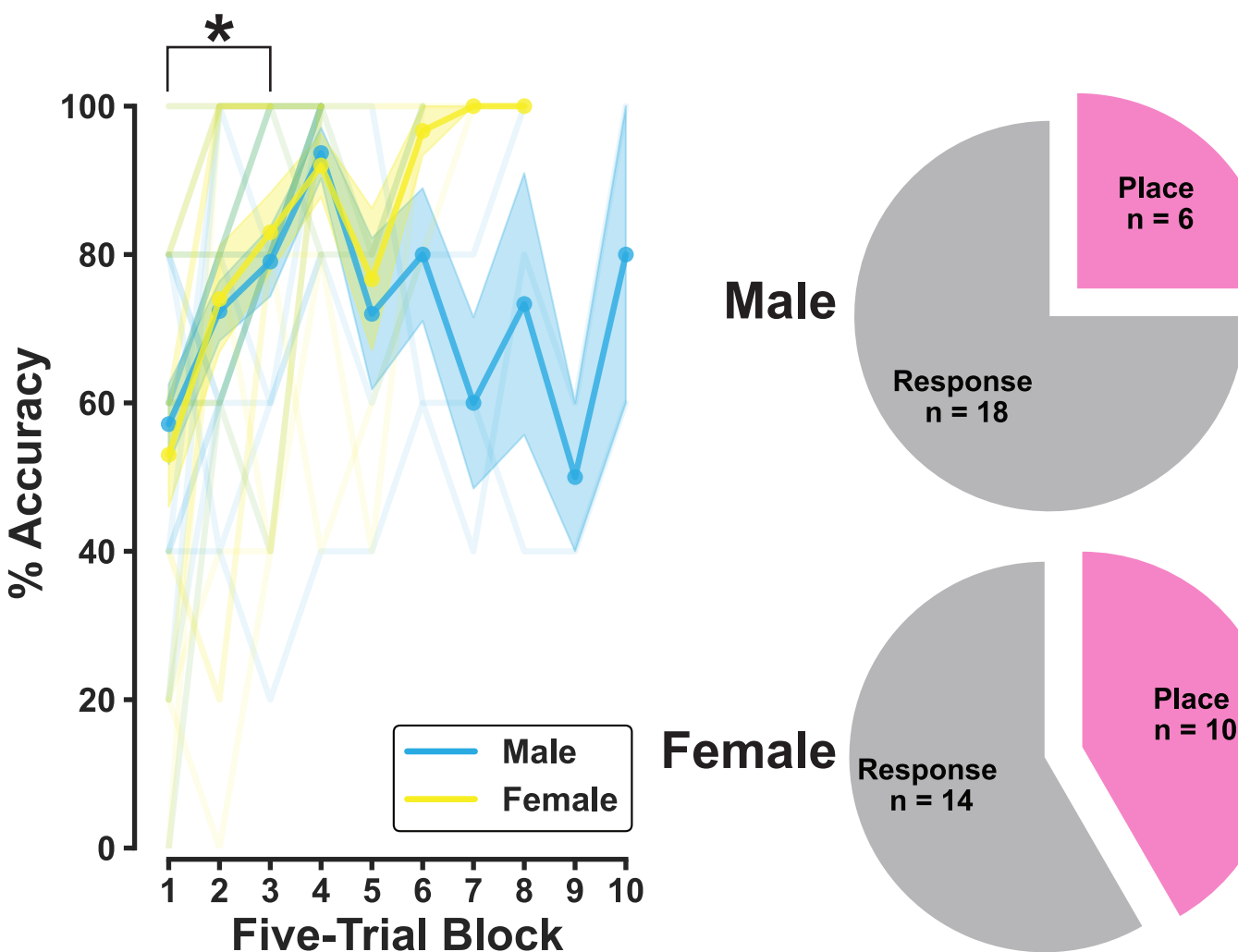


Intra-aDLS infusions of α -flu
Devolvement of stress coping responses to the aDLS dopamine-dependent habit system

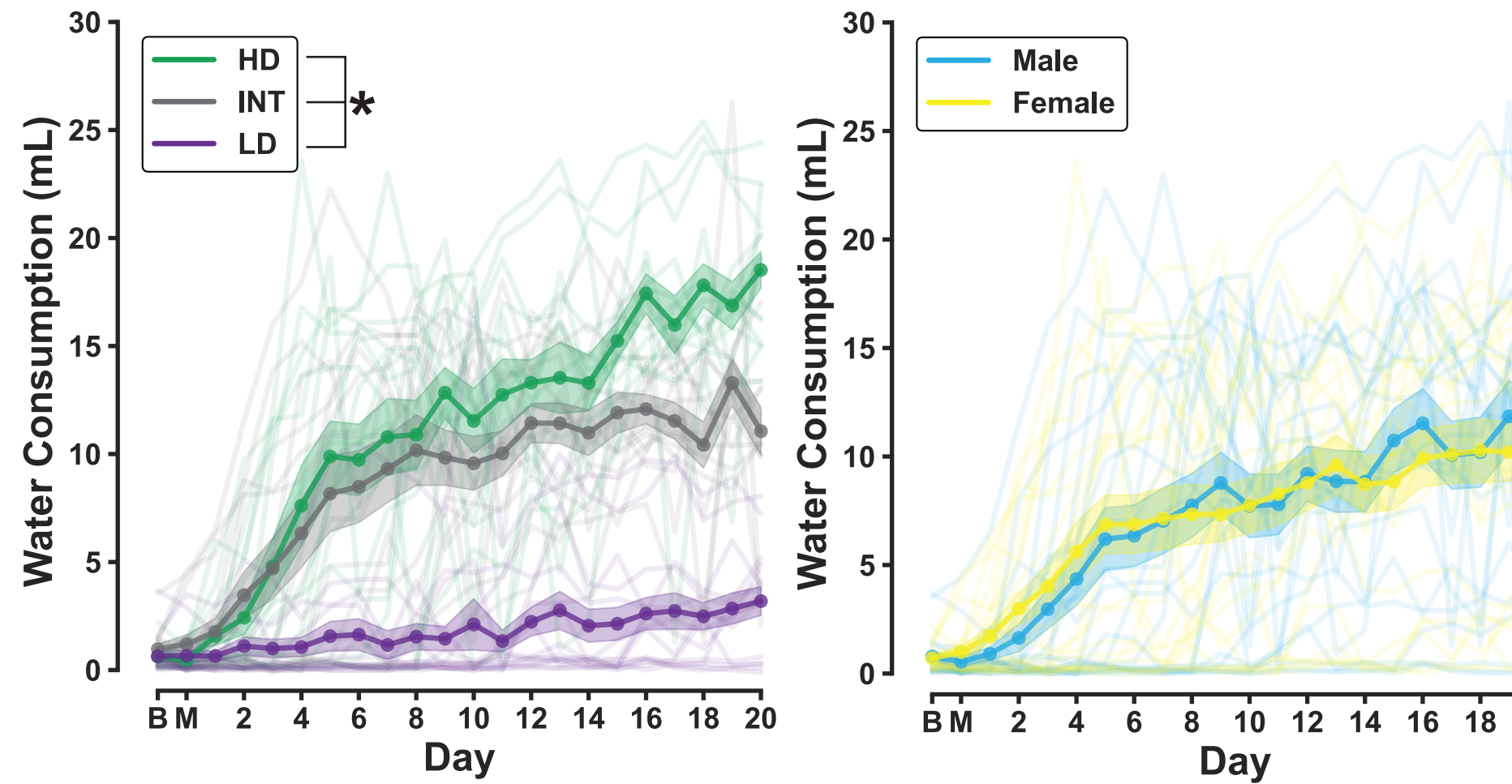


Results

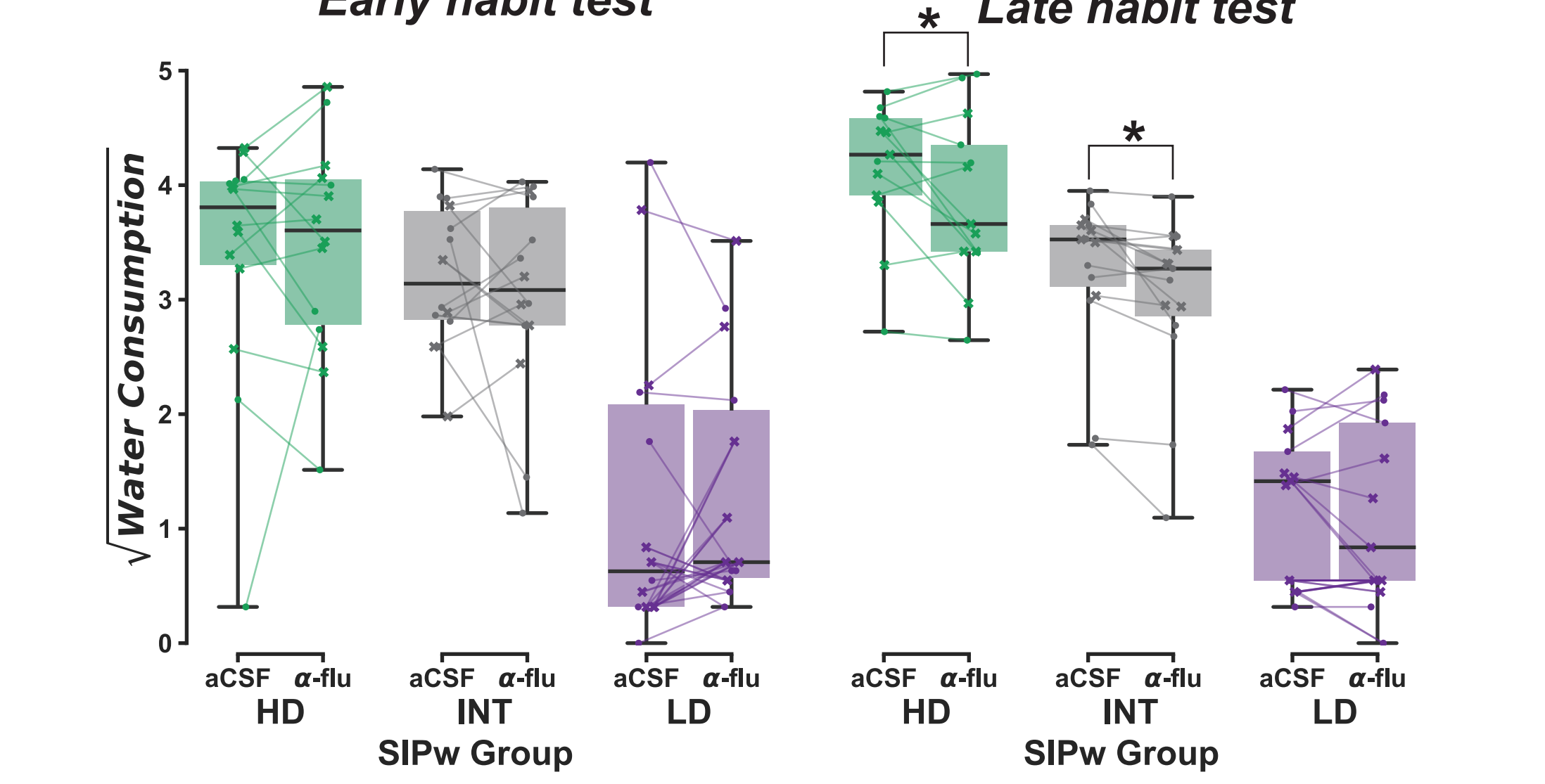
Identifying place and response learners in a cohort of male and female rats



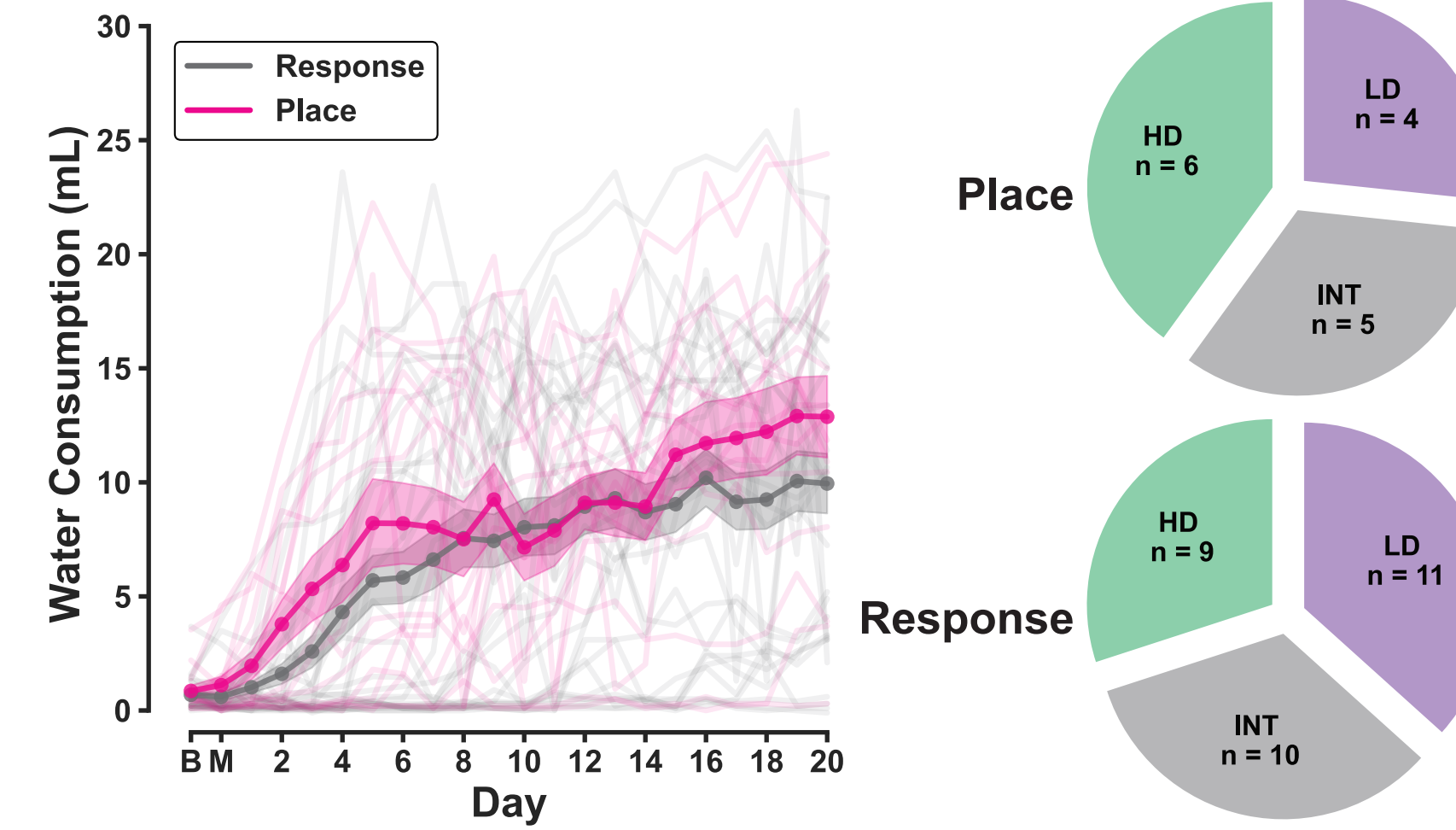
There are pronounced individual differences in the tendency to acquire and compulsively express a stress coping response



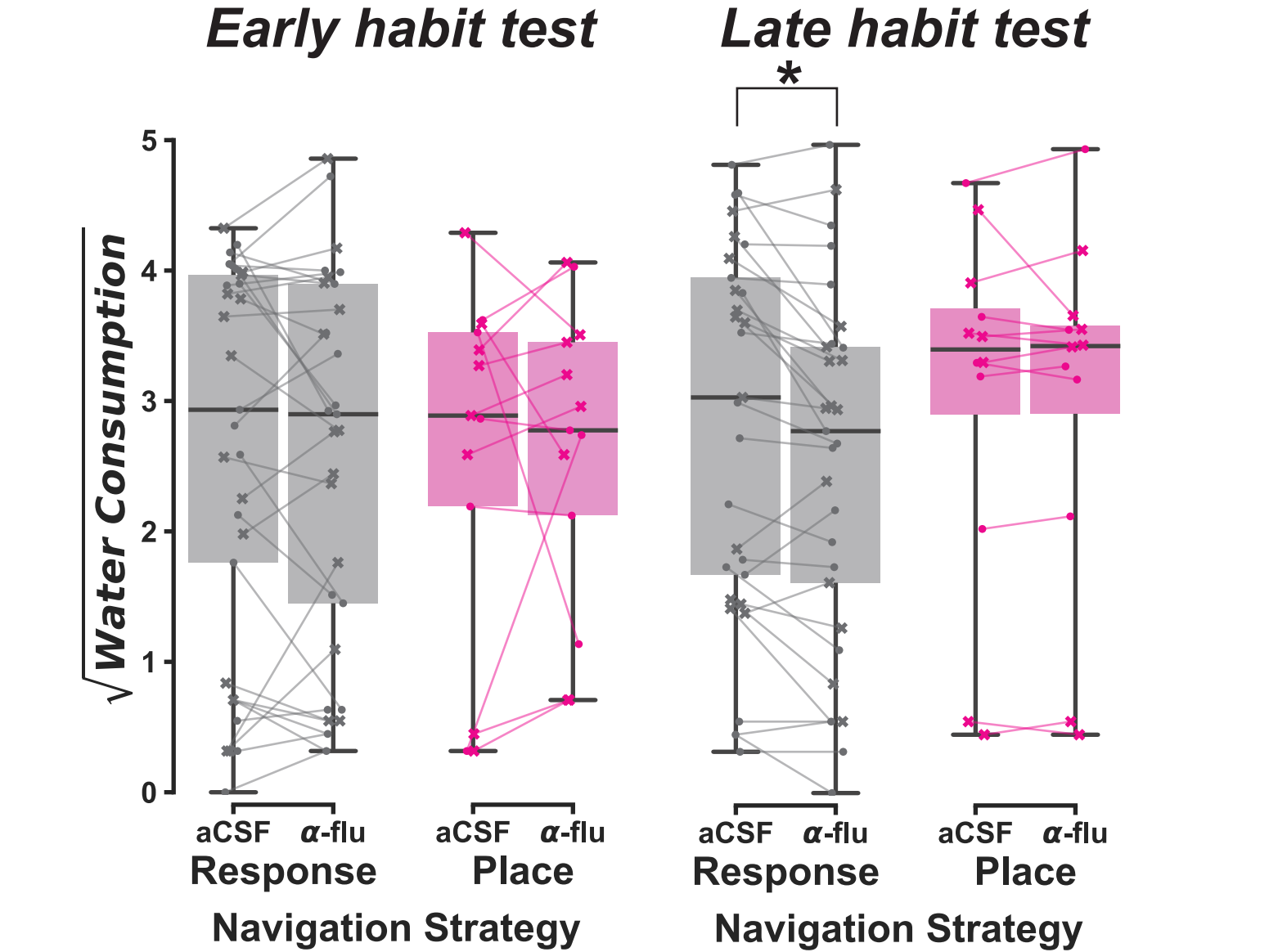
The acquisition of SIP and its compulsive expression is associated with the devolvement of drinking, once well-established, to the control of the S-R habit system



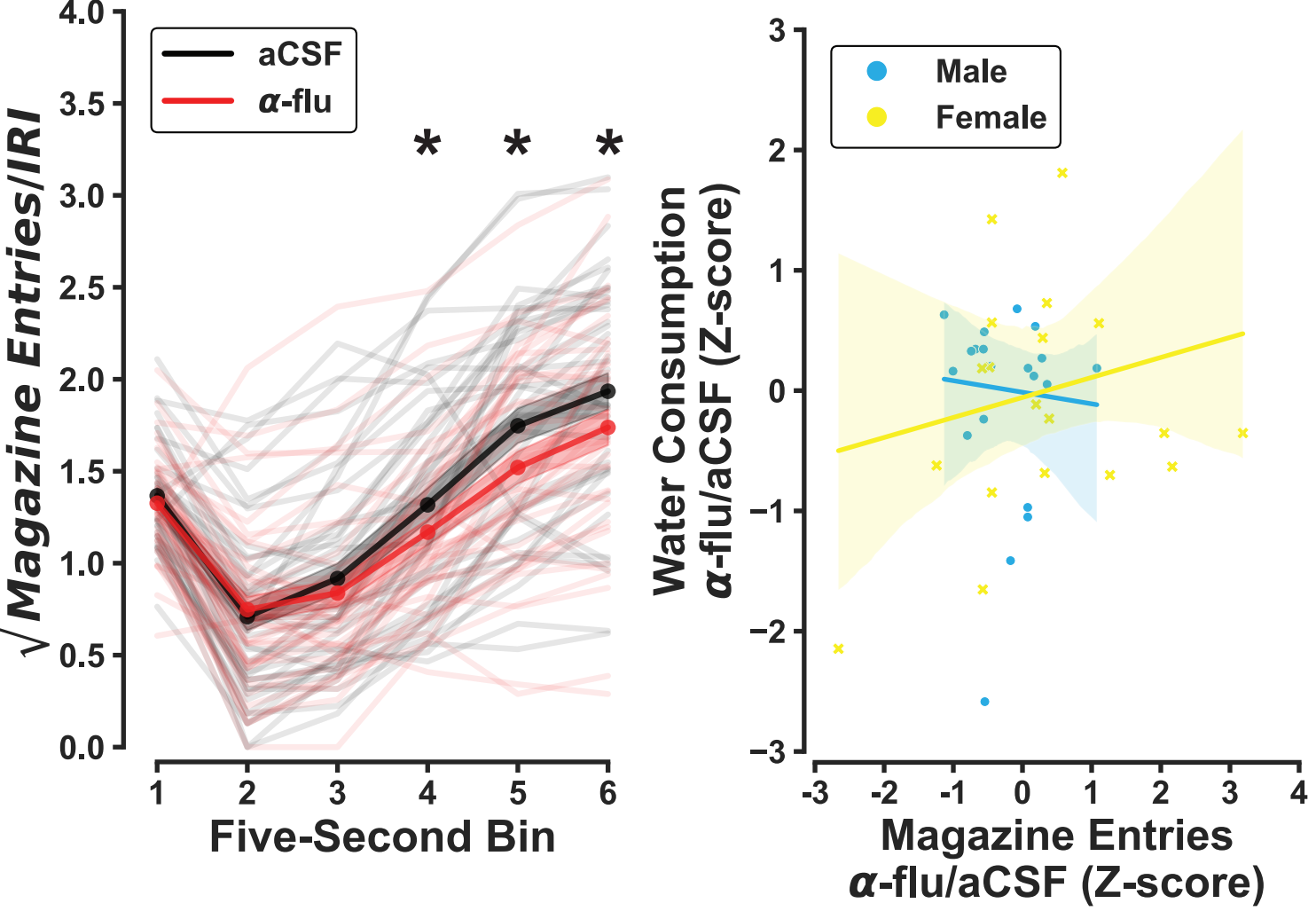
Place and response learners are equally prone to acquire polydipsic coping and to develop hyperdipsia



Response learners are more prone than place learners to the devolvement of SIP to S-R habitual control

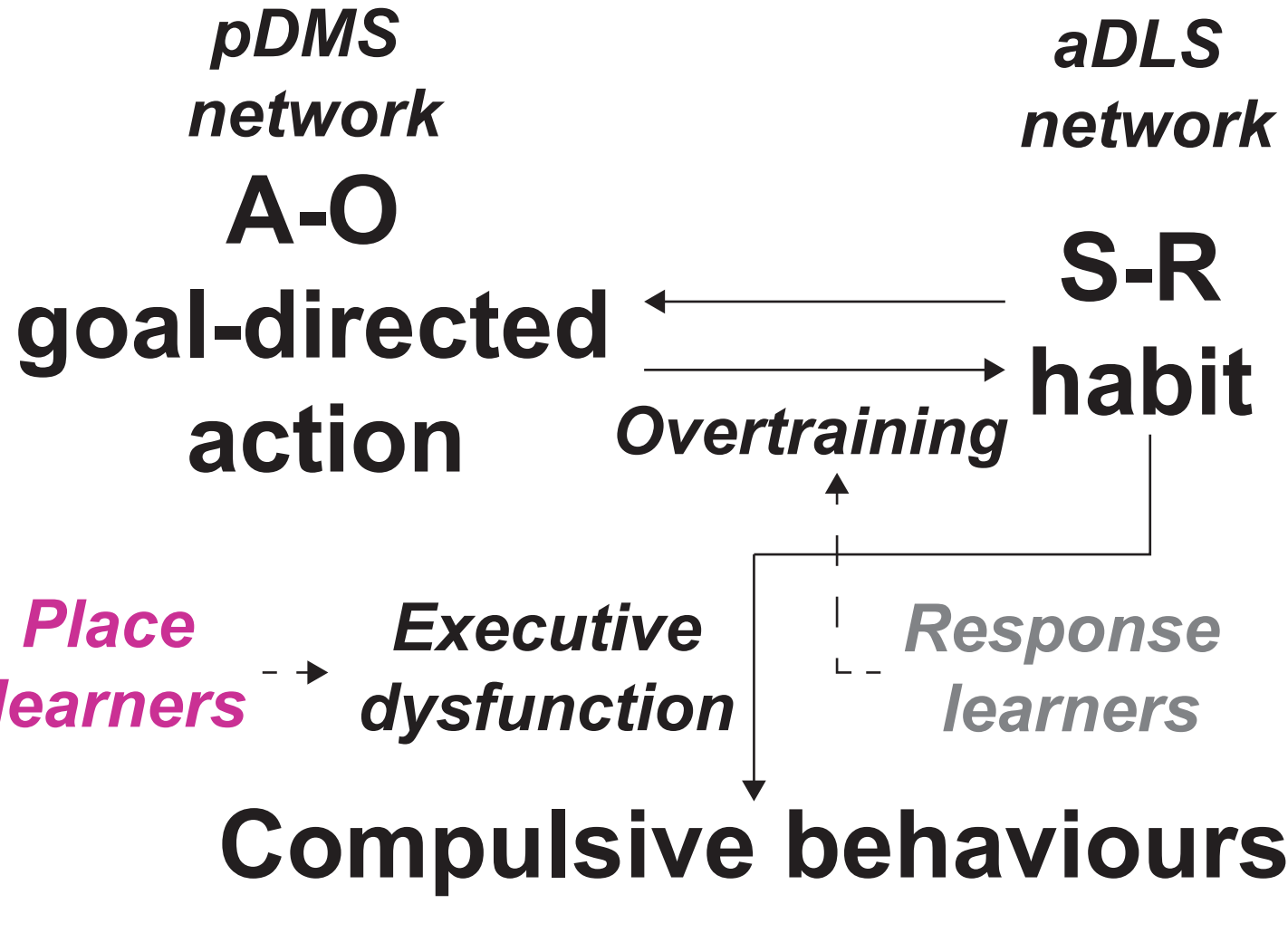


Intra-aDLS dopamine receptor blockade independently attenuates well-established terminal behaviours



Discussion

- That the development of hyperdipsia was associated with the devolvement of stress coping responses manifested in SIP to the control of the S-R habit system, as determined by its sensitivity to dopamine receptor blockade in the aDLS, is consistent with a previous report in rats¹² and in line with the maladaptive habit theory of compulsive behaviours³⁻⁶.
- That SIP once well-established devolves to the S-R system additionally in animals that develop SIP but do not compulsively express it is also consistent with the maladaptive habit theory in that the devolvement of instrumental behaviour to S-R control is a prerequisite but does not suffice for its compulsive manifestation³⁻⁶.
- Place and response learners do not differ in their acquisition of SIP and their vulnerability to develop hyperdipsia, despite response learners being more predisposed to develop S-R habitual control over SIP once well-established. This could reflect two equally offsetting processes: first, a greater predisposition to develop S-R habitual control over a stress coping response in response than in place learners; and second, a greater vulnerability to lose control over stress coping habits, once developed, in place than in response learners.
- The latter is indicated by human studies showing relatively lower levels of top-down executive function (e.g., cognitive flexibility, working memory capacity) in place than in response learners^{20,21}, with this being implicated as the "second factor" that dysregulates habits, once established, such that they become compulsive⁴.
- We also demonstrated an unreported function for aDLS dopamine-dependent mechanisms in some terminal behaviours under intermittent deliveries of food at predictable time intervals in hungry rats.



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