Box 8.2. Strain Differences in the Cage Stereotypies of Laboratory Mice

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Cabib convincingly proposes that stress-induced brain sensitization contributes to stereotypy. Her paradigm is a comparison of C57BL/6 ('C57') and DBA/2 ('DBA') mice in their reactions to long-term stress, sensitivity to drug sensitization and climbing responses to sustained food deprivation. However, she does not describe their behaviour in typical laboratory housing conditions: do the strain differences discussed here predict the degree of stereotypy shown night after night in their cages? The answer is yes, at least according to the one published study to systematically compare cage stereotypies across multiple strains. Nevison *et al.* (1999) kept *ad libitum*-fed male groups in two cage-types: standard barren cages merely lined with bedding; and semi-enriched cages additionally containing nesting and shelter. For 4 weeks, these were repeatedly videoed overnight. As predicted, DBAs showed more cage stereotypy than C57s. In barren cages, they spent a mean of 1.7% observations stereotyping, compared to the C57s' 0.5%; while in standard conditions these levels increased to 10.0% for DBAs and 1.3% for C57s. These data thus beautifully meet Cabib's prediction for her two focal strains (though the husbandry effect is rather unexpected; perhaps the barren conditions induced the 'behavioural despair' also discussed in this chapter?).

This study also collated data on four other strains, allowing further predictions to be tested – for if Cabib's framework has generality, the highest-stereotypy strains should also be least prone to 'behavioural despair' and most susceptible to stimulant sensitization. Nevison *et al.* (1999) found that CBA/Cas always showed the most cage stereotypies, and TOs and C57s, the least. The rank order of the intermediate stereotypers varied, however, being DBA > ICR(CD-1) > BALB/*c* in semi-enriched cages, but ICR(CD-1) = BALB/c > DBA in barren. Comparative data on drug sensitization have not been published for these strains. However, pre-pulse inhibition (PPI) data have been (Willott *et al.*, 2003). These are consistent with Cabib's prediction, although only if we assume that the subjects were housed in semi-enriched, not barren, cages (unspecified in the paper). Like schizophrenic humans and animals treated with DA agonists, DBAs showed low PPI: less than BALB/cs, which in turn showed less than C57s. Turning to models of depression, only two studies have investigated anhedonia/learned helplessness for three or more of these strains: Lucki *et al.* (2001) and Pothion *et al.* (2004). Both found the DBA versus C57 difference described by Cabib in this chapter; but other strain differences did *not* inversely correlate with cage stereotypy. Thus CBAs were most prone, *not* least, to anhedonia; while ICR(CD-1)s were more prone than BALBc/s to immobility in forced swim tests – *not* less prone or similar as their cage stereotypy would have predicted. Thus so far, this only partially supports Cabib's hypothesis beyond her two model strains – with three possible explanations. First, with data from so few strains, there may simply be insufficient replicates to test her idea reliably (Box 3.2, Chapter 3, illustrates how good comparative studies require a large N [here, of different strains] plus also need to control for phylogenetic relatedness). Second, the Nevison cage stereotypy data may have come from mice housed differently from the 'depression study' subjects. Housing-type clearly affects the magnitude – and even the rank order – of strain differences in cage stereotypy, and the extent to which similar variation occurs from one laboratory to the next is simply unknown. Last, it could be that, just as Cabib herself proposes here, stress-sensitization is only part of the full explanation: thus strain differences in mouse stereotypy are determined by multiple additional factors too (e.g. Chapter 4, this volume), which need factoring out before the hypothesis is tested further.