Effects of experimental housing conditions on recovery of laboratory mice

Paulin Jirkof, PhD[1, 2]

The beneficial effects of environment and social support during disease recovery in humans are widely accepted. Because laboratory mice are social animals and are highly motivated to interact with each other and with their environment, it is very likely that environmental and social factors are also beneficial to their recovery from experimental interventions or spontaneous diseases. The beneficial effects of enriched environments have been particularly well analyzed in the field of brain disorders, but several studies suggest that positive social contact and a complex and familiar environment may also support recovery from injury, from invasive procedures such as surgery or from spontaneously occurring diseases. The author reviews relevant publications on the effects of environment and social housing on recovery from disease or surgery in laboratory mice and other rodents. She concludes that in addition to promoting animal welfare, provision of optimal experimental housing conditions might also contribute to the clinical relevance of preclinical animal models by more closely simulating the environmental and social characteristics of disease recovery in humans.

Identification of the beneficial effects of environment and social support during disease and recovery in humans has led to the development of multimodal and psychosocial approaches in the treatment of disease and pain[1–5]. As laboratory mice are social animals and are highly motivated to interact with each other and with their environment[6], social and environmental factors are likely to have a role in their wellbeing and recovery from experimental interventions or spontaneously developing diseases. But the application of multimodal approaches to disease management in laboratory animal and preclinical science is still in its infancy, and studies analyzing the beneficial or detrimental influences of different housing conditions on rodent recovery are still relatively scarce. Notable exceptions are reports from some branches of neuroscience about the beneficial effects of environmental enrichment on the development or severity of neurodegenerative disorders and brain injuries.

Although the proximate effects of housing conditions may not always be evident in healthy mice, they might affect the way animals respond to stressors. Even if normal behavior and general condition are unaffected, individually housed or isolated animals are more reactive to stressors[7,8], suggesting that individual housing may increase vulnerability to stressful episodes. Animals' responses to invasive experimental procedures or reduced health condition may be dependent on environmental and social factors.

DEFINING ENVIRONMENTAL ENRICHMENT

The term environmental enrichment is used somewhat inconsistently to describe both an experimental neurobiological paradigm as well as a welfare-oriented husbandry approach. In the neurosciences, environmental enrichment is regularly defined as a housing condition combining complex inanimate (cage size, novel materials and objects) and social (cage mates) stimuli[9] that is supposed to enhance sensory, cognitive, motor and social skills compared with standard housing conditions[10]. A variety of environmental enrichment conditions have been used, and the lack of standardization has been criticized[11]. Enrichment efforts in routine housing systems are, in terms of costs and practicability, less complex than cage enrichment in neurobiology research. Often these efforts involve the addition of

[1]Division of Surgical Research, University Hospital Zurich, Zurich, Switzerland. [2]Neuroscience Center Zurich, University of Zurich & ETH Zurich, Zurich, Switzerland. Correspondence should be addressed to P.J. (Paulin.Jirkof@usz.ch).

biologically relevant features to the cage, creating a more natural setting, with the aim of facilitating or enabling the animals to engage in natural behaviors[12,13].

EFFECTS OF ENVIRONMENTAL ENRICHMENT

The enrichment of laboratory animal housing systems is thought to enhance animals' physical and emotional wellbeing[12], thereby improving their welfare. Although a growing body of literature supports the idea that some environmental enrichment strategies benefit general and emotional wellbeing in animals, contradictory results also exist, leading to an ongoing discussion of whether and under which conditions environmental enrichment can bring about a measurable improvement in animal welfare[13–15].

Environmental enrichment may alter behavioral and physiological responses, such as hypothalamic-pituitary-adrenal (HPA) axis responses, and may induce cellular and molecular changes in the brain[10,12]. Therefore, beneficial effects of environmental enrichment have been analyzed particularly well in the field of neuroscience, where environmental enrichment consisting of inanimate factors, like boxes, chains, metal barrels and ladders (changed daily), and social stimulation is used to promote recovery in neurological disorders[11]. Different kinds of environmental enrichment result in delayed onset of or reduced functional deficits in several central nervous system disorders[10,16]. For example, complex environments have beneficial effects in animal models mimicking two human cognitive disorders, Down syndrome and fragile X syndrome. Environmental enrichment (social housing as well as the provision of inanimate objects like running wheels, tunnels, shelters and stairs that were repositioned or replaced regularly) decreases the effects of phenotype in a model of Down syndrome[17] and leads to fewer deficits and promotes recovery in a murine model of fragile X syndrome[18]. Additionally, inanimate and social environmental enrichment seems to be protective against brain damage in several rodent species[19]. For example, environmental enrichment offers neuroprotection against the neurotoxic agent 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, which is used to induce syndromes resembling Parkinson's disease in mice. The prevalence and outcome of this neurodegenerative disorder are less pronounced in mice living under enriched housing conditions consisting of a combination of exercise, social interaction and cognitive enrichment (learning, novelty)[20,21]. Enriched housing conditions enhance motor and cognitive performance after stroke and traumatic brain injury in rats compared with standard or impoverished housing conditions[22–25]. Additionally, environmental enrichment, like tunnels, shelters, toys and running wheels as well as social interaction, improves functional recovery by transplanted adipose stem cells after chronic hypoxic brain injury in mice[26]. The ability of environmental enrichment to support recovery from brain disorders may be mediated by the induction of neural plasticity in the brain via enhanced stimulation of brain sensory, cognitive and motor systems[19].

Environmental enrichment can also benefit recovery from conditions like psychological stressors, physical injury or illness, presumably by modulating the HPA axis[27,28]. A combination of inanimate and social environmental enrichment buffers reactivity of the immune system in response to stress in mice[29], decreases the display of a submissive phenotype and depressive-like behaviors during chronic psychosocial stress[30] and reduces immobility in the forced swim test[31,32]. These data hint at an improved ability to cope with stressful life events, which might help substantially to improve recovery after injury, surgery or spontaneous disease. For example, rats housed in cages enriched with cotton nesting squares had better wound healing after burning injury than rats housed without nesting material[33]. In addition, socially and physically enriched housing affects sensitivity to thermal stimuli and leads to less inflammation-induced nociception in rats[34,35].

EFFECTS OF SOCIAL HOUSING

Laboratory mice are social animals and are highly motivated to interact with each other[6]. Social context influences both mouse wellbeing and experimental results[6]. Although social housing of mice is common in animal facilities, mice are often separated for scientific reasons, such as for monitoring purposes or surgical procedures. The findings of studies analyzing the effects of individual housing on mouse wellbeing are ambiguous. Some findings suggest that individual and social housing do not have different effects on endocrine stress indicators[36], physiological indexes[37] or behavioral tests[36]. On the contrary, several other studies show that individual and social housing have different effects on sympathetic neurotransmission[38], basal heart rate[7,39] and thymus weight[7]. Furthermore, individual housing of mice is associated with disruptions to circadian activity patterns[39]; effects on memory, emotionality and anxiety; a tendency to show hyperactivity in behavioral tests[40–42]; and greater fluctuating asymmetry, or deviation from physical symmetry in growing organisms in response to stress[43]. Some studies show that, even if normal behavior and general condition are unaffected, individually housed or isolated animals are more sensitive to stress, and mice housed in stable groups recover faster from mild stressors[7,8,44]. Both corticosterone release induced by housing stress and oxytocin release induced by social interaction can modulate stress reactivity as well as other HPA axis and immune system responses, the former in a detrimental way and the latter in a beneficial way[45–47].

Beneficial effects of social housing of mice can be observed in several disease models. After stroke, both male and female mice show better recovery, decreased infarct size, reduced functional deficits and increased survival rate when housed in pairs or groups, especially when housed with healthy companions[48–52]. Social isolation seems to modulate the neuroinflammatory and HPA axis response, both of which have a role in stroke outcome; IL-6 gene expression and corticosteroid secretion seem especially affected by isolation stress[48,50,51]. The positive effects of social housing on stroke recovery depend on direct physical contact; animals separated from their cage mates with a grid partition show the same outcomes as isolated animals[51].

In a murine model of coronary heart disease, social isolation accelerates disease progression, an effect more pronounced in females than in males. Changes in oxytocin levels, which can regulate the reactivity of the HPA axis, are assumed to cause these alterations[53]. Conversely, single housing of male mice decreased resistance to Ehrlich tumor growth (increase in volume of ascitic fluid and number of tumor cells) and led to shorter survival times compared with group housing[54].

Social housing can also influence the perception of pain. Male mice housed singly after electrode implantation show increased visceral hypersensitivity and defecation[55]. Surgery and postsurgical recovery are potentially painful and stressful episodes for mice. Individual housing during these episodes may exacerbate an animal's vulnerability to surgical pain and stress and interfere with postsurgical recovery. Hence, the common practice of housing mice individually after surgery for monitoring purposes, though scientifically justifiable, might in fact be detrimental. Several studies support the hypothesis that social housing promotes postsurgical recovery. After laparotomy and cecal manipulation, social housing had a pronounced beneficial impact on recovery of female mice as measured by Q1 less self-administration of analgesics[56]. Socially housed mice are less affected by abdominal telemetric transponder implantation than individually housed mice as indicated by heart rate and behavior measures[57]. After minor surgery, singly housed female mice show reduced burrowing and other behavioral differences compared with socially housed female mice[58]. Wound or tissue healing is also important in postsurgical recovery, and delays in healing may have profound effects[59]. Social housing facilitates wound healing in rats, deer mice and hamsters[59–61].

EFFECTS OF FAMILIAR ENVIRONMENTS

Scent marks, originating from urine smears or other glandular sources of secretion such as salivary, plantar or preputial glands and deposited on the substrate, are a key source of information for laboratory mice[62,63]. Many aspects of mouse behavior rely on their ability to use odor cues: orientation, detection of novel objects and differentiation of individuals, which is essential for maintenance of stable groups[64–66]. A common and rather drastic disturbance of these cues that all mice in the laboratory undergo is cage cleaning. Although this procedure is essential for hygiene, it disrupts the olfactory cues of mice and can be described as a repetitive and frequent stressful event in the lives of laboratory rodents[62,65,67]. Novel cage exposure is also used as a moderate experimental stressor or to assess emotional reactivity in mice[68]. Such exposure increases plasma corticosteroid concentrations in proportion to the degree of difference between the novel cage and the home cage[69,70].

The placement of an animal into a clean cage after surgery is a standard procedure in many facilities for several reasons (e.g., elimination of the potential health risk of soiled bedding). This procedure combines the stresses of in-house transport and cage cleaning and probably has a large impact on the animal during the critical postsurgical recovery phase. Animals in new cages are more sensitive to transportation stress, whereas mice housed in their home cages recover faster from transport stress[72]. Postsurgical transfer to a new environment might act as an additional stressor to female mice after an exhausting experimental procedure and, compared with housing them in their familiar home cages after surgery, might have a detrimental effect on postsurgical recovery[27].

IMPLICATIONS FOR IMPROVING EXPERIMENTAL HOUSING CONDITIONS

The aforementioned studies suggest that positive social contact as well as a complex and familiar environment may support animal recovery from invasive procedures or from diseases. Besides promoting animal welfare, providing mice with optimal experimental housing conditions might also improve the clinical relevance of animal models, as complex housing environments and social interaction are more reflective of human lifestyles[73].

The effects of environmental enrichment are sex-dependent[12], with female mice deriving greater benefit, especially from social enrichment. Most of the studies reviewed here involved female mice or male–female pairs, and so some of the findings might not apply generally to male mice of all strains and lines, particularly when housed with other males. In addition, negative social interactions can modulate the HPA axis and other factors that might affect recovery; therefore, social interaction can also be a source of stress for mice[47]. Chronic subordinate colony housing in single-sex male groups may cause stress-induced disease such as colitis[74], and aggression in male groups is a well-known problem that might be amplified by environmental enrichment[75]. Nevertheless, males may also benefit from a same-sex cage mate during challenging health conditions[49,54]. Problems with male aggression might be overcome with use of more docile strains, careful group composition, or ovarectomized female companions and informed selection of enrichment strategies[62,76].

Ultimately, the appropriate housing for mice during and after experiments should be determined on a case-by-case basis, considering various aspects of laboratory routine, experimental design, legislation and—most importantly—animal wellbeing. If changes in housing environment increase uncontrollable variation, due to inadequate enrichment strategies, for example, then standard housing may be the best choice to reduce variation and therefore animal numbers. Similarly, if social or inanimate enrichments to housing hamper experimental results (e.g., by enabling cage mates to damage equipment like microdialysis cannulas), then standard or single housing may be preferred. Individual housing also offers the advantage of allowing accurate monitoring of individuals, which may be advisable in situations such as determining whether an animal has reached a humane endpoint. But researchers should keep in mind how environmental and social factors can improve animal welfare and scientific results in animal experimentation and should choose to house laboratory mice in a familiar and enriched environment and in stable and harmonious groups whenever possible.

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The authors declare no competing financial interests.

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