Neurobiology of Learning and Memory 124 (2015) 97–103

Contents lists available at ScienceDirect

Neurobiology of Learning and Memory

journal homepage: www.elsevier.com/locate/ynlme

Review

The effects of acute social isolation on long-term social recognition memory

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ARTICLE INFO

Article history:
Received 9 March 2015
Revised 25 June 2015
Accepted 3 July 2015
Available online 10 July 2015

Keywords:
Social recognition memory
Social isolation
Long-term memory
Olfactory bulb
Medial amygdala
Hippocampus

ABSTRACT

The abilities to recognize individual animals of the same species and to distinguish them from other individuals are the basis for all mammalian social organizations and relationships. These abilities, termed social recognition memory, can be explored in mice and rats using their innate tendency to investigate novel social stimuli more persistently than familiar ones. Using this methodology it was found that social recognition memory is mediated by a specific neural network in the brain, the activity of which is modulated by several molecules, such the neuropeptides oxytocin and vasopressin. During the last 15 years several independent studies have revealed that social recognition memory of mice and rats depends upon their housing conditions. Specifically, long-term social recognition memory cannot be formed as shortly as few days following social isolation of the animal. This rapid and reversible impairment caused by acute social isolation seems to be specific to social memory and has not been observed in other types of memory. Here we review these studies and suggest that this unique system may serve for exploring of the mechanisms underlying the well-known negative effects of partial or perceived social isolation on human mental health.

1. Introduction

Social species, by definition, form organizations that extend beyond the individual. Since the survival of members of these species is threatened when they are socially isolated, various behavioral, neural, hormonal, cellular, and genetic mechanisms have evolved to support their social organizations (Adolphs, 2009; Robinson, Fernald, & Clayton, 2008). Humans too do not fare well alone, whether they live solitary lives or simply perceive that they live in isolation. An ever growing body of evidence shows that social isolation in general, and perceived social isolation (loneliness) in particular, have significant negative effects on human health (reviewed by Umberson & Montez, 2010). Moreover, loneliness was found by many studies to have negative influence on human mental health and cognition in all ages (reviewed by Cacioppo & Hawkley, 2009).

For example, loneliness was shown to be a powerful risk factor for cognitive decline and Alzheimer's disease (AD) in elderly people. A longitudinal study (Wilson et al., 2007) revealed that the risk of AD was more than doubled in lonely persons compared with persons who were not lonely. Loneliness was also associated with lower level of cognition at baseline and with more rapid cognitive decline during follow-up. Two more independent longitudinal studies found that being part of larger social networks has a protective influence on cognitive function among elderly people (Crooks, Lubben, Petitti, Little, & Chiu, 2008; Fratiglioni, Wang, Ericsson, Maytan, & Winblad, 2000). Although the relative contribution of objective vs. perceived social isolation to dementia are in controversy (Cacioppo, Hawkley, Norman, & Berntson, 2011; Steptoe, Shankar, Demakakos, & Wardle, 2013), it is clear that social isolation is a strong risk factor for age-related cognitive decline and dementia (Heinrich & Gullone, 2006). Yet, loneliness is a very common experience in adulthood; as many as 40% of adults over 65 years of age report being lonely at least sometimes and 15% report feeling lonely most of or all the time (Andersson, 1982; Pinquart & Sorensen, 2001; Weeks, 1994).

Obviously, the problem of social isolation becomes more acute in elderly people, as the percentage of subjects who have lost their spouse and/or close friends increases with age. Therefore, unraveling the biological processes underlying the damaging effects of partial or perceived social isolation in adulthood on mental health should be highly beneficial. Yet, only few studies have dealt with this issue so far in a mechanistic approach, mainly due to the lack of a proper animal model.

The common animal model used for exploring the effects of social isolation in rodents is post-weaning isolation rearing, which involves isolation of the animals with no handling, starting at a

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http://dx.doi.org/10.1016/j.nlm.2015.07.002
1074-7427/

very early stage (postnatal day 20–28) for an extended period of several months (Heidbreder et al., 2000). This rigorous isolation procedure was shown to cause a plethora of behavioral, physiological, and molecular abnormalities (comprehensively reviewed by Fone & Porkess, 2008). However, it is unlikely to serve as a proper model for the effects of the much later and milder condition of reduced social interactions experienced by adult people, not to mention perceived social isolation which seems to be more of an emotional state than objective condition. Nonetheless, during the last 15 years several studies have repeatedly shown that acute social isolation of adult rats and mice impairs a specific type of long-term memory, termed social recognition memory. This impairment may serve as a model for exploring the mechanisms underlying the influence of social isolation in adulthood. Here we review these studies and the mechanisms that are suggested to be involved.

2. Social recognition memory

The abilities to recognize individual animals of the same species (conspecifics) and to distinguish them from other individuals are the basis for all mammalian social organizations and relationships (Insel & Fernald, 2004). These social relationships may be divided into two classes: (1) those involving a critical period associated with significant hormonal and physiological changes, such as infancy, motherhood, or mating. The type of memory associated with these relationships seems to involve unique mechanisms which resemble imprinting (Bielsky, Hu, Ren, Terwilliger, & Young, 2005) or addiction (Chiodera et al., 1991). (2) Relationships which are not associated with a unique period or event but rather based upon daily experience, such as the relationships humans tend to develop with friends or colleagues. The type of memory associated with these social relationships is called social recognition memory (Gheusi, Bluthe, Goodall, & Dantzer, 1994).

A behavioral paradigm for studying social recognition memory was initially put forward by Thor and Holloway more than three decades ago (Thor, Wainwright, & Holloway, 1982). Since then, several other paradigms have been developed, each with its own advantages and limitations (reviewed by McEwen, 2004). The common denominator of all these paradigms is their use of the innate tendency of rats and mice to investigate novel social stimuli more persistently than they investigate familiar ones. The paradigm initially proposed by Thor and Holloway, simply termed social recognition, involves two short (2–5 min) encounters of the subject with the same stimulus, separated by a certain time interval. A reduction in investigation time, measured by a trained observer, between the first and second encounters, presumably due to the decrease in stimulus novelty, is considered to reflect social recognition memory. It should be noted that in order to avoid aggressive or reproductive behavior towards the stimulus, in most cases social stimuli consisted of either juvenile males or ovariectomized females.

A second, more elaborate test used for studying short-term social recognition memory is the social habituation–dishabituation paradigm (Ferguson, Young, & Insel, 2002; Sekiguchi, Wolterink, & van Ree, 1991b). This test is comprised of four consecutive 2–5 min encounters with the same social stimulus, separated by 10–30 min intervals and followed by a fifth encounter with a novel social stimulus. Normally, rats and mice display a continuous reduction in investigation time as they repeatedly encounter the same stimulus (habituation phase), followed by the return of investigation time to its original value during the fifth encounter with the novel stimulus (dishabituation phase), confirming a stimulus-specific habituation.

A third paradigm, which is considered more accurate, is the social discrimination paradigm in which following an encounter with a social stimulus, the subject is simultaneously exposed to the same stimulus and to a novel one, each located within a corral which enables restricted social investigation (Engelmann, Wotjak, & Landgraf, 1995). Normally, the subject explores the corral harboring the novel stimulus more rigorously that the one containing the familiar one, reflecting the recognition of the familiar social stimulus. This test is easily accessible for automatic, computer-based analysis. Moreover, the corralling of social stimuli enables the use of a wider range of stimuli, such as gonadally-intact females (Macbeth, Edds, & Young, 2009). Nevertheless, during the test the stimuli are restricted to their corrals, a relatively artificial and possibly stressing condition, which may influence the behavior of the subject.

2.1. Neural and molecular mechanisms underlying social recognition memory

Despite the intuitive conception that social recognition memory should not be different from any other type of memory, a large body of studies shows that it is mediated by a dedicated brain neuronal network and regulated by molecules which act specifically to modulate this type of memory (for several recent papers reviewing this issue see Gabor, Phan, Clipperton-Allen, Kavaliers, & Choleris, 2012; Harony & Wagner, 2010; Wacker & Ludwig, 2012). The most convincing evidence for this conclusion came from experiments with genetically modified mice in which the neurohypophyseal hormones oxytocin and vasopressin were manipulated.

Oxytocin and vasopressin are "twin" 9-amino acid peptides (nonapeptides) that in mammals are produced mainly in non-overlapping populations of neurons in the same three hypothalamic nuclei, the supraoptic nucleus (SON), the accessory nucleus (AN) and the paraventricular nucleus (PVN) (Gainer, 2012; Rhodes, Morrell, & Pfaff, 1981). These nuclei contain large magnocellular peptidergic neurons which project their axons to the posterior pituitary gland (neurohypophysis), where they release vasopressin and oxytocin into the blood. Many of these neurons (mostly in the PVN and AN) also release vasopressin and oxytocin in the brain either via direct projections to various locations (Knobloch et al., 2012) or through dendritic release to the third ventricle (Landgraf & Neumann, 2004; Ludwig & Leng, 2006). In the last two decades a plethora of studies in various organisms has pointed to a central role of oxytocin and vasopressin in the regulation of social behavior in vertebrates (for review see Caldwell, Lee, Macbeth, & Young, 2008; Lee, Macbeth, Pagani, & Young, 2009).

In a seminal work, Ferguson et al. (2000) used the social habituation-dishabituation paradigm to show that mice in which the gene encoding oxytocin (*Oxt*) was knocked-out (*Oxt*-KO mice) lack short-term social recognition memory. These mice thoroughly investigate the same stimulus presented to them repeatedly as if it were a novel one, despite the short time interval (10 min) between two consecutive encounters. No difference between *Oxt*-KO mice and their wild-type (WT) littermates was found in their investigation of a novel social stimulus or in their performance in an olfactory-guided foraging task, suggesting no impairment in detection of novelty or of olfactory stimuli. Moreover, *Oxt*-KO mice did not differ from their WT littermates in their habituation to olfactory or acoustic stimuli, or in their performance in spatial memory tests. Finally, the researchers showed that intracerebroventricular (ICV) administration of oxytocin immediately before the beginning of the test restored short-term social recognition memory in *Oxt*-KO mice. Similar results were obtained using mice in which the *Oxtr* gene encoding the oxytocin receptor was knocked out (Lee et al., 2008; Takayanagi et al., 2005), as well as in *CD38*-KO mice in which oxytocin cannot be released from nerve terminals (Aragona & Wang, 2004). These studies convincingly showed that

oxytocin is necessary specifically for social recognition memory, but not for other types of memory. An equivalent conclusion was drawn for vasopressin by several lines of evidence. First, social recognition memory is impaired in Brattleboro rats, which cannot synthetize biologically active vasopressin due to a spontaneous mutation in the corresponding gene (Engelmann & Landgraf, 1994; Feifel, Melendez, Priebe, & Shilling, 2007). Second, in male rats, social recognition memory is impaired by antagonists and facilitated by agonists of vasopressin (Bluthe & Dantzer, 1992; Bluthe, Schoenen, & Dantzer, 1990; Dantzer, Bluthe, Koob, & Le Moal, 1987; Le Moal, Dantzer, Michaud, & Koob, 1987; Popik, Wolterink, De Brabander, & van Ree, 1991; Sekiguchi, Wolterink, & van Ree, 1991a). Third, Social recognition memory was found to be impaired in mice lacking either one of the two vasopressin receptors expressed in the brain, Avpr1a and Avpr1b (Bielsky et al., 2005; DeVito et al., 2009). Altogether, these results signify the involvement of unique oxytocin- and vasopressin-dependent mechanisms, specifically in social recognition memory.

In rodents, social memory was shown to be mediated mainly by chemical cues (semiochemicals) perceived via the main and accessory olfactory systems (Dulac & Torello, 2003). Upon binding of semiochemicals to the receptors expressed by the sensory neurons of the main olfactory epithelium and the vomeronasal organ, sensory information is conveyed to the main (MOB) and accessory (AOB) olfactory bulbs, respectively (Dulac & Wagner, 2006). Both bulbs project, either directly or indirectly, to the medial nucleus of the amygdala (MeA) (Kang, Baum, & Cherry, 2011; Pro-Sistiaga et al., 2007). In turn, the MeA is thought to transfer the information to the lateral septum (LS) (Bielsky & Young, 2004), which is strongly connected, either directly or indirectly, with various hippocampal regions (Risold & Swanson, 1997). Other brain areas which are associated with modulation of social recognition memory are the hypothalamic medial preoptic area (MPOA), bed nucleus of stria terminalis (BNST), and medial prefrontal cortex (mPFC) (Adolphs, 2009; Goodson, 2005; Goodson & Kabelik, 2009). Interestingly, *Oxtr* expression levels were found to be especially high in most regions associated with the main and accessory olfactory systems (Gimpl & Fahrenholz, 2001; Gould & Zingg, 2003). Nevertheless, it was clearly shown by multiple studies that the MeA is the brain region where oxytocin action is necessary and sufficient for formation of social recognition memory (Choleris et al., 2007; Ferguson, Aldag, Insel, & Young, 2001). Similarly, the LS was shown to be the area where vasopressin activity is most critical to this memory form (Bielsky et al., 2005; Dantzer, Koob, Bluthe, & Le Moal, 1988; Everts & Koolhaas, 1997), although its activity in the olfactory bulb (OB) (Tobin et al., 2010) was also shown to be important.

2.2. Social recognition memory and acute social isolation

All early studies using the social recognition paradigm (mainly with rats) reported that social recognition memory may be observed only for a limited time period ranging between 1 and 2 h following the first encounter with the social stimulus (reviewed in Popik & van Ree, 1998). Therefore, social recognition memory was considered to be a short-term memory that for unknown reasons cannot be consolidated into a long-term form (Ferguson et al., 2002).

This concept was challenged by the seminal study of Kogan et al. (2000). In contrast to all previous studies which isolated the subject animals for several days prior to the social recognition test, these authors used group-housed mice, which displayed a reduction in investigation time during the second encounter with a particular social stimulus even a week after the first encounter. In contrast, animals which were singularly caged for a week showed no memory of the social stimulus even one day after the first encounter with the same stimulus. Yet, these animals displayed an intact social memory when tested 30 min after the first encounter, suggesting that only long-term, but not short-term social recognition memory was impaired by social isolation. Moreover, the week-long isolation caused no change in the anxiety level of the animals, as assessed by the elevated plus maze test. Thus, it seems as if the isolation of the animals directly impaired the conversion of short-term social recognition memory into a long-term form. When the authors examined how fast this impairment is induced, they surprisingly found that the mice lost their ability to acquire long-term social recognition memory following as shortly as one day of isolation.

Using group-housed mice Kogan et al. showed that, similarly to other types of long-term memory, long-term social recognition memory is hippocampal-dependent and requires protein synthesis and cAMP responsive element binding protein (CREB) activity. These results were later confirmed by other studies exploring mechanisms underlying long-term social recognition memory (Pena, Pereira-Caixeta, Moraes, & Pereira, 2014; Richter, Wolf, & Engelmann, 2005; Wanisch, Wotjak, & Engelmann, 2008). Yet, the issue of acute social isolation-induced impairment of long-term social recognition memory had not been directly addressed until recently, when several studies characterized the phenomenon and started to investigate its mechanism.

The study of Gusmão et al. (2012) started with confirming the results of Kogan et al. using both the social recognition and social discrimination paradigms in adult male mice to show that long-, but not short-term social recognition memory, is abolished by one week of social isolation. They also confirmed that one week of social isolation does not increase the level of anxiety of the animals, thus ruling out the involvement of anxiety in the impairment induced by acute social isolation. When examining other types of long-term memory, the authors found no difference between group-housed and isolated mice in the inhibitory avoidance and novel object recognition tests. Thus, similarly to Kogan et al. (2000) they concluded that the impairment induced by acute social isolation is restricted to long-term social recognition memory.

Interestingly, the authors found that odor-enriched housing restored the long-term social memory of the isolated animals. In a follow-up experiment, Monteiro, Moreira, Massensini, Moraes, and Pereira (2014) showed a link between the restoring effect of an odor-enriched environment and adult neurogenesis. They investigated the number of newborn neurons in the two main brain areas harboring newborn neurons in adult mice, the dentate gyrus (DG) sub-region of the hippocampus and the OB. Notably, the only location where one week of social isolation caused a significant reduction in the abundance of newborn neurons was the mitral cell layer of the OB, but this reduction was not compensated for by odor-enriched housing. In contrast, housing the animals in an odor-enriched environment, whether in groups or in isolation, caused significant elevation in the number of newborn neurons in both the DG and glomerular layer of the OB. In the granule cell layer of the OB an increase in newborn neurons was observed only in group-housed mice subjected to an odor-enriched environment.

To strengthen the link between adult neurogenesis and long-term social recognition memory, the authors examined the effects of chronic ICV infusion of the mitotic inhibitor cytosine arabinoside (AraC) to mice housed in an odor-enriched environment during the course of one week of social isolation. Indeed, in contrast to saline, AraC infusion eliminated long-term social recognition memory and reduced the number of newborn neurons in the DG and granule cell layer of the OB, with no effect on other layers of the OB. However, since the effect of AraC on long-term memory was not examined on group-housed mice, it is possible that a week-long AraC infusion impairs social memory regardless of the housing conditions. Moreover, the reduction in abundance of

newborn neurons due to AraC administration was found only in the DG and granule-cell layer of the OB, areas where no reduction in newborn neurons was observed in isolated mice as compared to group-housed animals. Thus, causality relationship between adult neurogenesis and acute social isolation was not proved by this study.

Other characteristics of the social memory-impairing effect of acute social isolation were revealed by a recent study by Shahar-Gold et al. (2013). These authors extended the results of the aforementioned studies to rats and used the social recognition test to show that the long-term social recognition memory of both male and female rats is indeed severely impaired by acute social isolation (Figs. 1 and 2). They also examined whether this impairment is in the acquisition or retrieval phases of the test. For this purpose, they compared between three groups: (1) rats housed in groups throughout the experiment (grouped), (2) rats kept in social isolation starting one week before the experiment and throughout the experiment (isolated), (3) rats kept in group-housing before the test, and delivered to solitary cages immediately after the acquisition phase. This phase comprised three consecutive 5-min encounters with the same social stimulus, separated by 10-min intervals. The animals were tested one and seven days later by two consecutive 5-min encounters, one with the same stimulus and another with a novel stimulus, separated by 30 min (Fig. 1).

As expected, the grouped animals showed intact long-term social recognition memory, expressed as a shorter duration of investigation of the familiar social stimulus as compared to the novel one, both one day and seven days following memory acquisition. In contrast, the isolated animals, males or females, did not show any difference between the stimuli even one day after memory acquisition, demonstrating a lack of long-term social

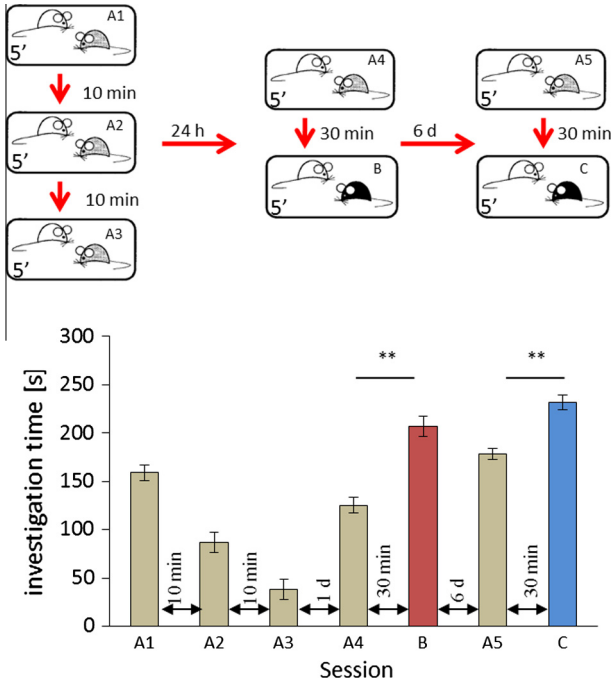

Fig. 1. Long-term social recognition memory in adult male rats. Adult male rats ($n = 8$) showed a reduction in social investigation time during three consecutive 5 min encounters, 10 min apart, with the same juvenile rat (A1-3). The rats displayed long-term social recognition memory 1 day and 7 days later, as assessed by the significant difference in investigation time between the encounters with the same juvenile rat and novel one 30 min later (1 d – A4 vs. B; 7 d – A5 vs. C). Paired t-test: $^{**}p < 0.01$. Bars represent mean ± SEM. Adapted from Shahar-Gold, Gur, and Wagner (2013) according to Creative Commons public domain license.

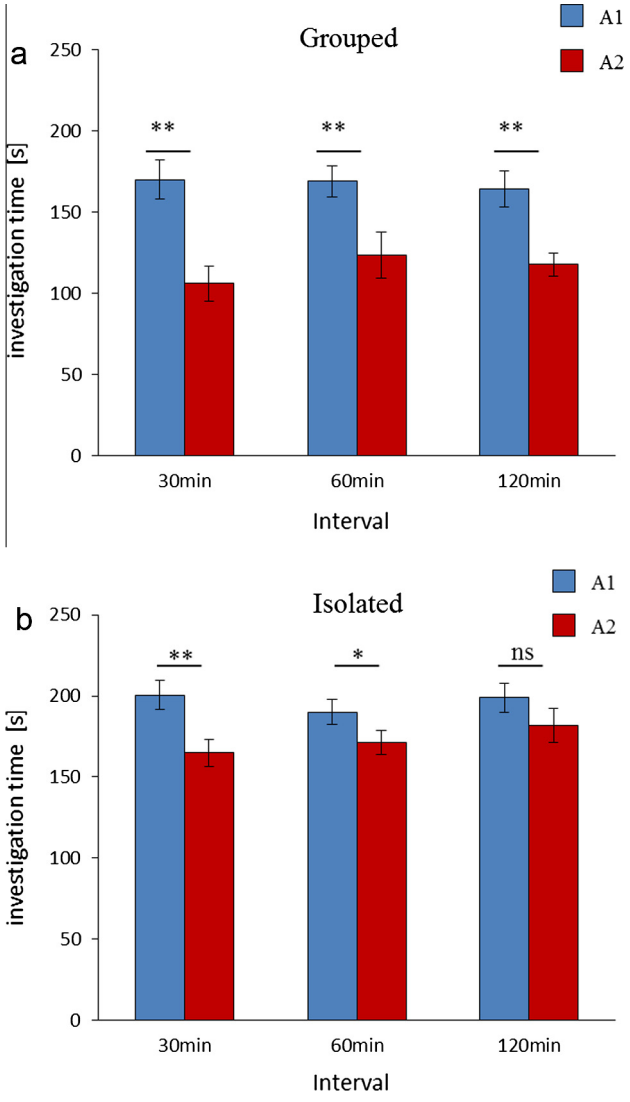

Fig. 2. Acute social isolation impairs long-term social recognition memory. (a) Rats in group housing displayed a significant decrease in investigation time during the second 5 min encounter (A2, red bars) compared to the first (A1, blue bars), regardless of the time interval between the encounters. Paired t-test: $^{**}p < 0.01$, $n = 10$ per group. (b) Socially isolated rats displayed a significant decrease in investigation time measured during the second encounter only for intervals of 30 and 60 min but not for a 120 min interval. Paired t-test: $^{**}p < 0.01$, $^{*}p < 0.05$, $n = 10$ per group. Bars represent mean ± SEM. Adapted from Shahar-Gold et al. (2013) according to Creative Commons public domain license. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

recognition memory. Notably, the group that was delivered to isolation following memory acquisition showed intact memory even after seven days of social isolation. This result suggests that it is memory acquisition rather than its retrieval which is impaired by acute social isolation. Another important conclusion from this experiment was that even after a week in isolation the animals still display social novelty seeking, reflected by their reduced interest in a familiar animal, similarly to group-housed rats. Thus, the impairment induced by acute social isolation resides in the social memory rather than in the social behavior of the animals.

The authors then explored the time course and reversibility of the impairment induced by acute social isolation in the long-term social memory of the adult rats. To that end they examined the time interval between encounters which enables discrimination between the isolated and group-housed rats. They found

that as shortly as 120 min after the first encounter, the isolated animals treat the same stimulus as if it were a novel one, while group-housed rats recognize it as familiar (Fig. 2). Therefore, the authors used a test comprised of two 5-min encounters separated by 120 min to determine the long-term social memory of the animals. This test was repeatedly performed with the same group of adult male rats, while the housing conditions of the animals were changes (Fig. 3). The animals showed intact long-term memory at the beginning of the experiment, while kept in group housing. Then they were delivered to solitary cages and examined one day later. As previously reported for mice (Kogan et al., 2000), this short period of time in social isolation was sufficient to induce severe impairment of long-term memory in the rats. The animals were tested again after a whole week in isolation, and still showed no long-term social recognition memory. Then the animals were delivered back to group housing. A day later they still did not show any recovery of social memory, but following seven days in group housing the animals regained intact long-term memory. Thus, the impairment in long-term social recognition memory, which is rapidly induced within a day of social isolation, can be reversed by several days in group housing.

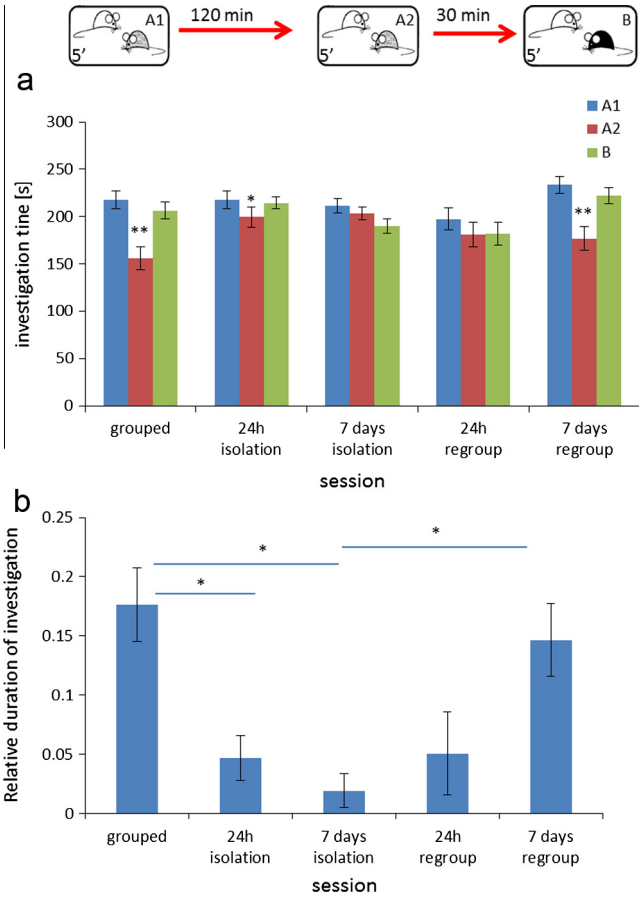

Fig. 3. Social isolation rapidly induces a reversible impairment in long-term social recognition memory. (a) Social investigation time during two 5 min encounters, 120 min apart, with the same juvenile rat (A1, A2) and a third encounter with a novel juvenile rat (B) 30 min later. The test was repeated with the same group of adult animals ($n = 13$) while their housing conditions were changed, using new stimuli for every session. After isolation for 1 day (24 h isolation) the rats showed a minor reduction in investigation time between the first and second encounters and following 7 days of isolation the reduction was abolished. This effect was reversed following 7 days (7 days regrouping), but not 1 day (24 h regrouping) of return to group housing. Paired t-test: $^{**}p < 0.001$, $^{*}p < 0.05$. (b) Relative duration of investigation (A1 − A2/A1 + A2) values of the results shown in (a). Repeated ANOVA, $F(4,48) = 7.573$, $p < 0.001$, Bonferroni post hoc: $^{*}p < 0.05$. Adapted from Shahar-Gold et al. (2013) according to Creative Commons public domain license.

The authors also found that, as opposed to findings in mice (Kogan et al., 2000), acute social isolation of rats caused impairment in short-term social recognition memory as well. This impairment is reflected by the need of socially isolated rats for more time for the acquisition of short-term memory than group-housed rats. Thus, while group-housed rats were able to show short-term memory even when 2 min encounters were used, the isolated rats did not seem to acquire the memory within such a short time, but did show short-term social recognition memory when 5 min encounters were used. The impairment in short-term memory had a different time course than the impairment in long-term memory, with longer induction time (>1 day), and full reversal as shortly as one day following regrouping of the animals. Moreover, only the impairment in long-term memory could be compensated for by systemic injection of vasopressin immediately following memory acquisition. These results suggest that the impairments in short- and long-term social recognition memory, which are induced by acute social isolation of adult rats, are caused by distinct mechanisms.

In a follow-up study Gur et al. (2014) showed that long-term social recognition memory is mediated by oxytocin-dependent synaptic plasticity in the MeA, and that this type of synaptic plasticity is abolished in adult rats isolated for seven days. Thus, acute social isolation seems to impair some of the molecular processes underlying long-term social recognition memory at the level of the MeA, which gets direct inputs from the AOB. Since these processes were shown to be oxytocin-dependent, an appealing possibility is that at least one of the components of the oxytocin-mediated neuromodulatory mechanism in the MeA is malfunctioning during social isolation. Such a component, like the expression, trafficking or release of oxytocin, may reside in the hypothalamic oxytocinergic neurons innervating the MeA. However, since Gur et al. used exogenously applied oxytocin in their study, this possibility seems unlikely, Alternatively, the malfunctioning component may reside in the MeA network, for example in the expression or function of the *Oxtr*. This possibility, which is supported by the known epigenetic regulation of the *Oxtr* gene by DNA methylation (Harony-Nicolas et al., 2014; Mamrut et al., 2013), should be further examined. This does not exclude the possibility that other molecular processes in other brain regions which are involved in social memory, such as neurogenesis in the DG or OB (Monteiro et al., 2014), are also impaired by acute social isolation.

3. Summary

During the last fifteen years since the report of Kogan et al. (2000), several independent studies, reviewed in this paper, have repeatedly confirmed that long-term social recognition memory is rapidly impaired by acute social isolation of adult mice and rats. This impairment, which seems to be specific to social memory, is induced within one day of solitary-housing, and is reversed following several days in group-housing. The mechanisms mediating this impairment and their whereabouts in the brain are yet to be discovered. Nevertheless, reduced adult neurogenesis in the DG and OB as well as impaired synaptic plasticity in the MeA were both observed following acute social isolation and shown to be involved in long-term social recognition memory. The fact that only social memory, but not other types of memory, was found to be impaired may be related to the specific neural network which processes social information in the mammalian brain which includes, among other regions, the OB, MeA, LS, and the CA2 region of the hippocampus. Nevertheless, the rapid induction and reversal of this impairment suggests that revealing the underlying molecular mechanisms may pave the way to unraveling the processes mediating the damaging effects of partial or perceived social isolation

on human mental health. Such a progress, coupled with experiments in other animal models, for example voles, (Lieberwirth, Liu, Jia, & Wang, 2012; Pournajafi-Nazarloo et al., 2011), would facilitate clinical trials with various interventions, such as intranasal delivery of oxytocin and vasopressin, to compensate for the damaging effects of social isolation. Moreover, these mechanisms may be relevant to other psycho-social diseases in which oxytocin and vasopressin may be involved, such as autism and schizophrenia (Harony & Wagner, 2010; MacDonald & Feifel, 2013).

Acknowledgment

This research was supported by the Israel Science Foundation Grant #1350/12.

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