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Co-learning facilitates memory in mice: A new avenue in social neuroscience

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ABSTRACT

Social context affects brain function but our understanding of its neurobiology is at an early stage. The mere presence of one individual can alter the cognitive capacities of another and social learning has been demonstrated in many species, including the mouse. We asked several questions: 1. How can active engagement of two familiar mice in the same learning activity (co-learning) alter their memory? 2. Under which environmental conditions (aversive vs non-aversive) can we expect the memory to be enhanced, impaired, or not affected? 3. Can a genetic factor modify the co-learning effect on memory? More specifically, can co-learning correct memory deficits in autistic-like BTBR inbred mice with deficient sociability? We demonstrated that pairs of familiar inbred mice of the same or different genotypes (C57BL/6J and BTBR) that were habituated to new objects and their spatial location, had enhanced episodic memory in the spatial object recognition test, whereas individually-trained animals failed to solve this task. Notably, the co-learning effect was genotype-dependent. BTBR mice paired with BTBR cage-mates in the habituation session modestly ameliorated their performance in the object recognition test but co-learning with a familiar C57BL/6J mouse completely normalized episodic memory deficit. Next, we explored the co-learning effect on fear memory in these inbred strains. Interestingly, mice of both genotypes displayed significantly enhanced contextual fear memory once they had been conditioned together with BTBR animals. The same influence of BTBR presence was observed on cued fear memory in C57BL/6J mice, whereas a modest co-learning effect was found on cued fear conditioning in the BTBR strain. Taken together, we demonstrated for the first time the co-learning effect on cognitive capacities in mice, which can be modified by genetic background and environmental conditions. The possible implications of this methodological approach in social neuroscience are discussed.

This article is part of a Special Issue entitled 'Cognitive Enhancers'.

1. Introduction

The main focus of cognitive neuroscience is to study neuronal substrates of mental processes to address questions of how cognitive functions are produced by the brain. Multiple experimental paradigms assess the neuronal mechanisms of behavioral processes of one individual by isolating a human or animal in a testing room/chamber. However, humans and many species of animals are social by nature, acquiring social skills in early development and remain apart of the social world throughout life. Accumulating knowledge points out that social context influences cognitive capacities in different species and the interdisciplinary field of social neuroscience, dedicated to the study of multiple-brains rather than a single-brain in neuroscience, has been formed in recent years (Hasson et al., 2012).

Social learning is the capacity of animals to obtain experience related to their interactions with other subjects. Social learning can be classified in terms of two experimental paradigms: *audience effects* and *co-action effects* (Zajonc, 1965). The first paradigm involves the observation of behavior when it occurs in the presence of passive spectators. The second examines behavior when it occurs in the presence of other individuals also engaged in the same activity.

The audience effect of social learning includes several types of behavior from the lowest, e.g. *social facilitation* (ability to perform specific actions only in presence of others) to more complex such as *instructing*, which is the basis of "cultural traditions" within an animal population. Social facilitation means that animals would express particular behavior with higher probability (facilitated response) in the presence of conspecifics rather than in isolation.

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Social facilitation influences feeding behavior, ambulation, emotionality and cognitive capacities (Wills et al., 1983). *Social contagion* is seen, for example, as fear reaction in fish shoals, bird flocks or hoofed animals. Mobbing is another example of social contagion in animals, which is an anti-predator behavior that occurs when individuals of a certain species mob a predator by cooperatively attacking or harassing it to protect their offspring. Stimulus enhancement is a simple form of social learning: the presence of one subject attracts the attention of another animal to the whole object in general, or to its functional part. The most complex forms of social learning are *imitation* and *active instructing* (teaching or tutoring), seen in humans or animals with highly developed central nervous system (Reznikova, 2004). Imitation may consist of one action to repeat or the consequence of actions in a more complex situation whereas active instructing contributes to the distribution of cultural traditions in population. Complex forms of social learning were considered parameters of cognitive capacities in animals at an early stage of experimental zoo-psychology. Chickens, in experiments of Thorndike (1911), must solve how to escape from the "puzzle box". However, by observing how this task was solved by others, chicken learned faster. Next, chicken-"demonstrators" were split into two groups and each of them had been trained to solve the "puzzle box" differently. Chicken-"observers" preferred the previously seen approach to solve the problem, suggesting that imitation plays an important role in learning. Observational fear learning was recently demonstrated in mice, regulated by the anterior cingulate cortex, parafascicular or mediodorsal thalamic nuclei, which comprise the medial pain system representing pain affection (Jeon et al., 2010).

The co-action effect is another type of social learning in terms of experimental paradigms and its neurobiology was not well studied. However, many human actions ranging from a handshake to playing basketball to theatrical performance require tight coordination across team members (Knoblich et al., 2011). Moreover, even actions that can be performed in isolation, such as playing a musical instrument or dancing, are faster and more accurate when performed within an ensemble. Accumulating evidence shows that during joint actions, people become implicitly coupled at motor, perceptual and cognitive levels (Knoblich et al., 2011). At a cognitive level, joint activity occurs when two people respond to different aspects of a stimulus, e.g. using the same hand, and the response times sped up when the other participants' responses were compatible and slowed down when they were incompatible (Keller, 2008). Comparative analyses of different species, including monkeys, parrots, rodents and insects suggest that social learning is a universal phenomenon involved in the processes of evolution of human society and animal populations.

Although neurobiological mechanisms of social learning are still poorly understood, fast-developing new tools in neuroscience such as brain imaging, molecular-cellular techniques or optogenetics will shed a light on social neuroscience and open a new avenue for the treatment of diverse mental disorders. Indeed, the nature of the social environment has been long recognized as a powerful emotional modulator contributing to both susceptibility to and recovery from mental illnesses. For instance, depression was proposed as an adaptation to deal with social competition, loss of social attachments, and avoiding social exclusion (Allen and Badcock, 2006). A wide array of social behavioral intervention programs have been developed to correct mental disorders in humans, such as anxiety, depression, post-traumatic stress disorder, Alzheimer' disorder, autism, and schizophrenia (Goldstein et al., 1997; National Research Council, 2001; Onwumere et al., 2011; Rodrigues et al., 2011; Gaebel et al., 2012). Beneficial effects of social training with familiar partners were reported on cognitive deficits in aging people (Rauers et al., 2011), humans with Alzheimer' disorder (Bourgeois, 1990), and autistic children (Stichter et al., 2012).

In the current study we sought to probe if joint learning or co-learning can facilitate aversive and non-aversive memories in "regular" C57BL/6 mice and "autistic-like" BTBR animals. We focused our efforts on autistic-like mice to elaborate a new methodological approach in social neuroscience that can be applied to different animal models of human mental illnesses.

Autism is a complex neurodevelopmental disorder characterized by poor communication with others, low capacity of mimicking behavior, accompanied by restricted and repetitive behavior and moderate cognitive deficit (Rommelse et al., 2011). BTBR T + tf/J (BTBR) is a reliable mouse model of autism with deficient social affiliation, social transmission of food preference, ultrasonic vocalizations in response to social cues, high repetitive self-grooming and gaze aversion-like behaviors (McFarlane et al., 2008; Scattoni et al., 2008, 2011; Defensor et al., 2011). In parallel, BTBR mice also show a severe contextual fear memory deficit (MacPherson et al., 2008). To date there are no pharmacological treatments for autism, and behavioral interventions are the most effective interventions to correct the diagnostic symptoms of autism. Recent findings of Crawley's group revealed that BTBR juvenile mice raised together with C57BL/6J control mice during adolescence improved their social approach behavior (Yang et al., 2011), further supporting the strategy of behavioral intervention with normally developing peers for correcting social behavior in autistic children. Peer intervention programs, e.g. the Integrated Play Group, or Learning Experiences: An Alternate Program, significantly improved not only social-communicative skills, but also ameliorated such intellectual abilities in children with autism as joint attention, language expression, and academic performance (Wolfberg and Schuler, 1993; Betz et al., 2008; Eikeseth et al., 2002; Zercher et al., 2001). Therefore, the BTBR inbred strain offers a unique opportunity to assess the effect of social context on their deficient cognitive capacities. Given that BTBR mice were able to improve their social skills when exposed to the peer enrichment environment (Yang et al., 2011), we asked if BTBR mice can be "instructed" by normal C57BL/6J mice during their active engagement (co-learning) in the same learning activity and therefore, improve their performance in the spatial object recognition and fear conditioning behavioral tasks. We found that co-learning enhanced spatial object recognition in mice of both inbred strains however, only co-learning of BTBR with C57BL/6J completely normalized deficit of their episodic memory in this task. Deficient contextual but not cued fear conditioning was ameliorated in BTBR mice once they had been co-trained with BTBR but not with C57BL/6J partners, suggesting distinct neurobiological pathways for fear memory. Overall, we demonstrated for the first time the co-learning effect on cognitive performance in mice, which can be modified by genetic background and environmental conditions.

2. Materials and methods

2.1. Animals

C57BL/6J (C57BL) and BTBR T + tf/J (BTBR) inbred mice have been bred at the Toronto Center of Phenogenomics (TCP). Mice were weaned at 21 days of age and couples of juvenile mice of each inbred strain (2C57BL and 2 BTRB) were raised together until adulthood (social enrichment conditions) under a 12 h light/dark cycle (lights on at 07.00) with *ad libitum* food (Purina mouse chow). Behavioral testing was conducted on male mice at 12–14 weeks of age between 09.00 and 16.00 h. Independent cohorts of mice have been used for each behavioral experiment (spatial object recognition; fear conditioning; elevated plus-maze; USV recording in the object recognition test and USV recording in fear conditioning). All animal procedures were approved by the Animal Management Committee of Mount Sinai Hospital and were conducted in accordance with the requirements of the Province of Ontario Animals for Research Act 1971 and the Canadian Council on Animal Care.