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Short communication

Episodic-like memory in Ts65Dn, a mouse model of Down syndrome

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Abstract

Ts65Dn mice, like individuals with Down syndrome (DS), demonstrate a functional dissociation between explicit and implicit forms of memory, showing selective impairment in explicit or declarative learning tasks. Here, we explored Ts65Dn explicit memory deficits further by evaluating the ability of these mice to assimilate the temporal and spatial contexts under which previously novel objects had been encountered. We found that Ts65Dn mice could in fact form contextual representations of objects over the course of a few hours, contrary to their inability to discriminate object novelty over a more prolonged period of 24 h. These results suggest that Ts65Dn mice might have particular difficulties in declarative tasks requiring long-term memory, presenting an especially important putative therapeutic target for pre-clinical and clinical DS research.
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Keywords: Ts65Dn; Object recognition; Medial temporal lobe; Down syndrome

Accumulating evidence suggests that declarative learning and memory systems associated with the medial temporal lobe (MTL) are disproportionately influenced in people with Down syndrome (DS), leading to severe shortcomings in information processing and in the acquisition of new knowledge [19]. As such, these findings reinvigorate the need to determine the dynamic range of cognitive deficits displayed by Ts65Dn mice, the foremost animal model of DS [15,23]. Specifically, do Ts65Dn have performance deficits in what are largely considered MTL-mediated tasks? Do they have behavioral signatures of episodic-like memory? If so, to what degree? In rodents, declarative memory can be delineated most parsimoniously along two domains: spatial and recognition memory [25]. Like individuals with DS, Ts65Dn mice are generally impaired in cognitive tasks requiring the use of spatial cues. Herein, they show navigation problems in the Morris water maze (i.e., increases in time necessary to reach the hidden platform) [15,23], difficulties in the radial arm maze task (i.e., increases in reference memory errors) [5,9,10,16], lower percentage alternation in a T-maze [14], and learning deficits during contextual fear conditioning (i.e., decreased time spent freezing in a shock-associated chamber) [17]. Their performance in the novel object recognition task is similarly affected, as they are unable to discriminate between familiar and novel items over a 24 h stretch [14]. Nonetheless, Ts65Dn mice do exhibit normal reactivity to spatial displacement and to object novelty within set object arrays over short time periods (∼3 min), suggesting that they possess some rudimentary – albeit limited – ability to process object-based information [18].

The interwoven structures that comprise the MTL, namely the hippocampus and perirhinal, entorhinal and parahippocampal cortices, jointly oversee the proper encoding, consolidation and retrieval of information related to discrete events [25]. This processing ultimately gives way to recognition memory, itself consisting of two components: (1) familiarity, a general awareness of the features of a stimulus, and (2) recollection, knowledge of the stimulus in the context of other information, such as when, where, or under what circumstances the stimulus was encountered [25]. Considering that the "episodic" or recollective component of recognition memory is defined by an integrated conceptualization of the "what" – "where" – and – "when" particulars of a situation, it has been difficult to establish whether active recollection (as opposed to familiarity) occurs in rodents as it does in humans. In other words, can rodents behaviorally demonstrate that they remember seeing a specific object in a specific place at a given time? To address this issue, Dere et al. recently developed a test that combines different versions of the novelty preference paradigm, dubbed the episodic-like

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memory task [11]. The authors took advantage of the fact that mice show innate preferences for exploring novel objects versus familiar ones, preferences for exploring familiar objects that have been moved versus familiar ones that have remained stationary, and preferences for exploring familiar objects that they have seen less recently versus those that they have seen more recently. Subsequently, we have used this task in the current study to evaluate episodic-like memory in Ts65Dn mice, asking whether these mice have the ability to form "what–where–when" representations over the course of a few hours (a model MTL function).

Ts65Dn mice were obtained by mating female carriers of the 17^{16} chromosome (B6EiC3H – a/ATs65Dn) with (C57BL/6JEi × C3H/HeJ)F1 (JAX #JR1875) males [8]. Ts65Dn mice were thus maintained on the B6/C3H background. Two cohorts of wild-type (WT) and Ts65Dn mice ($n = 9$ and 11, respectively; 4–6 months of age; male) were submitted to daily experimenter handling, and given an opportunity to habituate to a black acrylic,

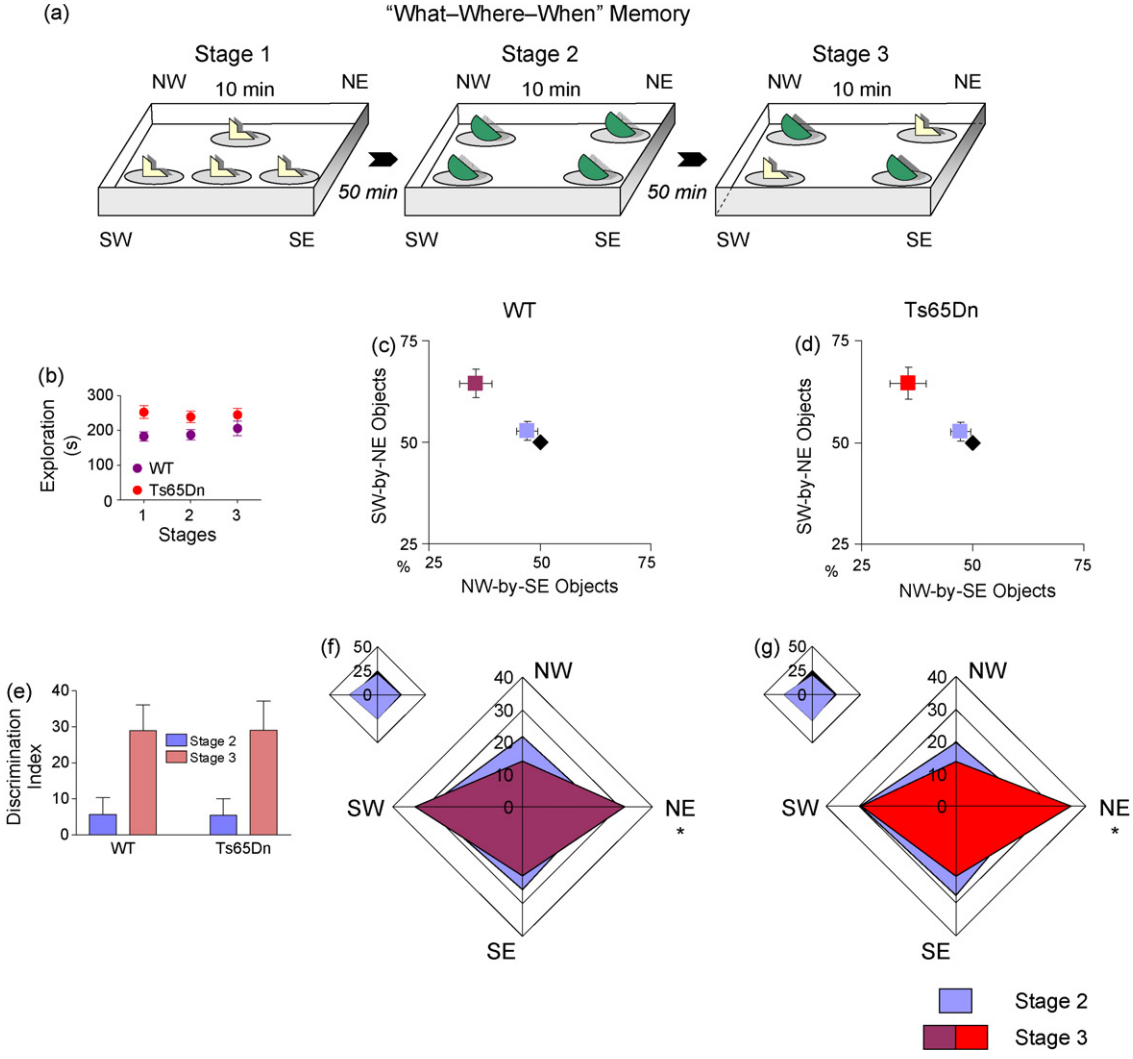

Fig. 1. Ts65Dn mice form "what–where–when" representations in the episodic-like memory task. (a) Schematic of the episodic-like memory task. Here, the animals are simultaneously "asked" when and where they encountered two different never-before-seen objects (please see text for technical details). (b) WT (purple circles) and Ts65Dn (red circles) do not show any differences in total object exploration time between stages in the Dere protocol, suggesting that the cognitive performance of both groups of mice is not secondary to general changes in the amounts of explorative activity across the Dere sequence. (c, d) WT and Ts65Dn mice do not differentially explore SW-by-NE related objects (i.e., objects in the SW and NE corners of the arena) versus NW-by-SE related objects (i.e., objects in the NW and SE corners of the arena) in Stage 2 (blue squares), suggesting that they do not exhibit directional biases in the quadratic-shaped object configuration (for reference, a theoretically perfect split in exploration between both object sets is depicted with black diamonds). However, mice from both genotypes exhibit recency preferences in Stage 3 (WT, purple squares; Ts65Dn, red squares), spending almost twice as much time with old familiar objects versus recent familiar objects. (e) WT and Ts65Dn recency preferences calculated alternatively with discrimination indices (DI's), where DI = [SW-by-NE object exploration time/total exploration time] − [NW-by-SE object exploration time/total exploration time] × 100. (f, g inserts) WT and Ts65Dn mice do not differentially explore individual, NW-NE-SW-SE objects in Stage 2 (blue plots). Notably, there is a symmetrical distribution of explorative activity (for reference, a theoretically perfect 25% split in exploration between individual objects is depicted with the black plot). (f, g) Animals from both genotypes polarize their exploration towards the NE-shifted old familiar object in Stage 3 (WT, purple plot; Ts65Dn, red plot; see Table 1 for a complete statistical breakdown of the episodic-like memory task). Please note that all experimental procedures were approved by the Stanford University Institutional Animal Care and Use Committee (IACUC), and were conducted in compliance with the NIH's *Guide for the Care and Use of Laboratory Animals*. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article).