Title: Spatial reconstruction deficits in Down syndrome

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Introduction: Previous studies suggested delayed maturation of the medial temporal lobe, especially the hippocampus, in people with Down syndrome (DS, trisomy 21; Edgin, 2013; Pennington et al., 2003). The hippocampus is critical for remembering spatial information and relational information. To test the ability of binding spatial relations, spatial reconstruction (SR) paradigms are used. Specifically, these tasks require the placement or identification of objects within a scene array, and then allow for the analysis of the precision of these reconstructions. The link between hippocampal damage and deficits in SR performance has been discovered in patient populations (Watson et al., 2013), but how it is affected in children and individuals with DS is far less known. Therefore, this study employs a novel task to determine how SR performance differs in typically developing (TD) group and in DS.

Method: The participants in this study were children with Down syndrome (n=44) and typically developing controls (n=72) recruited across three sites. All children were trained to perform the Alien Object task, an adapted version of the SR task previously administered with selective damage to the hippocampus. The task required them to remember the spatial location of two (three trials) or three (three trials) objects on a desert scene picture. The presentation of the objects was followed by a 5s delay period. After this delay, participants were required to place the objects back into their studied location using a touchscreen interface. Misplacement error was defined by the sum of the Euclidean distance between each item's studied location and the reconstructed location. Swap error (or the complete position misplacement of the items) was calculated by counting the frequency that the vector connecting each pair of objects reversed direction (i.e., the sign of the vector's x and y components changed simultaneously between study and reconstruction; Watson et al., 2013). Linear mixed-effects models were used to evaluate the task performance of DS group and TD group, via the *lmerTest* (Kuznetsova et al., 2017) packages in R. Tukey's multiple comparisons test was used for post hoc analysis.

Results: Both misplacement errors and swap errors decreased with age in the TD group, while no such pattern was found in the DS group. Accordingly, we divided the TD group into three sub-groups (3 ~ 5, 6 ~ 8, and > 9 years old). A linear mixed-effects model with age, set size as fixed effects and participant ID being a random effect, revealed a significant effect of age for misplacement errors (p = 6.077e-16) and swap errors (p = 6.219e-06), respectively. The 3 ~ 5 years old TD group generated more misplacement errors than the 6 ~ 8 years old TD group (adj. $p < 0.0001$) and the > 9 years old group (adj. $p < 0.0001$). The 6 ~ 8 years old TD group made more misplacement errors than the > 9 years old group (adj. p = 0.0001). For swap errors, the 3 ~ 5 years old TD group also showed more swap errors than the 6 ~ 8 years old TD group (adj. p = 0.0037) and the > 9 years old group (adj. $p < 0.0001$). No significant effect of set size or interaction was found. Further, we built three linear mixed-effects models to compare the DS group with three TD groups respectively, finding that DS group showed more misplacement errors than the 6 ~ 8 years old TD group (p = 2.261e-06), and the > 9 years old TD group (p = 6.438e-10), while no significant effect were found when compared with the 3 ~ 5 years old TD group. The DS group and the 6 ~ 8 years old TD group made more misplacement errors in set size 3 than in set size 2 (p = 0.0482). The same procedure implemented with swap errors showed that DS group generated more swap errors than the 6 ~ 8 years old TD group (p = 0.0154), and the > 9 years old TD group (p = 0.0003), while no significant difference when compared with the 3 ~ 5 years old TD group.

Discussion: In summary, we found that in typically developing children, compared with the younger group (3 ~ 5 years old), the older group (6 ~ 8 and > 9 years old) showed fewer misplacement errors and swap errors when performing the spatial reconstruction task, which suggested the development of relational binding ability as age increased, with age six being the potential critical period of maturation. Additionally, while there were no significant differences between the DS group and the youngest TD group on those two measurements, the DS group generated more misplacement errors and swap errors compared with the two older TD groups respectively, suggesting that the development of the relational binding ability of the DS group

might be delayed. These errors are similar to the data from patients with selective hippocampal damage and suggest that this measure may be one useful metric for hippocampal development. Future analyses will relate these spatial reconstruction errors to standard and novel measures of memory outcomes, including delayed memory retention over a 1-month interval.

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