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Bigger is better and worse: On the intricate relationship between hippocampal size and memory

Katalin Molnár [a,b,c], Szabolcs Kéri [a,b,c,*]

[a] Nyírő Gyula Hospital, National Institute of Psychiatry and Addictions, Budapest, Hungary
[b] University of Szeged, Faculty of Medicine, Department of Physiology, Szeged, Hungary
[c] Budapest University of Technology and Economics, Department of Cognitive Science, Budapest, Hungary

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ABSTRACT

The structure–function relationship between the hippocampal region and memory is a debated topic in the literature. It has been suggested that larger hippocampi are associated with less effective memory performance in healthy young adults because of a partial synaptic pruning. Here, we tested this hypothesis in individuals with Fragile X Syndrome (FXS) with known abnormal pruning and IQ- and age-matched individuals with hypoxic brain injury, preterm birth, and obstetric complications. Results revealed larger normalized hippocampal volume in FXS compared with neurotypical controls, whereas individuals with hypoxic injury had smaller hippocampi. In neurotypical controls and individuals with hypoxic injury, better general memory, as indexed by the Wechsler Memory Scale-Revised, was associated with larger hippocampus. In contrast, in FXS we observed the opposite relationship: larger hippocampus was associated with worse general memory. Caudate volume did not correlate with memory in either group. These results suggest that incomplete pruning in young healthy adults may not contribute to less efficient memory capacity, and hippocampal size is positively associated with memory performance. However, abnormally large and poorly pruned hippocampus may indeed be less effective in FXS.

1. Introduction

Despite the well-known fact that the hippocampus is implicated in learning and memory (Squire & Wixted, 2011), there is an intriguing controversy on a simple structure–function relationship: are larger hippocampi necessary for effective learning and remembering? In a recent study, Pohlack, Meyer, Cacciaglia, Liebscher, Ridder, and Flor (2014) highlighted the remarkable scarcity of studies investigating this structure–function relationship in healthy young individuals and the nature of the controversial data. In contrast to the common and intuitive belief that larger hippocampi are better, the meta-analysis of Van Petten (2004) demonstrated a negative correlation between hippocampal size and memory in young adults, whereas the correlation was positive in older participants. Foster et al. (1999) suggested that in healthy young people, the seemingly paradoxical negative correlation between hippocampal volume and memory might be related to incomplete synaptic pruning during childhood and adolescence, which refers to the elimination of unnecessary neurons and synapses to achieve more economic information processing. The essence of the hypothesis is that if pruning is not effective or completed in young people, a not appropriately pruned and hence larger hippocampus might be less optimal for learning and memory (Foster et al., 1999; also discussed by Pohlack et al., 2014).

We can directly test this hypothesis by the investigation of patients characterized by decreased synaptic pruning. Ample evidence suggests that synaptic pruning is less effective in Fragile X Syndrome (FXS) (Beckel-Mitchener & Greenough, 2004; Gatto & Broadie, 2011; Grossman, Elisseou, McKinney, & Greenough, 2006). FXS is one of the most common forms of inherited neurodevelopmental disorders leading to intellectual disability and autism (Reiss & Hall, 2007). The syndrome is caused by the absence of Fragile X Mental Retardation Protein (FMRP), which is a consequence of the silencing of the *FMR1* gene. Gene silencing is due to the expansion of a CGG trinucleotide repeat (Xq27.3, >200 repeats in the full syndrome), which results in the hypermethylation of the promoter region and decreased gene transcription (Rousseau, Labelle, Bussières, & Lindsay, 2011).

Reiss, Lee, and Freund (1994) showed that the right and left hippocampal volumes were significantly larger in young people with FXS compared with a typically developing control group (see also Kates, Abrams, Kaufmann, Breiter, & Reiss, 1997). Jäkälä et al. (1997) also found slightly enlarged hippocampi in FXS, but this

* Correspondence to: University of Szeged, Department of Physiology, Dóm sq. 10, H6720 Szeged, Hungary. Tel.: +36 20 448 3530; fax: +36 62 545 842.
E-mail addresses: keri.szabolcs.gyula@med.u-szeged.hu, szkeri2000@yahoo.com (S. Kéri).

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phenomenon was much less definitive when hippocampal volume was normalized for brain area and coronal intracranial area. Normalized hippocampal volume negatively correlated with the Similarities and Picture Arrangement subtests of the Wechsler Adult Intelligence Scale (Jäkälä et al., 1997). The finding of enlarged hippocampi in FXS and autism has been confirmed by a meta-analysis (Geuze, Vermetten, & Bremner, 2005), but its neuropsychological relevance is still controversial. One plausible hypothesis is that the excessive number of unnecessary neurons and their connections lead to inefficient information processing, low signal-to-noise ratio, and consequently lower behavioral performance in FXS. The opposite pathological process may occur after hypoxic injury (HIN) resulting in the loss of neurons and their synaptic connections in vulnerable brain regions such as the hippocampal formation. Early perinatal HIN has long-term developmental consequences including lower number of neurons and poorer connectivity in adulthood (Nyakas, Buwalda, & Luiten, 1996; Rees, Harding, & Walker, 2011; Vannucci & Vannucci, 2005).

Here, we aimed to clarify this issue by assessing a homogeneous group of young men with FXS and autism using a standard neuropsychological procedure for memory testing focusing on several domains (the revised version of the Wechsler Memory Scale). We also recruited IQ- and age-matched control individuals who live with intellectual disability due to perinatal HIN and preterm birth. Given that structural anomalies are not confined to the hippocampus in FXS and several other subcortical brain regions are enlarged (Hessl, Rivera, & Reiss, 2004), we also measured the volume of the caudate nucleus. This structure served as a control brain region in the correlation analysis between memory performance and brain structure. We selected this brain region because several recent studies highlighted its enlargement and pathophysiological role in FXS (e.g., Gothelf et al., 2008; Hallahan et al., 2011; Hazlett et al., 2012). The caudate nucleus also seems to be an optimal control region from a functional point of view because recent evidence suggests that its morphology is related to frontal lobe-associated cognitive and behavioral deficits in FXS rather than different aspects of declarative memory (Peng et al. in press).

2. Method

2.1. Participants

We recruited the study volunteers at the Nyírő Gyula Hospital – National Institute of Psychiatry and Addictions, Budapest, Hungary. Participants were referred by specialists from the whole country. The neurotypical control group (NT) included 25 healthy men (mean age: 21.6 years, SD=4.5, range: 18–27) with negative history for neurological and psychiatric disorders. We also investigated 14 men with FXS and autism (mean age: 22.6 years, SD=6.2, range: 19–29). The diagnosis of FXS was confirmed through DNA analysis using standard Southern blot techniques (Macpherson & Sawyer, 2005). The third group ($n=17$, mean age: 22.0 years, SD=5.1, range: 18–28) consisted of individuals matched for IQ and age to the FXS patients. The IQ-matched group included patients with a history of obstetric complications, perinatal hypoxia, preterm birth, and low birth weight with no known genetic abnormalities. All medical records were available to confirm the diagnosis. Individuals with FXS and hypoxic injury (HIN) live with intellectual disability as defined by the American Association on Intellectual and Developmental Disabilities (2010) (Table 1). The study was approved by the institutional ethics committee and was done in accordance with the Declaration of Helsinki. Study participants or their legal representatives gave written informed consent.

2.2. Neuropsychological assessment

All participants were assessed with the Wechsler Adult Intelligence Scale – Third Edition (WAIS-III) (Wechsler, 1997). The Wechsler Memory Scale-Revised (WMS-R) was administered to evaluate memory functions (Wechsler, 1981). The test provides 5 indices based on 13 subtests: verbal, visual and general memory, delayed recall, and attention/concentration. The raw data were converted to age-corrected standard scores according to the test manual (Wechsler, 1981). We also applied the Mini-Mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975), which is not a specific test in neurodevelopmental disorders, but it is useful to compare our findings with previous results on brain structure–function relationship in FXS (Jäkälä et al., 1997).

2.3. Structural brain imaging

We used the standard FreeSurfer protocol for structural neuroimaging (Martinos Center for Biomedical Imaging, Boston, MA, USA; http://surfer.nmr.mgh.harvard.edu; version: v5.1.0, Dell XPS workstation, Linux system) (Desikan et al., 2006; Fischl et al., 2002, 2004). We applied a multiecho FLASH sequence with a 1 mm^3 isotropic resolution (Siemens Trio 3T scanner; 256 × 256 matrix, 176 sagittal slices with a thickness of 1 mm, TR 2530 ms, TI 1100 ms, TE 1.64/3.5/5.36/7.22 ms, bandwidth 651 Hz, non-selective excitation at 7°). The dependent measures were right, left, total hippocampal, and caudate volumes. FreeSurfer region-of-interests (ROIs) were visually inspected before the analysis. No manual correction was needed. In a pilot study, two independent experts performed the manual parcellation of the hippocampal region in 20 healthy controls with a high reliability. The intraclass correlation coefficients (ICCs) for FreeSurfer and manual parcellation methods were high (ICCs > 0.8). Hippocampal volumes were normalized to total intracranial volume (ICV), which was measured with FreeSurfer (Whitwell, Crum, Watt, & Fox, 2011). Given that this normalization process minimizes within-group variability, we also analyzed uncorrected data with ICV as a covariate.

2.4. Statistical analysis

We used STATISTICA 11 (StatSoft, Inc., Tulsa) for data analysis. Analyses of variance (ANOVAs) were used to evaluate neuropsychological and brain imaging data if Kolmogorov–Smirnov tests did not indicate a deviation from normal distribution. For brain volumes not normalized to ICV, analysis of covariance (ANCOVA) was used with ICV as a covariate. Fisher's Least Significant Difference (LSD) tests were used for post-hoc comparisons. Pearson's product moment correlation coefficients were calculated between normalized hippocampal and caudate volumes and WMS-R scores. To eliminate the confounding effect of age and intelligence, we also calculated partial correlations. Correlations between hippocampal volume and WMS-R measures were reported with and without Bonferroni corrections.

Table 1
IQ, memory, and MMSE scores.

	Neurotypical controls (NT) ($n=25$)	Fragile X Syndrome (FXS) ($n=14$)	Hypoxic injury (HIN) ($n=17$)	F	p	Post-hoc
IQ	111.4 (11.8)	64.1 (9.0)	63.1 (10.2)	138.62	< 0.001	NT > HIN = FXS
Wechsler Memory Scale-Revised						
Verbal	107.4 (12.8)	55.9 (11.5)	61.2 (7.0)	135.8	< 0.001	NT > HIN = FXS
Visual	106.3 (14.0)	57.2 (9.8)	60.8 (9.7)	110.0	< 0.001	NT > HIN = FXS
General	107.4 (11.7)	53.3 (11.3)	66.5 (10.4)	126.6	< 0.001	NT > HIN > FXS
Delayed	106.5 (13.2)	56.6 (8.6)	59.9 (7.8)	139.4	< 0.001	NT > HIN = FXS
Attention	109.1 (11.9)	61.0 (12.9)	64.6 (9.2)	113.7	< 0.001	NT > HIN = FXS
MMSE[a]	29.7 (0.6)	16.1 (4.8)	15.5 (4.0)	–	< 0.001	NT > HIN = FXS

Data are mean (standard deviation) from the Wechsler Adult Intelligence Scale – Third Edition (IQ) and the Wechsler Memory Scale-Revised. The three groups were compared with one-way ANOVA (df=2,53). Post-hoc comparisons were performed with Fisher's LSD tests.

[a] In the Mini-Mental State Examination (MMSE), data were not normally distributed in the neurotypical control group, and therefore we used Mann–Whitney U tests.