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Congenital absence of the mammillary bodies: A novel finding in a well-studied case of developmental amnesia

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ABSTRACT

Individuals with developmental amnesia experience compromised development of episodic memory for details of personal life events, believed to relate to changes to the hippocampus after birth. Here we report the very rare discovery of aplasia of the mammillary bodies, hypogenesis of the fornix, and abnormal hippocampal shape and orientation in H.C., a well-documented case of selectively compromised episodic memory development who is the subject of numerous published empirical articles. These anatomical abnormalities are highly suggestive of disrupted extended hippocampal system development very early in gestation, despite an original diagnosis of developmental amnesia and assumed perinatal hypoxia. These findings provide a unique window into the normal function of the mammillary bodies, fornices, and related anterior nuclei of the thalamus bilaterally. The results also encourage re-examination of the pathological basis of developmental amnesia in other cases reported in the literature.

1. Introduction

Our understanding of memory has greatly benefited from the study of individuals with developmental amnesia, believed in many cases to be due to early-onset neonatal hypoxia (Cooper et al., in press; Vargha-Khadem et al., 1997, 2003). These individuals experience selectively compromised development of episodic memories of personal life events in the context of spared capacity for forming new semantic memories of factual information. Similar distinctions can be seen in the laboratory on tests of recognition memory: cases of developmental amnesia have difficulty recollecting the contextual details associated with previously studied items and yet maintain a sense of familiarity that those items appeared on the study list (Bindschaedler et al., 2011; Brandt et al., 2008; Maguire et al., 2001). Hippocampal tissue loss in these cases has been estimated at roughly 50% bilaterally and is believed to contribute to the failure to develop normal episodic memory (Cooper et al., in press).

But what if there is a congenital origin predisposing an individual to develop a similar, but not necessarily identical, course of memory difficulties? We have identified such an instance in a young woman, H.C., who shares a partially overlapping behavioral profile with other developmental amnesic cases. Like other cases of developmental amnesia, H.C. has selectively impaired episodic memory (Rosenbaum et al., 2011). A parallel pattern of worse recollection than familiarity of recognized items was observed on laboratory tests of episodic memory. Most striking in the anterograde memory domain, unlike control participants, H.C.'s recognition memory performance does not appear to benefit from semantic encoding of verbal study material, a feature that has been noted in individuals with Korsakoff syndrome in whom mammillary bodies are reduced (Cermak et al., 1974). Her memory retrieval nevertheless benefits from repetition when repeated items in a study list are spaced rather than presented in immediate succession (Green et al., 2014), an effect that has also been demonstrated in Korsakoff patients (Cermak et al., 1996). Areas of cognitive function that had not undergone rigorous investigation in developmental amnesia until H.C. include memory for public events, which was found to be impaired (Rosenbaum et al., 2011; see Maguire et al. (2001) for initial findings of intact public event memory in Jon), and

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the ability to hold information online in working memory, which was intact for famous faces and known vocabulary but impaired when the information was previously novel (Rose et al., 2012; see Allen et al. (2014) and Baddeley et al. (2011) for complementary evidence in Jon). Mental state inference on standard tests of theory of mind was found to be intact (Rabin et al., 2012), consistent with an average sized social network (Davidson et al., 2012). Reports are mixed with respect to H.C.'s ability to imagine future personal events (cf. Kwan et al., 2010; Hurley et al., 2011), though her ability to imagine other people's experiences is intact when the imagined events involve unfamiliar others and impaired when they involve close others (Rabin et al., 2013), and she can make future-oriented decisions on tests of inter-temporal choice (Kwan et al., 2013).

In an effort to provide a richer understanding of how her well-documented behavioral profile relates to her underlying brain pathology, the mammillary bodies and other structures closely connected to the hippocampus and medial temporal lobes (MTL) were systematically investigated for signs of abnormal fetal development. If confirmed, H.C. would represent the first documented case of developmental amnesia of prenatal origin. This discovery could bring new ways of understanding the function of these structures and previous findings in developmental amnesia.

2. Materials and methods

2.1. Participants

H.C. was born prematurely in gestational week 32 and was assumed to have suffered respiratory distress soon after birth. Despite impaired episodic memory, first noted at age 4, H.C. completed high school and 2 years of college, and has successfully held several jobs. She was most recently scanned at age 22 on a 3T MRI scanner with an established high-resolution MTL protocol for volumetric analysis of the MTL and hippocampal subregions (Olsen et al., 2013; see also Lee et al., 2014). Results indicated hippocampal volume reduction of 29.5% on the left and 31.2% on the right compared to controls, limited to the hippocampal formation and equally distributed across the subfields and the anterior–posterior axis, which is significantly lower than previous estimates of 48.1% on the left and 43.5% on the right based on averaged patient group volumes (Adlam et al., 2005). The finding of equivalent volume loss across hippocampal subfields in H.C. is inconsistent with reports of a selective vulnerability of the CA1 subfield to the effects of hypoxia (Kawasaki et al., 1990; Warren et al., 2012). Although abnormal orientation of the hippocampi, absence of the mammillary bodies, and other anatomical anomalies were also noted in H.C., the possibility of congenital maldevelopment and hypoplasia of limbic structures was not contemplated until the current study. Comparisons were made with 10 normally developing young women (mean age = 19.40 years, SD = 1.51; mean education = 13.60 years, SD = 0.97; no history of psychiatric or neurological illness; Olsen et al., 2013).

2.2. MRI acquisition

Participants were scanned at the Rotman Research Institute, Baycrest Health Sciences, on a 3T MRI scanner (Magnetom Trio, Siemens, Erlangen, Germany) with a 3D T1-weighted MPRAGE sequence (TR/TE = 2000 ms/2.63 ms, inversion time = 1100 ms; flip angle = 9 degrees; matrix = 256 × 192; field of view = 256 mm; number of oblique axial slices = 176; slice thickness = 1 mm, giving a voxel size of $1 \times 1 \times 1\ mm^3$; acquisition time = 6 min 26 s). A high-resolution oblique coronal T2-turbo-spin-echo image was also acquired in a plane perpendicular to the long axis of the hippocampus (TR/TE = 3000 ms/68 ms; flip angle = 165°; matrix = 512 × 512; field of view = 220 mm; number of slices = 22–28; slice thickness = 3 mm, giving a voxel size of 0.43 × 0.43 × 3 mm; no interslice gaps, acquisition time = 6 min 8 s). Its high in-plane resolution ($0.43 \times 0.43\ mm^2$) greatly reduced artifacts by pulse triggering during the acquisition, and permitted fine discrimination and analysis of the hippocampal subfields, fornices, and mammillary bodies.

2.3. Image processing

All raw digital MR images were transferred to a Dell workstation running Windows 7 in the Brain Imaging Analysis Laboratory of the LC Campbell Cognitive Neurology Research Unit and the Canadian Partnership in Stroke Recovery at Sunnybrook Health Sciences Center. 3D T1-weighted MPRAGE images were re-aligned to the anterior commissure – posterior commissure (AC–PC) plane, using ANALYZE AVW™ Software (Biomedical Imaging Resource, Mayo Foundation, Rochester, MN).

2.4. Image analysis

H.C.'s brain was visually inspected by an experienced research radiologist (F.G.) slice-by-slice in comparison to controls in axial, coronal, and sagittal views of AC–PC aligned 3D T1 images, and in high-resolution coronal T2-weighted images, using ANALYZE. The frontal, parietal, temporal, and occipital lobes, and the basal ganglia, thalamus, brainstem, and cerebellum were examined bilaterally to determine any structural or signal abnormalities. Ventricular size and shape as well as vasculature, dura mater, and venous sinuses were also carefully assessed. Special attention was paid to key brain structures within and in close proximity to the MTL, including the hippocampus and perirhinal, entorhinal, and parahippocampal cortices; fusiform gyrus; and midline structures of the diencephalon, including the mammillary bodies of the hypothalamus and associated white matter tracts and the thalamus.

2.5. Volumetric measurement of the thalamus and its subdivisions

As it is difficult to visually determine the size of the thalamus and its subdivisions, the left and right thalami were traced separately on inverted axial AC-PC aligned 3D T1-weighted images using the regions-of-interest module of ANALYZE software. The anterior pillar of the fornix was used as the anterior boundary, the internal capsule as the lateral boundary, the third ventricle as the medial boundary, and the AC–PC plane as the inferior boundary. The posterior boundary was defined by where the hemispheres of the thalamus merged under the crux of the fornix. The body of the lateral ventricle served as the superior boundary. Measurements were made by a well-trained and reliable rater (K.H.) who was blind to the study hypothesis, participant identities, and clinical data.

Thalamic subdivisions, especially the anterior and dorsomedial nuclei, were further delineated using a modified published method (Callen et al., 2001), which was based on the Talairach atlas (Talairach and Tournoux, 1988). The approximate boundaries of these nuclei were defined in each participant using the standard Talairach grid. Both are located medially between the midline and a plane 10 mm from the midline, with inferior boundaries at a plane 4 mm above the AC–PC line for the dorsomedial nucleus and 8 mm above the AC–PC line for the anterior nucleus; the posterior boundary of the dorsomedial nucleus was the plane through the PC; the plane separating the anterior from dorsomedial nucleus was drawn through the anterior one-third between the AC and PC in the inferior and middle sections of the thalamus, and through the anterior two-thirds between the AC and PC in the superior sections of the thalamus.

To account for potential differences in head size, thalamic volumes were extracted and corrected for head size variation by accounting for the total brain volume (TBV). TBV was obtained using an adapted version of the ANIMAL algorithm (Collins et al., 1995). TBV was accounted for in each ROI using a regression-based technique; each ROI is regressed on TBV and the residual value (i.e., the structure's actual size minus its predicted value based on the individual's TBV) is accounted for in each thalamic volume for each individual (Free et al., 1995). All measurements reported below are TBV-adjusted values. Volumetric differences between H.C. and controls were assessed with Bayesian hypothesis testing using modified *t*-tests (Crawford and Garthwaite, 2007).

3. Results

H.C.'s total brain volume ($1270.83\ cm^3$) did not differ significantly from the mean volume of controls ($P = 0.20$). The left and right hemispheres were symmetrical. There were no signal abnormalities on T1 and T2 images across all brain regions. The corpus callosum was generally intact in shape and size. Lateral ventricles were slightly prominent, and the interventricular foramina were also prominent. The third ventricle was normal in width but had an unusually long anterior–posterior dimension, which was 36.1 mm compared to the control mean of 25.1 mm. The fourth ventricle was normal in shape and size. The hemispheres of the cerebellum were intact.

Neither of the mammillary bodies was identifiable on the posterior ventral surface of the hypothalamus in axial, coronal, and sagittal sections of the 3D-T1 and high-resolution coronal T2 images (Figs. 1A; 2A; 3A and B; 4A). The ventral surface of the hypothalamus was flat, rather than having paired round mammillary bodies bulging into the interpeduncular fossa as would normally appear.