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Neuropathology of a remarkable case of memory impairment informs human memory

Andrew F. Gao [a,b], Julia L. Keith [a,b], Fu-qiang Gao [c], Sandra E. Black [c], Morris Moscovitch [d,e], R. Shayna Rosenbaum [d,f,*]

[a] Department of Anatomic Pathology, Sunnybrook Health Sciences Centre, Toronto, ON, Canada
[b] Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, ON, Canada
[c] L.C. Campbell Cognitive Neurology Research Group, Sunnybrook Health Sciences Centre, Toronto, ON, Canada
[d] Rotman Research Institute, Baycrest Centre for Geriatric Care, Toronto, ON, Canada
[e] Department of Psychology, University of Toronto, Toronto, ON, Canada
[f] Department of Psychology and Vision: Science to Applications (VISTA) Program, York University, Toronto, ON, Canada

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ABSTRACT

Kent Cochrane (K.C.) has been investigated by researchers for nearly three decades after intracranial trauma from a motorcycle accident at age 30 resulted in a striking profile of amnesia. K.C. suffered severe anterograde amnesia in both verbal and non-verbal domains which was accompanied by selective retrograde amnesia for personal events experienced prior to the time of his injury (episodic memory), with relative preservation of memory for personal and world facts (semantic memory), and of implicit memory. This pattern of spared and impaired memory extended to spatial memory for large-scale environments and beyond memory to future imagining and decision-making. Post-mortem brain findings at age 62 included moderate diffuse atrophy, left orbitofrontal contusion, left posterior cerebral artery infarct, and left anterior frontal watershed infarct. Notably, there was severe neuronal loss and gliosis of the hippocampi bilaterally. The left hippocampus was severely affected anteriorly and posteriorly, but CA2, CA4, and the dentate gyrus (DG) were focally spared. There was associated degeneration of the left fornix. The right hippocampus showed near complete destruction anteriorly, with relative preservation posteriorly, mainly of CA4 and DG. Bilateral parahippocampal gyri and left anterior thalamus also showed neuron loss and gliosis. There was no evidence of co-existing neurodegenerative phenomena on beta-amyloid, phosphorylated tau, or TDP-43 immunostaining. The extent of damage to medial temporal lobe structures is in keeping with K.C.'s profound anterograde and retrograde amnesia, with the exception of the unexpected finding of preserved CA2/CA4 and DG. K.C.'s case demonstrates that relatively clean functional dissociations are still possible following widespread brain damage, with structurally compromised brain regions unlikely to be critical to cognitive functions found to be intact. In this way, the findings presented here add to K.C.'s significant contributions to our understanding of clinical-anatomical relationships in memory.

Research in neuropsychology and cognitive neuroscience has shown clearly that there are different forms of memory, each governed by different principles, represented in different ways, mediated by different brain structures, and expressed under different conditions (e.g., Dudai, 2004; Eichenbaum, 2017; Milner et al., 1968; Squire, 2004; Moscovitch, 1992; Tulving, 2002). A widely recognized distinction is between episodic memory of personally experienced events that occurred in a particular time and place and semantic memory of context-free factual information. Endel Tulving proposed this distinction in 1972 (Tulving, 1972) and supported the neuropsychological foundations for it in partnership with the single amnesic case K.C., who helped make it a biological reality (Rosenbaum et al., 2005; Tulving et al., 1988). Extensive brain damage in K.C. from a severe head injury resulted in "episodic amnesia," which encompassed an entire lifetime of personal experiences but left relatively undisturbed semantic memory for personal and world facts acquired before his accident (Rosenbaum et al., 2005; Tulving et al., 1988; Westmacott et al., 2001). K.C. also helped solidify and extend Tulving's proposal for multiple memory systems by showing a further dissociation between explicit memory, for which there is conscious awareness of previous exposure to studied material, and

* Corresponding author. Department of Psychology, York University, 4700 Keele St., Toronto, ON, M3J 1P3, Canada.
E-mail address: shaynar@yorku.ca (R.S. Rosenbaum).

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implicit memory, for which conscious awareness of previous exposure is absent (Schacter, 1985, 1987; 2019; Tulving and Schacter, 1990).

K.C. differed from many other amnesic patients in severity but not pattern of spared and impaired function. He acted as a primary participant in over 25 published studies, many of which include multiple experiments, collectively cited at least 2500 times, and had been tested as a member of a group of participants in many others. Numerous reviews and book chapters mention K.C. or were influenced by his case. K.C.'s long-standing involvement in psychological science has changed the way we think about memory and the brain, greatly influencing memory theory and clinical practice to this day.

K.C. died unexpectedly of unknown cause at the age of 62, on March 30, 2014. His contributions to our field did not end there. He and his family donated his brain to science. An autopsy was performed on K.C.'s brain and neuropathological data were collected. As a tribute to Endel Tulving, and to K.C., we first review K.C.'s contributions to memory, and extend them to other functions such as decision making and theory of mind. We complement this review with novel ex-vivo MRI and neuropathological autopsy findings, including macroscopic neuroanatomy and histopathology. To determine the presence of a disease process not yet resulting in cognitive changes, we investigate histopathological changes representative of Alzheimer's disease or chronic traumatic encephalopathy (CTE). We then consider clinicopathological correlations in a case that has contributed greatly to our understanding of mechanisms of memory and to theory development.

At a cognitive level, K.C. displayed three prominent dissociations related to memory: 1. Impaired episodic memory but spared semantic memory (Kwan et al., 2012; Rosenbaum et al., 2005, 2009; Westmacott et al., 2001; Westmacott and Moscovitch, 2001, 2002), 2. Impaired explicit memory but spared implicit memory (Glisky et al, 1986a, 1986b; Glisky and Schacter, 1988; Goshen-Gottstein et al., 2000; McAndrews et al., 1987; Schacter, 1985; Schacter and Graf, 1986), and 3. Impaired detailed spatial memory but spared remote schematic spatial memory, sufficient for navigating within environments learned long ago (Rosenbaum et al., 2000, 2005, , Rosenbaum et al., 2007a). Despite deficits in episodic memory that extended to future imagining, a number of functions that were thought to depend on it, such as social, moral, and future decision-making, were all spared (Craver et al., 2014a, 2016; Kwan et al., 2012, 2013; Rosenbaum et al., 2007b, 2016). The ex-vivo MRI and neuropathological findings that we present shed light on K.C.'s behavioural profile and inform theories on memory and its interactions with other cognitive domains. To anticipate our findings, some support previous theories relating brain to behaviour, whereas others question the validity of these theories and invite re-examination. In this regard, K.C.'s postmortem radiological and neuropathological findings will stand alongside those of other prominent amnesic cases, notably H.M. (Annese et al., 2014; Augustinack et al., 2014), E.P. (Insausti et al., 2013), and N.T. (Warrington and Duchen, 1992).

1. Case history

K.C. was a right-handed man with 16 years of formal education. Born prematurely in 1951, his development was reported as normal. He led a boisterous lifestyle and experienced several head injuries that varied in severity throughout his childhood and adolescence, most notably when he was hit in the head by a bale of hay that required hospitalization and anti-seizure medication, and prevented him from attending school for a year. He completed high school and a three-year degree in business administration at a community college. At the age of 27, he became employed at an engineering and manufacturing plant, where he was responsible for delivery, pickup, and quality control of products. He continued to have a carefree personality, spending late nights at bars, travelling to Mardi Gras with fraternity brothers, and engaging in adventurous but risky behaviours that likely contributed to several mishaps. The most severe of these mishaps occurred in October 1981.

At 30 years old, K.C. had a motorcycle accident resulting in a severe traumatic brain injury (TBI) that had a dramatic, lasting effect on his memory and personality. Upon arrival to hospital, he was unconscious with dilated fixed pupils and had clonic seizures. He underwent neurosurgery for the removal of a left-sided subdural hematoma. He returned to consciousness at 72 h post-trauma. At around seven days, he appeared to recognize his mother. A follow-up CT scan performed during week three showed chronic bilateral frontal subdural hematomas, slightly enlarged ventricles and sulci, and left occipital lobe infarction presumed to be secondary to compression of the left posterior cerebral artery (PCA) from increased intracranial pressure. He remained in intensive care for one month and was then transferred to a rehabilitation hospital, where he was noted to be reading and conversing quite well and began to recognize friends. He nonetheless showed slowed mentation as well as hemiparesis (which mostly resolved) and a homonymous hemianopia, both affecting the right side.

When he returned home at 6 months post-injury, the severity of his inability to commit new information of any type to memory became more evident, forewarning what was to remain apparent on later MRI scans: widespread brain damage that included severe injury to his medial temporal lobes, with extensive hippocampal loss bilaterally (Rosenbaum et al., 2005; Tulving et al., 1988). It also became increasingly clear that any details of episodic memories, however meaningful at the time of occurrence, had been severely affected. Not even a relatively preserved corpus of mental faculties such as perception, language, and reasoning skills would enable K.C. to relive a personal episodic past or imagine possible future events in which he might participate.

1.1. In-vivo MRI findings

MRI scanning was conducted to provide a neural basis for the remarkable pattern of functional dissociations observed in K.C., with a primary focus on explaining severely impaired episodic memory in the face of seemingly intact semantic memory. MRI scans acquired in 1990 (Tulving et al., 1991) and in 1996 and 2002 (Rosenbaum et al., 2005) showed widespread damage including diffuse atrophy, left PCA infarct, and left anterior frontal encephalomalacia. Notably, there was severe atrophy of the bilateral hippocampi, parahippocampal gyri, and the left amygdala, mammillary body, and anterior thalamus (after adjusting for generalized atrophy). Visual inspection of the resulting images across the different examinations revealed no apparent structural changes.

Overall, K.C.'s severe head injury and related PCA compression resulted in brain damage that was diffuse and multifocal. What is unique about this double pathology is that the medial temporal lobes were effectively impacted from both directions, having affected the anterior portion in the right hemisphere from the head injury and the posterior portion in the left hemisphere.

1.2. Key behavioural findings

K.C. underwent detailed neuropsychological examination across multiple sessions in the late 1980s and mid-1990s, and was re-examined in 2003, 2009, and 2011 on abridged versions of the test battery. The presence of a sharp contrast between severely impaired episodic memory and intact semantic memory was the subject of subsequent research with K.C. in the late 1990s and 2000s. Work with K.C. contributed to our understanding not only of episodic and semantic memory but also to the development of other aspects of memory theory. These include the distinction between explicit memory (memory with conscious awareness) and implicit memory (memory without conscious awareness); the prospect of new learning in amnesia; the fate of recent and remote memory for autobiographical and public events, people, and spatial locations (Rosenbaum et al., 2000, 2005, Rosenbaum et al., 2007a, Rosenbaum et al., 2007b; Westmacott et al., 2001; Westmacott and Moscovitch, 2001, 2002); the relationship between memory, time, and the self (Kwan et al., 2012, 2013; Rosenbaum et al., 2009); and contributions of episodic memory to financial, social, and moral

decision-making (Craver et al., 2014a, 2016; Rosenbaum et al., 2007b, 2016).

1.3. Cognitive status and intellectual function

Testing across the decades showed that K.C.'s intellectual and cognitive functions outside the domain of episodic memory were largely, although not completely, preserved. Performance on mental status screening tests administered in 1994, 2003, and 2011 was above the cut-off for dementia, with most points lost on the memory subscale. His verbal, performance, and full-scale IQ on the Wechsler Adult Intelligence Scale–Revised (WAIS-R; Wechsler, 1987) and Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999) were in the average range. Results of detailed neuropsychological testing are summarized in Supplemental Table 1.

1.4. Visuoperceptual and visuospatial function

K.C. continued to experience a right homonymous hemianopia involving the upper field with lower quadrant and macular sparing. Corrected visual acuity was 20/40 on the right, which was within normal limits, and less than 20/400 on the left due to glaucoma. Eye movements were full in the horizontal and vertical planes, and there was no nystagmus. K.C. showed difficulties in perception of colour on the City University Colour Vision Test (Fletcher, 1980) and Farnsworth-Munsell 100-hue test (Farnsworth, 1957) and face matching under degraded conditions on the Benton Facial Recognition Test (Benton et al., 1983). Nevertheless, other aspects of his perception and recognition were preserved, including tasks requiring basic visual feature analysis, such as line orientation and form discrimination on the Judgment of Line Orientation and Visual Form Discrimination tests, respectively (Benton et al.). Preserved as well were more complex processes such as reading, and recognition of objects and faces that had been familiar prior to his head injury. He was also unimpaired in visuospatial reproduction of the Rey Osterrieth Complex Figure (ROCF; Osterrieth, 1944) and reconstruction of designs with blocks (WASI Block Design subtest; Wechsler, 1999). The possibility that damage to posterior neocortical areas contributed to K.C.'s autobiographical episodic memory loss by affecting his visual imagery (Rubin and Greenberg, 1998) was tested and deemed unlikely (Rosenbaum et al., 2004a).

1.5. Cognitive control

K.C. exhibited markedly reduced fluency for spontaneous verbal output, including poor performance on the FAS phonemic fluency task (Spreen and Strauss, 1998). No other deficits were observed on tests of executive function, including the Wisconsin Card Sorting Test, the ratio of Trails B to Trails A, working memory, and tests of abstract reasoning. Nonetheless, because cognitive control functions contribute to strategic retrieval on tests of retrograde memory (see next), it was important to test the possibility that any deficits may impact autobiographical memory, but this, too, was deemed unlikely (Gilboa et al., 2006; Rosenbaum et al., 2004a).

1.6. Anterograde memory: implicit vs. explicit memory

The majority of initial studies involving K.C. focused on the distinction between explicit and implicit memory. Early observations indicated intact procedural memory: K.C. could describe the steps to changing a tire, and play piano and chess, without recalling the source of the learning episodes. By contrast, assessment on standard neuropsychological tests indicated a pattern of severely impaired explicit (episodic) memory, whether the material was verbal or non-verbal. This included the Wechsler Memory Scale-Revised (WMS-R; Wechsler, 1987), California Verbal Learning Test (CVLT; Delis et al., 1987), Warrington Recognition Memory test for words and faces (WRMT; Warrington, 1984), and recall of the ROCF (see Table S1).

More systematic studies of new learning in K.C. focused on priming, a form of implicit memory that refers to a change in response to an item as a result of prior exposure to that item (Schacter, 2019; Tulving and Schacter, 1990). At the time that K.C. began participating in research, studies of other amnesic individuals with impaired explicit memory revealed surprisingly intact implicit memory when the first few letters of recently studied words were used as cues (e.g., Graf et al., 1984). Preservation of implicit memory in the face of impaired explicit memory was confirmed in K.C. in studies showing that even without a functional hippocampus, priming can occur for pre-existing and self-generated novel word associates (Schacter, 1985; Schacter and Graf, 1986) and is modality-specific (Köhler et al., 1997). The latter finding helped show that evidence of cross-modal priming in separate studies of healthy adults (Craik et al., 1994) was likely an artefact of explicit memory (Jacoby et al., 1996). Explicit contamination was a pervasive issue in studies of implicit memory that was addressed in later years with methods that distinguish process from task, such as the process dissociation procedure (PDP; Jacoby, 1991).

Other studies in which K.C. participated indicated that priming can last on the order of 30 minutes in some cases (Goshen-Gottstein et al., 2000) and up to one year in others, and is possible following a single study exposure (Goshen-Gottstein et al., 2000; McAndrews et al., 1987). Yet other work with K.C. demonstrated considerable procedural or complex learning, again in the absence of hippocampal support, such as the acquisition of computer-related knowledge through the "method of vanishing cues" (Glisky et al., 1986a, 1986b; Glisky and Schacter, 1988). This finding alone prompted rehabilitation efforts that are still in practice today (e.g., Kapur et al., 2002; Svoboda et al., 2012, 2015). Also notable is evidence of limited learning of semantic facts relating to the self (trait self-knowledge, familiarity with family and friends; Tulving, 1993; Westmacott et al., 2001) and the world (famous people, vocabulary terms; Westmacott and Moscovitch, 2001, 2002) and a very limited amount of information that may be regarded as episodic (i.e., mnemonic precedence; Schacter and Graf, 1986). For the most part, however, such learning depends heavily on repeated exposure of meaningful study materials under conditions in which associative interference is kept to a minimum, and the contents of learning are generally inflexible, inaccessible in novel situations, or impoverished in some way (Hayman et al., 1993; Tulving et al., 1991).

1.7. Retrograde memory: episodic vs. semantic memory

Despite the widely held view that retrograde amnesia is relatively brief and temporally graded, not all evidence is consistent with this pattern (for reviews, see Fujii et al., 2001; Kapur, 1999; Nadel and Moscovitch, 1997, 2001; Squire et al., 2015). K.C. did appear to have remote memory loss that was not extensive in duration, but only for factual information; his memory loss for personal episodes encompassed his entire past. Across several detailed investigations, he consistently demonstrated severely impaired autobiographical memory that covered his whole life, whether in response to actual visits to houses that he had lived in and schools that he had attended (Tulving et al., 1988) or to family photographs of past and more recent events (Westmacott et al., 2001). Though he often recognized the people and even some of the locations in the photographs, there was no sign that they triggered any feeling of re-experiencing, so that any narratives that he managed to produce lacked the subjective re-evoking of the emotional and contextual details that distinguish a personal from a non-personal episodic experience. Severe remote autobiographical episodic memory loss was formally confirmed on the Autobiographical Memory Interview (AMI; Kopelman et al., 1990), the Galton-Crovitz word-cue task for autobiographical information (Crovitz and Schiffman, 1974), and early (Moscovitch et al., 2000) and later (Levine et al., 2002) versions of the Autobiographical Interview. His performance improved only minimally when he was provided with additional prompts aimed at facilitating

recall (Rosenbaum et al., 2008), and he was not prone to confabulating (Rosenbaum et al., 2005). Similarly, he performed at chance on a recognition test of his autobiographical episodic memory, with no difference between recollection and familiarity of details (Gilboa et al., 2006).

In stark contrast to K.C.'s profoundly impaired episodic memory, general and personal semantic memory was relatively spared (Moscovitch and Melo, 1997; Rosenbaum et al., 2004a, 2005). Performance on standard neuropsychological tests indicated preserved language and general semantic memory on the Western Aphasia Battery (Kertesz, 1982), Boston Naming Test (BNT; Kaplan et al., 1983), category (semantic) fluency, and vocabulary subtest of WAIS. A temporal gradient in remote memory for general semantics has also been demonstrated; K.C. showed worse performance for famous names and vocabulary terms that came into popular use in the 5-year time period predating his injury relative to those that became popular in earlier years (Westmacott and Moscovitch, 2002). Interestingly, however, this temporal gradient was found to be attenuated on implicit testing, such that his performance for names and words from 5 years pre-injury improved when asked to guess their familiarity. Likewise, in Tulving et al.'s (1988) earlier experiment, repeated visual exposure of knowledge unique to the job that K.C. held during the three years before his accident allowed for the progressive improvement of such expert knowledge. This knowledge included the names of co-workers as well as familiarity with work-related technical terms and equipment presented in photographs. He was, however, unable to comment on his own personal experience with the co-workers or equipment, even after viewing photographs of himself with them (Tulving, 1972, 1983). K.C. showed a similar pattern of impaired and intact performance when family photos were used to cue autobiographical memory: he successfully retrieved the names of people in each photo that he knew prior to his 1981 accident but was unable to recollect details of any event depicted in the photos (Westmacott et al., 2001). As discussed next, a parallel pattern was seen within remote spatial memory.

1.8. Spatial cognition

Initial observations in K.C. indicated that like his intact semantic memory, he was able to remember how to navigate in neighborhoods learned many years before the onset of his amnesia, despite classic theories of spatial memory that would have predicted otherwise (O'Keefe and Nadel, 1978). More systematic testing in K.C. confirmed that at least some aspects of remote spatial memory are spared following hippocampal damage (Rosenbaum et al., 2000). K.C. was able to accurately locate gross geographical features on outline maps of the world. He performed normally on more structured mental navigation tests of his neighbourhood, such as those requiring accurate placement of streets in relation to one another in a sketch map, recognition and identification of neighbourhood landmarks, estimating absolute distances and relative distances and directions between landmarks, sequencing randomly ordered landmarks along a route, and selecting the most direct route between locations while avoiding an obstructed street (for comparable data on other amnesic patients, see Beatty et al., 1987; Teng and Squire, 1999). Functional MRI (fMRI) scanning of K.C. and controls while performing these tasks indicated that they engaged a common network of right-sided brain structures previously implicated in spatial navigation that, importantly, did not include the hippocampus (Rosenbaum et al., 2004b Rosenbaum et al., 2007a).

Findings of remote spatial memory preservation contrasted with K.C.'s dramatic inability to acquire spatial information in a new environment. He failed to recall the spatial locations of common objects on a board following a short delay (Smith and Milner, 1981), a floor plan of a library in which he has worked since 1997 (for the 5 years preceding testing), and a simple route after receiving extensive training. Even remote spatial memory, however, did not appear to be completely intact (Rosenbaum et al., 2000). This was first suggested by K.C.'s impoverished sketch map with respect to landmark inclusions in his home neighbourhood and his difficulty in identifying specific features on outline maps of Canada and Ontario. More extensive examination of his ability to identify detailed aspects of his neighbourhood revealed that he was unable to distinguish photographs of houses that he had visited often in the past from those of foil houses, whether the foils were similar in appearance or not. K.C.'s loss of memory for topographical details and environmental features resembles loss of contextually rich and detailed memories of autobiographical episodes (Moscovitch et al., 2005; Rosenbaum et al., 2001). This overall pattern of spared and impaired spatial memory has been found in other hippocampal amnesic cases (Herdman et al., 2015; Maguire et al., 2006).

1.9. Non-mnemonic abilities

Future imagining and narrative construction. Another interesting observation that was made early on was that K.C.'s ability to imagine a personal future appeared to be as compromised as his ability to describe personal events from his past. Tulving and Schacter confirmed this relationship in extensive interviews with K.C. (Tulving, 1985), which supported parallel work by Ingvar relating episodic memory to future thinking and planning (Ingvar, 1985) and laid the groundwork for future theories and research on autonoetic consciousness and future thinking (e.g., Clayton et al., 2003; Craver et al., 2014b; Klein, 2013; Schacter et al., 2012; Suddendorf and Corballis, 2007; Tulving, 2002). More systematic investigation confirmed impaired imagining of fictitious past episodes (Rosenbaum et al., 2009) and future episodes in K.C. (Kwan et al., 2012), consistent with findings of impaired mental time travel in other amnesic cases (e.g., Klein et al., 2002; Kwan et al., 2015; Race et al., 2011). Further support for this relationship comes from fMRI studies demonstrating that episodic memory and future imagining (along with spatial memory and theory of mind, discussed next) engage a common core "default" network of brain regions that includes the medial temporal lobe and that is present when participants are at rest in the scanner (for reviews, see Andrews-Hanna et al., 2014; Schacter et al., 2008).

Impaired imagining, however, did not seem to be confined to past and future events in K.C., as it was also found that he could not reconstruct details of well-learned semantic narratives (fairy tales and Bible stories; Rosenbaum et al., 2009; see also Verfaellie et al., 2014). Other cases have been found who were unable to construct spatially coherent scenes in imagination (Hassabis et al., 2007). Importantly, these studies included conditions that did not require participants to orient in time, suggesting that impaired performance may reflect a deficit in a more fundamental ability to generate details and/or to bind details into coherent narratives rather than an inability to travel mentally through time (Keven et al., 2018; Barry and Maguire, 2019).

Future orientation and decision-making. Another way to distinguish between deficits in future thinking vs. narrative construction is to test performance on a paradigm that requires future-oriented opinions and decisions without the need to construct narratives. The Zimbardo Time Perspective Inventory fulfills this requirement by asking participants to endorse items that reflect the extent to which they are positive or negative about the past, are fatalistic or hedonistic about the present, and/or tend to orient to the future (Zimbardo and Boyd, 1999). Importantly, the use of forced choice responses circumvents the need for participants to generate their own scenarios, teasing out future-orientation from event construction. Surprisingly, K.C. most frequently endorsed items reflecting past positive and future orientations; he seldom endorsed items indicating that he is bound to the present (Kwan et al., 2013).

Performance on a test of inter-temporal choice may be taken as further evidence that K.C. can engage in future thinking in the absence of episodic memory when not required to construct detailed narratives. The ability to choose between smaller, immediate rewards and larger, later rewards is a fundamental aspect of future-oriented decision-

making and one that is plausibly influenced by the ability to imagine one's possible future (Boyer, 2008; Schacter et al., 2012). However, results of studies investigating inter-temporal choice in K.C. suggest that the ability to evaluate future consequences does not require hippocampal integrity and can occur in the absence of the ability to construct imagined future events (Kwan et al., 2012, 2013). K.C. further showed a "magnitude effect" (shallower discounting of a larger compared to smaller delayed amount), a standard finding in the inter-temporal choice literature that appears to be uniquely human. In the absence of the ability to imagine using future rewards, however, it is possible that the patients' decision-making was qualitatively different from that of controls (Kwan et al., 2015; Palombo et al., 2015). In a separate study involving hypothetical monetary rewards, K.C. was found to be as prone as neurotypical controls to making irrational choices in the form of the certainty effect (Kahneman and Tversky, 1979) and the common ratio effect (Allais, 1953). For example, he showed a counterintuitive bias to accept a certain reward of $3000 over an 80% chance of receiving $4000 (and 20% of receiving $0) on the one hand, and a 20% chance of winning $4000 over a less risky 25% chance of winning $3000 on the other, even though the probabilities in the second scenario are reduced by a common factor (Craver et al., 2014a). K.C.'s performance might be interpreted as an intact future-oriented capacity to anticipate the regret that would come if he were to fall within the unfortunate 20% that received no reward, as proposed by Loomes and Sugden (1982). Alternatively, his performance might suggest that anticipation of future regret, if impaired in K.C., does not underlie the normal human tendency to engage in such irrational decision-making.

Theory of Mind. Although it was apparent from early observation that K.C. had difficulty imagining future events of a personal nature, including how he might think or feel, he seemed to have a "theory of mind" (ToM) that enabled him to have access to his own current thoughts and feelings and those of other people. This dissociation might not seem so surprising if it were not for evidence of shared default network activity underlying episodic memory, future imagining, and ToM that emerges from comparisons across separate fMRI studies of each ability. K.C.'s intact ToM was confirmed in formal investigations: his performance was indistinguishable from that of controls on a variety of standard tests that are known to be sensitive to impaired ToM in patients with damage to ventromedial prefrontal cortex (vmPFC; Rosenbaum et al., 2007b). The same held true in two other cases with documented memory impairment (Rosenbaum et al., 2007b; Rabin et al., 2012). Dissociations in activity were evident in subsequent fMRI studies directly comparing episodic memory and ToM within a single paradigm (Rabin et al., 2010; Spreng and Grady, 2010), unless the subject of the mental state inference is personally familiar, in which case no dissociations were found (Rabin et al., 2013; Rabin and Rosenbaum, 2012). Overall, these results suggest that one need not draw upon episodic memories of one's own experiences in order to infer the contents of other people's minds. Nevertheless, despite his intact social skills, his social network was considered small in the years since his accident, which was assumed to be due to the severity of his anterograde amnesia (Davidson et al., 2012).

Gambling. Unlike ToM, amnesic individuals (Gutbrod et al., 2006; Gupta et al., 2009), including K.C. (Rosenbaum et al., 2016), have been shown to perform poorly on another test that is sensitive to vmPFC function, the Iowa Gambling Test (Bechara et al., 1994). It requires learning which two of four decks of cards deliver large payoffs per trial but, when averaged over many trials, lead to a greater overall loss than gain, and which two deliver more modest gains and losses per trial but, on balance, lead to a greater overall gain than loss. An inability to anticipate future consequences of one's actions, due to impulsive or risk-taking tendencies, impedes the ability to develop a preference for the advantageous decks over time, but so might an inability to explicitly remember which cards belonged to which decks.

To differentiate impulsivity from risk-taking without placing demands on explicit memory, K.C. was tested on the Toronto Gambling Task (Floden et al., 2008). In an "ascending" condition, cards appear on the screen one at a time until a maximum of five cards is reached. In a "descending" condition, five cards appear on the screen, and one is removed at a time until only one card remains. Participants can stop the dealer at any time. If the "winning card" is in their hand when they stop the dealer, the participant wins a payout inversely proportional to the number of cards in their hand. A risk-taker will tend to stop the presentation with very few cards in both the ascending and the descending condition. An impulsive person will tend to choose the first available option in each condition. K.C. was neither risk-prone nor impulsive on this task, preferring to wait until three or more cards had been dealt in both the ascending and descending conditions (Rosenbaum et al., 2016). Consistent with this result, K.C. also did not show any risk-taking or impulsive tendencies on a probability discounting task that was similar to the delay discounting task mentioned above but that involved a choice between a smaller, certain reward and a larger, riskier (uncertain) reward (Kwan et al., 2013).

Moral reasoning. It has also been hypothesized that the ability to assess moral actions depends on constructing or reconstructing personal happenings in episodic memory (Casebeer and Churchland, 2003; Thagard, 2007; Darwin, 1871). Individuals are more likely to treat a scenario in a more abstract, utilitarian way (for the greater good) when personally removed from the scenario, whereas deontological (person-centred) judgments are more likely when individuals can vividly imagine themselves within the scenario. K.C. was tested as part of a group of individuals with episodic amnesia on a battery of moral scenarios (Craver et al., 2016), designed to assess moral decision-making in healthy adults (Greene et al., 2001, 2004) and sensitive to vmPFC function (Greene et al., 2004; Shenhav and Greene, 2014). Consistent with Greene's motivating hypothesis, K.C. did show a significant bias toward utilitarian answers: he explained in each case that the good of the many outweighs the good of the few. By contrast, the other patients tested did not show such an extreme utilitarian bias, and one patient whom we had tested and a group of five patients tested by McCormick et al. (2016) showed greater deontological tendencies. These discrepancies may be due to differences in premorbid moral response profiles, extent of episodic memory impairment, the way in which questions were posed, or the location and extent of vmPFC damage. As described next, ex-vivo MRI and neuropathological findings in K.C. might provide the most parsimonious account.

2. Materials and methods

2.1. Acquisition of post-mortem brain

Informed consent for donation of K.C.'s brain for a research-oriented neuropathological autopsy was obtained from K.C.'s mother, as approved by the Ethics Review Board of Sunnybrook Health Sciences. The brain was fixed in 10% neutral buffered formalin.

2.2. Ex-vivo MRI

2.2.1. Imaging acquisition

Ex-vivo brain MRI was acquired using a 3T GE Signa MRI scanner. The brain was placed in a water-filled chamber and scanned using an eight-channel transmit-receiving head coil. The images included 3D-T1 weighted (TR/TE, 12.90/5.68 ms, 11° flip angle, 400 inversion time, 1 NEX, 512 × 512 acquisition matrix, 0.5 × 0.5 in-plane resolution, 0.5 mm slice thickness, 23 min scanning time) and axial 2D fluid attenuation inversion recovery (FLAIR) sequences (TR/TE, 9000/146 ms, 125° flip angle, 2250 inversion time, 1 NEX, 256 × 256 acquisition matrix, 0.94 × 0.94 mm in-plane resolution, 1.5 mm slice thickness, 8 min scanning time).

2.2.2. Post-acquisition processing

ANALYZE AVW™ imaging software (Biomedical Imaging Resource,

Mayo Foundation, Rochester, MN) was used in the post-acquisition imaging processing and analysis. Ex vivo 3D-T1-weighted images were aligned to the anterior-posterior commissure plane (AC-PC). Brain with stereo 3D volume rendering and all slices were displayed in neurological convention.

2.2.3. Quantitative analysis of the medial temporal lobe

Manual tracing of medial temporal lobe (MTL) structures was performed every slice on the coronal T1-weighted images perpendicular to the AC-PC plane, using protocols described previously (Pruessner et al., 2000, 2002). Briefly, the length of the hippocampus from head to tail was traced including the hippocampus proper, dentate gyrus, alveus and subiculum. The most anterior slice showing the hippocampal head was identified by the emergence of the uncal recess in the superomedial region of the hippocampus. The most posterior part of the hippocampus was identified in the slice where an ovoid mass of gray matter began to disappear inferomedially to the trigone of the lateral ventrical. The amygdala was traced on the coronal view, with the boundary confirmed on the sagittal view for differentiation from the adjacent hippocampal head, basal ganglia, and entorhinal cortex (ERC). The ERC tracings began 2 mm posterior to the frontotemporal junction and ended at the level 2 mm posterior to the intralimbic gyrus. The perirhinal cortex (PRC) tracings began at the level of the frontotemporal junction and ended 4 mm posterior to the intralimbic gyrus. The parahippocampal cortex (PHC) (or the posterior PHC) started immediately from the caudal end of the PRC to the level on which the caudal tip of the hippocampal tail disappears. The lateral and medial boundaries of the ERC, PRC, and PHC were delineated based on their relationship with the amygdala and collateral sulcus as described in the tracing protocol (Pruessner et al., 2002). The ERC and PRC were assigned to the anterior MTL cortices and the PHC was attributed to the posterior MTL cortex for descriptive and illustration purposes in the post-mortem MRI analysis.

2.3. Neuropathology and neurohistology

Coronal sections of the cerebral hemispheres and axial sections of the brainstem and cerebellum were obtained manually to a 0.5–1.0 cm thickness and selected slices were further cut to 4 mm thickness using a custom aluminum mold as a guide to allow adequate penetration of tissue processing reagents. Whole slices were processed using a custom processing schedule in an automated tissue processor (Shandorn Pathcentre Enclosed Tissue Processor, Thermo Scientific) and whole-mount slices were paraffin-embedded, sectioned (6 μm) using a sliding microtome (Leica SM2500), mounted on 5 in x 7 in coated slides, and stained with Luxol fast blue-hematoxylin & eosin (LFB/H&E) in large 2L reagent containers. Stained slides were digitized using a large slide scanning system (TISSUEscope 4000, Huron Technologies Inc.), at a resolution of 0.5 μm/pixel, approximately equivalent to 20× optical magnification. Selected hemispheric, brainstem, and cerebellar regions were processed in standard fashion and stained with LFB/H&E and immunohistochemistry for beta-amyloid, tau (AT8), TDP-43, p62, and/or alpha-synuclein. Details of the immunohistochemical techniques are provided in Supplemental Table 2.

3. Results

3.1. Ex-vivo MRI findings

High resolution 3D T1- and FLAIR-weighted ex-vivo MR images were used in brain and lesion analyses. The 3D T1 images in particular, with 500 μm spatial resolution, allow a more detailed brain structural and lesion analysis than did previous in-vivo MRI.

3.2. Extra-medial temporal lobe lesions

Ex-vivo MRI showed multiple lesions in both left and right hemispheres. In the cortical and subcortical regions of the left superior frontal gyrus, a lesion, approximately 50 mm in the anteroposterior dimension, had a cystic or encephalomalasic appearance on the T1 images (L1 in Figs. 1A-B and 2I-J), surrounded by hyperintensities on the FLAIR images. This is known to be related to a subdural hematoma and surgical intervention following K.C.'s TBI. Another large lesion was in the left superomedial occipital lobe. It was wedge-shaped on the T1 sagittal, approximately 30 mm in the longest dimension (L2 in Fig. 1C-D). The lesion appeared to have extended into the adjacent left parietal lobe. The left occipital horn of the lateral ventricle was markedly enlarged (Fig. 1D-E). This lesion was consistent with a chronic infarction within the posterior cerebral artery territory.

There were a few small lesions. One lesion in the left and another in the right posteromedial orbitofrontal cortex (R3 in Fig. 1G) were 5 mm and 20 mm in length, respectively, in the longest lesion dimension along the anteroposterior axis. They presented as cortical tissue loss, consistent with brain contusion. There was a lesion (8 mm in diameter) in the left superior medial parietal lobe (R1 in Fig. 1A), consistent with a cortical infarct. In the left anteromedial thalamus, there was also an area, approximately 12 mm long, showing signal attenuation on T1 (L3 in Fig. 1F), likely related to ischemia. There was a cystic lesion in the left posteromedial thalamus, 4 mm in diameter, consist with a chronic lacunar infarct (L4 in Figs. 1F and 3N).

The left thalamus was significantly smaller than the right based on visual radiological assessment. Both cerebellar hemispheres and the brainstem appeared to be intact.

3.3. Medial temporal lobe assessment

MTL structures and their damage were visually assessed and quantitatively measured on the high resolution T1-weighted postmortem MRI. Currently, normative data of postmortem MRI is not available for comparison with KC's quantitative measures. As an alternative, we compared KC's postmortem MTL volumes to a published control sample based on 22 healthy subjects with mean age of 62 years (matched to 62-year-old K.C.) (Teipel et al., 2006). Both studies used the same MTL tracing protocol (Pruessner et al., 2002). Note that the presumed volume shrinkage of the brain is about 8% during formalin fixation (Schulz et al., 2011). Thus the volumes of K.C.'s MTL measures were compensated for that shrinkage when comparing to control sample from in vivo MRI (Teipel et al., 2006).

Hippocampus. In visual inspection, the most striking abnormality was the absence of the right anterior hippocampus (approximately two-thirds), suggestive of complete destruction (Figs. 2J-L and 3M). The right hippocampal tail (about 10 mm long) was identifiable, but it was small in size with marked enlargement of the temporal horn and choroidal fissure (Fig. 3N-O). The overall left hippocampus was shrunken, especially in the left posterior hippocampus (Fig. 3M-O). In the volumetric analysis, the right hippocampus was 295 mm^3 or 91% reduction, compared to 3321 mm^3 ($p < 0.001$), and the left hippocampus was 537 mm^3 or 83% reduction, compared to 3159 mm^3 ($p < 0.001$), of the age-matched control sample (Table 1).

Amygdala and mammillary body. The amygdala was quantitatively measured, with 457 mm^3 in the left and 567 mm^3 in the right, comparing to 976 mm^3 ($p = 0.055$) and 1001 mm^3 ($p = 0.17$) of the control sample, respectively (Table 1). The amygdala did not show signal abnormalities on the T1 and FLAIR images. The slightly smaller left amygdala could be attributed to hemispheric asymmetry or mild atrophy (Fig. 2I-J). The mammillary bodies were small based on qualitative neuroradiological assessment (Figs. 1H and 2J).

Entorhinal and perirhinal cortex. There were cortical injuries in the PRC and ERC, which presented as partial or complete absence of the cortical rims (see Fig. 2) based on visual inspection. The ERC volume was 183 mm^3 or 74% reduction in the left compared to 709 mm^3 ($p = 0.015$), and 245 mm^3 or 70% reduction in the right compared to 806 mm^3 ($p = 0.024$) of the control sample. The left and right PRC volumes

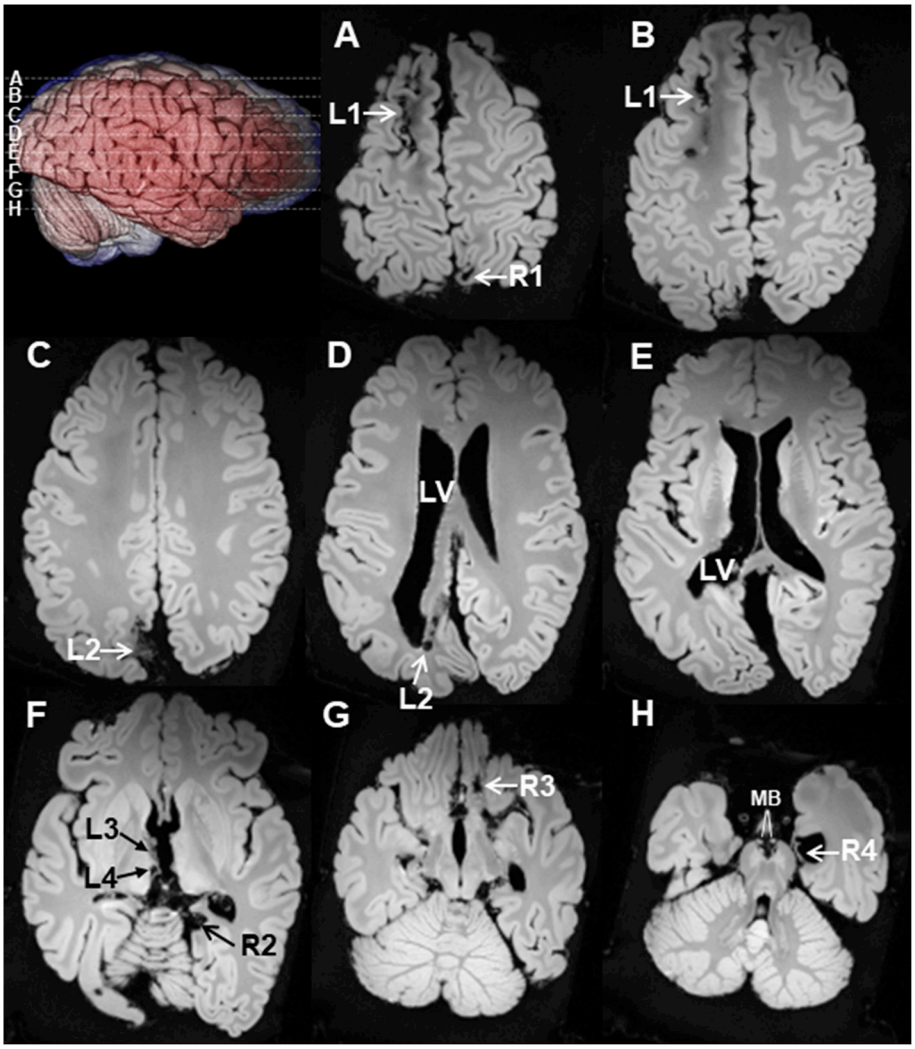

Fig. 1. Ex-vivo MRI of brain lesions. Ex-vivo transverse T1-weighted MRI from A (superior) to H (inferior) slices at 10mm intervals, as illustrated on the right lateral surface of K.C.'s brain. All images are parallel to the anterior-posterior commissure (AC-PC) plane with right hemisphere on the right. Cerebral infarcts were seen in the left superior frontal (L1 in A-B), right superior medial parietal (R1 in A), left medial occipitoparietal (L2 in C-D), left medial thalamus (L3-4 in F), and right anterior medial occipital (R2 in F). Brain contusions were seen in right orbitofrontal (R3 in G) and right medial temporal lobe regions (R4 in H). LV, lateral ventricle; MB: mammillary bodies.

showed no differences between K.C. and controls (p-values >0.05) (see Table 1).

Parahippocampal Cortex. Similar to PRC and ERC damage, part of the PHC in the posterior MTL showed absence of the cortical rim or cortical destruction (Fig. 3M-O). The posterior PHC has two subregions, one medial (known as area TH) and one lateral (known as area TF) of von Economo-Koskinas, according to their cytoarchitectural organization (Thangavel et al., 2008) (Fig. 3, pMTL). The medial portion of the PHC (area TH) showed greater absence of the cortical rim in the left than in the right based on visual estimation. The lateral portion of the PHC (area TF) suffered little injury (Fig. 3M-O). The volumes of the overall PHC in K.C. were 1091 mm^3 or 34% reduction in the left and 1322 mm^3 or 18% reduction in the right, compared to 1656 mm^3 ($p = 0.167$) and 1606 mm^3 ($p = 0.454$) in the control sample, respectively.

4. Neuropathological findings

Neuropathologic findings are presented in Figs. 4–6. The fresh brain weight was 1240 g. There were numerous focal lesions of varying morphology affecting both the medial temporal structures and non-medial temporal structures.

The left superior frontal lobe contained an area of cavitation and gliosis with relative sparing of the superficial cortex and scattered macrophages within the cavity (Fig. 4A). The left occipital cortex, including part of the primary visual cortex, showed severe laminar necrosis and gliosis with infiltration by macrophages (Fig. 4B). The left posterior thalamus contained a similar area of cavitation (Fig. 5D). These three lesions were consistent with remote infarction. The right orbitofrontal cortex showed a focal area of severe atrophy, neuronal loss, and gliosis involving the crest and adjacent depths of the gyrus, consistent with remote contusion. The superomedial parietal lobe showed a gliotic tract, consistent with prior ventricular drain placement. There was a lesion in the left anterior thalamic nucleus with uncertain etiology, which included marked neuronal loss and gliosis (Fig. 5A).

4.1. Medial temporal structures

Bilateral medial temporal structures were markedly abnormal. On the left side, at the level of the amygdala, which itself was mostly preserved, there were focal, well-demarcated areas of severe neuronal loss and gliosis in the ERC and PRC, most accentuated around the depth of the collateral sulcus (Fig. 5A-[L]). More posteriorly, the ERC appeared largely destroyed with sparing of a superficial rim of gliotic cortex containing few neurons (Fig. 5C-[L]), while the PRC was relatively preserved. The anterior hippocampus showed marked neuronal loss in the Cornu Ammonis. In the posterior hippocampus at the level of the lateral geniculate nucleus, CA1, CA3, and presubiculum (Duvernoy et al., 2013; Mai et al., 2015) showed severe and near-total neuronal loss and gliosis (Fig. 5C-[L]). This was accompanied by pallor and secondary degeneration of the ipsilateral fornix (Fig. 6). Interestingly, CA2, CA4, and the granule cell layer of the dentate gyrus were remarkably preserved (Fig. 5B-[L]). However, at further posterior levels, CA2 and CA4

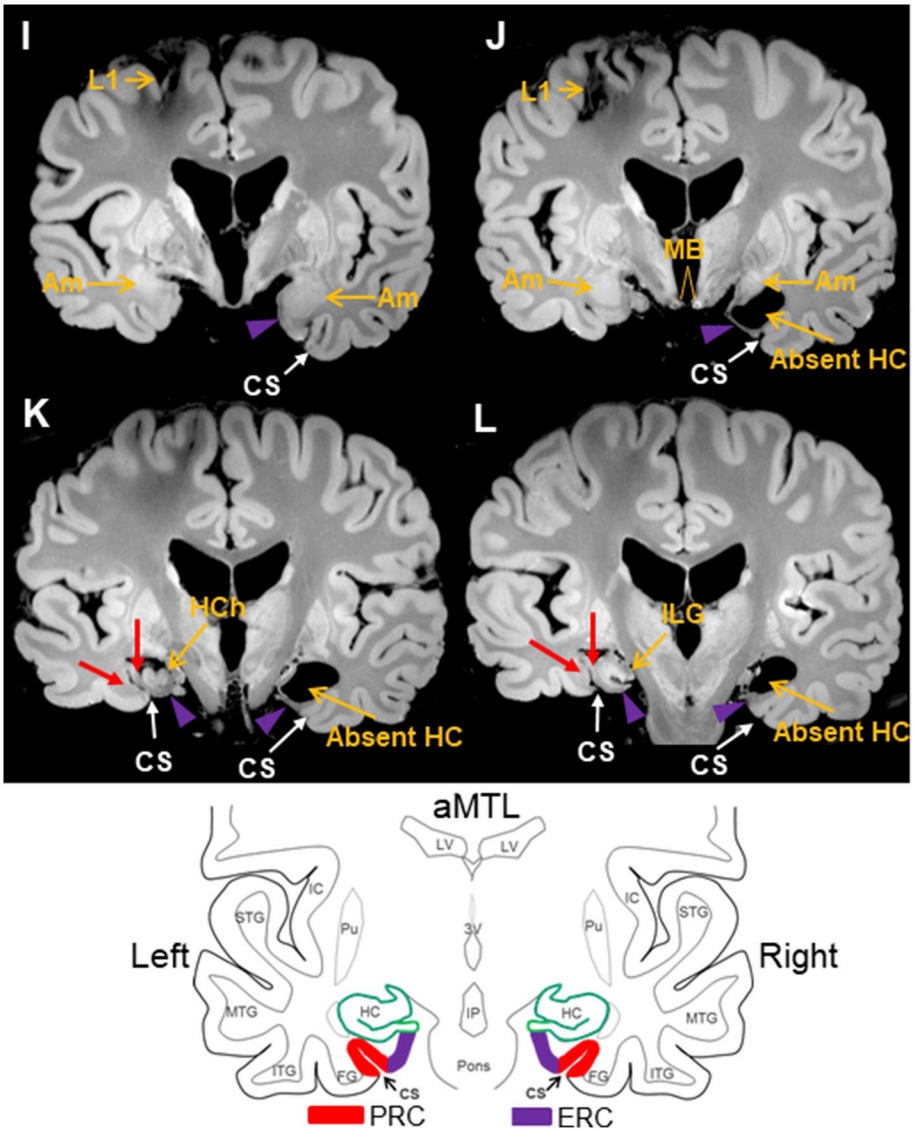

Fig. 2. Ex-vivo MRI of anterior medial temporal lobe (aMTL) lesions. Coronal sections of ex vivo T1-weighted MRI perpendicular to the AC-PC plane going through the levels between the amygdala (I) and intralimbic gyrus (L), at 5mm intervals. Compared to normal anatomy in the diagram of the aMTL below, the right hippocampus was completely absent (yellow arrows to absent HC in J-L), the entorhinal cortex was entirely lost in the right (purple arrows in J and K) and markedly lost in the left (purple arrows in K and L), and the cortical rims of the left perirhinal cortex showed signal intensity loss (red arrows in K and L) suggesting cortical injury.Am, amygdala; aMTL, anterior medial temporal lobe; CS, collateral sulcus; ERC, entorhinal cortex; HC, hippocampus; HCh, hippocampal head; ILG, intralimbic gyrus; L1, left superior frontal infarct; MB, mammillary body; PRC, perirhinal cortex.

both showed neuronal loss and gliosis, accompanied by severe neuronal loss and gliosis of the medial PHC (Fig. 5C-[L], 5D-[L]).

On the right side, at the level of the amygdala, which was preserved, there was neuronal loss and gliosis of most of the medial aspect of the ERC and a small well-demarcated focus of laminar necrosis within the ERC (Fig. 5-A). Posterior to this, there was marked dilatation of the temporal horn of the lateral ventricle with an adjacent focally cavitating gliotic scar and largely unidentifiable hippocampal structures (Fig. 5A-[R], 5B-[R]). ERC, likewise, was extremely atrophic and gliotic, with a sharp demarcation from relatively normal PRC (Fig. 5A-[R]). ERC and PRC were spared at a more posterior level (Fig. 5B-[R]). The lateral geniculate nucleus also showed neuronal loss and gliosis (Fig. 5B-[R]). The posterior hippocampus could be partially identified and CA4 and the granule cell layer of the dentate gyrus were relatively preserved (Fig. 5C-[R], 5D-[R]); CA1 showed neuronal loss and gliosis (Fig. 5C-[R]).

The etiology of the medial temporal pathology is likely complex. In some areas, morphology favours a hypoxic-ischemic etiology, such as the depth of the left collateral sulcus being preferentially affected (Fig. 5A-[L]) and hippocampal neuronal loss with relative sparing of CA2 (Fig. 5B-[L]). In other areas, such as the posterior aspect of the left hippocampus (Fig. 5C-[L]), this pattern was not observed, with all sectors of the hippocampus affected except for the dentate gyrus. Moreover, the severe parahippocampal pathology bilaterally may be a consequence of herniation and traumatic compression against the tentorium. Yet, the near-total loss of the right anterior hippocampus with a less severely affected parahippocampal gyrus (Fig. 5B-[R]) is unlikely to be explained by traumatic causes. The relative sparing of the granule cell layer of the dentate gyrus is likewise difficult to explain. Overall, the pathogenesis of these lesions is not completely understood and may involve multifactorial causes.

4.2. Cortical and subcortical structures

The neuronal population of the cerebral cortex was well-preserved and the supratentorial white matter was unremarkable. The brainstem showed a well-populated substantia nigra and locus coeruleus. The cerebellum was unremarkable.

4.3. Immunohistochemistry

There was no evidence of neurodegenerative phenomena on immunostaining for beta-amyloid, phosphorylated tau (AT8), TDP-43, p62, or alpha-synuclein.

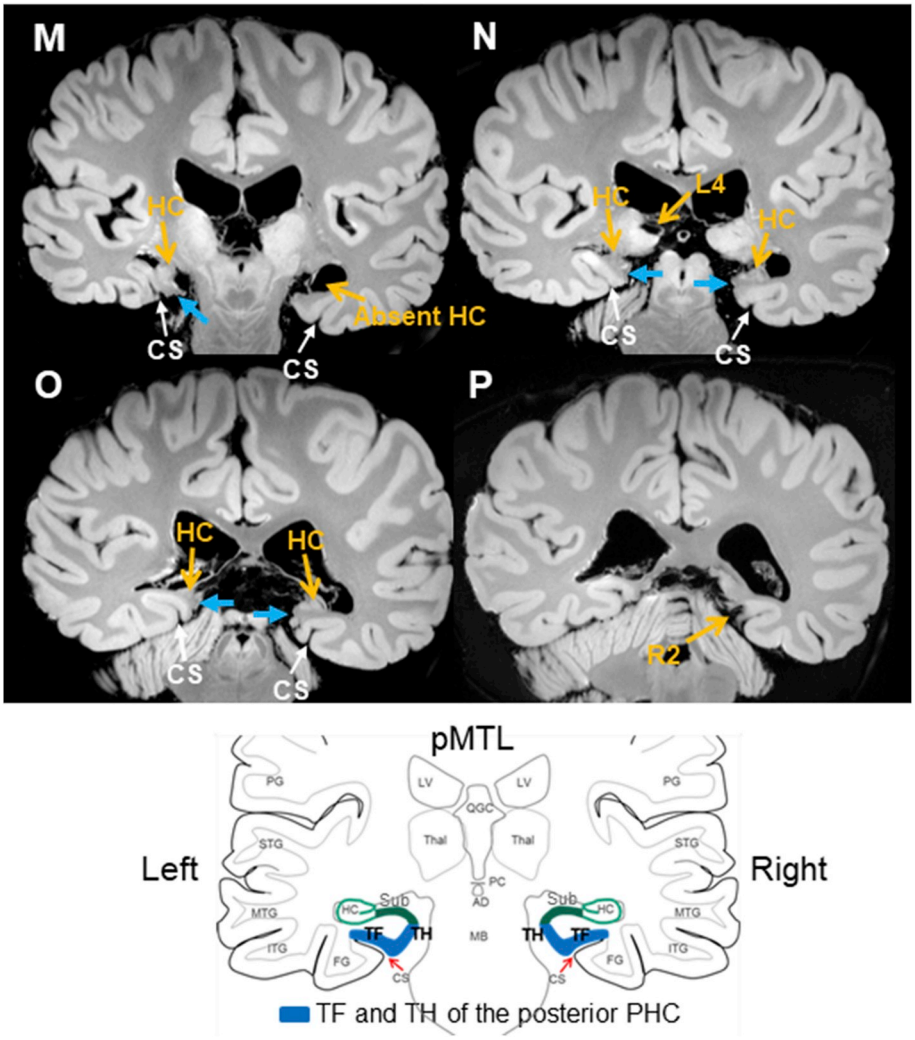

Fig. 3. Ex-vivo MRI of posterior medial temporal lobe lesions (pMTL). Coronal sections of ex vivo T1-weighted MRI perpendicular to the AC-PC plane going through the levels from the posterior commissure (M) to the splenium of corpus callosum (P), at 5mm intervals. The right hippocampus was still absent (yellow arrow to Absent HC in M) and its posterior portion was severely atrophic (arrows in N and O). The posterior left hippocampus was markedly reduced in size (N-O). Compared to normal anatomy in the diagram of the pMTL below, the cortical rims were partially lost in the medial portion (cytoarchitectural area TH) (blue arrows) and relatively preserved in the lateral portion (cytoarchitectural area TF) – e.g., the superomedial bank of the collateral sulcus of the parahippocampal cortex in both hemispheres (M-P).

CS, collateral sulcus; HC, hippocampus; L44: lacunar infarct in the posterior thalamus; PHC, parahippocampal cortex; R2, right anterior medial occipital lesions; TF, von von Economo-Koskinas cytoarchitectural area TF; TH, von Economo-Koskinas cytoarchitectural area TH.

Abbreviations in the diagrams of aMTL in Fig. 2 and pMTL in Fig. 3. AD, aqueduct; CS, collateral sulcus; ERC, entorhinal cortex; FG, fusiform gyrus; HC, hippocampus; IC, insular cortex; IP, interpeduncal cistern; ITG, interior temporal gyrus; LV, lateral ventricle; MTG, middle temporal gyrus; PC, posterior commissure; PHC, parahippocampal cortex; PRC, perirhinal cortex; Pu, putamen; QGC, quadrigeminal cistern; STG, superior temporal gyrus; Sub: subiculum; TF, area TF of von Economo-Koskinas; TH, area TH of von Economo-Koskinas; Th, thalamus; 3V, third ventricle.

5. Discussion

In recognizing the valuable contributions that research with K.C. has made to our understanding of memory and the meaning that it added to his own life, K.C.'s family donated his brain as a lasting gift to the scientific community. Here we report findings of post-mortem MRI together with neuropathological autopsy to confirm the true extent of damage to the MTLs and to other brain regions that may have contributed to K.C.'s profound memory impairment, damage that might not have been detected with in-vivo neuroimaging. It is difficult, if not impossible, to determine how a particular deficit corresponds to a specific lesion site when brain damage is so widely and unevenly distributed. Post-mortem examination, however, provides a unique window into how a severe brain injury that left few brain structures and connections between them untouched (Argyropoulos et al., 2019; Carrera and Tononi, 2014) could nevertheless leave some functions preserved in memory itself and in multiple other cognitive domains.

5.1. Medial temporal lobes

Ex-vivo MRI and neuropathologic results largely confirmed what was long suspected based on in-vivo MRI, adding significant precision to the overall anatomical picture.

In previous studies of K.C. (Rosenbaum et al., 2000, 2005), parahippocampal cortices were not specifically evaluated, but rather included in the overall parahippocampal gyrus estimate. MTL findings based on ex-vivo high-resolution MRI appeared to be in agreement with postmortem neuropathology. Overall, K.C. had the most significant injuries to the left hippocampus, left PRC, and bilateral ERC, whereas the posterior PHC, especially area TF, was well-preserved bilaterally.

The pattern of severe neuronal loss within the MTLs was more extreme in anterior portions bilaterally and posteriorly within the left hemisphere compared to the right. An exception to this pattern was the dentate gyrus, which was unexpectedly spared along the entire length of the hippocampus on the left and posteriorly on the right. One possibility is that although spared structurally, the areas are not viable functionally. Assuming that this is not the case, does K.C.'s profile of spared and impaired memory fit with recent conceptualizations of the functional specialization along the long axis of the hippocampus and within hippocampal subfields?

Older theories of laterality of function view the right hemisphere, including the hippocampus, as dominant for non-verbal, spatial abilities and the left hemisphere for verbal abilities (Milner, 1974; Moscovitch, 1979). Others have proposed that the posterior hippocampus (dorsal in the rodent) mediates spatial navigation and the anterior (ventral) hippocampus mediates fear and anxiety (Ekstrom et al., 2018; Strange et al., 2014). Sparing of right posterior hippocampus in K.C. might explain intact aspects of remote spatial memory. When scanned in an fMRI experiment, hippocampal activity was not detected in K.C. while he judged distances and directions, and imagined routes between well-known landmarks (Rosenbaum et al., 2007a), but it is possible that we lacked the sensitivity and spatial resolution to detect statistically

Table 1
Medial temporal lobe volumes of K.C. and healthy comparison subjects.

	Comparison participants[a]	K.C.[b]	p-values
	Mean volume (SD), mm^3	Volume, mm^3 (%-loss)[c]	(2-tailed)
Left hippocampus	3159 (582)	537 (0.83)	0.000
Right hippocampus	3321 (544)	295 (0.91)	0.000
Left entorhinal	709 (194)	183 (0.74)	0.015
Right entorhinal	806 (226)	245 (0.70)	0.024
Left perirhinal	2262 (929)	810 (0.64)	0.141
Right perirhinal	2434 (974)	2089 (0.14)	0.732
Left parahippocampal	1656 (386)	1091 (0.34)	0.167
Right parahippocampal	1606 (364)	1322 (0.18)	0.454
Left amygdala	976 (250)	457 (0.47)	0.055
Right amygdala	1001 (299)	567 (0.43)	0.170

[a] Comparison healthy participants are based on a published control sample (n = 22) with mean age of 61.5 (SD = 8.9) (Teipel et al., 2006), matched to K.C.'s age of 62, using the Pruessner et al. (2002) tracing protocol of the medial temporal lobe (MTL).

[b] MTL volumes are based on the Pruessner et al. tracing protocol, but the volumes were adjusted upward for the presumed 8% brain shrinkage during formalin fixation described by Schulz et al. (2011).

[c] Percent loss of KC's MTL volumes = 1-KC's volume/mean volume of comparison subjects. Significance on difference of the MTL volumes between the single case of K.C. and control sample was analyzed using Crawford et al.'s *t*-test (Crawford et al., 2003).

meaningful differences at the time. However, findings of hippocampal activity in K.C. during a house recognition task cast doubt on this explanation.

More recent theories that consider functional segregation along the long axis of the hippocampus propose an organization along a gradient that reflects receptive field organization with respect to hippocampal place cells. According to this scheme, more fine-grained analysis of stimuli occurs more posteriorly, with a gradual increase in coarseness as one moves anteriorly that is conducive to extracting a broader perspective or gist (Poppenk et al., 2013 Strange et al., 2014). If it is the case that more anterior portions of the hippocampus handle gist, as has been shown in recent work (Brunec et al., 2018), then we would expect impaired memory for gist in K.C. Although details should be handled by more posterior portions of the hippocampus, which are spared in K.C., at least within the right hemisphere, one might expect that details would also be lost, as without a gist, there is nothing on which to hang those details (Conway and Pleydell-Pearce, 2000). In line with this view, for episodic memory and, by extension, future episodic imagining and narrative construction, K.C. was unable to provide the gist or the details of stories or events. Details may be lost, however, even when the gist is spared, as was the case for K.C.'s spatial memory. In the absence of anterior hippocampal tissue, K.C.'s intact coarse representation of a well-known environment, which can be conceptualized as spatial gist, may have been supported by a schema mediated by intact portions of vmPFC (Gilboa and Marlatte, 2017) or by interactions among more posterior structures implicated in spatial cognition, such as TF and posterior parietal cortex (Ciaramelli et al., 2010; Rosenbaum et al., 2004b). K.C.'s right fornix might also have been sufficiently spared to support the gist of remote spatial memories. Coordination between information mediated by extra-hippocampal neocortical structures and the hippocampus may require the entire hippocampus or posterior hippocampus in both hemispheres for spatial details to survive. A question that arises in K.C. is whether there was sufficient tissue in the posterior hippocampus to be functionally viable. Work in rodents suggests that, as far as memory is concerned, once 60% of the hippocampal tissue is damaged, remaining tissue is not viable, with no gradient in performance with increases in hippocampal damage (i.e., Sutherland

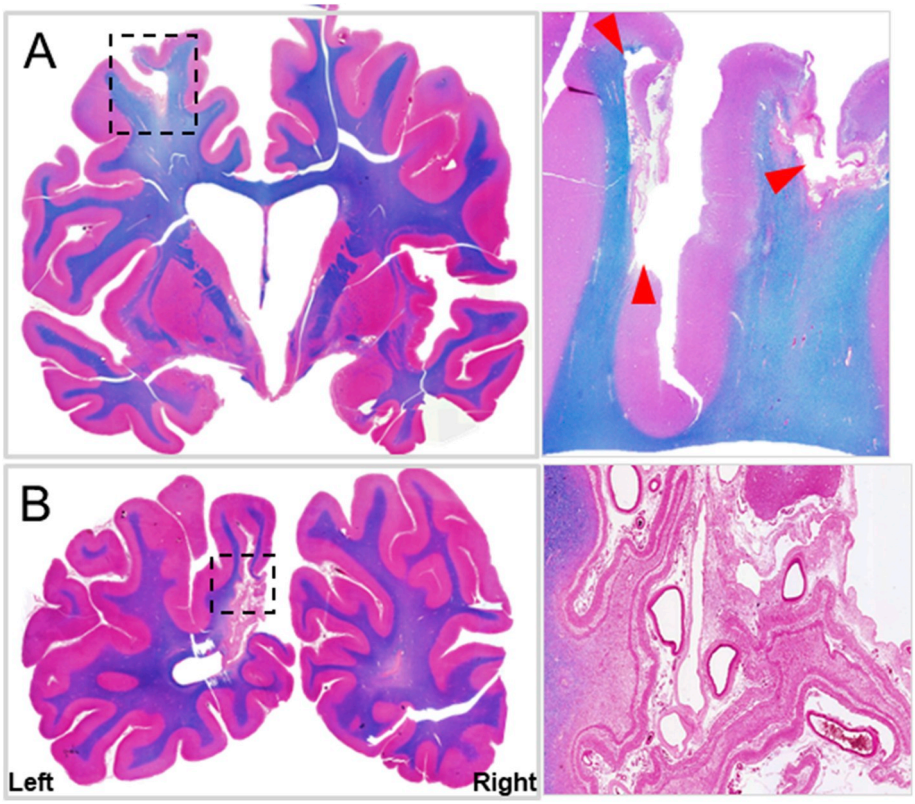

Fig. 4. Large left frontal and occipital infarcts.Whole-mounted H&E/LFB coronal sections show lesions (black boxes) in the left superior frontal (A) and medial occipital (B) lobes. Higher magnifications of the lesions are illustrated beside each whole-mounted section, showing areas of cystic cavitation in the left frontal lobe (arrows) and pseudolaminar necrosis in the occipital (primary visual) cortex, consistent with infarction.

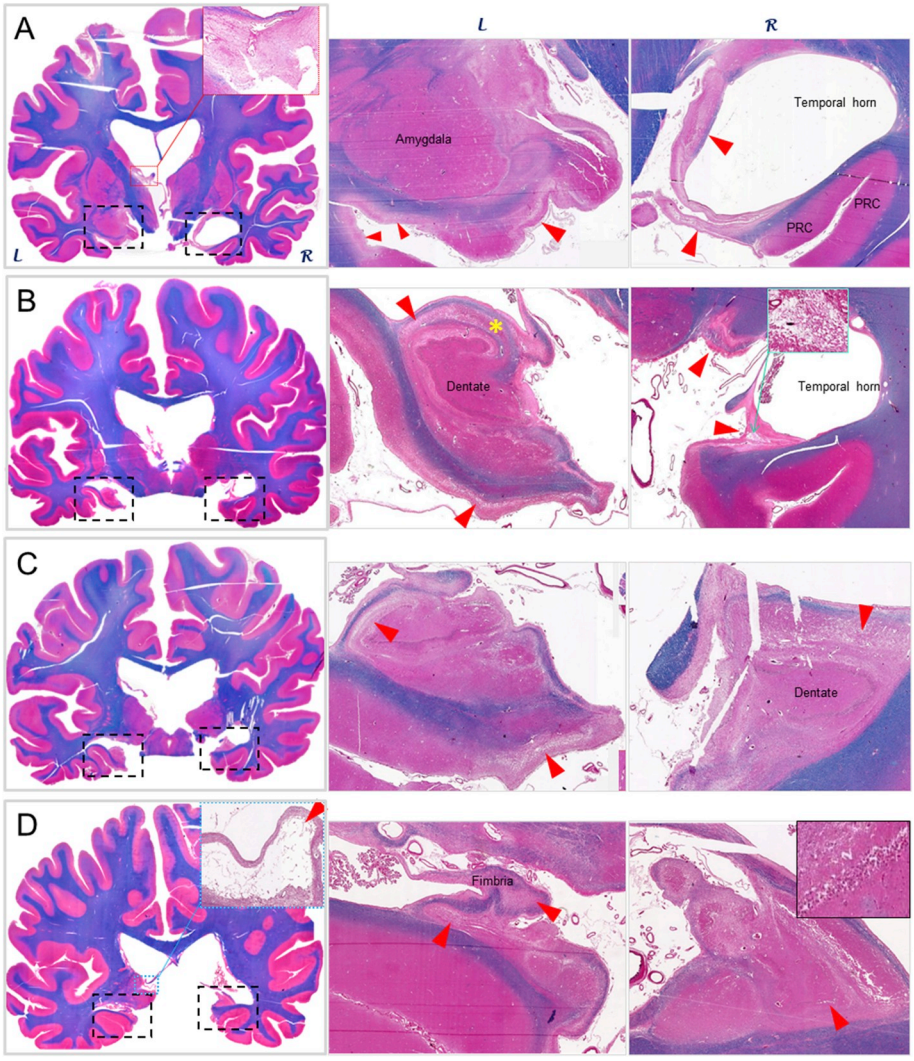

Fig. 5. Medial temporal lobe structural abnormalities. Whole-mounted H&E/LFB coronal sections through the mesial temporal lobes. A-D (from anterior to posterior slices) showed focal mesial temporal lesions. Higher magnifications of the left (L) and right (R) mesial temporal lobes (black boxes) are illustrated beside each whole-mounted section. A: Whole-mounted coronal section through the uncus of the anterior mesial temporal lobe. A-[L]: There were well-demarcated areas of severe neuronal loss and gliosis in the left entorhinal (right arrow) and perirhinal (left arrows) cortices. A-[R]: marked dilatation of the right temporal horn of the lateral ventricle with largely unidentifiable hippocampal structures (top arrow) and an extremely atrophic and gliotic entorhinal cortex (bottom arrow), with a sharp demarcation from normal perirhinal cortex (PRC). In addition, an inset in the whole-mounted section showed a higher magnification of the lesion in the left anterior thalamic nucleus (red box) with marked neuronal loss and gliosis. B: Whole-mounted coronal section through the lateral geniculate nucleus. B-[L]: Left CA1 (top arrow), CA3, presubiculum, parasubiculum, and entorhinal cortex (bottom arrow) showed severe and near-total neuronal loss and gliosis with relative preservation of CA2 (asterisk), CA4, and the granule cell layer of the dentate. B-[R]: Hippocampal structures on the right were largely unidentifiable (bottom arrow), with the lateral geniculate nucleus showing neuronal loss and gliosis (top arrow). Inset showed higher magnification of cavitary hippocampal structures (green arrow). C: Whole-mounted coronal section through the posterior commissure. C-[L]: At this more posterior level, all hippocampal sectors (top arrow) and the parahippocampal gyrus (bottom arrow) on the left showed neuronal loss and gliosis. C-[R]: The right side showed relatively preserved dentate and CA4. There was neuronal loss and gliosis in CA1 (arrow). D: Whole-mounted coronal section through the crus of fornix in the posterior mesial temporal lobe. D-[L]: Degeneration of the left fimbria (right arrow) and further neuronal loss and gliosis in the hippocampus (left arrow). D-[R]: The right side showed relatively preserved dentate and CA4 (arrow). Inset shows higher magnification of preserved dentate granule cell neurons. In addition, inset in the whole-mounted section was a higher magnification of the cystic cavitation (arrow) in the left posterior thalamus (blue box), consistent with infarction.

et al., 2020; Winocur et al., 2013).

Other research has focused on a division of labour across subregions of the hippocampus and MTL cortices. The CA subfields, together with the dentate gyrus and subiculum, form a network that segregates input from ERC and the CA1 subfield at encoding via a process of pattern separation, and assembles details of memories at retrieval via a process of pattern completion (Knierim and Neunuebel, 2016; Rolls, 2016). Proliferation of new granule cells, known as neurogenesis, is believed to take place throughout life within the dentate gyrus (Kuhn et al., 2018; Snyder, 2019), making it a prime candidate for pattern separation, whereas the CA3 subfield's recurrent collaterals make it a prime candidate for pattern completion (Baker et al., 2016; Bakker et al., 2008; Berron et al., 2016). The possibility of neurogenesis within K.C.'s dentate gyrus bilaterally cannot be ruled out, and his dentate gyrus may have supported intact aspects of his remote spatial memory. Though behavioural estimates of pattern separation and completion were never formally tested in K.C., episodic memory (Rosenbaum et al., 2005) and memory for spatial details (Rosenbaum et al., 2000) were severely impaired in the face of dentate gyrus sparing, suggesting that even if functional, it was not sufficient to support pattern separation. Indeed, it is unlikely that the dentate gyrus received the necessary inputs from ERC and CA1, which were damaged bilaterally in K.C.

5.2. Cortical structures

5.2.1. Implicit memory and priming

Why was K.C.'s implicit memory so good? Current theories propose that implicit memory relies on posterior regions, such as regions of occipital cortex that support perceptual details (Gabrieli et al., 1995), anterior temporal cortex (Feng et al., 2016; Kensinger et al., 2003) and PRC (Wang et al., 2010; Wang et al., 2014) that support conceptual details, and dorsolateral prefrontal cortex regions that support categorization and decisions based on those details (Schacter, 2019; Schacter et al., 2007). Because substantial portions of these structures were spared in K.C., his performance on virtually all tests of perceptual and conceptual priming was spared. The preservation of these structures may also account for his ability to acquire new vocabulary and knowledge of famous people's names since his accident, at least in the sense

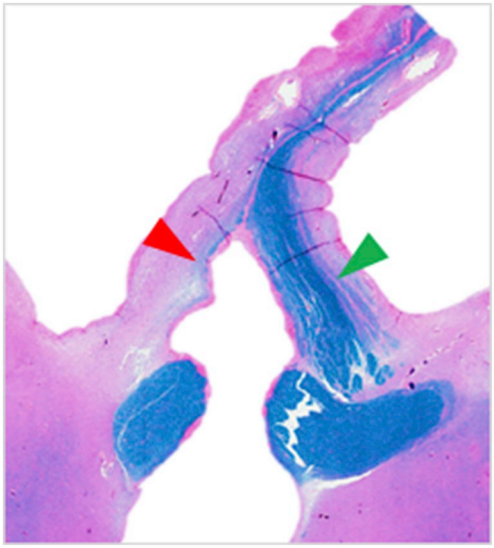

Fig. 6. Degeneration of the left fornix. A magnified H&E/LFB coronal section through the fornix showed pallor and secondary degeneration of the left fornix (red arrow) compared to the right side (green arrow). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

that he could distinguish them as familiar (Westmacott and Moscovitch, 2001). Exactly which of the various structures, or combination of them, is crucial to support this intact performance is not known. In retrospect, it was unfortunate that we did not conduct fMRI studies of priming in K.C. to answer this question, and to see if both neural and behavioural priming were spared and supported one another. Nor did we make any attempt to target priming that was hypothesized to be mediated by some regions that were damaged in K.C., such as priming of associations, or of conjunctions of targets and responses, that are suspected to be mediated by the medial temporal lobes (Schacter et al., 2007). Finally, the manner in which K.C.'s conceptual priming was tested (word stem completion following incidental learning of fact triads) was not exhaustive and might not have captured the type of conceptual priming that is within the domain of PRC (e.g., in relation to visual objects). Word stem completion may also depend on lexical priming via input from the word-form system (e.g., Gabrieli et al., 1994; Richardson-Klavehn and Gardiner, 1998), and it is this aspect that is spared in K.C. and may have supported his performance.

5.3. Orbitofrontal cortex contributions to non-mnemonic abilities

K.C.'s future imagining was impaired together with his episodic memory. Similar impairment has been documented in follow-up studies of amnesic cases with more selective MTL lesions (Klein et al., 2002; Kwan et al., 2015; Race et al., 2011), but other studies have demonstrated intact episodic memory and future imagining (Dede et al., 2016). Deficiencies in both episodic memory and future imagining are present in yet other patients with damage to vmPFC (Bertossi et al., 2016; Irish et al., 2013). In light of K.C.'s additional lesion within right orbitofrontal cortex, it is not possible to decipher which area of damage is responsible for his inability to engage in mental time travel. Although it is difficult to map function to structure when a patient exhibiting impaired function has multiple brain lesions, as in the case of K.C., inferences of what a brain region *does not do* can be made based on examination of preserved function (Rosenbaum et al., 2005, 2014).

We applied this logic to better understand when episodic memory and future imagining and, by extension, MTL function, are not needed for other forms of future thinking and decision-making. To do so, we selected several tests originally used in an effort to understand orbitofrontal cortex/vmPFC function. Inter-temporal choice and ToM, which were found to be intact in K.C., may depend on regions of vmPFC that are dorsal to the area of the frontal lobes that was lesioned in K.C (Abu-Akel and Shamay-Tsoory, 2011; Fellows and Farah, 2005; Hiser and Koenigs, 2018; but see Sellitto et al., 2010). Or, in the case of ToM, on more posterior regions such as temporoparietal junction (Saxe and Kanwisher, 2003; Saxe, 2006), which was relatively unaffected structurally.

By contrast, on the Iowa Gambling Test, patients with more ventral lesions, particularly within orbitofrontal cortex, consistently choose from "bad" decks that result in large immediate gains but a larger overall loss. This "impaired" performance has been hypothesized to result from an inability to assign emotional value to the outcome of past decisions to guide future choices (Bechara et al., 1997, 1999; 2005; Bechara et al., 2003). People with bilateral hippocampal damage and declarative memory deficits also fail to develop a gradual preference for advantageous decks over disadvantageous decks across many trials (Gutbrod et al., 2006; Gupta et al., 2009; Rosenbaum et al., 2016). We originally thought that K.C.'s impaired declarative (explicit) memory affected his ability to form and maintain an inventory of associations between choice of deck and outcome (gain vs. loss) over multiple trials, but an inability to assign emotional value to future outcomes is also plausible in light of K.C.'s lesion to orbitofrontal cortex. It is notable, however, that he performed well on the Toronto Gambling Task, which does not place demands on anterograde memory and has proven sensitive to impulsive and risk-taking tendencies in individuals with lesions to orbitofrontal cortex and vmPFC (Floden et al., 2008). Moreover, unlike individuals with frontal lobe lesions, amnesic cases choose randomly from the decks on the Iowa Gambling Test, suggesting that perhaps they are not encoding or storing the results of previous choices. This finding holds whether or not a delay is interposed between card selections (Gupta et al., 2009).

More difficult to explain in the context of K.C.'s right orbitofrontal lesion is his extreme utilitarian performance on a test of moral reasoning, which also lacks a memory component (Craver et al., 2016). Indeed, other hippocampal amnesic patients appear to exhibit greater deontological tendencies than controls (Craver et al.; McCormick et al., 2016). Patients with orbitofrontal cortex lesions, by contrast, are more likely to show utilitarian tendencies (Koenigs et al., 2007), but the relationship between these tendencies and degree of episodic memory impairment in these patients remains unknown. It is still the case that K.C.'s episodic memory impairment is more severe than most of the other patients tested. That the utilitarian nature of his moral judgments are due to his orbitofrontal cortex damage, either alone or in combination with his episodic memory impairment, cannot be dismissed in light of the neuropathological findings reported here. In light of findings from patients with hippocampal lesions, but spared orbitofrontal cortex, is that the hippocampus modulates deontological responses mediated by orbitofrontal cortex. When both are damaged, utilitarian responses prevail.

5.4. Immunohistochemistry

The severity of K.C.'s functional impairment, primarily affecting his episodic memory, future imagining, and moral decision-making, is offset by the degree and magnitude of preservation that he exhibited in most other cognitive domains, including memory. This profile remained unchanged until his untimely death. However, though he was asymptomatic, the possibility remained that a neurodegenerative process, such as Alzheimer's disease or CTE, was quietly underway, and this theory required postmortem examination to confirm or refute.

Despite the extreme nature of K.C.'s neurological history and the multiple decades between his head injuries and neurohistological examination, there was no evidence of tau immunopositive inclusions suggestive of either Alzheimer's disease or CTE. This is consistent with formal neuropsychological and neurological exams, conducted every

few years, indicating a largely stable cognitive profile, with intact function in most domains outside of memory (Kwan et al., 2012; Rosenbaum et al., 2005; Tulving et al., 1988; Tulving et al., 1991).

5.5. Comparisons with other amnesic cases

Only a handful of well-characterized MTL amnesic cases whose brains were donated for postmortem neuropathologic exam have been documented in the literature, and of these, none to our knowledge involved whole mounting as a means of visualizing histopathology along complex anatomical systems (Clarke et al., 2007). R.B., who suffered anoxia due to cardiac arrest, had very limited damage that was confined bilaterally to the CA1 subfield of the hippocampus (Rempel-Clower et al., 1996; Zola-Morgan & Squire, 1986). N.T., who underwent surgical resection of her right medial and lateral temporal lobe for treatment of intractable epilepsy, was found to have a sclerotic lesion of the unoperated left hippocampus that affected CA2 and volume reduction of CA3 and CA4, leaving CA1 relatively spared (Warrington and Duchen, 1992; Warrington, 1996). H.M., who underwent bilateral resection of his temporal lobes to treat epilepsy (Annese et al., 2014), and E.P., who had viral encephalitis (Insausti et al., 2013), both had more extensive damage to the MTL, including most or all of the ERC, PRC, amygdala, and subiculum bilaterally, and to the temporal pole bilaterally. Postmortem examination of H.M.'s brain revealed significant preservation of hippocampal tissue posteriorly in both hemispheres, including the CA4 subfield and granule cell layer of the dentate gyrus, parahippocampal cortex, and a circumscribed lesion within left orbitofrontal cortex (Annese et al., 2014); similar preservation was noted in K.C. but in the right hemisphere, with the exception of the dentate gyrus, which was spared bilaterally. E.P.ks lesion extended into rostral portions of parahippocampal cortex, fusiform gyrus, and into lateral temporal cortex, with only the most caudal portions of the dentate gyrus, subiculum, and presubiculum within the hippocampus spared bilaterally (Insausti et al., 2013). Gliosis of the white matter underlying E.P.'s orbitofrontal cortex/vmPFC and cell loss within the medial septum were also noted. Frontal cortex appeared intact in H.M., and parietal and occipital cortices were normal in appearance in H.M. and E.P. Here we describe similarities and differences across cases in areas of function that were tested in common.

The hallmark pattern in all patients was severe anterograde amnesia for episodic information with largely intact intellectual, perceptual, and executive function. An exception was K.C.'s impaired colour perception and face matching under degraded conditions, reflecting damage to occipital cortex, and E.P.'s impaired sorting on the Wisconsin Card Sorting Test. Despite MTL lesions of various extents, H.M., like K.C., showed intact perceptual and conceptual priming (Gabrieli et al., 1990; Keane et al., 1995), the former attributed to intact occipital cortex and the later to intact parietal and lateral temporal cortex (Augustinack et al., 2014). E.P. showed intact perceptual priming, and all three patients had the capacity for new skill learning (Glisky et al., 1986a, 1986b; Glisky and Schacter, 1988). H.M. and K.C. showed blunted affect, but both were able to recognize a range of facial emotions, whereas E.P. had difficulty detecting fear and sadness, likely owing to more extensive amygdala damage. E.P. also showed poor face discrimination, possibly due to rostral fusiform gyrus damage (Levy et al., 2005; Shrager et al., 2006), and difficulty distinguishing possible from impossible objects (Insausti et al., 2013) but surprisingly no difficulty discriminating objects and scenes on other complex visual discrimination tasks (Levy et al., 2005; Shrager et al., 2006) despite complete destruction of his PRC, which has been shown to be necessary for task performance in separate patient studies (see Graham et al., 2010). The discrepancy in findings across labs may be due to differences in the nature of the tasks.

All patients appeared to retain personal and general semantic memories that had been acquired in their early years (Bayley et al., 2006; Milner et al., 1968; Steinvorth et al., 2005; Westmacott et al., 2001), and there was evidence of intact schematic representations within remote spatial memory in those patients who were tested (H.M., E.P., and K.C.). However, more extensive tissue loss within temporal cortex in E.P. and H.M. was reflected in their semantic knowledge, which was severely affected in E.P (Reed and Squire, 1998; Schmolck et al., 2002; Stefanacci et al., 2000). and mildly to moderately affected in H.M. (Schmolck et al., 2002). Evidence of some new, but imperfect, semantic knowledge over multiple exposures was reported in both K.C (Hayman et al., 1993; Tulving et al., 1991; Tulving, 1993; Westmacott et al., 2001; Westmacott and Moscovitch, 2001, 2002). and H.M. (Freed et al., 1987; Gabrieli et al., 1988; O'Kane et al., 2004; James & MacKay, 2001; MacKay et al., 1998). In contrast, E.P. was said not to exhibit any form of declarative learning (Reed et al., 1997); findings suggestive of limited learning of household items in E.P. were interpreted as reflecting premorbidly established preferences of certain items over others (Bayley et al., 2008). Impaired declarative learning appeared to extend to spatial memory of a neighbourhood lived in by E.P (Teng and Squire, 1999) and acquisition of a simple route in K.C. (Rosenbaum et al., 2000). By contrast, there was anecdotal evidence in H.M. of intact memory of the layout of a house in which he had lived after his surgery (Corkin, 2002) and in K.C. of intact memory for the route to a library where he worked within the last 15 years of his life. The possibility of "fast mapping," rapid incidental learning of arbitrary associations via neocortex (cf. Sharon et al., 2011; Smith et al., 2014; Warren and Duff, 2014), had not been tested in any of these cases.

Like K.C., H.M.'s memories for personal events that took place as far back as childhood, which were initially thought to be preserved, were found to be severely impoverished (Steinvorth et al., 2005), with additional anecdotal evidence of impaired future imagining (Corkin, 2013). R.B., who had selective damage to CA1, and E.P., who had extensive bilateral hippocampal damage, showed sparing of episodes experienced long ago, even when more sensitive testing measures were used (Bayley et al., 2006). However, participants who served as controls for E.P. seemed to retrieve episodic memories that were impoverished relative to those recovered by similarly aged older adults tested in studies of autobiographical memory conducted in other labs (e.g., Levine et al., 2002; Rosenbaum et al., 2008), calling into question the extent of deficit in E.P., at least under conditions of free recall (Dede et al., 2016). Moreover, equally sensitive measures have been used to test other cases with selective hippocampal lesions who were found to be impaired, including N.T. The results indicate severe deficits in recollecting episodic details for a lifetime of events, even when the damage is limited to the CA1 or CA3 subfield as indicated by ultra high-resolution neuroimaging (Bartsch et al., 2011; Miller et al., 2020).

Although there is agreement in the literature that semantic memory is relatively spared, and that anterograde memory is severely affected, there is not universal agreement about the extent of remote, episodic memory loss in these cases of amnesia. The majority of reports of patients with more selective lesions indicate that damage to the hippocampus, regardless of etiology, leads to deficits in detailed, episodic memory across the lifespan; some studies, however, report that memory from more remote time periods is spared. To date, none of the explanations for the discrepancy account for all the findings, including explanations regarding the location and extent of the lesion, and the sensitivity of the tests used to assess remote episodic memory.

6. Conclusions

K.C. is an individual who illuminated our understanding of memory by participating in neuropsychological research for over 25 years, from the time that a closed head injury left him with a striking pattern of impaired and preserved memory and cognition until his untimely death. K.C.'s episodic memory was severely impaired in the context of damage that encroached on most, but not all, of the hippocampus and surrounding MTL cortices, with sparing of right posterior hippocampus and the granule cell layer of the dentate gyrus bilaterally. It is possible,

though unlikely, that this residual hippocampal tissue supported intact aspects of K.C.'s remote spatial memory. Perhaps most remarkable was the degree of spared function in other domains that K.C. exhibited in the face of widespread damage that affected other memory-related brain structures as well as parts of his frontal, parietal, and occipital cortices. He showed intact performance on tests of perceptual and conceptual implicit memory, remote semantic memory, and some new semantic and spatial learning. He was unable to imagine future personal events and was utilitarian in his moral reasoning, which may be explained by his MTL damage and/or right orbitofrontal lesion. Nevertheless, he showed intact inter-temporal choice, could represent other people's mental states, and his inability to develop preferences for advantageous decks on the Iowa Gambling Test seemed to be consistent with anterograde amnesia rather than poor decision-making.

In light of the current neuropathological evidence in K.C. indicating more extensive damage within some brain areas and less extensive damage in others, previous conclusions regarding brain-behaviour relations may need to be reconsidered. Nevertheless, previously reported behavioural findings in K.C. have been replicated in patients with more restricted lesions, allowing firmer conclusions about the neural correlates of cognitive deficits in K.C. Even in seemingly "clean" neurological cases, however, differences in patterns of disconnection suggestive of diaschisis should be investigated (Argyropoulos et al., 2019; Carrera and Tononi, 2014). We are also reassured by negative findings with respect to Alzheimer's pathology and CTE. Most of all, we are confident that, like the cases H.M., E.P., and N.T., the wealth of behavioural data that K.C. provided, now understood in light of postmortem examination of his brain, will continue to influence the field.

Declaration of competing interest

The authors declare no conflicts of interest.

Acknowledgments

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Appendix A. Supplementary data

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