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Pierre-Yves Jonin, Gabriel Besson, Renaud La Joie, Jérémie Pariente, Serge Belliard, et al.. Superior explicit memory despite severe developmental amnesia: In-depth case study and neural correlates. *Hippocampus*, 2018, 28 (12), pp.867-885. 10.1002/hipo.23010 . inserm-01916086v4

HAL Id: inserm-01916086

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3 **Superior explicit memory despite severe developmental amnesia: in-depth case**
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5 **study and neural correlates**
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15 Serge BELLIARD^(3,4), Christian BARILLOT⁽²⁾ and Emmanuel J. BARBEAU⁽¹⁾
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33
34 Abbreviated title : The extended hippocampal system and context-free memory
35

36 Number of text pages: 48
37

38 Number of figures: 6
39

40 Number of tables: 6
41
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53 **Keywords**: amnesia; single case study; new learning; recognition memory; RRID:
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Abstract

The acquisition of new semantic memories is sometimes preserved in patients with hippocampal amnesia. Robust evidence for this comes from case reports of developmental amnesia suggesting that low-to-normal levels of semantic knowledge can be achieved despite compromised episodic learning. However, it is unclear whether this relative preservation of semantic memory results from normal acquisition and retrieval or from residual episodic memory, combined with effortful repetition. Furthermore, lesion studies have mainly focused on the hippocampus itself, and have seldom reported the state of structures in the extended hippocampal system. Preserved components of this system may therefore mediate residual episodic abilities, contributing to the apparent semantic preservation. We report an in-depth study of Patient KA, a 27-year-old man who had severe hypoxia at birth, in which we carefully explored his residual episodic learning abilities. We used novel speeded recognition paradigms to assess whether KA could explicitly acquire and retrieve new **context-free memories**. Despite a pattern of very severe amnesia, with a 44-point discrepancy between his intelligence and memory quotients, KA exhibited **normal-to-superior levels of** knowledge, even under strict time constraints. He also exhibited **normal-to-superior** recognition memory for new material, again under strict time constraints. Multimodal neuroimaging revealed an unusual pattern of selective atrophy within each component of the extended hippocampal system, contrasting with the preservation of anterior subhippocampal cortices. A cortical thickness analysis yielded a pattern of thinner but also thicker regional cortices, pointing toward specific temporal lobe reorganization following early injury. We thus report the first case of **superior** explicit learning and memory in a severe case of amnesia, raising important questions about how such knowledge can be acquired.

Introduction

The formation of long-term declarative memories relies on medial temporal lobe (MTL) structures that include the hippocampus and entorhinal, perirhinal and parahippocampal cortices. Many studies have demonstrated that the retrieval of facts or general knowledge acquired before the onset of amnesia can be preserved. For example, Patient HM performed normally when asked to retrieve lexical knowledge acquired before the onset of amnesia, across a wide variety of tasks (Kensinger et al., 2001). However, the question of whether amnesic patients can acquire new knowledge still remains debated.

Patients EP and GP, who both had extensive damage to the whole MTL, were unable to recall or recognize information about famous people or events from the post-onset period (Bayley and Squire, 2005). In the case of Patient EP, intensive repetition of stimuli across 24 learning sessions (controls only required two sessions) failed to yield any evidence of new learning. Even when damage was limited to the hippocampal formation, five other patients performed at chance level when asked to make *living/deceased* judgments on famous names (Manns et al., 2003). When new explicit learning is observed in amnesia, this learning is usually described as being 1) slower than in controls, 2) achieved through extensive, repeated exposure to the to-be-learned material (Stark et al., 2005), and 3) the result of dedicated learning techniques such as vanishing cues or errorless learning. These features of new knowledge acquisition in amnesia have led some authors to suggest that this kind of learning cannot be considered as declarative, as it relies upon perceptual learning processes (Bayley and Squire, 2002).

Even so, some researchers have found that patients with adult-onset amnesia can acquire a certain amount of new factual knowledge (e.g., Tulving et al., 1991; Van der

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3 Linden et al., 1996; Kitchener et al., 1998; Verfaellie et al., 2000; Westmacott and
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5 Moscovitch, 2001; O’Kane et al., 2004; Stark et al., 2005). More robust evidence for this
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7 acquisition has come from patients with developmental amnesia (DA). These patients
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9 (e.g., Vargha-Khadem et al., 1997; Brizzolara et al., 2003; Martins et al., 2006; Gardiner et
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11 al., 2008; Bindschaedler et al., 2011; Picard et al., 2013; D’Angelo et al., 2015)
12
13 consistently exhibit low-to-normal levels of knowledge acquisition. They usually have
14
15 hippocampal atrophy but relatively preserved subhippocampal structures, leading to the
16
17 suggestion that these structures support the acquisition of new *context-free* knowledge,
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19 such as vocabulary, concepts, semantic facts, and familiarity (i.e., whether stimuli have
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21 previously been encountered) (Mishkin et al., 1998). However, interpreting these
22
23 findings as evidence for preserved semantic learning must be undertaken cautiously, for
24
25 three main reasons.
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29 First, the conclusion of preserved semantic learning is usually based on the results of
30
31 tests measuring academic achievement or general knowledge, such as the Information,
32
33 Vocabulary and Comprehension subtests of the Wechsler Adult Intelligence Scale (WAIS;
34
35 Vargha-Khadem et al., 1997; Gadian et al., 2001; Brizzolara et al., 2003; Vargha-Khadem
36
37 et al., 2003; Martins et al., 2006; Bindschaedler et al., 2011; Rosenbaum et al., 2011;
38
39 Picard et al., 2013; D’Angelo et al., 2016). It should be noted that more thorough
40
41 assessments of semantic knowledge always elicit performances in the low-to-normal
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43 range (Brizzolara et al., 2003; Martins et al., 2006; Bindschaedler et al., 2011) or, in some
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45 cases, impaired performances (e.g., Patient KF, Martins et al., 2006; Patient CL, Vicari et
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47 al., 2007; Patient Jocelyn, Picard et al., 2013). However, just because some patients with
48
49 DA perform the Vocabulary or Information subtest of the WAIS correctly does not mean
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51 that they have normal semantic memory. Recent findings suggest that their semantic
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53 knowledge structure differs from that of healthy individuals (D’Angelo et al., 2016;
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3 Patient HC, Blumenthal et al., 2017). There is also the question of whether these patients
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5 acquire new semantic knowledge in a similar way to healthy individuals, with available
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7 evidence suggesting that they do so at a slower pace (e.g., Martins et al., 2006; Gardiner
8
9 et al., 2008). Furthermore, it is unclear at present whether patients with DA use
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11 semantic knowledge as quickly and efficiently as controls. Time constraints need to be
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13 used at retrieval to assess this point properly, but to our knowledge this has yet to be
14
15 done.
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18 Second, a careful examination of published cases of adult-onset amnesia or DA
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20 suggests that some patients exhibit residual episodic learning abilities (e.g., Vargha-
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22 Khadem et al., 1997; Verfaellie et al., 2000; Brizzolara et al., 2003; Martins et al., 2006;
23
24 Bindschaedler et al., 2011; Picard et al., 2013; D'Angelo et al., 2015). For example,
25
26 Patient PS, whose damage was thought to be limited to the hippocampal formation
27
28 (Verfaellie et al., 2000), achieved a general memory index of 90 (Wechsler Memory
29
30 Scale-Revised; WMS-R), clearly denoting considerable residual abilities for episodic
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32 learning. In such cases, apparently preserved semantic learning may very well be the
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34 result of these residual episodic learning abilities, albeit requiring more time and effort
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36 than in controls (Squire and Zola, 1998).
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41 Third, lesion studies have mostly focused on distinguishing between patients with
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43 damage limited to the hippocampal formation or else spread across the whole MTL.
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45 However, episodic learning is thought to depend on the so-called *extended hippocampal*
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47 *system*, which includes the hippocampus, fornix, mammillary bodies, mammillothalamic
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49 tract, anterior thalamic nuclei, and retrosplenial cortex (Aggleton et al, 2010). Damage to
50
51 any part of this system has been shown to result in anterograde amnesia, with context-
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53 rich memories being particularly vulnerable (Aggleton and Saunders, 1997; Vann and
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55 Nelson, 2015). Accordingly, a detailed investigation of each component of the extended
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3 hippocampal system is crucial if we are to draw any further inferences about the
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5 cognitive profiles of patients with amnesia. Interestingly, in DA, recent evidence has
6
7 confirmed that damage is not limited to the hippocampal formation. Despite early
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9 evidence of abnormalities in the putamen, brainstem, thalamus, and/or retrosplenial
10
11 cortex (Gadian et al., 2000; Vargha-Khadem et al., 2003), diencephalic abnormalities
12
13 have only been reported comparatively recently (Bindschaedler et al., 2011; Rosenbaum
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15 et al., 2011; Olsen et al., 2013; Rosenbaum et al., 2014). A group study has just confirmed
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17 that mammillary body atrophy is quite common (Dzieciol et al., 2017), as is anterior
18
19 thalamus atrophy. We now have substantial evidence suggesting that some parts of the
20
21 so-called *extended hippocampal system* can be affected in DA. Thus, in case reports
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23 where damage is restricted to the hippocampal formation, we cannot rule out the
24
25 possibility of residual explicit learning abilities, owing to the functional preservation of
26
27 intact components of the extended hippocampal system.
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32 Taken together, evidence of normal knowledge acquisition (i.e., as fast and as efficient
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34 as in controls) in amnesia is therefore still lacking. This needs to be demonstrated in
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36 cases of severe amnesia with extensive damage to the extended hippocampal system
37
38 and no residual episodic ability. Here, we describe the case of a new patient with DA
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40 who displayed several novel and outstanding features. This patient had the extremely
41
42 rare condition of selective damage to the whole of the extended hippocampal system. He
43
44 was severely amnesic, with close to zero residual episodic ability, but displayed **superior**
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46 **(i.e. significantly better than controls)** abilities on many semantic memory tasks.
47
48 Experiments involving speeded recognition memory paradigms yielded evidence that he
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50 could retrieve and acquire new knowledge as efficiently as controls. We also
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52 performed-for the first time in DA to our knowledge a cortical thickness analysis that
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54 revealed a pattern of thicker subhippocampal cortex, indicative of profound
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3 reorganization. This case study suggests that in some instances, and in conditions that
4 remain to be fully elucidated, novel knowledge can be acquired up to a very good level in
5 severe amnesia.
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9 10 11 12 **1. Case description** 13

14 KA is a right-handed male who was 27 years old at first testing, when he was referred
15 to our memory clinic for persistent memory issues he and his family had had to face
16 since he was a child. His only notable antecedent was severe neonatal hypoxia. KA was
17 delivered prematurely at 32 weeks of gestation. He suffered from cardiac arrest and
18 hypoxia at birth, requiring intubation and ventilation and a 40-day stay in the intensive
19 neonatal care unit. His development thereafter was unremarkable, and his parents even
20 reported precocious knowledge of the alphabet at age 3, with a normal acquisition rate
21 for language and motor abilities. We did not find any medical history in KA's family, his
22 parents and his brother being free of any specific medical condition. All completed at
23 least 12 years of education and reported normal socio-occupational integration.
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36 However, very early on in his development, his parents also reported a series of
37 everyday situations where KA obviously exhibited marked anterograde amnesia. When
38 asked to perform two simple things, KA always forgot one, and at age 4 years, his
39 teachers worried about his inability to complete the activities he was instructed to
40 perform. By age 7 years, KA's learning disabilities had become a serious concern at
41 school. Despite many consultations in different clinical settings, no clear diagnosis
42 emerged. These difficulties persisted throughout secondary school, leading KA to repeat
43 his first year, then to go to a vocational school where he failed to obtain his vocational
44 diploma despite two attempts. In 2009, his mother heard about memory clinics, which is
45 when KA was referred to us. KA is currently unemployed. He cannot live fully
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3 independently without the supervision of his parents for administrative tasks, but he
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5 can drive, orient himself in very familiar surroundings, and generally take care of
6
7 himself. KA systematically records most events or thoughts in a notebook he always
8
9 keeps with him, together with at least three pencils, just in case. In this notebook, he can
10
11 write ideas shared in conversations he has just had, as well as the place where he left his
12
13 sunglasses, or something he should think about the next day. Nonetheless, KA is known
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15 by his close relations to have an impressive amount of general knowledge.
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20 **2. Neuropsychological background**

21 **2.1. General cognitive assessment**

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23 KA underwent various neuropsychological assessments between March 2009 and
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25 July 2015, without any noticeable change. To qualify KA's performance by reference to
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27 controls, we followed the recommendations from Spreen, Sherman & Strauss (2006).
28
29 Thus, we used the term "Superior" for scores corresponding to point estimates interval
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31 falling in the [0.950 - 0.979] percentile range, and "Very Superior" for scores falling
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33 above that range. As shown in Table 1, KA was found to have preserved cognitive
34
35 abilities in virtually all domains, except memory. For the sake of clarity, every score has
36
37 been converted to percentile ranks, based on published normative data. KA had a 44-
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39 point discrepancy between his memory and intelligence quotients (MQ and IQ derived
40
41 from the Wechsler scales), scoring 53 and 97, respectively. After Patient HC (Hurley et
42
43 al., 2011; Rosenbaum et al., 2011), this is the second greatest discrepancy between IQ
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45 and MQ ever to be reported in DA to our knowledge. An ecological assessment of
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47 memory was performed with the Rivermead Behavioral Memory Test. For the sake of
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49 comparison, results are provided in Table 2 alongside the values reported for two
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3 similar well-known cases: Patient Jon (Vargha-Khadem et al., 1997) and Patient HC
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5 (Rosenbaum et al., 2011). These data confirm severe anterograde amnesia in KA.
6

7 ***INSERT TABLES 1 & 2 HERE***

8 ***2.2. Recall tests***

9
10 We extensively tested KA's recall abilities across different modalities, to further
11 investigate the severity of his amnesia. Across 11 different standardized recall tests and
12 30 corresponding scores, KA's mean percentile rank was 3.1. When we only considered
13 delayed recall scores, performance dropped to a mean percentile rank of 0.1 (see Table
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21 3).

22 ***INSERT TABLE 3 HERE***

23 24 25 26 27 ***2.3. Recognition memory tests***

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29 Turning to recognition memory, we first administered five delayed matching-to-
30 sample (DMS) tests, keeping the testing format constant while varying the types of
31 stimuli. These tests were also administered to 19 male control participants matched
32 with KA for age (mean = 29.3 years, $SD = 3.2$, range = 25-35), but with a slightly higher
33 education level (mean = 14.8 years, $SD = 2.1$, range = 10-18).
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40 First, we administered the DMS 48 test (Barbeau et al., 2004), which involves the
41 incidental encoding of 48 colored pictures (16 abstract designs and 32 concrete
42 pictures). After a 3-minute break filled with a verbal fluency task, participants
43 underwent a two-alternative forced-choice recognition task. After a 1-hour break, the
44 same two-alternative forced-choice task was administered with new foils. Second, the
45 same procedure was used with 16 concrete words, 16 abstract words and 16 pseudo
46 words as stimuli (verbal version of the DMS 48) using a similar procedure (we used the
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60 Lexique database (New, 2006; New, Brysbaert, Veronis, and Pallier, 2007;

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3 <http://www.lexique.org/docLexique.php>) to match words for frequency: median=6.02
4
5 per million, [0.05 - 77.3]; number of letters: median=7, [4 - 11]; number of syllables:
6
7 median=2, [1 - 4]; pseudo words were also matched to words for the number of letters:
8
9 median= 6, [5 - 8]). Third, participants performed the Recognition Memory Test for
10
11 Faces (Warrington, 1984).

12
13
14 Modified *t* test procedures (Crawford and Howell, 1998; Crawford and Garthwaite,
15
16 2002; Crawford and Garthwaite, 2007a) revealed normal performances on all tasks (see
17
18 Table 4) by KA, with the exception of the 1-hour delayed DMS 48 score, where KA failed
19
20 on only two items, yielding overall accuracy of 96% (46/48).

21
22
23 We further used two four-alternative forced-choice visual recognition memory tests
24
25 (Doors test; Baddeley et al., 1994) and the “Reconnaissance de dessins” subtest of the
26
27 Batterie d’Efficience Mnésique 144 (BEM 144, Signoret, 1991). The latter drawings
28
29 recognition test involves explicit encoding of 24 abstract black-and-white drawings,
30
31 displayed one at a time for 5 seconds. After a 15-minute interval, participants had to
32
33 identify each target drawing among three distractors. In both tests, Patient KA again
34
35 performed within the fully normal range (see Table 4). Finally, since prior studies had
36
37 suggested that the forced-choice test format may enhance recognition memory in
38
39 amnesic patients compared with the old/new test format (Holdstock et al., 2002), we
40
41 administered the Face Recognition subtest of the WMS-III (Wechsler, 1997). Again, KA
42
43 achieved normal scores for both immediate and delayed trials (see Table 4).

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47 ***INSERT TABLE 4 HERE***

48 49 50 51 ***2.4. Source memory***

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54 A common feature of anterograde amnesia is the inability to perform context-rich
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56 memory tasks, where both the item but also its context of acquisition must be correctly
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3 recalled. We therefore adapted the item versus visual spatial memory experiment (Wolk
4
5 et al., 2008) to further investigate whether Patient KA exhibited any dissociation
6
7 between item-only (i.e., context-free) and item-plus-context (i.e., context-rich) memory.
8
9 During an explicit encoding phase, two living and two nonliving objects were displayed
10
11 on a screen, each located in one of the four quadrants (labeled 1 to 4). Participants were
12
13 explicitly asked to learn the association between the nonliving objects and their location
14
15 on the screen. 20 arrays of four pictures were successively presented in a self-paced
16
17 manner. The recognition test started 3 minutes after the encoding phase. Participants
18
19 were shown a total of 80 photographs of nonliving objects (40 studied, 40 novel). For
20
21 each item, they were instructed to make an *old/new* judgment, and for each *old*
22
23 response, the correct location of the item had to be retrieved by pressing the
24
25 corresponding key. Signal detection theory (Snodgrass and Corwin, 1988) was applied
26
27 to measure both discriminability (d' index; i.e., [zHits - zFalse Alarms(FAs)]) and bias (C
28
29 index; i.e., $0.5 \times [zHits + zFAs]$). Source memory was estimated by calculating the ratio of
30
31 correct locations to hits. Patient KA and five healthy male controls underwent the
32
33 experiment (mean age = 28.0 years, $SD = 2.1$; mean education level = 13.2 years, $SD =$
34
35 3.0), and modified t test procedures were applied. KA performed normally in terms of
36
37 accuracy (81%), and although his d' index was impaired, owing to a higher false alarms
38
39 rate, it remained at a reasonable level (Fig. 1). However, KA massively failed to recall the
40
41 locations of the targets, with a source memory score of just 21% (chance level = 25%;
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43 controls' median score > 90%).
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49 **INSERT FIGURE 1 HERE**

50 51 52 53 3. Neuroradiological findings

54 55 3.1. MRI examination

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3 Visual examination of MRI scans revealed severe bilateral atrophy of the
4 hippocampus (see Fig. 2a). We used the VolBrain system (Manjón and Coupé, 2016) to
5 obtain gross volumetric information about the main brain structures. As recently
6 described in a group of children who had sustained neonatal acute respiratory failure
7 (Cooper et al., 2015), we found a slightly lower cerebral white matter volume in KA,
8 despite normal overall gray matter volume. The thalami and caudate nuclei, as well as
9 the left nucleus accumbens, also showed reduced volumes, and severe bilateral
10 hippocampal atrophy was confirmed (see Table 5). Visual comparison between a normal
11 brain and KA's brain (see Fig. 2b) further revealed that neither the body nor the columns
12 of the fornix were clearly discernible, and only some vestiges of the crura were
13 identifiable. Moreover, both the mammillary bodies and the mammillothalamic tract
14 remained unidentifiable, which is an extremely rare condition in the literature. Figure 2c
15 illustrates additional bilateral atrophy of anterior thalamic nuclei.
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31 ***INSERT FIGURE 2 HERE***

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33 ***INSERT TABLE 5 HERE***
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38 ***3.2. Hippocampal subfields***

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40 To further examine Patient KA's hippocampus, a dedicated high-resolution (0.375 *
41 0.375 * 2 mm) proton density-weighted MRI sequence was acquired on a 3T-scanner
42 perpendicular to the long axis of the hippocampus. This sequence allowed us to segment
43 the hippocampal subfields according to a protocol developed by La Joie et al. (2010) on
44 the basis of anatomical atlases (Harding et al., 1998; Duvernoy, 2005), **successfully**
45 **applied to neurodegenerative disorders (La Joie et al., 2013), and which reliability has**
46 **specifically been assessed recently (de Flores et al., 2015).** Three *subfields* (CA₁,
47 subiculum, and *other subfields*, i.e., CA₂₋₃-dentate gyrus) were traced along the head and
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3 body of the hippocampus, based on macroscopic landmarks and heuristic geometric
4 rules (La Joie et al., 2010). After normalizing for total intracranial volume, Patient KA's
5 volumes were compared with those of a group of 20 healthy males who underwent the
6 same MRI sequences, in the same scanner, and were matched for age (mean = 28.4
7 years, $SD = 3.4$), but were more educated than KA (mean education level = 14.5 years, SD
8 = 3.0). In line with the VolBrain results, we found severe bilateral hippocampal volume
9 loss (volume loss exceeding 55%, z score = -5.6), and further showed that volume loss
10 was marked in every segmented subfield in both hemispheres, particularly in the CA₁
11 and subiculum (see Fig. 3).
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22 **INSERT FIGURE 3 HERE**
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27 **3.3. Whole-brain cortical thickness**

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29 Finally, we performed a whole-brain cortical thickness analysis of Patient KA's brain,
30 comparing it with 10 healthy male controls aged 19-36 years (mean = 24.2), using the
31 CortiZon MATLAB toolbox, derived from a successful application to early Alzheimer's
32 disease (Querbes et al., 2009). This toolbox uses a Laplace-based technique to estimate
33 cortical thickness after segmenting the brain into 96 Brodmann areas (BAs). Cortical
34 thickness measures were z -transformed to create a z -score map, as illustrated in Figure
35 4. Crawford's modified t tests (Crawford and Howell, 1998; Crawford and Garthwaite,
36 2002) were applied to compare KA's cortical thickness values with those of controls. We
37 found abnormally thin cortex within the left BA 34 ($p = 0.014$) and right BA 24 ($p =$
38 0.041), as well as a trend for the left BA 30 ($p = 0.074$), these areas corresponding to the
39 dorsal entorhinal cortex, anterior cingulate area, and a subdivision of the retrosplenial
40 area, respectively. Furthermore, we found a trend toward significantly *thicker* cortex
41 within the left BA 38 ($p = 0.064$), which corresponds to the temporal pole region.
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3 Importantly, no abnormal estimates of cortical thickness were found for critical
4 subhippocampal structures within the medial temporal lobe, not least the perirhinal and
5 ventral entorhinal cortices (z scores for bilateral BAs 35 and 36, as well as bilateral BA
6 28, within 1 SD of controls, with the exception of Right BA 28; z score = 1.05).
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11 ***INSERT FIGURE 4 HERE***
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16 To the best of our knowledge, Patient KA is the first reported case of selective and
17 massive damage restricted to the whole extended hippocampal system, providing a
18 unique window onto the role of that system in learning and memory, and most
19 importantly onto the functions of the preserved cortices in KA. In the following three
20 sections, we therefore address three critical questions: 1) could Patient KA retrieve
21 context-free (i.e., semantic) memories?; 2) could he access these memories in the same
22 way as controls do?; and 3) was he able to acquire new context-free knowledge like
23 controls?
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34 **4. Semantic memory retrieval**

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36 Patient KA performed a series of tasks involving the retrieval of semantic knowledge
37 about objects, buildings, events or people listed in Table 6. All raw scores were
38 converted to percentile ranks for the sake of clarity.
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43 **4.1. Standard tests**

44
45 A series of individual tests or batteries of tests tapping semantic (i.e., context-free)
46 memory was used to extensively assess Patient KA's abilities. The BECS-GRECO battery
47 (Merck et al., 2011) is a French battery of five tests assessing semantic knowledge about
48 objects, either living entities ($n = 20$) or manufactured objects ($n = 20$), matched on
49 various dimensions and presented in both verbal (words) and visual (line drawings)
50 modalities. The Mill Hill Vocabulary test (Raven, 1965) is a well-known graded-difficulty
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3 test requiring participants to select the correct synonym for each of 44 words (only Part
4 B was administered) from a list of six alternatives. The EVE-30 and TOP-30 batteries (all
5 details about these batteries available in Thomas-Antérion and Puel, 2012) include a
6 series of tests of semantic knowledge about 30 famous public events and 30 famous
7 people (color photographs), respectively. The EVE-30 battery involves 30 public events
8 spanning the early 1920's to the late 2000's, 3 events pertaining to each decade (1920-
9 1929; 1930-1939; etc.) and 9 for the last decade (2000). Each event was presented
10 visually through a short sentence (e.g. "death of Lady Di"). Three subtests were
11 administrated in a fixed order for each event, presented in a pre-determined random
12 order: the evocation subtest required subjects to provide as many information as he/she
13 could about the event; the multiple-choice recognition subtest consisted in the written
14 presentation of three definitions of the event, the target definition together with two
15 lure definitions, the subject being asked to select the right one (e.g. "Was the death of
16 Lady Di 1/ the assignation of a princess by a terrorist; 2/ the death of a princess due to a
17 car accident; 3/ the suicide of a princess?"); in the last subtest, subjects had to answer a
18 question of detail about the event (e.g. "What was the car's brand?"); subjects also had to
19 to point to the correct date of the event on a visual timeline. A similar logic of
20 assessment (except for the date subtest) is used in the TOP-30 battery, but with famous
21 faces as stimuli.

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KA's performances are set out in Table 6. For the 13 scores derived from the
standardized tasks, Patient KA's performances were in the high range, and it is worth
noting that KA even outperformed controls on the Eve-30 and Top-30 batteries, with
percentile scores above 95, reaching 99 in one subtest.

INSERT TABLE 6 HERE

4.2. *Experimental tasks*

We further designed or adapted three series of tasks to assess Patient KA's context-free retrieval abilities for famous buildings, famous people and recent concepts. The famous buildings task featured 16 color photographs of famous buildings taken from the web and chosen during pilot testing. Participants were asked to 1) make a familiarity judgment, 2) recall the corresponding country, 3) provide as many details as they could about that building, and 4) name the item. Their responses were recorded and independently scored by two raters.

The famous people battery (SemPer battery; Laisney et al., 2009) featured 16 black-and-white photographs of famous people from different domains and 16 matched unknown faces. The latter closely matched the former on several dimensions. Participants had to 1) make a familiarity judgment for each of the 32 faces, and 2) perform a semantic matching task including an easy part (the foil celebrity had a completely different occupation from the target items) and a difficult part (all the celebrities shared the same occupation, but one foil was closer to the target, e.g., three famous politicians displayed, two belonging to the same party). The matching task was administered first with faces as stimuli, then with written names. Finally, each target face was presented again for an oral naming task.

The recent concepts questionnaire was adapted from the New Words Questionnaire developed by Thomas-Antérion et al. (2009). A total of 22 newly coined French words were selected from the Larousse dictionary. Of these, 11 entered the dictionary in 1996 or 1997, and the remaining 11 in 2006 or 2007. Since we administered the questionnaire in 2009, the use of two sets of words coined 10 years apart allowed us to look for differences when KA was asked to retrieve knowledge about the corresponding

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3 concepts. In amnesia, we would expect repeated exposure to new concepts for more
4
5 than 10 years to lead to better performances than more recent exposure.
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7 The 22 words were presented orally, one at a time, and participants were asked to
8
9 give their best definition of each one (free recall). They then answered a multiple-choice
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11 questionnaire in which they had to choose one of three possible short definitions of each
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13 word. Finally, they were asked to decide which of two short sentences made the correct
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15 usage of each word.
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18 Five healthy male controls matched with Patient KA for age (KA was 28 years old at
19
20 the time of testing, and the healthy controls' mean age was 29 years, range: 27-30), but
21
22 slightly more educated (mean years of education: 12, range: 10-14), underwent these
23
24 tasks, in addition to Patient KA.
25
26

27 The same modified *t* test procedures as those mentioned above were used, and
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29 corresponding percentile ranks were estimated (see Table 6). For a total of 15 scores,
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31 KA's mean percentile rank was 69, with a range of 22-88, thus falling within the high
32
33 range of controls' scores.
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38 These results for Patient KA confirmed prior studies (Kensinger et al., 2001; Schmolck
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40 et al., 2002; O'Kane et al., 2004). However, our tasks did not allow us to speculate about
41
42 how KA actually accessed these context-free memories. It may be that, as previously
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44 suggested for Patient Jon (Bird et al., 2008), KA made use of idiosyncratic strategies to
45
46 access semantic memories, and/or this access, though quantitatively normal, was far
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48 slower than that of controls. In the following series of experiments, we therefore sought
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50 to strongly constrain the way KA could retrieve semantic memories, to investigate
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52 whether he would still perform normally.
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5. Speeded semantic memory retrieval

The following series of three experiments were adapted from Besson et al. (2017). Participants for these three experiments were 13 right-handed men (mean age = 25 years, range = 22–27; mean education level = 15 years, range = 12–21). Patient KA was 32 years old at the time of these experiments, and thus slightly older and less educated than the controls.

5.1. *Experimental setting*

For all experiments, stimuli were presented on a CRT computer screen, using E-Prime 2.0 software (<http://www.pstnet.com/eprime.cfm>, E-Prime, RRID: SCR_009567). Participants responded by raising their fingers from a dedicated infrared response pad, and the need for a speedy response was always emphasized in the instructions.

5.2. *General method: speed and accuracy boosting (SAB) procedure*

The speed and accuracy boosting (SAB) procedure was introduced by Besson et al. (2012) to constrain participants to use their fastest strategy, and has been used in several studies (Barragan-Jason et al., 2013; Besson et al., 2015; Besson et al., 2017). Based on a classic go/nogo task, the SAB procedure constrains participants to provide a go response for targets within a given response time following stimulus onset. The deadline was set at 600 ms in the present experiments, based on previous studies. A go response before this deadline was followed by audio feedback, which was positive if the item was a target (hit), and negative if the item was a distractor (FA). Similarly, a no-go response was followed by either positive (correct no-go response for a distractor, i.e., correct rejection) or negative (incorrect no-go response for a target, i.e., omission) audio feedback. Before each item was presented, a fixation cross was displayed with a jittered

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3 duration ranging from 300 to 600 ms. Stimuli were flashed for 100 ms, after which
4
5 participants had up to 500 ms to give their answer. Each of the following experiments
6
7 comprised two consecutive blocks of 140 items. As the SAB procedure is a very
8
9 demanding task, two training blocks where 10 target stimuli had to be recognized
10
11 among 10 distractors preceded each block for each experiment.
12

13
14 The SAB procedure provides a continuous distribution of responses times, allowing
15
16 the minimum reaction time (minRT) for recognition to be estimated (see below). As
17
18 recognition memory is known to rely upon two processes (recollection and familiarity),
19
20 and as familiarity is supposed to be a rapid and automatic process, in contrast to the
21
22 slow, controlled processes that support recollection (Brown and Aggleton, 2001;
23
24 Yonelinas, 2002), the SAB procedure is assumed to rely mainly on familiarity (Sauvage
25
26 et al., 2010; Besson et al., 2012).
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29 **5.3. Experiment 1: Speeded go/no-go human face categorization task**

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31 We took 140 photographs of unknown faces and 140 photographs of animal faces
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33 from the web. We then selected 70 pictures of each kind to build two lists of 140 stimuli.
34
35 Upright and inverted presentations were randomly assigned to the lists (half inverted,
36
37 half upright). Participants were told that the human faces were the targets (go
38
39 responses), and the animal faces the distractors (no-go responses).
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42 **5.4. Experiment 2: Speeded go/no-go famous face recognition task**

43
44 We took 140 photographs of unknown faces and 140 photographs of famous faces
45
46 from the web. Famous faces were selected on the basis of pilot studies showing that they
47
48 were recognizable to healthy individuals the same age as KA. Unknown faces were
49
50 selected because they looked like they could be famous faces (attractiveness and quality
51
52 of the photographs), and were matched to the famous faces for sex, head orientation and
53
54 emotional expression. We then selected 70 pictures of each kind to build two lists of 140
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3 stimuli. Again, upright and inverted images were randomly assigned to the lists as in
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5 Experiment 1. Participants were told that the famous faces were the targets (go
6
7 responses), and the unknown faces the distractors (no-go responses).
8

9 **5.5. Experiment 3: Speeded go/no-go individual face recognition task**

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11 We took 140 photographs of two French celebrities from the web: 70 photographs of
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13 former French President Nicolas Sarkozy and 70 photographs of the famous and now
14
15 deceased French singer Johnny Hallyday. Two sets of 70 photographs of unknown faces
16
17 were then selected from the web so that they matched the famous photographs as
18
19 closely as possible (i.e., each unknown face looked like it could be famous, had the same
20
21 orientation, emotion, hair color, apparent age, etc.). This resulted in two lists of 140
22
23 photographs. Upright and inverted images were randomly assigned to the lists as before,
24
25 i.e. 70 items upright and 70 inverted within each list. Participants were given the name
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27 of a celebrity (i.e., either Nicolas Sarkozy or Johnny Hallyday) and told that the
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29 photographs of that celebrity were the targets (go responses), and the unknown faces
30
31 the distractors (no-go responses).
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35 **5.6. Analyses**

36
37 Performances were analyzed according to signal detection theory (Snodgrass and
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39 Corwin, 1988): correct *go* responses were regarded as hits, and incorrect *go* responses
40
41 as FAs, thus providing measures of discriminability (d' index) and bias (C index), both
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43 indices being corrected according to Snodgrass and Corwin (1988). We applied χ^2 tests
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45 ($p < 0.05$) to hits and FAs for targets and distractors to determine whether participants
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47 successfully performed each task. As stated earlier, the SAB procedure provides a
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49 continuous distribution of response times, allowing the minimum processing time
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51 required for each task to be estimated. The minRT was computed as the latency at which
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53 the number of hits started to significantly outnumber the number of FAs. For each
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3 participant, we used Fisher's exact test ($p < 0.05$) with 40-ms time bins to determine
4 whether the hit-to-FA ratios differed significantly. Some participants had low overall
5 performances (i.e., low d' index), when hit and FA distributions tended to overlap,
6
7 meaning that their minRT could not be computed. Patient KA's performances were
8
9 compared with those of controls using the modified t test procedure.
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14 ***INSERT FIGURE 5 HERE***
15

16 17 18 **5.7. Results** 19

20 Figure 5 illustrates Patient KA's performances on all three experiments. He
21 successfully performed each and every task, despite the strict time constraints (all χ^2
22 tests yielded p values > 0.05). For upright stimuli, Patient KA exhibited normal
23 discriminability between targets and distractors in all the tasks, and strikingly even
24 outperformed controls on the famous face recognition experiment, achieving a d' of 2.17
25 (controls' mean $d' = 0.711$, range = 0–1.053, $t = 5.204$, $p < 0.01$). Regarding bias, Patient
26 KA again had normal C indices, with the exception of the human face categorization task,
27 where he proved to be more conservative than controls. Regarding minRTs for upright
28 stimuli, four controls performed too poorly on the famous face recognition task to
29 achieve a minRT. By contrast, Patient KA achieved a normal minRT and even
30 outperformed controls on the famous face recognition experiment, with a minRT of 360
31 ms (controls' mean = 489, range = 400–560, $t = -2.22$, $p < 0.05$). Furthermore, Patient KA
32 had a minRT of 280 ms in the inverted stimulus condition of the individual face
33 recognition task, again outperforming controls (controls' mean = 354 ms, range =
34 280–400, $t = -3.43$, $p < 0.01$).
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53 When we considered the inverted stimulus results, we found that Patient KA and
54 controls did not differ on either discriminability performances or bias (all $ps > 0.05$; see
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3 Fig. 5). Moreover, the inversion effect on performances was similar in both Patient KA
4
5 and controls.

6
7 The following experiment assessed whether KA could explicitly acquire and retrieve
8
9 new context-free knowledge as well as controls.
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11 12 13 14 **6. Speeded learning of new knowledge**

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16 Control participants for the following experiment were eight right-handed men
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18 matched with Patient KA for age but more educated (mean age = 28 years, range = 22–
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20 34; mean education level = 19 years, range = 14-21). Patient KA was 31 years old when
21
22 he performed this experiment.
23

24 25 **6.1. Experimental setting and stimuli**

26
27 The experimental setting and analyses were the same as those described above for
28
29 the SAB procedure. The stimulus set consisted of 280 color photographs of easily
30
31 nameable objects. The experiment required participants to explicitly learn blocks of 30
32
33 pictures of items and to recognize them among distractors after an interval of 3 minutes.
34
35 The rationale behind using pictures of objects rather than faces as in the first three
36
37 experiments was that faces are regarded as having a particular status in amnesia.
38
39 Research has consistently shown that unfamiliar face recognition can be preserved after
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41 hippocampal damage (Aggleton and Shaw, 1996; Carlesimo et al., 2001; Cipolotti et al.,
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43 2006; Bird et al., 2007; Taylor et al., 2007; Bird et al., 2008; Bird and Burgess, 2008; Aly
44
45 et al., 2010; Smith et al., 2014; Bird, 2017; but see Coleshill et al., 2004; Kafkas et al.,
46
47 2017 for divergent findings). As our aim here was to assess whether Patient KA could
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49 acquire new context-free knowledge normally, we wished to rule out any material-
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51 specific account of either preserved or impaired new learning.
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6.2. *Experimental procedure*

Participants were shown 120 pictures of objects, one at a time, across four 30-item blocks of explicit study. Each time, the instructions emphasized the need to remember each photograph for subsequent recognition. After each study block, participants had to watch a 3-minute cartoon randomly chosen from a set of 12 different videos. Following this interference phase, participants were given the instructions for the test blocks. During these blocks, the 30 target pictures were randomly mixed with 30 distractor pictures. Participants had 600 ms to answer, in line with previous studies. Participants were instructed to provide *go* responses for old items, and *no-go* responses for new items as quickly as possible.

Given the difficulty of this task, even for healthy young controls, two study blocks of 10 target items and two test blocks with 10 target pictures mixed with 10 distractors were used as practice trials for each participant. None of these 40 pictures were used in any of the subsequent study and test trials. These practice trials generally had to be repeated, to allow participants to become accustomed to the task's speed constraints.

INSERT FIGURE 6 HERE

6.3. *Results*

Results are displayed in Figure 6. Patient KA correctly discriminated between targets and lures, with a d' index of 1.20, which fell within the low-to-normal range of controls (z score = -1.41, t = -1.329, p = 0.226). He exhibited a response bias, in that he tended to be more conservative than controls (Patient KA = -0.54, z score = -2.00, t = -1.89, p = 0.06). One interesting possibility is that Patient KA's discriminability may have been underestimated because of his tendency to be more conservative (i.e. he tended to give fewer *go* responses overall). We therefore used a regression approach adapted to single-

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3 case analyses (Crawford and Garthwaite, 2007b) to roughly estimate the range of d'
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5 index values expected for a given response bias. Patient KA's C index (-0.54) predicted a
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7 d' index of 2.5 ($SE = 0.66$), which tended to be significantly better than the d' index that
8
9 was actually found for KA (1.20, $z = -3.8$, $p = 0.06$). The conservative bias we observed in
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11 Patient KA may therefore have led to an underestimation of his actual discriminability
12
13 abilities.
14

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16 Regarding response times, Patient KA's median response time was significantly
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18 shorter than that of controls (median RT = 398 ms, controls' mean = 469 ms, range =
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20 432-499, $t = -2.91$, $p < 0.05$), but he did not differ from controls on minRT (KA = 390 ms,
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22 controls' mean = 420 ms, range = 390-450, $t = -1.01$, $p = 0.35$).
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27 7. Discussion

28
29 We report the case of Patient KA, who has early-onset amnesia characterized by
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31 extremely rare selective and massive damage to each component of the extended
32
33 hippocampal system. We found that Patient KA displayed few, if any, residual episodic
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35 abilities. However, not only was he able to accurately retrieve semantic memories, but
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37 he was also the first patient to show clear evidence of superior or even very superior
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39 access to these memories. Even more strikingly, KA performed faster and more
40
41 accurately than controls on identifying famous faces, despite very strict speed
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43 constraints. In addition, we found evidence for preserved abilities of new knowledge
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45 acquisition in KA, again in the context of a speed-constraint paradigm limiting the range
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47 of available learning strategies. These findings suggest that under certain circumstances,
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49 a very powerful and efficient learning system can allow new knowledge to be acquired
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51 independently of any episodic support. Finally, we performed the first ever cortical
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53 thickness analysis in DA. This yielded novel findings suggesting profound functional
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3 reorganization of the brain in Patient KA. Although we have yet to establish the exact
4
5 nature of the system preserved in KA and how it developed, the present results are
6
7 extremely valuable, not least from a clinical perspective.
8
9

10 11 ***A case of selective and massive damage to the extended hippocampal system*** 12

13
14 Since 1997, when Vargha-Khadem and colleagues first described cases of DA, case
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16 studies have mainly focused on hippocampal atrophy, with a typical 30-40% bilateral
17
18 reduction (Vargha-Khadem et al., 2001). Until very recently, little was known about the
19
20 status of the other brain structures, either within or outside the MTL. As stated in the
21
22 Introduction, evidence for extrahippocampal damage was rather sparse, but suggested
23
24 that structures like the putamen, brainstem, thalamus and retrosplenial cortex might be
25
26 affected (Gadian et al., 2000; Vargha-Khadem et al., 2003; Rosenbaum et al. 2011).
27
28 Importantly, abnormalities of the mammillary bodies and the fornix were described in
29
30 Patients VJ and HC (Bindschaedler et al., 2011; Olsen et al., 2013; Rosenbaum et al.,
31
32 2014). Quite recently, a group study found that mammillary body atrophy was present
33
34 in 66% of participants with DA, and there was a mild reduction in thalamus volumes at
35
36 the group level (Dzieciol et al., 2017). This research confirmed that in DA, damage
37
38 probably extends far beyond the hippocampal formations, and may include some other
39
40 components of the extended hippocampal system, with an apparent variability between
41
42 patients. Our findings for KA suggest that the entire hippocampal system is
43
44 compromised, and not just some components.
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49 Hippocampal subfield segmentation indicated severe and homogeneous impairment
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51 of hippocampal development across each and every subfield, extending beyond the CA₁
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53 subfield as one might expect following hypoxia (Kawasaki et al., 1990). Hippocampal
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55 subfield volumetry has only been reported once in DA (Patient HC; Olsen et al., 2013),
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3 and this study also pointed to damage beyond the CA₁ subfield. However, KA's
4 hippocampal atrophy was fully symmetrical compared with that of Patient HC, who was
5 found to have relative preservation of the CA₂₋₃-dentate gyrus subfields in the left
6 hemisphere. Atrophy was very severe in KA: the volumes we measured were below the
7 lowest measures of the 20 controls, and volume reduction exceeded 55%. Patient KA
8 therefore exhibited the most severe hippocampal atrophy of all reported DA cases.
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16 The hippocampus was not the only structure to be severely atrophied in KA. We also
17 report evidence for severe bilateral atrophy of the fornix, as well as an apparent absence
18 of mammillary bodies. Complete agenesis of the mammillary bodies is an extremely rare
19 condition (but see Patient HC, Rosenbaum et al., 2014). Moreover, we failed to visually
20 identify the mammillothalamic tract in KA, suggesting complete agenesis of this tractus,
21 which has not previously been reported, to the best of our knowledge. Thalamus
22 volumetry also showed significant bilateral atrophy. Last, whole-brain cortical thickness
23 analyses in KA revealed thinner left dorsal entorhinal, left retrosplenial and right
24 anterior cingulate cortices. The whole extended hippocampal system was therefore
25 compromised in KA. It is noteworthy that Patient KA and Patient HC were found to have
26 atrophy of the left and right retrosplenial cortices, respectively. Vann and Albasser
27 (2009) argue that the retrosplenial cortex may be the target of covert lesions after
28 damage to the hippocampal/mammillothalamic system (see also Aggleton, 2008). This
29 region is thought to play a specific role in episodic learning and retrieval, beyond its
30 acknowledged function linking the anterior thalamus nucleus and hippocampus.
31 Evidence of an abnormal retrosplenial cortex in DA therefore reinforces findings of
32 damage extending well beyond the hippocampal formation.
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53 Such extensive injury, together with hippocampal subfield atrophy extending beyond
54 CA₁, raises the question of the potential combined effects of an additional etiology (see
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3 Rosenbaum et al., 2014), and of complex patterns of antero- and retrograde
4 degeneration following early injury (e.g. Caine and Watson, 2000; Loftus et al., 2000).
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7 Nonetheless, hypoxia remains the main probable cause, as recently suggested in Cooper
8
9 et al. (2015)'s case series.
10

11
12 By contrast, in line with previous studies (Vargha-Khadem et al., 1997; Gadian et al.,
13 2000; Vargha-Khadem et al., 2003; Brizzolara et al., 2003; Martins et al., 2006;
14 Bindschaedler et al., 2011; Olsen et al., 2013), we found that subhippocampal structures
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16 (perirhinal, entorhinal and parahippocampal cortices) were preserved in KA.
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20 To the best of our knowledge, Patient KA represents the first reported example in
21 humans of such severe damage extending to each and every structure of the
22 hippocampal system. This system is therefore highly unlikely to be functional. If, as
23 Aggleton and Brown (1999) and Aggleton et al. (2010) suggest, this system is the core
24 brain network underlying episodic learning, the patterns of both preserved and
25 impaired memories in Patient KA are of considerable interest.
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36 ***A case of knowledge acquisition without episodic learning***

37
38 As stated in the Introduction, prior reports of patients with amnesia consistently
39 showed preserved semantic memory retrieval despite compromised episodic memory,
40 the most striking results coming from patients with DA. However, evidence for
41 preserved semantic knowledge relied upon very limited assessments-mainly tests of
42 academic skills like the Vocabulary and Information subtests of the WAIS, where
43 patients typically perform in the low-to-normal range. This is of great importance, as it
44 has been pointed out that some residual level of episodic learning abilities may allow
45 patients-given sufficient time and repetition-to reach close-to-normal levels of
46 knowledge (see Squire and Zola, 1998). Interestingly, Kan et al. (2009) suggested that in
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3 cases of adult-onset amnesia where key brain structures for the semantic system are
4 preserved (anterior and lateral parts of the temporal lobes), prior knowledge about to-
5 be-learned items enhances some residual episodic learning. Thus, in cases of early-onset
6 amnesia, any residual episodic learning ability may allow, after sufficient repetition, the
7 acquisition of a limited but substantial amount of semantic knowledge, which may, in
8 turn, boost further learning, leading to the putative semantic-episodic distinction
9 reported in prior DA cases. Accordingly, previous investigations of new learning (rather
10 than semantic retrieval) in DA have shown that patients' performances critically rely on
11 the number of repetition trials (Brandt et al., 2006; Gardiner et al., 2006 Martins et al.,
12 2006).

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Episodic learning in Patient KA was clearly close to zero, with delayed recall scores for a wide variety of stimuli at floor level, and immediate source memory performances also at chance level. In many tasks, we showed that KA did indeed perform more poorly than most previous DA cases. These findings clearly demonstrate that little, if any, residual episodic learning could occur in KA. Even so, his memories about public events, famous people, objects and famous buildings, as well as his lexical knowledge for concepts coined only 2-3 years before testing, were found to be in the **normal, superior, or even very superior range**. KA indeed outperformed controls on some tasks involving the recall and forced-choice recognition of famous people and public events. It is hard to see how a slow, inefficient and gradual process of episodic learning can lead to this pattern of semantic memory performances. **One limitation that must be mentioned here is the absence of control for media exposure, which may have altered the results (Kapur, Thompson, Kartounis, Abbot, 1999). However, across multiple interviews with the patient and his family, and across several meetings at the patient's home, we did not collect any information that may suggest that KA differs from people of his age regarding**

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3 media exposure. More specifically, the patient reads the newspaper several times a
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5 week, and watches TV once a day, which falls in the normal range in France. Our findings
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7 for KA are therefore difficult to explain without making the assumption of some
8
9 functional distinction within declarative memory.
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11 We sought to control for the range of processes involved in semantic memory
12 retrieval, in order to explore whether this apparent preservation of semantic knowledge
13 in KA could be the result of alternative, putatively abnormal, strategies (Gardiner et al.,
14 2006; see also Bird et al., 2008, in Patient Jon). To this end, we carried out a series of
15
16 recognition experiments featuring time constraints, which greatly limited the range of
17 possible strategies. Experiments 2 and 3 (Section 5) involved the detection and
18 identification of famous faces, respectively. We argue that these tasks could only be
19 successfully performed if a normal representation of each famous face had been built
20 across prior encounters. Moreover, the identification experiment (Exp. 3) further
21 required these representations to include sufficiently detailed visual knowledge for the
22 celebrity to be distinguished from the foils. The fact that KA outperformed controls on
23 both speed and accuracy in Experiment 2, and performed at the controls' level in
24 Experiment 3, strongly supports the idea that not only did he have normal access to
25 context-free knowledge for faces, but also that the representations he had built of these
26 faces were quite similar to those of controls. The normal reductions in accuracy
27 observed in KA when inverted faces were used, further supports this interpretation,
28 suggesting that the holistic processing of faces had similar costs for KA and for controls
29 (Rossion, 2008). However, we acknowledge that both experiments 2 and 3 can be
30 achieved at a pre-semantic level, on the basis of "Face Recognition Units" (FRUs)
31 activation solely within a typical face-processing framework (Bruce and Young, 1986).
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33 Nonetheless, we argue that these tasks can inform us about the stored context-free, or
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3 semantic, knowledge in patient KA, for several reasons. First, the fact that patient KA
4 succeeds in Experiment 3 and outperforms controls in the Experiment 2, despite
5 suffering amnesia from birth, is in itself a surprising finding. This result might indicate
6 that some learning system independent of the hippocampal system has allowed the
7 building of context-free knowledge about faces at least as efficiently as controls do. The
8 fact that KA outperformed controls in the “TOP-30” task involving famous faces as
9 stimuli strengthens this idea. Second, the most recent revision of the Bruce and Young
10 framework (Burton, Bruce and Johnson, 1990) adds the “Semantic Information Units”
11 (SIUs) to the above-mentioned FRUs. Within that framework, SIUs activation is expected
12 to result in faster recognition for faces with pre-experimental knowledge like the famous
13 faces we used in Experiment 2 (e.g. Herzmann and Sommer, 2010). The fact that
14 Experiment 2 yielded slower RTs than face categorization (Experiment 1) and individual
15 face recognition (Experiment 3) strengthens the idea that late processing stages are
16 involved in the task. While controls reached min RTs around 490ms and a median d'
17 around 0.85, patient KA was on average 100ms faster and far more accurate ($d' > 2.0$)
18 (see Figure 5). We therefore speculate that such an unexpected finding can be at least
19 partly explained by the overreliance of the patient KA on his preserved semantic
20 knowledge (i.e. SIUs) to make familiarity decisions, thus abnormally speeding up his RTs
21 within the Famous Face Recognition task. Future work is however clearly needed to
22 assess more directly the acquisition of semantic knowledge in patients with
23 developmental amnesia (Blumenthal et al., 2017 for a recent report).

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26 Taken together, the results of these experiments speak for normal-to-very-superior
27 abilities in Patient KA for retrieving semantic memories.

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30 Regarding the acquisition of new explicit knowledge, rather than its retrieval, we
31 found that strict speed constraints did not prevent Patient KA from performing just as

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3 fast and as accurately as controls (see Section 6). Strikingly, Patient KA even had shorter
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5 median reaction times during the test phase, and his minRT was within the controls'
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7 shorter range, suggesting that the cognitive processes associated with the judgment of
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9 prior occurrence for newly learned material were at least as efficient in KA as they were
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11 in controls. This was not achieved after extensive repetition trials, but after a single
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13 study trial. It is noteworthy that when he gave *go* responses to targets, KA proved to be
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15 just as fast as controls, strongly supporting the idea that he used fast, automatic,
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17 familiarity-based processes.

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20 In summary, despite no evidence for any residual context-rich memories, Patient KA
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22 was able to acquire normal or superior levels of context-free memories just as efficiently
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24 as controls, independently of the modalities or kinds of concepts we explored in the
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26 present study. It is unclear for the time being how he acquired such massive amount of
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28 knowledge. Given that he has no episodic memory, he necessarily uses learning
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30 strategies that are different from healthy subjects who can use their episodic memory
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32 whenever they learn new facts. However, it is very unlikely that his abilities can be
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34 explained in terms of residual episodic abilities, and instead it supports the theoretical
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36 assumptions that episodic learning is not a prerequisite for semantic knowledge
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38 acquisition. Further understanding of how such a powerful learning system could be so
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40 efficient in KA is warranted, given the opportunities it might bring for the rehabilitation
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42 of amnesic patients. Apart from controversial findings of rapid arbitrary learning in four
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44 amnesic patients that presumably resulted from the so-called *fast-mapping* mechanism
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46 (Sharon et al., 2011), we are not aware of any previous findings suggesting normal
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48 knowledge acquisition in amnesia without extensive repetition and/or dedicated
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50 learning techniques.
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3 ***Cortical thickness in KA: an explanation for his superior semantic memories?***
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5 We found that left temporal pole cortices tended to be thicker in Patient KA, while we
6 observed thinner cortices within structures of the extended hippocampal system. Given
7 the critical role of the left anterior temporal lobe in semantic or context-free memories
8 (e.g., Jefferies, 2013; Lambon Ralph, 2014; Guido, 2017), and prior well-known studies
9 relating higher brain volumes to superior abilities or expertise (e.g. Woolett and
10 Maguire, 2011), this requires further discussion.
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18 Cortical thickness is a relevant measure when investigating neurodevelopmental
19 disorders, as it is thought to reflect both synaptogenesis and synaptic pruning, two
20 major maturation processes of the brain (Huttenlocher, 1990; Gogtay et al., 2007;
21 Khundrakpam et al., 2016). Surprisingly, we did not find any prior cortical thickness
22 analyses for DA. Nonetheless, neonatal anoxia-hypoxia has been found to have a specific
23 impact on cortical thinning within medial temporal regions (Bregant et al., 2013; see
24 also Phillips et al., 2011; Zubiaurre-Elorza et al., 2012, for the specific influence of
25 preterm birth on regional cortical thinning patterns). In Patient KA, we found
26 abnormally thin cortices in regions supposed to follow a cubic developmental trajectory,
27 with an initial rapid increase in thickness followed by an asymptotic decrease (i.e., right
28 cingulate cortices), and thicker cortex within the left temporal pole, a region supposed to
29 follow a quadratic trajectory (i.e., inverted U-shaped curve; Shaw et al., 2008). We can
30 therefore speculate that neonatal hypoxia in KA may have altered the developmental
31 trajectory of cortical thickness, leading to functional reorganization within
32 extrahippocampal structures (for evidence in monkeys and humans, see Lavenex et al.,
33 2007; Braun et al., 2008). Interestingly, the morphology of the temporal pole has already
34 been associated to extraordinary memory performance in subjects with Highly Superior
35 Autobiographical Memory (HSAM). These subjects are able to recall with very high
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3 accuracy a large amount of events of their own past, including days and dates when they
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5 occurred (Parker, Cahill & McGaugh, 2006). LePort et al. (2012) have shown that a
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7 sample of HSAM subjects presented with lower estimates of grey matter density in the
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9 bilateral temporal poles (i.e. Brodmann Area 38). Thus, while HSAM is characterized by
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11 very superior autobiographical episodic memory but average levels of declarative
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13 memory otherwise, including semantic memory, KA presents with dramatically
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15 impaired autobiographical episodic memory but superior to very superior semantic
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17 knowledge. It is therefore tempting to consider the possibility that the neuronal
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19 plasticity within the area of the temporal poles plays a critical role in the differential
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21 development of episodic autobiographical and semantic memories.
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25 However, as stated above, **borderline or low-average** ranges of performances across
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27 semantic knowledge tasks are the rule in DA. Evidence for **very superior** explicit
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29 memory in KA was therefore unexpected (**but see Kapur, 2011, for an extensive review**
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31 **and discussion of such paradoxical profiles**). Whereas bilateral hippocampal atrophy
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33 typically does not exceed 30-40%, it was more than 50% in KA. A similar
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35 counterintuitive finding of better performance despite more severe damage had already
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37 been reported (Murray and Mishkin, 1998; Baxter and Murray, 2001; see also Heuer and
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39 Bachevalier, 2011; in humans, see Barbeau et al., 2005; but see Zola and Squire, 2001).
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41 For example, using DMS procedures, greater impairment in recognition memory
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43 following smaller hippocampal lesions has been highlighted in monkeys (Murray and
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45 Mishkin, 1998). These authors suggested that in the case of mild hippocampal damage,
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47 for example, irrelevant signal processing coming from that partly inefficient subsystem
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49 may compete with the relevant physiological signal processing from preserved
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51 surrounding subsystems. Earlier studies in monkeys had suggested that the amount of
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53 hippocampal damage required to produce a significant deficit in DMS tasks is around
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3 20% (Zola and Squire, 2001), which is close to the suggested 20-30% cut-off reported by
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5 Isaacs et al. (2003) for a DA syndrome. Thus, an interesting hypothesis that requires
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7 further investigation -possibly in a group study- is that an inverted (convex) quadratic
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9 function characterizes the relationship between the degree of context-free memory
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11 preservation and the amount of damage to the hippocampal system or the thickness of
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13 temporal neocortical areas in DA.
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16 17 18 **Conclusion**

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20 We have reported the case of Patient KA, who has developmental amnesia, and was
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22 found to have damage beyond the hippocampus itself, encompassing the whole of the
23
24 extended hippocampal system. As expected, KA was densely amnesic, with no evidence
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26 of residual episodic learning abilities. Despite this, he had **normal-to-very-superior**
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28 semantic knowledge, and was able to retrieve that knowledge with the same speed and
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30 accuracy as controls. Besides, new explicit learning was found to be possible in for KA,
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32 again within the fully normal range regarding accuracy and speed, even under strong
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34 strict temporal time constraints. Our findings are consistent with the existence of a
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36 functional dissociation, (or division of labor), for declarative memory within the medial
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38 temporal lobes. Importantly, they add to the growing body of evidence suggesting that
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40 rapid learning may occur outside the hippocampus. However, we have yet to fully
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42 understand how such rapid, explicit, learning can occur and be promoted in amnesic
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44 patients.
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Acknowledgments

We are very grateful to Patient KA for his enthusiasm and tenacity. We are indebted to KA's parents for their participation in providing key elements of KA's early development. We are also grateful to Dr Eduardo Pasqualini for his visual analysis of KA's hippocampi and for his insightful commentaries on this case. KA and his parents gave their explicit consent for the publication of this case study. The authors of the present study have no conflict of interest to declare.

For Peer Review

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Cognitive domains / tests	Raw scores	Percentile Ranks
French National Adult Reading Test		
Raw score, max=40	21	
Estimated Full Scale IQ (mean=100, SD=15)	100	50
Estimated Verbal IQ (mean=100, SD=15)	100	50
Estimated Performance IQ (mean=100, SD=15)	101	50
Intelligence / Wechsler Adult Intelligence Scale, III		
List of subtests		
Vocabulary	36	50
Information	22	75
Comprehension	20	37
Similarities	23	63
Digit Span	13	16
Letter Number Sequencing	8	9
Arithmetic	13	37
Picture Completion	22	63
Digit Symbol - Coding	62	16
Block design	29	6
Matrix reasoning	22	63
Symbol search	29	25
Standard scores, mean=100, SD=15		
Verbal Comprehension	105	63
Perceptual Organization	93	32
Working Memory	84	14
Processing Speed	84	14
Memory / Wechsler Memory Scale III		

List of subtests – raw scores

Information and orientation	14	>56
Logical Memory I	11	0.1
Face Recognition	36	25
Verbal Paired Associates I	4	1
Family Pictures I	8	0,1
Words List, 1st recall	9	23
Words List, Total recall	23	2
Letter Number Sequencing	8	9
Spatial Memory	12	9
Mental Control	35	95
Digit Span	13	9
Logical Memory II	1	0.1
Logical Memory II, retention (%)	12.5	0.1
Face Recognition II	39	50
Verbal Paired Associates II	0	0.1
Family Pictures II	9	2
Words List II	0	0.1

Standard scores, mean=100, SD=15

Verbal Immediate Recall	58	0.3
Verbal Delayed Recall	54	0.1
Visual Immediate Recall	67	1
Visual Delayed Recall	75	5
Delayed Recognition	56	0.2
Working Memory	77	6

Attention & Executive Functions

2 & 7 Ruff Selective Attention Test

	Speed	267	45
	Efficiency	1.166	57
	Verbal fluency		
	Letter P	20	46
	Letter R	20	59
	Fruits category	16	35
	Ruff Figural Fluency Test		
	Unique designs (raw score corrected for age & education)	74	21
	Perseverative errors ratio (raw score corrected for age & education)	0.086	68
	Trail Making Test		
	Part A (seconds)	33	72
	Part B (seconds)	72	80
	Hayling Test		
	Part A, total response time (seconds)	8427	31
	Part B, total response time (seconds)	8130	-
	Part B, raw score	0	80
	Dual task interference paradigm		
	Mu index	92.02	50

Table 1. Neuropsychological background

	KA Aged	Jon Aged	HC Aged
	27	19	22
Rivermead Behavioural Memory Test			
Profile score	5	10	10
Wechsler adult intelligence scale III			
<i>(standard scores, mean = 100; SD = 15)</i>			
Full-Scale IQ	97	114	109
Verbal IQ	97	108	105
Performance IQ	98	120	113
Wechsler memory scale III			
<i>(standard scores, mean = 100; SD = 15)</i>			
Memory Quotient (General Memory)	53	93	49

Table 2. Overall memory & intelligence scores in patient KA vs. patients Jon and HC

Recall Tests	Raw scores	Accuracy, %	Percentile
Immediate, verbal			
<i>Words List I, 1st recall (WMS, 3rd Ed.)</i>	5	42	9
<i>Words List I, Total recall (WMS, 3rd Ed.)</i>	23	48	0.4
<i>Logical Memory I, total recall (WMS, 4th Ed.)</i>	18	36	16
<i>Verbal Paired Associates I, total recall (WMS, 4th Ed.)</i>	1	2	0.1
<i>Selective Reminding Test, Mean Recall across 10 trials</i>	5	33	0.1
<i>Selective Reminding Test, Consistent Recall</i>	18	35	0.1
<i>California Verbal Learning Test, 1st Recall</i>	2	13	0.1
<i>California Verbal Learning Test, Total Recall List A</i>	18	23	0.1
<i>California Verbal Learning Test, Recall List B</i>	3	19	3
Immediate, visual			
<i>Family Pictures I, Recall (WMS, 3rd Ed.)</i>	8	13	0.1
<i>Visual Reproduction I, Recall (WMS, 4th Ed.)</i>	38	88	50
<i>Visual Paired Associates I, 1st Recall (WMS, Revised Ed.)</i>	1	17	
<i>Visual Paired Associates I, Total Recall (WMS, Revised Ed.)</i>	6	33	0.6
<i>Rey Osterreith Complex Figure, Recall</i>	7	19	0.1
<i>"La Ruche, spatial localization learning test", 1st Recall</i>	2	20	7.5
<i>"La Ruche, spatial localization learning test", Total Recall</i>	9	18	0.1
Delayed, verbal			
<i>Words List II, Delayed recall (WMS, 3rd Ed.)</i>	0	0	0.1
<i>Logical Memory II, Delayed recall (WMS, 4th Ed.)</i>	1	2	0.1
<i>Verbal Paired Associates II, Delayed recall (WMS, 4th Ed.)</i>	0	0	0.1
<i>Selective Reminding Test, Delayed recall</i>	0	0	0.1
<i>California Verbal Learning Test, Post interference Free Recall</i>	0	0	0.1

<i>California Verbal Learning Test, Post interference Cued Recall</i>	1	6	0.1
<i>California Verbal Learning Test, Delayed Free Recall</i>	0	0	0.1
<i>California Verbal Learning Test, Cued Recall</i>	0	0	0.1
<i>Double Memory Test, Delayed cued recall</i>	10	21	0.1

Delayed, visual

<i>Family Pictures II, Delayed recall (WMS, 3rd Ed.)</i>	9	14	0.4
<i>Visual Reproduction II, Delayed Recall (WMS, 4th Ed.)</i>	0	0	0.1
<i>Visual Paired Associates II, Delayed recall (WMS, Revised Ed.)</i>	2	33	0.1
<i>Rey Osterreith Complex Figure, Delayed recall</i>	1.5	4	0.1
<i>"La Ruche, spatial localization learning test", Delayed Recall</i>	1	10	0.1

Table 3. Recall memory performances of patient KA. "La Ruche" test was taken from Violon & Wijns (1984)

Recognition tests	Stimuli	Nb. targets	Test format	Delay (min)	Accuracy KA (%)	Accuracy HC Mean (SD)	Percentile	p value
<i>DMS 48, Set 1</i>	Concrete & Abstract designs	48	2 AFC	3	100	98 (2)	83	0.171
<i>DMS 48, Set 2</i>	Concrete & Abstract designs	48	2 AFC	60	96	99 (1)	0.5	0.009
<i>DMS 48 Words, Set 1</i>	Words & pseudo-words	48	2 AFC	3	92	89 (8)	64	0.719
<i>DMS 48 Words, Set 2</i>	Words & pseudo-words	48	2 AFC	60	92	89 (1)	72	0.556
<i>Doors test (A+B)</i>	Doors pictures	24	4 AFC	0	71	-	10 - 25	-
<i>'Reconnaissance de dessins' (see text)</i>	Abstract drawings	24	4 AFC	15	83	-	69	-
<i>Faces I (WMS, 3rd Ed.)</i>	Faces	24	Y / N	0	75	-	25	-
<i>Faces II (WMS, 3rd Ed.)</i>	Faces	24	Y / N	35	81	-	50	-

Table 4. Recognition memory performances of patient KA

	Patient KA raw volumes (cm ³)	Patient KA Normalized volumes (%)	Healthy Controls Normalized volumes (95%IC)
Segmented structures			
Tissue segmentation			
<i>White Matter</i>	478.62*	32.26	[32.95 - 45.17]
<i>Grey Matter</i>	782.89	52.76	[44.17 - 55.44]
<i>Cerebro Spinal Fluid</i>	222.26	14.98	[5.83 - 16.44]
Subcortical structures			
<i>Lateral Ventricles</i>	48.24*	3.25	[0.00 - 1.97]
<i>Caudate</i>	4.72*	0.32	[0.41 - 0.60]
<i>Putamen</i>	7.72	0.52	[0.50 - 0.71]
<i>Thalamus</i>	9.77*	0.66	[0.73 - 0.93]
<i>Globus pallidus</i>	2.02	0.14	[0.14 - 0.21]
<i>Hippocampus</i>	3.30*	0.22	[0.46 - 0.64]
<i>Amygdala</i>	1.63	0.11	[0.09 - 0.15]
<i>Accumbens</i>	0.48*	0.03	[0.03 - 0.07]

Table 5. Results of automated MRI brain volumetry in Patient KA (VolBrain system, Manjón & Coupé, 2016). * = p<.05

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Controls

Stimuli	KA's Raw scores	Mean (SD)/ cut-off	Percentile	p value
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Standardized tasks**BECS-Greco battery**

<i>Words matching test, max = 40</i>	Words (objects)	40	Cut-off= 38	-	-
<i>Pictures matching test, max = 40</i>	Drawings (objects)	40	Cut-off=38	-	-
<i>Identity matching test, max = 20</i>	Drawings (objects)	19	Cut-off=19	-	-
<i>Pictures naming, max = 40</i>	Drawings (objects)	39	Cut-off=38	-	-
<i>Questionnaire, max = 240</i>	Words (objects)	235	Cut-off=233	-	-

Mill Hill Vocabulary scale

<i>Part B</i>	Words (concepts)	32		75-90	-
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EVE 30 battery

<i>Evocation, max=60</i>	Famous events	48		99	-
<i>Multiple-choice recognition, max = 30</i>	Famous events	29		91	-
<i>Details, max = 60</i>	Famous events	39		95	-
<i>Datation, max = 30</i>	Famous events	20		95	-

TOP 30 battery

<i>Evocation, max = 60</i>	Famous faces	55		96	-
<i>Multiple-choice recognition, max = 30</i>	Famous faces	28		37	-
<i>Details, max = 60</i>	Famous faces	50		93	-

Experimental tasks**Famous buildings task**

<i>Familiarity decision, max = 16</i>	Famous buildings pictures	16	15.3 (0.5)	48	0.272
<i>Free recall (country), max = 16</i>	Famous buildings pictures	16	15.3 (1.0)	73	0.535
<i>Free recall, details</i>	Famous buildings	54	38.0 (15.8)	78	0.431

		pictures				
		Famous buildings				
	<i>Naming, max = 16</i>		14	11.3 (3.4)	74	0.529
		pictures				
	SEMPer battery					
	<i>Familiarity decision for names, max = 32</i>	Famous names	32	30.2 (1.3)	86	0.275
	<i>Names matching, Part A, max = 16</i>	Famous names	16	14.4 (1.1)	87	0.270
	<i>Names matching, Part B, max = 16</i>	Famous names	14	14.2 (2.2)	47	0.937
	<i>Familiarity decision for faces, max = 32</i>	Famous faces	32	30.2 (1.5)	84	0.329
	<i>Faces matching, Part A, max = 16</i>	Famous faces	16	14.4 (1.5)	80	0.391
	<i>Faces matching, Part B, max = 16</i>	Famous faces	15	12.0 (3.4)	77	0.465
	<i>Naming, max = 32</i>	Famous faces	32	24.8 (4.7)	88	0.231
	Recent Concepts Questionnaire					
	1996-1997 period					
	<i>Free recall (definition), max = 11</i>	Words	10	9.4 (1.5)	63	0.737
	<i>Multiple Choice Questionnaire, max = 11</i>	Words	11	10.6 (0.9)	65	0.703
	<i>Real usage forced choice, max = 11</i>	Words	11	11 (0)	-	-
	Recent Concepts Questionnaire					
	2006-2007 period					
	<i>Free recall (definition), max = 11</i>	Words	8	9.6 (1.7)	22	0.431
	<i>Multiple Choice Questionnaire, max = 11</i>	Words	11	10.6 (0.9)	65	0.703
	<i>Real usage forced choice, max = 11</i>	Words	11	11 (0)	-	-

Table 6. Patient KA's context-free memory retrieval performances

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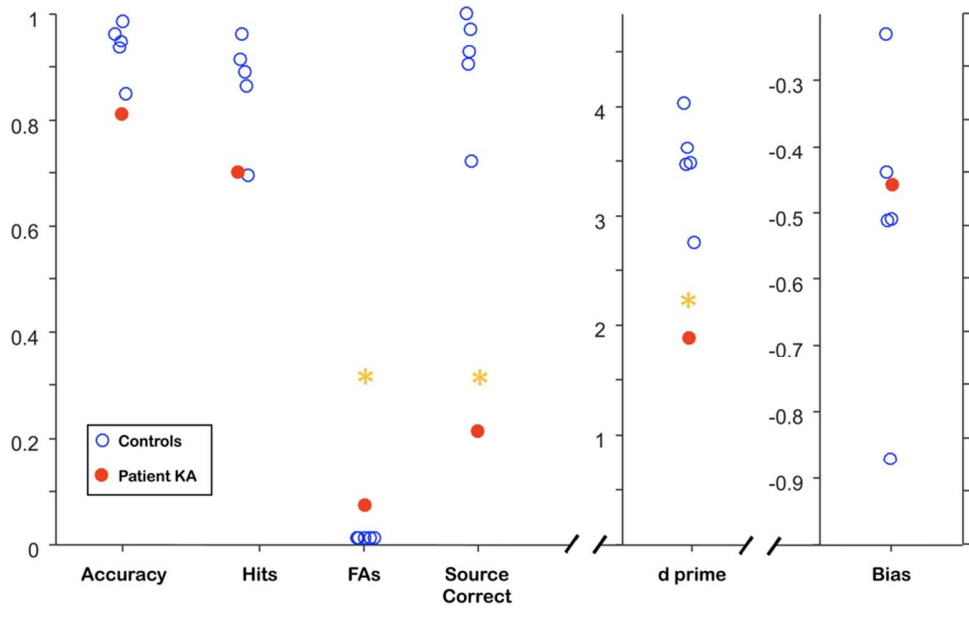


Figure 1. Source Quadrant Location Memory task. Yellow asterisks indicate impaired performances ($p < .05$).

361x270mm (72 x 72 DPI)

view

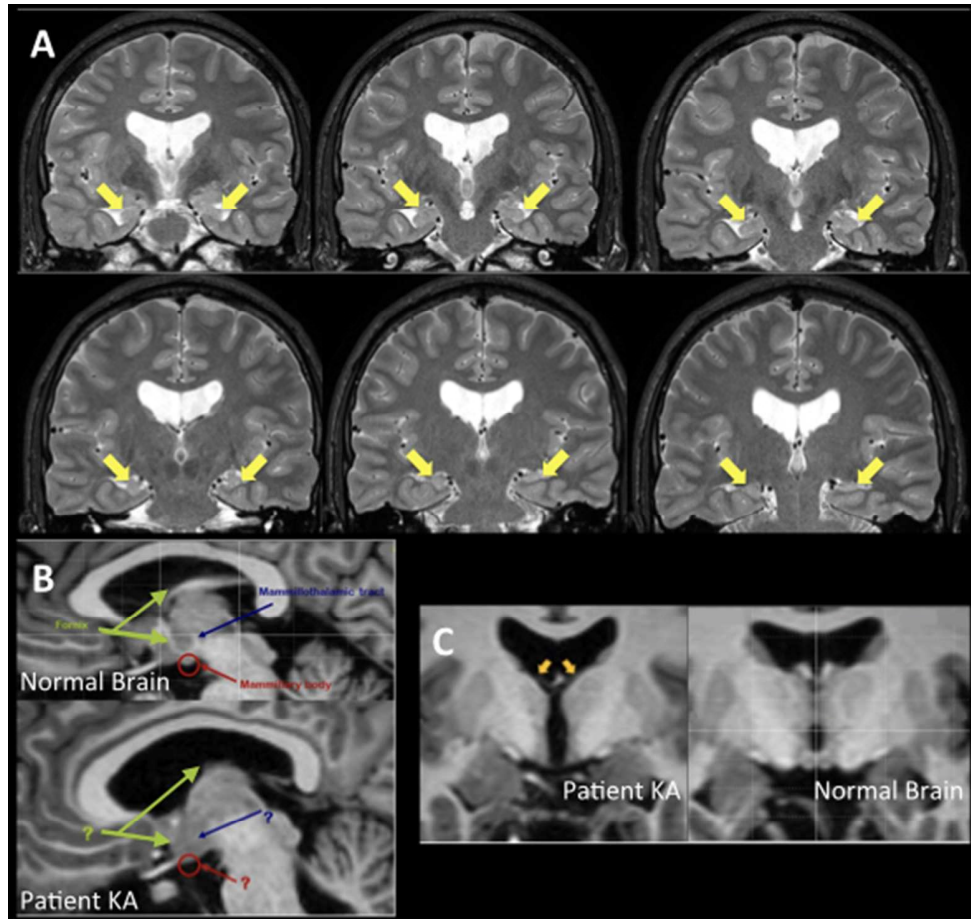


Figure 2. (A) Patient KA's T2-weighted MRI scans. Yellow arrows indicate bilateral hippocampal atrophy; (B) Fornix, mammillary bodies and mammillo-thalamic tract abnormalities in patient KA (bottom) vs a healthy control (top); (C) Anterior thalamic nuclei atrophy in patient KA (left image, yellow arrows) vs a healthy control (right image).

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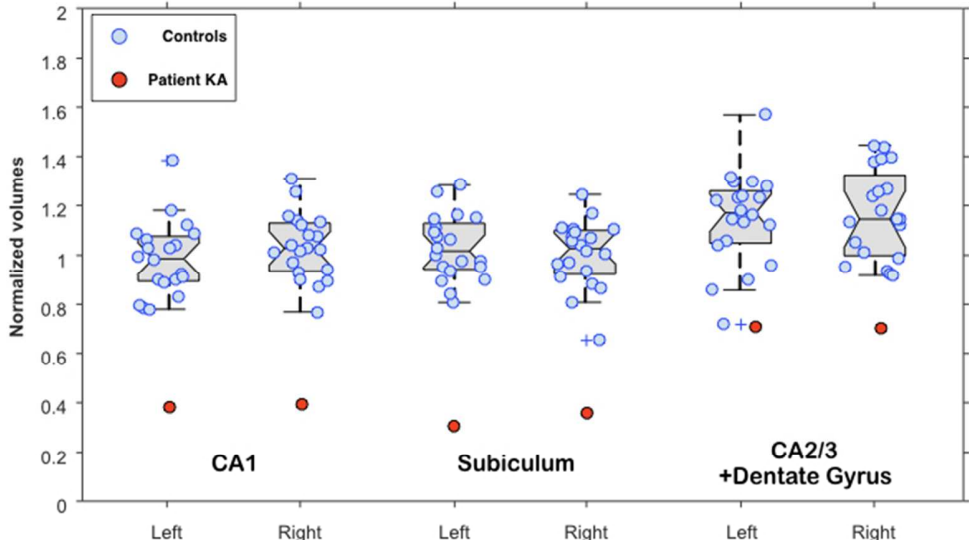
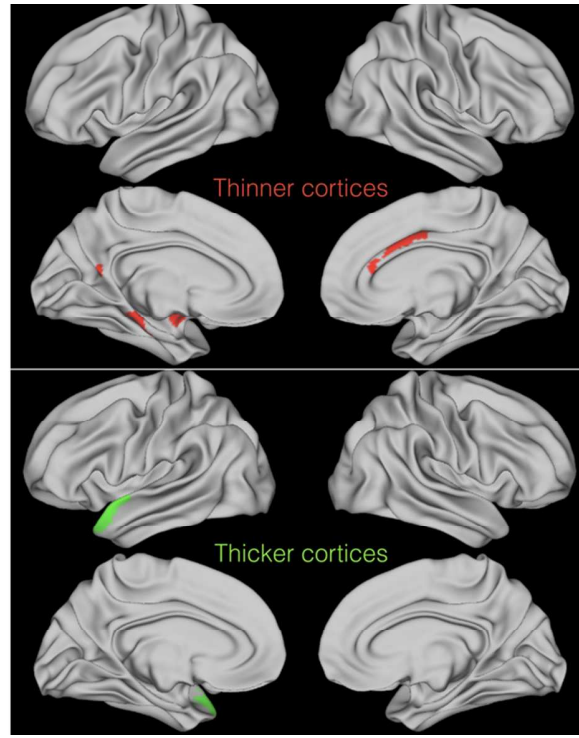


Figure 3. Hippocampal subfields volumetry in patient KA vs 20 healthy controls. (Crawford's modified t-tests, all p values <0.05).

238x135mm (72 x 72 DPI)

Peer Review



31 Figure 4. Z-score map for whole-brain cortical thickness estimates in patient KA vs 10 healthy controls. Red
32 indicates abnormally thick cortices, blue indicates abnormally thin cortices. Cut-off set at 1.65 standard
33 deviation of the mean. See text for detailed results.

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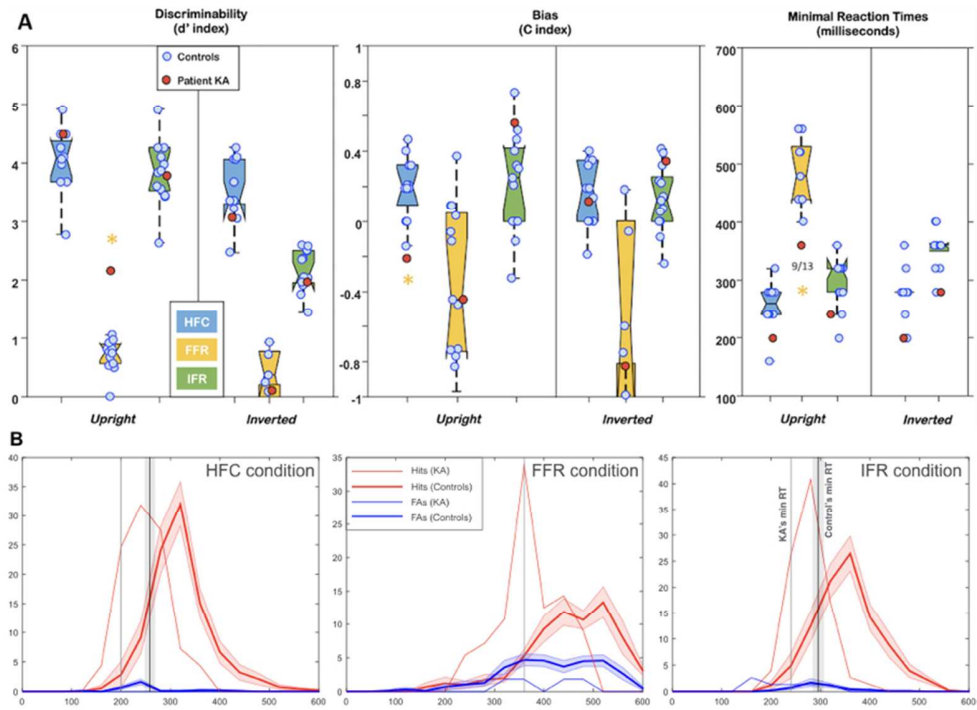


Figure 5. (A) Patient KA's performances during experiments 1 (Human Face Categorization [HFC], blue boxplots), 2 (Famous Faces Recognition [FFR], yellow boxplots), and 3 (Individual Faces Recognition [IFR], green boxplots). Yellow asterisks indicate $p < 0.05$. [HFC = Human Face Categorization, experiment 1; FFR = Famous Faces Recognition, experiment 2; IFR = Individual Face Recognition, experiment 3]; (B) Reaction times distributions for each task (Upright conditions only), where Y axis shows % responses and X axis time bins. Dashed areas represent standard error of the mean.

318x231mm (72 x 72 DPI)

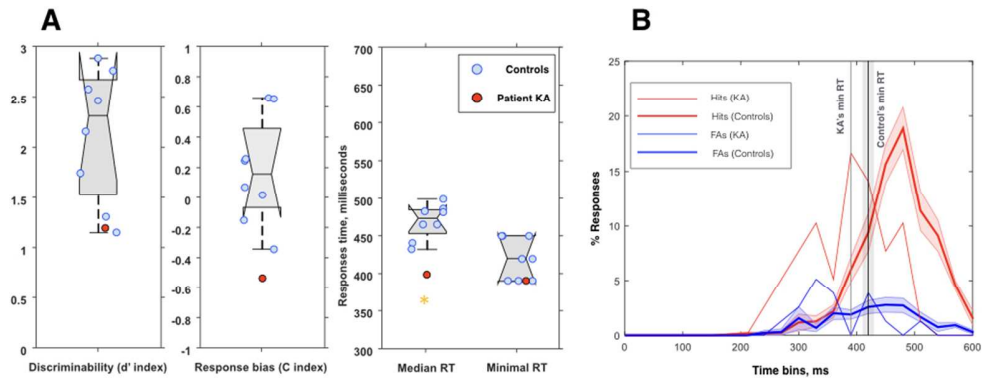


Figure 6. Context-free learning experiment. (A) Learning performances of patient KA (red circle) and controls (blue circles) assessed through discriminability (d' index, left plot), response bias (C index, middle plot) and response times (Median response time and Minimal reaction time, right plot). Yellow asterisk indicate $p < 0.05$. (B) Reaction times distributions, where Y axis shows % responses and X axis time bins. Dashed areas represent standard error of the mean.

356x137mm (72 x 72 DPI)

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