Impaired assessment of cumulative lifetime familiarity for object concepts after left anterior temporal-lobe resection that includes perirhinal cortex but spares the hippocampus

Ben Bowles a,b, Devin Duke a, R. Shayna Rosenbaum c,d, Ken McRae a, Stefan Köhler a,c

a Brain and Mind Institute and Department of Psychology, Western University, London, Ontario, Canada
b Department of Psychology, UC Berkeley, Berkeley, California, United States
c Rotman Research Institute, Baycrest Centre, Toronto, Ontario, Canada
d Department of Psychology, York University, Toronto, Ontario, Canada

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The ability to recognize the prior occurrence of objects can operate effectively even in the absence of successful recollection of episodic contextual detail about a relevant past object encounter. The pertinent process, familiarity assessment, is typically probed in humans with recognition-memory tasks that include an experimentally controlled study phase for a list of items. When meaningful stimuli such as words or pictures of common objects are employed, participants must judge familiarity with reference to the recent experimental encounter rather than their lifetime of autobiographical experience, which may have involved hundreds or thousands of exposures across numerous episodic contexts. Humans can, however, also judge the cumulative familiarity of objects concepts they have encountered over their lifetime. At present, little is known about the cognitive and neural mechanisms that support this ability. Here, we tested an individual (NB) with a rare left anterior temporal-lobe lesion that included perirhinal cortex but spared the hippocampus, who had previously been found to exhibit selective impairments in familiarity assessment on verbal recognition-memory tasks. As NB exhibits normal recollection abilities, her case presents a unique opportunity to examine potential links between both types of familiarity. In Experiment 1, we demonstrated that NB’s impairment in making recognition judgments affects cumulative frequency judgments for exposure to concept names in a recent study episode. Experiments 2 and 3 revealed, with a task borrowed from the semantic-memory literature, that NB’s impairments do indeed extend to abnormalities in judging cumulative lifetime familiarity for object concepts. These abnormalities were not limited to verbal processing, and were present even when pictures were offered as additional cues. Moreover, they showed sensitivity to concept structure as reduced in semantic feature norms; we only observed them for judgments on object concepts with high feature overlap. In Experiment 4, we found that an amnesic patient (HC) with previously established deficits in autobiographical recollection, due to a selective lesion of the extended hippocampal system, does not exhibit any abnormalities in assessing lifetime familiarity. Together, these findings provide support for a functional link between the assessment of recent changes in familiarity, as probed with experimental study-test paradigms, and cumulative lifetime familiarity based on autobiographical experience accrued outside the laboratory. They argue in favor of the notion that familiarity is closely related to the representation of concept knowledge, likely through computations in perirhinal cortex.

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1. Introduction

The ability to recognize the prior occurrence of objects in the environment is critical to many aspects of adaptive behavior. There is a consensus in the psychological literature that recognition memory can operate effectively even in the absence of successful recollection of episodic contextual detail about a pertinent past object encounter (Yonelinas, 2002). The process that allows for recognition independent of episodic recollection is often referred to as familiarity assessment. Familiarity is typically probed in humans with recognition-memory tasks that include an initial experimentally controlled study phase for a list of items. Familiarity-based responses are those in which an item is endorsed as studied, with no reported
recovery of contextual detail about that study encounter. Critically, when meaningful stimuli such as words or pictures of common objects are employed, as is the case in the majority of published studies in cognitive neuroscience research on recognition memory (Eichenbaum et al., 2007; Kim, 2013), participants must judge familiarity with reference to the recent experimental encounter rather than with respect to their lifetime of autobiographical experience, which may have involved tens, hundreds, or thousands of exposures in many different episodic contexts. From this perspective, extant cognitive neuroscience research has primarily probed recent incremental changes in familiarity rather than absolute or cumulative levels (Bridge et al., 2014; see also Coane et al., 2011; Mandler, 1980). Humans can, however, also judge the cumulative familiarity of objects concepts (i.e., the concrete object that a word or picture refers to; Martin, 2015) they have encountered over their lifetime as the outcome of many learning episodes outside the laboratory. Such judgments show considerable consistency across participants in normative studies of concept knowledge, and are also known to have some external validity, as reflected in moderate correlations with objective word frequency (Cree and McRae, 2003; Moreno-Martinez et al., 2014; Schröder et al., 2012). At present, little is known about the cognitive and neural mechanisms that support this ability.

Cumulative familiarity judgments for object concepts acquired over a lifetime and familiarity-based responses in recognition-memory tasks for items from a studied list can be considered similar in that both require an assessment of prior item occurrence without any requirement to recover contextual information about a specific episodic encounter. Perhaps owing to this similarity, it has often been assumed that the recognition-memory paradigm can provide a model to understand lifetime familiarity that hinges on the effects of accumulated semantic knowledge (e.g., Atkinson and Juola, 1974). Whether this assumption is justified, however, is a question that can ultimately only be answered through systematic empirical investigation (see Mandler, 2008, for further discussion).

A well-known and robust empirical finding in cognitive psychology that addresses the relationship between cumulative lifetime and recent incremental changes in familiarity is the mirror effect in recognition memory. It refers to the observation that hit rates are typically higher, and false alarm rates are lower, for low frequency as compared to high-frequency words (Glanzer and Adams, 1990). It has been suggested that high-frequency lures are more often falsely recognized as ‘old’ because participants mistake familiarity associated with prior lifetime experience as familiarity based on a recent encounter (Greene, 1999; Joordens and Hockley, 2000; Reder et al., 2000). In support of this notion, for example, Reder et al. demonstrated, using the Remember-Know paradigm, differential increases in ‘know’ responses for high as compared to low frequency lure words. Such findings suggest that, in phenomenological experience, it is not always apparent whether a stimulus feels familiar due to a recent laboratory exposure or due to frequent pre-experimental experience with it in daily life. As such, the effect could also hint at shared neural mechanisms.

There is a consensus in the neuroscience literature across rodents, non-human primates, and humans that recognition memory requires contributions of perirhinal cortex (PrC) in the medial temporal lobe (MTL; Brown and Aggleton, 2001; Murray et al., 2007; Squire et al., 2007; Suzuki and Naya, 2014). There is also considerable evidence to suggest that within the MTL, mechanisms that allow for familiarity assessment are, at least in part, distinct from those that support recovery of contextual detail about a specific recent item encounter (for reviews see Aggleton and Brown, 2006; Diana et al., 2007; Eichenbaum et al., 2007; Montaldi and Mayes, 2010; but see Squire et al., 2007). Although it remains contentious how best to characterize the unique functional contributions of different MTL structures, we note that a number of lesion studies have revealed dissociations in patterns of memory impairments that can be captured with the broad distinction between item-based familiarity assessment and episodic recollection (Aggleton et al., 2005; Bowles et al., 2010; Brandt et al., 2009; Horner et al., 2012; Jäger et al., 2009; Mayes et al., 2002; Tsivilis et al., 2008; Turritziani et al., 2008; Vann et al., 2009; Yonelinas et al., 2002; but see Cipolotti et al., 2006; Manns et al., 2003; Wais et al., 2006). Critically, it has been shown that anterior temporal lobe lesions that spare the hippocampus can produce deficits in familiarity assessment that leave recollection intact. We found this pattern of performance in an individual (patient NB) who underwent a rare tailored surgical resection of the left anterior temporal lobe for treatment of intractable temporal-lobe epilepsy that included PrC but spared the hippocampus (Bowles et al., 2007; Martin et al., 2011; see Brandt et al., 2016, Cohn et al. (2010), Davidson et al. (2006), Martin et al., (2012), for other patients with selective familiarity impairments). Furthermore, we reported that a stereotaxic surgical treatment for temporal-lobe epilepsy that is restricted to the hippocampus and amygdala can produce selective recollection impairments on the same task, and at the same level of overall recognition performance, as the familiarity impairment that was observed in NB (Bowles et al., 2010). This double dissociation provides particularly strong support for the notion that familiarity assessment in the study-test paradigm relies on brain mechanisms that are, at least in part, distinct from those that support recollection. However, these findings to not speak to any potential role of PrC in judgments of cumulative lifetime familiarity.

Recent evidence from functional neuroimaging research suggests that PrC is involved in processing of object concepts even in tasks that do not make explicit reference to any recent experimental encounter (Dew and Cabeza, 2011; Heusser et al., 2013; O’Kane et al., 2005; Yoss et al., 2009; Wang et al., 2010, 2014), and even in paradigms that do not include any experimental study phase (Bruffaerts et al., 2013; Clarke and Tyler, 2014; Liuzzi et al., 2015). In the latter set of studies, multivariate pattern analyses have revealed that PrC carries information that allows for fine-grained distinctions among similar object concepts. Neuropsychological research in patients with focal temporal-lobe lesions has also demonstrated that the extent of damage to PrC predicts differential behavioral impairments in naming confusable objects with high semantic feature overlap (Wright et al., 2015; for similar evidence in neurodegenerative disease see Kivisaari et al. (2012)). Overall, these findings are part a growing body of research that points to an important role of PrC in disambiguating objects and object concepts with high perceptual or semantic feature overlap in task contexts other than classic recognition-memory tasks (see Clarke and Tyler, 2015; Graham et al., 2010, for review).

A recent functional neuroimaging study from our lab provides, to our knowledge, the first evidence that implicates left PrC in the assessment of cumulative lifetime familiarity for object concepts. We examined fMRI BOLD responses when participants judged cumulative lifetime familiarity of object concepts based on perceived cumulative lifetime familiarity with object concepts based on recent item encounter (for reviews see Aggleton et al., 2005; Dew and Cabeza, 2013; Henson et al., 2003) while tracking perceived cumulative lifetime familiarity (Henson et al., 2003) while tracking perceived cumulative lifetime familiarity with object concepts based on perceived cumulative lifetime familiarity with object concepts based on.
autobiographical experience. Specifically, we tested patient NB on variants of the two types of tasks that revealed left PrC involvement in our prior fMRI study (Duke et al., submitted). Given that NB is known to exhibit selective impairments in familiarity-based recognition memory in the study-test paradigm (Bowles et al., 2007, 2010; Martin et al., 2011), we asked whether these impairments extend to frequency judgements and to assessment of cumulative lifetime familiarity. Note that in our past published work on NB, we examined graded familiarity decisions based on the use of a confidence scale for items presented once at study (Bowles et al., 2007; see Yonelinas (2002), for rationale). Another way to probe graded differences in recent changes in memory strength is to manipulate the number of item exposures (repetitions) in the experimental study phase, and to administer frequency judgements at test (see Hintzman and Curran 1994, for rationale). Therefore, we began the current investigation by examining whether NB’s familiarity impairments also manifest in abnormal frequency judgments for degree of recent laboratory exposure to names of object concepts (Experiment 1). In Experiments 2 and 3, we then presented the entire set of 541 items included in McRae and colleagues’ normative database for object concepts (McRae et al., 2005), and asked NB to judge the cumulative lifetime familiarity for each item. Given that our task was designed to probe the familiarity of concepts that words refer to, rather than the familiarity of the words themselves, we also tested NB under conditions in which visual images of exemplars were provided in addition to concept names as cues (Experiment 3). This modification was introduced in order to explore whether any abnormalities would be limited to the input modality of verbal cues, or whether they might be multimodal and affect processing of object concepts based on picture cues as well (see Gainotti, 2011; Rice et al., 2015a, 2015b, for discussion). Finally, in Experiment 4, we sought evidence to establish some specificity with respect to the nature of MT! damage that causes behavioral abnormalities in judging cumulative lifetime familiarity. Here, we tested an amnesic individual (HC) with documented bilateral lesions of the hippocampus and connected subcortical structures, but intact PrC (Olsen et al., 2013; Rosenbaum et al., 2015). HC is known to exhibit deficits in episodic recollection of autobiographical experiences (Kwan et al., 2010; Rabin et al., 2012; Rosenbaum et al., 2011). Given that lesions limited to the hippocampus, or the extended hippocampal system, can spare item familiarity with reference to recent laboratory exposure, we asked whether such a lesion could also spare the assessment of cumulative lifetime familiarity of object concepts.

2. Experiment 1 – Frequency judgements of recent laboratory exposure to object concepts in NB

2.1. Methods

2.1.1. Participants

NB is a right-handed, university-educated woman whose memory deficits and lesion characteristics have previously been documented in detail elsewhere (Bowles et al., 2007, 2010, 2011; Martin et al., 2011). She is a native English speaker who was 26 years old at testing. About 5 years prior to testing, NB underwent a left unilateral lesionectomy as treatment for intractable epilepsy, which was caused by a mass in the left amygdala and limited to the input modality of verbal cues, or whether they might be multimodal and affect processing of object concepts based on picture cues as well (see Gainotti, 2011; Rice et al., 2015a, 2015b, for discussion). Finally, in Experiment 4, we sought evidence to establish some specificity with respect to the nature of MT! damage that causes behavioral abnormalities in judging cumulative lifetime familiarity. Here, we tested an amnesic individual (HC) with documented bilateral lesions of the hippocampus and connected subcortical structures, but intact PrC (Olsen et al., 2013; Rosenbaum et al., 2015). HC is known to exhibit deficits in episodic recollection of autobiographical experiences (Kwan et al., 2010; Rabin et al., 2012; Rosenbaum et al., 2011). Given that lesions limited to the hippocampus, or the extended hippocampal system, can spare item familiarity with reference to recent laboratory exposure, we asked whether such a lesion could also spare the assessment of cumulative lifetime familiarity of object concepts.

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To determine whether NB's performance was abnormal, we examined item-based correlations (across the 541 concepts) between the ratings NB provided and those of control participants. We computed the mean value of the correlations between NB's ratings and each of the 22 control participants. For purpose of comparison, we also correlated each of the controls' ratings with those of the other controls (as displayed in Fig. 2a). To analyze the effects of feature overlap on assessment of concept familiarity, we took advantage of a cosine similarity measure from the normative data base (McRae et al., 2005) that was computed based on a matrix of 541 concepts × 2526 features obtained in the feature generation task. The cosine between each pair of concepts was calculated based on feature production frequencies. This measure of concept similarity is similar to those used in prior fMRI experiments on object concept representations in PrC (e.g., Bruffaerts et al. (2013)). For examination of the effect of feature overlap, concepts were rank-ordered based on this measure; the 100 concepts with the highest score (i.e., highest feature overlap) were chosen and compared with the 100 concepts with the lowest scores in the distribution. We then computed item-based correlations across each set of 100 concepts between the ratings NB provided and those of control participants, following the same approach as employed in our main analyses. Table 1 provides data on the category composition of these two subsets of items. As in prior related studies (e.g., Wright et al. (2015)), items with high feature overlap primarily belonged to categories of living things.

3.1.4. Results

To examine the sensitivity of NB's frequency judgments to degree of recent exposure, we calculated the mean perceived frequency, separately for each study frequency (see Fig. 1a). We conducted linear regression analyses to assess this relationship, regressing the average perceived frequency values onto the number of presentations for each participant. The regression coefficient reflects the slope of the lines plotted in Fig. 1a. To assess whether NB's performance was abnormal as compared to controls for this measure, and for those in all subsequent experiments, we present z-scores for descriptive purposes and report the significance (i.e., p-value) of the corresponding modified t-test, which was specifically developed for experimental single-case studies (Crawford and Howell, 1998). NB exhibited the lowest slope estimate for her frequency judgments, and this estimate was found to be significantly different from the values obtained in control participants (NB, b = -0.18; control mean, b = -0.43, z = -2.02, p < .05; see Fig. 1b). Although abnormal, NB's regression slope did differ from 0 (F(1,4) = 23.13, p < .01), revealing some remaining sensitivity to frequency of prior occurrence in her judgments. This pattern of results suggests that NB's previously documented impairments in familiarity-based recognition memory extend to frequency judgments of the degree of recent laboratory exposure to object concepts.
lowest and differed significantly from control participants \( (z = -1.91, p < .05; \text{see Fig. 2a}) \). Thus, her ratings are abnormal by virtue of not following the pattern of relative differences in familiarity observed in controls across the large set of tested concepts. Additional analyses also suggested that these abnormalities in rated concept familiarity were present against a background of otherwise normal task performance. Specifically, NB’s life-time familiarity ratings were in the normal range in terms of rating latency \( (\text{control mean} = 2751 \text{ ms; NB} = 2843 \text{ ms; } z = 0.04, p > .9) \), mean rating \( (\text{control mean} = 4.98; \text{NB} = 4.60; z = -0.36, p > .7) \), and the standard deviation of the ratings \( (\text{control mean} = 2.54; \text{NB} = 2.98; z = 1.31, p > .7) \). NB’s distribution of responses across the nine options also did not appear to differ from that of control participants \( (\text{see Fig. 3}) \). To investigate this issue statistically, we used Chi-square tests that compared the distribution for NB, and each individual control participant, to the mean response distribution for all control participants. We found that NB’s response distribution did not differ from the control mean any more than that of the 22 control participants \( (\text{control mean } \chi^2 = 84.52; \text{NB } \chi^2 = 24.22; z = -1.20, p > .2; \text{see Fig. 3}) \).

Returning to NB’s abnormalities in judged lifetime familiarity, we also examined NB’s ratings separately for concepts that show a high versus a low degree of similarity to other concepts in the set of 541 items \( (\text{as indexed by a cosine similarity measure from the normative data base; McRae et al., 2005}) \). The correlation value for NB’s ratings differed from those of controls for object concepts that had a high degree of semantic similarity \( (z = -2.07, p < .05; \text{Fig. 2b}) \) but not for object concepts that had a low degree of

Fig. 2. Behavioral results in Experiments 2–4. (a) Mean correlation of NB’s (Experiment 2) and HC’s (Experiment 4) lifetime familiarity ratings with those of 22 control participants and mean correlations between individual controls. (b) Mean correlations for NB and controls separated for items with high and low feature overlap in Experiment 2. (c) Mean correlation of familiarity ratings for NB and 6 controls in Experiment 3 in which photographs of concepts were added as cues. (d) Correlations for NB and controls separated for items with high and low feature overlap in Experiment 3. Error bars reflect SEM.

Table 1

| Percentage of object concepts from different semantic categories in the item sets with high or low feature overlap as probed in Experiments 2 and 3. |
|---------------------------------|-------|-------|-------|-------|
|                                | High Overlap |                  |                  |                  |
|                                | Animals     | Fruits/Veggies | Non-living      | Other            |
|                                | 43.9%       | 12.3%          | 43.9%           | 0%               |
|                                | Low Overlap  |                  |                  |                  |
|                                | Animals     | Fruits/Veggies | Non-living      | Other            |
|                                | 0%          | 0%              | 89.5%           | 10.5%            |

Fig. 3. Response distributions for patients NB, HC, a representative control participant, and the control mean in Experiments 2 (NB) and 4 (HC). Different colours indicate different response options on the 1–9 scale for familiarity ratings (warm colours reflect higher ratings). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
similarity \((z = -1.08, p > .3)\) with the other items in the set. This pattern of abnormalities across item sets also held when object concepts that had a high versus a low degree of semantic similarity were matched in terms of normative concept familiarity \((z = -2.27, p < .05; z = -1.47, p = .17)\). As such the specificity of these abnormalities in NB do not reflect difficulties in judging concept familiarity in a particular range of familiarity values, but rather appear to relate to requirements to make fine-grained concept distinctions.

4. Experiment 3 – Lifetime familiarity judgements in NB with picture cues

4.1. Methods

4.1.1. Participants

NB and six female university-educated controls (Mean age = 26.8, SD = 6.6) participated in Experiment 3. NB performed this task 9 months after offering lifetime familiarity judgments on this set of items with verbal cues only. The samples of control participants differed between Experiments 2 and 3.

4.1.2. Materials

Stimuli were the same concept names as used in Experiments 2, complemented by 541 photographs of corresponding exemplars. Exploratory pilot work was conducted to ensure that images consistently elicited the targeted concept names in healthy participants. We performed this item selection in iterative cycles with varying image sets, and finalized the set when average performance levels in naming were at a level of 70% accuracy. Effects of feature overlap were examined based on the same two subsets of items as employed in Experiment 2.

4.1.3. Procedure

The procedure for judgments of long-term exposure to these object concepts was identical to Experiment 2 with the exception that, prior to the presentation of each concept name, the photograph of the corresponding object was shown for 3 s and participants were asked to name it. Even though our primary interest was in probing lifetime familiarity through picture cues, names were presented at the end of each trial in order to ensure that participants always rated familiarity of the depicted objects in combination with correct identification, and at the targeted level of specificity (e.g., ‘apple’ rather than ‘Granny Smith’ or ‘fruit’). Trials were separated by a 750 ms ISI.

4.1.4. Results

Given that our task was designed to probe concept rather than word familiarity, we aimed to determine in Experiment 3 whether NB’s ratings would stay abnormal even when visual images were provided as additional cues with a requirement to name the object shown. When we examined participants’ naming accuracy, NB’s performance across the 541 photographs was in the normal range (NB: 73.8%, control mean = 77.4%, range = 66.4–79.1%, z = 0.77, \(p > .4\)). Notably, this pattern held regardless of whether object concepts had high or low feature overlap with the other items in the set examined (NB [high overlap] = 78.9%, control mean = 71.3%, range = 59.6–80.7%; NB [low overlap] = 84.2%, control mean = 77.5%, range = 77.2–82.5%). Contrasting with her naming performance, NB’s familiarity ratings were found to be abnormal (see Fig. 2c; \(z = -4.91, p < .003\)). In further exploratory analyses, we also confirmed NB’s impairment when excluding concepts that NB named incorrectly (excluding 120/541 in this case; \(z = -5.77, p < .003\)), or when excluding any concept that any of the controls or NB named incorrectly (excluding 293/541 in this case; \(z = -5.07, p < .005\)). NB was again impaired in both cases (\(z < -5\) for both). Critically, as in Experiment 2, these abnormalities were again noticeable only for object concepts that had high feature overlap with other items in the set (high feature overlap: \(z = -4.26, p < .006\); low feature overlap: \(z = -0.97, p > .4\); see Fig. 2d). Although these results were obtained with a smaller sample of control participants, they offer a statistically significant replication of our main findings in Experiment 2, with a pattern that mirrors the influence of feature overlap as well. Critically, the results of Experiment 3 also suggest that NB’s abnormalities in judging cumulative lifetime familiarity generalize to conditions in which object concepts can be accessed through pictorial cues. As such they suggest that these abnormalities are multi-modal in nature and do not reflect a problem limited to accessing objects concepts through verbal cues.

5. Experiment 4 – Lifetime familiarity judgements in patient HC

5.1. Methods

5.1.1. Participants

HC is a well-documented developmental amnesic patient who has participated in several previous studies (Adlam et al., 2005; Kwan et al., 2010; Hurley et al., 2011; Olsen et al., 2013; Rabin et al., 2012; Rosenbaum et al., 2011; Vargha-Khadem et al., 2003). She is a right-handed female who was 22 years old at the time of testing, with a total of 14 years of education. HC suffered hypoxia perinatally as a result of premature birth. MR-based volumetric analyses have revealed a selective hippocampal lesion with significantly reduced volume in anterior sections bilaterally and additional volume reductions in the right posterior hippocampus (Olsen et al., 2013). Critically, perirhinal (PRC), entorhinal (ERC), and parahippocampal cortices appear to be fully preserved and show no volume reduction. Additionally, it has been found that HC has abnormal morphology of the fornix and absent mammillary bodies, suggesting that a prenatal etiology, rather than perinatal hypoxia, may account for her amnesia (Rosenbaum et al., 2015). HC exhibits clear signs of amnesia with pronounced impairments on clinical neuropsychological tests of long-term memory, in experimental tasks of recognition memory, and in tasks of autobiographical memory. To illustrate, on the California Verbal Learning Test, HC’s impaired performance is reflected in a z-score of −4 for short delay free recall, −3 for long-delay free recall, and −2 for long-delay recognition memory. Her WASI Full Scale IQ is in the 66th percentile, and semantic fluency (animals) is above the 90th percentile (see Rosenbaum et al., 2011), for full neuropsychological profile). Testing of autobiographical memory with the Autobiographical Interview (AI) and the Galton–Crovitz paradigms has revealed that HC’s autobiographical recollections lack episodic detail across her life-span (see Kwan et al. (2010), Rosenbaum et al. (2011), Rabin et al. (2012)). Ten healthy control participants (Mean age = 22.1, SD = 1.9; 9 females) also took part in Experiment 4 \((z = -0.05)\). They were closely matched with HC in educational background \((\text{duration } M = 14.2 \text{ years}, \text{SD} = 9.3; z = -0.21)\). Research on HC was part of a larger program (directed by Rosenbaum) that was approved by the Research Ethics Boards of York University and Baycrest Center in Toronto and Fanshawe College in London, Ontario.

5.1.2. Materials and procedures

Materials and procedures were identical to those in Experiments 2.

5.1.3. Results

We first compared HC to the sample of individuals who had
erved as control participants for NB in Experiment 2. HC's performance was normal on every measure examined, including the mean correlation between her ratings and those of the controls \((z = 0.17, p = .8; \text{ see Fig. 2a and Fig. 3})\). We also tested a second sample of 10 control participants who were matched more closely to HC in terms of educational background. Critically, the correlation between HC's concept familiarity ratings and those of controls again did not differ \((z = 1.10, p > .3)\). Moreover, when we split the item set into subgroups of object concepts with high or low feature overlap (as reported for Experiments 2 and 3), we did not observe any abnormalities in this comparison for either set \((p > .05)\). Overall, these data suggest that judging the familiarity of concepts based on lifetime experience does not depend on the integrity of the hippocampus and can be preserved even when impairments in autobiographical recollection of specific lifetime episodes are clearly present.

6. General discussion

In the present study, we conducted three experiments with an individual (NB) who had previously been found to exhibit selective impairments in familiarity assessment on verbal recognition-memory tasks based on a recent experimental study exposure. Here we asked whether NB might also exhibit impairments in assessing cumulative prior experience with object concepts. As NB exhibits entirely normal recollection abilities, her case presents a unique opportunity to examine links between familiarity impairments in study-test paradigms and possible impairments in familiarity judgments tied to autobiographical life experience more generally. In the first experiment, we demonstrated that NB's impairment in making recognition judgments extends to cumulative frequency judgments for exposure to concept names in a recent study episode. Experiments 2 and 3 revealed that NB's impairments also extend to abnormalities in judgments of cumulative lifetime familiarity for object concepts. These abnormalities were not limited to making judgments based on verbal input but were present even when pictures were offered as additional cues. Moreover, they had some behavioral specificity; in both experiments, we observed them only for judgments on object concepts with high feature overlap. Finally, in Experiment 4, we found that an amnesic patient (HC) with previously established deficits in autobiographical recollection, due to a well-documented lesion of the extended hippocampal system, does not exhibit any abnormalities in assessing cumulative lifetime familiarity.

Taken together, the pattern of behavioral results from NB and HC strongly suggest that contributions of anterior temporal-lobe structures other than the hippocampus are essential for the assessment of cumulative lifetime familiarity for object concepts. That NB's anterior temporal lesion included left PrC is of particular relevance given that PrC has previously been shown to play a role in familiarity-based recognition-memory for recent experimental item exposures (for review see Aggleton and Brown (2006), Eichenbaum et al. (2007), Montaldi and Mayes (2010)), as well as in conceptual processing across a variety of semantic tasks (for review, Clarke and Tyler, 2015). We note that fMRI data in healthy young adults from our laboratory have specifically implicated left PrC in performance on the two tasks employed here (Duke et al., submitted). A region of left PrC tracked the perceived frequency of recent experimental exposure with a decrease in signal, and the perceived cumulative lifetime familiarity of object concepts with an increase in signal. Critically, in that study, we found no other region in left anterior lateral or temporopolar cortex that tracked perceived lifetime familiarity. The latter result is important because left anterior lateral and temporopolar cortex have been implicated in conceptual processing in other semantic task contexts (see Mehta et al., 2016; Rice et al., 2015a,2015b, for review), and these structures were also resected in NB. Although the findings of the present study do not allow us to rule out that the behavioral abnormalities we observed are due to the inclusion of left anterior lateral or temporopolar cortex in NB's lesion, those from our previous fMRI study argue against this interpretation. Taken together, the data from both studies converge on linking assessment of perceived lifetime familiarity to neighboring left PrC.

The notion that PrC carries signals about cumulative prior item exposure over extended time periods is consistent with findings obtained with neurophysiological recordings in non-human primates. In this work, it has been shown that some PrC neurons track the degree of exposure to objects that accumulates through hundreds of repetitions over the course of weeks (Hölscher et al., 2003; see Peissig et al. (2007), for related findings from event-related scalp potentials). There is also evidence to suggest that PrC neurons differ in their sensitivity to effects of recent versus long-term exposure when monkeys perform recognition memory tasks. For example, Xiang and Brown (1998) reported that some PrC neurons (termed 'recency neurons') respond to repetition of a recent (i.e., within-session) stimulus encounter while others respond to whether stimuli have been encountered frequently on prior days ('familiarity neurons'). It is noteworthy that in prior neurophysiological research, long-term familiarity signals in PrC were observed in the absence of any behavioral requirement to judge cumulative exposure across multiple sessions (Fahy et al., 1993; Hölscher et al., 2003; Xiang and Brown, 1998). In the current study, by contrast, we observed abnormalities in NB's performance in a task context that required her to make explicit judgments about cumulative lifetime exposure to object concepts. Taken together with our previously mentioned fMRI findings, this evidence suggests that PrC computations have direct behavioral relevance for the assessment of lifetime concept exposure.

The current findings are of special relevance to a growing body of evidence that has revealed involvement of human PrC in processing of object concepts in tasks other than classic recognition-memory paradigms. In several conceptual priming studies, repeated exposure to object concepts, often across different stimulus formats and modalities, led to changes in fMRI signal in PrC; these fMRI effects were associated with benefits in behavioral performance on tasks that made no reference to any prior experimental exposure (Dew and Cabeza, 2011; Heusser et al., 2013; O'Kane et al., 2005; Voss et al., 2009; Wang et al., 2010,2014). Past fMRI research has also implicated human PrC in conceptual processing in tasks that did not involve any experimental manipulation of stimulus repetition, including tasks that required naming of visually presented objects or judging the presence of specific semantic features in object concepts denoted by words (Bruffeaets et al., 2013; Clarke and Tyler, 2014; Liuzzi et al., 2015). These studies relied on multi-voxel pattern analyses techniques and have shown that the semantic similarity of object concepts, as reflected in the degree of semantic feature overlap calculated based on feature norms, is reflected in the similarity of fMRI response patterns in left PrC. Such evidence has been interpreted as support for theoretical models of PrC functioning that emphasize its critical role in differentiating between visually (Cowell et al., 2010; Graham et al., 2010; Murray and Bussey, 1999) and semantically similar objects (Clarke and Tyler, 2015; Taylor et al., 2011).

Most relevant for the interpretation of the current findings, it has been proposed that PrC supports computations that are necessary for establishing fine-grained representations of object concepts and that allow for the resolution of semantic confusability (Clarke and Tyler, 2015). Although abnormalities were revealed in the present study when NB's performance measures
were calculated across the entire set of 541 items, follow-up analyses showed that they were driven by abnormal ratings for confusible concepts with high feature overlap (as reflected in the cosine-similarity value in the semantic feature norms; Cree and McRae, 2003; McRae et al., 2005). NB's judgements for object concepts with limited feature overlap tended to be in the normal range. Differential impairments in discriminating between concepts with high semantic feature overlap have previously been reported in the context of object naming. In two group studies, lesion overlap analyses that focused on the extent of damage in the anterior temporal lobe allowed the authors to attribute these impairments specifically to damage in PrC (Kivisaari et al., 2012; Wright et al., 2015). The present study revealed no deficits in object naming in patient NB, which is in line with other observations showing that patients with unilateral temporal lesions sometimes only exhibit abnormalities in semantic processing when concept knowledge is probed under more demanding task conditions (e.g., speeded naming; Wright et al., 2015; Ralph et al., 2012). The present findings provide, to our knowledge, the first neuropsychological evidence to reveal differential abnormalities in processing confusible object concepts in the context of judgments of cumulative lifetime familiarity. That these abnormalities were present even when object names were accompanied by picture cues is consistent with functional neuroimaging evidence showing that left PrC supports conceptual processing across multiple input modalities (Bruffaerts et al., 2013; Clarke and Tyler, 2014). The pattern of results we observed is also in keeping with evidence from other lesion studies showing that unilateral left temporal lobe epilepsy, or left anterior temporal lobe resection for treatment of epilepsy, can lead to multi-modal impairments in conceptual processing (Ralph et al., 2012; Giovagnoli et al., 2005; Antonucci et al., 2008; but see Gainotti (2011)).

The notion that PrC is critical for establishing fine-grained representations of object concepts that allow for the resolution of perceptual or semantic confusability is of direct relevance to computational work that has focused on the principle of pattern separation. Pattern separation can be defined as the outcome of computational transformations that make similar, overlapping neural representations more distinct (Yassa and Stark, 2011). Pattern separation has attracted most attention in research on hippocampal functions, specifically those of the dentate gyrus (e.g., Neunuebel and Knierim (2014), Bakker et al. (2008), Leutgeb et al. (2007)). As others have argued, however, pattern separation may be a computation that is not restricted to hippocampal processing (Kent et al., 2016; Cowell, 2012). In fact, it has been suggested that pattern separation takes place in many cortical regions, and that it is fundamental to many aspects of cognition, including but extending beyond recognition memory. What may distinguish pattern separation across different cortical structures is the type of representation it operates on. Within such a framework, PrC has been proposed to constitute an extension of the representational hierarchy within the ventral visual pathway for object identification (Kent et al., 2016; Cowell, 2012; Murray and Bussey, 1999). It may provide a highly-integrated representation of the conjunctions of object features that are critical for task performance when individual features are insufficient for unique object identification. Complementing the role of PrC, the dentate gyrus may allow for pattern separation of more complex representations that also carry episodic contextual information, which would allow for the distinction of specific object encounters and other experienced events. As mentioned previously, the present findings in NB, which revealed a sensitivity of her abnormalities to semantic feature overlap, are compatible with a framework that emphasizes the role of PrC in the individuation of specific object concepts. An important direction for future research is to link the characterization of the nature of representations supported by PrC to specific processes of neural plasticity that allow for judgment of cumulative prior lifetime exposure.

Although the structure of the task we employed to probe lifetime familiarity did not require any reference to a specific past episodic encounter, it is interesting to consider whether episodic recollection may have still played a role in performance. This possibility deserves consideration in light of prior evidence that implicates hippocampal functioning in ostensibly semantic tasks, such as object naming or conceptual fluency, i.e., the speeded generation of exemplars from different semantic categories (Klooster and Duff, 2015; Greenberg et al., 2009; Ryan et al., 2008; Sheldon et al., 2013; Westmacott and Moscovitch, 2003; Whatmough and Chertkow, 2007). Building on the widely held view that the hippocampus plays a critical role in binding items to episodic contexts (Cohen and Eichenbaum, 1993), such evidence has led to the suggestion that episodic and semantic memory may interact even on tasks that do not require any recollection, and that recollection of a pertinent autobiographical episode can help generate or retrieve semantic information (see Sheldon and Moscovitch (2012), for detailed discussion). To explore this issue in the context of the current task, we conducted a supplementary behavioral experiment in a separate group of healthy young participants (n = 31), in which we asked participants to judge not only lifetime familiarity but also the perceived ease of recovery of a relevant autobiographical episode for object concepts taken from the normative dataset (McRae et al., 2005). Both types of ratings were obtained in separate blocks of the experiment. Indeed, the resulting data revealed a moderate correlation (r = .49 across items; averaged across participants p < .05) between perceived lifetime familiarity and perceived ease of autobiographical recollection of a pertinent past episodic encounter. Although these results are in line with a possible contribution, the current data in patient HC argue against any necessary role for autobiographical recollection in assessing lifetime familiarity. Even though HC experiences autobiographical recollection impairments that have been documented in several previous studies, including in response to the names of object concepts in the Galton-Crovitz task (Kwan et al., 2011), her ratings for lifetime familiarity of object concepts did not differ from those we observed in two different samples of healthy control participants. This pattern of results suggests a functional distinction between the recollection of the time and place of particular autobiographical instances of object encounters, and the assessment of degrees of experience over hundreds or thousands of encounters across different episodic contexts. We note, however, that due to the early onset of her lesion, HC may have developed idiosyncratic strategies to compensate for her deficits in recollection in memory judgments. Moreover, this early onset may also have had an impact on knowledge acquisition and conceptual structure. Thus, further evidence from patients with adult onset amnesia and hippocampal damage is clearly desirable.

In conclusion, the neuropsychological findings reported in the current study provide support for a functional link between the assessment of recent changes in familiarity of object concepts, as probed with experimental study-test paradigms, and cumulative lifetime familiarity based on autobiographical experience accrued outside the laboratory. Moreover, they argue in favor of the notion that recognition of prior occurrence of objects is closely related to the representation of concept knowledge, likely through computations in PrC. As such they also offer a new bridge between the typically distinct cognitive neuroscience literatures on recognition memory and semantic knowledge representation.
References

Duke, D., Martin, C.B., Bowles, B., McRae, K., Köhler, S., Role of left perirhinal cortex in assessing the cumulative familiarity of object concepts. Submitted for publication.