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Independent contributions of fMRI familiarity and novelty effects to recognition memory and their stability across the adult lifespan

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ABSTRACT

The impact of age on the neural correlates of familiarity-driven recognition memory has received relatively little attention. Here, the relationships between age, the neural correlates of familiarity, and memory performance were investigated using an associative recognition test in young, middle-aged and older participants. Test items comprised studied, rearranged (items studied on different trials) and new word pairs. fMRI 'familiarity effects' were operationalized as greater activity for studied test pairs incorrectly identified as 'rearranged' than for correctly rejected new pairs. The reverse contrast was employed to identify 'novelty' effects. Estimates of familiarity strength were slightly but significantly lower for the older relative to the younger group. With the exception of one region in dorsal medial prefrontal cortex, fMRI familiarity effects (which were identified in medial and lateral parietal cortex, dorsal medial and left lateral prefrontal cortex, and bilateral caudate among other regions) did not differ significantly with age. Age-invariant 'novelty effects' were identified in the anterior hippocampus and the perirhinal cortex. When entered into the same regression model, familiarity and novelty effects independently predicted familiarity strength across participants, suggesting that the two classes of memory effect reflect functionally distinct mnemonic processes. It is concluded that the neural correlates of familiarity-based memory judgments, and their relationship with familiarity strength, are largely stable across much of the healthy adult lifespan.

Introduction

It is well established that long-term memory declines with increasing age (Nyberg et al., 2012). Age-related memory decline is especially prominent when performance depends upon recollection of associative information about a specific episode as, for example, in tests of source memory or associative recognition (e.g., Bender et al., 2010; see Old and Naveh-Benjamin, 2008, for review). By contrast, memory judgments that can be supported by undifferentiated information, such as an acontextual sense of familiarity, are less affected by age. Indeed, null or relatively small effects of age on familiarity-based recognition memory have been reported in numerous studies (see Koen and Yonelinas, 2014; Yonelinas, 2002, for reviews; see also Henson et al., 2016). Here, we examine neural correlates of familiarity-based memory judgments as a function of age. In doing so, we add to what is currently a sparse literature on this topic, generalizing and extending prior findings by operationalizing familiarity in the context of an associative recognition task, and sampling participants from across the adult lifespan rather than just from its extremes.

Recollection and familiarity are supported by functionally dissociable memory signals (Ingram et al., 2012; Wixted and Mickes, 2010; Yonelinas, 2002) that depend upon distinct neural regions and networks (Aggleton and Brown, 2006; Eichenbaum et al., 2007; Skinner and Fernandes, 2007). Notably, studies employing fMRI have identified largely non-overlapping patterns of neural activity associated with recollection- and familiarity-based memory judgments (e.g., Johnson et al., 2013; Montaldi et al., 2006; for reviews, see Kim, 2010, 2013). When recollection is operationalized by the contrast between correctly recognized memory test items for which recollection succeeded or failed, enhanced activity is evident in a characteristic brain network (the 'core recollection' network) that includes the hippocampus and medial prefrontal, posterior cingulate, middle temporal and ventral parietal cortex (Rugg and Vilberg, 2013) (The reverse contrast, identifying where activity is greater for familiar than recollected items, has frequently been employed to study the neural correlates of 'retrieval monitoring'; see de Chastelaine et al., 2016a, and Wang

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et al., 2016, for recent examples). Familiarity (operationalized, for example, by the contrast between recognized but unrecollected items and unstudied items) is associated with enhanced activity in a different set of regions, including the intra-parietal sulcus (IPS), precuneus, lateral and antero-lateral prefrontal cortex and caudate nucleus (Kim, 2010, 2013).

When contrasted with unstudied ('novel') items, familiar items are also associated with *reductions* in neural activity. Familiarity-related reductions are especially prominent in the anterior medial temporal lobe (MTL), including the perirhinal cortex (e.g., Henson et al., 2003; Staresina et al., 2012; Wang et al., 2014; see Diana et al., 2007, for review of early studies) and the anterior hippocampus (e.g., Daselaar et al., 2006a; Staresina et al., 2012; see Kim, 2013, Nyberg, 2005, and Rugg et al., 2012, for reviews). Perirhinal 'novelty effects' are of particular significance in light of findings from studies of experimental animals indicating that perirhinal cortex is necessary for familiarity-based recognition memory (Aggleton and Brown, 2006; Winters et al., 2008), and that single neuron activity (e.g., Xiang and Brown, 1998) and immediate early gene expression (e.g., Zhu et al., 1995; see Aggleton et al., 2012, for review) in the region are lower for neural activity elicited by familiar rather than novel stimulus events. In light of this evidence, perirhinal cortex has been proposed as a neural region crucial for familiarity-based memory in humans also (Diana et al., 2007; see Bowles et al., 2007, for supporting lesion evidence).

Analogous fMRI effects in anterior hippocampus have typically not been interpreted as neural correlates of a familiarity signal, however, but rather as reflecting the engagement of the region in novelty-driven memory encoding (Johnson et al., 2008; Köhler et al., 2005; Nyberg, 2005; Stark and Okado, 2003). There is however currently little direct evidence to suggest that familiarity-related reduction in fMRI BOLD responses (or, equivalently, novelty-related enhancement of activity) in perirhinal cortex and anterior hippocampus are functionally dissociable (although see Staresina et al., 2012, for electrophysiological evidence that memory-related effects can have different time-courses in the two regions). By contrast, there is some evidence that familiarity-driven activity enhancements and reductions (henceforth, respectively, 'familiarity' and 'novelty' effects) are functionally dissociable. Note that we have adopted this terminology for the sake of clarity, and not to imply that the effects necessarily reflect functionally distinct processes or mechanisms (although see Daselaar et al., 2006a and Kafkas and Montaldi, 2014, for evidence that the two classes of effect are indeed functionally distinct). In a study in which participants rated their confidence that a recognition test item was old or new (on a scale varying from high confidence 'old' to high confidence 'new'), Daselaar et al. (2006a) reported that neural correlates of novelty (operationalized as activity that was positively correlated with confidence that an item was new) were localized primarily to anterior hippocampus and 'rhinal' cortex, whereas correlates of familiarity (activity that correlated positively with confidence that an item was 'old') were identified in, among other regions, parahippocampal and lateral parietal cortex and the precuneus. These two classes of effects were independently predictive of recognition memory performance, suggesting that they reflect processes with distinct mnemonic roles. We return to this issue in the Discussion.

As alluded to previously, there is a substantial behavioral literature examining the effects of age on recollection- and familiarity-based memory judgments. Motivated by the vulnerability of recollection to increasing age (see above), several studies have been reported where fMRI was employed to contrast recollection-related neural activity according to age (see de Chastelaine et al., 2016a, and Wang et al., 2016, for two recent examples, and Wang and Cabeza, 2016, for review). There are fewer reports describing age effects on neural correlates of familiarity-based memory judgments (Angel et al., 2013; Daselaar et al., 2006b; Duarte et al., 2010; Wang and Giovanello, 2016), and only a handful of fMRI studies that have examined the influence of age on novelty processing more generally (Bowman and Dennis, 2015; Moriguchi et al., 2011; Wang et al., 2015). The findings for familiarity-related enhancements of cortical activity range from null effects of age in one study (Daselaar et al., 2006b), to broadly similar effects across age groups in two others (Angel et al., 2013; Duarte et al., 2010), albeit in combination with the identification of familiarity-sensitive regions where effects were attenuated (Angel et al., 2013; Duarte et al., 2010) or enhanced (Duarte et al., 2010) in older adults. The findings of Angel et al. (2013) and Duarte et al. (2010) converged in identifying infero-lateral and dorsal medial prefrontal cortex (mPFC) as regions where familiarity effects are attenuated with increasing age.

The balance of the evidence from the aforementioned studies suggests that MTL novelty effects are largely preserved with increasing age (see Bowman and Dennis, 2015, for an exception). Indeed, age-related *enhancement* of novelty effects was reported in two studies: in perirhinal cortex in Daselaar et al. (2006b), and in the hippocampus in Wang et al. (2015). The age differences in perirhinal effects were accounted for by the proposal that older individuals are more reliant on familiarity than are younger individuals when making recognition memory judgments. The finding for the hippocampus was interpreted as an example of age-related 'de-differentiation' (e.g., Li et al., 2006), reflecting a breakdown in functional segregation between the hippocampus and perirhinal cortex.

The somewhat modest effects of age on fMRI familiarity and novelty effects seemingly align well with the relatively weak influence of age on familiarity-based memory judgments (see above). Nonetheless, reliable age effects were identified in five of the above-cited studies (six, if one also includes the finding that age influenced the time-course of novelty effects in the amygdala in one other study; Moriguchi et al., 2011). Here, we further examine the question of whether familiarity or novelty effects are age-sensitive. We took advantage of a previously described large dataset (N =136; de Chastelaine et al., 2016a) to examine the neural correlates of familiarity and novelty processing with participant samples that spanned the adult lifespan more continuously than was the case in prior studies (all of which employed extreme age group designs), and that provided statistical power sufficient to allow a sensitive assessment of whether these correlates co-vary with memory performance.

As we have discussed in detail elsewhere (de Chastelaine et al., 2016a, 2016b; Rugg, 2016), examination of brain-behavior relationships as a function of age is of considerable theoretical interest. A relationship between neural activity and performance that is constant across age groups (an age-invariant relationship) is consistent with the idea that performance is similarly constrained across the lifespan by the functional capacity of the region or regions manifesting the activity. By contrast, a relationship that is stronger, or only evident, in older individuals (an age-dependent relationship) suggests that the relevant region plays an increasingly important role in mediating performance with advancing age, perhaps reflecting individual differences in the vulnerability of the region to age-related degradation (de Chastelaine et al., 2016a, 2016b).

We examine these issues here through further analysis of data acquired in the study of associative recognition that was first reported by de Chastelaine et al. (2016a). In our original report we focused on the neural correlates of successful recollection and post-retrieval monitoring, and did not describe the outcomes of contrasts that identified familiarity or novelty effects. In the present paper, we describe these effects, contrast them according to age, and examine their relationship with memory performance. On the basis of prior findings (see above), we expected to find little evidence of age differences in novelty effects, along with differences in familiarity effects that, if present, are confined to dorsal medial and left lateral prefrontal cortex. Whether either class of effect demonstrates age-invariant or age-dependent relationships with performance is an open question.