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The gist and details of sex differences in cognition and the brain: how parallels in sex differences across domains are shaped by the locus coeruleus and catecholamine systems

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20 1. Introduction

21 Males and females have been consistently reported to differ on aspects of emotional
22 memory (Buck *et al.*, 1974; Fujita *et al.*, 1991; Hall and Matsumoto, 2004; Kring and Gordon,
23 1998; Seidlitz and Diener, 1998), and spatial ability (Astur *et al.*, 1998; Beatty, 1984; Dawson *et*
24 *al.*, 1975; Galea and Kimura, 1993; Grön *et al.*, 2000; Isgor and Sengelaub, 1998; Jonasson,
25 2005; Linn and Petersen, 1985; Postma *et al.*, 2004; Voyer *et al.*, 1995). Buttressing these
26 differences in behavior and memory are findings that the predominant neural regions for each of
27 these cognitive domains, the amygdala for emotional memory (for review see, Roozendaal and
28 Hermans, 2017) and hippocampus for spatial abilities (among other abilities; for review see,
29 Eichenbaum and Cohen, 2014), also are reported to show morphological and/or functional
30 differences depending on sex (for amygdala see, Cahill *et al.*, 2001; Cahill *et al.*, 2004; Canli *et*
31 *al.*, 2002; Killgore and Yurgelun-Todd, 2001; Kilpatrick *et al.*, 2006; Stevens and Hamann,
32 2012; for hippocampus see, Isgor and Sengelaub, 1998; Jacobs *et al.*, 1990; Pfaff, 1966; but see,
33 Gur *et al.*, 2002; Tan *et al.*, 2016).

34 These sex differences in emotional memory and spatial ability have typically been
35 considered as arising from independent and separate brain mechanisms (but see, Pletzer, 2014,
36 2015; Pletzer *et al.*, 2017). However, in this paper we discuss the parallels between the nature of
37 the sex differences in the two domains and a third domain (perceptual processing) and evaluate
38 potential general mechanisms that might lead to systemic sex differences across these domains.

39 Recently, sex differences have also been reported in perceptual processing and
40 hemispheric brain activation associated with perceptual processing (Kimchi *et al.*, 2009; Kramer
41 *et al.*, 1996; Müller-Oehring *et al.*, 2007; Pletzer and Harris, 2018; Pletzer *et al.*, 2013; Pletzer *et*
42 *al.*, 2014; Roalf *et al.*, 2006; Scheuringer and Pletzer, 2016). Here, perceptual processing refers

43 to the order of processing of a scene, where the global scene, or the scene as a whole, is
44 processed before local information, or the detail items that make up the scene (Navon, 1977,
45 1981). Interestingly, sex differences in global-to-local processing are also seen in both the
46 emotional and spatial domains. In the domain of emotional memory, women show a bias towards
47 “detail” and men show a bias towards “gist” (Cahill and van Stegeren, 2003; Nielsen *et al.*, 2013,
48 2014; Nielsen *et al.*, 2011). The domain of spatial abilities does not share the same parallels in
49 nomenclature observed in emotional memory, however, there is evidence suggesting that global-
50 to-local processing performance is related to some forms of spatial ability, such as performance
51 on the Judgment of Line Orientation Test (Basso and Lowery, 2004). As a result, sex differences
52 in visuo-spatial processing and the accompanying sex differences in the brain while processing
53 global-to-local stimuli have been proposed to account for sex differences in other cognitive
54 domains including spatial abilities and emotional memory (Pletzer, 2014; Pletzer *et al.*, 2013).

55 There are likely widespread and complex mechanisms underlying these similar sex
56 differences across cognitive domains and the brain. We propose that sex differences in the locus
57 coeruleus (LC) structure and function (Bangasser *et al.*, 2010; Bangasser *et al.*, 2011; Curtis *et*
58 *al.*, 2006; De Blas *et al.*, 1990; Guillamón *et al.*, 1988; Pinos *et al.*, 2001) contributes to sex
59 differences in encoding and retrieval processes via the many connections the pontine nucleus
60 shares with both the amygdala, hippocampus, and throughout the brain (Abercrombie *et al.*,
61 1988; Aston-Jones, 2004; Buffalari and Grace, 2007; Canteras *et al.*, 1995; Cedarbaum and
62 Aghajanian, 1978; Jones and Moore, 1977; Loughlin *et al.*, 1986a; Loughlin *et al.*, 1986b;
63 Morrison *et al.*, 1978; Pasquier and Reinoso-Suarez, 1978; Segal and Landis, 1974; Segal *et al.*,
64 1973; Wallace *et al.*, 1992).

65 The LC is relevant for understanding how sex differences occur in preferences for details
66 vs. gist because the LC helps identify and re-orient attention to salient stimuli in the environment
67 (for reviews see, Roozendaal and Hermans, 2017; Sara, 2009; Sara and Bouret, 2012) and
68 selectively increases processing of salient stimuli via interactions with local cortical salience
69 signals (Mather *et al.*, 2016). However, despite parallels in sex differences across cognitive
70 domains and the ability of the LC to influence what information is identified as salient and how
71 strongly it is weighted, little work has been geared towards understanding whether and how the
72 locus coeruleus-norepinephrine (LC-NE) system might contribute to any parallel sex differences
73 in memory processes. In this review, we first summarize sex differences in these three disparate
74 domains of emotional memory, spatial ability, and perceptual processing. We then summarize
75 sex differences in brain morphology, function, and/or activation related to each of these domains,
76 followed by discussion of possible mechanisms contributing to parallels in sex differences across
77 cognitive domains and the brain.

78

79 **2. Sex differences in gist and detail memory are observed across** 80 **domains**

81

82 2.1 Defining gist versus detail memory

83 Gist and detail memory are defined as follows; gist refers to the information central to the
84 event, or, “any fact or element pertaining to the ‘basic story’ that could not be ‘changed or
85 excluded without changing the basic story line’” (Heuer and Reisberg, 1990, pg. 499), while
86 detail refers to peripheral information that has no bearing on the context of the story line (Heuer

87 and Reisberg, 1990). Heuer and Reisberg (1990) showed participants a slideshow, with each
88 slide having a short accompanying narrative. The images and accompanying narrative either had
89 an emotional component or not. In the non-emotional version, a mother and son visit the son's
90 father at a garage where he is a mechanic and is fixing a broken-down car shown in an earlier
91 slide. In the emotional version, the mother and son visit the son's father at a hospital where he is
92 a surgeon and is operating on a victim of a car accident shown in an earlier slide. Memory for
93 gist and detail information was enhanced for the emotional story over the neutral story. As we
94 will review below, this emotion-related enhancement for gist and detail information differs
95 between men and women and may relate to sex differences in other aspects of episodic memory,
96 with parallels in sex differences even extending to perceptual processing.

97

98 2.2 Gist and Detail: sex differences in emotional memory

99 Research suggests that men and women process and communicate emotional information
100 differently. For instance, women are reported to more accurately communicate emotional
101 information nonverbally (Buck *et al.*, 1974), show more facial expressivity despite reporting the
102 same amount of emotion as men (Kring and Gordon, 1998), are more accurate at identifying
103 emotional expressivity in others (Hall and Matsumoto, 2004), experience greater affect intensity
104 (Fujita *et al.*, 1991), and recall more positive and negative life events than men (Fujita *et al.*,
105 1991). Yet the underpinnings of such behavioral differences have only been examined recently,
106 with studies showing that these sex differences do not stop at expressivity but extend to what
107 type of information is encoded and retrieved under emotional circumstances. The differences in
108 encoding and retrieval seem to reside mainly in what features of emotional stimuli are
109 remembered, typically studied in the context of emotional scenes or situations. In particular, as

110 will be reviewed below, women appear to show preferential encoding and retrieval of item
111 details for emotional stimuli encountered in the lab and emotional autobiographical memories. In
112 contrast, men appear to preferentially encode and retrieve more gist-like information from the
113 same experiences.

114

115 2.2.1 Sex differences in gist and detail memory for autobiographical memories

116 While Heuer and Reisberg (1990) examined memory for gist and detail in the laboratory
117 without concern for sex of participants, as outlined below, others have reported sex differences in
118 recall patterns associated with gist and detail in autobiographical memories.

119 Findings that women recalled more positive and negative life events than men (Fujita *et*
120 *al.*, 1991), raises the question of at what stage of information processing such differences occur.
121 For instance, a difference in recall performance can stem from differences in encoding,
122 organization, retrieval, and/or response generation. A series of three studies eliminated a number
123 of potential explanations, including sex differences in response generation, mood congruence
124 between memory valance and current mood, tendency to ruminate, and even sex differences in
125 semantic memory (Seidlitz and Diener, 1998). A lack of sex differences in semantic memory
126 juxtaposed against sex differences in autobiographical memory in the same people suggests that
127 women and men may be encoding life events differently. To test this possibility, participants
128 were instructed to log event descriptions at the end of each day over a 6-week journaling period.
129 When asked to recall as many journaled events as possible, men and women recalled a similar
130 number of events, however, women recalled more positive events, while men reported more
131 repeat events than women, suggesting they may not differentiate events to the same degree as
132 women (Seidlitz and Diener, 1998). A word count for each event logged over the 6-week

133 journaling period revealed a significant sex effect on the amount of detail recorded for events,
134 with women recording more detail per event than men(Seidlitz and Diener, 1998), suggesting
135 that women may encode more peripheral detail information in their daily life (e.g., I went to
136 dinner at The District with Dave) whereas men may encode more gist-type information (e.g., I
137 went to dinner with a friend).

138

139 2.2.2 Sex differences in gist and detail emotional memory in the laboratory setting

140 The tendency for women to record more detail for autobiographical events than do men
141 (Seidlitz and Diener, 1998) has also been observed in the laboratory setting for emotional
142 information. In particular, Cahill and colleagues have used the three-phase story¹ to better
143 understand what features of emotional information men and women are more likely to recall.

144 After exposure to the emotional version of the three-phase story, men recalled more gist
145 information (e.g., the mother and son were leaving the house), while women recalled more
146 peripheral detail information (e.g., the mother and son were standing in front of a house with a
147 blue door; Nielsen *et al.*, 2013). These mnemonic effects appeared to be modulated by sex
148 hormones, as women only differed from men during the high-female-sex-hormone luteal phase
149 of the menstrual cycle. Women tested during the low-female-sex-hormone follicular phase of the
150 menstrual cycle showed no preference for one type of information over the other, exhibiting

¹ The three-phase story is a slideshow of images with accompanying narrative (adapted from, Heuer and Reisberg, 1990). There is a neutral and a negative version, each consisting of a beginning, middle, and end. The middle phase differs between the neutral and negative version. The neutral version explains the middle set of slides as an emergency drill viewed by a mother and son. The negative version explains the same set slides as the son being seriously injured. The middle phase of the emotional version of the story is typically better recalled than the same phase of the neutral version (Cahill et al., 1994).

151 similar recall rates for gist and detail information. Consistent with this finding, women's
152 hormonal contraceptive status also relates to differences in gist versus detail recall (Nielsen *et*
153 *al.*, 2014; Nielsen *et al.*, 2011). Both studies found that women using hormonal contraception
154 performed similarly to men, showing better recall of gist information in the emotional condition.
155 In contrast, women not using hormonal contraception, and who therefore had higher endogenous
156 female sex hormones, showed better memory for detail information in the emotional condition.
157 Interestingly, in each of Nielsen *et al.*'s aforementioned studies, pupil and eye tracking data
158 indicated that all groups showed similar attention and arousal while viewing the slideshow,
159 suggesting that sex differences in gist versus detail memory profile are not driven by differences
160 in attention but rather by differences in how the same information is encoded, consolidated
161 and/or later retrieved.

162

163 2.3 Orientation and Landmarks: Gist and detail in spatial abilities

164 There has been much research on sex differences in spatial abilities, with men
165 outperforming women on some but not all tasks (Jonasson, 2005; Linn and Petersen, 1985;
166 Voyer *et al.*, 1995). Gonadal and stress hormones influence these behavioral differences, and
167 show interactions as well in studies of sex differences in spatial memory (Bowman *et al.*, 2003;
168 Bowman *et al.*, 2001; Conrad *et al.*, 2004; Luine *et al.*, 1994; Shors *et al.*, 1998; Williams *et al.*,
169 1990; Wood *et al.*, 2001). In the following sections, we first review evidence of sex differences
170 in spatial memory under non-stressful conditions. We then discuss how these differences in
171 spatial memory may be explained by differences in gist and detail memory biases in males and in
172 females.

173

174 2.3.1 Sex differences in spatial ability

175 A great deal of work on sex differences in spatial memory has been conducted in animals.
176 A reliable finding across many of these studies is that males outperform females on a battery of
177 spatial tasks, such as the radial arm maze, symmetrical maze, and the Morris water maze (Beatty,
178 1984; Dawson *et al.*, 1975; Isgor and Sengelaub, 1998). In humans, even though it has been
179 demonstrated that males perform better on various measures of spatial ability and spatial
180 memory, the particular components of spatial memory giving rise to these sex differences are
181 still unclear (Postma *et al.*, 1999). However, as will be reviewed below, the pattern of males
182 outperforming females does not hold true for every measure of spatial ability (Eals and
183 Silverman, 1994; Galea and Kimura, 1993; James and Kimura, 1997; McBurney *et al.*, 1997;
184 Silverman and Eals, 1992).

185 Clear sex differences in humans have been identified in tasks measuring route learning,
186 mental rotation, and spatial perception, with males outperforming females (Astur *et al.*, 1998;
187 Galea and Kimura, 1993; Grön *et al.*, 2000; Linn and Petersen, 1985; Postma *et al.*, 2004). Men
188 also are reported to outperform women on spatial working memory tasks. For instance, in the
189 Corsi Block-Tapping task, a task requiring the participant to repeat back a sequence of taps on a
190 set of spatially separated blocks, men show significantly larger spatial working memory spans
191 than women evidenced by men completing increasingly longer spatial sequences than women
192 (Capitani *et al.*, 1991; Orsini *et al.*, 1986; Orsini *et al.*, 1987).

193 However, this pattern of better performance by men is less consistent in tasks of object
194 location memory, as women often remember the locations of objects better (Eals and Silverman,
195 1994; James and Kimura, 1997; Silverman and Eals, 1992) and tend to recall more landmarks

196 visible on maps (Galea and Kimura, 1993). Women also outperform men on a memory game that
197 relies on remembering the location of a previously seen item in a grid (McBurney *et al.*, 1997).

198 As observed with emotional memory, gonadal hormones appear to play an important role
199 in the observed sex differences in spatial memory (e.g., Williams *et al.*, 1990). In animals, male
200 rodents receiving anti-androgens during an embryonic critical period and then orchietomized
201 (testes removed) after birth showed decrements in water maze performance compared with
202 intact, untreated males in adulthood. Conversely, masculinization of females via androgen
203 administration during the same critical period led to improved spatial learning, such that they
204 were similar to intact males and better than intact females (Isgor and Sengelaub, 1998). Similar
205 to the effects of anti-androgen administration on spatial performance in male rodents, men
206 undergoing a sex-change operation and receiving high doses of cross-sex hormones combined
207 with androgen deprivation performed worse on a mental rotation task (Van Goozen *et al.*, 1995).
208 In contrast, female-to-male transsexuals improved on the mental rotation task after cross-sex-
209 hormone treatment. Overall, it appears that androgens are associated with better performance on
210 spatial tasks measuring the ability to “orient oneself in relation to objects or places, in view or
211 conceptualized across distances...” (Eals and Silverman, 1994, pg.96), such as locating target
212 shapes within a larger pattern, and mental rotation/manipulation (Christiansen and Knusmann,
213 1987; Janowsky *et al.*, 1994). In contrast to the beneficial effects of androgens on spatial
214 cognition, high estradiol levels during the menstrual cycle have been associated with worse
215 performance on these types of tasks in females (Hampson, 1990).

216 Thus, when looking at the spatial tasks in which males outperform females and vice
217 versa, one can see that the spatial abilities being measured differ, with males performing better

218 on tasks that require orienting oneself in space or mentally manipulating objects in space and
219 women performing better on tasks requiring one to recall the location of objects in space.

220

221 2.3.2 Gist and detail in spatial ability

222 There appear to be some parallels between the sex differences seen in which features of
223 emotional scenes are recalled and which features of spatial information are recalled. In recalling
224 emotional scenes, males favor gist and females details relatively more. Similar sex differences
225 are seen in the spatial domain. Men tend to focus on the gist of where they or objects are in
226 space, allowing them to more flexibly manipulate themselves or objects within that space.
227 Women, on the other hand, tend to recall the details of the space they occupy, allowing them to
228 better remember objects in an array.

229 Similar differences are also seen in how men and women navigate in space and provide
230 directions. Studies show that men do not necessarily outperform women on these tasks, but that
231 men and women use different strategies, with men relying more on Euclidean, or allocentric
232 navigation, and women relying more on landmarks, or egocentric navigation (Cherney *et al.*,
233 2008; Lawton, 1994; Saucier *et al.*, 2002). Nevertheless, eye-tracking revealed men and women
234 attend to the same features on a map, suggesting that the sex differences arise from differences in
235 encoding and/or consolidation rather than from differences in attention (MacFadden *et al.*, 2003).

236 Thus, in both laboratory tasks assessing spatial ability (e.g., mental rotation or object
237 location) and navigation, it seems as though women are encoding and retrieving detail
238 information (e.g., location of objects), allowing them to better identify changes in their local
239 environment, while men are encoding and recalling gist information (e.g., orientation of objects),
240 which allows them to find alternate routes over large areas.

241 Creating detail- and gist-type distinctions for spatial memories is not new. The multiple
242 trace theory (Moscovitch *et al.*, 2005) posits that some spatial memories are akin to episodic
243 memories, with detailed representations not only of the route but also of the details of the scenes
244 that allow re-experiencing the environment as one mentally walks through it. This level of detail
245 may be useful for re-experiencing the environment but not for navigation. In contrast, other
246 spatial memories are akin to semantic memories, with schematic representations that include
247 only features which are salient cues, which may be more useful for navigation but not for re-
248 experiencing the environment. This would suggest that spatial memories in women tend to be
249 encoded in a more egocentric, episodic fashion, while spatial memories in men tend to be
250 encoded in a more allocentric, semantic fashion.

251 As with non-spatial episodic vs. semantic memories, evidence suggests that the kind of
252 detailed spatial memory which shares features with episodic memory is hippocampal-dependent,
253 while the kind of spatial memory sharing features with semantic memory is less hippocampal-
254 dependent (Moscovitch *et al.*, 2005). This pattern suggests that the detail associated with female
255 spatial memory performance would be hippocampal-dependent, while the gist associated with
256 male spatial memory performance would not be hippocampal-dependent. However, as we will
257 review in section 3, below, this is not the case. Brain activation in humans during recall of
258 episodic autobiographical memories indicates that men tend to recruit hippocampal circuits,
259 whereas women tend to recruit more prefrontal cortical regions (Piefke *et al.*, 2005; St. Jacques
260 *et al.*, 2011). This pattern of brain activation aligns with other findings showing male animals
261 and humans tend to show greater hippocampal reliance during spatial learning and memory tasks
262 than females, while females tend to rely more on frontal regions (Grön *et al.*, 2000; Roof *et al.*,
263 1993).

264

265 2.4 Global and local processing is the gist and detail of perceptual processing

266 Sex differences in gist and detail processing also extend to perceptual processing.
267 Perceptual processing, here, refers to the temporal order in which a scene and its individual
268 features are recognized by an individual. In studies examining these processes, the overall scene
269 is the global level of processing, whereas the individual features making up the scene are the
270 local level of processing (Navon, 1977, 1981). This is often tested using the Navon task (Navon,
271 1977, see Figure 1 for example of hierarchical stimuli), which requires participants “...to respond
272 to an auditorily presented name of a letter while looking at a visual stimulus that consisted of a
273 large character (the global level) made out of small characters (the local level)” (Navon, 1977,
274 pg. 353). Two findings suggest that the global level is typically processed first (Navon, 1977).
275 First, when participants were given no instruction on whether to attend to the global or local
276 level (divided attention), interference in responding to the auditory stimuli occurred only when
277 there was a mismatch between the global level character and the auditory stimulus, not between
278 the local level character and the auditory stimulus (Navon, 1977). Second, when participants
279 were asked to focus on only the global or local features (selected attention paradigm), in the
280 absence of auditory stimuli, participants were unable to identify the local features when asked to
281 focus on the global level, but could identify the global features when asked to focus on the local
282 level (Navon, 1977). Interestingly, these global and local features of a scene can be likened to the
283 gist and detail of an emotional story or spatial paradigm, where the gist represents the global,
284 overall theme/location and detail represents the local, individual non-essential features within the
285 theme/location. If the sex differences in memory for gist and detail information extend to this

286 perceptual domain, men should have a greater global advantage and women a greater local
287 advantage.

288

289 **Figure 1 should go here.**

290 Figure 1. Example of hierarchical stimuli used for testing global and local perceptual processing.

291 On the left, the large letter 'T' is at the global level and the small letter 'E's creating the shape of

292 the large 'T' are at the local level. On the right, the letter 'T' is used at both the global and local

293 level. The global level is processed prior to the local level (Navon, 1977).

294

295 2.4.1 Sex differences in global and local processing

296 Although the literature examining global vs. local processing biases does not always

297 show sex differences, there are some findings indicating a male bias towards global processing

298 versus a female bias towards local processing. In one study reporting sex differences using an

299 adaptation of the Navon task (Kimchi and Palmer, 1982), effects are seen as early as

300 preadolescence, with boys aged 4-12 showing more global selections than girls of the same age

301 (Kramer *et al.*, 1996). In this adaptation, hierarchical stimuli consist of large shapes (global)

302 constructed from smaller shapes (local) and rather than recording reaction time to identify target

303 stimuli at the global or local level, participants choose which two out of three stimuli are similar;

304 choices about match can be made at the local level or global level (Kimchi and Palmer, 1982).

305 This effect in the Kimchi-Palmer task has not been replicated in adults, with men and women

306 making a similar number of global choices (Basso and Lowery, 2004; Scheuringer and Pletzer,

307 2016). However, when reaction time to selection is examined, sex differences have been

308 reported, with women showing faster reaction times than men for local choices and men showing
309 faster reaction times than women for global choices (Scheuringer and Pletzer, 2016).

310 In contrast to the Kimchi-Palmer task, sex differences are more consistently observed in
311 the Navon task using both letters and shapes. In one study, participants were asked to respond
312 anytime a particular letter appeared. The letter could appear at either the global or local level.
313 Women responded faster when the target appeared at the local level compared to the global level,
314 whereas men did not differ in their response times between global and local location of the target
315 (Roalf *et al.*, 2006). In another study, while men and women showed a general global advantage
316 in a divided attention paradigm (given no instruction on which level to attend to), such that
317 reaction times were faster for global than local targets, women showed decreased global
318 advantage compared with men during trials when asked to focus on either the global or local
319 level (selected attention paradigm) only during the high-hormone luteal phase, not during lower
320 hormone states (Pletzer *et al.*, 2014). Following this pattern, testosterone was positively
321 correlated with global advantage during the selected attention paradigm in men and women
322 during the low-hormone follicular phase but negatively correlated with the global advantage
323 during the high-hormone luteal phase (Pletzer *et al.*, 2014).

324 Sex differences in adults in global and local processing have also been reported in a study
325 using numerical stimuli rather than the traditional letter stimuli (Pletzer *et al.*, 2013). In this
326 study, participants were required to compare two two-digit numbers and determine which
327 number was larger. While men and women showed slower reaction times to numbers within the
328 same decade (e.g., 62 vs 66) versus those in different decades (e.g., 62 vs 48), men showed less
329 of a difference in reactions times between the two conditions than women during the low-
330 hormone follicular phase of the menstrual cycles (Pletzer *et al.*, 2013). This pattern suggests that

331 men are likely processing multi-digit numbers as unitary, whereas women may be processing
332 multi-digit numbers as individual items placed together. This interpretation was supported when
333 looking at trials where number pairs were mismatched in whether both digits within a number
334 were larger or smaller than both digits in the other number (e.g., 62 vs. 51 or 62 vs. 57). In these
335 trials, women also showed slower reaction times (Pletzer *et al.*, 2013), suggesting that women
336 allocated attention resources to the second digit of the numbers even though larger or smaller
337 judgements could be made on the first digit alone.

338 However, as was seen for the Kimchi-Palmer adaptation to the Navon task, sex
339 differences in global vs. local attention have not been consistently reported. One study only
340 found differences when examining response facilitation effects between congruent and
341 incongruent trials (Müller-Oehring *et al.*, 2007). Congruent trials were those where both the
342 global and local level contained the same target letter (e.g., small “T”s forming one large “T”),
343 while incongruent trials were those where one level consisted of one target letter and the other
344 level consisted of the second target letter (e.g., small “E”s forming one large “T”, or vice versa).
345 In this instance, while men showed response facilitation (i.e., faster reaction times on congruent
346 trials) regardless if attention was focused on the global or local level, women only showed
347 response facilitation when attention was focused on the global level and the local level was also a
348 target, but did not show facilitation when attention was focused on the local level and the global
349 level was also a target (Müller-Oehring *et al.*, 2007).

350 The variability in sex differences have been elsewhere attributed to stimuli selection, with
351 letter stimuli purported to pick up sex differences whereas shape or line stimuli are less likely to
352 pick up such differences (Pletzer and Harris, 2017). Sex differences are also less likely to be
353 observed in divided attention paradigms compared with selective attention paradigms (Pletzer

354 and Harris, 2017). Despite these inconsistencies, there do appear to be some sex differences in
355 global and local processing, with men trending toward more gist or global processing of
356 hierarchical stimuli and women trending toward more detail or local processing of hierarchical
357 stimuli (see Figure 2).

358

359 **Figure 2 should go here.**

360 Figure 2. Sex differences in global and local processing. Pictorial depiction of the trend for men
361 toward more gist or global processing of hierarchical stimuli and women toward more detail or
362 local processing of hierarchical stimuli.

363

364 2.5 Overview

365 We have reviewed three disparate domains, which all appear to share a similar theme in
366 terms of sex differences. In emotional autobiographical and episodic memory, we see that men
367 appear to encode and retrieve more gist-type information, such as limited detail information for
368 daily events or the central theme to a story, while women appear to encode and retrieve more
369 detail-type information, such as more detailed information for daily events or more peripheral
370 information from a story with no bearing on the central theme. We see this phenomenon extend
371 to spatial abilities where men appear to encode more long-distance gist-type information when
372 processing spatial information, which allows them to perform better on tasks requiring they
373 orient themselves or objects in space, while women appear to encode more short-distance detail-
374 type information when processing spatial information, allowing them to perform better on tasks
375 requiring they remember where in space objects are located. Lastly, although less robustly, we
376 see this theme carry through to perceptual processing, where men show instances of greater

377 global advantage, or better identification of central, gist-type information, while women show
378 instances of better identification of local, detail-type information within hierarchical stimuli.

379 We propose it is not just coincidence that at least three cognitive domains share similar
380 sex differences in allocation of encoding and/or retrieval processes. In the next section, we will
381 review the neural underpinnings and sex differences in these processes which may contribute to
382 the sex differences in behavior.

383

384 **3. Are sex differences in the brain regions associated with these tasks** 385 **responsible for sex differences in emotional memory, spatial** 386 **memory, and perceptual processing?**

387 The sex differences in behavior and memory we have covered so far are associated with
388 sex differences in the brain. We first will cover sex differences in the primary regions associated
389 with emotional memory, spatial behaviors, and perceptual processing, the amygdala,
390 hippocampus, and hemispheric laterality, respectively². However, as we will note, while sex
391 differences in these regions do reflect sex differences in their associated cognitive domains, they

² It is important to note that the hippocampus also is involved in emotional memory processes, such that amygdala activation modulates hippocampal function when forming these emotional memories. The amygdala aids in the formation of episodic memories containing emotional components, such that activation of the amygdala signals the hippocampus to maintain that information for future use (Phelps, 2004). The relationship between structures also is bidirectional, highlighting that episodic memories for information, in other words, for things that have not happened, to also lead to increased amygdala activation. For example, once one hears the phrase “leaves of three, leave them be” they may show an amygdala response to “leaves of three” similar to the response exhibited by someone who has experienced the negative effects of coming in contact with such leaves.

392 do not address the overall pattern of a bias toward gist information in males and toward detail
393 information in females. As such, a more unifying mechanism which can lead to this kind of
394 widespread differentiation should also be considered.

395

396 3.1 Sex differences in the amygdala and emotional stimuli

397 The amygdala is integral to processing emotional stimuli and memory formation for
398 events with emotional import (Anderson *et al.*, 2003; Cahill *et al.*, 1995; Fox *et al.*, 2001; Phelps,
399 2004; Roozendaal and Hermans, 2017). Given the sex differences in reactivity and memory for
400 emotional information, it is not surprising that men and women also display differences in
401 amygdalar responses to emotional information as measured using functional magnetic resonance
402 imaging (fMRI) and positron emission tomography (PET). For instance, using PET, men showed
403 greater right amygdala glucose metabolism while viewing negative video clips compared to
404 neutral video clips, but women showed greater left amygdala glucose metabolism while viewing
405 the negative video clips (Cahill *et al.*, 2001).

406 These patterns of amygdala activity were also observed using an fMRI paradigm. In one
407 study, participants were scanned while viewing negative and neutral images (Cahill *et al.*, 2004).
408 Two weeks later, participants returned and completed a recognition test of the photos they had
409 seen during the prior session intermixed with new emotional and neutral images. Amygdala
410 activation during the first session, when images were first viewed, was then examined for those
411 images correctly recognized versus those not correctly recognized. Men showed significantly
412 greater right amygdala activation and women showed significantly greater left amygdala
413 activation in response to correctly recognized negative images (Cahill *et al.*, 2004). Additionally,
414 men tended to show greater activation of right hemisphere brain regions, including the anterior

415 hippocampus, globus pallidus, frontal cortex, and bilateral parietal, whereas women showed
416 more left hemisphere brain activation, including posterior cingulate, middle temporal gyrus, and
417 inferior parietal cortex. Others replicated this sex difference in amygdala laterality in brain
418 responses during viewing of negative images correctly recognized three weeks later, although
419 only women showed an overall trend to exhibit more activation in left hemisphere brain regions,
420 with the significant laterality effect in men limited to only the amygdala (Canli *et al.*, 2002).

421 Others have failed to find this same task-based effect of sex on laterality, but still report
422 sex differences in amygdala and brain activation during the viewing of emotional stimuli
423 (Killgore and Yurgelun-Todd, 2001). A meta-analysis also reported a lack of consistency in the
424 laterality differences, but still found sex differences in brain activation patterns to emotional
425 stimuli (Stevens and Hamann, 2012). This meta-analysis revealed that the only significant
426 amygdala activation men had over women was in the left amygdala when viewing positive
427 emotional stimuli, but not negative stimuli. Other brain regions differed between men and
428 women, with more sex differences driven by women in studies using negative stimuli, such as
429 the left hippocampus, suggesting women may be more likely to encode negative images. Other
430 regions also suggest that women may internalize and ruminate over negative stimuli more than
431 men, with women showing greater activation in regions such as anterior cingulate and medial
432 prefrontal cortex, which show increased activity corresponding to self-reports of anger (Denson
433 *et al.*, 2009) and rumination (Denson *et al.*, 2009; Ray *et al.*, 2005). Meanwhile, men exhibited
434 greater activation in the right anterior insula and bilateral inferior frontal gyrus in response to
435 both negative and positive stimuli. Men also showed greater activation of the entorhinal cortex in
436 response to positive stimuli (Stevens and Hamann, 2012), suggesting that while women show
437 activation suggesting increased encoding of negative stimuli, men show activation suggesting

438 increased encoding of positive stimuli. This positivity bias in memory may help explain why
439 men show greater risk-taking behaviors than women (among other reasons; see e.g., Mather and
440 Lighthall, 2012).

441

442 3.2 Sex differences in the hippocampus and spatial memory

443 There is little dispute that the hippocampus supports spatial memory in animals
444 (Eichenbaum and Cohen, 2004; Morris *et al.*, 1982; O'Keefe and Nadel, 1978, 1979; Scoville
445 and Milner, 1957) and in humans (Abrahams *et al.*, 1999; Burgess *et al.*, 2002; Maguire *et al.*,
446 1998; Maguire *et al.*, 1999; Maguire *et al.*, 1996; Spiers *et al.*, 2001; Vargha-Khadem *et al.*,
447 1997). In particular, much work in animals implicates hippocampal processes in behaviors
448 dependent on spatial location, such as food storage and homing, based on evidence that species
449 that practice these behaviors have much larger hippocampal size compared to species that do not
450 share these behaviors (Sherry *et al.*, 1992).

451 Similar to the effects of stress and sex hormone-stress interactions on spatial task
452 performance, these factors can also modulate hippocampal morphology (Arbel *et al.*, 1994;
453 Conrad *et al.*, 1996; Magariños *et al.*, 1996; McEwen *et al.*, 1968; Olton *et al.*, 1978; Sousa *et*
454 *al.*, 2000; Vyas *et al.*, 2002) and function during these tasks (Bowman *et al.*, 2003; Bowman *et*
455 *al.*, 2001; Conrad *et al.*, 1996; Conrad *et al.*, 1999; Galea *et al.*, 1997; McEwen, 2000; Park *et*
456 *al.*, 2001). Here, we will focus on the hippocampal involvement in spatial memory and abilities
457 under normal, non-stressful conditions.

458 The hippocampus has a high density of sex hormone receptors (Brailoiu *et al.*, 2007;
459 Simerly *et al.*, 1990), allowing gonadal steroids to modulate hippocampal structure and function
460 (Foy *et al.*, 1984; Gould *et al.*, 1990; Roof and Havens, 1992; Woolley *et al.*, 1990). Thus,

461 unsurprisingly, a number of animal studies have noted various sex differences in the
462 hippocampal formation, including larger volume in males than females (Jacobs *et al.*, 1990;
463 Pfaff, 1966). The pattern of larger hippocampal volume in males is less established in human
464 neuroimaging studies. Although a recent meta-analysis reported that relative to cranial size men
465 have larger hippocampal volume (Ruigrok *et al.*, 2014), others, including another recent meta-
466 analysis, reported that men and women have comparable hippocampal size (Gur *et al.*, 2002; Tan
467 *et al.*, 2016), others that women have larger hippocampal volumes (for review, Cahill, 2006),
468 while still others noted that the difference in size may shift across the lifespan with girls having
469 larger hippocampi than boys, but with women experiencing greater hippocampal decline than
470 men (for review, Cosgrove *et al.*, 2007).

471 Despite the inconsistent results in humans for hippocampal volume, other work in rodents
472 report larger hippocampal subfields in males which may relate to differences in spatial learning.
473 In addition to having faster completion times during a maze task, male rats showed CA1 and
474 CA3 pyramidal cell field volumes approximately 20% larger than females and pyramidal neuron
475 soma sizes 14-18% larger than females (Isgor and Sengelaub, 1998). This pattern of larger cell
476 fields and better performance in males suggests that CA1 and CA3 pyramidal cells are highly
477 involved in spatial tasks associated with better performance in males over females.

478 Perhaps more influential than structural differences on sex differences in behavior, are
479 the observations suggesting there are sex differences in the recruitment of other brain regions
480 during spatial tasks. Lesions of the entorhinal cortex, located in the parahippocampal gyrus and
481 sharing connections with CA1 and CA3, cause greater impairment in males than in females on
482 the Morris water maze (Roof *et al.*, 1993). By contrast, female rats show greater deficits on most
483 measures of a radial maze and Morris water maze tasks when they received frontal cortex lesions

484 (Kolb and Cioe, 1996). In humans, a similar reliance on the hippocampus in men and frontal
485 cortex regions in women was observed using a maze task. It was reported that in addition to
486 finding their way out of the maze faster, men showed greater activation of the left hippocampus,
487 right parahippocampal gyrus, and the left posterior cingulate, whereas women consistently
488 recruited right parietal and right prefrontal cortex during the maze task (Grön *et al.*, 2000).

489 That women tend to rely on and recruit more frontal regions during spatial tasks aligns
490 with the above-discussed behavioral studies showing women navigate using landmarks, while
491 men navigate using more allocentric strategies. In strategies using landmarks, working memory
492 processes should come online in order to maintain the landmarks in accessible short-term
493 memory. Working memory relies on frontal regions more than on hippocampal regions (Curtis
494 and D'Esposito, 2003), which may account for why females show frontal recruitment during the
495 spatial tasks and males do not (Grön *et al.*, 2000).

496

497 3.3 Sex differences in brain laterality and perceptual processing

498 Sex differences in the relationship between brain activation and global/local processing
499 also have been observed (Müller-Oehring *et al.*, 2007; Pletzer *et al.*, 2013; Roalf *et al.*, 2006),
500 although as seen with the global/local behavioral findings, patterns of brain activation
501 differences are less robust and consistent than such differences seen for emotional memory and
502 spatial ability.

503 Earlier, we discussed findings showing women responded faster when a target letter
504 appeared at the local versus global level, while men did not differ in their response times (Roalf
505 *et al.*, 2006). Brain event related potential (ERP) recordings from this same study revealed some
506 differences in ERP responses for those components related to early visual processing (P100 and

507 N150) and cognitive processing (P300). In contrast to bilateral P100 responses in the occipital
508 lobes when women were viewing global targets, women only showed P100 responses in the right
509 occipital hemisphere when viewing local targets (Roalf *et al.*, 2006). Meanwhile, men showed
510 larger amplitude ERPs for the N150 component when the target letter was in a global location
511 (Roalf *et al.*, 2006). The ERP for the cognitive P300 component followed the behavioral
512 responses, with men showing no difference between global and local location of the target letter,
513 whereas women showed higher amplitude P300 components when the target letter was locally
514 located versus globally located (Roalf *et al.*, 2006).

515 Brain activation measured via fMRI also revealed sex differences. In the task where
516 participants made judgements about which number in a pair of numbers was larger, women
517 showed greater bilateral activation throughout, with greater recruitment of fronto-parietal regions
518 during within-decade pairs and posterior superior parietal lobule during different-decade pairs
519 than men during the high-hormone luteal phase of the menstrual cycle (Pletzer *et al.*, 2013).

520 Sex differences in lateralization have also been observed using letter and shape stimuli
521 (Pletzer and Harris, 2017). Performance of the Navon task was generally associated with
522 bilateral increased activation in the parietal and occipital lobes and decreased activation in the
523 inferior parietal gyri, precuneus, anterior cingulate cortex, and medial prefrontal cortex.
524 However, brain activation in the occipital lobes was largely right lateralized for global targets
525 and left lateralized for local targets (Pletzer and Harris, 2017). Lateralization scores, which
526 indicate greater activation in one hemisphere over the other, showed that women displayed
527 greater left lateralization in the occipital lobe than men for local targets particularly during
528 selected attention blocks. Such an effect was not observed in men unless inter-hemispheric
529 connectivity was taken into account. In this regard, greater negative parieto-parietal connectivity

530 was associated with greater left lateralization in the parietal lobe and greater global advantage.
531 This pattern suggests that men may require more energetic resources to process local details than
532 women, while women may not require a complimentary increase in energetic resources to
533 process global items.

534

535 3.4 Overview

536 In the above section, we reviewed evidence that sex differences in behavior show
537 corresponding differences in the brain, although differences for emotional memory and spatial
538 ability are more consistent than for perceptual processing. Given the importance of these brain
539 structures for the successful execution of their relative cognitive tasks, it is likely that sex
540 differences in these regions contribute to sex differences in behavior and cognition. One
541 remaining question is whether these sex differences developed independently from one another
542 (e.g., sex differences in the amygdala developed with no relation or consequence to sex
543 differences in hippocampus or hemispheric activation, all of which, coincidentally, led to similar
544 sex differences in behavioral/cognitive outcomes) or whether some additional mechanism led to
545 a more favorable gist versus detail strategy in males and females leading to similar sex
546 differences to take shape in the brain, behavior, and cognition. Concluding that the similarity of
547 sex differences across these three domains all developed as independent systems, with no
548 common guiding mechanism, suggests that brain development occurs in an unorganized,
549 stochastic fashion, which is not the case (Schottdorf *et al.*, 2015; Sporns *et al.*, 2004). As a result,
550 it seems more likely that more specific pressures or mechanisms led to common sex differences
551 across these domains and related brain regions. Below we review possible mechanisms for why
552 and how these differences developed.

553

554 **4. Are there any general brain mechanisms that could help account**
555 **for the similar sex differences seen across multiple domains?**

556 There are multiple possibilities for why this gist and detail parallel is observed across
557 multiple domains. Each of which can account for the parallel to some extent, but generally fall
558 short when the questions of “why and “how” are posed. Ideally, a mechanism able to explain this
559 parallel would address both *why* the difference occurs and *how* the difference occurs. Below we
560 review three possible explanations, and their individual strengths and weaknesses.

561

562 4.1 Sex differences in global and local perceptual processing as a mechanism for sex
563 differences in gist and detail encoding and retrieval in emotional and spatial memory

564 It has been proposed that sex differences in visuospatial processing of global and local
565 features drive sex differences in other aspects of cognition, including spatial abilities, emotional
566 memory, and verbal abilities (Pletzer, 2014; Pletzer *et al.*, 2013). In one such account, men and
567 women attend to different aspects of presented scenes, leading to sex differences in recall or
568 navigation performance (Pletzer, 2014). However, this account ignores work showing that men
569 and women scan, fixate, and attend to emotional scenes (Nielsen *et al.*, 2013, 2014; Nielsen *et*
570 *al.*, 2011) and maps (MacFadden *et al.*, 2003) in a similar fashion. Nonetheless, one study
571 examining the relationship between global-to-local processing and other cognitive domains
572 (spatial navigation and verbal fluency), did find that global advantage in the Navon task during
573 selected attention blocks was related to better performance on a spatial task requiring allocentric
574 navigation, however, the effect was stronger in women than men (Pletzer *et al.*, 2017).

575 Some studies have examined how manipulating the spatial nature of hierarchical stimuli
576 (line orientation vs. shape judgement) might modulate sex differences in global and local
577 processing. In one study (Kimchi *et al.*, 2009), men and women both showed global advantage
578 (i.e., faster reaction times to global targets than local targets), and did not differ in local
579 processing reaction times. However, sex differences did emerge when stimulus type was taken
580 into consideration. For instance, women were sensitive to differences in line orientation between
581 global and local levels, such that they showed global interference of classification of local line
582 orientation when the global line orientation differed. Men, on the other hand, did not show global
583 interference resulting from differences in line orientation (Kimchi *et al.*, 2009). Conversely,
584 women more accurately classified shape stimuli as either open or closed patterns than men
585 (Kimchi *et al.*, 2009). This pattern follows sex differences in spatial ability, suggesting that men
586 outperform women on tasks centered on orienting oneself or objects in space and women
587 outperform men on tasks centered on object recognition.

588 While sex differences in global versus local processing may contribute to sex differences
589 in gist versus detail encoding and retrieval in spatial tasks, it does not account for *why* scenes and
590 spaces are encoded and later retrieved differentially between males and females. Evolution and
591 natural selection suggest that these differences would have been selected to increase survival.
592 Thus, while sex differences in visuospatial processing may contribute to sex differences in
593 encoding and retrieval across domains, that explanation still does not address why males and
594 females would develop sex differences in and across these domains.

595 One proposal, aimed at explaining how sex differences occur across domains, suggests
596 that sex differences in brain laterality related to visuospatial processing drive sex differences in
597 and across different cognitive functions (Pletzer, 2014). Problematically, laterality differences

598 have been observed in emotional memory and global/local processing, but not in an entirely
599 coherent manner across the two domains. While sex differences in emotional memory show
600 greater left amygdala and hemisphere activation in women and right amygdala and hemisphere
601 activation in men (Cahill *et al.*, 2001; Cahill *et al.*, 2004; Canli *et al.*, 2002; Stevens and
602 Hamann, 2012), the findings for sex differences in left versus right hemisphere activation for
603 global versus local stimuli is less consistent (Pletzer and Harris, 2017; Pletzer *et al.*, 2013; Roalf
604 *et al.*, 2006). This is problematic given the striking conceptual parallel between the gist and
605 detail differences in emotional memory and the global and local differences in visuospatial
606 processing (see Section 3 for discussion). Furthermore, as discussed in Section 3, sex differences
607 in laterality of the amygdala for emotional memory and more generally between hemispheres for
608 perceptual processing do not account for why and how these differences came to exist.
609 Importantly, this account also does not adequately explain sex differences in the hippocampus
610 and elsewhere in the brain as they pertain to spatial abilities where laterality does not play a
611 robust or consistent role. Thus, in order to make progress toward what forms these sex
612 differences take in the brain and behavior, we could benefit from a more cohesive and efficient
613 mechanism to account for sex differences across cognitive domains and the brain.

614

615 4.2 Differential evolutionary pressures favored different encoding and retrieval 616 strategies between males and females

617 One possible explanation for “why” sex differences exist in such a uniform manner
618 across cognitive domains are theories of differing evolutionary pressures for males and females.
619 Evolutionary pressures associated with spatial navigation may account for biases toward
620 encoding and retrieving gist versus detail information in males and females. When looking at the

621 spatial tasks in which males outperform females and vice versa, one can see that the spatial
622 abilities being measured differ, with males performing better on tasks requiring orienting oneself
623 in space or mentally manipulating objects in space (Astur *et al.*, 1998; Beatty, 1984; Cherney *et*
624 *al.*, 2008; Dawson *et al.*, 1975; Galea and Kimura, 1993; Grön *et al.*, 2000; Isgor and Sengelaub,
625 1998; Linn and Petersen, 1985; MacFadden *et al.*, 2003; Postma *et al.*, 2004; Saucier *et al.*,
626 2002) and females performing better on tasks requiring the recall of object locations in space
627 (Cherney *et al.*, 2008; Eals and Silverman, 1994; Galea and Kimura, 1993; James and Kimura,
628 1997; MacFadden *et al.*, 2003; McBurney *et al.*, 1997; Saucier *et al.*, 2002; Silverman and Eals,
629 1992). These features may also relate to findings that men tend use allocentric navigation
630 strategies while women tend to use egocentric navigation strategies (Cherney *et al.*, 2008;
631 Lawton, 1994; Saucier *et al.*, 2002).

632 The Hunter-Gatherer Theory (Eals and Silverman, 1994) posits that the pattern of sex
633 differences observed in spatial ability arises from different evolutionary pressures facing men
634 and women, where early man needed to travel over large areas to hunt, and women were more
635 likely to live and forage in one region (Silverman *et al.*, 2007; Silverman and Eals, 1992). Thus,
636 the types of tasks men excel in are abilities allowing for a more allocentric approach to encoding
637 spatial information and navigation (Dabbs *et al.*, 1998; Silverman and Eals, 1992). For instance,
638 when hunting prey males do not know where or how far from home the hunt will come to end. If
639 males encoded and retrieved landmark information they would need to retrace their steps to
640 return home. However, that may not be the most direct route home, making egocentric
641 navigation (e.g., using landmarks and “right”/“left” direction) a less adaptive strategy for males
642 than the allocentric strategy that males tend to utilize. By contrast, the types of tasks women
643 excel in would, for example, allow women to better recall the locations of items fixed in place,

644 such as a particular food source and better monitor their immediate surroundings (Dabbs *et al.*,
645 1998; Silverman and Eals, 1992).

646 Evolution is aimed at balancing optimal efficiency of each system within an organism
647 (Noor and Milo, 2012; Schuetz *et al.*, 2012; Shoval *et al.*, 2012; Yun *et al.*, 2006). Hunting and
648 foraging for food was essential for survival, making evolutionary pressures for spatial strategies
649 of utmost importance. Given that systems would be geared toward efficiency, these encoding and
650 retrieval processes should then be utilized for other behavioral and cognitive domains. These
651 pressures offer an account of “why” sex differences occur, but still do not address “how” they
652 are occurring.

653 We propose that the “how” mechanism results from differences in the brain. However,
654 following the concept of efficiency within and across systems, it seems unlikely that the
655 aforementioned sex differences in the brain regions related to these behavioral and cognitive
656 processes developed independent of one another in a stochastic fashion. Rather, it is possible that
657 another brain region, able to effect change throughout the brain, modulates these processes
658 differently in males and females leading to different patterns of brain activation and different
659 patterns of performance.

660 One brain region that may be able to exert the level of widespread neural modulation
661 required to affect each of these domains is the locus coeruleus (LC). The LC regulates vigilance
662 and re-orienting attention to all manner of salient stimuli, regardless of valence. Through its
663 broad and diffuse release of norepinephrine (NE) across most of the brain (Abercrombie *et al.*,
664 1988; Aston-Jones, 2004; Morrison *et al.*, 1978), the LC is ideally positioned to modulate
665 activity in various regions implicated in attention and memory (for reviews see, Sara, 2009; Sara
666 and Bouret, 2012), and importantly, to exert different effects throughout the brain via sex

667 differences in its own structure and function. Furthermore, local cortical NE-glutamate
668 interactions spark “hot spots” of high excitation that promote processing of whatever is most
669 salient at that moment (Mather *et al.*, 2016).

670

671 4.3 LC-NE system as a potential mechanism for facilitating these differential strategies

672 The LC is a small pontine nucleus whose role is identifying and orienting attention to
673 salient stimuli, which makes the LC an ideal candidate for mediating sex differences between
674 gist and detail memory. It is possible that while men and women are attending to the same scene,
675 LC signaling may inform a female system that detail-level stimuli are salient and should be
676 attended to. This would be adaptive based on the aforementioned evolutionary pressures
677 hypothesized to affect women more than men. In contrast, those pressures hypothesized to affect
678 men more than women may make the male LC less likely to identify detail features as salient and
679 worth encoding for later retrieval. The question then becomes, *how* the LC effects the neural
680 milieu exerting such sex differences.

681

682 4.3.1 Sex differences in the locus coeruleus

683 Sex differences in the LC-NE system, particularly with respect to a higher prevalence of
684 stress- and anxiety-related disorders in women, have been skillfully and extensively reviewed
685 elsewhere (Bangasser *et al.*, 2017; Bangasser and Valentino, 2012, 2015; Bangasser *et al.*, 2016).
686 Here, we briefly review evidence showing that male and female LC differ on various indices,
687 including size/volume, morphology, and function. Given the small size and location of this
688 nucleus, much of the structural and activational work is conducted in animals, unless otherwise
689 indicated.

690 Sex differences in this midbrain pontine structure are documented to begin during
691 adolescence, with males and females showing differences in LC volume and neuron number
692 during puberty. Continued LC neurogenesis in females through puberty and discontinued
693 neurogenesis in males at the onset of puberty drive these sex differences (Pinos *et al.*, 2001).
694 Evidence suggests that the onset of estradiol cyclicity in females is the catalyst for differences
695 appearing at the onset of puberty. Disruption of estradiol production and concentration, even
696 after puberty, has been shown to abolish the formation of larger LC volume and higher neuron
697 count in females (De Blas *et al.*, 1990). Further evidence for the driving role of estradiol leading
698 to larger LC volume and neuron number in females is the androgenizing effect of testosterone
699 propionate when administered to females on postnatal day 1. These females no longer differed
700 from males and had smaller LC volume and neuron count than normal intact females, however,
701 orchietomy of males had no effect on LC volume or neuron number (Guillamón *et al.*, 1988).
702 Showing that testosterone resulted in smaller LC volume and lower neuron count in females,
703 while loss of testosterone in males did not lead to changes in LC volume or neuron number,
704 suggests that the observed effect in females was not a result of testosterone action on the female
705 LC but rather disruption of the normal estradiol-induced organization and modulation of LC
706 development resulting from the testosterone administration in early development.

707 Others have shown that larger LC volume in females compared with males is driven by
708 sex differences in the overall volume and number of NE neurons in the LC, particularly in the
709 intermediate anterior regions of the LC in females (Luque *et al.*, 1992). Interestingly, however,
710 some evidence suggests that males do have a larger LC volume depending on the LC subregion
711 of interest (Babstock *et al.*, 1997). This study found that adult male Sprague-Dawley rats
712 exhibited larger dorsal LC volume, a difference driven by a subregion of the dorsal LC that

713 heavily innervates the hippocampus (Babstock *et al.*, 1997), which may have important
714 implications for spatial abilities in males.

715 Perhaps more importantly from a functional standpoint, adult females are reported to
716 exhibit larger density of the dendritic field throughout the LC and peri-LC regions, including the
717 core, ventromedial LC, and dorsolateral LC, likely resulting from females showing greater
718 number of dendritic nodes and ends, dendritic length, and higher branch order (Bangasser *et al.*,
719 2011). The length of longest dendritic tree was also longer in females than in males. As would be
720 expected with a greater number of dendrites, females also appear to have more synapses based
721 on higher levels of synaptophysin in the core and dorsolateral LC (Bangasser *et al.*, 2011).

722 Another set of important functional findings show that the female LC is more responsive
723 to stressful stimuli. For instance, females show a greater increase in tonic LC neuronal firing
724 rates in response to hypotensive stress than males (Curtis *et al.*, 2006). This larger neuronal
725 response to the same stressor was driven by greater sensitivity of LC neurons to corticotropin-
726 releasing factor (CRF) in females, such that a lower dose of CRF resulted in a greater increase of
727 tonic LC firing rates in females than in males (Curtis *et al.*, 2006). The sex difference in CRF
728 sensitivity appears at the level of receptor signaling. The CRF receptor involved in this process is
729 a G-protein coupled receptor (Grammatopoulos *et al.*, 2001; Hillhouse and Grammatopoulos,
730 2006), which increases LC tonic firing rates via activation of a cAMP-dependent intracellular
731 signaling cascade (Jedema and Grace, 2004). In contrast with unstressed males, the larger LC
732 neuronal response to a low dose of CRF in females was found to be completely mediated by this
733 cAMP-dependent cascade. However, when males were first exposed to a stressor, they exhibited
734 a sensitized LC response, such that neurons responded to a lower dose of CRF. This sensitization
735 of LC neurons in males was completely cAMP-dependent (Bangasser *et al.*, 2010). This pattern

736 suggests that females experience a near maximal response in the LC to stressors that do not
737 affect the male LC system. This increased sensitivity may have important implications for the
738 LC even in the absence of stress. Recall that the LC plays an integral role in identifying and
739 orienting to salient stimuli (Sara, 2009; Sara and Bouret, 2012). Thus, if the female system is
740 more sensitive to stressors, it might be the case that the female system also identifies different
741 stimuli as salient, which would result in encoding of different features of the same scene than
742 males.

743

744 4.3.2 Sex differences in the locus coeruleus and norepinephrine drive sex differences in 745 emotional memory

746 The LC shares bidirectional projections with the amygdala (Buffalari and Grace, 2007;
747 Canteras *et al.*, 1995; Cedarbaum and Aghajanian, 1978; Jones and Moore, 1977; Segal *et al.*,
748 1973; Wallace *et al.*, 1992), and NE activation of the amygdala is necessary for successful
749 encoding and consolidation of emotional memory (Hermans *et al.*, 2014; Roozendaal and
750 Hermans, 2017). For instance, in humans NE facilitates memory enhancement for the middle
751 portion of the negative version of the three-phase story (Cahill *et al.*, 1994), and NE must act
752 centrally, not peripherally, to yield such memory enhancement effects (van Stegeren *et al.*,
753 1998). Given the sex differences that exist in the NE system and in emotional memory, it should
754 not be surprising that there are sex differences in how NE influences emotional memory.

755 Following up on their work showing propranolol, a β -adrenoreceptor blocker, abolished
756 enhancement for the middle phase of the negative version of the three-phase story (Cahill *et al.*,
757 1994; van Stegeren *et al.*, 1998), Cahill and van Stegeren (2003) found that the effects of
758 propranolol on gist and detail memory differed by sex. As reviewed previously, men typically

759 recall the gist, while women recall the details (depending on menstrual cycle phase and
760 contraceptive status) of a scene. In line with the observed sex difference under control
761 conditions, administration of propranolol prior to encoding diminished emotion-related
762 enhancement of gist memory in men and detail memory in women (Cahill and van Stegeren,
763 2003). This pattern suggests that LC-NE modulation of the amygdala not only plays a role in
764 encoding emotional memories, but also plays a role in the sex differences observed for encoding
765 of detail versus gist information in women and men, respectively.

766

767 4.3.3 Sex differences in the locus coeruleus and dopamine may drive sex differences in spatial 768 memory

769 The LC and hippocampus are also highly interconnected. The LC innervates the
770 hippocampus (Jones and Moore, 1977; Loughlin *et al.*, 1986a; Loughlin *et al.*, 1986b; Pasquier
771 and Reinoso-Suarez, 1978; Segal and Landis, 1974; Segal *et al.*, 1973) and receives afferents
772 from the subiculum (Swanson and Cowan, 1977). In addition to sharing efferents and afferents,
773 the LC-NE system contributes to spatial abilities (Lemon *et al.*, 2009; Lemon and Manahan-
774 Vaughan, 2012; Nakao *et al.*, 2002) via modulation of long-term plasticity within the
775 hippocampus related to spatial memory formation (Hansen and Manahan-Vaughan, 2015a, b).
776 Recent work suggests that the LC specifically modulates spatial learning and memory
777 (Kempadoo *et al.*, 2016), via dopaminergic innervation of the hippocampus (Kempadoo *et al.*,
778 2016; Kentros *et al.*, 2004). While not the primary source of neural dopamine (DA), the LC is
779 also involved in DA release throughout the brain (Devoto and Flore, 2006; Devoto *et al.*, 2005;
780 Grenhoff *et al.*, 1993; Kempadoo *et al.*, 2016; Lategan *et al.*, 1990; Lemon and Manahan-
781 Vaughan, 2006), an effect that appears to be mediated by NE action.

782 Recent work demonstrated that LC modulates spatial memory via DA action (Kempadoo
783 *et al.*, 2016). This study found that while dopaminergic and noradrenergic neurons send
784 projections to the CA1, of the two catecholamines, increasing dopaminergic tone to the dorsal
785 hippocampus by stimulating LC dopamine release resulted in enhanced spatial performance
786 across a battery of spatial tests, including a spatial object recognition test, the Barnes maze, and a
787 conditioned place preference test, in animals that otherwise would not have learned. This effect
788 occurred primarily through activation of the dopamine D1/D5 receptor complex (Kempadoo *et*
789 *al.*, 2016). Dopamine D1/D5 receptors are featured prominently on pyramidal neurons in the
790 hippocampus and other cortical regions (Bergson *et al.*, 1995), where they are important for
791 long-term plasticity in the hippocampus (Hansen and Manahan-Vaughan, 2014) and for spatial
792 learning (Granado *et al.*, 2008).

793 While little work has examined sex differences in LC projections to, or LC modulation of
794 activity in, the hippocampus, extant data suggest that men receive greater LC input to the
795 hippocampus than women. In animals, the dorsal region of the LC, which heavily innervates the
796 hippocampus (Mason and Fibiger, 1979), is larger in males than females (Babstock *et al.*, 1997).
797 In humans, one resting-state fMRI study also suggests that fluctuations in LC activity are more
798 tightly coupled with activity in the hippocampus and other medial temporal lobe regions in males
799 than females (Zhang *et al.*, 2016). This preferential LC modulation of the hippocampus in males
800 may at least partially explain why males exhibit better performance on spatial tasks requiring
801 orienting oneself or objects in space (Zhang *et al.*, 2016).

802 Unlike investigation of sex differences in LC-hippocampus interactions, there is ample
803 evidence of sex differences in the DA system, although much of this research is confined to the
804 domain of reward learning. Nonetheless, much of this research shows that males show

805 overproduction of DA receptors in the striatum until puberty and retain greater D1 receptor
806 density in the nucleus accumbens (Andersen *et al.*, 1997) and greater DA release in the striatum
807 in response to amphetamine administration (Munro *et al.*, 2006). On the other hand, females
808 show greater DA clearance efficiency (Mozley *et al.*, 2001), suggesting the male system
809 maintains higher levels of DA. Given the importance of DA and the D1/D5 receptor complex in
810 spatial learning and memory, this pattern of greater DA may speak to the aforementioned greater
811 reliance on the hippocampus for spatial tasks in males compared to females who also recruit
812 frontal regions during spatial tasks (Grön *et al.*, 2000; Kolb and Cioe, 1996; Roof *et al.*, 1993),
813 as discussed in section 3.

814

815 4.3.4 Can sex differences in the locus coeruleus and arousal speak to sex differences in global
816 and local processing

817 Recall that while there is a general effect of global precedence in perceptual processing,
818 sex differences in global and local processing suggest that men show a tendency to perform
819 better on global processing and women on local processing (Kimchi *et al.*, 2009; Kramer *et al.*,
820 1996; Müller-Oehring *et al.*; Pletzer and Harris, 2017; Pletzer *et al.*, 2013; Pletzer *et al.*, 2014;
821 Roalf *et al.*, 2006; Scheuringer and Pletzer, 2016). Given the role of the LC/NE system to
822 identify salient stimuli and reorient attention to those salient stimuli (for reviews see, Sara, 2009;
823 Sara and Bouret, 2012), it would be expected that arousal would amplify this pattern of
824 differences in men and women. However, limited work has examined the effects of arousal on
825 global and local perceptual processing. This limited work in humans has examined how
826 manipulating arousal levels via presentation of a tone might affect performance on these tasks,
827 but do not account for sex (Weinbach and Henik, 2011, 2014). In these studies, flanker tasks

828 were modified to mimic Navon stimuli³ and auditory tones were played prior to congruent or
829 incongruent trials. The measure of performance on these tasks was the “congruency effect”
830 (mean reaction time for incongruent trials minus mean reaction time for congruent trials). In a
831 version of the study where the salience of the local and global interfering information was
832 manipulated, arousal increased attentional biases to whichever aspect of the stimuli was most
833 salient in that context (Weinbach and Henik, 2014). Thus, these findings suggest that if there are
834 sex differences in whether global vs. local stimuli are more salient, increased LC activation due
835 to arousal should increase those sex differences.

836

837 4.4 Overview

838 As seen in sections 4.3.2 and 4.3.3, although structural differences in LC have been
839 reported between males and females, LC structure alone cannot account for why women appear
840 to encode more detail information and men appear to encode more gist information. However,
841 given the known role of NE in re-orienting attention and in regulating vigilance (for reviews see,
842 Sara, 2009; Sara and Bouret, 2012), LC modulation of the NE system and the sex differences
843 indicating the female LC-NE system is more responsive to detail items within a scene or
844 environment may account for this difference. Recall that the female LC is more sensitive to

³ The arrow-flanker task requires participants to indicate the direction of a central arrow in a line of arrows. The arrows can either be congruent (→ → → → →) or incongruent (→ → ← → →). In the modified version of the task used in the reviewed studies (Weinbach, 2011, 2014), the arrows were arranged similar to Navon task stimuli, where one large arrow was made out of smaller arrows. In this formation, congruent trials were where the large, global, arrow and smaller, local, arrows were facing the same direction, while incongruent trials were where the large, global, arrow was facing one direction and the smaller, local, arrows were facing the opposite direction.

845 stressors than the male LC (Bangasser *et al.*, 2010; Curtis *et al.*, 2006). This increased sensitivity
846 has often been discussed in its relation to stress- and anxiety-related psychiatric disorders
847 (Bangasser *et al.*, 2017; Bangasser and Valentino, 2012, 2015). However, this increased
848 sensitivity may not be limited to events commonly considered stressors. In particular,
849 evolutionary pressures resulting in differential encoding of detail and gist information between
850 females and males could have capitalized on the widespread influence of the LC throughout the
851 brain to instantiate such differences in other perceptual, cognitive, and neural domains. In doing
852 so, the LC may promote different thresholds in females and males of determining that features of
853 a scene are salient or behaviorally relevant, leading to a preferential encoding of details or local
854 information in females and a preferential encoding of gist or global information in males.

855

856 **5. Future directions and limitations**

857 Importantly, this is just one possible account for how similarities in sex differences are
858 observed across these three domains and there is still a great deal of research that must be done
859 to test the veracity of this theoretical account. Behaviorally, these effects appear to be stable in
860 emotional memory, but less so in spatial ability and perceptual processing. For instance,
861 experiments linking gist versus detail memory and spatial ability, in particular preferring
862 allocentric or egocentric navigation strategies, remain to be conducted. There is also a need to
863 further explore whether and how increased arousal or direct norepinephrine manipulation affects
864 performance on global-to-local processing tasks. The clearest experimental design to address this
865 issue would involve manipulating LC activation independently from the stimuli used to examine
866 attentional biases toward detail and gist information (for examples of this approach of

867 independently manipulating LC activation levels and stimuli salience see, Clewett *et al.*, 2018;
868 Lee *et al.*, in press)

869 Another challenge is to determine whether there are sex differences in which aspects of
870 stimuli or scenes the LC tends to amplify processing of during baseline states (i.e., not under
871 states of stress or arousal). Molecular and cellular studies examining neuronal LC response to
872 stimuli typically focus on LC response to stressors, which lead to robust neuronal and
873 neuromodulatory responses, however, our proposed model does not directly benefit from such
874 paradigms. Our model proposes that under normal conditions the LC is differentially identifying
875 whether detail-level items within a global scene are salient and worth encoding in males and
876 females. Testing this would require electrophysiological studies which can measure how LC
877 neurons are responding to different individual stimuli within a scene or environment. A similar
878 model could be tested in humans using the constantly improving technology and imaging
879 sequences for fMRI. LC responses could then be related to performance on memory tasks for
880 global vs. local stimuli within a scene or environment.

881 A final caveat is the proposed influence of evolutionary pressures on the development of
882 these parallel sex differences across domains. Evolutionary theories are subject to criticism, in
883 particular, the concept of spandrels (Gould and Lewontin, 1979) which discusses how theories
884 centered on evolutionary psychology are in danger of ignoring alternative explanations. In this
885 regard, evolutionary foundation for modern behaviors are at risk of missing alternative causes for
886 said behaviors. As such, it is important to note that evolutionary pressures are not the only
887 possible driving force for shaping and selecting the observed sex differences. One possibility for
888 testing the potential influence of these evolutionary pressures would be to begin incorporating
889 tasks which can decipher detail versus gist memory in anthropological studies focused on

890 current-day hunter-gatherer societies. Alternatively, or additionally, pre-existing data from such
891 hunter-gatherer studies (e.g., Reyes-García *et al.*, 2016) might be reexamined to determine
892 whether some tasks within the datasets may be able to speak to detail versus gist memory and
893 whether performance on those tasks differ by sex.

894

895 **6. Conclusions**

896 Men and women differ on a range of indices related to perceptual processing, emotional
897 memory, and spatial ability. In these tasks, women tend to show greater encoding of detail
898 information, leading to better performance on recall tasks for peripheral information in an
899 emotional scene and landmarks in a route. Men tend to show greater encoding of gist
900 information, leading to better performance on recall tasks for central information in an emotional
901 scene and allocentric navigation. In a related domain, men and women also show differences in
902 perceptual processing of hierarchical stimuli, with men performing better for global targets and
903 women performing better for local targets. Such differences in perceptual processing seem
904 attractive for explaining sex differences in encoding and retrieval for emotional memory and
905 spatial ability, however they do not account for why and how these low-level sex differences in
906 perception occur. The failure of perceptual processing to account for sex differences suggests
907 that the sex differences observed in perceptual processing are a byproduct of another effect, just
908 as seems likely for emotional memory and spatial ability.

909 Differing evolutionary pressures and LC innervation throughout the brain may help
910 explain why and how these sex differences occur. Specifically, the greater sensitivity of the
911 female LC-NE system may lead women to activate the LC-NE system in response to stimuli and
912 goals that do not lead to increased activation in males. This non-stress level activation of the LC-

913 NE system may lead to a greater level of vigilance in women when interacting with such stimuli
914 and enhance encoding of detail information.

915

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