RESEARCH ARTICLE

Age but no sex effects on subareas of the amygdala

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Abstract

The amygdala, an anatomical composite of several nuclei that have been grouped anatomically and functionally into three major subareas, has been reported to decrease in size with increasing age and to differ in size between male and female brains. However, findings are rather inconsistent across existing studies, possibly reflecting differences in the cohorts examined or the approaches chosen to define and measure the dimensions of the amygdala. Here, we investigated possible effects of age and sex on the amygdala as well as age-by-sex interactions in 100 healthy subjects (50 men/50 women) aged 18–69 years. For this purpose, we enhanced conventional imaging-based information with microscopically defined cytoarchitectonic probabilities to discriminate between different subareas. We observed significant negative correlations between age and all subareas of the amygdala indicating decreases over time, but with subarea-specific trajectories. In addition, we detected a significant quadratic association with age for the left superficial subarea suggesting an accelerating volume loss over time. Such regional information may serve as a frame of reference in future studies, not only for normative samples but also potentially for clinical populations known to present with an atypical atrophy of the amygdala. There were no sex differences and no interactions between sex and age, suggesting that the size of the amygdala is similar in male and female brains (at least when properly accounting for total intracranial volume) and that its age-related decline follows a similar trajectory in both sexes.

KEYWORDS

aging, amygdala, brain, gender, MRI, sex

1 | INTRODUCTION

The amygdala is a conglomerate of multiple nuclei that are highly interconnected (Sah, Faber, Lopez De Armentia, & Power, 2003). Based on their underlying cytoarchitecture, these nuclei have been grouped into three main compartments, namely the centromedian subarea, the laterobasal subarea, and the superficial subarea (Amunts et al., 2005; Heimer et al., 1999). While this parcellation has been originally established anatomically using post mortem data and cytoarchitectonic mapping, it was more recently replicated functionally using imaging data and meta-analytic connectivity modeling (Bzdok, Laird, Zilles, Fox, & Eickhoff, 2013).

The amygdala has frequently been reported to decrease in volume with increasing age (Fjell, Walhovd, et al., 2009a; Fjell, Westlye, et al., 2009b; Fjell et al., 2013; Pfefferbaum et al., 2013; Walhovd et al., 2005, 2011; Ziegler et al., 2012), but reports differ substantially with respect to the magnitude and trajectories of its decline. Such

discrepancies across studies may reflect differences in the cohorts examined with respect to the age range, sex ratio, and/or the existence of any (pre)clinical conditions (Cherbuin, Sachdev, & Anstey, 2012; Janowitz et al., 2015; Ruigrok et al., 2014; Zanchi, Giannakopoulos, Borgwardt, Rodriguez, & Haller, 2017). Another source of discrepancy could be the amygdala's immediate proximity to surrounding brain structures and the difficulty in accurately and consistently identifying its borders (Amunts et al., 2005), which often leads to approximations rather than precise delineations. Moreover, there is a lack of visible macro-anatomical landmarks to discriminate between functionally distinct subregions of the amygdala. While some studies have assessed the possible modulating effects of sex on amygdala size, findings are rather conflicting (for meta-analyses see Marwha, Halari, & Eliot, 2017; Ruigrok et al., 2014), which might be due to the inconsistency in accounting for the different brain sizes in men and women across studies (Marwha et al., 2017). To our knowledge, research assessing age effects on different subareas is entirely missing.

The goal of the current study was therefore to (i) investigate associations between age and amygdala size while discriminating between its different subareas, (ii) to assess possible sex differences in amygdala size while properly adjusting for individual brain size, and (iii) to test whether any age-by-sex interactions exist. For this purpose, we analyzed brain data from a healthy sample of 50 men and 50 women covering a broad age range and applied a state-of-the-art brain mapping technique combining MRI-based signal intensities and cytoarchitectonically defined probabilistic maps (Kurth, Cherbuin, & Luders, 2015a, 2017a; Kurth, Jancke, & Luders, 2017b, 2018; Luders, Kurth, Toga, Narr, & Gaser, 2013). This approach allows investigating the amygdala and its centromedian (CM), laterobasal (LB), and superficial (SF) subareas in a highly standardized way. In accordance with the literature (Fjell, Walhovd, et al., 2009a; Fjell, Westlye, et al., 2009b; Fjell et al., 2013; Pfefferbaum et al., 2013; Walhovd et al., 2005, 2011; Ziegler et al., 2012), we hypothesized that the amygdala would decline with increasing age, and that this decline might even accelerate over time. However, different trajectories may exist in CM, LB and SF, similar as has been reported, for example, for subregions of the hippocampus (Kurth, Cherbuin, et al., 2017a). Our hypothesis on sex differences (as well as on age-by-sex interactions) was undirected as previous reports of larger amygdalae in men than in women may have been driven by the overall larger dimensions of male brains (Marwha et al., 2017).

2 | METHODS

2.1 | Study sample

The study included data of 100 healthy adults (mean age $\pm$ SD: 43.32 ± 13.72 years; range 18–69 years), specifically 50 men and 50 women, who did not differ significantly in terms of age (men: 41.64 ± 13.52 years; women: 45.00 ± 13.85 years). Image and meta-data were obtained from the International Consortium for Brain Mapping (ICBM) database of normal adults (<http://www.loni.usc.edu/ICBM/Databases/>). The ICBM database contains subjects without any medical disorders and conditions that could potentially affect brain structure or function, and the extensive set of exclusion criteria applied (see Mazziotta et al., 2009) differs substantially from the usually less strict screening protocols for healthy controls. All subjects had given their informed consent in accordance with the policies and procedures of UCLA's Institutional Review Board.

2.2 | Data acquisition and preprocessing

All brain images were collected on a 1.5 Tesla Siemens Sonata scanner (Erlangen, Germany) using an 8-channel head coil and a T1-weighted magnetization-prepared rapid acquisition gradient echo (MPRAGE) sequence with the following parameters: 1,900 ms repetition time, 4.38 ms echo time, 15° flip angle, 160 contiguous sagittal slices, 256×256 mm² field-of-view, $1 \times 1 \times 1$ mm³ voxel size. The T1-weighted images were then processed using SPM12 (<http://www.fil.ion.ucl.ac.uk/spm>) and the CAT12 toolbox (<http://dbm.neuro.uni-jena.de/cat/>), as previously described (Kurth, Cherbuin, et al., 2015a, 2017a; Kurth, Jancke, et al., 2017b, 2018; Luders et al., 2013). Briefly, images were

first corrected for magnetic field inhomogeneities and subsequently classified into gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF). The resulting gray matter partitions were then spatially normalized to the DARTEL template within the CAT12 toolbox using linear (12-parameter affine) transformations and nonlinear (high-dimensional) warping (Ashburner, 2007). Finally, the normalized gray matter segments were divided by the linear and nonlinear components of the Jacobian determinant derived from the normalization matrix to preserve the original gray matter (Ashburner & Friston, 2000; Good et al., 2001; Kurth, Luders, & Gaser, 2015b). In addition, total intracranial volume (TIV) was calculated by adding the volumes of the tissue classes in native space ($TIV = GM + WM + CSF$) to be later included as co-variate in the statistical model.

2.3 | Data analyses

In order to investigate the impact of age and sex on the amygdala, we assessed the amygdala as a whole as well as its centromedian (CM), laterobasal (LB), and superficial (SF) subareas within the left and right hemisphere. As detailed in Amunts et al. (2005), those subareas were originally established by first defining them in cell body-stained histological sections, then warping them into MNI single-subject space, and finally converting them into voxel-wise probabilities. The resulting color-coded probability maps (see Figure 1), were then integrated with the gray matter segments from the current study. More specifically, we multiplied our preprocessed gray matter segments (see Section 2.2) with the subarea-specific probability maps (Amunts et al., 2005) as provided by the Anatomy toolbox, version 2.2c (Eickhoff et al., 2005). The entire procedure is described in detail elsewhere (Kurth, Cherbuin, et al., 2015a, 2017a; Kurth, Jancke, et al., 2017b, 2018; Luders et al., 2013). Ultimately, this voxel-wise integration yields a probability-weighted measure of gray matter content within left and right CM, LB, and SF (in mm³). Gray matter content for the amygdala as a whole (AMG) was calculated by adding the volumes of its subareas ($AMG = CM + LB + SF$).¹ The resulting means as well as adjusted means of the (sub)volumes of the amygdala are provided in Table 1.

All statistical analyses were conducted in Matlab (The MathWorks, Natick, MA) using a mass-univariate general linear model. Specifically, the left and right volumes for AMG, CM, LB, and SF were used as dependent variables, age and sex as the independent variables, and TIV as a variable of no interest. Age was centered at 50 years to facilitate interpretation of the results. Significance levels were Bonferroni-corrected for multiple comparisons and set at $p \leq .05/4 = 0.0125$, accounting for the assessments of AMG, CM, LB, and SF. In addition, age-by-sex interactions as well as quadratic effects of age were assessed. Since the addition of the interaction term neither improved the model nor resulted in significant results (even when omitting Bonferroni corrections), interaction terms were not included in the final model. The beta estimates as well as the adjusted R^2 , ΔR^2 , and F statistics for the final model are provided in Table 2.

¹In terms of percentages, the left AMG was composed of 16% CM, 69% LB, and 15% SF, while the right AMG was composed of 17% CM, 63% LB, and 20% SF.

FIGURE 1 Cytoarchitectonic probabilities. Maps of the centromedial (CM), laterobasal (LB), and superficial (SF) subarea, displayed on coronal sections of the MNI single-subject template at $y = -8$, $y = -4$, and $y = 0$. The color bar encodes the regional probability as derived from cytoarchitectonic mapping in 10 postmortem brains (Amunts et al., 2005) [Color figure can be viewed at wileyonlinelibrary.com]

3 | RESULTS

There were significant linear associations between age and all (sub-)volumes of the amygdala. However, the magnitude and significance of these negative correlations varied slightly between the different areas, with the strongest correlation for the right SF ($r = -0.471$; $p < .001$)

and the weakest for the left LB ($r = -0.351$; $p < .001$). In contrast, quadratic associations only survived Bonferroni corrections for the left SF ($r = -0.261$; $p = .005$). When Bonferroni corrections were omitted, additional significant quadratic associations were observed for the left AMG and the left CM. The subarea-specific trajectories are depicted in Figure 2; the t -statistics and indicators of effects sizes

TABLE 1 (Sub)volumes of the amygdala in mm^3 (mean $\pm$ SD)

Side	Area	Whole sample		Women		Men	
		Raw	Adjusted for TIV	Raw	Adjusted for TIV	Raw	Adjusted for TIV
Left	AMG	1,478 $\pm$ 208	1,478 $\pm$ 134	1,395 $\pm$ 196	1,488 $\pm$ 128	1,561 $\pm$ 187	1,469 $\pm$ 141
	CM	242 $\pm$ 31	242 $\pm$ 22	230 $\pm$ 28	242 $\pm$ 20	254 $\pm$ 29	241 $\pm$ 24
	LB	1,018 $\pm$ 147	1,018 $\pm$ 95	960 $\pm$ 138	1,026 $\pm$ 88	1,075 $\pm$ 133	1,010 $\pm$ 101
	SF	218 $\pm$ 35	218 $\pm$ 25	205 $\pm$ 32	220 $\pm$ 24	231 $\pm$ 32	217 $\pm$ 26
Right	AMG	1,252 $\pm$ 169	1,252 $\pm$ 114	1,183 $\pm$ 142	1,255 $\pm$ 100	1,322 $\pm$ 166	1,249 $\pm$ 127
	CM	213 $\pm$ 28	213 $\pm$ 20	201 $\pm$ 23	212 $\pm$ 18	224 $\pm$ 28	213 $\pm$ 22
	LB	792 $\pm$ 108	792 $\pm$ 72	748 $\pm$ 92	795 $\pm$ 63	836 $\pm$ 106	789 $\pm$ 81
	SF	248 $\pm$ 36	248 $\pm$ 26	234 $\pm$ 30	248 $\pm$ 24	262 $\pm$ 36	248 $\pm$ 29
	TIV	1,539 $\pm$ 178 cm^3		1,435 $\pm$ 133 cm^3		1,643 $\pm$ 156 cm^3	

AMG = amygdala as a whole; CM = centromedial subarea; LB = laterobasal subarea; SF = superficial subarea; TIV = total intracranial volume. For each (sub)area, raw volumes as well as volumes adjusted for the mean TIV ($1,539 \text{ cm}^3$) are presented.

TABLE 2 Final statistical model used to assess the effects of age and sex on the (sub)volumes of the amygdala

	Left AMG	Right AMG	Left CM	Right CM	Left LB	Right LB	Left SF	Right SF
Age	−6.4550* (1.4737)	−5.7933* (1.2060)	−1.1232* (0.2208)	−0.9878* (0.1977)	−3.7157* (1.0168)	−3.1776* (0.7351)	−1.2564* (0.2525)	−1.3374* (0.2572)
Age ²	−0.1442# (0.0749)	−0.0674 (0.0613)	−0.0231# (0.0112)	−0.0105 (0.0101)	−0.0826 (0.0517)	−0.0363 (0.0374)	−0.0339* (0.0128)	−0.0213 (0.0131)
Sex	−43.3888 (31.9267)	−16.4825 (26.1268)	−3.3883 (4.7843)	0.0064 (4.2827)	−30.8636 (22.0280)	−13.3178 (15.9253)	−5.9553 (5.4696)	−3.2204 (5.5721)
TIV	0.9695* (0.0911)	0.7237* (0.0746)	0.1205* (0.0137)	0.0983* (0.0122)	0.6566* (0.0629)	0.4424* (0.0455)	0.1395* (0.0156)	0.1327* (0.0159)
Constant	1,595.2251* (24.2863)	1,342.9656* (19.8743)	241.4615* (3.6393)	208.4366* (3.2578)	1,027.6315* (16.7564)	785.6538* (12.1142)	220.8690* (4.1607)	245.5409* (4.2386)
Adjusted R ²	0.6537	0.6655	0.6155	0.6234	0.6367	0.6511	0.5949	0.6135
ΔR ² (vs. TIV only)	0.0748	0.1250	0.1209	0.1545	0.0554	0.1028	0.1048	0.1461
F statistic (df = 4; 95)	48.53*	50.24*	40.62*	41.98*	44.38*	47.19*	37.34*	40.28*

AMG = amygdala as a whole; CM = centromedial subarea; LB = laterobasal subarea; SF = superficial subarea; * $p \leq .0125$; # $p < .050$. The table shows all beta weights (standard errors) as well as adjusted R^2 and F statistics for the complete model.

are provided in Table 3. As shown in Table 3, there were no significant sex differences with respect to the (sub)volumes of the amygdala, regardless of whether Bonferroni corrections were applied or not. Similarly, there were no significant age-by-sex interactions with or without Bonferroni corrections.

4 | DISCUSSION

We investigated the effects of age on the amygdala and its subareas (CM, LB, and SF) in a carefully selected (i.e., extremely healthy) sample of individuals covering a broad age range (i.e., 18–69 years). Specifically, we set out to determine the magnitude and trajectories of age-related decline, while additionally assessing the modulating impact of sex on amygdala volume as well as on age-related volume loss. This was achieved by integrating voxel-wise cytoarchitectonic probabilities with MR-based signal intensities, not only for the amygdala as a whole, but also for each of its three main compartments. Our findings indicate a significant age-related atrophy of the amygdala with regional variations, but no sex differences and no modulating effects of sex on age-related volume loss. Overall, these findings are in good agreement with prior studies, as subsequently discussed. Given that there is a lack of studies assessing differential effects across the amygdala, our present findings additionally enhance this field of research by discriminating between different subareas as guided by micro-structure.

4.1 | Pronounced age effects

We detected significant negative linear associations between age and all (sub)volumes of the amygdala, suggesting that increasing age is associated with decreasing volumes overall. In addition, significant quadratic associations were evident in the left hemisphere, which points to an acceleration of volume loss over time in some (but not all) subareas. Overall, these findings are in good agreement with prior studies indicating a significant age-related atrophy of the amygdala (Fjell, Walhovd, et al., 2009a; Fjell, Westlye, et al., 2009b; Fjell et al.,

2013; Pfefferbaum et al., 2013; Walhovd et al., 2005, 2011; Ziegler et al., 2012). However, while some of those studies reported a constant atrophy (Fjell, Walhovd, et al., 2009a; Fjell et al., 2013; Narvican et al., 2017; Walhovd et al., 2005, 2011), others observed an accelerating decline (Pfefferbaum et al., 2013; Ziegler et al., 2012). Our results suggest that both linear and nonlinear trajectories exist for different subareas of the amygdala, which may have contributed to some of the inconsistencies in the literature. Other contributors might be the inclusion/exclusion of certain areas surrounding the amygdala, such as the entorhinal and perirhinal cortices (Jernigan et al., 2001). Similarly, different age ranges examined might affect study outcomes. For example, a lack of age-related volume loss was reported in a prior study, but perhaps due to only including subjects aged 18–42 years (Pruessner, Collins, Pruessner, & Evans, 2001). That is, if linear (or nonlinear) decreases only occur later in life (Pfefferbaum et al., 2013; Ziegler et al., 2012), examinations in younger cohorts may not necessarily capture significant volume losses.

Finally, the region-specific age effects might reflect a differential susceptibility to aging-related processes. More specifically, the strongest association with age was observed in the right SF. Moreover, the significant quadratic association in the left SF indicates an acceleration of atrophy with increasing age. Functionally, the SF has been described to play a role in olfactory processing (Bzdok et al., 2013). Olfactory perception, in turn, is well-known to decrease with increasing age (Attems et al., 2015; Doty & Kamath, 2014), and functional imaging studies reported a lower activation of the amygdala in response to olfactory stimuli in older versus younger cohorts (Cerf-Ducastel & Murphy, 2003; Rolls, Kellerhals, & Nichols, 2015). The observed strong association between age and SF volume may therefore reflect a structural correlate of an age-related decrease in olfactory processing, setting it apart, for example, from emotion processing which is less affected by age (Mather, 2016) and involves all subregions of the amygdala (Bzdok et al., 2013). However, since no information on olfactory or emotion processing is available for the current dataset, such considerations remain conjecture and must await assessment in future studies.

FIGURE 2 Links between the adjusted (sub)volumes of the amygdala (in mm^3) and age (in years). Depicted are the area-specific trajectories (i.e., after removing the variance associated with sex and TIV) for the amygdala as a whole (AMG), as well as the centromedian (CM), laterobasal (LB), and superficial (SF) subareas

4.2 | Lack of sex effects and of age-by-sex interactions

Brain size differed between men and women in the current sample, with significantly larger TIVs in male than female brains. Consequently, raw (sub)volumes of the amygdala were larger in men than in women by up to 11%. However, following correction for TIV, significant sex differences disappeared. While this finding might be somewhat surprising considering that functional imaging studies have

revealed sex differences in amygdala activation in response to several tasks (Filkowski, Olsen, Duda, Wanger, & Sabatinelli, 2017; Fusar-Poli et al., 2009; Hill, Laird, & Robinson, 2014; Stevens & Hamann, 2012—but also see Garcia-Garcia et al., 2016)—our current observation corroborates the outcomes from a recent meta-analysis (Marwha et al., 2017). More specifically, the meta-analysis included 49 studies investigating sex differences in amygdala volume (14 studies with and 35 studies without brain size corrections): When brain size corrections

TABLE 3 Effects of age and sex on (sub)volumes of the amygdala

Side	Area	Age		Age ²		Sex	
		<i>r</i>	<i>T</i>	<i>r</i>	<i>T</i>	Cohen's <i>d</i>	<i>T</i>
Left	AMG	−0.407	−4.342*	−0.197	−1.957#	−0.271	−1.322
	CM	−0.463	−5.086*	−0.207	−2.060#	−0.145	−0.708
	LB	−0.351	−3.654*	−0.162	−1.598	−0.288	−1.401
	SF	−0.455	−4.976*	−0.261	−2.640*	−0.223	−1.089
Right	AMG	−0.450	−4.907*	−0.122	−1.195	−0.140	−0.680
	CM	−0.456	−4.997*	−0.107	−1.048	<0.001	0.001
	LB	−0.405	−4.323*	−0.099	−0.972	−0.172	−0.836
	SF	−0.471	−5.200*	−0.165	−1.629	−0.119	−0.836

AMG = amygdala as a whole; CM = centromedial subarea; LB = laterobasal subarea; SF = superficial subarea; * $p \leq .0125$; # $p < .050$.

were applied, sex differences were only small and not significant. In contrast, without brain size corrections, men had significant larger amygdala volumes than women, and interestingly the magnitude of this sex difference in amygdala volume was comparable to the magnitude of the sex differences in overall brain volume (Marwha et al., 2017). Similarly, another three large-scale analyses (which are not part of the aforementioned meta-analysis) observed only minute effects of sex when brain size was controlled for: More specifically, two of those studies contained more than 800 subjects and concluded that sex effects did not reach significance or explained only very little (about 1%) of the variance (Inano et al., 2013; Jancke, Merillat, Liem, & Hanggi, 2015). The third study contained more than 5,000 subjects (Ritchie et al., 2018) and revealed that, although men had a larger amygdala than women, the effect was only small ($d = 0.18$, bilaterally). Of note, this effect is comparable in size to the currently observed nonsignificant sex difference (left $d = 0.27$; right $d = 0.14$). Similar small and nonsignificant sex effects were observed in the current sample for all subareas of the amygdala. Since all our measures were adjusted for brain size, these findings suggest that apparent sex differences in AMG as well as CM, LB, and SF are due to sex-specific brain size. The current analysis also did not reveal any significant age-by-sex interactions, which suggests that the age-related decline in amygdala (sub)volume tends to follow a similar trajectory in men and women over time. This observation is in line with previous reports of only minute (if any) effects of sex on age-related amygdala decline (Fjell, Westlye, et al., 2009b; Marwha et al., 2017).

4.3 | Potential modulators: Sample characteristics and methodology

The heterogeneity of findings across studies may be due to the characteristics of the study-specific subject sample examined and/or the methodology applied. For example, the pool of subjects of the present study originates from the ICBM project, aimed to create a database of brains free from conditions that impact brain structure (Mazziotta et al., 2009). This led to a strict and extensive set of exclusion criteria and an unusually low inclusion rate (i.e., only 10.7% out of the initial sample who considered themselves “normal” were ultimately included in the ICBM database). In other words, given the high exclusion rate, the current (i.e., extremely healthy) sample differs from most other samples of healthy subjects compiled using less strict criteria. While

less restrictive samples are more representative of the general population, they are also more likely to be affected by clinical conditions (e.g., diabetes) or by preclinical manifestations of anxiety, depression, posttraumatic stress disorder, etc., altogether known to affect amygdala volume and/or aging trajectories (Cherbuin, Sachdev, & Anstey, 2012; De Winter et al., 2016; Fjell, Walhovd, et al., 2009a; Horinek, Varjassova, & Hort, 2007; O'Doherty, Chitty, Saddiqui, Bennett, & Lagopoulos, 2015; Sacher et al., 2012; Zanchi et al., 2017). In addition, study-specific mean ages as well as age ranges are likely to impact (age-related) findings, especially if nonlinear aging trajectories exist (see Fjell, Walhovd, et al., 2009a; Pruessner et al., 2001).

4.4 | Summary and implications for future studies

Our study significantly enhances this field of research by mapping the effects of age on the amygdala, while discriminating between different subareas as guided by micro-structure. Overall, the present findings in this extremely healthy sample suggest that the amygdala loses volume over time, but with area-specific trajectories of volume loss. Follow-up research is warranted to explore the functional relevance of such regional effects and assess, for example, whether age-related anatomical changes correspond to age-related changes in cognitive and emotional processing. Perhaps equally relevant, future longitudinal studies are necessary to confirm the current cross-sectional findings, not only in individuals selected for their excellent health status but also in well-characterized and potentially large-scale normative cohorts. If confirmed, such well-validated results may establish a useful baseline against which measures from various clinical conditions and diseases can be compared. Aberrations in amygdala volumes have been reported, for example, in individuals with high fasting plasma glucose levels (Cherbuin et al., 2012), obesity (Masouleh et al., 2016), dementia and cognitive decline (De Winter et al., 2016; Fjell, Walhovd, et al., 2009a; Horinek et al., 2007; Zanchi et al., 2017), depression (Sacher et al., 2012), and posttraumatic stress disorder (O'Doherty et al., 2015).

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CONFLICT OF INTEREST

There are no actual or potential conflicts of interest.

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