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Article *in* Brain Structure and Function · October 2018

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ORIGINAL ARTICLE

Comparison of bonobo and chimpanzee brain microstructure reveals differences in socio-emotional circuits

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Received: 2 May 2018 / Accepted: 9 September 2018

Abstract

Despite being closely related, bonobos and chimpanzees exhibit several behavioral differences. For instance, studies indicate that chimpanzees are more aggressive, territorial, and risk-taking, while bonobos exhibit greater social tolerance and higher rates of socio-sexual interactions. To elucidate the potential neuroanatomical variation that accompanies these differences, we examined the microstructure of selected brain areas by quantifying the neuropil fraction, a measure of the relative tissue area occupied by structural elements of connectivity (e.g., dendrites, axons, and synapses) versus cell bodies. In bonobos and chimpanzees, we compared neuropil fractions in the nucleus accumbens (NAc; core and shell), amygdala (whole, accessory basal, basal, central and lateral nuclei), anterior cingulate cortex (ACC; dorsal and subgenual), anterior insular cortex (AIC), and primary motor cortex (M1). In the dorsal ACC and frontoinsular cortex (FI) we also quantified numbers of von Economo neurons (VENs), a unique subset of neurons thought to be involved in rapid information processing during social interactions. We predicted that the neuropil fraction and number of VENs in brain regions associated with socio-emotional processing would be higher in bonobos. In support of this hypothesis, we found that bonobos had significantly greater neuropil in the central and accessory basal nuclei of the amygdala, as well as layers V–VI of the subgenual ACC. However, we did not find a difference in the numbers of VENs between the two species. These findings support the conclusion that bonobo and chimpanzee brains differ in the anatomical organization of socio-emotional systems that may reflect species-specific variation in behavior.

Keywords Microstructure · Neuropil · Amygdala · Social cognition · Bonobo · Chimpanzee · Von Economo neurons

Introduction

Bonobos (*Pan paniscus*) and chimpanzees (*Pan troglodytes*) are African great apes and the closest living relatives of humans. Despite their close genetic relatedness to each other (estimated divergence 1–2 million years ago) and striking phenotypic similarities, it has become increasingly clear that bonobos and chimpanzees exhibit several behavioral differences. Bonobos, like chimpanzees, live in fission–fusion societies where females are the dispersing sex (Goodall 1986; Boesch and Boesch-Acherman 2000; Furuichi 2011). Unlike chimpanzees, however, where males are dominant to females (Goodall 1986; Boesch and Boesch-Acherman 2000), in bonobos there is partial female dominance (Furuichi 1997; Vervaecke et al. 2000; Stevens et al. 2007). Furthermore, some have reported that adult chimpanzees engage in more severe aggression, are more risk-taking, and less socially tolerant toward non-group members relative to

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00429-018-1751-9) contains supplementary material, which is available to authorized users.

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Published online: 10 October 2018

bonobos (Goodall 1986; Hare et al. 2007; Haun et al. 2011; Wilson et al. 2014; Tan and Hare 2013). Bonobos, on the other hand, are neophilic, risk-averse (Herrmann et al. 2011; Haun et al. 2011; Rosati and Hare 2012a, b) and show significantly higher levels of adult social play and socio-sexual behaviors compared to chimpanzees (Palagi and Cordoni 2012; Woods and Hare 2011; Wrangham 1993). Bonobos also outperform chimpanzees on tasks related to their sensitivity in responding to socio-communicative cues and theory of mind, whereas chimpanzees perform better on physical cognition tasks (Herrmann et al. 2010; Hopkins et al. 2017).

Studies have examined the proximate mechanisms underlying the reported behavioral variation between bonobos and chimpanzees by identifying species differences in hormone levels (Wobber et al. 2013; Behringer et al. 2014), neurotransmitter systems, neuropeptides and their receptor genes (Donaldson et al. 2008; Hopkins et al. 2012; Staes et al. 2014; Stimpson et al. 2015), as well as neuroanatomy (Rilling and Insel 1999; Schenker et al. 2005; Hopkins et al. 2009, 2017). For example, bonobos and chimpanzees show differences in the timing of urinary thyroid hormone levels during development that may be linked to the distinct ontogenetic changes found between the two species, and potentially reflect the lower intensity of aggression found in bonobos (Behringer et al. 2014). Chimpanzees show a deletion in the gene coding for the vasopressin receptor 1A, which may be associated with lower levels of sociability and sensitivity to socio-communicative cues compared to bonobos (Staes et al. 2015, 2016; Hopkins et al. 2012, 2017). Bonobo brains have a higher density of serotonin transporter-immunoreactive axons in the amygdala, particularly in the basal and central nuclei, potentially modulating a variety of behavioral responses to stimuli that elicit emotional arousal (Stimpson et al. 2015; LeDoux 2007). Studies comparing brain anatomy have also revealed differences between chimpanzees and bonobos in neural systems supporting social cognition. Relative to chimpanzees, bonobos have larger volumes of the anterior insula, frontoinsular cortex, and lateral nucleus of the amygdala (Bauernfeind et al. 2013; Barger et al. 2007). Coupled with species differences in risk aversion (Haun et al. 2011; Rosati and Hare 2012a, b), novelty avoidance (Herrmann et al. 2011), social sensitivity (Herrmann et al. 2010) and severe aggression (Wilson et al. 2014), these findings point to overall differences in (socio-) emotional control between bonobos and chimpanzees.

To determine further if the organization of brain regions involved in social cognition and emotion differ between bonobos and chimpanzees, in this study we examined neuroanatomical variation by comparing neuronal architecture and distribution in histological sections at the microstructural level. One quantitative approach that has been used in previous studies is to measure the proportion of neuropil space in the gray matter from histological sections (Schenker et al. 2008; Spocter et al. 2012). The neuropil is defined as the space between neuronal and glial cell bodies, which is comprised by dendrites, axons, synapses, and microvasculature. Therefore, it provides a measure of connectivity within a region. Microstructural indicators of connectivity have been shown to vary in association with disorders that impact social cognition and affect (Dajani and Uddin 2016; Courchesne and Pierce 2005; Alexander-Bloch et al. 2010; Casanova et al. 2002, 2006). Accordingly, quantification of neuropil space may give insight into species differences in the brain regions supporting these behaviors.

A second approach is to focus on total numbers of specific neuron types. For example, studies have examined von Economo neurons (VENs), which are large bipolar projection neurons located in the frontoinsular cortex (FI) and anterior cingulate cortex (ACC) (Allman et al. 2010). In humans, VENs are hypothesized to be involved in processing networks associated with empathy, social awareness, and self-control (Allman et al. 2005; Kim et al. 2011; Senatorov et al. 2014). Across primates, VENs have been identified in humans, great apes, and macaques (Allman et al. 2010; Evrard et al. 2012; Stimpson et al. 2011), with the greatest densities in humans and African great apes (Nimchinsky et al. 1999). Based on available data, it may be speculated that greater numbers of VENs are associated with specializations for social cognition within and between species (Watson et al. 2006; Butti et al. 2009). For example, quantification of VENs in small samples of captive orangutan brains has revealed the highest numbers in female Sumatran orangutans (*Pongo abelii*) compared to Sumatran males and Bornean males and females (Allman et al. 2010). Given that within orangutans, in the wild females represent the philopatric sex (Singleton and Van Schaik 2002) and are more gregarious with more spatial overlap in Sumatra (Galdikas 1985; Wich et al. 2004; Delgado and van Schaik 2000, 1999), it is possible that variation in numbers of VENs is related to these different levels of sociability. In humans, lower VEN counts are linked to diseases that involve impairments to emotional expression and social cognition, including the behavioral variant of frontotemporal dementia (Kim et al. 2011), agenesis of the corpus callosum (Kaufman et al. 2008), autism spectrum disorder (Butti et al. 2013; Santos et al. 2011), and early-onset schizophrenia (Brüne et al. 2010).

The goals of the present study were to test the hypothesis that bonobos and chimpanzees differ in microstructure of brain regions supporting socio-emotional function, by measuring neuropil fraction, and to test whether bonobos have higher numbers of VENs than chimpanzees. The neuropil fraction was determined for the anterior cingulate cortex (ACC; dorsal and subgenual), anterior insular cortex (AIC) and amygdala (whole and accessory, basal, central and lateral nuclei), as these regions are implicated in empathy, anxiety, and affect (Devinsky et al. 1995; Gu et al. 2013;

Lovero et al. 2009; Davis 1992). We subdivided the ACC because a number of fMRI studies have found that the dorsal and subgenual components are differentially activated during cognitively demanding and affective tasks, respectively (Margulies et al. 2007; Gray and Braver 2002; Holroyd et al. 2004). We hypothesized that a higher neuropil fraction in bonobos would be found in the subgenual compared to the dorsal ACC. We also analyzed the nucleus accumbens (NAc; whole, core, and shell). The NAc, as a whole, is a central generator of motivated behaviors (for review see Floresco 2015). The core of the NAc is most associated with risk-taking (Knutson et al. 2001), whereas the shell is more involved with behavioral control, spatial learning, and memory (Barrot et al. 2002; Ito et al. 2008; Heysieattalab et al. 2016; Kerfoot and Williams 2018). Given the reported species differences, with greater risk-taking and the spatial memory abilities of chimpanzees (Haun et al. 2011; Menzel 1973; Rosati and Hare 2012a, b, but see; Herrmann et al. 2010), we predicted that bonobos might have a higher neuropil fraction in the NAc core, while chimpanzees would have relatively greater neuropil in the NAc shell. The primary motor cortex (M1) and the putamen were also included in the current analysis as they are principally involved in motor control, which is not thought to differ considerably between these two species (Marchand et al. 2008; Graziano 2005; Holdefer and Miller 2002). VENs were quantified in both the ACC and FI.

Materials and methods

Subjects

This study compared postmortem brain samples from 7 bonobos (*Pan paniscus*) and 7 chimpanzees (*Pan troglodytes*) that were age and sex matched (see Table S1). Brains were collected opportunistically after necropsy from apes that died of natural causes at various zoos and research facilities. For some chimpanzees, sections were not available for all brain regions; therefore, data from brain regions of a total of 14 individuals (6 females: mean age at death = 28.3 years; standard deviation (SD) 12.5; range 12–45, and 8 males: mean age at death 20.4 years; SD 5.3; range 11–28) were included to compare to the 7 bonobos (3 females: mean age at death = 29.9 years; SD 16.4; range 12–52, and 4 males: mean age at death = 19.7 years; SD 11.0; range 4–34).

Tissue preparation and Nissl stain

All brains were obtained after death and immersion fixed in 10% formalin within a 14-h postmortem interval. Brain hemispheres were blocked into three large slabs coronally and cryoprotected by immersion in graded sucrose solutions (up to 30%) in PBS, pH 7.4. Tissue blocks were frozen on dry ice, and sectioned at 40 µm on a freezing sliding microtome, with the exception of one bonobo brain that had been sectioned at 100 µm thickness. From these blocks, adjacent sections were collected for histological staining and stored in anatomical order. Every 10th section (spaced 400 µm apart) from each block was mounted on chromalum-subbed slides, stained using 0.5% cresyl violet to visualize cytoarchitecture, and coverslipped with DPX. For this study, only the left hemisphere was analyzed, as right hemisphere samples were not available for all individuals. Therefore, our results should be interpreted with the understanding that hemispheric asymmetry in function has been reported for autonomic processing (for review see Craig 2005), although often such activity is complementary or bilateral with regard to socio-emotional processing (Duerden et al. 2013; Oberlin et al. 2015; Craig 2005).

Neuropil fraction

Neuropil fraction was measured using high-resolution images of Nissl-stained sections. Imaging of the regions of interest was performed with a Zeiss Axioplan 2 photomicroscope (Zeiss, Thornwood, NY) equipped with a Ludl XY motorized stage (Ludl Electronics, Hawthorne, NY), Heidenhain z-axis encoder and an Optronics MicroFire color video camera coupled to a Dell PC using StereoInvestigator software (MBF Bioscience, Williston, VT). Area identification was based on published regional and cytoarchitectural definitions (Bauernfeind et al. 2013; LeDoux 2007; Paus 2001; Groenewegen et al. 1996; Fig. 1a). For each bonobo or chimpanzee brain, three evenly spaced coronal sections were sampled throughout the region of interest (Fig. 1b, c). For each section, regions of interest were contoured under low magnification (2.5× objective lens) underneath a representative portion of the area (for cortical regions this was approximately 3 mm in length along the cortical surface). At least 30 systematic random sampled (SRS) images were taken within the contours of each section using a 20× objective lens, resulting in images at 0.53 pixels/µm resolution (Fig. 1f). Each image was imported into Image J (v.1.32j) and subjected to background subtraction with a rolling ball radius of 50 pixels and then converted to binary by an automated threshold routine (Spocter et al. 2012) (Fig. 1g). Before calculation of the neuropil fraction, images that contained artifacts were removed from the batch and the remaining images were blind-coded to avoid observer bias. We considered the one bonobo brain that was sectioned at 100 µm acceptable for inclusion in neuropil fraction analyses because it has been previously shown that values for imaging of cell profile areas in brain sections reach asymptote around 15 µm (Wree et al. 1982). Furthermore, we ran all analyses both including and excluding this individual and it did not have an impact on the overall pattern of results.

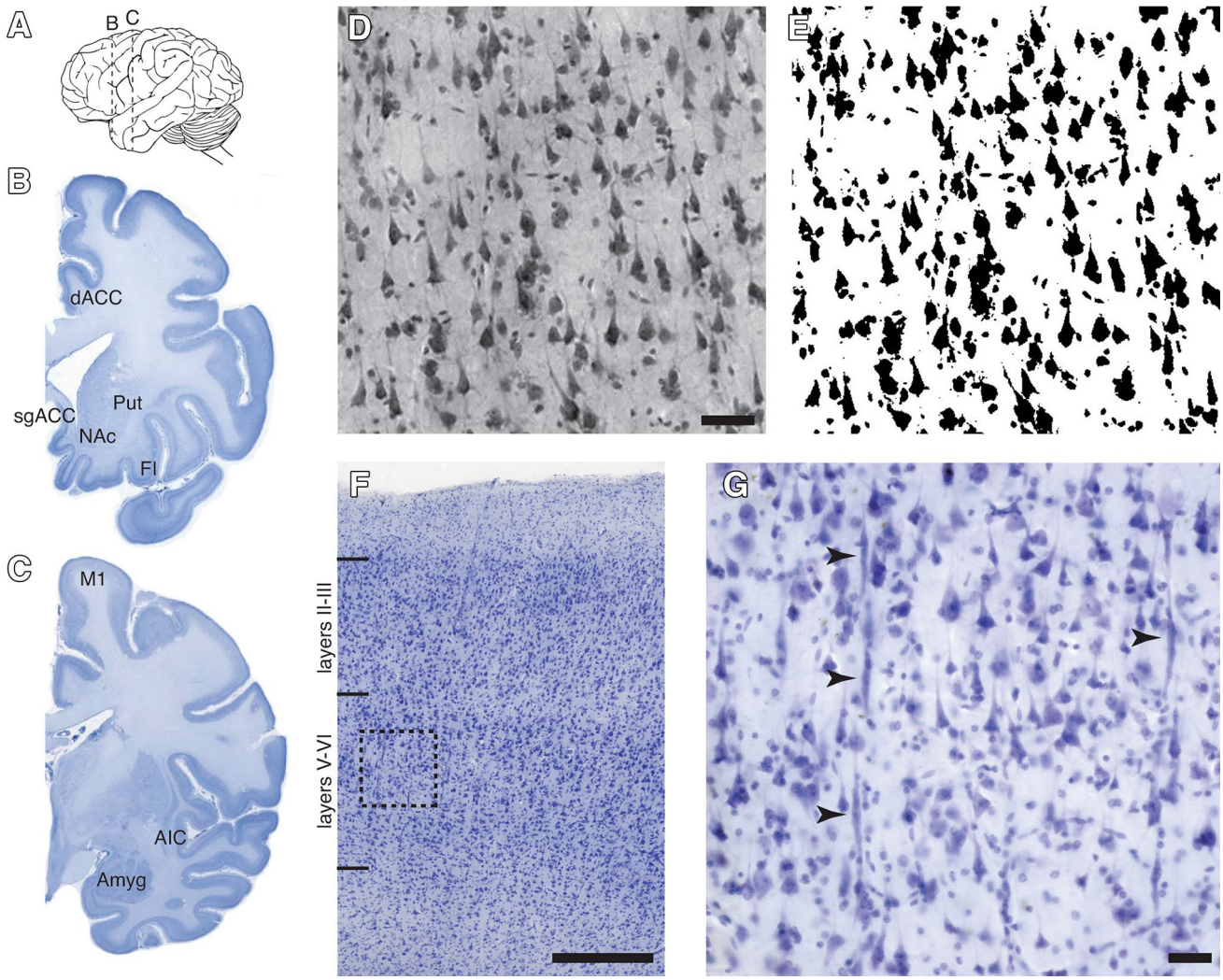

Fig. 1 **a** Lateral view of chimpanzee brain showing location of sections B and C. **b, c** Coronal sections showing regions in the study. **d** An image captured for neuropil fraction measurements from a chimpanzee M1 layers II–III. **e** The binarized output of image D. **f** Fronto-insular cortex in a bonobo. The box indicates the location of higher magnification view of layer V in **g** arrowheads indicate VENs. Scale bars in **f** 1 mm, **d, g** 100 µm

In cortical regions, layers II–III and V–VI were contoured separately. In addition to the whole amygdala, measurements from the accessory, basal, central and lateral nuclei were also collected using anatomical boundaries as previously described (Sah et al. 2003; Stimpson et al. 2015). The ACC was also subdivided into dorsal and subgenual components, which are separated by the corpus callosum (Allman et al. 2001). Finally, the nucleus accumbens was measured whole and subsequently subdivided into its ventromedial and dorsolateral components, which approximately correspond to the shell and core in primates (Friedman et al. 2002). An estimate of inter-rater reliability (IRR) was performed by a second rater retracing at least 3 slides per region of interest from 3 different regions to recalcuate the neuropil fraction independently. IRR was calculated in R using the intraclass coefficient in a two-way mixed model measuring consistency. The IRR cutoff was 0.70, and IRR across all regions was greater than 0.72. Additionally, an analysis of variance (ANOVA; alpha = 0.05) revealed no significant differences between raters.

Von Economo neuron quantification

For each individual, every 10th section that spanned the region of interest was sampled. We examined FI and dorsal ACC. VENs were identified as having a spindle-like shape with a thin cell body giving rise to a single apical and basal dendrite extending in opposite directions. Since VENs are most dense in cortical layer V, only this layer was contoured in each section (see Fig. 1d, e). Within each contour, systematic random sampling (SRS) placement of counting frames was used to quantify neurons using the optical fractionator in StereoInvestigator (software version

11, MBF Bioscience, Wiliston, VT). To quantify VENs, a 100 × 100-µm counting frame was used with a 320 × 320-µm SRS grid. To quantify other layer V neurons, a 40 × 40-µm counting frame was used with a 320 × 320-µm SRS grid. A counting frame height of 6-µm was used and mounted section thickness was measured at every 10th sampling site. Each type of neuron—VEN and "other neuron"—was quantified using a different marker. Glial cells were identified and excluded based on a combination of criteria, including smaller soma size and the absence of stained proximal neurites. The estimated population of total layer V neurons allowed for a calculation of the percentage of VENs within the regions of interest. The Gundersen coefficient of error was obtained for counts of both VENs and "other" neurons and the cutoff was set to 0.1 (Gundersen et al. 1999). A few cases of 0.11 and 0.12 were tolerated for VENs in the ACC due to the scarcity of these cells overall. All slides were blind-coded to avoid observer bias. To increase the sample size, data for two bonobo individuals were taken from Allman et al. 2010 and included in our analysis.

Statistical analysis

We calculated statistical differences in neuropil fraction and VEN numbers between bonobos and chimpanzees using ANOVA models with the EZ ANOVA function of the R package EZ (version 3.3.3, R Core Team 2015). A repeated measures design took into account multiple measures across brain regions per individual. For analysis of neuropil fraction in cortical regions (AIC, dACC, sgACC, and M1) the overall model tested for the effects of region, species, sex and layers (layers II–III versus layers V–VI) and all interactions. If there was a significant interaction effect of species by region, simplified models were run per region to determine those that differed. The follow-up models included species, sex and layers and all two-way and three-way interaction terms. Given the relatively small sample size in relation to the complexity of these models, we reran models excluding sex or layers when they showed no significant main effects or interactions. For subcortical regions (NAc and putamen) the overall model tested for the effects of species, sex and region and all interactions between these terms. If a species by region interaction was significant, follow-up models were analyzed per region including species and sex as factors and their interactions. The amygdala was tested separately from cortical and other subcortical regions and separate models were run for total amygdala and its separate nuclei, testing the effects of species and sex and the interaction between the two. Finally, ANOVA models were analyzed for VEN numbers and percentages in dACC and FI testing for effects of species and sex.

Results

Neuropil fraction

Subcortical regions

Significant species differences in neuropil fraction were found in certain nuclei of the amygdala (Fig. 2). Specifically,

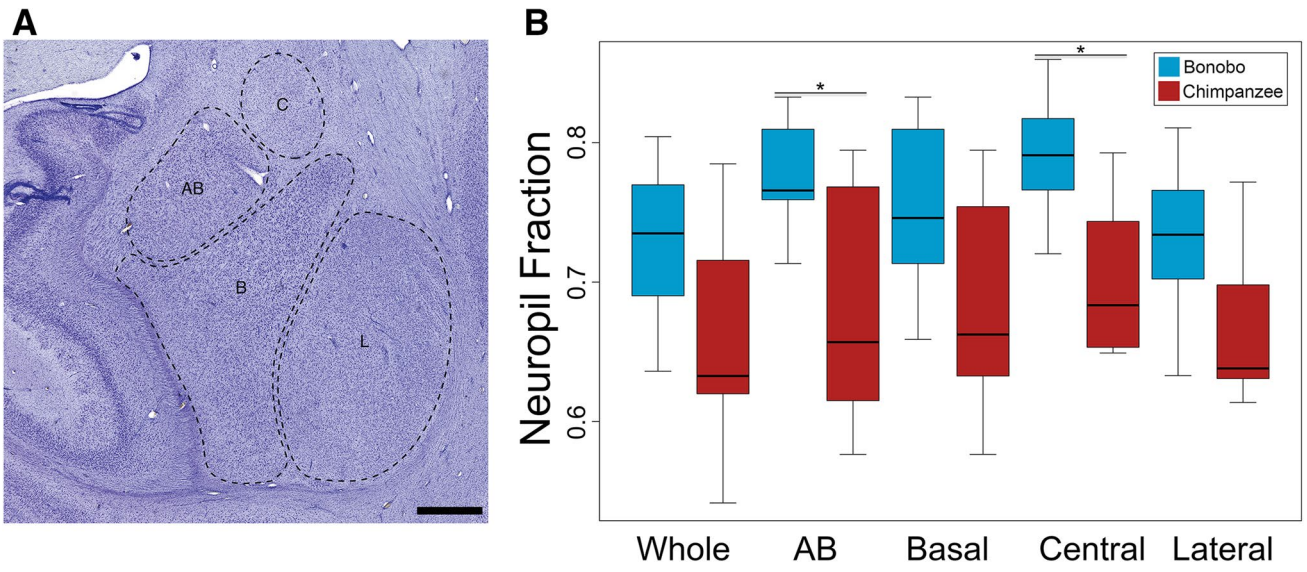

Fig. 2 Amygdala neuropil fraction. **a** Photomicrograph showing amygdala nuclei. *C* central, *AB* accessory basal, *B* basal, *L* lateral. Scale bar = 1 mm. **b** Neuropil fraction results are shown in the whole amygdala as well as its separate nuclei in bonobo (blue) and chimpanzee (red). Bars indicate the interquartile range, whiskers represent range and horizontal lines represent the median. Significant effects are indicated by an asterisk

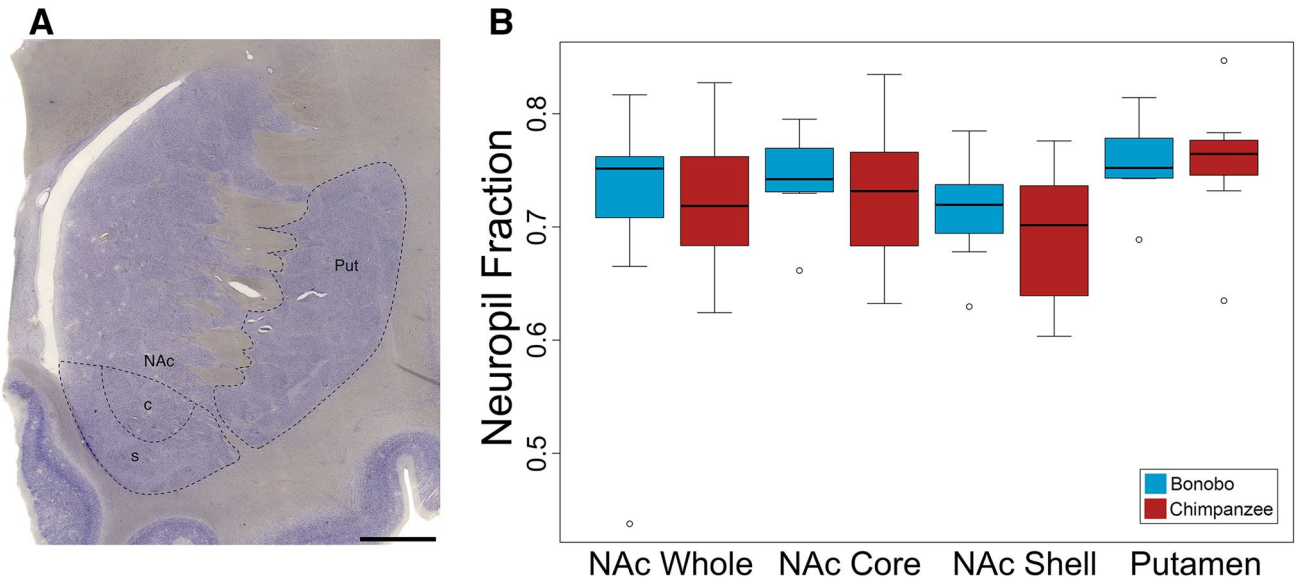

Fig. 3 Basal ganglia neuropil fraction. **(A)** Photomicrograph showing basal ganglia. *Put* putamen, *NAc* nucleus accumbens, *c* core, *s* shell. Scale bar = 2 mm. **b** Neuropil fractions for the whole, core and shell of the NAc in bonobos (blue) and chimpanzees (red) and the putamen. Bars indicate the interquartile range, whiskers represent range and horizontal lines represent the median. Open dots signal outliers

bonobos had significantly more neuropil than chimpanzees in the central ($F(1, 11) = 7.82$, $p = 0.017$) and accessory basal ($F(1, 11) = 5.22$, $p = 0.043$) nuclei. Bonobos also had higher neuropil fraction in the lateral ($F(1, 12) = 3.44$, $p = 0.088$) and basal nuclei ($F(1, 12) = 3.05$, $p = 0.106$) as well as the whole amygdala, ($F(1, 12) = 2.78$, $p = 0.123$), though none of these results reached conventional levels of statistical significance. No significant species or interaction effects were found for neuropil fraction differences in any of the other subcortical regions that were tested (whole NAc: $F(1, 12) = 0.09$, $p = 0.769$; NAc shell: $F(1, 12) = 0.586$, $p = 0.459$; NAc core: $F(1, 12) = 0.209$, $p = 0.656$; putamen: $F(1, 12) = 0.00$, $p = 0.971$) (Fig. 3). No significant sex differences were found (Table S2).

Cortical regions

The overall model for the cerebral cortex revealed a significant three-way interaction between region, species and layer ($F(3,40) = 5.24$, $p = 0.004$). Follow-up analyses within each region revealed a significant species by layer interaction for sgACC ($F(1, 10) = 7.52$, $p = 0.021$) and M1 ($F(1, 10) = 8.38$, $p = 0.016$) (Fig. 4). In sgACC, there was relatively greater neuropil in layers V–VI of bonobos, whereas in chimpanzee layers V–VI had comparatively less neuropil than layers II–III. Conversely, in M1, chimpanzees had more neuropil in layers V–VI than layers II–III. No significant species or interaction effects were found in any of the other regions (Table S3). No significant sex differences were found.

Von Economo neurons

The total number of VENs did not differ significantly between species (ACC: $F(1,11) = 0.11$, $p = 0.743$; FI: $F(1 ,17) = 0.03$, $p = 0.857$) (Fig. 5a). No significant sex differences were found (Table S4). The percentage of VENs also did not differ significantly between bonobos and chimpanzees in any of the regions sampled (ACC: $F(1,10) = 3.13$, $p = 0.107$; FI: $F(1 ,11) = 2.24$, $p = 0.163$) (Fig. 5b).

Discussion

Our results show that, compared to chimpanzees, bonobos have significantly higher neuropil fractions in certain nuclei of the amygdala, as well as relatively greater neuropil in layers V–VI of sgACC. We did not find species differences in the total number or percentage of VENs.

The bonobo amygdala had more neuropil than chimpanzees in the central and accessory basal nuclei. It has been suggested that while the amygdala is involved in emotion generation and behavioral responses in a global sense (Aggleton 1992; Whalen et al. 1998), its individual components are highly functionally distinct (Savonenko et al. 1999; Saygin et al. 2011; Roozendaal and McGaugh 1997; Campbell-Smith et al. 2015; Butler et al. 2017). Central and accessory basal nuclei of the amygdala are involved in generating emotional, physiological, and behavioral responses to fear

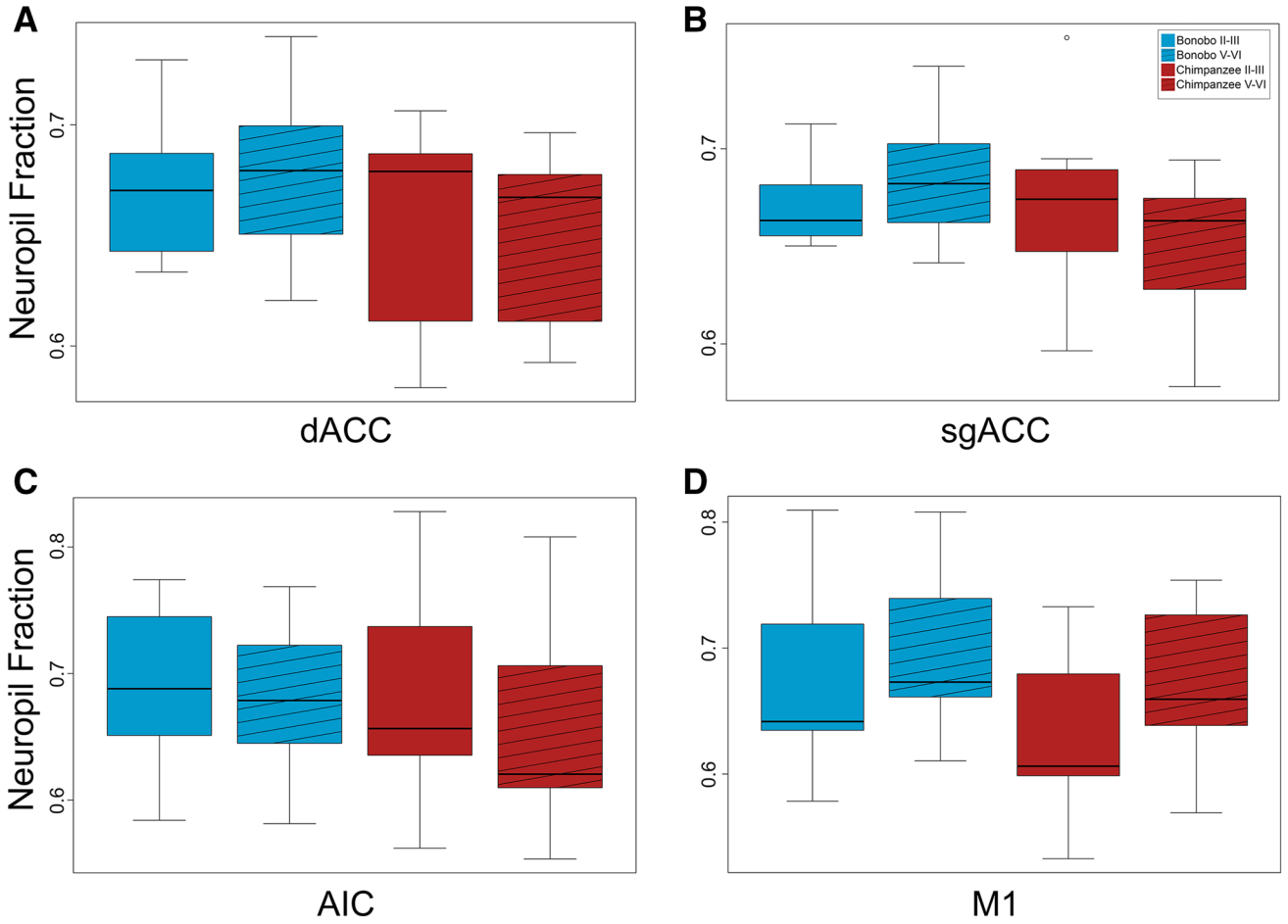

Fig. 4 Cortical neuropil fraction. Neuropil fraction for layers II–III followed by layers V–VI in bonobos (blue) and chimpanzees (red) in **a** the dorsal ACC, **b** subgenual ACC, **c** AIC and **d** M1. Bars indicate the interquartile range, whiskers represent range and horizontal lines represent the median. Open dots signal outliers

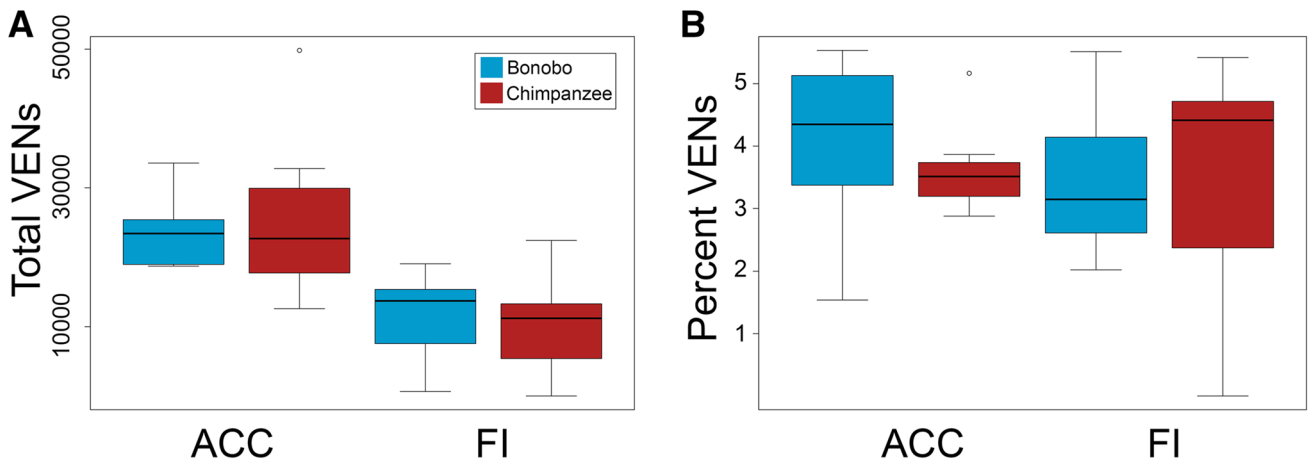

Fig. 5 Von Economo neurons in the ACC and FI. Both **a** total and **b** percentage of VENs were compared in bonobos (blue) and chimpanzees (red). Bars indicate the interquartile range, whiskers represent range and horizontal lines represent the median. Open dots signal outliers

and stress-inducing stimuli (LeDoux et al. 1988; Moga and Gray 1985; Pitkänen et al. 1997; Kalin et al. 2004). The central nucleus is considered the major output center of the amygdala (Yu et al. 2016; Han et al. 2017; for review see; Fadok et al. 2018). Patterns of intra-amygdaloid connections indicate that it integrates sensory and internal-state information primarily from basolateral nuclei (Hrybouski et al. 2016; for review see; Ledoux 2007), and reciprocal connections are found with areas such as the parabranchial nucleus, periaqueductal gray, and dorsomedial nucleus of the hypothalamus, suggesting an autonomic role involved in generating visceral and internal-state stress responses (Veening et al. 1984; Moga and Gray 1985; Rizvi et al. 1991; Amaral and Price 1984). The accessory basal nucleus is an input center, providing information about internal states via projections from the hypothalamus (Pitkänen et al. 1997). The differences in neuropil of these particular amygdala nuclei are especially interesting since they may be associated with variation in sympathetic-autonomic activation related to the reported behavioral differences between these species (Herrmann et al. 2011; Rosati and Hare 2013).

We found no significant variation in neuropil fraction between bonobos and chimpanzees in the lateral and basal nuclei of the amygdala. Nevertheless, bonobos did have higher neuropil fractions in both these nuclei, with statistical differences that approached conventional levels of significance. The relatively small sample size available for the current study should be noted. The lateral nucleus is considered the major input center to the amygdala and is responsible for relaying sensory information from external stimuli (Romanski and LeDoux 1993; Turner and Herkenham 1991; for review see; LeDoux et al. 1990). Neurons in the basal nucleus project to brain regions outside the amygdala, with the responses generated by its connections to striatal areas resulting in active (e.g., running) rather than reactive (e.g., freezing) behaviors, which can oppose central nucleus function and decrease the likelihood of fear-based emotional arousal (Lázaro-Muñoz et al. 2010; Moscarello and LeDoux 2013; Ramirez et al. 2015). Previous studies examining species differences in bonobos and chimpanzees have found significant volumetric differences and variation in serotonergic innervation in these nuclei (Barger et al. 2007; Stimpson et al. 2015). Neuropil fraction, however, may be more reflective of the integrated interconnectivity within the amygdala, complicating precise one-to-one mapping of our results to the function of specific nuclei (LeDoux 2007; Aggleton and Mishkin 1986). For example, the accessory basal nucleus is thought to attenuate central nucleus responses to external stimuli based on internal states via projections to the lateral nucleus (Pitkänen et al. 2002). Thus, the trend for greater neuropil in the lateral nucleus of bonobos might be related to its participation in the overall network of connections among other nuclei of the amygdala, which also show increased neuropil in bonobos.

Recent studies on the functional heterogeneity of the ACC have found its dorsal and subgenual components are involved in "cognitive" versus "affective" information processing, respectively (Margulies et al. 2007; Gray and Braver 2002; Holroyd et al. 2004). While we did not predict species differences in the dorsal subdivision, we did hypothesize that differences would be evident in the sgACC. Interestingly, the greatest species difference was found in layers V–VI of the sgACC, where bonobos had relatively higher neuropil fraction than chimpanzees. Diffusion tensor imaging has previously shown that relative to chimpanzees, bonobos have a larger white matter tract connecting the sgACC to the amygdala (Rilling et al. 2012). Because only the sgACC is directly connected to the amygdala (Etkin et al. 2011; Koski and Paus 2000) and layers V–VI preferentially project to subcortical regions, our results provide further support for the conclusion that there are neural specializations in bonobos selectively localized to the pathway connecting ACC to the amygdala.

No significant species differences were found in the AIC, a region that also plays a role in regulating social emotion and communication (Seeley 2010; Nestor et al. 2003), as well as anxiety (Paulus and Stein 2006; Klumpp et al. 2012; Simmons et al. 2011). Given reported species differences in social affiliative and communication behaviors (Clay et al. 2015; Pollick and de Waal 2007; de Waal 1988; Wrangham 1993; Palagi and Cordoni 2012), we hypothesized that bonobos would also have higher neuropil fractions in this region, but this was not the case. In addition, the stereological quantification of VENs in the present study did not reveal significant differences between bonobos and chimpanzees in numbers or percentages of VENs in the ACC or FI (which is the anterior portion of AIC defined by the presence of VENs).

VENs are a unique subpopulation of cells, hypothesized to be involved in the rapid processing of social information (Allman et al. 2005, 2010). In the absence of an animal model and specific biomarkers, their function and connectivity has been difficult to study directly (Evrard et al. 2012). VENs were initially thought to be uniquely present in only humans and great apes (Nimchinsky et al. 1999; Allman et al. 2005), but have since been identified in elephants and cetaceans (Hakeem et al. 2009; Butti et al. 2009; Hof and Van der Gucht 2007) among several other mammalian species (Evrard et al. 2012; Butti et al. 2014; Raghanti et al. 2015). This has led to the suggestion that their occurrence may be due to convergent evolution for this neuronal phenotype in certain mammalian lineages with large brain sizes (Hof and Van der Gucht 2007). It is possible that they play a role in socio-emotional behaviors in some of the species where they are found (Allman et al. 2005). Interestingly, a comparison of these neurons in hominoids has found that humans have significantly higher proportions of VENs that

express the proteins ATF3 and IL4Ra than other ape species (Stimpson et al. 2011). Such neurochemical variation of VENs may be involved in social and emotional processing capabilities across primates (Nawa and Takei 2006; Dijkstra et al. 2018). It remains a possibility, therefore, that there are differences between bonobo and chimpanzee VENs in terms of gene or protein expression profiles. It should also be noted that due to limitations of tissue availability, our study only analyzed the left hemisphere. Thus, an additional possibility is that greater species differences may be present in the right hemisphere, which has significantly more VENs in humans and great ape species (Allman et al. 2010), consistent with sympathetic-autonomic asymmetry in function in ACC and FI for processing emotion (Wittling et al. 1998; Lorberbaum et al. 2002). In any case, a more comprehensive survey of the biochemical, gene expression, and developmental profile of these neurons in bonobos and chimpanzees is needed, since many of the current hypotheses surrounding VEN function rely only on data from neuronal morphology (Watson et al. 2006; Allman et al. 2005). It should be noted, however, that recent work has shown VEN expression of transcription factors and neurotransmitter-related genes indicative of subcerebral projection and monoaminergic function respectively (Cobos and Seeley 2013; Dijkstra et al. 2018).

In the NAc, we observed no significant species difference, in the region as a whole, or in subdivisions (core and shell). The NAc is involved in a diverse range of functions including attention, risk–reward evaluation, and motor control (Mikhailova et al. 2016; Morrison et al. 2017; Cole and Robbins 1989; Groenewegen et al. 1996). While no major species differences in neuropil fraction were found in the NAc, other studies have reported interesting species-specific variation in this region in the expression of neuropeptides and their receptors that are known to play important roles in regulation of aggression, anxiety (Bosch and Neumann 2012; Neumann and Landgraf 2012), and affiliative behaviors (Campbell 2008; Bales and Carter 2003). For example, variation in oxytocin and vasopressin 1A receptor densities in the NAc have been shown to be associated with social affiliative behaviors in different species of voles (Ross et al. 2009; Keverne and Curley 2004), and interactions between oxytocin and dopamine in the NAc are crucial for pair bonding in female voles (Liu and Wang 2003). Previous studies have shown that bonobos and chimpanzees differ in the genes coding for the OXTR and AVPR1a (Staes et al. 2014), but to date receptor distribution patterns in these brain regions has not been investigated.

No significant species effect was observed in the putamen, which served as a subcortical control in our study. However, there was a significant species by layer effect in the primary motor cortex. Interestingly, chimpanzees had a relatively greater neuropil fraction in layers V–VI compared to layers II–III; this effect might be related to species differences in performance on spatial and motor tasks. While captive bonobos demonstrate skilled tool use capability, only chimpanzees are known for frequent tool use in the wild (Gruber et al. 2010; Goodall 1986). Compared to bonobos, chimpanzees also perform better at tool use and spatial memory tasks (Rosati and Hare 2012a, b; Herrmann et al. 2010) and neuroimaging comparisons between species indicate relative expansion of regions such as M1, the cerebellum, and hippocampus in chimpanzees (Rilling et al. 2012; Hopkins et al. 2009).

In summary, our results demonstrate important differences between bonobos and chimpanzees in the microstructure of brain regions implicated in socio-emotional processing, with the most pronounced species differences found in the amygdala (Pitkänen et al. 1997; Veening et al. 1984). Consistent with previous studies, our results suggest that the amygdala is a major focal point of evolutionary differences in the brain underlying affective behaviors of bonobos and chimpanzees (Barger et al. 2007; Stimpson et al. 2015; Gruber and Clay 2016; Hopkins et al. 2017; Woods and Hare 2011). Further comparative studies between bonobos and chimpanzees concerning the neuromodulation, gene expression and cytoarchitecture of brain regions that regulate emotion will further our understanding of how social systems drive changes in primate brain evolution.

Acknowledgements The authors would like to thank Yerkes National Primate Research Center (supported by National Institutes for Health Grant ORIP/OD P51 OD011132), the National Chimpanzee Brain Resource (supported by National Institutes for Health Grant R24 NS092988-02), Milwaukee County Zoo, Jacksonville Zoo, and veterinary technicians for the donation of specimens. We would also like to thank Dr. Amy Bauernfeind for helpful discussion and Dr. John Allman for providing bonobo samples. This work was supported by the National Science Foundation (SMA-1542848) and the James S. McDonnell Foundation (220020293).

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All applicable international, national, and/or institutional guidelines for the care and use of animals were followed.

References

Aggleton JP (1992) The functional effects of amygdala lesions in humans: a comparison with findings from monkeys. In: Aggleton JP (ed) The amygdala: neurobiological aspects of emotion, memory, and mental dysfunction. Wiley-Liss, New York, pp 485–503

Aggleton JP, Mishkin M (1986) The amygdala: sensory gateway to the emotions. In: Plutchik R, Kellerman H (eds) Emotion: theory, research and experience, vol 3. Academic Press, Orlando, pp 281–299

Alexander-Bloch AF, Gogtay N, Meunier D, Birn R, Clasen L, Lalonde F, Lenroot R, Giedd J, Bullmore ET (2010) Disrupted modularity and local connectivity of brain functional networks in childhood-onset schizophrenia. Front Syst Neurosci 4:147

Allman JM, Hakeem A, Erwin JM, Nimchinsky E, Hof PR (2001) The anterior cingulate cortex. Ann N Y Acad Sci 935:107–117

Allman JM, Watson KK, Tetreault NA, Hakeem AY (2005) Intuition and autism: a possible role for von Economo neurons. Trends Cogn Sci 9:367–373

Allman JM, Tetreault NA, Hakeem AY, Manaye KF, Semendeferi K, Erwin JM, Park S, Goubert V, Hof PR (2010) The von Economo neurons in frontoinsular and anterior cingulate cortex in great apes and humans. Brain Struct Funct 214:495–517

Amaral DG, Price JL (1984) Amygdalo-cortical projections in the monkey (*Macaca fascicularis*). J Comp Neurol 230:465–496

Bales KL, Carter CS (2003) Sex differences and developmental effects of oxytocin on aggression and social behavior in prairie voles (*Microtus ochrogaster*). Horm Behav 44:178–184

Barger N, Stefanacci L, Semendeferi K (2007) A comparative volumetric analysis of the amygdaloid complex and basolateral division in the human and ape brain. Am J Phys Anthropol 134:392–403

Barrot M, Olivier JDA, Perrotti LI et al (2002) CREB activity in the nucleus accumbens shell controls gating of behavioral responses to emotional stimuli. Proc Natl Acad Sci 99:11435–11440

Bauernfeind AL, de Sousa AA, Avasthi T, Dobson SD, Raghanti MA, Lewandowski A, Zilles K, Semendeferi K, Allman JM, Craig AD, Hof PR, Sherwood CC (2013) A volumetric comparison of the insular cortex and its subregions in primates. J Hum Evol 64:263–279

Behringer V, Deschner T, Murtagh R, Stevens JMG, Hohmann G (2014) Age-related changes in thyroid hormone levels of bonobos and chimpanzees indicate heterochrony in development. J Hum Evol 66:83–88

Boesch C, Boesch-Achermann H (2000).The chimpanzees of the taï forest. Behavioural ecology and evolution. Boesch C, Boesch-Achermann H (eds), Oxford University Press New York. p 316

Bosch OJ, Neumann ID (2012) Both oxytocin and vasopressin are mediators of maternal care and aggression in rodents: from central release to sites of action. Horm Behav 61:293–303

Brüne M, Schöbel A, Karau R, Benali A, Faustmann PM, Juckel G, Petrasch-Parwez E (2010) Von Economo neuron density in the anterior cingulate cortex is reduced in early onset schizophrenia. Acta Neuropathol 119:771–778

Butler RK, Ehling S, Barbar M et al (2017) Distinct neuronal populations in the basolateral and central amygdala are activated with acute pain, conditioned fear, and fear-conditioned analgesia. Neurosci Lett 661:11–17

Butti C, Sherwood CC, Hakeem AY, Allman JM, Hof PR (2009) Total number and volume of von Economo neurons in the cerebral cortex of cetaceans. J Comp Neurol 515:243–259

Butti C, Santos M, Uppal N, Hof PR (2013) Von economo neurons: clinical and evolutionary perspectives. Cortex 49(1):312–326

Butti C, Ewan Fordyce R, Raghanti MA, Gu X, Bonar CJ, Wicinski BA, Wong EW, Roman J, Brake A, Eaves E, Spocter MA, Tang CY, Jacobs B, Sherwood CC, Hof PR (2014) The cerebral cortex of the Pygmy Hippopotamus, (Cetartiodactyla, Hippopotamidae): MRI, cytoarchitecture, and neuronal morphology. Anat Rec 297(4):670–700

Campbell A (2008) Attachment, aggression and affiliation: the role of oxytocin in female social behavior. Biol Psychol 77:1–10

Campbell-Smith EJ, Holmes NM, Lingawi NW et al (2015) Oxytocin signaling in basolateral and central amygdala nuclei differentially regulates the acquisition, expression, and extinction of context-conditioned fear in rats. Learn Mem 22:247–257

Casanova MF, Buxhoeveden DP, Switala AE, Roy E (2002) Minicolumnar pathology in autism. Neurology 58:428–432

Casanova MF, van Kooten IAJ, Switala AE et al (2006) Minicolumnar abnormalities in autism. Acta Neuropathol 112:287–303

Clay Z, Archbold J, Zuberbühler K (2015) Functional flexibility in wild bonobo vocal behaviour. PeerJ 3:e1124

Cobos I, Seeley WW (2013) Human von Economo neurons express transcription factors associated with layer V subcerebral projection neurons. Cereb Cortex 25:213–220

Cole BJ, Robbins TW (1989) Effects of 6-hydroxydopamine lesions of the nucleus accumbens septi on performance of a 5-choice serial reaction time task in rats: implications for theories of selective attention and arousal. Behav Brain Res 33:165–179

Courchesne E, Pierce K (2005) Why the frontal cortex in autism might be talking only to itself: local over-connectivity but long-distance disconnection. Curr Opin Neurobiol 15:225–230

Craig AD (2005) Forebrain emotional asymmetry: a neuroanatomical basis? Trends Cogn Sci 9:566–571

Dajani DR, Uddin LQ (2016) Local brain connectivity across development in autism spectrum disorder: a cross-sectional investigation. Autism Res 9:43–54

Davis M (1992) The role of the amygdala in fear and anxiety. Annu Rev Neurosci 15:353–375

De Waal FM (1988) The communicative repertoire of captive bonobos (*Pan paniscus*), compared to that of chimpanzees. Behav 106:183–251

Delgado RA, Van Schaik CP (2000) The behavioral ecology and conservation of the orangutan (*Pongo pygmaeus*): a tale of two islands. Evol Anthropol 9:201–218

Devinsky O, Morrell MJ, Vogt BA (1995) Contributions of anterior cingulate cortex to behaviour. Brain 118:279–306

Dijkstra AA, Lin L-C, Nana AL et al (2018) Von Economo neurons and fork cells: a neurochemical signature linked to monoaminergic function. Cereb Cortex 28:131–144

Donaldson ZR, Kondrashov FA, Putnam A, Bai Y, Stoinski TL, Hammock EAD, Young LJ (2008) Evolution of a behavior-linked microsatellite-containing element in the 5′ flanking region of the primate AVPR1A gene. BMC Evol Biol 8:180

Duerden EG, Arsalidou M, Lee M, Taylor MJ (2013) Lateralization of affective processing in the insula. NeuroImage 78:159–175

Etkin A, Egner T, Kalisch R (2011) Emotional processing in anterior cingulate and medial prefrontal cortex. Trends Cogn Sci 15:85–93

Evrard HC, Forro T, Logothetis NK (2012) Von Economo neurons in the anterior insula of the macaque monkey. Neuron 74:482–489

Fadok JP, Markovic M, Tovote P, Lüthi A (2018) New perspectives on central amygdala function. Curr Opin Neurobiol 49:141–147

Floresco SB (2015) The nucleus accumbens: an interface between cognition, emotion, and action. Annu Rev Psychol 66:25–52

Friedman DP, Aggleton JP, Saunders RC (2002) Comparison of hippocampal, amygdala, and perirhinal projections to the nucleus accumbens: combined anterograde and retrograde tracing study in the Macaque brain. J Comp Neurol 450(4):345–365

Furuichi T (1997) Agonistic interactions and matrifocal dominance rank of wild bonobos (*pan paniscus*) at wamba. Int J Primatol 18:855–875

Furuichi T (2011) Female contributions to the peaceful nature of bonobo society. Evol Anthropol 20:131–142

Galdikas BMF (1985) Orangutan sociality at Tanjung Puting. Am J Primatol 9:101–119

Goodall J (1986) The Chimpanzees of Gombe: patterns of behavior. Harvard University Press, Cambridge

Gray JR, Braver TS (2002) Personality predicts working-memory-related activation in the caudal anterior cingulate cortex. Cogn Affect Behav Neurosci 2:64–75

Graziano M (2005) Arm movements evoked by electrical stimulation in the motor cortex of monkeys. J Neurophysiol 94:4209–4223

Groenewegen HJ, Wright CI, Beijer AV (1996) The nucleus accumbens: gateway for limbic structures to reach the motor system? Prog Brain Res 107:485–511

Gruber T, Clay Z (2016) A comparison between bonobos and chimpanzees: a review and update. Evol Anthropol 25:239–252

Gruber T, Clay Z, Zuberbühler K (2010) A comparison of bonobo and chimpanzee tool use: evidence for a female bias in the Pan lineage. Anim Behav 80(6):1023–1033

Gu X, Hof PR, Friston KJ, Fan J (2013) Anterior insular cortex and emotional awareness. J Comp Neurol 521:3371–3388

Gundersen HJG, Jensen EBV, Kieu K et al (1999) The efficiency of systematic sampling in stereology—reconsidered. J Microsc 193:199–211

Hakeem AY, Sherwood CC, Bonar CJ, Butti C, Hof PR, Allman JM (2009) Von Economo neurons in the elephant brain. Anat Rec 292:242–248

Han W, Tellez LA, Rangel MJ, Motta SC, Zhang X, Perez IO, Canteras NS, Shammah-Lagnado SJ, van den Pol AN, de Araujo IE (2017) Integrated control of predatory hunting by the central nucleus of the amygdala. Cell 168(1–2):311–324.e18

Hare B, Melis AP, Woods V, Hastings S, Wrangham R (2007) Tolerance allows bonobos to outperform chimpanzees on a cooperative task. Curr Biol 17:619–623

Haun DBM, Nawroth C, Call J (2011) Great Apes' risk-taking strategies in a decision making task. PLoS One 6(12):e28801

Herrmann E, Hare B, Call J, Tomasello M (2010) Differences in the cognitive skills of bonobos and chimpanzees. PLoS One 5:2–5

Herrmann E, Hare B, Cissewski J, Tomasello M (2011) A comparison of temperament in nonhuman apes and human infants. Dev Sci 14:1393–1405

Heysieattalab S, Naghdi N, Zarrindast MR et al (2016) The effects of GABAAand NMDA receptors in the shell-accumbens on spatial memory of METH-treated rats. Pharmacol Biochem Behav 142:23–35

Hof PR, Van Der Gucht E (2007) Structure of the cerebral cortex of the humpback whale, *Megaptera novaeangliae* (Cetacea, Mysticeti, Balaenopteridae). Anat Rec 290:1–31

Holdefer RN, Miller LE (2002) Primary motor cortical neurons encode functional muscle synergies. Exp Brain Res 146:233–243

Holroyd CB, Nieuwenhuis S, Yeung N, Nystrom L, Mars RB, Coles MGH, Cohen JD (2004) Dorsal anterior cingulate cortex shows fMRI response to internal and external error signals. Nat Neurosci 7:497–498

Hopkins WD, Lyn H, Cantalupo C (2009) Volumetric and lateralized differences in selected brain regions of chimpanzees (*Pan troglodytes*) and bonobos (*Pan paniscus*). Am J Primatol 71:988–997

Hopkins WD, Donaldson ZR, Young LJ (2012) A polymorphic indel containing the RS3 microsatellite in the 5′ flanking region of the vasopressin V1a receptor gene is associated with chimpanzee (*Pan troglodytes*) personality. Genes Brain Behav 11:552–558

Hopkins WD et al (2017) Social cognition and brain organization in chimpanzees (*Pan troglodytes*) and bonobos (*Pan paniscus*). In: Hare (ed) Bonobos: unique in mind, brain and behavior. Oxford University Press, B

Hrybouski S, Aghamohammadi-Sereshki A, Madan CR et al (2016) Amygdala subnuclei response and connectivity during emotional processing. Neuroimage 133:98–110

Ito R, Robbins TW, Pennartz CM, Everitt BJ (2008) Functional interaction between the hippocampus and nucleus accumbens shell is necessary for the acquisition of appetitive spatial context conditioning. J Neurosci 28:6950–6959

Kalin NH, Shelton SE, Davidson RJ (2004) The role of the central nucleus of the amygdala in mediating fear and anxiety in the primate. J Neurosci 24:5506–5515

Kaufman JA, Paul LK, Manaye KF, Granstedt AE, Hof PR, Hakeem AY, Allmamn JM (2008) Selective reduction of von Economo neuron number in agenesis of the corpus callosum. Acta Neuropathol 116:479–489

Kerfoot EC, Williams CL (2018) Contributions of the nucleus accumbens shell in mediating the enhancement in memory following noradrenergic activation of either the amygdala or hippocampus. Front Pharmacol 9:47

Keverne EB, Curley JP (2004) Vasopressin, oxytocin and social behaviour. Curr Opin Neurobiol 14:777–783

Kim EJ, Sidhu M, Gaus SE, Huang EJ, Hof PR, Miller BL, DeArmond SJ, Seeley WW (2011) Selective frontoinsular von Economo neuron and fork cell loss in early behavioral variant frontotemporal dementia. Cereb Cortex 22:251–259

Klumpp H, Angstadt M, Phan KL (2012) Insula reactivity and connectivity to anterior cingulate cortex when processing threat in generalized social anxiety disorder. Biol Psychol 89:273–276

Knutson B, Adams CM, Fong GW, Hommer D (2001) Anticipation of increasing monetary reward selectively recruits nucleus accumbens. J Neurosci 21:RC159

Koski L, Paus T (2000) Functional connectivity of the anterior cingulate cortex within the human frontal lobe: a brain-mapping meta-analysis. Exp brain Res 133:55–65

Lázaro-Muñoz G, LeDoux JE, Cain CK (2010) Sidman instrumental avoidance initially depends on lateral and basal amygdala and is constrained by central amygdala-mediated pavlovian processes. Biol Psychiatry 67:1120–1127

LeDoux J (2007) The amygdala. Curr Biol 17:868–874

LeDoux JE, Iwata J, Cicchetti P, Reis DJ (1988) Different projections of the central amygdaloid nucleus mediate autonomic and behavioral correlates of conditioned fear. J Neurosci 8:2517–2529

LeDoux J, Ciocchetti P, Xagoraris A, Romanski L (1990) The lateral amygdaloid nucleus: sensory interface of the amygdala in fear conditioning. J Neurosci 10(4):1062–1069

Liu Y, Wang ZX (2003) Nucleus accumbens oxytocin and dopamine interact to regulate pair bond formation in female prairie voles. Neurosci 121:537–544

Lorberbaum JP, Newman JD, Horwitz AR et al (2002) A potential role for thalamocingulate circuitry in human maternal behavior. Biol Psychiatry 51:431–445

Lovero KL, Simmons AN, Aron JL, Paulus MP (2009) Anterior insular cortex anticipates impending stimulus significance. Neuroimage 45:976–983

Marchand WR, Lee JN, Thatcher JW, Hsu EW, Rashkin E, Suchy Y, Chelune G, Starr J, Barbera SS (2008) Putamen coactivation during motor task execution. Neuroreport 19:957–960

Margulies DS, Kelly AMC, Uddin LQ, Biswal BB, Castellanos FX, Milham MP (2007) Mapping the functional connectivity of anterior cingulate cortex. Neuroimage 37:579–588

Menzel EW (1973) Chimpanzee spatial memory organization. Science 82:943–945

Mikhailova MA, Bass CE, Grinevich VP et al (2016) Optogenetically-induced tonic dopamine release from VTA-nucleus accumbens projections inhibits reward consummatory behaviors. Neuroscience 333:54–64

Moga MM, Gray TS (1985) Evidence for corticotropin-releasing factor, neurotensin, and somatostatin in the neural pathway from the central nucleus of the amygdala to the parabrachial nucleus. J Comp Neurol 241:275–284

Morrison SE, McGinty VB, du Hoffmann J, Nicola SM (2017) Limbic-motor integration by neural excitations and inhibitions in the nucleus accumbens. J Neurophysiol 118(5):2549–2567

Moscarello JM, LeDoux JE (2013) Active avoidance learning requires prefrontal suppression of amygdala-mediated defensive reactions. J Neurosci 33:3815–3823

Nawa H, Takei N (2006) Recent progress in animal modeling of immune inflammatory processes in schizophrenia: implication of specific cytokines. Neurosci Res 56:2–13

Nestor PJ, Graham NL, Fryer TD, Williams GB, Patterson K, Hodges JR (2003) Progressive non-fluent aphasia is associated with hypometabolism centered on the left anterior insula. Brain 126:2406–2418

Neumann ID, Landgraf R (2012) Balance of brain oxytocin and vasopressin: implications for anxiety, depression, and social behaviors. Trends Neurosci 35:649–659

Nimchinsky EA, Gilissen E, Allman JM, Perl DP, Erwin JM, Hof PR (1999) A neuronal morphologic type unique to humans and great apes. Proc Natl Acad Sci 96:5268–5273

Oberlin BG, Dzemidzic M, Tran SM, Soeurt CM, O'Connor SJ, Yoder KY, Kareken DA (2015) Beer self-administration provokes lateralized nucleus accumbens dopamine release in male heavy drinkers. Psychopharmacology 232(5):861–870

Palagi E, Cordoni G (2012) The right time to happen: play developmental divergence in the two *Pan* species. PLoS One 7:e52767

Paulus MP, Stein MB (2006) An insular view of anxiety. Biol Psychiatry 60:383–387

Paus T (2001) Primate anterior cingulate cortex: where motor control, drive and cognition interface. Nat Rev Neurosci 2:417–424

Pitkänen A, Savander V, LeDoux JE (1997) Organization of intra-amygdaloid circuitries in the rat: An emerging framework for understanding functions of the amygdala. Trends Neurosci 20:517–523

Pitkänen A, Kelly JL, Amaral DG (2002) Projections from the lateral, basal, and accessory basal nuclei of the amygdala to the entorhinal cortex in the macaque monkey. Hippocampus 12:186–205

Pollick AS, de Waal FBM (2007) Ape gestures and language evolution. Proc Natl Acad Sci 104:8184–8189

Raghanti MA, Spurlock LB, Robert Treichler F, Weigel SE, Stimmelmayr R, Butti C, Thewissen JMGH, Hof PR (2015) An analysis of von Economo neurons in the cerebral cortex of cetaceans, artiodactyls, and perissodactyls. Brain Struct Funct 220:2303–2314

Ramirez F, Moscarello JM, LeDoux JE, Sears RM (2015) Active avoidance requires a serial basal amygdala to nucleus accumbens shell circuit. J Neurosci 35:3470–3477

Rilling JK, Insel TR (1999) The primate neocortex in comparative perspective using magnetic resonance imaging. J Hum Evol 37:191–223

Rilling JK, Scholz J, Preuss TM, Glasser MF, Errangi BK, Behrens TE (2012) Differences between chimpanzees and bonobos in neural systems supporting social cognition. Soc Cogn Affect Neurosci 7:369–379

Rizvi TA, Ennis M, Behbehani MM, Shipley MT (1991) Connections between the central nucleus of the amygdala and the midbrain periaqueductal gray: Topography and reciprocity. J Comp Neurol 303:121–131

Romanski LM, LeDoux JE (1993) Information cascade from primary auditory cortex to the amygdala: corticocortical and corticoamygdaloid projections of temporal cortex in the rat. Cereb Cortex 3(6):515–532

Roozendaal B, McGaugh JL (1997) Basolateral amygdala lesions block the memory-enhancing effect of glucocorticoid administration in the dorsal hippocampus of rats. Eur J Neurosci 9:76–83

Rosati AG, Hare B (2012a) Chimpanzees and bonobos exhibit divergent spatial memory development. Dev Sci 15:840–853

Rosati AG, Hare B (2012b) Decision making across social contexts: competition increases preferences for risk in chimpanzees and bonobos. Anim Behav 84:869–879

Rosati AG, Hare B (2013) Chimpanzees and bonobos exhibit emotional responses to decision outcomes. PLoS One 8(5):e63058

Ross HE, Freeman SM, Spiegel LL, Ren X, Terwilliger EF, Young LJ (2009) Variation in oxytocin receptor density in the nucleus accumbens has differential effects on affiliative behaviors in monogamous and polygamous voles. J Neurosci 29:1312–1318

Sah P, Faber ES, Lopez DA, Power J (2003) The amygdaloid complex: anatomy and physiology. Physiol Rev 83:803–834

Santos M, Uppal N, Butti C, Wicinski B, Schmeidler J, Giannakopoulos P, Heinsen H, Schmitz C, Hof PR (2011) von Economo neurons in autism: a stereologic study of the frontoinsular cortex in children. Brain Res 1380:206–217

Savonenko A, Filipkowski RK, Werka T, Zielinski K, Kaczmarek L (1999) Defensive conditioning-related functional heterogeneity among nuclei of the rat amygdala revealed by c-Fos mapping. Neurosci 94:723–733

Saygin ZM, Osher DE, Augustinack J, Fischl B, Gabrieli JDE (2011) Connectivity-based segmentation of human amygdala nuclei using probabilistic tractography. Neuroimage 56:1353–1361

Schenker NM, Desgouttes AM, Semendeferi K (2005) Neural connectivity and cortical substrates of cognition in hominoids. J Hum Evol 49:547–569

Schenker NM, Buxhoeveden DP, Blackmon WL, Amunts K, Zilles K, Semendeferi K (2008) A comparative quantitative analysis of cytoarchitecture and minicolumnar organization in Broca's area in humans and great apes. J Comp Neurol 510:117–128

Seeley WW (2010) Anterior insula degeneration in frontotemporal dementia. Brain Struct Funct 5–6:465–475

Senatorov VV, Damadzic R, Mann CL, Schwandt ML, George DT, Hommer DW, Heilig M, Momenan R (2014) Reduced anterior insula, enlarged amygdala in alcoholism and associated depleted von Economo neurons. Brain 138:69–79

Simmons AN, Stein MB, Strigo IA, Arce E, Hitchcock C, Paulus MP (2011) Anxiety positive subjects show altered processing in the anterior insula during anticipation of negative stimuli. Hum Brain Mapp 32:1836–1846

Singleton I, Van Schaik CP (2002) The social organization of a population of Sumatran orang-utans. Folia Primatol 73:1–20

Spocter MA, Hopkins WD, Barks SK, Bianchi S, Hehmeyer AE, Anderson SM, Stimpson CD, Fobbs AJ, Hof PR, Sherwood CC (2012) Neuropil distribution in the cerebral cortex differs between humans and chimpanzees. J Comp Neurol 520:2917–2929

Staes N, Stevens JMG, Helsen P, Hillyer M, Korody M, Eens M (2014) Oxytocin and vasopressin receptor gene variation as a proximate base for inter- and intraspecific behavioral differences in bonobos and chimpanzees. PLoS One 9:1–9

Staes N, Koski SE, Helsen P, Fransen E, Eens M, Stevens JMG (2015) Chimpanzee sociability is associated with vasopressin (Avpr1a) but not oxytocin receptor gene (OXTR) variation. Horm Behavior 75:84–90

Staes N, Weiss A, Helsen P, Korody M, Eens M, Stevens JMG (2016) Bonobo personality traits are heritable and associated with vasopressin receptor gene 1a variation. Sci Rep 6(1):38193

Stevens JMG, Vervaecke H, De Vries H, Van Elsacker L (2007) Sex differences in the steepness of dominance hierarchies in captive bonobo groups. Int J Primatol 28:1417–1430

Stimpson CD, Tetreault NA, Allman JM, Jacobs B, Butti C, Hof PR, Sherwood CC (2011) Biochemical specificity of Von Economo neurons in hominoids. Am J Hum Biol 23:22–28

Stimpson CD, Barger N, Taglialatela JP, Gendron-Fitzpatrick A, Hof PR, Hopkins WD, Sherwood CC (2015) Differential serotonergic innervation of the amygdala in bonobos and chimpanzees. Soc Cogn Affect Neurosci 11:413–422

Tan J, Hare B (2013) Bonobos share with strangers. PLoS One 8(1):e51922

Turner BH, Herkenham M (1991) Thalamoamygdaloid projections in the rat: a test of the amygdala's role in sensory processing. J Comp Neurol 313:295–325

Van Schaik CP (1999) The socioecology of fission-fusion sociality in orangutans. Primates 40:69–86

Veening JG, Swanson LW, Sawchenko PE (1984) The organization of projections from the central nucleus of the amygdala to brainstem sites involved in central autonomic regulation: a combined retrograde transport-immunohistochemical study. Brain Res 303:337–357

Vervaecke H, De Vries H, Van Elsacker L (2000) Dominance and its behavioral measures in a captive group of bonobos (*Pan paniscus*). Int J Primatol 21:47–68

Watson KK, Jones TK, Allman JM (2006) Dendritic architecture of the von economo neurons. Neurosci 141:1107–1112

Whalen PJ, Rauch SL, Etcoff NL, McInerney SC, Lee MB, Jenike MA (1998) Masked presentations of emotional facial expressions modulate amygdala activity without explicit knowledge. J Neurosci 18:411–418

Wich SA, Utami-Atmoko SS, Mitra Setia T, Rijksen HD, Schürmann C, van Hoof JARAM, van Schaik CP (2004) Life history of wild sumatran orangutans (*Pongo abelii*). J Hum Evol 47:385–398

Wilson ML, Boesch C, Fruth B et al (2014) Lethal aggression in Pan is better explained by adaptive strategies than human impacts. Nature 513:414–417

Wittling W, Block A, Schweiger E, Genzel S (1998) Hemisphere asymmetry in sympathetic control of the human myocardium. Brain Cogn 38:17–35

Wobber V, Hare B, Lipson S, Wrangham R, Ellison P (2013) Different ontogenetic patterns of testosterone production reflect divergent male reproductive strategies in chimpanzees and bonobos. Physiol Behav 116–117:44–53

Woods V, Hare B (2011) Bonobo but not chimpanzee infants use sociosexual contact with peers. Primates 52:111–116

Wrangham RW (1993) The evolution of sexuality in chimpanzees and bonobos. Hum Nat 4:47–79

Wree A, Schleicher A, Zilles K (1982) Estimation of volume fractions in nervous tissue with an image analyzer. J Neurosci Methods 6:29–43

Yu K, Garcia da Silva P, Albeanu DF, Li B (2016) Central amygdala somatostatin neurons gate passive and active defensive behaviors. J Neurosci 36:6488–6496