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Morphological Characterization of the African Giant Rat (*Cricetomys gambianus*, Waterhouse) Brain Across Age Groups: Gross Features of Cortices

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Summary: This experiment was designed to investigate the morphological characterization of the brain cortices of African giant rats, AGR (*Cricetomys gambianus*, Waterhouse) across age groups as related to function. A total of 15 male AGR were used for this study comprising of 5 neonates, 5 juveniles and 5 adults. Brains were described as having typical rodent features; the falx cerebri, the dura modification of interest, was partly inserted between the lobes of the olfactory bulb and extended towards the corpus callosum. Gross parameters extrapolated include cerebral and cerebellar cortical dimensions using a one-way ANOVA ($p \leq 0.05$). Most values showed highest significant value bias for juveniles over adults and neonates. The average brain weight was 5.60±0.06g, 4.64±0.17g and 0.62±0.08g; cortex volume: 2.84±0.04cm^3, 3.16±0.10cm^3 and 0.23±0.02cm^3 and antero-posterior dimensions: 11.93±0.26mm, 14.54±0.22mm and 6.00±0.16mm for adult, juvenile and neonates respectively. There was however adult bias in the cerebellum weight (0.83±0.02g, 0.76±0.02g and 0.04±0.02g); vermis length (13.23±0.32mm, 11.27±0.014mm and 0.24±0.02mm) and the antero-posterior length values (8.79±0.19mm, 6.97±0.03mm and 0.29±0.01mm) for adults, juveniles and neonates AGR respectively. Cortical parameters were related as a function of the brain development and plasticity, while age was described to play functional roles in intelligence determination of the AGR. The result of this study will be useful as baseline information for post mortem studies, medical imaging and useful as diagnostic tool for future research work on the AGR brain.

Keywords: African giant rats, Brain, Morphology, Cerebrum, Cerebellum, Olfactory bulb

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INTRODUCTION

The brain cortices i.e. cerebrum and cerebellum are regions known for the control of cognition, memory and coordination (Ibe *et al.*, 2014). The African giant rat (AGR) is a subject of great media and scientific reviews in the last decade owing largely to its sheer size, olfactory acuity with applications in landmine detection and tuberculosis diagnosis (Weetjens *et al.*, 2009). In recent times, work has been ongoing to link the brain morphology to the functional aspects of different parts of the brain (Nzalak *et al.*, 2005; Ibe *et al.*, 2010 & 2014; Olude *et al.*, 2014a&b). Therefore, this study seeks to investigate and describe the useful morphometric parameters of the brain cortices of the AGR to evaluate functional capabilities across age groups and proffer which age group of this rodent is best suited for research.

MATERIALS AND METHODS

Fifteen male rats consisting of five Neonates, five Juvenile and five Adult AGRs were utilized to study gross morphometric characteristics of the AGR brain. Age groups were estimated in accordance to Ajayi (1974) (Neonates: 0–70g; Juveniles: >70g but <500g; Adult: >500g). Sedation was achieved using chloroform inhalation. Morphometric characteristics of the body weights were ascertained for each rat using a digital electronic balance, with a sensitivity of 0.01g. Intracardiac perfusion was carried out first with normal saline then with 4% paraformaldehyde (PFA) through the left ventricle and a snip at the right atrium (Olopade *et al.*, 2011; Mustapha *et al.*, 2014). Brains were harvested after removal of the bony cranium, weighed and post-fixed in perfusion solution. Cortices were severed and weighed. Gross observation was done using hand lens and the naked eye.

Definitions of gross anatomical structures were drawn from Anatomy of the Domestic Rat (Hebel and Stromberg, 1975). This include:

Brain weight absolute (g): weight of the whole dissected brain without the meninges

Body weight (kg): weight of the rodent in the nearest kilogram

Relative brain weight: weight of brain parts divided by the total brain weight, multiplied by 100

Cerebellum weight (g): weight of the dissected cerebellum (grams)

Cerebellar weight relative: cerebellar weight/brain weight, multiplied by 100

Cerebral weight relative: cerebral weight /brain weight, multiplied by 100
Maximum hemisphere width (mm): maximum width of the lobes of the cerebellum from left to right hemispheres
Vermis length (mm): maximum rostro-caudal length of the cerebellar vermis
Antero-posterior (A-P) length (cm): maximum dorso-ventral length of the dissected cerebellar cortex.
Maximum cortex width (mm): maximum length across the most lateral portion of the parietal lobes of the cerebral cortex.
Maximum cortex length (mm): the maximum length from the tip of the frontal lobe to the caudal most portion of the occipital lobe of the cerebral cortex.
Cortex volume (cm^3): volume of displaced fluid from a measuring cylinder by the cerebral cortex dissected at the cerebral peduncle.
Cortex A-P length (mm): maximum thickness of the dissected cerebral cortex.
Left olfactory bulb length (LOB) (cm): length of the left olfactory bulb from the tip of the bulb to the rhinal sulcus.
Right olfactory bulb length (ROB) (cm): length of the right olfactory bulb from the tip of the bulb to the rhinal sulcus.

Statistical Analysis
Data are presented as Mean ± SEM. Statistical analysis was done with one- way ANOVA using the SPSS for windows version 16 and statistical significance was set at $p \leq 0.05$

RESULTS

Body brain parameters across age groups

The mean brain weights were 5.60±0.06g, 4.64±0.17g and 0.62±0.08g, while the mean body weights were 1010.00±25.10g, 343.11±17.78g and 21.65±2.40g for adults, juvenile and neonates respectively. The relative brain to body weight index was found to be 0.56±0.01, 1.36±0.06 and 2.85±0.16, being significantly highest in neonates and lowest in the adult group. All the parameters were statistically significant across age groups, with adult having the largest values followed by juveniles except the relative brain:body weight (Table 1).
The brain was grossly lissencephalic in neonates and juveniles but showed slight gyrencephaly in the putative caudomedial and visual cortex in adults (Fig.1a-c). The dura meninx appeared typical as a transparent colourless membrane

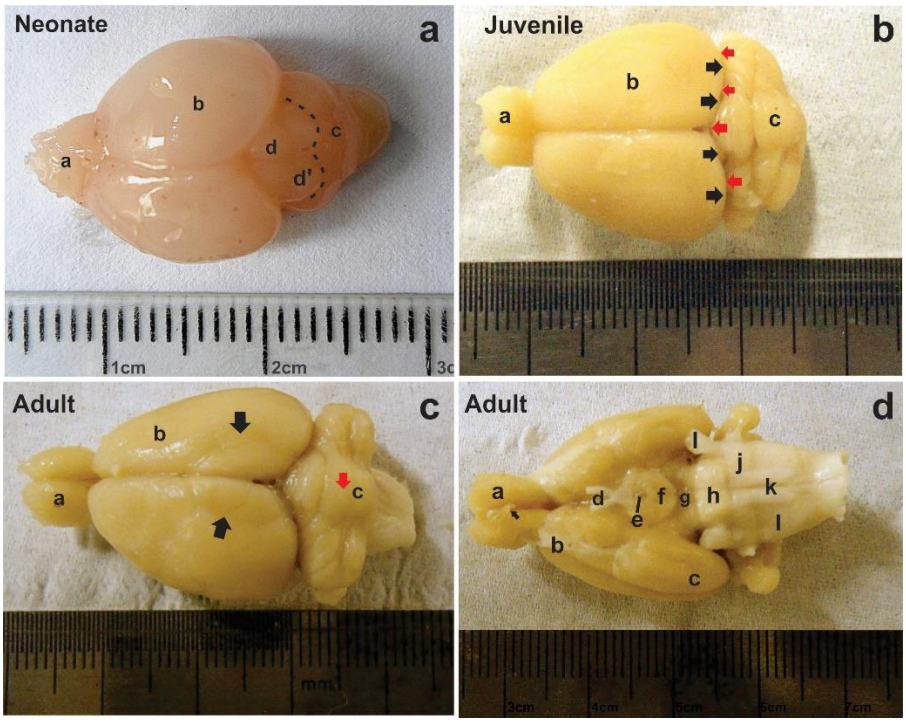

Figure 1: (a) Photograph of neonate AGR brain showing the fully extracted dorsal view. Note the separation of the cortices by the mesencephalic tectum delieanated at the caudal extent by broken dotted lines. a = olfactory bulb, b = cerebral cortex, c = cerebellum, d = rostral colliculus, d' = caudal colliculus. **(b)**Picture showing the fully extracted dorsal view of a juvenile AGR brain with lissencephalic conformity and apposed cerebral and cerebellar cortices (black and red arrows). a = olfactory bulb, b = cerebral cortex, c = cerebellum. (**c)** Picture showing the fully extracted dorsal view of an adult AGR brain. The putative caudomedial visual cortex shows slight gyrencephally (black arrows). a = olfactory bulb, b = cerebral cortex, c = cerebellum. Note the cerebellar vermis (red arrow). (**d)** Picture showing the fully extracted ventral view of an adult AGR brain. a = olfactory bulb, b = olfactory tract, c = priform lobe, d = optic nerve, e = stalk of hypophysis cerebri, f = mamillary body, g = interpenduncular fossa h = pons, i = trigeminal nerve (cranial nerve V), j = trapezoid body k = pyramid, l = medulla oblongata. Note the insertion of falx cerebri par bulbous olfactorius (black arrow).

Table 1: Mean Body Parameters Across AGR Age Groups

Parameters	Adult (n=5)	Juvenile (n=5)	Neonate (n=5)
Brain weight (g)	5.60±0.06[a]	4.64±0.17[b]	0.62±0.08[c]
Body weight (g)	1010.00±25.10[a]	343.11±17.78[b]	21.65±2.40[c]
Relative brain weight (%)	0.56±0.01[c]	1.36±0.06[b]	2.85±0.16[a]

Means with same superscript letters are not significantly different at p≤0.05. Adult had significantly higher brain weight and body weight than the juvenile and neonate stages (p≤0.05). However, neonate stage significantly had higher relative brain weight than juvenile and adult stages (p≤0.05)

Table 2: Mean Cerebral Cortical Parameters Across AGR Age Groups

Parameters	Adult (n=5)	Juvenile (n=5)	Neonate (n=5)
Max cortex width (mm)	19.27±0.21[b]	20.67±0.18[a]	11.75±0.58[c]
Max cortex length (mm)	17.81±0.03[a]	18.93±0.39[a]	8.13±0.81[b]
Cortex volume (cm^3)	2.84±0.04[b]	3.16±0.10[a]	0.23±0.02[c]
Cortex A-P length (mm)	11.93±0.26[b]	14.54±0.22[a]	6.00±0.16[c]
LOB (cm)	6.43±0.24[b]	7.85±0.57[a]	3.25±0.19[c]
ROB (cm)	6.49±0.33[a]	7.51±0.57[a]	3.13±0.24[b]

Means with same superscript letters are not significantly different at p≤0.05. Juveniles had significantly higher max cortex width, cortex volume, Cortex A-P and LOB than adults and neonates stages (p≤0.05). However, there is no significant difference between adult and juvenile in their max cortex length and ROB (p>0.05) but different from the neonate stage (p≤0.05).

Table 3: Mean Cerebellar Cortical Parameters Across AGR Age Groups

Parameter	Adult (n=5)	Juvenile (n=5)	Neonate (n=5)
Brain weight absolute (g)	6.08±0.22[a]	5.02±0.03[b]	0.61±0.10[c]
Cerebellum weight (g)	0.83±0.02[a]	0.76±0.02[b]	0.04±0.02[c]
Cerebellar weight relative (g)	0.14±0.01[a]	0.15±0.003[a]	0.12±0.005[b]
Maximum hemisphere width (mm)	17.08±0.37[a]	16.76±0.16[a]	0.75±0.04[b]
Vermis length (mm)	13.23±0.32[a]	11.27±0.014[b]	0.24±0.02[c]
Antero-Posterior (A-P) Length (mm)	8.79±0.19[a]	6.97±0.03[b]	0.29±0.01[c]
Relative brain weight (%)	0.75±0.04[b]	0.97±0.01[b]	2.77±0.19[a]

Means with same superscript letters are not significantly different at p≤0.05. Adult AGR had significantly higher body weight, brain weight, absolute brain weight, vermis length, antero-posterior (A-P) length and relative brain weight than the juvenile and neonate (p≤ 0.05). However, there is no significant difference between adult and juvenile in their cerebellar weight and relative weight (p>0.05) but different from the neonate stage (p≤ 0.05).

which turned slightly whitish upon post fixation in PFA. The modification of the dura of interest was the falx cerebri which was partly inserted between the lobes of the olfactory bulb (OB) extending towards the corpus callosum. This feature made the bulb easily destroyed on removal of the brain and thus, the falx cerebri must be severed to successfully harvest the olfactory bulb along with the whole brain.

The olfactory bulbs were relatively big, making up about 25% of the brain size in juvenile and adult age groups. Neonate OB was relatively underdeveloped and was fragile to handle as was all the other neonatal brain parts. The OB structure lie in the cribriform fossa of the ethmoid bone. The piriform area was observed to be a conspicuously pear shaped cortical region ventral to the middle of the rhinal sulcus region at the temporal pole of the cerebrum (Fig.1d).

The cerebrum was observed to be the largest part of the brain, and laid immediately caudal to the OB, rostral to the cerebellum and dorsal to the brain stem. It accounted for about 55% of the total brain length and over 70% of the forebrain length in all the groups. The rhinal sulcus or fissure was found on the ventrolateral aspect of the cerebrum separated by the phylogenetically more recent neocortex. The maximum cortex widths were 19.27±0.21mm, 20.67±0.18mm and 11.75±0.58mm while maximum cortex lengths were 17.81±0.03mm, 18.93±0.39mm and 8.13±0.81mm for adults, juveniles and neonates respectively. The cortex volumes and A -P length across age groups (adults, juveniles and neonates) were 2.84±0.04cm3, 3.16±0.10 cm3 and 0.23±0.02 cm3; and 11.93±0.26mm, 14.54±0.22mm and 6.00±0.16mm respectively. Juveniles had significantly higher parameters than other groups though, except in their maximum cortex length and ROB (p>0.05) (Table 2). The hind brain comprised of medulla oblongata, pons and cerebellum. The pons and medulla formed portions of the brain stem. The cerebellum consisted of the three typical lobes of rodents in the median portion (rostral, central and caudal lobes); three lobes lateral to the median portion (lunate, ansiform, and paramedian lobes), and two prominent paraflocular lobes that were found deep

and lateral to the median and lateral portions of the cerebellum and the paraflocular lobe. The cerebellum of the AGR was observed caudal to the cerebrum and dorsal to the fourth ventricles in the region of the pons and rostral portion of the medulla oblongata. The dorsal view of the cerebellum revealed a typical worm-like appearance in juvenile and adults while it was relatively smooth without the typical vermis and was slightly separated from the cerebrum by an interposing and exposed mesencephalon (Fig.1a-c). The mean cerebellar weights were 0.83±0.02g, 0.76±0.02g and 0.04±0.02g while the relative cerebellar weight values were 0.14±0.01, 0.15±0.003 and 0.12±0.005 for adults, juveniles and neonates respectively. Other parameters such as the maximum hemisphere width were 17.08±0.37mm, 16.76±0.16mm and 0.75±0.04mm; Vermis length 13.23±0.32mm, 11.27±0.014mm and 0.24±0.02mm while the A-P lengths were 8.79±0.19mm, 6.97±0.03mm and 0.29±0.01mm for adults, juveniles and neonates respectively (Table 3).

DISCUSSION

It has been stated that morphometric analysis of organs may expose small structural changes that cannot be observed by ordinary qualitative analysis (Mayhew *et al.,* 1990; Oto *et al.,* 2009). Furthermore, quantitative evaluation has been used to reveal the state and functional capacities of brain regions in various animals (Donaldson 1924; Larsell and von Berthelsdorf, 1941; Sutter, 1943; Wirz, 1950 and Riese and Riese, 1952). Similar quantitative studies have been done on the human brain (Donaldson, 1909; Marsden & Rowland 1965). Morphometric studies have been useful to generate data for post mortem; medical imaging studies and as a diagnostic tool for diseases (Mayhew *et al.,* 1990; Ishikawa *et al.,* 2003). With the AGR proposed as a model for neuroscience studies in Africa (Olude *et al.,* 2014), morphometric data especially across age groups are of great value to set standards of comparison for research.

No literature exists on the shrinkage factor of the brain of the AGR but suggest negligible shrinkage following 3 days post fixation (Ibe *et al.,* 2010). An assumption that is adapted in this study also. The AGR brain exhibited lissencephaly of the neocortex similar to the smaller brained *Rattus norvegicus*. This pattern was expressed in all neonate and juvenile AGR except for adults (n=3) where gyrencephaly was seen in the caudomedial putative visual cortex. This pattern has been reported in the Armadillo (*Dasypus hybridus*), and Greater cane rat (*Thryonomys swinderianus*) (Dwarika *et al.,* 2008). The authors however view this as shrinkage with aging rather than selective gyrencephaly in adults and posit that those particular regions might have neurological effects on brain functions in the adult AGR. In the laboratory rats, the cerebral and cerebellar hemispheres have the falx cerebri and tentorium cerebelli respectively as modifications of the dura mater (Waibl, 1973). The dura mater forming the falx cerebri, the falx cerebri pars cerebri, is widely fused with the periosteum and penetrates deeply between the cerebral hemispheres (Hebel and Stromberg, 1975). However, in the AGR, the falx cerebri extended in between the lobes of the olfactory bulbs as an uncommon finding. The authors, therefore, proposed a name for this feature as the falx cerebri pars bulbus olfactorius. The occurrence of the pars bulbus olfactorius, made the successful whole removal of the olfactory bulb along with the brain difficult being always severed from the rest of the brain unless the falx cerebri pars is first dissected away.

Body - Brain parameters

The mean brain weight of the AGR (neonate=0.62±0.08g, juvenile = 4.64±0.17g, adult = 5.60±0.06g). Figures were unavailable for age groups of other animals as in this study. However, the adult AGR mean brain weight was comparatively higher when compared with that of the adult guinea pig (4g), sparrow (1g), but less than the porcupine (25g), adult greater cane rat (9.80±0.50g for males and 10.27±0.45g for females) (Byanet *et al.,* 2009), rabbit (10.00g), squirrel (7.6g) and marmoset (7.00g) in the studies of Nzalak *et al.,* (2005) and Eric (2006).

The ratio of brain to body weight has been reported to be 0.02 for man (Dyce *et al.,* 1996) and 0.006 for the Red Sokoto Sheep (Olopade & Onwuka, 2002). In the Greater cane rat, the ratios of 0.01 for males and 0.006 for females were recorded (Byanet *et al.,* 2009), while Russell (1979) noted the following: Squirrel monkey (0.04), Marmoset (0.03), Mouse (0.03), Squirrel (0.02), Fox (0.01), Cat (0.008), Rat (0.007), Dog (0.006), rabbit (0.004). In this present study, it was found to be 0.03, 0.01 and 0.006 in the neonate, juvenile and adult AGR respectively. Russell's hypothesis had stated that there exists a relationship between brain size and intelligence suggesting that brain size reflected intelligence (Russell, 1979). Based on this, the juvenile AGR can be said to be the most intelligent across age groups with the adults showing the least value. In general, the AGR can be said to be more intelligent than many other mammals e.g. the Squirrel monkey, greater cane rats, even the Cat (1:120=0.008), Rat (1:152=0.007), Dog (1:170=0.006), rabbit (1:300=0.004). While this point of view may add credence to the fact that, age plays a functional role in intelligence determination especially in the AGR, this hypothesis can however, be flawed based on age variations of recorded values in those animals and the fact that intelligence is beyond size to neurocellular and synaptic connections (Dwarika *et al.,* 2008).

The results of this study showed that the OB accounts for 20% as against 6% the total brain length in greater cane rats (Byanet, *et al.,* 2009); the cerebral cortex was 50% (62% in greater cane rats) of total brain length while cerebellar cortex was 30% of total brain length. The

larger cortical volumes, width and A-P dimensions in the cortex of the juvenile AGR were significantly above values for the adults and neonates. This has been reported in the cat (Zhang *et al.,* 2006) in humans (Bart *et al.,* 2001; Blakemore and Choudhury, 2006).

Early experiments on animals showed that sensory regions of the brain go through sensitive periods soon after birth, during which time environmental stimulation appears to be crucial for normal brain development (wave of synaptogenesis) and for normal perceptual development to occur (Hubel & Wiesel, 1962). It is then believed that a neuronal and synaptic trimming occurs towards adulthood.

The juvenile AGR had higher cortical volume, width and A-P dimensions than the adults. Shrinkage in adults may best be described on the basis of neuronal trimming following juvenile growth stimulation. This wave of synaptogenesis in the frontal cortex at the onset of puberty and the process of synaptic pruning that follows it after puberty is believed to be essential for the fine-tuning of functional networks of brain tissue, rendering the remaining synaptic circuits more efficient and to underlie sound categorization with effect on cognition (Zhang *et al.,* 2006).

Cortical parameters as a function of brain development and plasticity

Closely related to the above hypotheses are findings on adult neurogenesis studies on the AGR (Olude *et al.,* 2014b). It has been observed that postnatal induction of neuronal plasticity leads to reorganization of microtubules, for example during synaptic reorganization or axonal outgrowth (Nacher *et al.,* 2001). This hypothesis implies that the neocortex with its various cortical divisions e.g. the piriform cortex is a very plastic area and therefore adult neurogenesis could be one of the mechanisms of plastic changes affecting synaptic density.

In this present study, measurements were done on each bulb and the LOB was found to be significantly longer than the ROB with the juveniles also having larger bulbs than the adults. As earlier discussed, the synaptogenesis and neuronal trimming with progressing age might have similar effects on the olfactory bulbs and possibly on olfactory differentiation across age groups.

Olude *et al.,* (2014b) reported higher neural plasticity and cortical neuronal volume in juveniles AGR compared to neonates and adults. The authors posited the juveniles as having the best cognitive abilities. This observation is further strengthened by the on-field evaluations of APOPO, a registered Belgian nongovernmental organization. They train and use juvenile AGR to detect landmines and diagnose tuberculosis (Poling *et al.,* 2011; Mahoney *et al.,* 2012; Carrington, 2014) and it was observed that this age group were the best primed for this purpose compared to the adult AGR (Verhagen *et al.,* 2003; Weetjens *et al.,* 2009).

In conclusion, this work presents baseline information useful for post mortem studies, medical imaging and as diagnostic tool for future research work on the AGR brain. It also proffers the juvenile AGR as the most suitable for research across age groups.

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