Aging alters visual processing of objects and shapes in inferotemporal cortex in monkeys

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1. Introduction

The cognitive functions, including visual perception, decline with age. This deterioration of the perceptual processes can be attributed not only to optical defects such as cataract, glaucoma or presbyopia, but also to neurological aging and dysfunction in higher visual areas. This may have a major impact on the occurrence of home accidents, automobile driving and the quality of life in general (Carter et al., 1997; Desapriya et al., 2014; Kallstrand-Eriksson et al., 2013). Data from psychophysical studies indicate that older people tend to have decreased visual acuity, contrast sensitivity and contour integration (Hutman and Sekuler, 1980; Roudaia et al., 2008; Sekuler et al., 1980). They often demonstrate impairments in visual motion sensitivity, including the perception of apparent motion, and have poorer orientation-judging capabilities (Bennett et al., 2007; Betts et al., 2007; Roudaia et al., 2010)(for a review, see (Andersen, 2012). It has been reported that aging also has an impact on form perception and shape discrimination (Habak et al., 2009; McKendrick et al., 2010; Weymouth and McKendrick, 2012) and figure-background separation (Chee et al., 2006), but it is not clear what changes accompany these impairments.

A number of papers have addressed the connection between aging and the decline of visual functions (Liang et al., 2010; Schmolesky et al., 2000; Spear, 1993; Wang et al., 2006; Wang, 2001; Yang et al., 2008; Yang et al., 2009a; Yu et al., 2006), but we are not aware of any electrophysiological report concerning the effects of aging on the neuronal activity underlying object and shape vision in a high-level visual area such as the monkey inferotemporal cortex (IT). The monkey IT, the last stage of the ventral visual stream, is critical for object vision and recognition. Lesions of this area lead to an impairment of object discrimination (Dean, 1976). The inferotemporal cortex is in close connection to visual system (V1,V2,V4) as well as perirhinal and prefrontal cortex, amygdale and striatum (Tanaka, 1996). There are fibres between IT and hippocampus (Zhong and Rockland, 2004) furthermore parietal lobe (Baleydier and Morel, 1992; Zhong and Rockland, 2003) and superior

temporal lobe (Saleem et al., 2000) also elements of the dorsal visual stream (Yeterian and Pandya, 2010). On the other hand, it has an impact on perception. Microstimulation of the area influenced the face non-face categorisation (Afraz et al., 2006), and human perception models cause similarity cell firing pattern as IT neurons (Allred et al., 2005). For a recent review of the crucial role of this area in visual perception, see (Tompa and Sary, 2010).

Microelectrode-based electrophysiology in humans clearly has limitations, and most of our knowledge relating to the neuronal processes in object vision therefore originates from monkeys. Several papers have compared the visual systems of monkeys and humans (Denys et al., 2004; Orban et al., 2004; Tanaka, 1997). If it is accepted that a possible criterion for homologies is similarity in function and in retinotopy in the particular visual areas, then it is clear that the ventral cortical pathway serving object vision across primates into humans is conserved (DeYoe et al., 1996; Fize et al., 2003; Kourtzi et al., 2003). A homology for IT in humans is probably the lateral occipital complex (for a review, see: (Orban et al., 2004)), and the investigation of changes in the shape representation of the monkey IT may therefore facilitate an understanding of age-related changes in the human visual system.

The aging of monkeys is similar in many respects to human aging. A 30-35-year-old monkey is similar to a human aged 90-95 years (Tigges et al., 1988). On this basis, three human years may be assumed to correspond to one monkey year. Nonhuman primates are ideal for examining central nerve system aging since they share the same neuromorphological pattern as in humans during normal ageing (Gallagher and Rapp, 1997); (Lowenstine, 2003). Interestingly, the refractory power of the eye tends to decrease, which is appropriately compensated in monkeys (Fernandes et al., 2003; Ooj and Grosvenor, 1995). This supports the assumption that ocular pathology is not critically relevant in the changes in visual function. We hypothesized that changes in the neuronal coding of

objects may partially explain the perceptual deficit of aging monkeys (and humans). The establishment of similarities between the visual systems of human and nonhuman primates has a number of benefits; most importantly, it confirms and validates animal data and allows the design of paradigms for across-species studies concerning, for example aging.

In the study reported here, we compared data obtained from single-cell recordings from monkeys in two age groups: 7 years and 27-33 years (corresponding to 21 and 81-99 years, respectively, in humans) to determine how the neuronal coding of visual stimuli changes with age in the inferotemporal cortex.

2. Methods

All the participating animals (*Macaca mulatta*) had engaged in earlier studies in our laboratory. The animals performed a simple fixation task and were exposed to the same set of images at a certain stage during their training (for an example of the stimulus set, see (Sary et al., 2006)). To compensate for implicit learning, we took our sample from a later phase of the experiments, when the animals could be regarded as experienced or even overtrained. The animals all performed well, despite having a fixation spot consisting of only a few pixels. A stimulus preference was obvious, the analyzed cellular data and visual inspection not revealing apparent opalescence of the cornea or lens in any of the monkeys. All of them exhibited a performance better than 87% in the task, and we therefore regard these animals as having normal vision.

The 4 monkeys that participated in the study weighted between 6 and 9 kg at the time of the experiments. In the young group, two monkeys were males and the old animals were 2 females. Prior to their training, the animals underwent two session of aseptic surgery. All surgical procedures were carried out under full anesthesia, induced with an i.m. injection of ketamine (Calypsol; 15 mg/kg)

and atropine (0.05 mg/kg). An endotracheal tube was inserted into the trachea and anesthesia was maintained with Halothane (1-1.2 %), given in a mixture of N_2O and O_2 in a ratio of 2:1, or 0.5 mg/kg i.v. midazolam (Dormicum). An i.v. line was inserted for continuous access and physiological saline was given to compensate for fluid loss. Before the surgical procedure, a preventive dose (250 mg) of the antibiotic ceftriaxone (Rocephin) was given. The incision was infiltrated with local anesthetic (Procaine). Nalbuphin and nonsteroidal anti-inflammatory drugs were administered to the animals postoperatively. The arterial oxygen saturation, expired CO_2 level, heart rate and alveolar concentration of the inhalation narcotic were monitored continuously throughout the surgery. A stainless steel headpost was fixed to the head to keep the animal's head stable, and a search coil was implanted under the conjunctiva (Judge et al., 1980) to enable recording of the eye position.
The animals performed a fixation task. First, a red fixation point was presented on the monitor (distance: 57 cm) for 500 ms, followed by a gray background (500 ms) and then by the stimulus (500 ms). If the animal maintained fixation (fixation window ~ 0.5°) until the end of the trial, a reward was given (fruit juice). Biologically non-relevant colored geometrical forms and everyday objects served as stimuli (Sary et al., 2006). Stimulus presentation took place in a semi-random fashion. Once a responsive cell had been isolated, a set of effective and non-effective stimuli were chosen and the neuronal responses were recorded with the use of these stimuli. This allowed us to construct stimulus-preference tuning curves, a feature characteristic of IT cells. The neuronal activity from the IT was recorded by using standard electrophysiological methods. Cellular activity was analyzed off-line by means of Statistica (Statsoft) and MATLAB (Math Works). All procedures relating to the surgery and training of the animals conformed fully to the NIH standards and had been approved in advance by the Ethical Council of the University of Szeged.

To characterize the recorded neuronal responses, the following parameters were used:

- Baseline: the mean activity in a time window of 400 ms preceding stimulus onset.

- The response latency time: the time from stimulus onset to the start of the neuronal activity. We used the Poisson spike train analysis method, which has previously proved to be reliable in different experimental paradigms (Hanes et al., 1995; Sary et al., 2006; Thompson et al., 1996).
- The net firing rate: the mean baseline activity subtracted from the mean overall activity in a 400-ms time window starting 100 ms after stimulus onset.
- The signal to noise ratio: a value calculated by dividing the net firing rate by the baseline activity. This shows how much the stimulus-related activity differs from the background activity.
- The Fano factor: the standard deviation of probability distribution of the spike counts. This is one of the most widely used statistical parameters with which to describe the variability of the spike trains (Churchland et al., 2010).

. The following factors are considered special to neurons which play roles in the sensory perception and discrimination of, for example, the speed and direction of movement or shapes.

- The selectivity index (SI): this is used to describe the stimulus preference of cells.

  SI = $(R_{max} - R_{min})/(R_{max} + R_{min})$

  where R_{max} is the maximal and R_{min} is the minimum response, respectively, to a particular stimulus set. The closer the value is to 1, the better the cell discriminates between a preferred and a non-preferred stimulus.
- The depth of selectivity index (DSI). Long-term recordings have indicated that the cellular responses can best be characterized by a variable derived from the median of the firing rate (Bondar et al., 2009). In the optimal case, i.e. if the cell shows a stimulus preference, the value is 1 or close to it. It is a normalized variable, with the greatest response taken as 1 and the median of the responses being subtracted from it:.

$$DSI = [n - (\Sigma_{i=1,n} R_i / R_{max})] / [n - 1],$$

where R_i is the ith response to the n stimuli, while R_{max} is the maximum response. The value ranges from 0 to 1, where the highest value indicates that the examined cell reacts to only one stimulus.

- The sparseness index (SP): the ratio between the used and effective stimuli, i.e. the "tail" of the distribution of the cellular responses to the stimulus set (Rolls and Tovee, 1995).

$$SP = [\Sigma_{i=1,n} (R_i/n)]^2 / [\Sigma_{i=1,n} (R_i^2/n)],$$

where R_i is the ith response from the responses to a stimulus set containing n stimuli. The value can range between 0 and 1. A small SP value means that there are only a few stimuli in the set which can evoke large responses (i.e. there is a stimulus preference), while a large SP values means that most of the stimuli can trigger cellular responses which do not differ too much.

Statistics

Nonparametric tests were used throughout the analysis. To verify the differences between groups, we performed a Mann-Whitney U test. Results (U) were compared with the corresponding value of the χ^2-table at the same degree of freedom (df). Results were taken as significant if the type I error was less than 5% ($p<0.05$). All values are presented with the median and the interquartile range in the text and in the Figures. Correction for multiple comparisons was applied according to the Bonferroni method. In some cases, however, we present both corrected (p_{corr}) and uncorrected values, as we consider that the Bonferroni correction is too conservative and could mask relevant results so nonparametric permutation test was implemented (number of permutation=5000) (Winkler et al., 2014). Cluster analysis (Ward method) was used to reveal the relationship between possible groups among the variables.

3. Results

We recorded a total of 288 neurons from 4 *Macaca mulatta* monkeys to investigate the functional consequences of neuronal aging. Two groups of data were formed for comparison: a young group ("Young", 2 monkeys, aged 7 years, number of cells: 221) and an old group ("Old", 2 monkeys aged 27 and 33 years, respectively, number of cells: 67).

First to have an initial analysis of our data set we rana cluster analysis to determine whether our data form groups according to the age or not. Baseline activity, as the raw data with no modulation were chosen to explore internal pattern of groups. Secondary, latency data were used, as our hypothesis was that this is a primary measure of cell aging (Kuba et al., 2012; Wang et al., 2005). The cluster analysis revealed two main clusters, one comprising the data on the 2 Old animals and the other the data on the Young ones.

In the next step, we compared the data on all the registered cells by means of the Mann-Whitney U test.

The baseline of firing rate did not significantly differ in the 2 groups: 6.00 (2.81 - 9.69) spikes/s in the Young, and 5.23 (2.50 - 10.27) spikes/s in the Old animals, respectively.

The signal-to-noise ratio was 3.63 (2.19 - 6.10) in the Young and 3.26 (2.34 - 6.75) in the Old group. Once again, there was no significant difference between the groups.

The Fano-factor did not indicate differences between the groups either: 1.26 (0.76 - 1.85) and 1.31 (0.84 - 2.00) for the Young and Old groups, respectively.

The net firing rate were likewise not different: 15.67 (8.33 - 25.33) spikes/s vs. 14.33 (8.33 - 24.66) spikes/s, respectively, in the Young-Old comparison.

On the other hand, the latency revealed a difference between the Young and Old groups (Fig. 1): 128.73 (96.88 - 161.86) ms and 147.20 (124.54 - 179.83) ms, respectively; U= 4101.00; $p_{corr} < 0.05$.

SI too demonstrated a difference (U = 4810.50; $p_{corr} < 0.001$) in the Young vs. Old comparison : 0.89 (0.69 - 0.97) and 0.76 (0.47 - 0.90), respectively.

The SP values for the Young-Old groups (Fig. 2) were (0.47 (0.28 - 0.73) and 0.75 (0.56 - 0.90), respectively), this difference was significant, according to the Mann-Whitney test (U = 4245.50; $p_{corr} < 0.001$).

DSI similarly pointed to a group difference in the Young-Old comparison: (0.60 (0.44 - 0.79) vs. 0.46 (0.31 - 0.68), respectively; U= 5197.00; $p_{corr} < 0.01$).

To reduce the biasing effects of unequal samples, we repeated the analysis on 22 randomly chosen cells from all animal. Cells were selected from that stage of the experiments when the animals were considered overtrained. During this phase, the animals worked on a daily basis, achieving a > 87% performance rate in the task, and the effect of attentional fluctuation could therefore be minimized.

As in the analysis involving all the cells, the response latency values of the Young and Old data were statistically different: 124.85 (97.00 - 161.74) ms and 154.51 (129.33 - 178.64) ms, respectively (U = 567.00; $p_{corr} < 0.01$).

Here too, the SI values pointed to a significant difference between the groups (U = 713.50; $p < 0.034$) before the Bonferroni correction, which disappeared after it ($p_{corr} < 0.27$). Since in our opinion, this difference is essential for understanding neuronal aging and the perceptual decrease, we rerun this comparison with Monte –Carlo method, aside from Bonferroni correction ($p_{permutation} < 0.027$). The neuronal selectivity in the two groups were: 0.90 (0.69 - 0.97) vs. 0.81 (0.51 - 0.92).

DSI, the same way produced masked result (U = 670.00; $p < 0.013$, $p_{corr} < 0.10$), which after randomize, remained relevant (<0.02).

The SP parameters, were significantly different (U = 587.00; $p_{corr} < 0.05$): 0.46 (0.29 - 0.73) vs. 0.75 (0.51 - 0.88), in the Young and Old groups, respectively.

4. Discussion

Naturally, the best way to study age-related differences would be therefore long-term monitoring (> 10 years) of the same subjects, but that is technically not feasible. We compared results obtained from awake, behaving monkeys belonging in two appreciably differing age groups, young and old, while the animals performed the same task, with an identical stimulus set. Differences emerged between the different age groups in the response latencies and selectivity indices.

Baseline activity

The baseline activity did not appear to change with aging in these animals, whereas others have reported an elevation in baseline activity in older animals (Hua et al., 2006; Schmolesky et al., 2000; Yang et al., 2008). This, and other possible differences between our and other studies, may be explained by the methodological differences: our animals performed a fixation task, while the recordings in other studies were made on anesthetized monkeys, or in animals performing a demanding task (e.g., discrimination, categorization). Although a stimulus preference of neurons and tolerance against identity preserving changes (e.g. stimulus size and position) have been observed in anesthetized animals (Hung et al., 2005), it is well known that recording in awake animals has various benefits. It is not necessary to consider the sometimes undulating level of anesthesia, while the cellular response rate is generally higher (this may improve the signal to noise ratio), the latencies may be shorter and the stimulus preference becomes more explicit (Tamura and Tanaka, 2001; Tanaka et al., 1991). On the other hand, the task performed may also have an influence on the results.

Neuronal responsivity

Previous papers have reported an age-related changes in the neuronal response levels in V1, V2 and middle-temporal complex (MT) in monkeys (Leventhal et al., 2003; Schmolesky et al., 2000; Wang

et al., 2005; Yang et al., 2009b), which also affected the signal to noise ratio of the responses. We did not observe any significant change in the responsivity of the neurons between the Young and Old groups, and the signal to noise ratio was not affected either. Since we know of no study in which the age-related activity changes in V1, V2, MT and IT were compared in the same animal, we can not explain of this controversy. It may possible be caused by the differences between awake and anesthetized animals.

A number of neuroimaging studies have reported age-related changes in cerebral activity in human subjects that resemble those observed in our study. An object-identifying PET study demonstrated a decreased inferior temporal regional cerebral blood flow (rCBF) level (Schiavetto et al., 2002). Similarly, an age-related attenuation in blood-oxygen-leved dependent (BOLD) signal was detected in the temporal lobe during object recognition (Ramsoy et al., 2012). Other reports have shown that a possible impairment in areas needed for the performance of a task may be compensated by an increased activity in the basal ganglia (Madden et al., 2004) or frontal cortical regions (Grady et al., 1994; Gutchess et al., 2005; Gutchess et al., 2007) . However, as the coupling of the BOLD signal to neuronal activity has been reported to change with age, care must be taken when young and old subjects are compared in imaging studies (D'Esposito et al., 1999).

Increased latency

It is not possible to explain the origin of the delayed latency times from the data we report here. Some authors argue for a generalized slowing in processing speed during aging (Salthouse, 1996) and many papers describe age-related increases in response latencies. An increased response latency was recently observed in rats (Wang et al., 2006). Evoked potential studies revealed an increase in the peak latency time of P3 in human subjects during both passive and active tasks, indicating a slowing-down of cognitive tasks at higher ages (Morgan and Murphy, 2010). Similarly, the response latency time differences between good and poor performers increased with advancing age (Riis et al.,

2008), indicating age-dependent factors in visual processing during normal aging. In a PET experiment, a facematching task demonstrated an increase in reaction times (Grady et al., 1994). The underlying mechanism is not clear as no decrease was found in the number of retinal ganglion cells (Kim et al., 1996) or lateral geniculate body cells (dLGB) (Ahmad and Spear, 1993) during aging. On the other hand, changes have been discovered in layer 3 of V1, but these did not affect the electrophysiological properties (Luebke et al., 2013), and significant decreases were not found in the total numbers of V1 neurons and glias (Giannaris and Rosene, 2012). This might direct attention to age-related functional changes. Recent results suggest that myelin breakdown can affect the processing speed (Lu et al., 2011; Lu et al., 2013), and we hypothesize that this might be the reason for the increased response latencies observed. This idea is supported by the fact that there is a strong correlation between age-related myelin breakdown and the cognitive impairment in monkeys (Peters and Sethares, 2002). Moreover, the axonal conduction velocity is decreased in aged cats (Xi et al., 1999). The electrophysiological properties change together with the age-associated deterioration of the myelin in the cortex (Luebke et al., 2010). This slowing-down could be a general phenomenon in the nervous system, but certainly affects the corresponding visual cortical areas too (Peters et al., 2000).

Change in stimulus selectivity

The key to the perception of different aspects of the visual stimulus is probably a set of neurons with stimulus selectivity (or more precisely, stimulus preference) for a particular parameter (speed, direction, orientation, shape, color, etc.), and thus an altered preference or influencing the firing pattern of these neurons will have an impact on the perception of the particular item (Salzman and Newsome, 1994). Minor functional age-related changes have been observed in the dLGB (Spear et al., 1994), and in the higher stages of the visual hierarchy the changes are more expressed (Schmolesky et al., 2000). It is suggested, for instance, that V2 is more affected than V1 (Yu et al.,

2006), similarly to higher levels (Liang et al., 2010). Indeed, there is a clear distinction between the aging of simple and complex cells in V1 (Liang et al., 2012). Changes in speed representation and increased response variability in the MT, might well explain the altered speed perception in aging humans; such findings were interpreted by supposing a decreased number of glycinergic neurons (Yang et al., 2009a; Yang et al., 2009b), but a decreased number of interneurons in the cortex has also been reported (Coleman and Flood, 1987). The shape selectivity in IT receptive fields is formed by GABAergic neurons (Wang et al., 2002). It might be that the number of these neurons decreases with age, and that this leads to an altered shape preference. Further, microstructural changes including a deterioration of the myelin sheets (Inano et al., 2011) and changes in the white matter (fractional anisotropy in the occipital region) (Van Impe et al., 2012) were postulated to be possible predictors of sensory degeneration. Others have reported an accumulation of microglia and oligodendrocytes in the primary auditory and visual cortices (Tremblay et al., 2012). A possible explanation was suggested for the impairment of effectivity in sensory-perceptual processing following the finding of decrease in occipital gray matter and activity (Kalpouzos et al., 2012). A reduced gray matter volume and decreased discrimination capability reflecting aging of the brain have likewise been reported (Carp et al., 2010). Human experiments clearly demonstrated age-related changes in shape perception (McKendrick et al., 2010; Weymouth and McKendrick, 2012) and visuospatial memory (Carp et al., 2010), though the results appear to depend strongly on the experimental methods used (Habak et al., 2009).

It seems, that from middle age on, the changes in neuronal activity that result in perceptual deficits become increasingly explicit. This was recently illustrated by Riis (Riis et al., 2008).

As regards age-related deficits, several of the above papers suggested a structural deterioration of the neuronal mechanisms supporting visual perception. On the other hand, many findings lend support to the hypothesis that perceptual impairments in aging are due to functional rather than morphological

changes, which affect the communication between neurons (Hua et al., 2006; Leventhal et al., 2003; Mendelson and Wells, 2002; Schmolesky et al., 2000; Wang et al., 2006; Yang et al., 2008). Unfortunately our findings do not allow a decision between the mechanisms mentioned above; we have merely demonstrated a phenomenon that has previously not been described.

In summary, we have reported an increase in response latency and a worsening of the stimulus selectivity in the monkey homolog of the human LOC, which might, explain, at least partially the uncertainties in visual perception observed in the elderly.

Figure legends

Fig. 1.

Neuronal response latencies in the two age groups, calculated by the Poisson analysis method, and seen to be the longer in the Old group.

Fig.2.

Sparseness indices in the two age groups. Sparseness is the “tail” of the distribution of responses to a particular stimulus set. A low value indicates that s cell has a stimulus preference, i.e. there are only few stimuli that evoke high responses. The Old group displayed a significantly higher sparseness, indicating less stimulus selectivity.

Acknowledgements

This research was supported by Országos Tudományos Kutatási Alap (OTKA) K83671 awarded to Gy. Sáry. The authors thank P. Liszli, G. Dosai and L. Rácz for technical support and for taking care of the animals and J. Navracsics for proof-reading the manuscript. This research was supported by the European Union and the State of Hungary, co-financed by the European Social Fund in the framework of TÁMOP-4.2.4.A/ 2-11/1-2012-0001 'National Excellence Program'.

Disclosure Statement: there are no actual or potential conflicts of interest.

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