ELSEVIER

Brain Research Bulletin 67 (2005) 382–390

BRAIN RESEARCH BULLETIN

www.elsevier.com/locate/brainresbull

Reward-based decision-making and aging

A. Marschner[a,b,*], T. Mell[a,b,c], I. Wartenburger[a,b,d], A. Villringer[a,b], F.M. Reischies[c], H.R. Heekeren[a,b,*]

[a] *Berlin NeuroImaging Center, Charité, Campus Mitte, Schumannstr. 20/21, 10117 Berlin, Germany*
[b] *Department of Neurology, Charité, Campus Mitte, Berlin, Germany*
[c] *Department of Psychiatry, Charité, Campus Benjamin Franklin, Berlin, Germany*
[d] *Department of Neurology II, Otto von Guericke University, Magdeburg, Germany*

Available online 11 July 2005

Abstract

Healthy aging is associated with a number of neuroanatomical and neurobiological alterations that result in various cognitive changes. Both, the dopaminergic as well as the serotonergic system are subject to change during aging. Receptor loss and severe structural changes in PFC and striatum have been reported. Aging is associated with a progressive decline in several cognitive functions, such as episodic memory, working memory, and processing speed. Furthermore, it is associated with deficits in tasks requiring adaptation to external feedback of right or wrong, or task-switching. Here, we develop the hypothesis that this loss of behavioral flexibility is caused by structural and functional alterations of the reward system leading to impairments in reward processing, learning stimulus reinforcement associations, and reward-based decision-making. We review (a) data on neural correlates and substrates of reward processing in young healthy animals and humans, (b) evidence for age related functional and structural alterations of the reward system, and (c) behavioral and neuroimaging data of age effects on reward-based decision-making processes. Implications for neuroeconomics and neurodegenerative diseases are discussed.

Keywords: Reward; Dopamine; Aging; fMRI; Neuroimaging; PFC; Striatum; Reward association learning

1. Introduction

Decision-making is the process of choosing an option or course of action from among a set of alternatives. This process depends on the decision-maker's estimate of the outcome of the different options, which is based on rewards and punishments associated with these alternatives in the past. This indicates that reward processing and reward association learning are important components of the decision-making process.

The reward system has four major components: (1) dopaminergic midbrain neurons located in the ventral tegmental area (VTA), (2) the ventral striatum (VST), (3) the prefrontal cortex (PFC), and (4) the amygdala [5,83]. Both, the dopaminergic as well as the serotonergic system are subject to change during aging: several studies report severe receptor loss in PFC and striatum, which may cause decreased responses by target neurons [92,95]. Other studies report severe structural changes, such as volume loss most pronounced in PFC and striatum [64]. It is well known that aging is associated with a progressive decline in several cognitive functions, such as episodic memory, working memory, and processing speed. Furthermore, it has been shown that aging is associated with deficits in tasks requiring adaptation to external feedback of right or wrong, or task-switching [2,38,39,60]. Here, we develop the hypothesis that this loss of behavioral flexibility is caused by structural and functional alterations of the reward system leading to impairments in reward processing, learning stimulus reinforcement associations, and adapting existing ones to new situations. We review (a) data on neural correlates and substrates of reward processing in young healthy animals and humans, (b) evidence for

* Corresponding authors. Tel.: +49 30 450 560 169; fax: +49 30 450 560 952.
E-mail address: hauke.heekeren@charite.de (H.R. Heekeren).

0361-9230/$ – see front matter © 2005 Elsevier Inc. All rights reserved.
doi:10.1016/j.brainresbull.2005.06.010

age-related functional and structural alterations of the reward system, and (c) behavioral and neuroimaging data of age effects on reward-based decision-making processes.

2. Neural substrates and correlates of reward processing in animals and humans

Aging is associated with many changes in the brain across different behavioral as well as anatomical domains. To review age-related changes in reward-based decision-making we first focus on reward-based decision-making in young healthy animals and humans.

2.1. Reversal learning tasks

One of the very basic tasks that have been used for the investigation of reward association learning are reversal learning tasks. In this kind of task subjects have to adapt responses to a certain stimulus reward contingency and to inhibit previous responses. Originally, these tasks were used in animal studies [34] but were adopted for use in healthy human subjects and in patient populations [22,57,75]. The animals typically receive a certain primary reinforcer, such as food or liquid with pleasant flavor in response to a certain movement or behavior. After several trials the reward is omitted and the animal has to change its choice behavior in order to obtain the reward again.

More recently, probabilistic versions of reversal learning paradigms have been applied. In the probabilistic version, the feedback follows a probabilistic schedule and is thus less informative, i.e. there is a stochastic variation of the amount of reward. It has been shown that under this condition several clinical populations, such as patients with organic depression [68] or Huntington's disease [41] show impaired performance in stimulus reward association learning.

Choice selection decision-making paradigms, such as the Iowa gambling task [7] and Rogers' gambling task [72], are frequently used in neuropsychological studies of decision-making disturbances in frontal lobe damaged patients (for review, see [6,62]). A characteristic of these tasks is that participants have to choose between two options with different odds of success and different pay-offs (e.g. a small very likely or a larger less likely reward or punishment). For example, in Rogers' task, subjects have to weigh the probability of winning a reward with the amount of possible reward or punishment. In the Iowa gambling task, participants have to optimize their decision behavior by processing feedback from previous trials.

2.2. Neural correlates of reward processing in animals

Rolls found that neurons in orbitofrontal cortex (OFC) represent absolute as well as relative value [74]. Schultz et al. developed a model integrating different aspects of reward processing. This model proposes that reward processing relies on dopaminergic midbrain neurons that are sensitive to unpredicted rewards and show a short, phasic activation after the presentation of rewards in animal studies [82–84]. Phasic dopaminergic activity is also elicited by visual and auditory stimuli that predict rewards, but is depressed by the omission of predicted rewards [47]. These results have led to the suggestion that the dopamine response might represent a so-called "reward prediction error" (RPE). The RPE indicates the discrepancy between reward received for an action and reward that was predicted to occur as the result of this action. Specifically, the RPE is positive when a reward occurs unpredictably after a certain action, resulting in an activation of the dopaminergic neurons. Once a reward is expected with total certainty, the RPE becomes zero and there is no phasic dopaminergic activity. If a reward is expected but does not occur, the RPE is negative, and activity in dopaminergic neurons is depressed (for review, see [83]). Thus, this signal emitted by dopaminergic midbrain neurons might serve as a global reinforcement signal to neurons in the striatum and the PFC. Recently, Fiorillo et al. extended the model by showing increased sustained activity shortly before an expected reward was delivered. This activity varied as a function of probability of the occurrence of the rewarding object and was highest when the probability was 50%. The authors conclude that this pattern could reflect task uncertainty [21].

2.3. Neural substrates and correlates of reward processing in humans

A majority of neuroimaging studies have focused on subprocesses of reward processing, such as reward anticipation and reinforcement delivery using primary rewards (e.g. food, liquid with a pleasant flavor) and secondary rewards (e.g. money). In agreement with the animal literature most studies in humans have identified a number of brain regions including the PFC (different subregions, namely dorsolateral PFC (dlPFC), and OFC) [56,90]), the amygdala [11,55], the basal ganglia (including caudate nucleus, putamen and globus pallidus), and the VTA [55]. Other studies have focused on the above mentioned choice selection decision-making tasks, e.g. the Iowa gambling task or the Rogers' gambling task [19,73,93].

The striatum is suggested to show sustained activity after the presentation of a reward-predicting stimulus, during reward anticipation, and after the delivery of an unexpected reward [8,11,37,58,89,93,99].

The OFC is critically involved in the detection and prediction of rewards [74,88], as well as in the flexible relearning of associations between stimuli and rewards if required. Neurons in the OFC provide information about the motivational value and the identity of rewarding stimuli [83]. In neuroimaging studies the OFC is consistently activated when rewards are delivered [11,18,56]. But the OFC is not only involved in reward processing: several studies have shown

a critical involvement of the OFC for encoding information [23,24,40].

2.4. Neural correlates of probabilistic reward association learning

In a recent fMRI study, we investigated neural correlates of stimulus reward association learning in the human brain [51]. In a probabilistic object reversal task (pORT) [68] participants had to choose one out of four letters (decision-making phase) and received feedback (abstract non-monetary reward or punishment, "points"; reward processing phase) after a randomized delay (compare Fig. 1). Participants were instructed to collect as many points as possible so that they had to determine, by trial and error, which letter was the most profitable to choose. To assess flexible relearning the feedback schedule covertly changed after participants had reached a predefined learning criterion (most profitable letter chosen in more than 80% of successive trials), and another letter was associated with the maximum feedback. To make the task less predictable, the reward schedule was probabilistic, i.e. the letters were associated stochastically with the magnitude of received points. For example, the choice of letter "N" was rewarded with 40 points in 80% and with 20 points in 20% of its occurrences. Based on the predefined learning criterion, trials were divided into two groups: SEARCH and LEARNED (reward associations not yet learned and learned).

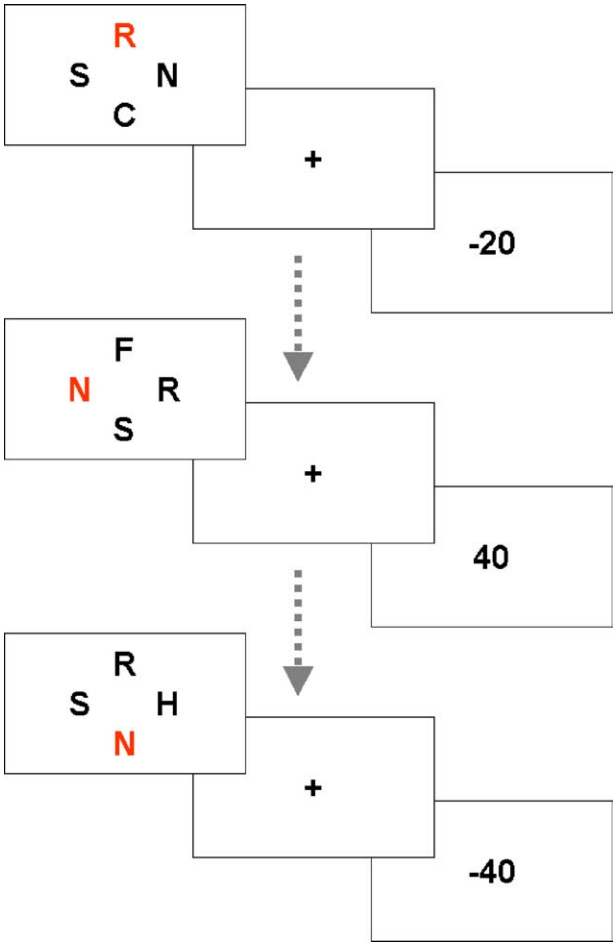

Fig. 1. Probabilistic object reversal task [68]. Four out of six letters (C, F, H, N, R, S) were presented simultaneously on a screen. The participants had to choose one of the letters via button-press on a four-button mouse (for the purpose of illustration chosen letters are marked in red here). After a randomized delay, participants received an abstract non-monetary feedback cue (40, 20, 0, −20, −40 points). To collect as many points as possible participants had to search for the most profitable letter ("N" in this case) by trial and error. To assess flexible relearning the feedback schedule covertly changed after participants had reached a predefined learning criterion, i.e. after the most profitable letter was chosen in more than 80% of successive trials, and another letter was associated with the maximum feedback (bottom row). (For interpretation of the reference to colour in this figure legend, the reader is referred to the web version of the article.)

To test in which brain regions the activity was modulated by reward association learning, we contrasted activity during SEARCH and LEARNED trials and vice versa during decision-making and reward processing, respectively (group average T-statistics).

Preliminary data show that during decision-making right hemispheric dlPFC was more active while reward associations were being learned and the new target had to be found, i.e. when comparing SEARCH and LEARNED trials. This is in line with the idea that this area's main function is response selection [77].

Comparing LEARNED to SEARCH trials during decision-making resulted in greater activation in left superior frontal gyrus, cingulate gyrus, amygdala, and insular brain regions.

The comparison of SEARCH and LEARNED trials during reward processing revealed significant activation in left frontal pole and left dlPFC. This activation could reflect the processing of behaviorally relevant rewards thus signaling that the most recent choice was good and had to be reinforced.

In contrast, the VST showed larger right hemispheric responses to reward cues during LEARNED trials compared to SEARCH trials which might reflect its role in processing expected rewards (compare Fig. 2).

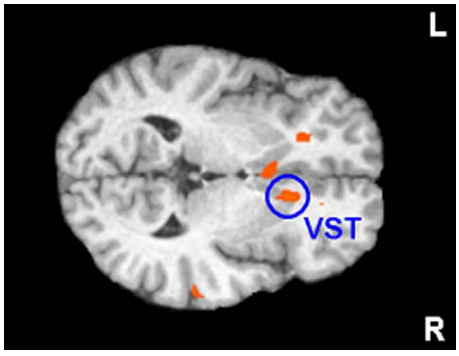

Fig. 2. Neural correlates of reward association learning in young subjects. Right ventral striatum ($x = 12/y = 18/z = 3$) showed greater responses to reward cues after stimulus reward associations had been learned (LEARNED > SEARCH trials; $n = 8$, $p < 0.005$; [51]). VST, ventral striatum.

3. Age effects on the neural substrates and correlates of reward processing

Healthy aging is associated with a number of neuroanatomical and neurobiological alterations that result in various cognitive changes. Reward-based decision-making and the underlying neural systems are affected in old age and might thus influence the decline of other cognitive functions during aging. A selection of the most prominent evidence will be briefly discussed below. In the following paragraph, we review age-related changes in brain structures relevant for reward processing.

3.1. Changes of brain structure in aging

Postmortem studies indicate a moderate reduction in brain weight and volume [36]. Significant reductions in overall cerebral volume are also shown by magnetic resonance imaging (MRI; [66,69]). The vulnerability of cortical circuits in normal aging seems to result from a loss of synaptic contacts [32].

Although structural neuroimaging and postmortem studies indicate a general loss of brain tissue (signs of overall atrophy), several cortical and subcortical brain areas are particularly more affected by aging than others. For example, frontal and parietal lobes appear more vulnerable to age-related decline than temporal and occipital lobes [69]. Specifically, prefrontal grey matter volume shows a stronger negative association with age than any other brain area [65–67]. These structural changes in PFC have been attributed to age-related declines in cognitive performance ("frontal lobe hypothesis"; [97]). Severe age effects have also been found in the basal ganglia including nucleus caudatus, putamen, and globus pallidus [25].

Conflicting findings have been reported regarding age-related morphological changes of the OFC. Age-related volume loss in the OFC is not as pronounced as volume loss in the dlPFC [64], however a more recent study by Salat et al. showed an increase of cortical volume in OFC in older adults ranging between 74 and 92 years [79]. Furthermore, this alteration significantly correlated with working memory performance. This study was the first to show that alteration in prefrontal areas other than the dlPFC could account for behavioral changes during aging.

3.2. Changes in brain physiology in aging—neuroimaging results

Indices of brain function also change with age. As observed with positron emission tomography (PET), age is associated with a moderate reduction in regional cerebral blood flow [49,50,96], which is an indirect measure of neural activity.

Age-related differences have been found within several neurotransmitter systems. In particular, there is evidence that the dopaminergic system undergoes gradual changes across the adult life span, indicating a negative relationship between adult age and dopamine (DA). In the human striatum, a number of studies have shown an age-associated decline of D_2-like receptors, which could be related to a decline in motor and cognitive abilities, such as speed of processing and episodic memory [3,92]. Additionally, Kaasinen et al. have shown an extrastriatal decline of D_2/D_3 receptors most pronounced in PFC and anterior cingulate cortex (ACC) compared to temporal and thalamic regions [35].

These results indicate that age-related decreases in DA function are associated with a decline in cognitive functioning. Hereby, DA may affect different systems that are critical for different cognitive abilities.

In sum, these data could lead to the prediction that at least some aspects of stimulus reinforcement learning, which relies on releasing DA in the striatum and the PFC, might be altered in the aging brain. It is plausible that either reduced DA release or an altered postsynaptic effect may affect information processing and thus task performance in older adults. However, although these PET studies using biochemical markers are highly reliable and provide a signal for radioligand binding to specific proteins of the neurotransmission system, PET studies cannot assess the rapid alterations in regional neural activity induced by changes in task demands.

3.3. Cognitive changes in aging

A large body of evidence has shown that cognitive abilities decline with age across different domains, such as episodic and working memory, tasks requiring executive functions, inhibition, processing speed, and reasoning [14,45,46]. Aging is associated with impairments in tasks involving executive functions whereas age-related differences are only modest in simple working memory tasks, such as digit span. In contrast, older participants perform significantly worse on tasks that require active maintenance and manipulation of information within working memory, such as monitoring of previous responses in the self-ordered pointing task [15,61,86,98] or the inhibitory control of working memory contents (for a review, see [27]). In contrast, measures of crystallized intelligence, such as vocabulary or semantic knowledge, are relatively stable until late life [43,59,80].

Taking into account the various structural, physiological, and cognitive changes, which occur during healthy aging, different components of reward-based learning could be specifically affected and possibly account for some of these cognitive deficits.

3.4. Neural correlates of cognitive changes in aging

To investigate possible neural correlates of the behavioral changes that are associated with aging, several recent studies have used PET and functional magnetic resonance imaging (fMRI). In working memory as well as episodic memory tasks, old people exhibited a bilateral activation in PFC whereas the PFC of young subjects was activated

only unilaterally [78] (for review, see [12]). Generally, bilateral functional activity could be related to higher cognitive performance in old age [13]. This commonly found pattern was interpreted as evidence for a compensational process and was called "hemispheric asymmetry reduction in old adults" (HEROLD) [12,70].

3.5. Reward processing in aging and its behavioral and neural correlates

In the context of reward-based decision-making, however, only few studies investigated possible age-related changes and animal reports showed controversial results. Some studies investigating this process in animals using simple reward discrimination and reward reversal learning paradigms found age-related deficits in learning and reversing a certain reward contingency [4,81,94]. Other authors report a small if any age-related decline [30,63].

Furthermore, different results about the nature of the errors in older animals are reported. Some authors showed that older animals tend to perseverate on task sets, which are no longer valid [4,87]. Others propose a failure in learning new stimulus reward associations as revealed in learning stage analyses [94].

In humans, studies investigated stimulus reinforcement learning using the Wisconsin Card Sorting Test (WCST) [26,71]. Differences in task performance between young and old participants were discussed controversially. Ridderinkhof et al. propose that older adults have the tendency to perseverate because of deficits in set shifting abilities [71]. In contrast, Hartman et al. argue that performance differences are due to a decline in updating items in working memory [26].

Using more complex reward-based decision-making tasks, such as the Iowa gambling task, thought to be sensitive to orbitofrontal functioning, age-related declines in task performance could not be found [48], suggesting little if any age-related orbitofrontal alteration in old age [48]. A recent study using Rogers' task demonstrated reduced risk-taking behavior and greater latency to respond along with a tendency to make poorer decisions in older adults [16]. The authors suggest that older adults may show slower learning in avoiding high risk choices, tend to be more conservative than the younger participants, and show reduced speed of performance which might be related to a general age-related factor, such as processing speed.

Levine et al. studied conditional associative learning in older adults and in patients with damage to the PFC [42]. Higher error scores were attributed to decline in inhibitory processes and it was argued that this deficit was due to dlPFC dysfunction.

Using the pORT (described above) in a behavioral study with 20 young and 20 older participants, we found deficits in reward association learning in older adults [52]. Compared to younger adults, older adults showed poorer performance, i.e. they collected less points throughout the task and needed more trials to learn the stimulus response associations. Interestingly, older adults did not show significantly more perseverative errors compared to young adults. The difference in task performance remained statistically significant after correcting for the age effect in other tests assessing executive functions, such as the self-ordered pointing task (SOPT), the Stroop Word Color Interference task (Stroop) and the Tower of London task (TOL). This suggests that the age effect found in the pORT can be separated from general age effects on executive functioning.

Taken together, older adults can learn stimulus response associations and are flexible to adapt existing ones to new situations but require more effort compared to young adults.

It is possible that structural as well as functional changes in the reward system may account for this altered processing. For example, reduced dopamine release may result in an increase of signal to noise ratio, i.e. behaviorally relevant rewards need more time to be integrated in a current contextual representation [10,44].

To date, only few studies have investigated the effect of aging on stimulus response learning by means of functional neuroimaging. In a study by Nagahama et al., the effect on executive functions was investigated, using the WCST [54]. Age-related reductions of activity were found in left PFC, parietal, and cerebellar gyrus. The right hemispheric ventrolateral PFC was activated in older adults but not in younger adults. Left dlPFC, precuneus as well as lingual and parahippocampal gyrus showed significant negative correlations between the number of perseverative errors and regional cerebral blood flow (rCBF). As the number of perseverative errors correlated with age, the authors suggest that these regions may reflect age-related deficits in set-shifting ability. Esposito et al. investigated executive functions using the WCST and Raven's progressive matrices (RPM) in young and old participants [20]. During WCST, participants showed activations in frontopolar cortex, cuneus, parahippocampal gyrus, and deactivations in left prefrontal cortex, ACC, and cerebellum not seen in the young subjects. These age-related differences may reflect a failure to engage appropriate networks and suppress inappropriate ones, or a compensatory use of alternative networks. Furthermore, this study suggests that age-related changes are task-specific. For example, in young adults left PFC was activated during both WCST and RPM, whereas in older adults it was activated during RPM but deactivated during WCST.

These above mentioned studies indicate that there is an age-related decrease of rCBF as measured with PET in dlPFC during tasks that require the detection of feedback and flexible relearning as contingencies change. However, because of the low temporal resolution of PET it remains unclear whether the dlPFC is less activated during the whole task or whether this alteration in dlPFC is process specific. In addition, the deficit in dlPFC could be related to a deficit in set-shifting rather than a deficit in stimulus reinforcement learning. Finally, while functional and morphological alterations during aging in dlPFC are well established, little data exist on functional integrity of the OFC or the basal ganglia.

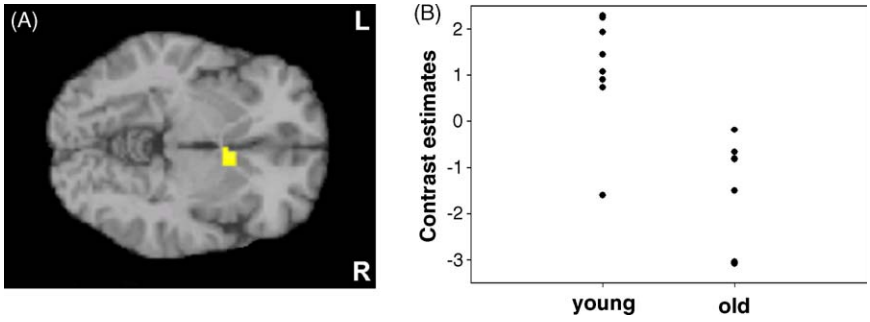

Fig. 3. Age effects on neural correlates of reward assocation learning. (A) Statistical map of a group comparison between young and older adults (preliminary data, 8 young and 8 older participants). Comparing LEARNED to SEARCH trials revealed greater activation of right ventral striatum ($x = 8/y = 12/z = -5$) during reward processing in young relative to older adults. (B) Contrast estimates in ventral striatum in the young and older participants, respectively [53].

Specifically, the interplay and differential age-related vulnerability within the reward system is unclear. Therefore, it is of special interest to know to what extent different aspects of reward processing and reward association learning are vulnerable to aging.

3.6. Age effects on neural correlates of probabilistic reward association learning

To address this issue we used event-related fMRI while older ($n = 9$, mean age = 67.5 years) and younger ($n = 9$, mean age = 24.3) participants performed the pORT [68], see above [52]. Similar to our previous behavioral study, older adults collected fewer points and needed more trials to learn stimulus response associations than younger adults ($p < 0.001$). This difference remained statistically significant after correcting for the age effect in other frontal tests. Preliminary fMRI results show that young participants recruited the dorsolateral PFC while learning stimulus response associations (i.e. a greater change in blood-oxygen-level-dependent (BOLD) signal to feedback cues while stimulus response associations have not yet been learned). FMRI signal changes in the ventral striatum showed the opposite pattern: after associations had been learned there was a greater BOLD response relative to trials in which associations had not yet been learned. In contrast, older adults showed additional activation in frontopolar regions during the decision-making phase (compare Fig. 1). Comparing signal changes in older and young adults, we found that the VST was less activated during reward processing in older than in young adults after stimulus reward associations had been learned (see Fig. 3). These data thus show age-related differences in reward association learning and are consistent with several studies showing additional recruitment of PFC in older adults. The differential activation in the ventral striatum could be related to age-related alterations of the reward system as outlined above.

When using functional imaging techniques, such as fMRI to study neural correlates of cognitive aging several caveats have to be mentioned. Healthy elderly participants might have risk factors for cerebrovascular pathology, such as diabetes, hypertension and hyperlipidaemia. All of these factors might affect the BOLD signal by altering cerebral blood flow (CBF) and neurovascular coupling [17,28,31]. Altered neurovascular coupling might also explain the finding that the hemodynamic response of older subjects reaches its peak earlier and is more variable across individuals compared to younger subjects [1,33]. When interpreting age-differences in neuroimaging data these caveats should be kept in mind.

4. Conclusion

The findings reviewed above help to gain a more complete picture of the neural basis of reward-based decision-making in the human brain and how this process is influenced by aging. Previous studies investigating mechanisms of decision-making used simple perceptual decision-making tasks (e.g. direction of motion discrimination [85], flutter discrimination [76], face-house discrimination [29]). In everyday behavior rewards play an important role. As reviewed above, alteration of the reward system might lead to impairments in cognitive flexibility. Therefore, better understanding reward-related processes, such as reward-based decision-making in the aging brain is an important goal for future research. From a neuroeconomical perspective it is important to keep in mind that in the future in many countries the proportion of elderly citizens will increase (e.g. in the year 2030, about 50% of the German population will be over 50) and that the over 50-year-old have a great buying power (about €90 billion in Germany). Specifically, the changes in choice behavior (lack in flexibility and perseveration) and reward processing are relevant for the accessibility for advertising effects. Understanding (altered) reward processing in the aging brain will be crucial for the nascent field of neuroeconomics.

The findings reviewed above are also important from a clinical perspective: Patients suffering from neurodegenerative diseases, such as Alzheimer's disease (AD) show deficits in reversal learning tasks [22]. Neurofibrillary tangle pathology in the OFC is extensive in early stages of Alzheimer's disease [9]. This widespread orbitofrontal damage in AD may contribute to the severe behavioral changes, such as

disinhibition, decision-making impairments, and executive control deficits [91]. The performance of stimulus reinforcement learning could gain significance in the early diagnosis of AD.

Acknowledgements

We thank Shu-Chen Li for very helpful comments on this manuscript. Financial support of DFG (Graduate Program "Neuropsychiatry and Psychology of Aging", Emmy-Noether-Program), BMBF (Berlin Neuroimaging Center), and International Leibniz Program Clinical and Cognitive Neurosciences are gratefully acknowledged.

References

[1] G.K. Aguirre, E. Zarahn, M. D'Esposito, The variability of human, BOLD hemodynamic responses, Neuroimage 8 (1998) 360–369.
[2] M.S. Albert, Age-related changes in cognitive function, in: M.L. Albert, J.E. Knoefel (Eds.), Clinical Neurobiology of Aging, Oxford University Press, New York, 1994, pp. 314–328.
[3] L. Backman, N. Ginovart, R.A. Dixon, T.B. Wahlin, A. Wahlin, C. Halldin, L. Farde, Age-related cognitive deficits mediated by changes in the striatal dopamine system, Am. J. Psychiatry 157 (2000) 635–637.
[4] R.T. Bartus, R.L. Dean III, D.L. Fleming, Aging in the rhesus monkey: effects on visual discrimination learning and reversal learning, J. Gerontol. 34 (1979) 209–219.
[5] M.G. Baxter, E.A. Murray, The amygdala and reward, Nat. Rev. Neurosci. 3 (2002) 563–573.
[6] A. Bechara, Neurobiology of decision-making: risk and reward, Semin. Clin. Neuropsychiatry 6 (2001) 205–216.
[7] A. Bechara, A.R. Damasio, H. Damasio, S.W. Anderson, Insensitivity to future consequences following damage to human prefrontal cortex, Cognition 50 (1994) 7–15.
[8] G.S. Berns, S.M. McClure, G. Pagnoni, P.R. Montague, Predictability modulates human brain response to reward, J. Neurosci. 21 (2001) 2793–2798.
[9] H. Braak, E. Braak, J. Bohl, Staging of Alzheimer-related cortical destruction, Eur. Neurol. 33 (1993) 403–408.
[10] T.S. Braver, D.M. Barch, A theory of cognitive control, aging cognition, and neuromodulation, Neurosci. Biobehav. Rev. 26 (2002) 809–817.
[11] H.C. Breiter, I. Aharon, D. Kahneman, A. Dale, P. Shizgal, Functional imaging of neural responses to expectancy and experience of monetary gains and losses, Neuron 30 (2001) 619–639.
[12] R. Cabeza, L. Nyberg, Neural bases of learning and memory: functional neuroimaging evidence, Curr. Opin. Neurol. 13 (2000) 415–421.
[13] R. Cabeza, N.D. Anderson, J.K. Locantore, A.R. McIntosh, Aging gracefully: compensatory brain activity in high-performing older adults, Neuroimage 17 (2002) 1394–1402.
[14] F.I.M. Craik, J.M. Jennings, Human memory, in: F.I.M. Craik, T.A. Salthouse (Eds.), Handbook of Aging and Cognition, Erlbaum, Hillsdale, NJ, 1992, pp. 51–109.
[15] S. Daigneault, C.M. Braun, Working memory and the self-ordered pointing task: further evidence of early prefrontal decline in normal aging, J. Clin. Exp. Neuropsychol. 15 (1993) 881–895.
[16] J. Deakin, M. Aitken, T. Robbins, B.J. Sahakian, Risk taking during decision-making in normal volunteers changes with age, J. Int. Neuropsychol. Soc. 10 (2004) 590–598.
[17] M. D'Esposito, L.Y. Deouell, A. Gazzaley, Alterations in the BOLD fMRI signal with ageing and disease: a challenge for neuroimaging, Nat. Rev. Neurosci. 4 (2003) 863–872.
[18] R. Elliott, R.J. Dolan, C.D. Frith, Dissociable functions in the medial and lateral orbitofrontal cortex: evidence from human neuroimaging studies, Cereb. Cortex 10 (2000) 308–317.
[19] R. Elliott, C.D. Frith, R.J. Dolan, Differential neural response to positive and negative feedback in planning and guessing tasks, Neuropsychologia 35 (1997) 1395–1404.
[20] G. Esposito, B.S. Kirkby, J.D. Van Horn, T.M. Ellmore, K.F. Berman, Context-dependent, neural system-specific neurophysiological concomitants of ageing: mapping PET correlates during cognitive activation, Brain 122 (Pt 5) (1999) 963–979.
[21] C.D. Fiorillo, P.N. Tobler, W. Schultz, Discrete coding of reward probability and uncertainty by dopamine neurons, Science 299 (2003) 1898–1902.
[22] M. Freedman, M. Oscar-Berman, Spatial and visual learning deficits in Alzheimer's and Parkinson's disease, Brain Cogn. 11 (1989) 114–126.
[23] S. Frey, M. Petrides, Orbitofrontal cortex: a key prefrontal region for encoding information, Proc. Natl. Acad. Sci. U.S.A. 97 (2000) 8723–8727.
[24] S. Frey, M. Petrides, Orbitofrontal cortex and memory formation, Neuron 36 (2002) 171–176.
[25] F.M. Gunning-Dixon, D. Head, J. McQuain, J.D. Acker, N. Raz, Differential aging of the human striatum: a prospective MR imaging study, AJNR Am. J. Neuroradiol. 19 (1998) 1501–1507.
[26] M. Hartman, E. Bolton, S.E. Fehnel, Accounting for age differences on the Wisconsin Card Sorting Test: decreased working memory, not inflexibility, Psychol. Aging 16 (2001) 385–399.
[27] L. Hasher, R.T. Zacks, Working memory, comprehension, and aging: a review and a new view, in: G.H. Bower (Ed.), The Psychology of Learning and Motivation, vol. 22, Academic Press, San Diego, 1988, pp. 193–225.
[28] T. Hedden, J.D. Gabrieli, Insights into the ageing mind: a view from cognitive neuroscience, Nat. Rev. Neurosci. 5 (2004) 87–96.
[29] H.R. Heekeren, S. Marrett, P.A. Bandettini, L.G. Ungerleider, A general mechanism for perceptual decision-making in the human brain, Nature 431 (2004) 859–862.
[30] J.G. Herndon, M.B. Moss, D.L. Rosene, R.J. Killiany, Patterns of cognitive decline in aged rhesus monkeys, Behav. Brain Res. 87 (1997) 25–34.
[31] C. Hock, F. Muller-Spahn, S. Schuh-Hofer, M. Hofmann, U. Dirnagl, A. Villringer, Age dependency of changes in cerebral hemoglobin oxygenation during brain activation: a near-infrared spectroscopy study, J. Cereb. Blood Flow Metab. 15 (1995) 1103–1108.
[32] P.R. Hof, J.H. Morrison, The aging brain: morphomolecular senescence of cortical circuits, Trends Neurosci. 27 (2004) 607–613.
[33] S.A. Huettel, J.D. Singerman, G. McCarthy, The effects of aging upon the hemodynamic response measured by functional MRI, Neuroimage 13 (2001) 161–175.
[34] B. Jones, M. Mishkin, Limbic lesions and the problem of stimulus-reinforcement associations, Exp. Neurol. 36 (1972) 362–377.
[35] V. Kaasinen, H. Vilkman, J. Hietala, K. Nagren, H. Helenius, H. Olsson, L. Farde, J. Rinne, Age-related dopamine D2/D3 receptor loss in extrastriatal regions of the human brain, Neurobiol. Aging 21 (2000) 683–688.
[36] T.L. Kemper, Neuroanatomical and neuropathological changes in normal aging and in dementia, in: M. Albert, J. Knoefel (Eds.), Clinical Neurology of Aging, Oxford University Press, New York and Oxford, 1994, pp. 3–78.
[37] B. Knutson, C.M. Adams, G.W. Fong, D. Hommer, Anticipation of increasing monetary reward selectively recruits nucleus accumbens, J. Neurosci. 21 (2001) RC159.
[38] A.F. Kramer, D.G. Humphrey, J.F. Larish, G.D. Logan, D.L. Strayer, Aging and inhibition: beyond a unitary view of inhibitory processing in attention, Psychol. Aging 9 (1994) 491–512.

[39] J. Kray, U. Lindenberger, Adult age differences in task switching, Psychol. Aging 15 (2000) 126–147.
[40] M.L. Kringelbach, E.T. Rolls, The functional neuroanatomy of the human orbitofrontal cortex: evidence from neuroimaging and neuropsychology, Prog. Neurobiol. 72 (2004) 341–372.
[41] A.D. Lawrence, B.J. Sahakian, R.D. Rogers, J.R. Hodge, T.W. Robbins, Discrimination, reversal, and shift learning in Huntington's disease: mechanisms of impaired response selection, Neuropsychologia 37 (1999) 1359–1374.
[42] B. Levine, D.T. Stuss, W.P. Milberg, Effects of aging on conditional associative learning: process analyses and comparison with focal frontal lesions, Neuropsychology 11 (1997) 367–381.
[43] S.C. Li, U. Lindenberger, B. Hommel, G. Aschersleben, W. Prinz, P.B. Baltes, Transformations in the couplings among intellectual abilities and constituent cognitive processes across the life span, Psychol. Sci. 15 (2004) 155–163.
[44] S.C. Li, U. Lindenberger, S. Sikstrom, Aging cognition: from neuromodulation to representation, Trends Cogn. Sci. 5 (2001) 479–486.
[45] U. Lindenberger, P.B. Baltes, Intellectual functioning in old and very old age: cross-sectional results from the Berlin Aging Study, Psychol. Aging 12 (1997) 410–432.
[46] U. Lindenberger, U. Mayr, R. Kliegl, Speed and intelligence in old age, Psychol. Aging 8 (1993) 207–220.
[47] T. Ljungberg, P. Apicella, W. Schultz, Responses of monkey dopamine neurons during learning of behavioral reactions, J. Neurophysiol. 67 (1992) 145–163.
[48] S.E. MacPherson, L.H. Phillips, S.S. Della, Age, executive function, and social decision making: a dorsolateral prefrontal theory of cognitive aging, Psychol. Aging 17 (2002) 598–609.
[49] D.J. Madden, J.M. Hoffmann, Application of positron emission tomography to age related cognitive changes, in: K.R.R. Krishnan, P.M. Doraiswamy (Eds.), Brain Imaging in Clinical Psychiatry, Marcel Dekker, New York, 1997, pp. 575–613.
[50] D.J. Madden, T.G. Turkington, R.E. Coleman, J.M. Provenzale, T.R. DeGrado, J.M. Hoffman, Adult age differences in regional cerebral blood flow during visual world identification: evidence from H215O PET, Neuroimage 3 (1996) 127–142.
[51] A. Marschner, H.R. Heekeren, T. Mell, D. Kronfeldt, I. Wartenburger, A. Villringer, F.M. Reischies, Reward association learning modulates activity in dorsolateral prefrontal cortex during decision-making processes, Neuroimage 16 (2002) 1077.
[52] T. Mell, H.R. Heekeren, A. Marschner, I. Wartenburger, A. Villringer, F.M. Reischies, Effect of aging on stimulus-reward association learning, Neuropsychologia 43 (2005) 554–563.
[53] T. Mell, I. Wartenburger, A. Marschner, A. Villringer, H.R. Heekeren, F.M. Reischies, Reward association learning and expectancy control: aging effects on the mesolimbic reward system, Biol. Psychiatry 55 (2004) 156.
[54] Y. Nagahama, H. Fukuyama, H. Yamauchi, Y. Katsumi, Y. Magata, H. Shibasaki, J. Kimura, Age-related changes in cerebral blood flow activation during a Card Sorting Test, Exp. Brain Res. 114 (1997) 571–577.
[55] J. O'Doherty, R. Deichmann, H.D. Critchley, R.J. Dolan, Neural responses during anticipation of a primary taste reward, Neuron 33 (2002) 815–826.
[56] J. O'Doherty, M.L. Kringelbach, E.T. Rolls, J. Hornak, C. Andrews, Abstract reward and punishment representations in the human orbitofrontal cortex, Nat. Neurosci. 4 (2001) 95–102.
[57] M. Oscar-Berman, S.M. Zola-Morgan, Comparative neuropsychology and Korsakoff's syndrome. I. Spatial and visual reversal learning, Neuropsychologia 18 (1980) 499–512.
[58] G. Pagnoni, C.F. Zink, P.R. Montague, G.S. Berns, Activity in human ventral striatum locked to errors of reward prediction, Nat. Neurosci. 5 (2002) 97–98.
[59] D.C. Park, A.D. Smith, G. Lautenschlager, J.L. Earles, D. Frieske, M. Zwahr, C.L. Gaines, Mediators of long-term memory performance across the life span, Psychol. Aging 11 (1996) 621–637.
[60] A.J. Parkin, A. Lawrence, A dissociation in the relation between memory tasks and frontal lobe tests in the normal elderly, Neuropsychologia 32 (1994) 1523–1532.
[61] M. Petrides, B. Milner, Deficits on subject-ordered tasks after frontal- and temporal-lobe lesions in man, Neuropsychologia 20 (1982) 249–262.
[62] S. Rahman, J. Sahakia, N. Cardinal, R. Rogers, T. Robbins, Decision-making and neuropsychiatry, Trends Cogn. Sci. 5 (2001) 271–277.
[63] P.R. Rapp, Visual discrimination and reversal learning in the aged monkey (*Macaca mulatta*), Behav. Neurosci. 104 (1990) 876–884.
[64] N. Raz, Aging of the brain and its impact on cognitive performance: integration of structural and functional findings, in: F.I.M. Craik, T.A. Salthouse (Eds.), Handbook of Aging and Cognition, Erlbaum, Mahwah, NJ, 2000, pp. 1–90.
[65] N. Raz, F.M. Gunning-Dixon, D. Head, J.H. Dupuis, J.D. Acker, Neuroanatomical correlates of cognitive aging: evidence from structural magnetic resonance imaging, Neuropsychology 12 (1998) 95–114.
[66] N. Raz, F.M. Gunning, D. Head, J.H. Dupuis, J. McQuain, S.D. Briggs, W.J. Loken, A.E. Thornton, J.D. Acker, Selective aging of the human cerebral cortex observed in vivo: differential vulnerability of the prefrontal gray matter, Cereb. Cortex 7 (1997) 268–282.
[67] N. Raz, F. Gunning-Dixon, D. Head, K.M. Rodrigue, A. Williamson, J.D. Acker, Aging, sexual dimorphism, and hemispheric asymmetry of the cerebral cortex: replicability of regional differences in volume, Neurobiol. Aging 25 (2004) 377–396.
[68] F.M. Reischies, Pattern of disturbance of different ventral frontal functions in organic depression, Ann. N. Y. Acad. Sci. 877 (1999) 775–780.
[69] S.M. Resnick, D.L. Pham, M.A. Kraut, A.B. Zonderman, C. Davatzikos, Longitudinal magnetic resonance imaging studies of older adults: a shrinking brain, J. Neurosci. 23 (2003) 3295–3301.
[70] P.A. Reuter-Lorenz, J. Jonides, E.E. Smith, A. Hartley, A. Miller, C. Marshuetz, R.A. Koeppe, Age differences in the frontal lateralization of verbal and spatial working memory revealed by PET, J. Cogn. Neurosci. 12 (2000) 174–187.
[71] K.R. Ridderinkhof, M.M. Span, M.W. van der Molen, Perseverative behavior and adaptive control in older adults: performance monitoring, rule induction, and set shifting, Brain Cogn. 49 (2002) 382–401.
[72] R.D. Rogers, B.J. Everitt, A. Baldacchino, A.J. Blackshaw, R. Swainson, K. Wynne, N.B. Baker, J. Hunter, T. Carthy, E. Booker, M. London, J.F. Deakin, B.J. Sahakian, T.W. Robbins, Dissociable deficits in the decision-making cognition of chronic amphetamine abusers, opiate abusers, patients with focal damage to prefrontal cortex, and tryptophan-depleted normal volunteers: evidence for monoaminergic mechanisms, Neuropsychopharmacology 20 (1999) 322–339.
[73] R.D. Rogers, A.M. Owen, H.C. Middleton, E.J. Williams, J.D. Pickard, B.J. Sahakian, T.W. Robbins, Choosing between small, likely rewards and large, unlikely rewards activates inferior and orbital prefrontal cortex, J. Neurosci. 19 (1999) 9029–9038.
[74] E.T. Rolls, The orbitofrontal cortex and reward, Cereb. Cortex 10 (2000) 284–294.
[75] E.T. Rolls, J. Hornak, D. Wade, J. McGrath, Emotion-related learning in patients with social and emotional changes associated with frontal lobe damage, J. Neurol. Neurosurg. Psychiatry 57 (1994) 1518–1524.
[76] R. Romo, E. Salinas, Flutter discrimination: neural codes, perception, memory and decision making, Nat. Rev. Neurosci. 4 (2003) 203–218.
[77] J.B. Rowe, I. Toni, O. Josephs, R.S. Frackowiak, R.E. Passingham, The prefrontal cortex: response selection or maintenance within working memory? Science 288 (2000) 1656–1660.
[78] B. Rypma, M. D'Esposito, Isolating the neural mechanisms of age-related changes in human working memory, Nat. Neurosci. 3 (2000) 509–515.
[79] D.H. Salat, J.A. Kaye, J.S. Janowsky, Greater orbital prefrontal volume selectively predicts worse working memory performance in older adults, Cereb. Cortex 12 (2002) 494–505.

[80] K.W. Schaie, Intellectual Development in Adulthood: The Seattle Longitudinal Study, Cambridge University Press, Cambridge, 1996.
[81] G. Schoenbaum, S. Nugent, M.P. Saddoris, M. Gallagher, Teaching old rats new tricks: age-related impairments in olfactory reversal learning, Neurobiol. Aging 23 (2002) 555–564.
[82] W. Schultz, Responses of midbrain dopamine neurons to behavioral trigger stimuli in the monkey, J. Neurophysiol. 56 (1986) 1439–1461.
[83] W. Schultz, Multiple reward signals in the brain, Nat. Rev. Neurosci. 1 (2000) 199–207.
[84] W. Schultz, R. Romo, Dopamine neurons of the monkey midbrain: contingencies of responses to stimuli eliciting immediate behavioral reactions, J. Neurophysiol. 63 (1990) 607–624.
[85] M.N. Shadlen, W.T. Newsome, Neural basis of a perceptual decision in the parietal cortex (area LIP) of the rhesus monkey, J. Neurophysiol. 86 (2001) 1916–1936.
[86] A.P. Shimamura, P.J. Jurica, Memory interference effects and aging: findings from a test of frontal lobe function, Neuropsychology 8 (1994) 408–412.
[87] P.D. Tapp, C.T. Siwak, J. Estrada, E. Head, B.A. Muggenburg, C.W. Cotman, N.W. Milgram, Size and reversal learning in the beagle dog as a measure of executive function and inhibitory control in aging, Learn. Membr. 10 (2003) 64–73.
[88] L. Tremblay, W. Schultz, Relative reward preference in primate orbitofrontal cortex, Nature 398 (1999) 704–708.
[89] M. Ullsperger, D.Y. von Cramon, Error monitoring using external feedback: specific roles of the habenular complex, the reward system, and the cingulate motor area revealed by functional magnetic resonance imaging, J. Neurosci. 23 (2003) 4308–4314.
[90] M. Ullsperger, D.Y. von Cramon, Decision making, performance and outcome monitoring in frontal cortical areas, Nat. Neurosci. 7 (2004) 1173–1174.
[91] G.W. Van Hoesen, J. Parvizi, C.C. Chu, Orbitofrontal cortex pathology in Alzheimer's disease, Cereb. Cortex 10 (2000) 243–251.
[92] N.D. Volkow, R.C. Gur, G.J. Wang, J.S. Fowler, P.J. Moberg, Y.S. Ding, R. Hitzemann, G. Smith, J. Logan, Association between decline in brain dopamine activity with age and cognitive and motor impairment in healthy individuals, Am. J. Psychiatry 155 (1998) 344–349.
[93] K.G. Volz, R.I. Schubotz, D.Y. von Cramon, Predicting events of varying probability: uncertainty investigated by fMRI, Neuroimage 19 (2003) 271–280.
[94] M.L. Voytko, Impairments in acquisition and reversals of two-choice discriminations by aged rhesus monkeys, Neurobiol. Aging 20 (1999) 617–627.
[95] G.J. Wang, N.D. Volkow, J. Logan, J.S. Fowler, D. Schlyer, R.R. MacGregor, R.J. Hitzemann, R.C. Gur, A.P. Wolf, Evaluation of age-related changes in serotonin 5-HT2 and dopamine D2 receptor availability in healthy human subjects, Life Sci. 56 (1995) L249–L253.
[96] F. Wenz, K. Rempp, G. Brix, M.V. Knopp, F. Guckel, T. Hess, G. van Kaick, Age dependency of the regional cerebral blood volume (rCBV) measured with dynamic susceptibility contrast MR imaging (DSC), Magn. Reson. Imaging 14 (1996) 157–162.
[97] R.L. West, An application of prefrontal cortex function theory to cognitive aging, Psychol. Bull. 120 (1996) 272–292.
[98] R. West, A.M. Ergis, G. Winocur, J. Saint-Cyr, The contribution of impaired working memory monitoring to performance of the self-ordered pointing task in normal aging and Parkinson's disease, Neuropsychology 12 (1998) 546–554.
[99] A.M. Young, M.H. Joseph, J.A. Gray, Increased dopamine release in vivo in nucleus accumbens and caudate nucleus of the rat during drinking: a microdialysis study, Neuroscience 48 (1992) 871–876.