Is getting older all that rewarding?

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The increasing public health impact of addictive disorders and obesity has led to an emphasis on studying the neurobiology of reward. Studies of reward integrate basic and cognitive neuroscience with *in vivo* approaches in humans. In this issue of PNAS, Dreher *et al.* (1) use neuroimaging to visualize the *in vivo* neurochemistry and neural circuitry of reward in older and younger adults. They show different relationships (1) between estimated dopa decarboxylase activity (DDC), assessed through PET measurement of the presynaptic dopamine (DA) system with [^{18}F]flurodopa (FDopa), a radiolabeled derivative of dopa (measure of DA), and reward measured by fMRI networks. They found that midbrain measures of FDopa correlated positively with the BOLD signal after tasks eliciting a reward mechanism in youth but negatively in aged subjects. There were also regional differences in brain activation between the two age groups.

This finding has implications for both normal and pathological forms of reward and physiological aging. This study is among the first to demonstrate differences in DA–reward relationships between the young and old.

Age effects in the DA system were observed in postmortem human studies, PET measurements of D_2/D_3 DA (2) receptors and DA transporters (DAT) (3). Dreher *et al.* (1) measured the influx constant (K_i), which does not fall with age and does not distinguish DDC activity (which does fall with age) from efflux rate. K_i is decreased in neurodegeneration and measures aspects of presynaptic DA and is not confounded by age effects, which enhances the observation of different correlations of DA and reward. Although the FDopa data are not age-specific, the fMRI data may reflect the functional consequences of DA deficit. These studies provide evidence for why reward may be different in older age groups.

Recently, more studies are looking into reward by building on animal models, which have assumed that DA is fundamental. These studies have impacted our understanding of the differences between normal and pathophysiological reward (Table 1). Further studies investigated human reactions to tasks eliciting reward mechanisms (money, sex, passionate love, and food intake). Reward has been shown via fMRI and PET in conjunction with tasks that elicit DA, as in alcoholism (4). Recently it has been possible to demonstrate that the pathways affect endogenous DA changes at the intrasynaptic level, e.g., in drug craving (5). A small number of investigations using PET-[^{11}C]raclopride have measured intrasynaptic DA release (DAR) during reward paradigms. These studies found DAR during expectation of reward but not during reward itself after administration of a placebo in the ventral striatum in patients with Parkinson's (6) and in different striatal regions during unexpected reward tasks (7), in variance with some animal studies. The findings of unanticipated reward appear to be more reproducible using fMRI (8), setting the stage for bringing together computational neuroscience with functional neurotransmitter neuroimaging and electrophysiologic recording of DA measurements in animals. This research indicates that anticipation of reward is more relevant than delivery of reward (9).

Table 1. Summary of aging and reward literature

Species	Findings	Refs.
Animal	Animal models of adolescent vs. adult brain in drug abuse	13
Human	D_2/D_3 fall with age	2
Human/animal	Increased risk of drug abuse in aged	11
Human	Food craving falls in aged	14
Human	Gastric bypass less effective in aged	17
Human	Predilection to fraud in aged	18
Human	Gambling problems in aged	18,19
Human	Anorexia in aging	16
Human	Dietary and appetite effects of anorexia	15
Human	AD in decision making/gambling tasks	20
Human	Apathy in AD	21
Human	Presynaptic DA PET measures fall with age	22
Human	DA in the ventral striatum relates to reward	6
Human/animal	Computational reward models	9
Human	Age decrease in striatal DAT	3
Human	Increased demands on drug abuse treatment over next 20 yr	10
Human	Suppressed putamen DA transmission	7
Human	Dorsal striatal DA involved with craving	5
Human	Cognitive enhancers in the elderly	12
Human	Differences in male vs. female brain	23
Human	fMRI of reward	8

How do these findings relate to what is known about reward in older populations? Studies predict a dramatic increase in the needs of drug treatment for the aged by 2020 (10). The different interaction between DA and reward in the aging gives further insight into the reward dysfunction risks in older patients. Substance abuse has a different pattern in the aging than in youth (11). This problem may worsen with the misuse of prescription drugs by the elderly. A related concern is the widespread use of cognitive enhancers in the aging population, even when they may not be indicated for cognitive decline. This attempt at enhancement of normal cognitive function may be misguided, especially in the aged, if reward mechanisms are altered (12). Several animal models have investigated this issue (13).

Age effects on reward relate to food intake and economic decision-making: The elderly tend to crave and intake food less (14), can be predisposed to anorexia (15), and can have decreased gut transit and desire to eat (16). In ad-

Author contributions: D.F.W. wrote the paper.

The author declares no conflict of interest.

See companion article on page 15106.

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dition, gastric bypass may be less effective in the elderly (17). It is of interest to examine the correlates of reward systems with DA D_2, D_1, or DAT, all of which fall dramatically with age and may fall differently in some patient groups vs. controls and extend beyond midbrain imaging.

Older adults may have diminished decision-making function, potentially contributing to the increased predilection to fraud possibly due to dysfunction in the ventral medial prefrontal cortex (18). As much as 35–40% of older adults may perform poorly in a decision-making task, and people over 60 may have greater gambling problems (19). Those with mild Alzheimer's disease (AD) showed poorer performance on gambling tasks and impairment for decisions where ambiguity was present (20).

Apathy may also represent a manifestation of abnormal reward processing (21). In mood disorders of the elderly, as well as in neurodegenerative disorders of late life, including AD and vascular diseases, apathy, in addition to other reward-related behavior (loss of appetite and libido), is prominent and more frequently observed in late versus early onset depression. Elderly patients have persistent apathy even after adequate treatment (e.g., depression) and because apathy affects cognition adversely in patients with dementia, as well as in those with globally normal cognition, it may be an early sign of incipient cognitive decline (21). Apathy may be a symptom of brain dysfunction in the elderly resulting from vascular, neurodegenerative, neurochemical, or hormonal mechanisms that have a final common pathway to affect DA reward pathways. Thus, numerous factors may affect self-gratification in the elderly based in part on differences in reward patterns and DA.

Future Directions

The results in Dreher *et al.* (1) provide insight into the neurobiology of reward–aging differences. Future studies should be extended across the life span of subjects to determine precisely where these reward patterns change the slope of correlations, given that this could affect treatment strategies.

Dreher *et al.* provide insight into the neurobiology of reward–aging differences.

Dreher *et al.* (1) chose to quantify FDopa with a composite measure K_i. Ideally, measures of DDC could be computed to directly measure DDC vs. efflux rates because they have been shown to decrease and increase with age (22), respectively. Correlation with more DDC activity might have shown a different relationship. Future studies could also correlate with other DA parameters, e.g., cortical D_2/D_3 or D_1 receptor binding, and ascertain whether the reward mechanisms are different in older vs. younger age groups because this could also affect therapy. In addition, using the recently available highest-resolution brain PET, such as the HRRT (high resolution research tomograph; 2-mm resolution), would allow imaging of very small brain areas relevant to reward. To provide a comprehensive understanding, future studies could include other neurotransmitter systems affected by the aging process.

Another issue is possible sex differences in reward mechanisms in older individuals. In Dreher *et al.* (1), younger women were randomly distributed across phase of the menstrual cycle, which could affect DA measures. There is evidence that the fall with age differs between the sexes and that menses is mediated by DA. Such age/sex differences would also have implications for pathophysiology and treatment because drug abuse and major mental illness have sex differences in onset, severity, and potential etiology (23).

Despite these age effects, there are many advantages of advancing age that are not easily quantifiable but contribute to reward (e.g., self-confidence, esteem, mentorship, peer recognition, etc.), but these advantages cannot be fully achieved unless society addresses the challenges to reward-related issues in aging. In summary, to paraphrase a TV commercial, "We hope we are not just getting older—we are getting better." Future research into the reward mechanisms in the aging population may help to achieve this more satisfying status for our citizens who have lived a productive life.

ACKNOWLEDGMENTS. This work was supported by National Institutes of Health Grant DA000412.

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