Age-Related Changes in Human and Nonhuman Timing

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Abstract

The capacity for timed behavior is ubiquitous across the animal kingdom, making time perception an ideal topic of comparative research across human and nonhuman subjects. One of the many consequences of normal aging is a systematic decline in timing ability, often accompanied by a host of behavioral and biochemical changes in the brain. In this review, we describe some of these behavioral and biochemical changes in human and nonhuman subjects. Given the involvement of timing in higher-order cognitive processing, age-related changes in timing ability can act as a marker for cognitive decline in older adults. Finally, we offer a comparison between human and nonhuman timing through the perspective of Alzheimer's disease. Taken together, we suggest that understanding timing functions and dysfunctions can improve theoretical accounts of cognitive aging and time perception, and the use of nonhuman subjects constitutes an integral part of this process.

Keywords

Aging, Alzheimer's disease, timing, time perception, animal models

1. Introduction

Temporal regularities in behavior are inextricably linked to an organism's continuity and survival — from a flowering perennial, to a hibernating black bear, to the fluctuating hormones that govern our daily sleep–wake cycle. That all creatures, both large and small, rely on the ability to perceive time highlights the role of timing as a central component of cognitive function, and a major determinant of behavior in both humans and nonhuman animals.

As another illustration of the profound role of timing, in a number of neuropsychiatric disorders including Parkinson's disease (Artieda et al., 1992; Pastor et al., 1992), Huntington's disease (Beste et al., 2007), or drug-induced brain states

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(Meck, 1996, 2005), the inability to represent temporal information can result in a myriad of behavioral disturbances that ultimately impede daily functioning. Even in healthy individuals, the experience of time is heavily influenced by a normal aging process, exhibiting gradual changes throughout life (Block et al., 1998; McCormack et al., 1999, 2002). Consider the experience of a young child, who has to wait a whole 365 days before their next birthday and before they will receive all those wonderful gifts. Now contrast this with the experience of an adult, who might be quite content with the same 365 days passing before their next birthday. Why is the subjective experience of the same 365 days so different in these two cases? Might the difference in age change the way we represent time? To address this question, a number of psychological (Meck, 1996, 2005) neurobiological (Buhusi & Meck, 2005; Merchant et al., 2013), and computational (Gibbon, 1977; Gibbon et al., 1984; Treisman et al., 1963) models have been posed.

In this review, we compare age-related changes in timing performance across human and nonhuman subjects. In addition, we consider how the representation of time differs in an abnormal aging process: Alzheimer's disease (AD). Understanding the relationship between chronological age and the experience of time will in turn offer theoretical insight and integrative avenues of therapeutic intervention for age-related psychiatric disorders (Davalos et al., 2005; Toplak et al., 2006).

2. Human Timing

Much of our daily routine relies on an accurate perception of time. Consider, for example, the preparation of a simple meal where multiple ingredients must be added in a sequential order and all within a specific time frame during the cooking process. Without the ability to estimate how much time is needed to finish cooking your current dish, or remember how long since you started preheating the oven, a simple meal might not turn out all that simple. As we age, changes in our perception of time make it increasingly difficult to carry out these daily tasks. While many of these changes can be attributed to a distorted experience of time (Friedman & Janssen, 2010; McAuley et al., 2006; Perbal et al., 2002; Wittmann & Lehnhoff, 2005;), many have far-reaching consequences for cognitive (dys)functioning at large (for reviews, see Balci et al., 2009; Fraisse, 1984; Turgeon et al., 2016). In the following section, we address two behavioral differences in timing between young and aged adults: the estimation and production of temporal intervals. Table 1 provides a summary of the studies discussed, the tasks and intervals used, as well as major results from these studies.

Effects of age on time perception can be most notably observed by a decrease in the accuracy of temporal estimates. For instance, in a temporal estimation task, participants are exposed to a standard interval (e.g., 8 s), and immediately asked to estimate the length of the interval to the best of their ability. In this case, the accuracy of their estimate is the measure of absolute deviation from the standard

Table 1.
Summary of recent studies investigating the relationship between aging and interval timing in humans.

Reference (year)	Subjects (age)	Task	Interval	Results
Anderson et al. (2014)	20 YA (19.95 ± 3.4 years),	Verbal estimation	10 s (short),	Mean errors did not differ between the two groups (both groups tend to underestimate); OA showed greater magnitude of error, regardless of direction; OA showed stability in their estimates over the course of one year
	20 OA (73.90 ± 8.16 years)		25 s (short),	
Bangert & Balota (2012)	66 YA (20.27 ± 1.56 years),	Continuation tapping	45 s (long),	
	119 OA (74.62 ± 7.42 years),		60 s (long)	
	46 CDR 0.5 (75.76 ± 7.54),		0.5 s, 1 s, 1.5 s	OA sped up their tapping at the longest target rate; YA showed similar CV, while OA showed increased CV with decreasing target rate; YA were more accurate, especially at slower tapping rates
	21 CDR 1 (79.76 ± 5.97)			
Bherer et al. (2007)	15 YA (25 ± 3.1 years),	Temporal production	2.5 s	Performance did not differ between groups in the no break condition; with a break, OA produced longer intervals
	15 OA (70.9 ± 5.7 years)	(with and without break)		
Carrasco et al. (2000)	8 OA (60 ± 9.95 years),	Temporal estimation	5 s, 10 s, 25 s	AD patients showed greater absolute error and variability than OA; AD group tends to overestimate short intervals, but the reproduced times are similar in the 25 s condition
	8 AD (62.13 ± 8.89 years)			
Carrasco et al. (2001)	13 YA (26.15 ± 6.64 years),	Temporal reproduction	10 s	OA produced shorter estimates than YA; no differences were found between OA and YA in accuracy and CV
	12 OA (79.1 ± 5.3 years)			
Caselli et al. (2009)	12 YA (mean age: 28.4),	Temporal bisection	0.1 s (short),	AD patients did not differ from OA and YA in the long bisection task (one to three seconds) but in the short bisection task (100 ms to 600 ms), AD patients (and to a milder degree, OA) showed greater response variability than YA
	12 OA (mean age: 71.4 years),		0.6 s (long),	
	12 AD (mean age: 70.6 years)		1 s (short), 3 s (long)	

Table 1.
(Continued)

Reference (year)	Subjects (age)	Task	Interval	Results
Lustig & Meck (2011)	12 children (mean = 8.24, SE = 0.08 years), 12 YA (mean = 20.3, SE = 0.53 years), 12 OA (mean = 68.7, SE = 1.29 years)	Temporal bisection	3 s (short), 6 s (long)	Auditory signals are judged as longer than visual signals by all groups, but children and OA showed a larger modality effect; performance of OA was similar to YA in the auditory modality, but OA underestimated visual signals
Lustig & Meck (2001)	34 YA (20.1 ± 1.2 years), 36 OA (69.3 ± 4.3 years)	Temporal bisection	3 s (short), 6 s (long)	Auditory signals are judged as longer than visual signals by both groups, but OA showed greater discrepancy; OA were less sensitive to time when both visual and auditory signals were presented
McCormack et al. (1999)	26 five-year olds, 32 eight-year olds, 34 ten-year olds, 26 YA 36 YA (19.6 ± 2.2 years), 55 Young-Old (69.6 ± 3.2 years), 33 OA (81.5 ± 5.8 years)	Temporal generalization; temporal bisection	0.125 s to 0.875 s	YA were more accurate than children and OA groups; the adult groups did not differ on the bisection task, but children were significantly impaired, showing greater overestimations on both tasks; age differences between children and YA were significant only at shorter durations, but not for intervals over 750 ms
Nichelli et al. (1993)	5 YA (mean age: 46 years), 15 OA (mean age: 65 years), 15 AD (mean age: 66 years), 4 Amnesics (mean age: 41 years)	Temporal reproduction; verbal estimation	Reproduction: 1 s Estimation: 5 s, 10 s, 20 s, 40 s	Amnesics performed similarly to the other groups on reproduction task, but significantly impaired on the estimation task; AD patients showed greater variability in reproduction, and greater error in the estimation task

Table 1.
(Continued)

Reference (year)	Subjects (age)	Task	Interval	Results
Pagagno et al. (2004)	21 OA (72.24 ± 6.80 years), 21 AD (71.86 ± 8.95 years)	Verbal estimation	15 s, 50 s	AD patients showed greater absolute error and variability than OA; when a demanding task was introduced (increased cognitive load), AD patients showed greater impairment than OA
Pouya et al. (2015)	250 participants aged 20 to 83 years (60.1 ± 14.4 years)	Temporal estimation (based on a virtual reality task)	40 s	Individuals under 70 years of age showed less absolute error (AE), directional error (over- and underestimation; DE) and variability than individuals over 70 years of age; significant correlations were found between age and AE and DE, but not between age and variability
Rakitin et al. (2005)	16 YA (18–28 years), OA 1: 16 OA (63.5 ± 9.2 years), OA 2: 16 OA (70.2 ± 6.2 years)	Temporal production (peak interval procedure)	6 s, 17 s	No differences between the groups during training, but following a 24h delay, both OA groups overestimated the 17-s interval as compared to YA. Accuracy was similar in YA and OA groups for the 6-s condition.
Rueda & Schmitter- Edgecombe (2009)	24 YA (19.83 ± 2.35 years), 24 OA (72.54 ± 8.84 years), 24 MCI patients (70.96 ± 9.79 years)	Verbal estimation	10 s (short), 25 s (short), 45 s (long), 60 s (long)	No differences were found between MCI and OA groups at short and long intervals, but their estimates were worse (greater absolute error) than YA
	17 OA (76.65 ± 6.64 years), 17 AD (78.06 ± 7.14 years)			AD patients had more absolute errors and response variability than OA; errors were greater for the two longer intervals for both groups

AD, Alzheimer's disease; CDR, clinical dementia rating; CV, coefficient of variation; MCI, mild cognitive impairments; OA, older adults; YA, young adults.

time. Using a temporal estimation task, Carrasco and colleagues compared the temporal estimates made by young (~26 years) and old (~79 years) adults. The length of the standard interval used in this study was 10 s. Every trial began with three rapid beeps and participants had to press the spacebar exactly 10 s after the last beep. Results from both age groups were analyzed based on three parameters: estimated time, amount of absolute error from the target time, and the standard deviation in their responses. While older adults produced intervals that were considerably shorter than those of young adults (that is, older adults consistently underestimated the interval), no differences were observed for the other two factors considered (Carrasco et al., 2001). Carrasco et al.'s findings suggest that the mechanisms underlying time perception may be preserved with age, but the content of older adults' representations may differ fundamentally from that of young adults (cf. Gunstad et al., 2006; Perbal et al., 2002). At shorter intervals (i.e., 1 s), older adults perform comparable to young adults if they were given feedback on their performance (Wearden et al., 1997). However at longer intervals, such as that used in the Carrasco et al.'s study — intervals that are necessary for the execution of daily activities — older adults showed a clear deficit compared to younger adults (Feifel, 1957; Kline et al., 1980; McGrath & O'Hanlon, 1968). Collectively, what these studies show is that age is negatively correlated with timing performance especially over longer intervals (Coelho et al., 2004).

In young children, a similar pattern of results is observed. McCormack et al. (1999) tested children (5–10 years), young adults (16–25 years), and older adults (63–99 years) on probe durations that were either the same as or different from a target duration. Compared to the other two groups, young adults were the most accurate in classifying each probe as being the same or different, though consistent with previous studies, there were no qualitative changes in the shape of the generalization gradient between groups (Droit-Volet & Clément, 2005; Droit-Volet & Wearden, 2001; Droit-Volet et al., 2001; Wearden et al., 1997). There are several different speculations about why children and older adults perform less optimally than young adults (McCormack et al., 1999, 2004). One hypothesis is that young children may not be proficient at controlling their attention towards relevant signals during the task (Droit-Volet et al., 2007), while older adults may not have the necessary attentional resources to attend to the signals (Lustig, 2003; Lustig & Meck, 2001, 2011). In a meta-analysis by Block, Zakay and Hancock, it was proposed that age-related differences may be exaggerated by the demands of the task (Block et al., 1998). Similarly, Lustig and Meck (2001) maintained that a reduction in the attentional resources associated with a normal aging process could account for at least some of these observed timing deficits. Whereas younger adults are able to allocate their attention flexibly to the relevant features of a task, the failure of executive attentional control in older adults may cause them to focus on other, irrelevant stimuli during the task (Lustig & Meck, 2001, 2011; McDowd & Craik, 1988; Vanneste & Pouthas, 1999; Vanneste et al., 2001). To test this

hypothesis, Bherer and colleagues (2007) compared the time productions given by young and older adults. In this paradigm, a break was inserted at some random time during the encoding of the target interval. This required participants to sum the 'pre-break' period and 'post-break' period in order to produce the correct duration (Fortin & Massé, 2000). It was hypothesized that attentional load was directly proportional to the pre-break interval and given that older adults exhibit a greater attentional deficit, they would show a greater impairment in maintaining the pre-break interval. Indeed, results revealed that older adults were much more affected by the length of the pre-break period as compared to younger participants. However, there were no differences in performance between the groups when no breaks were included, which indicates that both young and older adults are able to maintain representations of the pre-break interval, but that with the insertion of a break, older adults were unable to effectively 'share' attention between the relevant parts of the task (Bherer et al., 2007). Similarly, Craik and Hay showed that verbal estimates made by older adults were considerably shorter than that of younger adults when a concurrent task was involved (Craik & Hay, 1999). In addition, the inconsistency in response times has been reported in a few studies (e.g., Vasquez et al., 2014). Thus, while older adults show an age-related decline in timing accuracy, this decline may reflect changes in other executive controls necessary for timing function (Baudouin et al., 2006).

Another means of assessing age-related differences in timing is through the production of a temporal interval. Typically, older adults perform more slowly on tasks that require motor responses as compared to younger adults. For example, temporal production tasks often involve finger-tapping or continuation-tapping paradigms where a participant must maintain a target rhythm (e.g., metronome) and tap in sync with the beat. After some time, the beat is turned off and participants must continue to produce the target beat in the absence of any external rhythm (Wing & Kristofferson, 1973). Bangert and Balota compared continuous tapping accuracy of young and older adults as well as individuals in the earliest stages of dementia. Three target rates were used: 500, 1000, and 1500 ms. Young adults outperformed both older adult groups in both measures of accuracy and response variability (Bangert & Balota, 2012). Their results were interpreted as a 'slowing-down' of central executive functioning and a decline in information-processing speed which accompanies a normal aging process (Hedden & Gabrieli, 2004). Consistent with Lustig and Meck's (2001) interpretation, attentional resources necessary to monitor the passage of time may differ between different age groups such that older adults may not be able to divide attention among competing tasks. To control for this possibility, Krampe et al. (2010) combined a working memory task (N-Back memory task; Dobbs & Rule, 1989) in conjunction with a fast (550 ms) and slow (2100 ms) tapping duration. For the memory task, participants were required to either name the presented digit (low memory load), name the digit that was presented two cycles ago or silently monitor the number

of switches between odd and even digits (high memory load). As memory load increased, older adults showed a shortening of produced intervals as well as an increase in response variability. This effect was more pronounced for the fast tapping condition (550 ms) than the slow tapping condition (2100 ms; Krampe et al., 2010). These results suggest that attention and working memory processes cannot be entirely isolated from timing functions.

Another recent study investigated the temporal discrimination threshold (TDT) across age groups, which is the shortest inter-stimulus interval necessary to judge a successive stimulus to be distinct (rather than continuous). They found that over the 10 age groups they tested, age was a significant predictor of TDT with a 0.66 ms increase in TDT every year. The authors argued that the absence of any performance differences across test and retest conditions suggest that memory and decision mechanisms may be preserved with age (Ramos et al., 2016). Whereas, the pacemaker component of the clock-model (Gibbon, 1977), gated by attentional mechanisms (Treisman, 1963), may be responsible for explaining these aging differences in both the estimation and production of temporal intervals. Interestingly, studies have also found that the preferred tempo (freely tapping at one's preferred rate) exhibit marked changes over time. The preferred tapping rate is thought to reflect subjective time independent of attentional and memory mechanisms. In this case, older adults are still observed to tap at a slower pace than younger adults (Turgeon et al., 2011; Vanneste et al., 2001), which suggests that there may still be intrinsic age-related differences in timing across age groups.

3. Nonhuman Timing

Timing is not only essential for perception and action in humans, but serves an equally critical role in nonhuman populations (e.g., Glickstein et al., 1964; Niki & Watanabe, 1979). Macaque monkeys, for instance, share a similar representational system for spatial relationships (Georgopoulos et al., 1986; Hubel & Wiesel, 1968) and temporal order (Leon & Shadlen, 2003). Although it is still unclear whether nonhuman animals have a similar experience of space and time as we do, many lines of research have at least demonstrated a similar pattern of cortical involvement during timing tasks (Meck et al., 2008). In the field of aging, rodents are often the preferred organism based on their relatively short life expectancies (approx. three years), ease of care, and established history in other domains of biomedical research. The use of animal models in aging further affords experimenters the great flexibility of comparing neurological and behavioral changes within a controlled setting (for reviews, see Gallagher et al., 2011; Van der Staay et al., 2009). A list of studies examining the relationship between aging and timing in nonhuman subjects is summarized in Table 2. While the majority of experiments included here use rats as the model organism, their findings can be extended to other nonhuman organisms. The adoption of animal models is an

Table 2.
Summary of recent studies investigating the relationship between aging and interval timing in rats (nonhuman).

Reference (year)	Age	Strain of rat	Task	Interval	Results
Cheng et al. (2008)	20 months	Sprague–Dawley	Temporal bisection (visual and auditory)	2 s, 8 s	Prenatal choline supplementation increased timing sensitivities and modality effect (where auditory signals are consistently judged as longer than visual signals) in aged rats
Cheng et al. (2011)	10, 20, 30 months	Sprague–Dawley	Temporal bisection (visual and auditory)	2 s, 8 s	Aged rats were unimpaired in terms of the PSE and DL measures; aged rats show a stronger 'modality effect' (overestimate auditory signals and underestimate visual signals); 30-months-old rats also showed a fatigue effect where PSE and DL for visual signals increased as a function of session block (but not in the auditory modality)
Church et al. (2014)	3, 12, 20, 30 months	F344/BN	FI-schedule; PI-schedule	32 s, 64 s, 128 s	Behaviourally, young rats pressed the lever more rapidly, and frequently but aged rats were more precise in responding on the FI-schedule; biggest differences were observed between the 12- and 20-month rats; on the PI-schedule, aged rats showed lower response rates; biochemically, aging was characterised by increased AB40, AB42 and RAGE expression, and a decrease in LRP-1; the number of cells within the subventricular zone and dentate gyrus also decreased with age

Table 2.
(Continued)

Reference (year)	Age	Strain of rat	Task	Interval	Results
Leblanc & Soffié (1999)	6, 12, 18, 24 months	Wister	Temporal discrimination (symbolic-matching-to-sample)	2 s, 10 s	Older rats (18 and 24 months) needed more training sessions to reach criterion; all groups exhibited the 'choose short' effect where matching accuracy was lower after the long duration (responding as if it was short);
	6, 18 months				18-months-old rat needed more training sessions to reach criterion; only 6-months-old rats exhibited a shift in their psychophysical functions towards 'long' and increased PSE values as a function of the retention interval
Leblanc et al. (1996)	6, 12, 18, 24 months	Wister	Temporal discrimination (symbolic-matching-to-sample)	2 s, 10 s	Older rats (18 and 24 months) needed more training sessions to reach criterion; performances did not differ between the groups; older rats (18 and 24 months) had lower mean percentage of correct responses
Lejeune et al. (1986)	21 days, 3 months and 26 months	Wister	FI-schedule	60 s	Senescent rats generally emitted lower response rates and running rates than adult and weanling rats; they also showed less suppression during the FI-schedule
Lejeune (1989)	24 days, 3–7 months, 24 months	Wister	DRL schedule	delay of 5–20 s	Aged rats emitted lower response rates, earned more reinforcements, and longer inter-response times; after a 3 month retention interval, only adult rats (3–7 months) increased their efficiency; weanlings showed greater CV during training

Table 2.
(Continued)

Reference (year)	Age	Strain of rat	Task	Interval	Results
Meck (2002)	10–16 months, 24–30 months	Sprague–Dawley	PI-schedule	20 s	Aged rats emitted lower response rates; the level of SDHACU in the frontal cortex of both age groups were proportional the absolute error in performance; only aged rats had a correlation between hippocampal SDHACU levels and absolute error
Meck (2006)	6, 26 months	albino Norway	PI-schedule	20 s	Aged rats had later peak times than adult rats; when these groups were administered BW813U (a choline acetyltransferase inhibitor), peak times were increased
Soffié & Lejeune (1991)	7, 24–25 months	Wister	DRL schedule	delay of 5 s	Aged rats exhibited greater CV and lower response rates; no differences in efficiency across groups during training phase and no differences in performance were found between the last training and first testing session (memory retention)

CV, coefficient of variation; DL, difference limen; DRL, differential responding of lower rates; FI, fixed interval; PI, peak interval; PSE, perceived subjective equality; SDHACU, sodium-dependent high-affinity choline uptake.

especially attractive option in aging research due to their relatively short lifespans and functional homology to the human brain (Richelle & Lejeune, 1984).

Two common procedures used in nonhuman timing are the fixed interval (FI) and peak interval (PI) procedures. In a FI procedure, a rat's response is reinforced after a set amount of time (e.g., every 30 s). As the animal learns the length of the standard interval, they begin responding closer to the expected reward time and drop off quickly after receiving the reward. This results in a typical 'scallop-like' pattern of response rates. Like young rats, old rats have little difficulty acquiring this pattern of responding during initial stages of learning, however, their response rate distributions become considerably flatter following a 16-day retention interval (Campbell & Haroutunian, 1981; cf. Harrison & Pavlik, 1985). What this suggests is that older rats may suffer from a memory impairment that affects their ability to recall the learned interval prior to the retention period.

The PI procedure is a variant of the FI procedure where a small percentage of trials (i.e., 30%) are not reinforced. On unreinforced trials, response rate patterns typically yield a Gaussian distribution with a 'peak' approximating the expected reward time (Church & Broadbent, 1991; Meck, 1996). By examining the location of the peak in relation to the standard (expected) reward time, the PI procedure provides the experimenter a measure of timing accuracy and variability. Using this procedure, Lejeune et al. (1998) trained young and aged rats to respond on a 20-s and 40-s reinforcement schedule. The time of reinforcement changed from trial to trial, representing a "changing temporal criterion". This required animals to track both durations independently and respond according to each representation. While young rats were able to track these durations very closely (peak times were around the reinforced time), aged rats adjusted much more slowly to these transitions and produced peak times much later than the young rats (Lejeune et al., 1998). In addition, aged rats (18–24 months) are much slower to acquire the temporal discrimination task, as indexed by a higher number of trials needed to reach performance criterion in comparison to younger rats (6–12 months; Leblanc et al., 1996). It is suggested that aged rats may be misrepresenting the intervals necessary for accurate responding, which highlight the same finding in humans that age-related changes in timing are rarely observed in isolation, but involve a number of interactions with learning and memory systems.

Although there has been extensive research on the effect of age on timing by humans and rats, it has been difficult to equate the tasks. Typically humans are given verbal or written information, and they have less than an hour to complete the task. In contrast, rats are typically given a procedure that may last for many days or weeks. Some of the differences between age-related changes in timing by humans and rats presumably are due to the differences in these procedures. The normal assumption is that humans and rats gradually lose both mental and physical abilities as they age. There is some reason to consider that the changes may be relatively rapid (i.e., at 18 or 20 months the rats are doing well but by a greater age

many of the rats will clearly show mental and physical problems). The following two articles provide some evidence.

In the article by Leblanc, Weyers, and Soffié (1996), Wistar rats were 6, 12, 18, and 24 months old. In training, a duration of 2 s or 10 s was associated with light and sound signals. The two younger groups (6 and 12 months old) mastered the criterion about twice as quickly the older groups (18 and 24 months old). But when further training was provided, the different ages were similar. The article of Church et al. (2014) was a description of age-related changes in behavior, brain biochemistry, and the relationship between them. Twenty-four rats were Fischer 344/BN F1 male hybrid rats at 3, 12, 20, and 30 months. Accuracy and speed both decreased as a function of age. The most interesting feature of the results was the systematic decrease between 12 and 20 months for both accuracy and speed ($p = 0.003$). This suggests that therapies may have important functions for rats in these months.

4. A Case Comparison: Alzheimer's Disease

So far in this review, we have described a number of changes in time perception that take place over a normal developmental trajectory. However, the value in understanding these changes is not solely to infer about underlying mechanisms for timing, but to uphold that inference in cases of dysfunction. In the following section, we will focus on the pathological aging process associated with Alzheimer's disease (AD) and examine its effects on timing for human and nonhuman populations.

According to the National Institute on Aging (NIA), AD is a complex and progressive neurodegenerative disorder accounting for more than 60–80% of dementia in older adults. AD is characterized by a number of debilitating symptoms such as the inability to follow a conversation; difficulty concentrating, planning and organizing behavior; becoming confused and disoriented; as well as a number of other visuospatial deficits (Anand et al., 2014; Wuwongse et al., 2010). In a survey of over 58 caregivers for AD patients, levels of stress and psychological morbidity were much higher in the AD caregivers group as compared to a control group (elderly but non-demented), highlighting the increasing strain placed on their families and secondary caregivers (González-Salvador et al., 1999). As of 2015, it is estimated that more than 5 million individuals are diagnosed with AD, making Alzheimer's the 6th leading cause of death in the United States alone (NIA Annual Report, 2015). A key contributor to AD is the extracellular accumulation of toxic β -amyloid ($A\beta$) proteins (Abraham et al., 1988; Masters et al., 1985), as well as a build-up of intracellular tau-containing neurofibrillary tangles (Armstrong, 2012; Armstrong et al., 2013; Ubhi & Masliah, 2013). Accumulation of $A\beta$ in the cortex induces a large degree of neuronal and synaptic loss in the basal forebrain, and a progressive deterioration of cholinergic and dopaminergic systems, which are

often implicated in temporal processing (Meck, 2005; Meck et al., 2008; Sarter & Bruno, 2004).

Timing deficits associated with AD are well documented in a number of studies (e.g., Carrasco et al., 2000; Levy & Dreier, 1997; Nichelli et al., 1993; Wild-Wall et al., 2008). For example, Caselli and colleagues (2009) used a temporal bisection task to assess the performance of a group of young adults, older adults, and mild AD patients. The ‘short’ bisection task required participants to categorize intermediate intervals as being closer to the 100 ms or 600 ms interval. In the ‘long bisection’ task, 1000 ms and 3000 ms intervals were used. While AD patients were less sensitive to timing in the short bisection task, no differences were observed for the long bisection task. AD patients (but not young and old adults) also exhibited a greater variability in their responses across both short and long conditions (Caselli et al., 2009). A similar result was obtained in a verbal estimation task comparing older adults, AD patients, and patients with mild cognitive impairments (MCI). While no significant differences were observed in the timed responses between older adults and the two patient groups, the AD group had a greater measure of absolute error (Rueda & Schmitter-Edgecombe, 2009). Another finding is that AD patients typically exhibit a greater variability in their responses (Carrasco et al., 2000; El Haj et al., 2013; Papagno et al., 2004).

Amyloid proteins accrue naturally in both rodent and human brains (Price et al., 1991; Silverberg et al., 2010), but only a small number of studies have investigated the effects of A β on nonhuman timing. When toxic amyloid proteins were infused into the cerebral ventricles of rats, they showed a marked decrease in performance on the water maze as compared to controls. The effect was especially pronounced for frontal and hippocampal regions (Nitta et al., 1994). Interestingly, A β -treated rats exhibited a decrease in ChAT activity in the frontal and hippocampus regions, similar to human participants diagnosed with AD (Frautschy et al., 1996). In a more recent paper, increases in biochemical measures associated with aging (namely, A β 40, A β 42 and A β transporter) were found to correlate with the speed, accuracy, and precision of timing behavior in rats (Church et al., 2014). This suggests that early changes in timing behavior may serve as a surrogate marker for biochemical changes that take place in the brain. While few studies have focused on the relationship between pathological aging and timing in nonhuman species, we believe it can offer new insight into current models of functional aging in the brain.

5. Conclusion

A central goal in aging research is to establish a set of biochemical and behavioral standards that reliably predict changes associated with age. It is oftentimes challenging however, to tease apart results of a normal aging process from that of abnormal or diseased processes (e.g., AD). Based on the corpus of literature reviewed

here, we suggest that time perception can serve as an important step towards understanding the mechanisms behind age-related changes in cognitive function. The observation of a declining timing ability in both human and nonhuman subjects — as well as the integral role it plays in perception and action — makes timing a suitable candidate for examining aging processes across different species. While there are clear differences in basic concepts and classifications used in human and nonhuman research, consideration of nonhuman research results can greatly improve our understanding of the mechanisms underlying time perception and aging, and offer therapeutic intervention in age-related disorders.

References

- Abraham, C. R., Selkoe, D. J., & Potter, H. (1988). Immunochemical identification of the serine protease inhibitor α 1-antichymotrypsin in the brain amyloid deposits of Alzheimer's disease. *Cell*, 52, 487–501.
- Anand, R., Gill, K. D., & Mahdi, A. A. (2014). Therapeutics of Alzheimer's disease: Past, present and future. *Neuropharmacology*, 76, 27–50.
- Anderson, J. W., Rueda, A., & Schmitter-Edgecombe, M. (2014). The stability of time estimation in older adults. *Int. J. Aging Hum. Dev.*, 78, 259–276.
- Armstrong, R. A., (2012). What causes Alzheimer's disease? *Folia Neuropathol.*, 51, 169–188.
- Armstrong, R. A., Myers, D., & Smith, C. U. (1993). The spatial patterns of plaques and tangles in Alzheimer's disease do not support the 'cascade hypothesis'. *Dementia*, 4, 16–20.
- Artieda, J., Pastor, M. A., Lacruz, F., & Obeso, J. A. (1992). Temporal discrimination is abnormal in Parkinson's disease. *Brain*, 115, 199–210.
- Balci, F., Meck, W. H., Moore, H., & Brunner, D. (2009). Timing deficits in aging and neuropathology. In J. L. Bizon, & A. G. Woods (Eds), *Animal models of human cognitive aging* (pp. 1–41). New York, NY, USA: Humana Press.
- Bangert, A. S., & Balota, D. A. (2012). Keep up the pace: Declines in simple repetitive timing differentiate healthy aging from the earliest stages of Alzheimer's disease. *J. Int. Neuropsychol. Soc.*, 18, 1052–1063.
- Baudouin, A., Vanneste, S., Pouthas, V., & Isingrini, M. (2006). Age-related changes in duration reproduction: Involvement of working memory processes. *Brain Cogn.*, 62, 17–23.
- Beste, C., Saft, C., Andrich, J., Müller, T., Gold, R., & Falkenstein, M. (2007). Time processing in Huntington's disease: A group-control study. *PLoS One*, 2, e1263.
- Bherer, L., Desjardins, S., & Fortin, C. (2007). Age-related differences in timing with breaks. *Psychol. Aging*, 22, 398–403.
- Block, R. A., Zakay, D., & Hancock, P. A. (1998). Human aging and duration judgments: A meta-analytic review. *Psychol. Aging*, 13, 584–596.
- Buhusi, C. V., & Meck, W. H. (2005). What makes us tick? Functional and neural mechanisms of interval timing. *Nat. Rev. Neurosci.* 6, 755–765.
- Campbell, B. A., & Haroutunian, V. (1981) Effects of age on long-term memory: Retention of fixed interval responding. *J. Gerontol.*, 36, 338–341.
- Carrasco, M. C., Guillem, J., & Redolat, R. (2000). Estimation of short temporal intervals in Alzheimer's disease. *Exp. Aging Res.*, 26, 139–151.

- Carrasco, M. C., Bernal, M. C., & Redolat, R. (2001). Time estimation and aging: A comparison between young and elderly adults. *Int. J. Aging Hum. Dev.* 52, 91–101. doi: 10.1186/1744-9081-5-32.
- Caselli, L., Iaboli, L., & Nichelli, P. (2009). Time estimation in mild Alzheimer's disease patients. *Behav. Brain Funct.*, 5, 1.
- Cheng, R. K., Scott, A. C., Penney, T. B., Williams, C. L., & Meck, W. H. (2008). Prenatal choline availability differentially modulates timing of auditory and visual stimuli in aged rats. *Brain Res.*, 1237, 167–175.
- Cheng, R. K., Dyke, A. G., McConnell, M. W., & Meck, W. H. (2011). Categorical scaling of duration as a function of temporal context in aged rats. *Brain Res.*, 1381, 175–186.
- Church, R. M., & Broadbent, H. A. (1991) A connectionist model of timing. In: SGJERS Michael, & L. Commons (Eds), *Neural network models of conditioning and action. Quantitative analyses of behavior series* (pp. 225–240). Hillsdale, NJ, USA: Lawrence Erlbaum Associates.
- Church, R. M., Miller, M. C., Freestone, D., Chiu, C., Osgood, D. P., Machan, J. T., Messier, A. A., Johanson, C. E., & Silverberg, G. D. (2014). Amyloid-beta accumulation, neurogenesis, behavior, and the age of rats. *Behav. Neurosci.*, 128, 523–536.
- Coelho, M., Ferreira, J. J., Dias, B., Sampaio, C., Martins, I. P., & Castro-Caldas, A. (2004). Assessment of time perception: The effect of aging. *J. Int. Neuropsychol. Soc.*, 10, 332–341.
- Craik, F. I., & Hay, J. F. (1999). Aging and judgments of duration: Effects of task complexity and method of estimation. *Percept. Psychophys.*, 6, 549–560.
- Davalos, D. B., Kisley, M. A., & Freedman, R. (2005). Behavioral and electrophysiological indices of temporal processing dysfunction in schizophrenia. *J. Neuropsychiatry Clin. Neurosci.*, 17, 517–525.
- Dobbs, A. R., & Rule, B. G. (1989). Adult age differences in working memory. *Psychol. Aging*, 4, 500–503.
- Droit-Volet, S., & Clément, A. (2005) Time perception in children and adults: Effects of continuous and discontinuous signal. *Curr. Psychol. Cogn.*, 23, 229–248.
- Droit-Volet, S., & Wearden, J. H. (2001). Temporal bisection in children. *J. Exp. Child Psychol.*, 80, 142–159.
- Droit-Volet, S., Clément, A., & Wearden, J. (2001). Temporal generalization in 3-to 8-year-old children. *J. Exp. Child Psychol.*, 80, 271–288.
- Droit-Volet, S., Meck, W. H., & Penney, T. B. (2007). Sensory modality and time perception in children and adults. *Behav. Processes*, 74, 244–250.
- El Haj, M., Postal, V., & Allain, P. (2013). Destination memory in Alzheimer's disease: When I imagine telling Ronald Reagan about Paris. *Cortex*, 49, 82–89.
- Feifel, H. (1957). Judgment of time in younger and older persons. *J. Gerontol.*, 12, 71–74.
- Fortin, C., & Massé, N. (2000). Expecting a break in time estimation: Attentional time-sharing without concurrent processing. *J. Exp. Psychol. Hum. Percept. Perform.*, 26, 1788–1796.
- Fraisse, P. (1984). Perception and estimation of time. *Annu Rev. Psychol.*, 35, 1–37.
- Frautschy, S. A., Yang, F., Calderón, L., & Cole, G. M. (1996). Rodent models of Alzheimer's disease: Rat A β infusion approaches to amyloid deposits. *Neurobiol. Aging*, 17, 311–321.
- Friedman, W. J., & Janssen, S. M. (2010). Aging and the speed of time. *Acta Psychol.*, 134, 130–141.
- Gallagher, M., Stocker, A. M., & Koh, M. T. (2011). Mindspace: Lessons from rat models of neurocognitive aging. *ILARJ.*, 52, 32–40.
- Georgopoulos, A. P., Schwartz, A. B., & Kettner, R. E. (1986). Neuronal population coding of movement direction. *Science*, 233(4771), 1416–1419.

- Gibbon, J. (1977). Scalar expectancy-theory and Webers law in animal timing. *Psychol. Rev.*, 84, 279–325.
- Gibbon, J., Church, R., & Meck, W. (1984). Scalar timing in memory. In J. Gibbon & L. G. Allan (Eds), *Timing and time perception* (pp. 52–77). New York, NY, USA: New York Academy of Sciences.
- Glickstein, M., Quigley, W. A., & Stebbins, W. C. (1964). Effect of frontal and parietal lesions on timing behavior in monkeys. *Psychon. Sci.*, 1, 265–266.
- González-Salvador, M. T., Arango, C., Lyketsos, C. G., & Barba, A. C. (1999). The stress and psychological morbidity of the Alzheimer patient caregiver. *Int. J. Geriatr. Psychiatry*, 14, 701–710.
- Gunstad, J., Cohen, R. A., Paul, R. H., Luyster, F. S., & Gordon, E. (2006). Age effects in time estimation: Relationship to frontal brain morphometry. *J. Integr. Neurosci.*, 5, 75–87.
- Harrison, D. W., & Pavlik, W. B. (1985). Age differences in retention of fixed-interval responding: Memory or habitation effects? *Behav. Neural Biol.*, 44, 339–346.
- Hedden, T., & Gabrieli, J. D. (2004). Insights into the ageing mind: A view from cognitive neuroscience. *Nat. Rev. Neurosci.*, 5, 87–96.
- Hubel, D. H., & Wiesel, T. N. (1968). Receptive fields and functional architecture of monkey striate cortex. *J. Physiol.* 195, 215–243.
- Kline, D. W., Holleran, L., & Orme-Rogers, C. (1980). The estimation of short time intervals as a function of age and metronome pacing. *Int. J. Aging Hum. Dev.*, 11, 127–134.
- Krampe, R. T., Doumas, M., Lavrysen, A., & Rapp, M. (2010). The costs of taking it slowly: Fast and slow movement timing in older age. *Psychol. Aging*, 25, 980–990.
- Leblanc, P., & Soffié, M. (1999). Effects of age on short-term memory for time in rats. *Exp. Aging Res.*, 25, 267–284.
- Leblanc, P., Weyers, M. H., & Soffié, M. (1996). Age-related differences for duration discrimination in rats. *Physiol. Behav.*, 60, 555–558.
- Lejeune, H., Jasselette, P., Nagy, J., & Peree, F. (1986). Fixed interval performance in weanling rats: A comparison with adult and senile subjects. *Physiol Behav*, 38 (3), 337–343.
- Lejeune, H., Ferrara, A., Soffié, M., Bronchart, M., & Wearden, J. H. (1998). Peak procedure performance in young adult and aged adult rats: Acquisition and adaptation to a changing temporal criterion. *Q. J. Exp. Psychol. B*, 51, 193–217.
- Leon, M. I., & Shadlen, M. N. (2003). Representation of time by neurons in the posterior parietal cortex of the macaque. *Neuron*, 38, 317–327.
- Levy, B., & Dreier, T. (1997). Preservation of temporal skills in Alzheimer's disease. *Percept. Mot. Skills*, 85, 83–96.
- Lustig, C. (2003). Grandfather's clock: Attention and interval timing in older adults. In W. H. Meck (Ed.), *Functional and neural mechanisms of internal timing* (pp. 261–293). Boca Raton, FL, USA: CRC Press.
- Lustig, C., & Meck, W. H. (2001). Paying attention to time as one gets older. *Psychol. Sci.*, 12, 478–484.
- Lustig, C., & Meck, W. H. (2011). Modality differences in timing and temporal memory throughout the lifespan. *Brain Cogn.*, 77, 298–303.
- Masters, C. L., Multhaup, G., Simms, G., Pottgiesser, J., Martins, R. N., & Beyreuther, K. (1985). Neuronal origin of a cerebral amyloid: Neurofibrillary tangles of Alzheimer's disease contain the same protein as the amyloid of plaque cores and blood vessels. *EMBO J.*, 4, 2757–2763.
- McAuley, J. D., Jones, M. R., Holub, S., Johnston, H. M., & Miller, N. S. (2006). The time of our lives: Life span development of timing and event tracking. *J. Exp. Psychol. Gen.*, 135, 348–367.
- McCormack, T., Brown, G. D., Maylor, E. A., Darby, R. J., & Green, D. (1999). Developmental changes in time estimation: Comparing childhood and old age. *Dev. Psychol.*, 35, 1143–1155.

- McCormack, T., Brown, G. D., Maylor, E. A., Richardson, L. B. N., & Darby, R. J. (2002). Effects of aging on absolute identification of duration. *Psychol. Aging*, 17, 363–378.
- McCormack, T., Brown, G. D., Smith, M. C., & Brock, J. (2004). A timing-specific memory distortion effect in young children. *J. Exp. Child Psychol.*, 87, 33–56.
- McDowd, J. M., & Craik, F. I. M. (1988). Effects of aging and task difficulty on divided attention performance. *J. Exp. Psychol. Hum. Percept. Perform.*, 14, 267–280.
- McGrath, J. J., & O'Hanlon, J. F. (1968). Relationships among chronological age, intelligence and rate of subjective time. *Percept. Mot. Skills*, 26, 1083–1088.
- Meck, W. H. (1996). Neuropharmacology of timing and time perception. *Brain Res. Cogn. Brain Res.*, 3, 227–242.
- Meck, W. H. (2002). Choline uptake in the frontal cortex is proportional to the absolute error of a temporal memory translation constant in mature and aged rats. *Learn. Motiv.*, 33, 88–104.
- Meck, W. H. (2005). Neuropsychology of timing and time perception. *Brain Cogn.*, 58, 1–8.
- Meck, W. H. (2006). Temporal memory in mature and aged rats is sensitive to choline acetyltransferase inhibition. *Brain Res.*, 1108, 168–175.
- Meck, W. H., Penney, T. B., & Pouthas, V. (2008). Cortico-striatal representation of time in animals and humans. *Curr. Opin. Neurobiol.*, 18, 145–152.
- Merchant, H., Harrington, D. L., & Meck, W. H. (2013). Neural basis of the perception and estimation of time. *Annu. Rev. Neurosci.*, 36, 313–336.
- Nichelli, P., Venneri, A., Molinari, M., Tavani, F., & Grafman, J. (1993). Precision and accuracy of subjective time estimation in different memory disorders. *Brain Res.*, 1, 87–93.
- Niki, H., & Watanabe, M. (1979). Prefrontal and cingulate unit activity during timing behavior in the monkey. *Brain Res.*, 171, 213–224.
- Nitta, A., Itoh, A., Hasegawa, T., & Nabeshima, T. (1994). β -Amyloid protein-induced Alzheimer's disease animal model. *Neurosci. Lett.*, 170, 63–66.
- Papagno, C., Allegra, A., & Cardaci, M. (2004). Time estimation in Alzheimer's disease and the role of the central executive. *Brain Cogn.*, 54, 18–23.
- Pastor, M. A., Artieda, J., Jahanshahi, M., & Obeso, J. A. (1992). Time estimation and reproduction is abnormal in Parkinson's disease. *Brain*, 115, 211–225.
- Perbal, S., Droit-Volet, S., Isingrini, M., & Pouthas, V. (2002). Relationships between age-related changes in time estimation and age-related changes in processing speed, attention, and memory. *Aging Neuropsychol. Cogn.*, 9, 201–216.
- Pouya, O. R., Kelly, D. M., & Moussavi, Z. (2015). Tendency to overestimate the explicit time interval in relation to aging and cognitive decline. *Conf. Proc. IEEE Eng. Med. Biol. Soc.*, 2015, 4692–4695.
- Price, J. L., Davis, P. B., Morris, J. C., & White, D. L. (1991). The distribution of tangles, plaques and related immunohistochemical markers in healthy aging and Alzheimer's disease. *Neurobiol. Aging*, 12, 295–312.
- Rakitin, B. C., Gibbon, J., Penney, T. B., Malapani, C., Hinton, S. C., & Meck, W. H. (1998). Scalar expectancy theory and peak-interval timing in humans. *J. Exp. Psychol. Anim. Behav. Process.*, 24, 15–33.
- Rakitin, B. C., Stern, Y., & Malapani, C. (2005). The effects of aging on time reproduction in delayed free-recall. *Brain Cogn.*, 58, 17–34.
- Ramos, V. F. M. L., Esquenazi, A., Villegas, M. A. F., Wu, T., & Hallett, M. (2016). Temporal discrimination threshold with healthy aging. *Neurobiol. Aging*, 43, 174–179.
- Richelle, M., & Lejeune, H. (1984). Timing competence and timing performance: A cross-species approach. *Ann. N. Y. Acad. Sci.*, 423, 254–268.

- Rueda, A. D., & Schmitter-Edgecombe, M. (2009). Time estimation abilities in mild cognitive impairment and Alzheimer's disease. *Neuropsychology*, 23, 178–188.
- Sarter, M., & Bruno, J. P. (2004). Developmental origins of the age-related decline in cortical cholinergic function and associated cognitive abilities. *Neurobiol. Aging*, 25, 1127–1139.
- Silverberg, G. D., Miller, M. C., Messier, A. A., Majmudar, S., Machan, J. T., Donahue, J. E., Stopa, E. G., & Johanson, C. E. (2010). Amyloid deposition and influx transporter expression at the blood–brain barrier increase in normal aging. *J. Neuropathol. Exp. Neurol.*, 69, 98–108.
- Soffié, M., & Lejeune, H. (1991). Acquisition and long-term retention of a two-lever DRL schedule: Comparison between mature and aged rats. *Neurobiol. Aging*, 12, 25–30.
- Toplak, M. E., Dockstader, C., & Tannock, R. (2006). Temporal information processing in ADHD: Findings to date and new methods. *J. Neurosci. Methods*, 151, 15–29.
- Treisman, M. (1963). Temporal discrimination and the indifference interval: Implications for a model of the “internal clock”. *Psychol. Monogr.*, 77(13), 1–31.
- Turgeon, M., Wing, A. M., & Taylor, L. W. (2011). Timing and aging: Slowing of fastest regular tapping rate with preserved timing error detection and correction. *Psychol. Aging*, 26, 150–161.
- Turgeon, M., Lustig, C., & Meck, W. H. (2016). Cognitive aging and time perception: Roles of Bayesian optimization and degeneracy. *Front. Aging Neurosci.*, 8, 102. doi: 10.3389/fnagi.2016.00102.
- Ubhi, K., & Masliah, E. (2013). Alzheimer's disease: Recent advances and future perspectives. *J. Alzheimers Dis.*, 33(Suppl. 1), S185–S194.
- Van der Staay, F. J., Arndt, S. S., & Nordquist, R. E. (2009). Evaluation of animal models of neurobehavioral disorders. *Behav. Brain Funct.*, 5, 11. doi: 10.1186/1744-9081-5-11.
- Vanneste, S., & Pouthas, V. (1999). Timing in aging: The role of attention. *Exp. Aging Res.*, 25, 49–67.
- Vanneste, S., Pouthas, V., & Wearden, J. H. (2001). Temporal control of rhythmic performance: A comparison between young and old adults. *Exp. Aging Res.*, 27, 83–102.
- Vasquez, B. P., Binns, M. A., & Anderson, N. D. (2014). Staying on task: Age-related changes in the relationship between executive functioning and response time consistency. *J. Gerontol. B Psychol. Sci. Soc. Sci.*, 71, 189–200.
- Wearden, J. H., Wearden, A. J., & Rabbitt, P. M. (1997). Age and IQ effects on stimulus and response timing. *J. Exp. Psychol. Hum. Percept. Perform.*, 23, 962–979.
- Wild-Wall, N., Willemsen, R., Falkenstein, M., & Beste, C. (2008). Time estimation in healthy ageing and neurodegenerative basal ganglia disorders. *Neurosci. Lett.*, 442, 34–38.
- Wing, A. M., & Kristofferson, A. B. (1973). Response delays and the timing of discrete motor responses. *Percept. Psychophys.*, 14, 5–12.
- Wittmann, M., & Lehnhoff, S. (2005). Age effects in perception of time. *Psychol. Rep.*, 97, 921–935.
- Wuwongse, S., Chang, R. C. C., & Law, A. C. (2010). The putative neurodegenerative links between depression and Alzheimer's disease. *Prog. Neurobiol.*, 91, 362–375.