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Neural mechanisms underlying age-related changes in attentional selectivity

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Abstract

Distraction - or a lack of attentional inhibition - is perhaps the most recognized age-related difference in attention. Older adults are particularly impaired in attentional tasks that require self-directed inhibition of irrelevant information, despite relatively preserved ability in other attentional processes. What are the neural mechanisms underlying the age-related, decreased inhibition of distracting information? In this chapter, we make the case that age-related changes in the frontoparietal network play a critical role in older adults' decreased attentional selection. A number of age-related changes in frontoparietal network mechanisms are likely to contribute to impaired attentional inhibition in older adulthood, including slowing in alpha band activity, decreased GABAergic and dopaminergic densities, and impaired frontoparietal connectivity with noradrenergic release under arousal. Finally, we discuss other possible mechanisms underlying age-related impairments in attentional selectivity – including changes within the default mode network - and avenues for future research.

Introduction

One of the hallmarks of cognitive aging is the increase in distraction from goal-irrelevant information (e.g., Hasher & Zacks, 1988; Lustig, Hasher, & Zacks, 2007). Hasher and Zacks's (1988) seminal chapter outlined age-related decreases in the ability to ignore irrelevant information – and to date, their chapter has been cited over 3500 times on Google Scholar. Age and inhibition has thus been one of the most prominent and explored research areas in cognition and aging in the past thirty years, and the deficit in ignoring irrelevant information in older adults compared to younger adults has now been demonstrated across many contexts and paradigms (see Weeks & Hasher, 2014).

However, despite this relatively intensive focus on age-related declines in this aspect of attention, it is not well understood which brain changes contribute most to these behavioral changes. In this chapter, we review evidence suggesting that age-related deficits in frontoparietal networks play a key role in older adults' impaired ability to ignore distracting information. We discuss how these frontoparietal network impairments involve changes in alpha band activity, GABAergic processing, dopaminergic decreases, and changes in how noradrenergic release under arousal affects attention. In addition, we discuss alternative mechanisms of older adults' impaired attentional selectivity and directions for future research.

Distraction, inhibition, and aging

The amount of information in our environment far exceeds what we can process and retain. We thus prioritize information that is most important to navigate our world (see Wolfe & Horowitz, 2017 for a review). For our attentional system, priority can be determined by several factors, including the bottom-up features of information in our environment (such as motion or

contrast) or from top-down goals (such as items that share a feature being sought, e.g., blue items when searching for a friend known to be wearing blue). Top-down, goal-directed attention can be driven both by enhancing mental representations of stimuli that are more important and by inhibiting representations of stimuli that are less important.

Hasher and colleagues propose that older adults are less likely to actively inhibit representations, and that this decrease in inhibition is responsible not only for the increase in distractibility among older adults but also for more general cognitive decline issues (Hasher, Stoltzfus, Zacks, & Rypma, 1991; Hasher & Zacks, 1988; Lustig et al., 2007; Weeks & Hasher, 2014). Across multiple tasks that require ignoring distracting stimuli (e.g., Stroop: West & Alain, 2000; Flanker: e.g., Zeef, Sonke, Kok, Buiten, & Kenemans, 1996; and Simon tasks: e.g., Kubo-Kawai & Kawai, 2010), older adults show slower reaction times and greater distraction by task-irrelevant features. Consistent with the hypothesis that inhibition of task-irrelevant information is the basis for these performance differences, older adults perform similarly to younger adults in many cognitive tasks when inhibition is not involved (Andrés, Parmentier, & Escera, 2006; Commodari & Guarnera, 2000; Madden, 2007).

Moreover, older adults spontaneously learn task-irrelevant information that younger adults usually inhibit (Healey, Campbell, & Hasher, 2008). For example, in an experiment where participants were required to concentrate on a central task, younger adults failed to learn information about motion coherence that appeared in the background, whereas older adults performed well above chance in a later surprise test of the task-irrelevant information (Chang, Shibata, Andersen, Sasaki, & Watanabe, 2014). Similarly, when participants view common objects superimposed with task-irrelevant words, older adults are more likely than younger adults to demonstrate priming from the task-irrelevant words in a subsequent, surprise word

completion task (Campbell, Grady, Ng, & Hasher, 2012; Rowe, Valderrama, Hasher, & Lenartowicz, 2006).

Functional magnetic resonance imaging (fMRI) data mirror behavioral findings. Gazzaley and colleagues had participants view scene and face images, and instructed them to either 1) ignore scenes and remember faces, 2) remember scenes and ignore faces, or 3) passively view the images (Gazzaley, Cooney, Rissman, & D'Esposito, 2005). Younger adults showed an increase in scene-selective activation (in the left parahippocampal/lingual gyrus) when remembering scenes and ignoring faces compared to passively viewing them, and also showed a decrease in scene-selective activity when remembering faces and ignoring scenes. Although older adults also demonstrated an increase in scene-selective activity when remembering scenes and ignoring faces, they did not show any difference from passive viewing when they were remembering faces and ignoring scenes. The degree to which older adults demonstrated suppressed activation when ignoring scenes also correlated with their memory performance, suggesting that inhibition of irrelevant information is important to determining what information is retained (see also Campbell et al., 2012; Lustig et al., 2007)

A selection problem or a suppression problem?

To understand the underlying brain mechanisms involved in age-related attentional changes, it is helpful to identify the distinct cognitive processes involved. Could it be that older adults simply struggle to select and prioritize important information? Not all aspects of prioritization are impaired; activation of representations that are most important seems to remain intact. For example, older adults usually perform well in visual search tasks, but struggle when the search requires a greater amount of effort because distractors need to be ignored in the search environment (e.g., Foster, Behrmann, & Stuss, 1995). More specifically, search performance is

typically comparable between older and younger adults when they can utilize parallel search strategies – that is, when target items are distinctive from distractors due to a particular, single feature (Foster et al., 1995; Madden, 2007). However, when a visual search requires timely, serial search strategies (such as when task-relevant items are defined by a conjunction of features that make them similar to distractor items), older adults typically demonstrate greater impairments in search efficiency compared to young adults (Foster et al., 1995; Madden, 2007).

Since older adults can effectively search for single features, but struggle when they have to actively disregard distractors to identify targets in a more complex serial search, the impairment in inhibition mechanisms in older adults could be due to their failure to use goal-directed attention and maintain an attentional set for the target over distractors (Hasher, Zacks, & May, 1999). Indeed, aging was associated with impaired inhibition when tasks required executive attentional control (i.e., Stroop, Stop Signal), as opposed to tasks that only require automatic attentional inhibition (i.e., Negative Priming; Andrés, Guerrini, Phillips, & Perfect, 2008). Consistent with this, older adults performed similarly to younger adults in search efficiency when a colored distractor or distractor with a surprise onset appeared in a search array (Colcombe et al., 2003; Kramer, Hahn, Irwin, & Theeuwes, 2000), but, unlike younger adults, older adults did not improve performance when specifically made aware of the distractors (Kramer et al., 2000). Thus, older adults seem less able to employ a goal-directed attentional set to ignore upcoming distractors compared to younger adults. However, this may be specific for harder tasks, as when identifying the target amongst distractors is easier (e.g., when knowing that a task-relevant target will likely be a color singleton), knowing about the target does improve older adults' performance (Whiting, Madden, Pierce, & Allen, 2005). In a similar vein, older adults show less object-specific activation in the lateral occipital cortex (LOC) when passively

viewing objects imposed on scenes, but instructions to focus on objects enhance object-specific activation in the LOC in older adults (Chee et al., 2006). Taken together, these results suggest 1) that top-down control mechanisms may help overcome task-irrelevant distraction, 2) that older adults do seem able to recruit some of these top-down control abilities, but 3) that older adults cannot override distraction with their goal-directed attention to the extent that younger adults can.

Age-related changes in the frontoparietal networks

The nature of these age-related deficits rule out any mechanisms that do not account for how selectivity can be coordinated across relatively distant brain regions. Thus, to understand these age differences, we need to focus on brain mechanisms that coordinate which stimuli representations are enhanced and which are suppressed – even when they are represented in different cortical regions, such as when someone is selectively attending to a scene and ignoring a face shown at the same time. The prime candidate for this role coordinating attentional selectivity is the frontoparietal brain network (Hwang, Shine, & D’Esposito, 2018; Ptak, 2012; Scolari, Seidl-Rathkopf, & Kastner, 2015). The network includes areas in the posterior parietal cortex (PPC), the dorsolateral prefrontal cortex (DLPFC), and premotor cortex - including the anterior cingulate cortex (ACC), frontal eye field (FEF), and intraparietal sulcus (IPS; Ptak, 2012). Researchers posit that the frontoparietal network represents priority maps that identify and prioritize the spatial location of stimuli that are salient or important to the observer’s top-down goals (Jerde, Merriam, Riggall, Hedges, & Curtis, 2012; Ptak, 2012; Treisman, 1998). Thus, the frontoparietal network plays a key role in distinguishing task-relevant targets from task-irrelevant distraction.

Researchers have posited that age-related decline in frontal regions can account for attentional inhibition changes in older adults (Allen, Bruss, Brown, & Damasio, 2005; Gazzaley & D'Esposito, 2007; Reuter-Lorenz & Campbell, 2008). There has been less focus on the potential role of frontoparietal networks in age-related decline in selective attention and inhibition. However, emerging research examining functional connectivity reveals age-related changes in frontoparietal networks (Campbell et al., 2012; Geerligs, Renken, Saliassi, Maurits, & Lorist, 2015; Goh, 2011; Madden, 2007; Sala-Llloch, Bartrés-Faz, & Junqué, 2015) that are associated with cognitive performance (Avelar-Pereira, Bäckman, Wåhlin, Nyberg, & Salami, 2017; DuPre & Spreng, 2017; C. Grady, Sarraf, Saverino, & Campbell, 2016; Mitchell, Ankudowich, Durbin, Greene, & Johnson, 2013; Nashiro, Sakaki, Braskie, & Mather, 2017; Siman-Tov et al., 2017; Zanto & Gazzaley, 2016). Of particular interest, older adults' reduced frontoparietal network activity was associated with poorer attentional selectivity in a study in which participants viewed task-irrelevant words during a picture 1-back task (Campbell et al., 2012). In this study, young adults showed greater brain activity in the frontoparietal network when they were trying to ignore distracting words. Older adults did not demonstrate such activation during the task, and were worse at ignoring the words compared with young adults. Moreover, when participants were simply resting, parietal regions involved in ignoring stimuli correlated more strongly with regions of the rostral prefrontal cortex in young adults compared to older adults, suggesting that connectivity within the frontoparietal network is decreased in older adults (Campbell et al., 2012). Thus, both lowered brain activation in frontoparietal regions and decreased network connectivity of the frontoparietal network suggest that impairments in cognitive control may stem from diminished integrity within the frontoparietal network. Consistent with this, age-related decreases in brain volume in the frontoparietal dorsal stream

have been associated with worse visual search performance in conjunction search tasks (Müller-Oehring, Schulte, Rohlfing, Pfefferbaum, & Sullivan, 2013).

Compensation and dedifferentiation accounts of frontoparietal network changes

Traditional frameworks of age-related changes in the brain can be used to conceptualize underlying changes in the frontoparietal network. Compensation and dedifferentiation theories are two main hypotheses about age related changes in the brain, and they apply to both brain structures and functional networks.

Dedifferentiation refers to a process when neural processors lose their functional specificity or selectivity (see Park et al., 2004). If neural representations are no longer as specific as they used to be, dedifferentiation would make it harder to select target stimuli amongst distractors. Evidence of age-related dedifferentiation has been observed in individual brain structures and for particular functional networks and connectivity (Geerligs et al., 2015; Goh, 2011; Park et al., 2004) - including network connectivity and functionality of the frontoparietal network (Geerligs et al., 2015). Altogether, the lessened distinctiveness and modularity of regions responsible for particular processing in younger adulthood may make distinguishing task-relevant targets from task-irrelevant distractors more difficult in older age – and make it harder to direct goal-directed attentional inhibition.

Compensation theories also apply to the frontoparietal network. Despite deficits in performance, older adults often to show *more* activity in related brain areas compared to younger adults (Grady & Craik, 2000; Reuter-Lorenz, 2002; Reuter-Lorenz & Campbell, 2008). This has been interpreted as a “compensation” for underlying deficits (Reuter-Lorenz & Campbell, 2008). Compensation theories of aging suggest that greater activity reflects greater task-related effort

(Reuter-Lorenz & Campbell, 2008). However, when task demands are too great, frontoparietal activation in older adults decreases and is less active than for younger adults; a decrease that coincides with impaired task performance compared to younger adults (Campbell et al., 2012; Reuter-Lorenz & Campbell, 2008). Accordingly, compared with younger adults, older adults often demonstrate greater brain activation during cognitive tasks to achieve a similar level of performance – particularly in frontoparietal areas (Cabeza, 2002; Campbell et al., 2012; Madden, 2007).

While traditional dedifferentiation and compensation theories provide frameworks to understand age-related changes in frontoparietal network activity, specific underlying functional and chemical changes have been identified that relate to the ability to ignore distraction. For example, the frontoparietal network's involvement in attentional selectivity has been linked with both alpha rhythms (e.g., Capotosto et al., 2009) and with GABAergic action (Womelsdorf & Everling, 2015; Zhang et al., 2014). Both of these processes involved in implementing frontoparietal network function decline with aging, as reviewed in the following two sections.

Alpha EEG, selective attention, and the frontoparietal network

Oscillatory waveforms measured with electroencephalogram (EEG) are associated with mental processing and are correlated with performance on attentional tasks (see Kahana, 2006; Klimesch, 1999; Ward, 2003 for reviews). These waveforms are believed to represent synchronous activity in the brain, and unique waveforms can be distinguished based on their individual frequency and power bands (Klimesch, 1999). Alpha EEG, with frequency ranges between 7.5-12.5Hz, is the most dominant waveform in humans (Klimesch, 1999). It is also a waveform believed to reflect attention: alpha EEG changes amplitude with task-related stimuli presentation or increased task demands in attentional tasks.

Furthermore, there is much evidence indicating that alpha oscillations reflect inhibitory and selective aspects of attention (Foxe & Snyder, 2011; Händel, Haarmeier, & Jensen, 2011; Klimesch, 1999, 2012). Alpha amplitude is typically suppressed when people process events but it increases in situations when participants must exert top-down control over responses (for review see Klimesch, Sauseng, & Hanslmayr, 2007). The ability to perceive external stimuli oscillates in tandem with alpha oscillations, suggesting that alpha oscillations may provide rhythmic pulses that inhibit attentional processes (Mathewson et al., 2011). The causal role of alpha band rhythms in blocking stimuli processing was demonstrated in a study that applied rhythmic transcranial magnetic stimulation at a frequency within the alpha range (10 Hz) to parietal and occipital sites (Romei, Gross, & Thut, 2010). This alpha stimulation impaired visual detection contralateral to the stimulation site more than stimulation at higher or lower frequencies, while improving detection at an ipsilateral site.

Alpha EEG and activity in frontoparietal regions appear to be linked (Laufs et al., 2003). For example, in a study combining continuous EEG with fMRI, alpha rhythms were negatively correlated with activity specifically in frontal and parietal areas (Laufs et al., 2003). Attentional activity in the frontoparietal regions thus seems to be reflected through alpha rhythms. Frontoparietal brain regions also play a key role in modulating alpha activity (Mathewson et al., 2014). For instance, a transcranial magnetic stimulation study showed that interfering with activity in the intraparietal sulcus or frontal eye field (two nodes of the dorsal frontoparietal network) disrupted anticipatory alpha desynchronization and impaired identification of targets appearing a couple of seconds later (Capotosto et al., 2009).

Age-related changes in alpha EEG

Age-related slowing in alpha band oscillatory activity is a pronounced effect that is among the first documented observations of age differences in brain activity (e.g., Davis, 1941; Harvald, 1958) and has been replicated many times (e.g., Clark et al., 2004; McEvoy, Pellouchoud, Smith, & Gevins, 2001; Vlahou, Thurm, Kolassa, & Schlee, 2014; Woodruff & Kramer, 1979). Such slowing has been particularly observed in frontal areas of the brain (Clark et al., 2004), and has been linked with lowered reaction times on attentional tasks (Woodruff & Kramer, 1979) and decreased working memory performance (Clark et al., 2004; Sander, Werkle-Bergner, & Lindenberger, 2012).

Alpha-band activity is high during rest, and increases further when eyes are closed. In response to stimuli or task demands, it typically decreases in amplitude (showing an ‘alpha band desynchronization’). However, it can also increase in amplitude when stimuli are task irrelevant or potentially interfering with current goals. Thus, ‘alpha band synchronization’ in response to stimuli appears to reflect inhibition (Klimesch, 2012). For instance, when performing the inhibition-intensive Stroop task which requires inhibition, younger adults showed a tradeoff pattern between alpha and theta bands during a Stroop task, such that alpha was suppressed when participants resolved Stroop conflicts, and theta (theta band amplitude tends to increase with engaged attention; Klimesch, 1999) increased during these trials – but the trade-off was less pronounced in older adults compared with younger adults (Nombela et al., 2014). Furthermore, aging is associated with delays in the latency of alpha synchronization responses to task-irrelevant stimuli but not in the alpha band desynchronization responses to attended stimuli (Deiber et al., 2010). In other words, alpha band responses associated with inhibition show age-related decline whereas alpha band responses associated with focused attention do not.

Alpha EEG is also believed to act as an anticipatory signal for information, and the frontoparietal network modulates these anticipatory alpha rhythms (Capotosto et al., 2009). For instance, the anticipatory change in alpha rhythms can be seen when participants are presented with a short sequence of stimuli in which the second item should be ignored on some trials but remembered on other trials (Vaden, Hutcheson, McCollum, Kentros, & Visscher, 2012).

Younger adults show more alpha power from parietal electrodes in the 400 ms before that second stimulus when it should be ignored than when it should be remembered, indicating they increase alpha when anticipating the need to ignore something. In contrast, older adults did not show greater alpha power in the to-be-ignored than the to-be-remembered condition.

In younger adults, anticipatory shifts in alpha tend to be lateralized if cues indicate they should shift spatial attention to a left or right visual location (Sauseng et al., 2005). However, these spatially specific anticipatory shifts in alpha power are not seen in older adults even though older adults showed clear indications of spatial orienting and good task performance (Hong, Sun, Bengson, Mangun, & Tong, 2015; van der Waal, Farquhar, Fasotti, & Desain, 2017). The selective impairment of alpha was evident from classifier analyses that could decode the cue direction (left or right) on each trial from either ERPs or alpha lateralization in younger adults, but only from ERPs in older adults (van der Waal et al., 2017).

Thus, in the context of attentional suppression in older adults, increased age correlates with a decrease in alpha EEG frequency (particularly decreased in frontal areas), which often correlates with decreased performance on attentional tasks. Nevertheless, the mechanisms underlying alpha EEG remain unknown. The slowing of alpha EEG with age may represent changes in the higher and lower bands of the alpha frequency – such that age reduces upper band power and/or decreases lower band power of the alpha EEG (Clark et al., 2004). Altogether,

while the underlying brain areas associated with age-related decreases in alpha EEG remain relatively unknown, the frontally specific, attention-related decline suggest that frontoparietal regions are involved in its age-related change.

While it is not known what generates the alpha rhythms in the brain, they have been linked to thalamic oscillatory activity (e.g., Hughes & Crunelli, 2005) and rhythmic GABAergic activity (Lőrincz, Kékesi, Juhász, Crunelli, & Hughes, 2009). Gamma-Aminobutyric Acid (GABA) is a neurotransmitter that is widely distributed in the brain, and is known to be involved in inhibition. Diazepam, a drug that increases GABAergic neurotransmission, increases alpha frequency, the inverse of the alpha slowing that occurs with aging (Hall, Barnes, Furlong, Seri, & Hillebrand, 2010). However, the mechanism does not seem to be as simple as GABAergic processing increasing alpha oscillations in general. For instance, lorazepam, a drug enhancing GABAergic conductance, reduces alpha EEG power (Ahveninen et al., 2007; Lozano-Soldevilla, ter Huurne, Cools, & Jensen, 2014; Schreckenberger et al., 2004). In the next section, we review how GABAergic neurotransmission decreases in aging and how this might contribute to age-related impairments in attentional selection.

Age-related declines in GABA

GABA is the primary neurotransmitter driving inhibition in the brain. Compared with excitatory neurons, inhibitory neurons are less prevalent in the brain, making up only 10-20% of all neurons (Caputi, Melzer, Michael, & Monyer, 2013), but they are critical for maintaining effective brain function. In particular, GABA is associated with perceptual and attentional selectivity (Clark, 1996; Sumner, Edden, Bompas, Evans, & Singh, 2010) - for example, greater concentrations of GABA are associated with increased inhibitory function in visual receptive fields (Wolf, Hicks, & Albus, 1986), increased working memory performance (Yoon, Grandelis,

& Maddock, 2016), and faster eye-gaze movement toward task-relevant stimuli over task-irrelevant stimuli (Sumner et al., 2010). Moreover, inhibition in cognitive performance has been correlated specifically with GABA concentrations in frontal regions (Sumner et al., 2010; Yoon et al., 2016).

GABAergic interneurons are highly metabolically demanding (Bazzigaluppi, Amini, Weisspapir, Stefanovic, & Carlen, 2017), which may help explain why inhibitory GABA function seems to decline more in aging than excitatory glutamatergic function (Rozycka & Liguz-Leczna, 2017). With age in human prefrontal cortex, the ratio of excitatory pyramidal neurons to non-pyramidal neurons (a category including GABAergic neurons) shifts as the proportion of non-pyramidal neurons decreases while pyramidal neuron counts remain more constant (Braak & Braak, 1986). Likewise, in cat visual cortex, the ratio of GABAergic neurons to total neurons decreases with age (Hua, Kao, Sun, Li, & Zhou, 2008). In rats, aging reduces GABA but not glutamate efflux within the hippocampus, and leads to significant loss of GABAergic interneurons (Stanley, Fadel, & Mott, 2012). Furthermore, in older mice somatosensory cortex, the overall responses of neurons and astrocytes is unchanged, but fast-spiking GABAergic parvalbumin-positive interneuron shows reduced activity (Jessen, Mathiesen, Lind, & Lauritzen, 2017).

In humans, GABA concentrations quantified non invasively using magnetic resonance spectroscopy confirm that GABA concentrations decrease with age (Gao et al., 2013; Porges et al., 2017) and GABA concentration decrease in frontal regions of the brain are associated with age-related cognitive functioning (Porges et al., 2017).

Reductions in GABA are likely to have significant effects in the aging brain. In particular, fast-spiking GABAergic parvalbumin-positive interneurons serve as pacemakers that

help generate high-frequency gamma oscillations in local circuits associated with focused attention (Uhlhaas & Singer, 2012). Optogenetic techniques indicate that inhibiting parvalbumin interneurons suppresses gamma oscillations but increases oscillations in the alpha frequency range (Sohal, Zhang, Yizhar, & Deisseroth, 2009). And as already mentioned, pharmacological manipulations also link GABA to modulation of alpha EEG rhythms (Ahveninen et al., 2007; Hall et al., 2010; Lozano-Soldevilla et al., 2014; Schreckenberger et al., 2004).

Reductions in GABA are also likely to impair frontoparietal network function. The frontoparietal network relies on long-range communication across its subcomponent regions as well as with target regions (Womelsdorf & Everling, 2015). Although most inhibitory neurons make only local connections, recent research indicates that a small number of cortical GABAergic neurons have long-range connections to other cortical regions or to subcortical regions (Higo, Uchida, & Tamamaki, 2007; Tomioka et al., 2005), with the basal ganglia a frequent target (Tomioka, Sakimura, & Yanagawa, 2015). In addition, prefrontal GABAergic interneurons regulate the output of long-range excitatory pyramidal cells (Giustino & Maren, 2017; Lu et al., 2017) and long-range excitatory connections from frontal regions activate local GABAergic activity in visual cortex (Zhang et al., 2014). Thus, impaired GABA processing is likely to reduce the efficacy of frontoparietal network to coordinate attentional selectivity across the brain. Consistent with this potential link between GABA and frontoparietal function, in humans GABA levels in frontal and parietal regions are associated with selective attention effects such as the attentional blink (Kihara, Kondo, & Kawahara, 2016). Given its primary role in inhibition, and its change in frontal regions with age, GABA is a strong candidate as a contributor for age-related inhibitory changes.

Age-related declines in dopamine

Another neurotransmitter potentially involved in attentional selectivity changes in aging is dopamine. Dopamine is a neurotransmitter involved in motor processing and higher level cognitive processing (Bäckman, Nyberg, Lindenberger, Li, & Farde, 2006; Braver & Barch, 2002). This neurotransmitter is believed to play a role in cognitive control and also for gating information to further processing, such that dopaminergic phasic activity helps bias task-relevant information over task-irrelevant information (Braver & Barch, 2002).

Dopamine has been implicated in traditional models of age-related cognitive impairments of dedifferentiation (Abdulrahman, Fletcher, Bullmore, & Morcom, 2017; Li & Lindenberger, 1999). Moreover, connections have been drawn between dopamine and the integrity of the frontoparietal network. Dopamine appears to modulate the communication between the frontoparietal network and other attentional networks (Dang, Neil, & Jagust, 2012), and has been shown to play a role in synchronizing oscillations in prefrontal activity (Bäckman et al., 2006). Moreover, in a study of individual differences in caudate dopamine density, dopamine density was found to be predictive of connectivity between frontal and parietal brain areas, but not between areas of the default mode network or between bilateral prefrontal areas (Rieckmann, Karlsson, Fischer, & Bäckman, 2011). Thus, dopamine appears to play a modulatory role during attention, particularly to enhance communication within the frontoparietal network.

The density of dopamine - including both dopamine subtypes D₁, D₂, and the dopamine transporter (DAT) – decreases with age, and the rate of decrease seems to be relatively similar throughout areas of the brain (Bäckman et al., 2006). These decreases in dopamine density have been associated with poorer cognitive function with age (Bäckman et al., 2006; Braver & Barch, 2002), in a proposed theoretical “correlative triad” between aging, cognition, and dopamine (Bäckman et al., 2011, 2006). Although increasing dopamine levels in older adults

pharmacologically has failed to yield significant behavioral performance improvements, brain activation patterns under dopaminergic drugs have shown shifts in the right direction (Abdulrahman et al., 2017; Chowdhury et al., 2013; Morcom et al., 2010). Altogether, because of its role in the connectivity of the frontoparietal network, and the decrease of dopamine density with age, dopamine may well play a role in the decreased attentional inhibition in older adults.

Age-related changes in the LC-NE system and attentional selectivity

The locus coeruleus (LC) is the brain's primary source of norepinephrine and activates with arousal. The role of the locus coeruleus–norepinephrine (LC-NE) system in attentional selectivity is outlined in the GANE (Glutamate Amplifies Noradrenergic Effects) model (Mather, Clewett, Sakaki, & Harley, 2016). In this framework, glutamate spills over from active synapses in neural networks that are currently “high priority.” This spillover glutamate from highly active synapses reaches NMDA receptors on nearby axons from LC neurons. Glutamate activates these NMDA receptors if the associated LC neuron is simultaneously depolarized (activated), stimulating local norepinephrine release. This can allow norepinephrine levels to get high enough in that local area to stimulate high-threshold β -adrenergic receptors via both pre- and post-synaptic mechanisms (e.g., Ji et al., 2008) that stimulate even more glutamate release at the excited synapse. This feedback loop can ignite “hot spots” of prioritized representation when arousal is high and therefore the LC is active. In areas with lower priority, norepinephrine release will be limited to the relatively low levels induced by LC activation alone. This should lead to insufficient release to activate β -adrenergic receptors, but enough to stimulate lower threshold α_2 inhibitory receptors (see Mather et al., 2016 for more details).

A recent study used fMRI to examine age differences in the dynamics of LC interactions with cortical representations of salient high priority stimuli and with the frontoparietal network

(Lee et al., in press). On each trial in this study, participants were shown a place and an object image next to each other and had to indicate which one was more salient. On half of the trials, the place image was made more salient by highlighting it with a yellow border and by reducing the perceptual contrast on the other image. On the other trials, the object image was more salient. In addition, immediately before each trial, participants heard either a tone that had been previously conditioned to predict shock (CS+) or a tone conditioned to predict no shock (CS-). The GANE model predicts that high activation of stimuli representations should be further amplified when LC is activated at the same time. Consistent with this hypothesis, functional connectivity between the LC and the parahippocampal place area showed an arousal-by-salience interaction, such that the greatest functional connectivity was seen when both the place image was salient on that trial and it was an arousing (CS+) trial. This significant interaction in functional connectivity between the LC and a cortical brain area representing current stimuli was seen for both younger and older adults, suggesting that the GANE hot spot mechanisms are still intact in later life.

In contrast, the ability of the LC and arousal to modulate frontoparietal network activity was significantly diminished among the older adults in this study. Younger adults showed stronger functional connectivity between the frontoparietal network regions and the LC on high than on low arousal trials. In addition, for younger adults functional connectivity between the parahippocampal place area and frontoparietal network regions was modulated both by the salience of the place stimulus and by arousal. These modulations of frontoparietal connectivity to the LC and to the brain region representing a current salient stimulus were significantly diminished among older adults. Thus, for younger adults, arousal increased the coordination of

LC and frontoparietal activity, which in turn may have modulated how the frontoparietal network amplified or suppressed representations.

These findings suggest that even among older adults with intact ability of LC to differentially amplify cortical representations based on salience, the influence of the LC over frontoparietal selectivity processes is diminished. This may be due to decreases in the sensitivity of noradrenergic receptors in frontoparietal regions. Interestingly, in a sample aged 18-47, functional connectivity between the LC and the frontoparietal network during a resting state scan was positively correlated with age (Zhang, Hu, Chao, & Li, 2015). Higher circulating levels of norepinephrine among older adults at rest (e.g., Gannon & Wang, 2018) may lead to high levels of frontoparietal network stimulation at baseline with little capacity to increase frontoparietal resources when attentional demands (and arousal) increase. Furthermore, age-related decline in the LC itself may contribute to decreases in attentional selectivity under arousal. In general, recent findings indicate that age-related decreases in LC integrity are associated with decline in cognitive function (Clewett et al., 2015; Hämmerer et al., 2018; Mather & Harley, 2016; Wilson et al., 2013). The Lee et al. (in press) findings suggest that changes in the LC-NE system in aging may target some aspects of cognition more than others. In particular, older adults may get the benefits of arousal for amplifying activation of salient stimuli, but lose the benefits of arousal for inhibition of competing stimuli.

Alternative mechanisms and directions for future research

We've outlined several mechanisms that may contribute to age-related differences in goal-related inhibition of distracting information. We have focused on changes that occur within the frontoparietal network – a likely candidate for age-related decline in attentional selectivity. However, further work needs to examine how these mechanisms interact, whether their

contributions are specifically related to attentional selectivity, and how other brain areas or networks may also play a role.

Default mode network

While the frontoparietal network is a strong candidate for attentional selectivity changes with age, other candidates have been put forward. For example, changes within the default mode network have been proposed as contributors to age-related decline in attentional selectivity (e.g., Chadick, Zanto, & Gazzaley, 2014; Stevens, Hasher, Chiew, & Grady, 2008).

The default mode network tends to be active when people are not engaged in a particular task, and decreases activity – a pattern termed “deactivation” – with increased task demands (Anticevic et al., 2012; Mevel, Chételat, Eustache, & Desgranges, 2011). The network includes areas of the posterior cingulate cortex, precuneus, anterior cingulate cortex, dorsal and ventral medial prefrontal cortex, lateral parietal cortices, and medial temporal lobes (Hafkemeijer, van der Grond, & Rombouts, 2012; Mevel et al., 2011). Older adults tend to show lessened deactivation between rest and during cognitive tasks, to suggest that they are less able to transition between a task-free state and one that requires cognitive task demands (Hafkemeijer et al., 2012; Mevel et al., 2011). The functional connectivity of the default mode network also appears to decrease in older age (Hafkemeijer et al., 2012; Ng, Lo, Lim, Chee, & Zhou, 2016; Vidal-Piñeiro et al., 2014), and even more in individuals with mild cognitive impairment (Hafkemeijer et al., 2012; Zanchi et al., 2018) or Alzheimer’s Disease (Hafkemeijer et al., 2012).

In a task that required attentional selection for faces over scenes or vice versa, older adults demonstrated decreased deactivation in default network areas compared to younger adults – particularly in the medial prefrontal cortex – and older adult’s lowered suppression of the

medial prefrontal cortex was related to greater distraction in behavioral performance on the task (Chadick et al., 2014; see also Stevens et al., 2008). Moreover, connectivity between the medial prefrontal cortex and visual areas were associated with less suppression of distracting information in older adults compared to younger adults (Chadick et al., 2014). Thus, areas identified as within the default mode network in the medial prefrontal cortex were especially indicative of attentional selection with age.

Both the frontoparietal network and default network include areas of the prefrontal cortex, are related to attentional demands, and demonstrate decreased connectivity with age (Chadick et al., 2014; Sala-Llloch et al., 2015). Moreover, emerging evidence suggests that age-related changes in both networks can be predictive of performance (e.g., Zanchi et al., 2018), suggesting that underlying impairments in both networks should be considered for age-related changes. However, the default mode network is typically measured during non-task situations – and its coupling with other networks, such as the frontoparietal network, may vary by task-demands (Avelar-Pereira et al., 2017). While still in its infancy, more research exploring age-related connectivity changes seems a fruitful avenue for explaining complex age-related changes like attentional selectivity – whether it be a particular network or a combination of networks (see Amer, Anderson, Campbell, Hasher, & Grady, 2016; Avelar-Pereira et al., 2017; Ng et al., 2016; Zhao, Lu, Metmer, Li, & Lu, 2018).

Defining inhibition

We also discussed several functional and chemical mechanisms that change with age and likely contribute to impairments in the functions of the frontoparietal network. Nevertheless, it remains unclear which of these mechanisms and their interactions are most potent in the underlying impairments in attentional selectivity. We have also discussed “inhibition” as a

general concept, which may not be representative of the complex mechanistic underpinnings involved in different attentional, inhibitory situations (see Kramer, Humphrey, Larish, Logan, & Strayer, 1994). That is, just because inhibitory differences have been observed across many tasks does not mean that their underlying mechanisms are the same (e.g., Eich, Razlighi, & Stern, 2017) – for example, the mechanisms through which arousal amplifies inhibition of stimuli that are not perceptually salient (e.g., Lee, Sakaki, Cheng, Velasco, & Mather, 2014) may work differently than inhibition of goal-irrelevant stimuli (e.g., Sutherland, McQuiggan, Ryan, & Mather, 2017). Specifying differences between such inhibitory effects will help identify mechanisms responsible for specific aspects of attentional inhibition.

Mechanistic influences on individual stages of cognition

Inhibition may also rely on separable underlying mechanisms during different cognitive processing stages. In an fMRI study to compare activation related to older adults' inhibition during early vs. late memory processing, activation patterns reflected separable regions for inhibition during different memory processes (Eich et al., 2017). Different stages of attentional processing may thus involve different contributory mechanisms in inhibitory functionality (see also Turner & Spreng, 2012). Future research exploring the mechanisms underlying age-related inhibition changes should thus consider the specific contributory processing stages.

Conclusion

Goal-directed attentional selection requires selecting task-relevant information while simultaneously inhibiting task-irrelevant information. Across many studies and task designs, older adults demonstrate impaired attentional inhibition. We reviewed literature suggesting the frontoparietal network may play a key role in age-related changes in inhibitory processing, and

discussed mechanisms that may contribute to alterations in the integrity of the network, including alpha band activity, GABAergic processing, dopaminergic decreases, and noradrenergic influences via the LC-NE system under arousal. We also discussed the potential role of the default mode network. Future research will inform which of these mechanisms – or their interactions – play the largest role in driving age-related changes in attentional inhibition.

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