Mather, M., (in press). How arousal-related neurotransmitter systems compensate for age-related decline.
In Gutchess, A. & Thomas, A., ed. The Cambridge Handbook of Cognitive Aging: A Life Course Perspective. Cambridge University Press.

6 How Arousal-Related Neurotransmitter Systems Compensate for Age-Related Decline

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Abstract

Without brain systems that modulate arousal, we would not be able to have daily sleep-wake cycles, focus attention when needed, experience emotional responses, or even maintain consciousness. Thus, it is not surprising that there are multiple overlapping neurotransmitter systems that control arousal. In aging, most of these systems show decline in basic features such as number of receptors and transporters, and sometimes even in neuron count. These declines have the potential to disrupt basic arousal functions. Compensatory increases in activity in some of these systems allow for maintained levels of circulating neurotransmitters in those systems – but at the cost of reduced dynamic range in arousal responses.

Introduction

In the 1960s, opposing theories were proposed about arousal and aging. On the one hand, "overarousal" theory (Eisdorfer, 1968) proposed that older adults' learning and performance deficits were due to their overarousal during laboratory tasks. In contrast, "underarousal" theory (Birren, 1960; Birren, Cunningham, & Yamamoto, 1983; Falk & Kline, 1978) argued that performance deficits were due to a decreased baseline activation level and lessened reactivity of the central nervous system in older adults.

One might think that, fifty years later, this debate would either be resolved or irrelevant. However, decades of accumulated findings regarding arousal systems in the brain continue to provide data to support both perspectives. In this chapter, I outline the current cases for both underarousal and overarousal in aging. I then make the case that both processes occur simultaneously in aging. Most neurotransmitter systems involved in arousal show significant decline in aging, which could lead to chronic underarousal. However, increased tonic levels of some arousal-related neurotransmitters compensates for these declines. This compensation comes at the cost of a reduced dynamic range of responses.

What Is Arousal?

Arousal is a general term that can be broadly categorized as covering three domains: wakefulness, autonomic arousal, and affective arousal (Satpute et al., 2018). Brainstem nuclei and the hypothalamus, thalamus, posterior cingulate cortex, precuneus, and medial prefrontal cortex have been implicated in all three types of arousal. Autonomic and affective arousal involve additional regions including the amygdala, the insula, and the anterior cingulate cortex (Satpute et al., 2018).

Within the brainstem, five neurotransmitter systems – norepinephrine, dopamine, serotonin, acetylcholine, and histamine – have overlapping roles in increasing arousal (Pfaff, 2006), as does a neuropeptide, orexin. The fate of these systems in aging and the implications for arousal are the focus of this chapter. I first review each of these briefly below.

Norepinephrine

The locus coeruleus, a nucleus in the pons, is the source of most of the brain's norepinephrine. It receives direct inputs from all of the other arousal systems outlined below and serves as a hub region to integrate all categories of arousal (Mather, in press). Its tonic levels of activity are associated with wakefulness levels, and its phasic levels closely track momentary fluctuations in arousal induced by all sorts of conditions, including emotional arousal, cognitive or physical effort, and detection of salient stimuli. Locus coeruleus neurons have long axons that release norepinephrine throughout much of the brain. Typically, the release occurs at bulges along the axons known as varicosities, rather than at synapses. Thus, rather than having a specific postsynaptic target, norepinephrine is released into extrasynaptic space where it can have a broader impact.

Dopamine

Dopamine modulates behavioral motivation, playing central roles in both reward and movement (Cools, Nakamura, & Daw, 2011; Volkow, Wise, & Baler, 2017). Many motivated behaviors, such as eating, copulating, or taking addictive drugs, require activity and attention to be implemented. Thus, it is not surprising that the dopamine system interacts with the other arousal systems to modulate arousal levels, in order to increase response vigor when higher rewards are at stake (Niv et al., 2007). Dopaminergic signaling in the ventral tegmental area is correlated with vigilance levels and sleep/wake timing (Wisor, 2018). Dopamine neurons in the dorsal raphe are activated by salient stimuli and modulate wakefulness (Cho et al., 2017).

Serotonin

In some ways, serotonin plays an opposing role to dopamine, by modulating aversive processing and behavioral inhibition (Boureau & Dayan, 2011; Cools

et al., 2011). Thus, like dopamine, serotonin is linked with arousal via its role in motivated behavior. In addition, the predominant characteristic of most serotonin neurons in the raphe nucleus is that their activity is related to the sleep-wake cycle, although whether activity is associated with sleep or wake states depends on the current behavioral state and other factors (Ursin, 2002).

Acetylcholine

Acetylcholine plays a role in selective attention, orienting, and detecting behaviorally significant stimuli (Klinkenberg, Sambeth, & Blokland, 2011). Cholinergic neurons in the basal forebrain are most active during wakefulness, and the levels of their activity correlate with cortical activation (for a review, see Tyree & de Lecea, 2017). Acetylcholine neurons use GABA as a cotransmitter, which may increase the signal-to-noise ratio in sensory signals and increase control over cortical plasticity (Ma et al., 2018).

Histamine

Histamine, released broadly throughout the brain from the tuberomamillary nucleus of the hypothalamus, is responsible for modulating wakefulness and consciousness levels and is often a target of drugs used for anesthesia (Haas & Panula, 2003; Wada et al., 1991). Like norepinephrine, histamine is primarily released via varicosities into extracellular space rather than at specific synapses (Takagi et al., 1986). In addition to releasing histamine, histamine neurons release GABA into the extrasynaptic space, which seems to play an important role in calibrating the effects of histamine release and avoiding overarousal (Yu et al., 2015).

Orexin

In addition, orexin (or hypocretin), a neuropeptide synthesized in the lateral hypothalamus, also plays an important role in modulating arousal, promoting stable periods of wakefulness, and sustaining alertness needed during motivated behavior (Alexandre, Andermann, & Scammell, 2013), as well as promoting award-based feeding (Cason et al., 2010). Orexin neurons have reciprocal connections with all of the nuclei discussed above: the locus coeruleus (NE), tuberomammillary nucleus (histamine), dorsal raphe (serotonin), ventral tegmental area and nucleus accumbens (dopamine), basal forebrain, and laterodorsal and pedunculopontine tegmental nuclei (acetylcholine; Alexandre et al., 2013). Genetic mutations disrupting orexin lead to narcolepsy, or the inability to sustain long periods of wakefulness. However, microdialysis probes in the amygdala of human epilepsy patients revealed that orexin levels are not a simple function of arousal, as they are highest during positive emotion and social interactions, somewhat elevated during anger, and lowest during episodes of waking pain and during sleep (Blouin et al., 2013).

These findings suggest that orexin promotes approach-related arousal (associated with positive emotion and anger) rather than arousal in general.

Summary

This brief overview underscores the multifaceted nature of arousal. Throughout each day and night, multiple neurotransmitters interact to induce and maintain sleep and alertness. These neurotransmitters have overlapping influences, but also each has its own signature pattern of effects. As reviewed in the next section, there is evidence for age-related decline in all of these systems (see, e.g., Chapter 5 in this volume) that could support a characterization of aging as being associated with underarousal. However, as addressed in the section after that, the story is not that simple.

Evidence for Underarousal in the Aging Brain

Multiple Indicators of Decline in the Locus Coeruleus-Norepinephrine (LC-NE) System

Although modern unbiased stereology techniques (i.e., use of random sampling to count neurons within two-dimensional tissue samples to extract estimates of the count within a three-dimensional area) do not tend to find associations between age and postmortem count of LC neurons (Mouton et al., 1994; Ohm, Busch, & Bohl, 1997; Theofilas et al., 2017), there are other indicators of decline within the LC-NE system (Mather & Harley, 2016). In particular, tau pathology increases with age in the LC (Braak et al., 2011). In healthy neurons, tau protein is mostly found in axons, where it binds to tubulin, helping to stabilize and stiffen microtubules which help support the extended axon structure and transport within the axon (Arendt, Stieler, & Holzer, 2016). Hyperphosphorylation of tau reduces its binding to tubulin and is an initial phase before eventually becoming aggregated, as seen in Alzheimer's disease and other pathological conditions (Iqbal, Liu, & Gong, 2016). Initial signs of hyperphosphorylated tau are seen quite early in life in the locus coeruleus, and then the pathological tau slowly spreads from the brainstem to the entorhinal cortex and then other cortical regions in healthy aging, with this process presumably accelerated in those exhibiting signs of Alzheimer's disease (Braak et al., 2011).

It is not clear yet how hyperphosphorylated tau affects neuronal function in the absence of other pathology. Given its key role in microtubule stabilization, it may reduce axonal transport effectiveness. In addition, recent findings indicate that small amounts of tau in the dendritic compartment of neurons support both NMDA and AMPA receptor function, and so increasing tau phosphorylation reduces signal transduction and prevents excitotoxicity which otherwise could occur from overexcitation of NMDA receptors (Arendt et al., 2016).

There is some evidence that noradrenergic signaling processes change in aging. Positron emission tomography findings indicate less norepinephrine transporter binding (Ding et al., 2010). In the prefrontal cortex, postmortem findings indicate reduced α2-receptor binding (Javier Meana et al., 1992; Kalaria and Andorn, 1991) and changes in the relative ratio of β1- and β2-adrenergic receptors (Kalaria et al., 1989).

Another indication that the LC-NE system declines in aging is that NE levels are lower in older than younger adults, as found in sections of brain tissue from sites such as the cingulate gyrus (Arranz et al., 1996; Winblad et al., 1985), hippocampus (Winblad et al., 1985), hypothalamus (Winblad et al., 1985), and hindbrain (Robinson, 1975). One qualifying point that I will return to in the next section, however, is that in these studies, the tissue is blended into a solution that does not allow investigators to discriminate NE levels found in vesicles (storage sites) within a neuron from those in current circulation available to influence activity.

Declines in the Dopamine System Positron emission tomography studies indicate decline in D_1, D_2, and D_3 dopamine receptors and in dopamine transporters (for a review, see Bäckman et al., 2010). Postmortem studies also indicate loss of dopaminergic neurons in the substantia nigra with age (Fearnley & Lees, 1991; McGeer, McGeer, & Suzuki, 1977) and significant decline in dopamine levels in the striatum (Carlsson & Winblad, 1976; Kish et al., 1992), hippocampus (Adolfsson et al., 1979), and hypothalamus (Arranz et al., 1996).

Declines in the Serotonin System Postmortem studies reveal reduced density of serotonin receptors in the brain, while PET studies show reduced receptor binding (for reviews, see Meltzer et al., 1998; Rodríguez, Noristani, & Verkhratsky, 2012).

Declines in the Orexin System Postmortem analysis of the hypothalamus reveals a 10 percent decline in orexin neurons from young adulthood (between 22 and 32) and later adulthood (between age 48 and 60; Hunt et al., 2015). In a study with male rhesus monkeys, orexin neuron numbers did not differ with age, but there was less excitatory orexin innervation to the locus coeruleus (Downs et al., 2007). PET studies show decreases in histamine receptor binding (specifically, H_1 R-binding) with age throughout much of the cortex (Higuchi et al., 2000; Yanai et al., 1992).

The Acetylcholine System Does Not Decline Much In the 1970s and 1980s, the acetylcholine hypothesis of Alzheimer's disease emerged based on finding significant loss of basal forebrain cholinergic neurons in brains affected by Alzheimer's disease (Davies & Maloney, 1976; Perry et al., 1977; Whitehouse et al., 1982). However, more recent evidence indicates that notable cholinergic system deficits do not emerge until late stages of Alzheimer's disease (Davis et al., 1999; Gilmor et al., 1999; Schliebs & Arendt, 2011), and aspects of the system such as number of cholinergic neurons in the basal forebrain (Gilmor et al., 1999) and nicotinic acetylcholine receptors (Jogeshwar et al., 2018) are not correlated with age (although the volume of the basal forebrain cholinergic system declines throughout

adulthood; Grothe, Heinsen, & Teipel, 2012). However, a significant risk in late life for this system comes from anticholinergic medications prescribed for a variety of common ailments (e.g., depression, allergies, cold and flu symptoms, insomnia, and urinary incontinence). Estimates of how many older adults take anticholinergic medication are as high as 37 percent (Britt & Day, 2016), and higher cumulative use of anticholinergics is associated with greater risk of developing Alzheimer's disease (Gray et al., 2015). Consistent with acetylcholine's role in arousal, cholinesterase inhibitors that increase acetylcholine levels improve attention and concentration and reduce anxiety and restlessness in patients experiencing those symptoms (Lemstra, Eikelenboom, & van Gool, 2003).

Summary

The arousal-related neurotransmitter systems show decline in various aspects, including reduced receptor density and binding and reduced norepinephrine and dopamine transporter binding.

Evidence for Overarousal in Aging

The previous section reviewed an array of declines in arousal-related transmitter systems. This section presents evidence that such declines are associated with increases in transmitter activity that may help maintain function, especially within the hub arousal system, the LC-NE system.

The LC-NE System Shows Compensatory Increases in Activity As outlined in the previous section, there is evidence of decline in the LC-NE system in aging, and studies that examine NE levels within homogenized (i.e., blended into a consistent solution) brain tissue find decreases in older adults. However, this quantification of overall brain levels of NE may only tell part of the story, as there is also evidence of LC-NE hyperactivity in aging and in early stages of the AD process (Gannon & Wang, 2018; Weinshenker, 2018).

Norepinephrine levels in cerebrospinal fluid and in blood are greater in older adults than in younger adults (Elrod et al., 1997; Raskind et al., 1988; White et al., 1997). For instance, one estimate is that plasma norepinephrine increases 10–15 percent in concentration per decade during adulthood (Seals & Esler, 2000). The increases in norepinephrine in cerebrospinal fluid are even greater in patients with Alzheimer's disease than in healthy older adults (Elrod et al., 1997). While these estimates can be confounded by age differences in the rate of flushing out waste from cerebrospinal fluid, techniques that assess the rate of norepinephrine spillover into plasma find elevated rates in older compared with younger adults (Seals & Esler, 2000). In addition, muscle sympathetic nerve activity increases as people age (Fagius & Wallin, 1993), and in general, increasing sympathetic nerve activity seems to contribute to increasing blood pressure with age (Hart & Charkoudian, 2014).

Why would LC-NE system activity increase in aging? One possibility is that as LC neurons die in aging and Alzheimer's disease, surviving LC neurons go into overdrive to compensate for this loss (Gannon & Wang, 2018; Weinshenker, 2018). An impressive demonstration of the ability of surviving LC neurons to compensate for the loss of other LC neurons comes from a study that induced partial LC lesions in rats and then measured extracellular NE levels in the hippocampus using microdialysis both at baseline and during stress (Abercrombie & Zigmond, 1989). Reductions of hippocampal tissue NE (detected from homogenized postmortem tissue) of up to 50 percent had no effect on NE levels detected in extracellular space; it took more than a 50 percent decline in tissue NE to see a decline in NE detected using microdialysis. These findings suggest that remaining LC neurons increased their rate of NE release to compensate for declines in total LC neurons. Furthermore, destroying most of the noradrenaline terminals in the forebrain of rats led the intact LC neurons to increase firing rates for the next few weeks at about a fourfold rate (Chiodo et al., 1983), and destroying terminals in the hippocampus led to a rapid increase in the activity of the rate-limiting enzyme for NE production, tyrosine hydroxylase (Acheson & Zigmond, 1981; Acheson, Zigmond, & Stricker, 1980). Destruction of LC neurons can also lead to increases in NE axons in forebrain regions over the next twelve months (Fritschy & Grzanna, 1992). Most importantly, these results indicate that even if NE levels quantified from postmortem homogenized tissue are diminished, this does not mean that extracellular circulating levels of NE are diminished.

Consistent with these experimental findings in rats, patients with neuronal loss due either to Alzheimer's or dementia with Lewy bodies showed changes in the noradrenergic system consistent with compensation, including an increase in tyrosine hydroxylase mRNA expression in remaining neurons. This suggests that these neurons are compensating for the loss of other LC neurons by increasing the rate-limiting enzyme in the synthesis of NE (Szot et al., 2000, 2006). In addition, those with more loss of pigmented LC neurons showed higher ratios of the norepinephrine metabolite 3-methoxy-4-hydroxyphenylglycol (MHPG) to total norepinephrine levels in the frontal medial cortex (Hoogendijk et al., 1999). In the same study, no such upregulation of serotonin or dopamine metabolites was seen in the Alzheimer's patients.

Phasic pupil responses are associated with LC activity (Joshi et al., 2015), and interestingly, in middle-aged men, reduced phasic pupil responses during working memory were associated with greater tonic low-frequency BOLD variance during a resting-state fMRI scan in key nodes of the ventral attention network (Elman et al., 2017). Greater tonic activity in the ventral attention network in older adults may also help explain why arousing circumstances such as expecting an electric shock are less effective at increasing ventral attention network activity and less likely to increase coordination with LC activity than they are for younger adults (Lee et al., 2018).

Why might the LC-NE system show more upregulation of activity upon loss of neurons? The NE system may be ideally set up to allow for surviving neurons to

compensate for the loss of other neurons or for upregulation of release of NE from surviving varicosities when other release sites are damaged. This is because most NE release does not occur at specific synapses, but instead into the general extracellular space. If a specific synapse is damaged it is difficult for upregulation of another synapse to compensate for this, but because NE can use a "hormonal" mode of modulating activity, releasing more NE from nearby varicosities should be able to provide some compensation for loss of neighboring NE release points.

It has also been proposed that even before there is neuron loss in the LC-NE system, increasing tau pathology triggers changes that lead to hyperactivity, which may help compensate for the loss of noradrenergic axons, terminals, and NE in brain regions to which the LC projects (Weinshenker, 2018).

In general, stress and arousal manipulations show either similar or reduced increases in markers of sympathetic activity in older adults compared with younger adults. For instance, in response to postural stimulation, younger adults show greater increases in NE levels, heart rate, heart rate variability, and salivary alpha amylase (Lavi et al., 2007; Lipsitz et al., 1990; White et al., 1997; Yo et al., 1994). Salivary alpha amylase is another biomarker for NE, as sympathetic activity stimulates salivary glands to release this digestive enzyme (Nater & Rohleder, 2009). When several samples are collected each day to capture a diurnal profile, older adults have an overall greater daily output of salivary alpha amylase than younger adults (Birditt et al., 2017; Nater, Hoppmann, & Scott, 2013; Strahler et al., 2010), findings that seem consistent with the possibility of baseline NE hyperactivity reviewed in the previous section. In general, negative social interactions are associated with higher sustained levels of alpha amylase during that day, an effect that did not differ by age group (Birditt et al., 2017). Likewise, in another study with both a psychosocial stress and a control group, older adults had greater salivary alpha amylase release than younger adults, but there was no age difference in how much the stress task affected participants compared to the control group (Almela et al., 2011).

α2a noradrenergic receptors are the most common noradrenergic receptors in the brain, and they require less NE to activate than α1 or β-adrenergic receptors. They typically are inhibitory and often serve as autoreceptors right at the sites of NE release. Thus, their activity is critical for keeping tonic levels of NE low. Across studies, α2 antagonists have more of an effect on NE activity in older adults than younger adults (Peskind et al., 1995; Raskind et al., 1999), whereas α2 agonists have more of an effect on younger adults (Raskind et al., 1988). This suggests that α2 receptors are tonically more occupied in older adults, which may result in fewer remaining α2 receptors available to inhibit NE activity.

Likewise, administration of NE to the LC, which usually decreases LC firing due to α2a inhibitory noradrenergic receptors, was significantly less effective at reducing firing in surviving LC neurons with upregulated activity after most other LC neurons had been damaged (Chiodo et al., 1983). This indicates that some types of damage lead the LC to transition to a higher tonic mode of activity and to become less sensitive to autoregulation feedback mechanisms to adjust its activity levels.

The Dopamine System May Also Show Compensatory Increases in Activity There are emerging hints that, as seen in the LC-NE system, decline within the dopamine system is not uniform and that as much of the system declines, there may be upregulation of dopamine synthesis by remaining neurons to maintain dopamine levels. Cerebrospinal fluid (CSF) levels of a major dopamine metabolite, homovanillic acid, increase in aging (Brewerton et al., 2018; Gottfries et al., 1971). It could be that homovanillic acid remains in CSF for longer in older adults than in younger adults, such that it does not actually reflect greater dopamine metabolism in the brain (e.g., Rapoport, Schapiro, & May, 2004). However, a meta-analysis of positron emission tomography studies found that, across studies, there was no significant decline with age in dopamine synthesis – despite declines in dopamine transporters and receptors (Karrer et al., 2017).

The lack of age effect in dopamine synthesis may reflect an initial upregulation that eventually declines. Current models posit that some aspects of age-related impairments in episodic memory may be caused by reduced dopamine signaling (Bäckman et al., 2010; Li & Rieckmann, 2014). However, while a study that involved administering both a dopamine agonist and a dopamine antagonist found that older adults were more sensitive to the dopaminergic perturbation than younger adults, the dopamine agonist improved memory function only in those older adults with poor baseline memory, whereas the dopamine antagonist improved memory in the better-performing older adults (Abdulrahman et al., 2017). This raises the possibility that in higher-functioning older adults, there is some degree of overexcitation within the dopamine system. CSF levels of a major serotonergic metabolite, 5-hydroxyindoleacetic acid (5-HIAA), are higher in healthy older adults than in younger adults (Brewerton et al., 2018; Gottfries et al., 1971; Yoon et al., 2017), even though they also show decreased levels in patients with Alzheimer's disease.

Increases in Orexin In contrast with the age-related declines in orexin neurons, plasma levels of orexin are positively associated with age (El-Sedeek, Korish, & Deef, 2010; Matsumura et al., 2002). In addition, patients with Alzheimer's disease or mild cognitive impairment show higher CSF levels of orexin-A than controls (Gabelle et al., 2017; Liguori et al., 2016), and these higher levels are associated with disrupted sleep (Liguori et al., 2016). This may reflect greater production of the peptide to overcome reduced sensitivity associated with loss of orexin neurons, as in both rodents and humans, more than half of orexin neurons must be lost before significant decreases in CSF levels of orexin are detected (for a review, see Nixon et al., 2015). Thus, there may be an initial phase of upregulation of orexin-A associated with disrupted sleep followed by depleted levels of orexin-A in later stages of Alzheimer's disease, leading to excessive daytime sleepiness (Fronczek et al., 2012).

Increases in Histamine Mean levels of histamine metabolites are higher in CSF of older adults than in younger adults (Motawaj et al., 2010; Prell et al., 1990). Furthermore, in Alzheimer's disease, the tuberomammillary nucleus (the origin of histamine neurons) shows marked degeneration, yet the main histamine metabolite

is only slightly (Motawaj et al., 2010) or not at all (Gabelle et al., 2017) decreased in the CSF of Alzheimer's patients relative to controls. This suggests compensatory activation of remaining neurons. Furthermore, histamine levels in CSF were correlated with insomnia severity in patients with mild cognitive impairment and Alzheimer's disease, suggesting that compensatory histamine activity during this disease process leads to overarousal (Gabelle et al., 2017).

Summary

A number of neurotransmitter systems show signs of overarousal in aging insofar as their levels are increased in cerebrospinal fluid. In textbooks, neurotransmitter release is pictured as occurring at a synaptic gap. However, arousal-related neurotransmitters often are released into the extracellular space of the brain outside of specific synapses. CSF can provide a proxy measure of the level of these circulating neurotransmitters and their metabolites because interstitial fluid diffuses easily into the CSF (Spector, Snodgrass, & Johanson, 2015). While cerebrospinal fluid is one step removed from the brain, it provides an important piece of data that typical postmortem data does not. Typically, postmortem examination of neurotransmitter levels is done by taking brain tissue and blending it up. This mixes up the neurons and the extracellular fluid (known as interstitial fluid). However, if in aging there are fewer neurons containing a particular neurotransmitter in stored vesicles but upregulation of release of that neurotransmitter, this could lead to decreased total neurotransmitter sequestered within neurons but equivalent or even increased neurotransmitter levels in the extracellular space.

The CSF "overarousal" indications, however, require confirmation from other measures because age-related changes in CSF transit processes could potentially be the source of these differences. For instance, active transport processes help move HVA and 5-HIAA out of the brain, and these transport processes decline in Alzheimer's disease and also somewhat in healthy aging (Spector et al., 2015).

Conclusions

Modulating arousal is essential for so many everyday life functions, including consciousness. It is likely because of its essential nature that there are multiple overlapping neurotransmitter systems that help control arousal levels. In aging, there is clearly decline in these systems. Returning to the old debate introduced at the outset of this chapter as to whether aging involves overarousal or underarousal, the findings reviewed in this chapter suggest that loss of neurons, receptors, and other infrastructure involved in brain arousal systems threatens to create underarousal. However, as I argue in this chapter, these declines are compensated for by increased tonic levels of some of the involved neurotransmitters, which allows for maintained function at the cost of a diminished dynamic range. For older adults to maintain conscious awareness

and cognitive functioning, each neuron involved in these arousal-related systems appears to have to produce more neurotransmitters than it would in a younger brain. With these higher typical baseline levels, there may be less capacity to increase levels further.

This picture fits with a recent model of emotional well-being in aging called "strength and vulnerability integration" or SAVI (Charles, 2010), which posits that physiological flexibility decreases in aging. However, SAVI also posits that under stress, older adults will show greater and more prolonged physiological stress responses, whereas the evidence reviewed here suggests that older adults are chronically at a higher set point of physiological arousal but that stressful situations do not increase that arousal any more for older than for younger adults, and in fact, older adults sometimes even show less physiological responding to stress than younger adults.

In general, stress hormones and neurotransmitters help people adapt to the challenges of daily life in order to maintain homeostasis. These are essential functions, but if not turned off after stress or when overused by having too many stressors, this leads to a state of "allostatic overload" that is associated with wear and tear in the brain and body (McEwen, 2004). The findings reviewed in this chapter suggest that internal declines in arousal system capacity may similarly lead to allostatic overload by stimulating greater neurotransmitter release to help maintain function, but at a long-term cost.

Acknowledgements

I thank Chris Hertzog for pointing me to the over- versus underarousal debate. Work on this chapter was supported by NIH grant R01AG025340.

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