

Chapter 1

Introduction

1.1 Sustained attention

1.1.1 Psychological foundation, definitions and its significance

Sustained attention is the ability to actively process incoming information adequately over a prolonged period of time (Rogers, 2000; Durso et al., 2007) and also includes the ability to maintain a consistent behavioral response during continuous, repetitive, tedious and intellectually unchallenging activity (Langner and Eickhoff, 2013; Fleming, 2019). A recent integration of these definitions reframes sustained attention as the ability to maintain task performance over time against fatigue and distraction (Clayton et al., 2015; Al-Shargie et al., 2019; Esterman and Rothlein, 2019). The decline of sustained attention is delineated as performance reduction with time during vigilance tasks as a time on task (TOT) effect such as committing more lapses, omitting targets, having slower and less stable responses when people are required to stay alert to detect targets for a period of time (Mackworth, 1948; Warm et al., 2008; Esterman et al., 2013; Staub et al., 2014b).

Sustained attention plays a crucial role in daily life, such as public safety (Edkins and Pollock, 1997), academic (Steinmayr et al., 2010) and occupational performance (Royal et al., 2015). The monotonic nature of vigilance tasks distracts people, introduces fatigue in individuals, and leads to possible fatal consequences such as road accidents (Thiffault and Bergeron, 2003). The ability to stay vigilant not only keeps people away from lethal consequences and mishaps (Robertson, 2003), but also lays the groundwork for advanced cognitive functions (Debettencourt et al., 2018; Hakim et al., 2020) and motor performance (O'Halloran et al., 2011; Park et al., 2021). Many higher-level cognitive functions are closely associated with sustained attention, such as working memory (Unsworth and Robison, 2020), episodic memory (Debettencourt et al., 2018), and executive functions (Luna et al., 2022). For instance, individuals with high working memory capacity (WMC) are less distracted when facing cognitively challenging activities compared to low-WMC participants (Kane et al., 2007). Another study demonstrated that vigilance decrement was proportional to working memory load in both healthy and dementia participants (Baddeley et al., 1999), which had been confirmed in following studies (Helton and Russell, 2011; Epling et al., 2016). When working memory performance was compared with phases of slower or faster responses in sustained

attention tasks, synchronous fluctuations of sustained attention and working memory were observed (DeBettencourt et al., 2019).

Therefore, sustained attention, as the ability to stay vigilant, is pivotal in fulfilling the requirements for sufficiently performing everyday routines to keep individuals from dangers and providing foundations for advanced cognitive functions.

1.1.2 Neural mechanisms of sustained attention

Specific cortical areas, networks, and neurotransmitter systems have significant impact on the functioning of sustained attention, as manifested in behavioral performance, neurophysiological signals, and imaging results. Contributions from these factors to sustained attention are described below.

▪ Related cortical areas and cerebral networks

From the functional localization perspective, both frontal and parietal cortices are involved in sustained attention at behavioral, imaging, and neurophysiological levels (Corbetta and Shulman, 2002). Posner and Petersen (1990) laid the foundation for the contribution of the frontoparietal network (FPN) to sustained attention by introducing the anterior attention system in the frontal lobe for target detection (the “what” pathway) and the posterior attention system in the parietal cortex for target location (the “where” pathway) (Ungerleider, 1982; Posner and Petersen, 1990). Neurophysiological evidence from animal models as well as from epilepsy patients revealed that theta band oscillations mediated functional connectivity in the FPN, including the prefrontal cortex (PFC) and posterior parietal cortex (PPC), during sustained attention tasks (Sellers et al., 2016; Helfrich et al., 2018). The possible role of the FPN in sustained attention was fortified by brain network segregation based on functional connectivity patterns identified in functional magnetic resonance imaging (fMRI) studies (Langner and Eickhoff, 2013).

With respect to the frontal cortex, many studies support its importance on sustained attention (Manly and Robertson, 1997), particularly frontal lesion studies (Wilkins et al., 1987; Rueckert and Grafman, 1996; Shallice et al., 2008). Patients with right frontal lesion performed poorly on sustained attention tasks compared to patients with lesions in other regions (Wilkins et al., 1987). Furthermore, in comparison with healthy controls, frontal-lesioned patients made more errors and responded slower (Rueckert and Grafman, 1996). Moreover, frontomedial theta oscillations were found to be associated with sustained attention performance in both animal and human studies (Clayton et al., 2015). In addition,

the bilateral inferior frontal operculum, anterior cingulate, and bilateral premotor cortex were activated during sustained attention tasks in both visual and auditory modalities (Grahn and Manly, 2012). fMRI studies also manifested enlarged activations in the right DLPFC, inferior parietal cortex, and thalamus during attention tasks (O'Connor et al., 2004). The involvement of DLPFC was pervasively observed in sustained attention studies at behavioral, electrophysiological and neuroimaging levels. An animal study using the pharmaceutical pseudo-lesion technique in the PFC region found a vigilance decrement during an attention task (Dalley et al., 2004). Another animal study exhibited vigilance decrement after an infusion of γ -amino butyric acid (GABA) in the PFC region (Auger et al., 2017). In neuroimaging studies, one positron emission tomography (PET) study exhibited not only an increased activation in the right middle PFC when participants performed a discrimination task requiring sustained attention, but also a positive correlation between the middle PFC metabolic rate and the accuracy of the same vigilance task (Cohen et al., 1988).

Studies moreover showed contributions of the parietal cortex to sustained attention (Broussard et al., 2006; Thakral and Slotnick, 2009; Edwards et al., 2020). The P3b component of the classical P300, an event-related potential (ERP) component elicited by the oddball paradigm, presentation of rare events, in attention tasks, has the largest amplitude around the parietal electrode Pz (Pritchard, 1981; Picton, 1992). Animal studies revealed that activation of the PPC is positively related to sustained attention performance (Broussard et al., 2006). In humans, fMRI studies also found that the inferior parietal cortex (Coull et al., 1998), as well as the PPC (Lauritzen et al., 2009) manifested activations specific to sustained attention.

At the network level, a meta-analysis integrating coordinate-based computations of neural correlates of the TOT effects across neuroimaging studies and possible brain-behavioral causality from brain-lesion patients, identified several cerebral areas related to vigilance tasks performing in durations from more than 10 seconds up to several minutes, including the bilateral PFC and thalamus, and also the bilateral but right-hemispheric dominance in the presupplementary motor area and anterior insula, and the inferior parietal sulcus (IPS), temporoparietal junction (TPJ), and the mid-lateral PFC in the right hemisphere, as well as some subcortical areas (Langner and Eickhoff, 2013). Those regions constitute the Sustained Attention Network (SAN) (Pamplona et al., 2020), and later modified as the collective cerebral regions with elevated activations during

vigilance tasks, such as gradual-onset Continuous Performance Task (gradCPT) (Rosenberg et al., 2016) and Psychomotor Vigilance Test (PVT) (Drummond et al., 2005). Besides, sustained attention has also close associations with networks involved in goal-directed processing, namely top-down control, such as the Dorsal Attention Network (DAN), Frontoparietal Network (FPN, also known as Executive Central Network (ECN)).

For performing vigilance tasks by maintaining attention on targets with or without distractors, participants need to detect the target and make the required responses, which indicates an endogenous top-down control to invest internal attention resources to the target prior to the presence of incoming stimuli (Theeuwes, 2010). An elegant example of top-down control in allocating people's attention is the cue paradigm. When the target later appears in the location where it is correctly indicated by a prior cue, participants respond faster and more accurately due to the prior distribution of internal resources to the cued location via top-down control. On the contrary, when the target is presented in a location opposite to the cue position, slower and erroneous responses occur consequently because of an additional process, re-orientation from locations indicated by invalid cues to the target, is required for correct responses (Posner et al., 1980).

Selective attention to stimuli and mapping of a specific response involves the DAN which includes the bilateral frontal eye field (FEF) of the DLPFC region, IPS, and superior parietal lobule. Cortical activations of the DAN significantly increased in a sustained attention task with short breaks between runs requiring self-paced fast responses, in difference to other vigilance tasks of a fixed time frame with same or fewer stimulus-response mappings, albeit the TOT effects in response time and pupil diameter changes occurred in all three tasks (Teng et al., 2019). A similar activation pattern during a self-paced vigilance task applied to the FPN as well: cerebral activations of the FPN increased during the sustained attention task, and reduced to a lesser extent at rest after task completion compared to the baseline resting-state. Moreover, regional cerebral blood flow (rCBF) reductions in the FPN was found to be correlated to the performance decrease (Lim et al., 2010).

The default mode network (DMN) is crucial for sustained attention performance. The DMN was first spotted due to its characteristic inactivity during task-demanding processing while becoming active instead when not focusing on tasks, particularly in the awake state at rest, in both health and disease (Raichle et al., 2001; Buckner et al., 2008; Anticevic et al., 2012; Vemuri et al., 2016; Smallwood et al., 2021). The cortical regions of the DMN include the medial DLPFC, posterior cingulate cortex, and angular gyrus (Greicius et al., 2003; Esterman et al., 2013; Horn et al., 2014). The default mode of the

brain is physiologically characterized by its uniformly stable oxygen extraction fraction, the ratio of oxygen consumed by the brain to oxygen delivered by arterial blood flow, which is regarded as the baseline state of the brain (Raichle et al., 2001). One fMRI study found that the DMN was activated during the sustained attention task, meanwhile the anterior insula was inhibited compared to the resting state (Danckert and Merrifield, 2018). Another study described the modality independence, in visual and auditory presentation, of the DMN involvement in sustained attention (Zhang et al., 2022). Although correlations between the aforementioned networks and sustained attention were described, their activations might represent general responses to task-related demands (Parks and Madden, 2013), which might not be specific to sustained attention.

▪ **Neurotransmitter**

Besides the attribution of inter- and intra-network functional connectivity to sustained attention, the contribution of neurotransmitters, such as noradrenaline (Unsworth and Robison, 2017), acetylcholine (Himmelheber et al., 2000), and nicotine (Mirza and Stolerman, 1998; Shoaib and Bizarro, 2005) to sustained attention, has been examined in many studies as well.

Noradrenaline is primarily regulated by the locus coeruleus-norepinephrine (LC-NE) system, which is related to arousal and has an impact on sustained attention (Esterman and Rothlein, 2019). Deficient LC-NE functioning in participants of low working memory capacity led to overall more erroneous responses in attention control tasks, and a proneness to mind wandering associated with greater DMN activity compared to those with high working memory capacity (Unsworth and Robison, 2017).

For acetylcholine, one animal study using an operant task for sustained attention evaluation found that the release of acetylcholine was increased during operant task performance. Decreased acetylcholine release appeared during distractor presentation with a propelled response in the first half of the experiment, regardless of the types of stimuli, indicating a disrupted sustained attention performance at the start. Furthermore, the following recovered increase was revealed in both acetylcholine release and sustained attention performance in the late half of the experiment. The positive correlations manifested in both early and later stages of the experiment, suggested a strong association between acetylcholine level and sustained attention performance (Himmelheber et al., 2000).

Administration of a medium amount of nicotine was beneficial to accuracy increment and omission reduction in sustained attention tasks with low event frequency in rats.

Furthermore, both small and medium amounts of nicotine intake were advantageous to shorten response time and to enhance anticipatory response in sustained attention tasks in conditions of short stimulus presentation and low event frequency. However, performance in high event rate conditions was not affected by nicotine uptake (Mirza and Stoleran, 1998). Moreover, withdrawal of nicotine absorption after one week of constant consumption drastically worsened sustained attention performance in rats in comparison with the control group taking saline (Shoaib and Bizarro, 2005).

These findings from neuropharmacological studies suggested that neurotransmitters might also have a role in maintaining sustained attention, as do the brain networks associated with vigilance.

1.1.3 Sustained attention decline in elderly

As people age, a variety of functions in the cognitive spectrum inevitably decline, including sustained attention (Salthouse, 2010; Harada et al., 2013; Staub et al., 2013; Salthouse, 2016). Lower hits as well as higher false alarm rates of sustained attention tasks were manifested as age-dependent vigilance decrements in older adults, albeit similar commission error rates were reported in young and older adults (Deaton and Parasuraman, 1993). Furthermore, older adults displayed a larger vigilance decrement with respect to response time when responding to infrequent targets in comparison with young adults (Staub et al., 2014b). These age-dependent vigilance decrements are hardly compensated by practice (Parasuraman and Giambra, 1991; MacLean et al., 2010). A meta-analysis investigating age-related differences in Sustained Attention to Response Task (SART) performance found that older adults responded slower but committed fewer errors than young adults, suggesting a more cautious strategy might be adopted by older adults (Vallesi et al., 2021). One study using semantic stimuli obtained similar results as the aforementioned studies, supporting the notion that older adults prefer preservative strategies (Thomson and Hasher, 2017).

Sustained attention has a close relationship with functional independence as revealed in activities of daily living (ADL), such as gait. The accuracy of gradual-onset Continuous Performance Task (gradCPT) for sustained attention performance not only explained most of the variance of gait speed in both middle-aged and older participants, but also was a significant predictor of gait speed, even after filtering out factors including executive function performance, physical and vascular risks (Park et al., 2021).

The inevitable declining vigilance with age encounters elderly people with fundamental challenges of maintaining safety and life independence, which ignites research interest to find potential solutions through a sufficient understanding of possible mechanisms underlying the waning of sustained attention in aging.

1.1.4 Neurodegenerative mechanism behind vigilance decline in aging

The primary cause of vigilance decline in older adults may come from neurodegenerative aging through both brain atrophy (Dennis and Cabeza, 2011) at the structural level and reduced activations in whole-brain scale at the neurophysiological level (Lu et al., 2011; Ferreira and Busatto, 2013; Hausman et al., 2020). At the structural level, a longitudinal fMRI study revealed reductions of brain volume in distinct brain regions in older adults compared to young adults, including the hippocampus, the inferior temporal lobe, and the PFC areas, which were all shrinking with age (Raz et al., 2005).

At the cortical level, brain activation patterns in healthy aging are emerging in distinct age-dependent tendencies. Resting-state rCBF is decreased in aging brains, particularly in the PFC, insular cortex, and caudate (Lu et al., 2011). On the contrary, prominent larger activation as observed by blood oxygen-level dependent (BOLD) signals in the PFC of older adults was manifested in resting-state fMRI (rsfMRI), compared to young adults with more focal intensified cortical activations (Batouli et al., 2009). Enlarged prefrontal activations were noted to be positively associated with improved task performance in task-related fMRI studies (Davis et al., 2008; Cabeza and Dennis, 2012), implying a possible compensation mechanism in older adults for retaining performance to previous levels.

Another cause for age-dependent sustained attention decline might be derived from receding neurotransmitter activity. The decline of the cholinergic system in advanced age might be resulted from the interactions between reduced amyloid precursor protein metabolism and cerebral microvascular abnormalities. This could lead to cognitive decline with age (Sarter and Bruno, 2004). The cholinergic hypothesis states that acetylcholine (ACh) release or changes in the cholinergic system of the basal forebrain modulate attention-related processes through top-down regulation in the PFC region (Sarter et al., 2001).

Neuroimaging techniques have opened a window for researchers to look into neurodegenerative mechanisms behind age-related cognitive decline, which involves numerous cognitive functions, including processing speed (Salthouse, 2000; Davis et al.,

2012; O'Shea et al., 2016), perception (Baltes and Mayer, 2001; Monge and Madden, 2016; Roberts and Allen, 2016), attention (Madden et al., 2004), learning (Lighthall et al., 2018), working memory (O'Shea et al., 2016), episode memory (Cabeza et al., 2000; O'Shea et al., 2016), execution function (O'Shea et al., 2016) and reasoning (Chapman et al., 2015).

Accumulated results from resting-state fMRI and structural MRI studies in older adults have demonstrated age-related atrophy, reductions in cerebral blood flow, and ebbing functional connectivity in the whole brain of older adults (Dennis and Cabeza, 2011; Lu et al., 2011; Ferreira and Busatto, 2013; Hausman et al., 2020). The frontal lobe, a central region for cognitive functions, exhibits the most rapid atrophy rate compared to other cortical regions (Grothe et al., 2013; Kievit et al., 2014). Both functional connectivity within networks, especially the DMN, and between networks is waning in healthy aging brains (Goh, 2011; La Corte et al., 2016; Hausman et al., 2020; Jiang et al., 2022).

Task-related imaging research provides substantial correlations between cortical activation and the performance of specific cognitive functions affected by age. Several studies in visual perception have identified an age-related activation pattern revealing decreased occipital activity and increased prefrontal activity, termed the posterior-anterior shift in aging (PASA) (Grady et al., 1994; Davis et al., 2008; Abellana-Pérez et al., 2019), implying a role of the prefrontal cortex (PFC) in compensation mechanisms of the aging brain (Dolcos et al., 2002; Davis et al., 2012; Davis et al., 2017).

Furthermore, the tendency of PFC lateralization is fading with age (Cabeza, 2001), as demonstrated by substantial evidence across various cognitive functions, including episodic memory (Cabeza et al., 1997; Reuter-Lorenz, 2002; Cabeza et al., 2004; Bucur et al., 2008; Deng et al., 2021), working memory (Reuter-Lorenz, 2002), perception (Grady et al., 2000), and inhibitory control (Korsch et al., 2014). In older adults, the PFC lateralization evolves into a bilateral activation pattern, in contrast to the lateralized activation observed in younger adults when performing the same task.

These neuroimaging findings in different age cohorts had developed into several concepts for healthy aging, such as the model of Hemispheric Asymmetry Reduction in Old Adults (HAROLD) revealed in age-dependent differences of cerebral activations between young and older adults, with similar memory performance (Cabeza, 2002) and the Compensation-related Utilization of Neural Circuits Hypothesis (CRUNCH) (Reuter-Lorenz and Cappell, 2008). These models concordantly indicate a bilateral compensation mechanism propelled by brain aging, in order to achieve the requirements of demanding

cognitive tasks for healthy aging, which has also been verified by later studies (Piefke et al., 2012; Lee et al., 2015; Suzuki et al., 2018).

In a clinical study on older adults, the atrophy of bilateral PFC regions was strongly correlated with slower responses in sustained attention tasks (Brück et al., 2004). During a 1h sustained attention task, older adults revealed similar activations in bilateral frontal areas in contrast to a lateralized activation in young adults, while manifesting lower signal detections and a slower response time than young participants (Harwood et al., 2017). These age-dependent differences in behavioral and cortical changes were also corroborated by neurophysiological studies. Vigilance decrements in rare target detections and the greater electroencephalography (EEG) amplitudes were exhibited in older adults compared to young participants (Staub et al., 2015). One PET study demonstrated that both frontal and parietal regions were activated during sustained attention tasks in a modality-independent manner in older adults (Johannsen et al., 1997). Furthermore, a deficit of sustained attention might also be resulted from receding PFC activations in the elderly. One study using event-related fMRI found decreased PFC activations in older adults compared to young adults when longer blocks of items were required to be remembered (Dennis et al., 2007). In another fMRI study, the correlation variations between and within the FPN (Frontoparietal Network), DAN (Dorsal Attention Network), and DMN (Default Mode Network) were examined at rest and during a sustained attention task in young and older adults. The lower activation level of the resting DMN was indicative of the weakening anticorrelation of DAN and DMN during the task in older adults. Furthermore, an age-dependent reduction was apparent in the correlation of the FPN and DMN both at rest and during a sustained attention task in older adults compared to young adults, and the FPN-DMN connectivity was higher at rest than that during a vigilance task performance in both age groups. Moreover, no differences in FPN-DAN connectivity between the young and old groups in either states was observed. Additionally, the DMN-DAN anticorrelation did not differ at rest between these two groups either, while the young group manifested greater DMN-DAN anticorrelations than the older group during the vigilance task (Avelar-Pereira et al., 2017). And this DMN-DAN anticorrelation was positively associated with sustained attention performance (Kucyi et al., 2020). Instead, the greater DAN-DMN correlation was negatively correlated to distractor suppression (Poole et al., 2016).

In an event-related potential (ERP) study using the SART (Sustained Attention to Response Task) paradigm, older adults revealed not only enhanced resource allocation as

manifested in larger amplitudes in P2 and Go-P3 components, but also a broader frontal distribution in No-Go P3 of response inhibition for task-related processing, in comparison with the findings in younger participants (Staub et al., 2014a).

The results of these aforementioned studies in cognitive aging, across different methodologies, lead to the conclusion that the PFC region is of vital importance to possibly reverse vigilance decline in older adults via a compensation mechanism in healthy aging. Therefore, the exploration of approaches, such as cognitive training and tDCS aiming for inducing plasticity in cerebral activity to counteract cognitive aging in older adults, would be advantageous for healthy aging.

1.2 Cognitive training

To improve or enhance an individual's cognitive functions, such as attention, working memory and inhibitory control, by practicing specific cognitive tasks or performing intellectually challenging activities, is the current definition of cognitive training (Toril et al., 2014; Sala and Gobet, 2019; Smid et al., 2020).

For cognitive training, two mainstream methodologies, strategy-based and processing-based training, were developed according to distinct training focuses.

i. Strategy-based training: it aims to improve the performance of the trained function by providing cognitive strategies required for the specific ability, such as mnemonics for memory (Ball et al., 2002; Willis et al., 2006; Lustig et al., 2009). For instance, goal management, a key element of executive control that is crucial for problem-solving, involves breaking down the major goal into several small targets for easier attainment, and those schemes can be instructed (Levine et al., 2007; van Hooren et al., 2007; Stamenova and Levine, 2019). Substantial improvements via strategy-based approaches were achieved in performance of both trained tasks and near transfer tasks, but only restricted effects in far transfer tasks were reported (Noack et al., 2009; Shipstead et al., 2010; Zinke et al., 2012).

ii. Process-based training: this training methodology focuses on improving processing efficacy in cognitive processes required for diverse cognitive functions through repetitive practice, such as working memory training, with the aim of initiating neural plasticity mechanism from its fundamental information processes shared with other cognitive functions (Morrison and Chein, 2011; Studer-Luethi and Meier, 2020). Furthermore, maintaining the processing speed achieved in younger age might be pivotal in later life to