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Dissection of neuronal circuits underlying sustained attention with the five-choice serial reaction time task

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ABSTRACT

Attention deficits are common in psychiatric and neurological disorders. The transdiagnostic nature of impaired attention suggests a common set of underlying neural circuits. Yet, there are no circuit-based treatments such as non-invasive brain stimulation currently available due to the lack of sufficiently delineated network targets. Therefore, to better treat attentional deficits, a comprehensive functional dissection of neural circuits underlying attention is imperative. This can be achieved by taking advantage of preclinical animal models and well-designed behavioral assays of attention. The resulting findings in turn can be translated to the development of novel interventions with the goal of advancing them to clinical practice. Here we show that the five-choice serial reaction time task has greatly facilitated the study of the neural circuits underlying attention in a well-controlled setting. We first introduce the task and then focus on its application in preclinical studies on sustained attention, especially in the context of state-of-the-art neuronal perturbations.

1. Introduction

Attention is an indispensable element of cognitive functioning. Cortical lesions of brain regions involved in attentional processes can lead to the neglect syndrome, and mental disorders such as attention-deficit/hyperactivity disorder (ADHD) (Arnsten, 2006; Pillidge et al., 2014) and Alzheimer's disease (AD) (Cortese et al., 2019; Romberg et al., 2011; Shepherd et al., 2021) are often associated with attentional deficits (Robbins, 2002). However, the efficacy of current therapeutic treatments for attention deficits varies among individuals, and many patients are treatment resistant (Shim et al., 2016). This suggests that the malfunctioning neural circuits underlying attention deficits are complicated and deficits in attention may be highly individualized. Attention is not a unitary process but consists of multiple distinct mechanisms (Fizet et al., 2016; Robbins, 2002). The first form is sustained attention, a unique brain state with elevated vigilance over a considerable period for responding to rare and unpredictable events. The second form is divided attention, where animals must optimize the allocation of mental resources to respond according to different contingencies (e.g., sensory modalities) simultaneously. The third form is selective or focused attention, where animals should pay attention to the target and ignore the distractors (e.g., cues indicating the presence of a relevant stimulus in either the right or left visual field). These attentional processes engage distinct neural pathways yet work synergistically in real life. To examine these processes in isolation, the five-choice serial reaction time task (5CSRTT) was proposed 40 years ago (Carli et al., 1983). This task focuses on sustained attention, and due to its versatility, has been successfully adapted to various species (rat, mouse, zebrafish, ferret, non-human primates, etc.) for examining constructs such as attention, impulsivity, compulsivity, and decision making. In this review, we will first introduce the task, the training procedures, and the interpretation of the behavioral parameters. Next, we will summarize classical pharmacological studies and more recent findings using optogenetics and chemogenetics to decipher the neural circuits underlying cognitive control as assessed by the 5CSRTT.

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2. 5CSRTT: the task, the training, and the interpretation

2.1. Original human continuous performance tests

Successful recruitment of attention was conceptualized as continuous, stable task performance by behavioral psychologists decades ago (Rosvold et al., 1956). Based on the definition of sustained attention, i.e., continuous allocation of mental resources for the detection of rare and unpredictable events (Robbins, 2002), continuous performance tests (CPTs) are still the most widely used tests of sustained attention in human clinical practice (Rosvold et al., 1956). During these tests, the subject sits in front of a screen and is presented with a continuous stream of visual stimuli (usually letters) for a long period of time (usually 20–30 min). The subject is required to press a button when a predetermined target is presented on the screen (e.g., an A in a stream of Xs), and the numbers of correct responses and reaction times are recorded. Patients with attentional deficits are prone to make more mistakes (lower accuracy rates) and respond more slowly (longer reaction times) compared with healthy controls (Rosvold et al., 1956). About 40 years ago, Carli et al. reported their seminal work on the first adaptation of the CPTs for animal studies, namely, 5CSRTT (Carli et al., 1983). Although the CPT usually requires participants to ignore irrelevant stimulus and the classical 5CSRTT does not have this component (but see Adaptations), the 5CSRTT has been widely used and adapted to quantify sustained attention in various animal models. We will first review the original and basic experimental setup and training protocol and then turn our attention to recent adaptations to investigate other attention-related constructs.

2.2. Experimental setup and training protocol

The task is carried out in a conditioning operant box of a size appropriate for the animal model. The animal is water or food deprived before the task and learns the rules with conditioning. The front wall of the box is curved and has five horizontally evenly spaced holes so that the distances from each hole to the back of the box are approximately the same. The back wall has a hole with a food dispenser or waterspout attached for reward delivery. The box is also equipped with a speaker. A typical trial is shown in Fig. 1. To start the task, the animal is placed in the box and the box is closed. When the animal pokes into the hole on the back wall, a tone is played by the speaker, signaling the start of a trial. After a delay period, a visual stimulus is presented in one of the five holes on the front wall for a specific duration and then turned off. If the animal correctly pokes into the hole with the visual stimulus during its presentation or a specific period after it turned off (i.e., holding time), another tone is played, signaling the reward delivery, and this is recorded as a correct trial. The animal turns around and approaches the hole on the back wall to retrieve the reward. If the animal pokes into an incorrect hole without visual stimulus during stimulus presentation or holding time, this trial is recorded as “incorrect”, and white noise is played as punishment, followed by a time-out period. If the animal does not poke into any of the five holes during this period, this trial is labeled as “omission”, with the animal punished by a burst of white noise and time-out. Finally, if the animal pokes into any of the five holes during the delay period and before the visual stimulus, this trial is recorded as “premature”, and the animal is similarly punished as after an incorrect response or omission. An inter-trial interval is applied after each trial, regardless of being correct or incorrect, after which the animal can poke into the hole on the back wall to initiate another trial. The animal performs the task in a self-paced manner for about 30 min, and the total number of trials is recorded. The basic behavioral readouts include accuracy (percentage of correct trials), omission rate (percentage of omissions), premature rate (percentage of premature responses), incorrect rate (percentage of incorrect responses), reaction time (latency of the visual stimulus onset to the correct response), and reward retrieval time (latency of the correct response to retrieval of reward at the back wall). The interpretation of these numbers will be discussed in the following section (see Measurements and interpretation).

Animals undergo multiple training levels that are designed to become increasingly difficult in the training box described above, and they are moved to the next levels only when they are skilled at the current level. Animals are conditioned to use their best efforts to complete the task by allocating sustained attention, and this training process can take several months (Table 1). On Level 1, the animal is trained to poke into the back hole just to receive the reward, being familiar with the overall layout and functioning of the box. On Levels 2 and 3, the animal learns to poke into the hole(s) on the front wall with visual stimulus to get the reward. Note that on Levels 2 and 3, no delay period is introduced, the visual stimulus is kept on until the animal responds to it, and trials are initiated automatically. On Level 4, the animal needs to poke into the back hole first to start a trial, and the stimulus is turned off after a specific duration. If the animal fails to poke into the correct hole within a pre-determined window, white noise will be played as punishment. Finally, on Level 5, the delay period is implemented, and task difficulty is further gradually increased with shortened stimulus duration and variable delay period, which requires allocation of more attention; at this point, the animal is ready for the 5CSRTT. The task can be even more challenging with distractors (bursts of white noise) presented during the delay period or reduced brightness of the visual stimulus. These added features are useful to study the neural underpinnings with graded performance level and to separate animals into low- and high-performance groups for pharmacological studies (Robbins, 2002).

2.3. Adaptations

With the technical development and higher demand of more precise stimulus presentation and behavior recording, touchscreen and computer-aided automation have been implemented in the 5CSRTT (Birtalan et al., 2020; Bruinsma et al., 2019; Mar et al., 2013; Morais Gancz et al., 2022). Notably, the touchscreen version of 5CSRTT is now one of the most commonly used approaches (Bartko et al., 2011; Mar

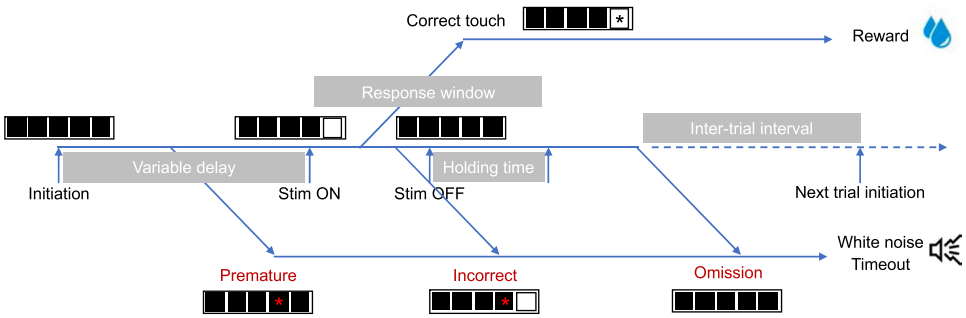

Fig. 1. Schematic flowchart of a typical trial in a 5CSRTT session.

Table 1
Example of 5CSRTT training schedule for ferrets (Sellers et al., 2016).

Level	Description	Graduation criteria
1	Habituate the animal to experimenter and behavior box. Manually trigger water release from the lick spout, following a tone. No visual stimulus is presented.	Three consecutive sessions with strong association between tone and water reward;
2a	A stimulus flashes in all five windows until touched. Once a touch is registered, a tone is played, and water is released.	Three consecutive sessions of 50 trials within 30 min;
2b	Similar to Level 2a, but the stimulus flashes in only two or three connected windows until touched. The stimulus position is updated after each trial.	The same as Level 2a;
3	Similar to Level 2b, but the stimulus flashes in only one window until touched. The stimulus position is updated after each trial.	The same as Level 2a;
4a	Similar to Level 3, but the animal must trigger a trial by poking into the lick spout and a static stimulus is presented in one window until touched.	The same as Level 2a;
4b	Similar to Level 4a, but a 5-sec timeout and a white noise are added as punishment for wrong touches.	The same as Level 2a;
5a	Similar to Level 4b, but a delay (increasing from 0.5 sec to 5 sec) is introduced before visual stimulation. A static stimulus is presented in one window for 10 sec. The animal has additional 5 sec to respond when the stimulus is turned off. A 5-sec inter-trial interval is counted before the animal can trigger the next trial.	Three consecutive sessions of at least 60 trials, less than 30 % omission;
5b	Similar to Level 5a, but a 5-sec delay is introduced, and the visual stimulus is presented only for 5 sec. The animal only has additional 2 sec to respond when the stimulus is turned off.	Four consecutive sessions of at least 60 trials, less than 30 % omission;
5c	Similar to Level 5b, a 5-sec delay is introduced, but the visual stimulus is presented only for 2 sec. The animal has additional 2 sec to respond when the stimulus is turned off.	Five consecutive sessions of at least 50 trials, less than 30 % omission;
5d	Similar as Level 5c, but a random delay of 4, 5, or 6 sec is used.	Five consecutive sessions of at least 50 trials, less than 30 % omission.

et al., 2013; Romberg et al., 2011), which allows comparison with other cognitive touchscreen tasks (Horner et al., 2013; Mar et al., 2013; Oomen et al., 2013) and can be directly translated to human neuropsychological approaches such as the Cambridge Neuropsychological Test Automated Batteries (CANTAB) for the comparative assessment of cognition from animals to humans (Fray and Robbins, 1996; J. Fray et al., 1996). Furthermore, the original task for the rat model has been adapted to other species. A fully automated operant box has been commercially available for mice, which greatly facilitates attention research given the rich set of available transgenic mouse lines (Mar et al., 2013). A similar automated behavior box has been designed for zebrafish (*Danio rerio*) (Parker et al., 2013). Interestingly, the rodent task has been back translated to non-human primates (Weed and Gold, 1998). In the task, the subject is asked to press a lever or button to start a trial and hold it until a visual stimulus appears briefly on one of the five predetermined positions on a screen after a variable delay period, and then release the level or button and reach the target as fast as possible within a period. More recently, the 5CSRTT has also been adapted for ferrets (*Mustela putorius furo*) (Sellers et al., 2016; Yu et al., 2018). In contrast to mice and rats, ferrets exhibit alpha oscillations (Stitt et al., 2018). Given the prominent role of alpha oscillations in human cognitive function (Clayton et al., 2015; Sadaghiani and Kleinschmidt, 2016; Samaha et al., 2020), ferrets are thus an ideal intermediate model system for the study of brain network dynamics that are altered in patients with psychiatric illness and cognitive deficits. Initial studies of the 5CSRTT in the ferret indeed demonstrated pronounced task-modulated oscillatory signatures in the frontoparietal and posterior visual network (Sellers et al., 2016; Yu et al., 2018). The classical 5CSRTT was further elaborated to include "No-go" trials as in the human CPT, namely the five-choice CPT (5CCPT), so that both attention and inhibitory control can be explicitly measured (Young et al., 2009). More importantly, the 5CCPT has recently been reverse-translated for use in humans and presented consistencies in target-locked theta activity across species (Cavanagh et al., 2021).

2.4. Measurements and interpretation

The most relevant measurements of sustained attention in the 5CSRTT are accuracy and omission rate. Increased accuracy and reduced omissions indicate robust and continuous attention allocation in the task, while decreased accuracy and elevated omission rate suggest disrupted allocation of attention and attentional deficits. It is important to note that in order to rule out the confounding influence of a motivational deficit, which could also contribute to an increased omission rate, it is necessary to check that the latency to retrieve the reward and initiate the next trial has not changed. The premature rate represents (waiting) impulsivity and inhibitory control, and the incorrect rate is more likely to be related to decision making. Disrupted sustained attention may be related to prolonged reaction time, which signals the slowdown of neural processing. Perseverative response (or compulsivity) can also be quantified by the number of consecutive pokes to the same hole regardless of the outcome. Note that a correct response requires sufficient motivation, sensory processing, sustained attention, decision making, and motor skill. Thus, to ascribe changes in accuracy and omissions to altered sustained attention, it is imperative to ensure other neural processes are unchanged, which can be inferred from auxiliary behavioral readouts. For example, the reward retrieval time and inter-trial interval are indicative of the motivation level, which is supposed to be maintained throughout one session. Also, accuracy and reaction time are presumably the same when the five target locations are analyzed separately, suggesting no visual or motor bias towards a specific position, and the same throughout a session, indicating no significant mental or physical fatigue. To emphasize the decision-making process (Go/No-go) in the 5CSRTT, "No-go" trials can be included, where visual stimuli are turned on in all five holes, and the animal should not respond to any of them to get the reward (Bhakta and Young, 2017). All the other trials are "Go" trials, as the animal needs to respond to the visual stimulus. Thus, hits (correct responses in "Go" trials), misses (omissions and incorrect responses in "Go" trials), correct rejections (no response in "No-go" trials), and false alarms (responses to any of the visual stimuli in "No-go" trials) can be quantified to derive the hit rate (HR = hits / (hits + misses)), the false alarm rate (FAR = false alarms / (false alarms + correct rejections)), and d′ (computed as the difference between the standard scores for HR and FAR), which indicate the discriminability between the "Go" versus "No-go" trials according to the signal detection theory. These behavioral measurements in the 5CSRTT together provide researchers with a rich and independent quantification of various aspects of cognitive control, such as sustained attention, impulsivity, compulsivity, and decision making, which popularized the use of the 5CSRTT in attention studies.

3. Applications of 5CSRTT in preclinical studies on sustained attention

3.1. Classical pharmacology studies on neuromodulatory systems

For the last few decades, the 5CSRTT has been mostly used in

conventional pharmacological behavioral studies in rodent models. These pioneering works have focused on classical neuromodulators, including norepinephrine (NE) from locus coeruleus (LC), 5-hydroxytryptamine (5-HT or serotonin) from raphe nuclei (RN), dopamine (DA) from ventral tegmental area (VTA) and substantia nigra (SN), and acetylcholine (ACh) from the basal forebrain nuclei, nucleus basalis (NB) and septal nuclei, and pontomesencephalic tegmentum. These studies documented the effects of neuromodulatory ascending signals on the sustained attention in the 5CSRTT using pharmacological approaches, such as systemic or local infusion of agonists or antagonists for specific receptors or chemical lesions. The pharmacological literature before 2010 has been comprehensively reviewed elsewhere (Chudasama and Robbins, 2004; Robbins, 2002). Here, we will focus on recent advances in sustained attention by the 5CSRTT over the past 10 years. (1) Boosting NE signaling by acting on the adrenergic receptors generally enhances attentional performance and cognitive processing, especially under challenging conditions, such as shortened stimulus duration, decreased stimulus brightness, and increased temporal unpredictability (Bari et al., 2008). Recent reports have further shown that atomoxetine, a noradrenergic reuptake inhibitor to treat ADHD, can reduce impulsive behaviors after dorsal noradrenergic ascending bundle (DNAB) lesion (Liu et al., 2015) or in high-impulsivity rats (Ansquer et al., 2014). (2) Forebrain 5-HT depletion impairs performance and increases impulsive premature touches (Harrison et al., 1997a, 1997b), while recent studies have found that augmented or suppressed 5-HT signaling can cause diverse behavioral effects depending on the functioning of specific receptor types. For example, 5-HT2C receptor agonist reduces premature responses (Fletcher et al., 2013). 5-HT1A receptor antagonist increases omissions and latency, while antagonism at 5-HT2C receptors causes the opposite effects (Quarta et al., 2012). Finally, selective antagonism at 5-HT(2 A) receptors in the striatum can partially rescue the accuracy deficit after blocking the glutamatergic cortical-striatal inputs (Agnoli and Carli, 2012). (3) Manipulations of DA system have produced profound attentional deficits in a baseline performance-dependent manner. Local infusion of D1R agonists into mPFC enhances performance in low-accuracy animals, while D1R antagonists reduce performance in animals of high accuracy (Granon et al., 2000). Systemic D2R antagonism also impairs the accuracy rate (Harrison et al., 1997a). Recently, local infusion of D2/3 R agonists in NAc increases premature responses only in high-impulsive but not low-impulsive rats (Moreno et al., 2013). D1, but not D2, inactivation in the central nucleus of amygdala reduces performance in the more demanding versions of the 5CSRTT (Smith et al., 2015). Also, pharmacological activation of D1R in dorsomedial striatum impairs accuracy but not compulsivity, while enhancing D2 signaling increases compulsivity without affecting accuracy (Agnoli et al., 2013), suggesting DA can differentially modulate attentional performance via D1R and D2R pathways. (4) Cholinergic lesions of NB projections to mPFC decrease accuracy but increase omissions (McGaughy et al., 2002). More recently, similar denervation of cortical NB cholinergic terminals has been shown to cause reduced accuracy and increased omissions in not only visual but also olfactory 5CSRTT, suggesting cholinergic involvement in modality-independent attentional processing (Ljubojevic et al., 2014). However, blocking cholinergic transmission in the thalamus instead does not affect performance (Mantanona et al., 2020). These results together demonstrate the important roles neuromodulatory systems play in sustained attention.

3.2. Recent studies on sustained attention using optogenetics and chemogenetics

Pharmacological approaches come with pronounced shortcomings, including dosage-dependent receptor specificity, lack of cell-type and projection-type specificity in nuclei with heterogeneous molecular identities, irreversibility, and long-term effects, which greatly hamper better understanding the neural circuits underlying sustained attention. Thanks to the recent development of viral tools and transgenic animal lines, optogenetics (manipulating brain activity with light after delivery of light-sensitive neuronal actuators such as channelrhodopsin) and chemogenetics (manipulating brain activity with chemicals that bind to specifically designed neuronal actuators, such as DREADDS) have begun to be applied in sustained attention studies, allowing instantaneous or temporally well-controlled reversible activation and suppression of spiking activity in neurons of a specific type (most often, excitatory and inhibitory neurons), located in a specific cortical layer or subcortical region, projecting to or receiving inputs from a specific target region, or activated under a specific contextual scenario. We will next elaborate on the latest results on the cortical and subcortical neural correlates of sustained attention with the 5CSRTT and opto-/chemogenetic methods. The brain targets, manipulations and main behavioral effects are summarized in Table 2.

3.2.1. Cortical regions and their projections

Cortical regions, including the prefrontal cortex (PFC) and the posterior parietal cortex (PPC) are engaged in sustained attention. The prefrontal cortex (PFC) is conventionally defined as frontal regions innervated by afferents from the mediodorsal nucleus of thalamus and consists of the following four anatomically distinguishable subdivisions: dorsomedial PFC (dmPFC, including the anterior cingulate cortex (ACC) and secondary motor area (MOs)), ventromedial PFC (vmPFC, including paralimbic (PL) and infralimbic areas (ILA)) and ventrolateral PFC (vlPFC, mainly the orbital areas (ORB)), which are common across mammals, and dorsolateral PFC (dlPFC), which is prominent mostly in the primates (Carlén, 2017; Le Merre et al., 2021). Neuronal activity and oscillatory dynamics in the (pre)frontal cortex have been shown to correlate to the attentional deployment during the 5CSRTT (Sellers et al., 2016). However, the causal role of these frontal neurons and their cortico-cortical and cortico-subcortical projections have yet to be elucidated.

Fast-spiking parvalbumin positive (FS-PV) inhibitory neurons in the medial prefrontal cortex (mPFC) show increased and sustained firing during attentional processing in the three-choice serial reaction time task (3CSRTT) (Kim et al., 2016). Successful allocation of attention is characterized by strong synchronization of FS-PV neurons and between FS-PV and pyramidal neurons in the gamma frequency (Kim et al., 2016). Optogenetic silencing of FS-PV neurons impaired attentional processing, while optogenetic activating FS-PV neurons at gamma frequencies improved behavioral performance mainly driven by a decrease in omission (Kim et al., 2016).

Chemogenetic suppression of the pyramidal neurons in the ACC during the 5CSRTT significantly decreases accuracy and increases omission and correct response latencies (Koike et al., 2016). Interestingly, a more recent study demonstrated that chemogenetic inhibition of the ACC pyramidal cells rather reduces challenge-evoked impulsivity and improves attention (van der Veen et al., 2021). This discrepancy may be due to the different coordinates and depth of the targeted region in the ACC (see Table 2). ACC neurons send long-range cortico-cortical projections to sensory cortices to modulate sensory responses and behaviors (Zhang et al., 2014). Selective chemogenetic inactivation of the ACC neurons that project to the visual cortex similarly decreases task performance during the 5CSRTT by increasing omission, with no concurrent changes in behavioral outcomes associated with locomotion, motivation, impulsivity, or compulsivity (Norman et al., 2021b). In contrast, optogenetic stimulation of visual cortex-projecting ACC neurons promotes performance after errors (incorrect touches or omissions) (Norman et al., 2021c). Interestingly, chemogenetic suppression of these top-down neurons during adolescence produces more pronounced attentional behavior deficits than that during later periods (Nabel et al., 2020). Note that these neurons can be dispensable for attentional behavioral performance with reduced task demand or difficulty (Norman et al., 2021a). Top-down ACC inputs also drive spiking responses in the claustrum (CLA) and optogenetic disruption of CLA-projecting ACC neurons impairs the 5CSRTT (White et al., 2018). On the other hand,

Table 2
Main targets of optogenetic and chemogenetic manipulations and the effects on sustained attention and inhibitory control.

Target	Manipulation	Main results			Ref.	Coordinates (mouse, from Bregma)
		Attention	Impulsivity	Motivation		
mPFC FS-PV neurons	Opto-inhibition	↓	↑	→	(Kim et al., 2016)	mPFC: AP + 1.76 mm; ML ± 0.25 mm; DV − 1.3 mm
mPFC FS-PV neurons	Opto-activation at gamma frequency	↑	→	→	(Kim et al., 2016)	mPFC: AP + 1.76 mm; ML ± 0.25 mm; DV − 1.3 mm
ACC neurons	Chemo- inhibition	↓	→	→	(Koike et al., 2016)	PL: AP + 1.7, + 1.1, + 0.4 mm; ML ± 0.2 mm; DV −0.7 mm
ACC neurons	Chemo- inhibition	↑	↓	→	(van der Veen et al., 2021)	ACC Site 1: AP + 0.7 mm; ML ± 0.3 mm, DV − 1.65 mm and − 1.1 mm ACC Site 2: AP + 1.8 mm, ML ± 0.25 mm, DV − 1.25 mm
VIS projecting ACA neurons	Chemo- inhibition	↓	→	→	(Norman et al., 2021b)	ACC: AP + 0.7, + 0.2, − 0.3 mm; ML ± 0.2 mm; DV − 0.7 mm
VIS projecting ACA neurons	Opto-activation	↑	→	→	(Norman et al., 2021c)	ACC: AP + 0.7, + 0.2, − 0.3 mm; ML ± 0.2 mm; DV − 0.7 mm
ACC to CLA projections	Opto-activation	↓	N/A	→	(White et al., 2018)	ACC: AP + 1.34, + 0.74 mm; ML ± 0.3 mm; DV − 1.25 mm
ACC to CLA projections	Opto- inhibition	↓	N/A	→	(White et al., 2018)	ACC: AP + 1.34, + 0.74 mm; ML ± 0.3 mm; DV − 1.25 mm
CLA neurons	Chemo-activation	↓	→	N/A	(Liu et al., 2019)	CLA Site 1: AP + 1.0 mm; ML ± 4.84 mm; DV − 6.08 mm CLA Site 2: AP + 1.8 mm; ML ± 4.22 mm; DV − 5.92 mm (4° angle)
CLA to PFC projections	Chemo-activation	→	↑	N/A	(Liu et al., 2019)	CLA Site 1: AP + 1.0 mm; ML ± 4.84 mm; DV − 6.08 mm CLA Site 2: AP + 1.8 mm; ML ± 4.22 mm; DV − 5.92 mm (4° angle)
CLA to PFC projections	Chemo-inhibition	→	↓	N/A	(Liu et al., 2019)	CLA Site 1: AP + 1.0 mm; ML ± 4.84 mm; DV − 6.08 mm CLA Site 2: AP + 1.8 mm; ML ± 4.22 mm; DV − 5.92 mm (4° angle)
MDL projecting dmPFC neurons	Chemo- inhibition	↓	↓	→	(de Kloet et al., 2021)	MDL: AP − 3 mm; ML ± ± 2.32 mm; DV − 5.89 mm (10° angle) dmPFC: AP + 2.76 mm; ML ± 1.30 mm; DV − 2.90 mm (10° angle)
MDM projecting vmPFC neurons	Chemo- inhibition	→	↑	→	(de Kloet et al., 2021)	MDM: AP − 3.00 mm; ML ± 1.42 mm; DV − 5.89 mm (10° angle) vmPFC: AP + 2.76 mm; ML ± 1.47 mm; DV − 4.87 mm (10° angle)
DMS projecting dmPFC neurons	Chemo- inhibition	→	↑	→	(de Kloet et al., 2021)	DMS: AP + 1.44 mm; ML ± 2.78 mm; DV− 4.47 mm (10° angle) dmPFC: AP + 2.76 mm; ML ± 1.30 mm; DV − 2.90 mm (10° angle)
VMS projecting vmPFC neurons	Chemo- inhibition	→	→	→	(de Kloet et al., 2021)	VMS: AP + 1.44 mm; ML ± 2.59 mm; DV + 7.41 mm, + 6.80 mm (10° angle) vmPFC: AP + 2.76 mm; ML ± 1.47 mm; DV − 4.87 mm (10° angle)
BLA neurons	Opto- inhibition	↓	↑	↓	(Yin et al., 2019)	BLA: AP − 1.4 mm; ML ± 3.5 mm; DV − 4.5 mm
BLA neurons	Opto-activation	↑	↓	↓	(Yin et al., 2019)	BLA: AP − 1.4 mm; ML ± 3.5 mm; DV − 4.5 mm
NAc FS neurons	Opto- inhibition and chemo-inhibition	→	↑	N/A	(Pisansky et al., 2019)	NAc: AP + 1.35 mm, ML ± 1.10 mm; DV − 4.40 mm
TH^+ DA neurons in VTA and SNc	Opto-activation and chemo-activation	↓	→	→	(Boekhoudt et al., 2017; Flores-Dourojeanni et al., 2021)	VTA: AP − 5.4 mm, ML ± 1.3 mm, DV − 8.0 mm (Boekhoudt et al., 2017) or AP − 5.8 mm, ML ± 1.3 mm, DV − 8.4 mm (Boekhoudt et al., 2017) or AP − 5.8 mm, ML ± 1.60 mm, DV − 8.40 mm (all with 5° angle) (Flores-Dourojeanni et al., 2021) SNc: AP − 5.2 mm, ML + 2.0 mm, DV − 7.2 mm (Boekhoudt et al., 2017)
VTA to NAc shell projections	Opto-activation	↓	↑	→	(Flores-Dourojeanni et al., 2021)	VTA: AP − 5.80 mm, ML ± 1.60 mm, DV − 8.40 mm (5° angle) NAc shell: AP + 1.20 mm, ML + 2.70 mm, DV − 7.50 mm (10° angle)
VTA to NAc core projections	Opto-activation	↓	→	→	(Flores-Dourojeanni et al., 2021)	VTA: AP − 5.80 mm, ML ± 1.60 mm, DV − 8.40 mm (5° angle) NAc core: AP + 1.20 mm, ML + 1.60 mm, DV − 6.80 mm
VTA to mPFC projections	Opto-activation	↓	→	→	(Flores-Dourojeanni et al., 2021)	VTA: AP − 5.80 mm, ML ± 1.60 mm, DV − 8.40 mm (5° angle) mPFC: AP + 2.70 mm, ML + 1.20 mm, DV − 5.70 mm (10° angle)
LC neurons	Opto-activation	↑	↓	→	(Bari et al., 2020)	LC: AP − 5.5 mm, ML ± 0.8 mm, DV − 3.6 mm
LC neurons	Opto-inhibition	↓	↑	→	(Bari et al., 2020)	LC: AP − 5.5 mm, ML ± 0.8 mm, DV − 3.6 mm
LC to dmPFC projections	Opto-activation	↑	→	→	(Bari et al., 2020)	LC: AP − 5.5 mm, ML ± 0.8 mm, DV − 3.6 mm
LC to vlPFC projections	Opto-activation	→	↓	→	(Bari et al., 2020)	LC: AP − 5.5 mm, ML ± 0.8 mm, DV − 3.6 mm
STN neurons	Chemo- inhibition	↓	↑	→	(Nishioka et al., 2020)	STN: AP − 1.90 mm, ML ± 1.70 mm, DV − 4.60 mm and − 4.25 mm

ACC, anterior cingulate cortex; BLA, basolateral amygdala; CLA, claustrum; DA, dopamine; dmPFC, dorsomedial prefrontal cortex; DMS, dorsomedial striatum; FS, fast-spiking; LC, locus coeruleus; mPFC, medial prefrontal cortex; MDL, lateral part of mediodorsal nucleus of thalamus; MDM, medial part of mediodorsal nucleus of thalamus; NAc, nucleus accumbens; PV: parvalbumin positive; SNc, substantia nigra pars compacta; STN, subthalamic nucleus; TH+, tyrosine hydroxylase positive; VIS, primary visual cortex; vlPFC, ventrolateral prefrontal cortex; vmPFC, ventromedial prefrontal cortex; VMS, ventromedial striatum; VTA, ventral tegmentum area. ↑, significantly increased; ↓, significantly decreased; →, no significant changes; N/A, not available or not tested.

chemogenetic activation of the bottom up CLA to PFC inputs reduces the overall PFC activity while increases the impulsivity level (i.e., premature touches) (Liu et al., 2019). Interestingly, vmPFC and dmPFC are temporally specifically recruited in the sustained attention. Transient suppression of vmPFC right before the stimulus onset impairs response accuracy and inhibitory control, while dmPFC has to be inhibited during the entire preparatory delay period to affect the behavioral performance (Luchicchi et al., 2016). vmPFC and dmPFC neurons further innervate anatomically and functionally distinct striatal and thalamic domains, suggesting frontal-striatal and frontal-thalamic projections differentially modulate attentional control (de Kloet et al., 2021). Not surprisingly, chemogenetic silencing of dmPFC and vmPFC projections to lateral and medial mediodorsal thalamus subregions bidirectionally regulate inhibitory control during the 5CSRTT (de Kloet et al., 2021). Furthermore, dmPFC neurons projecting to striatum and thalamus differentially regulate cognitive control (de Kloet et al., 2021).

The posterior parietal cortex (PPC) has reciprocal connections with the frontal areas and pulvinar, and has been shown to coordinate the alpha oscillations in the frontoparietal and posterior thalamocortical network in a brain state dependent manner (Huang et al., 2021; Stitt et al., 2018). However, whether this suppression causally contributes to the establishment and maintenance of sustained attention awaits future PPC opto- or chemogenetic perturbation studies.

3.2.2. *Subcortical regions and their projections*

In addition to the cortico-cortical and cortico-subcortical circuits, the functional roles of various subcortical nuclei and their projections in cognitive control are also assessed by the 5CSRTT using optogenetic or chemogenetic manipulations. For example, optogenetic suppression of the basolateral amygdala (BLA), a key player in emotional control, increases the impulsivity and decreases the compulsivity of mice in the 5CSRTT (Yin et al., 2019). Many subcortical nuclei consist of a mixture of neurons of diversified molecular identity, so that cell-type specific manipulations enabled by promoter-specific Cre-mouse line and Cre-dependent virus expression allow us to dissect the contribution from each neuronal type in the sustained attention. Opto- and chemo-genetic inhibition of the fast-spiking inhibitory neurons in the nucleus accumbens (NAc), which is involved in the dopamine system, also causes increased impulsivity (Pisansky et al., 2019). Chemogenetic activation of midbrain tyrosine hydroxylase (TH)-positive dopamine neurons in VTA and SNc impairs attention and increases omissions but not impulsivity (Boekhoudt et al., 2017) (but see (Fitzpatrick et al., 2019)). Also, most subcortical nuclei in the neuromodulatory systems project to multiple downstream targets, and thus projection-specific manipulations powered by synaptic terminal stimulation or inhibition together with retrograde virus or trans-synaptic anterograde viral tools and transgenic mouse lines reveal differential roles of each projection playing in the sustained attention. For example, selective optogenetic activation of VTA-NAc shell neurons, VTA-NAc core neurons and VTA-mPFC neurons impair attentional control by increasing both omissions and premature touches, omissions only, and incorrect touches, respectively (Flores-Dourojeanni et al., 2021). Also, optogenetic terminal activation of LC norepinephrinergic projections to dmPFC and to the vlPFC independently increases correct rates and reduces premature touches (Bari et al., 2020). Chemogenetic disruption of the subthalamic nucleus causes attentional deficits and increases impulsive responses in the 5SCRTT, especially under highly demanding trials with shortened stimulus duration (Nishioka et al., 2020). Finally, pulvinar is the largest and most evolved nucleus in the thalamus. Mutually connected with cortical (V1, V2, A1, A2, PPC, PFC) and subcortical regions (superior colliculus, amygdala), it plays important roles in sensory processing and cognitive control (Bennett et al., 2019; Chou et al., 2020; Fang et al., 2020; Fiebelkorn and Kastner, 2020; Saalmann et al., 2012; Zhou et al., 2018), and more recently and specifically in the sustained attention unveiled in the 5CSRTT (Yu et al., 2018). Pulvinar shows brain state dependent and task-modulated theta power activity (Huang et al., 2021; Stitt et al., 2018; Yu et al., 2018). However, whether pulvinar oscillatory network causally controls the attentional allocation needs further evidence from neuronal perturbations.

4. Application of 5CSRTT in preclinical rodent models of brain disorders

The 5CSRTT has been widely applied in drug-induced and transgenic rodent models of neurological (neurodevelopmental, movement, and neurodegenerative) and psychiatric disorders to quantitatively assess the attentional deficits and to determine how pharmacological, genetic, and optogenetic/chemogenetic perturbations can improve the symptoms.

First, the 5CSRTT has been adopted to evaluate the attention deficits in models of neurodevelopmental disorders, including ADHD, autism, Angelman syndrome (AS), fragile X syndrome, and early age adversary events. For example, mice with functional ablation of substance P-preferring neurokinin-1 receptor (NK1R-/- mice) display behavioral anomalies as in ADHD. In the 5-CSRTT, attention was increased with a low dose of guanfacine (an ADHD treatment) in NK1R-/- mice and impulsivity was decreased by a high dose of guanfacine (Pillidge et al., 2014). Also, in a mouse model with autism-associated R451C mutation in synaptic adhesion protein neuroligin-3 (NL3), the 5CSRTT showed that while $NL3^{R451C}$ and wild-type mice had similar accuracy and omissions, $NL3^{R451C}$ mice exhibited slower response speed but shorter reward collection latencies (Burrows et al., 2022). The $Ube3a^{m-/p+}$ transgenic mouse is a model of AS with loss-of-function mutations in the *UBE3A* gene. These animals had more omissions during the 5CSRTT training, while they showed normal response latencies to retrieve rewards, suggesting they retained normal motor function and motivation in the tests (Negrón-Moreno et al., 2022). Thus, the 5CSRTT can help to dissociate the cognitive and motor impartment in the AS model. Interestingly, in a knockout mouse model for Fragile X syndrome (the *Fmr1* KO mouse), adult mice exhibited visual attentional deficits in the 5CSRTT with disruptions in the balance of local and long-range inputs, as well as an increased nicotinic cholinergic tone in the ACC neurons that project to the visual cortex, which was rescued by Lynx1-dependent suppression of nicotinic cholinergic signaling from adolescence (Falk et al., 2021). Early age adversary events can cause significant cognitive and behavioral problem in adults, which can also be assessed with the 5CSRTT. For example, in an acute immune activation model of in utero inflammation exposure (IUI), the IUI-exposed offspring performed more trials and could respond accurately at a shorter stimulus length in the 5CSRTT. However, IUI exposed animals showed a greater decrease in test performance after a secondary hit of acute LPS administration, suggesting early life exposure to localized inflammation of the uterus can drive a vulnerability for adult cognitive performance deficits in response to acute infection(Makinson et al., 2019). Moreover, gestational exposure to a high-fat diet promoted impulsivity, whereas exposure to a low-protein diet resulted significant inattention in the 5CSRTT due to specific transcriptional changes in the prefrontal cortex (Grissom et al., 2015).

The 5CSRTT has also been used to examine the attention

impairments in addition to motor deficits in mouse models of extrapyramidal and movement disorders, such as Parkinson's disease (PD) and Huntington's disease (HD). For example, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) has been used extensively to model PD, as it induces robust executive deficits similar to those seen in PD. During the 5CSRTT, MPTP-lesioned mice exhibited attentional impairments, including slower reaction times when challenged with shorter cue durations, and a lack of impulse control with longer pre-cue duration, likely associated with altered prefrontal serotonergic signaling (Maiti et al., 2016). The HdhQ92 mouse is a model of HD and these Htt knock-in transgenic animals exhibited attentional deficits with reduced accuracy in the 5CSRTT when the stimulus duration is unpredictable (Trueman et al., 2012). The HdhQ111 mouse model of HD also demonstrated impaired attentional and executive function and motivation in the 5CSRTT in parallel to deficits in people with HD, although these cognitive and behavioral deficits did not progress over time (Yhnell et al., 2016).

In addition, 5CSRTT has also been used in mouse models of neurodegenerative diseases, such as AD. For example, the 3xTgAD mice contain three mutations associated with familial AD (APPSwe, MAPTP301L, and PSEN1M146V). These triple transgenic mice responded less accurately when the attentional demand of the task was high in a touchscreen version of the 5CSRTT, and also were prone to make more perseverative responses (Romberg et al., 2011). The APP/PS1 mouse model of AD also demonstrated increased impulsive and compulsive responding when task difficulty was high but normal attention in a touchscreen version of the 5CSRTT, indicating APP/PS1 mice may not be an ideal model for studying the attentional deficits of AD(Shepherd et al., 2021). Interestingly, chronic stress increased impulsive responses and impaired sustained attention in wild-type mice in the 5CSRTT. However, the same exposure to chronic stress reduced impulsivity but not did not affect sustained attention in arcAβ mouse model of cerebral amyloidosis (Cortese et al., 2019). Thus, the 5CSRTT helped to reveal an unexpected interaction between chronic stress and Aβ.

Moreover, the 5CSRTT is also applied as an integral part of behavioral assays to examine attention in mouse models of psychiatric disorders, such as schizophrenia, psychosis, alcohol use, drug use, and abnormal neurotransmitter signaling. For example, in a phencyclidine-induced schizophrenia mouse model, chronic oral administration of nicotine selectively reduced phencyclidine-induced impulsivity in 5CSRTT. This suggests that nicotine use by people with schizophrenia may relieve distinct symptoms that involve impulsive behaviors (Scott and Taylor, 2014). In addition, mice with psychosis-associated 22q11.2 deletion showed attentional control deficits (increased omissions but unchanged impulsivity) in the 5CSRTT (Nilsson et al., 2016a), which was ameliorated by an omega-3 polyunsaturated fatty acid-supplemented diet (Armando et al., 2020). Attention impairment with decreased accuracy was also observed in a mouse model of the 15q13.3 microdeletion syndrome using the touchscreen 5CSRTT, which reinforced the model's value in modeling schizophrenia-like pathology (Nilsson et al., 2016b). In an alcohol use mouse model, the alcohol preferring alcohol-naïve C57BL/6 J mice were more impulsive in the 5CSRTT than the alcohol averse DBA2/J mice. The alcohol preferring strain showed robust impairments in attention and more premature responses when stressed with increased attentional load (Sanchez-Roige et al., 2014). Similarly, mice with genetic DA signaling perturbations (such as DAT Val559 knock-in) displayed impulsivity dependent on the reward strength in the 5CSRTT, which suggests DA signaling problem can contribute to substance use behaviors (Davis et al., 2018). Finally, *ErbB4*$^{-/-}$ mice showed abnormal ErbB4-dependent GABAergic transmission in the hippocampus and impaired hippocampal-prefrontal synchrony and attention (Tan et al., 2018), in line with the finding that *ErbB4* is a susceptibility gene of schizophrenia (Del Pino et al., 2013).

5. Conclusions

Since the original application in the rat model 40 years ago, the 5CSRTT has been widely used in studies on cognitive control, especially sustained attention and adapted or even back translated for a variety of species, including mice, ferret, zebrafish, and non-human primates. Its versatile experimental design allows researchers to examine the neuronal network underlying different aspects of cognitive control, including sustained attention, impulsivity, compulsivity, and even decision-making. Although firstly applied in behavioral pharmacology studies where chemical agents are administered to manipulate neuromodulatory systems, with the advances of transgenic animals and viral tools, optogenetic and chemogenetic approaches have further enabled perturbations of cortical and subcortical attention circuits in a cell-type-specific, projection-specific, temporally well-controlled manner during normal attentional behavior and under pathological conditions in animal models. The combination of 5CSRTT and the-state-of-art neuronal manipulations and recording techniques will shed light on the causal neural dynamics of attentional control and contribute to the development of improved treatments for patients with attention deficits caused by neurological and psychiatric diseases.

Declaration of Competing Interest

F.F. is the lead inventor of IP filed on the topics of noninvasive brain stimulation by UNC and receives royalty payments. F.F. has received consulting honoraria and royalties from the following entities in the last twelve months: EPI, Academic Press, Insel Spital, and University of Michigan. Q.F. declares no competing interests.

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