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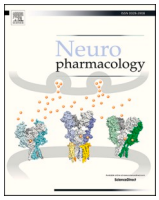

Alcohol, flexible behavior, and the prefrontal cortex: Functional changes underlying impaired cognitive flexibility

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ABSTRACT

Cognitive flexibility enables individuals to alter their behavior in response to changing environmental demands, facilitating optimal behavior in a dynamic world. The inability to do this, called behavioral inflexibility, is a pervasive behavioral phenotype in alcohol use disorder (AUD), driven by disruptions in cognitive flexibility. Research has repeatedly shown that behavioral inflexibility not only results from alcohol exposure across species but can itself be predictive of future drinking. Like many high-level executive functions, flexible behavior requires healthy functioning of the prefrontal cortex (PFC). The scope of this review addresses two primary themes: first, we outline tasks that have been used to investigate flexibility in the context of AUD or AUD models. We characterize these based on the task features and underlying cognitive processes that differentiate them from one another. We highlight the neural basis of flexibility measures, focusing on the PFC, and how acute or chronic alcohol in humans and non-human animal models impacts flexibility. Second, we consolidate findings on the molecular, physiological and functional changes in the PFC elicited by alcohol, that may contribute to cognitive flexibility deficits seen in AUD. Collectively, this approach identifies several key avenues for future research that will facilitate effective treatments to promote flexible behavior in the context of AUD, to reduce the risk of alcohol related harm, and to improve outcomes following AUD.

This article is part of the Special Issue on "PFC circuit function in psychiatric disease and relevant models".

1. Introduction

Alcohol use disorder (AUD) is a significant public health concern. In 2022 it was reported that 28.8 million adults in the United States, almost 1 in 10 people, had suffered from AUD at some point in the past year (SAMHSA Center for Behavioral Health Statistics and Quality, 2022). Alcohol consumption, especially heavy and binge-like drinking, functions as a risk factor for a variety of negative outcomes for individuals, such as premature death and disability, as well as deleterious social and public health impacts (Pihl and Peterson, 1995). The World Health Organization estimates that over 5% of deaths result from alcohol use, which is roughly 3 million people each year (World Health Organization, 2022).

AUD is characterized in part by persistent alcohol-seeking regardless of aversive outcomes such as tumultuous relationships or inability to maintain a job (American Psychiatric Association, 2022). Understanding the neural foundations of key features of AUD is criticasl for developing prevention and treatment for AUD. Alcohol acutely impacts neural systems involved in regulating cognitive functions such as memory, speech, decision-making, emotion, and goal-directed behavior (Witkiewitz et al., 2019). Moreover, a history of heavy alcohol use drives functional changes in these systems that make future abstinence difficult to achieve and even more difficult to maintain. Executive function is particularly vulnerable to excessive alcohol use, and this disruption is directly relevant to multiple major defining criteria of AUD. There is extensive evidence of reductions in flexible behavior in individuals with AUD (Dannenhoffer et al., 2021; Barker and Taylor, 2014). The transition from casual drinking, where alcohol acts as a positive reinforcer, to alcohol seeking despite negative consequences, an essential phenotype in AUD, exemplifies the loss of adaptive flexible behavior.

Executive functions required for many behaviors, including attentional control, response-inhibition and working memory, are known to

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be regulated by the prefrontal cortex (PFC) (Friedman and Robbins, 2021; Miller and Cohen, 2001). Together, these functions integrate to permit cognitive flexibility, often considered a core executive function (Diamond, 2013), which is key for adaptation and updating of goal-directed behaviors (Dickinson and Balleine, 1994). Multiple subregions of the PFC are relied upon for executive functions, which are impacted by both chronic alcohol exposure and binge-like drinking (Howland et al., 2022; Staples and Mandyam, 2016). This subversion of cognitive control mechanisms by alcohol may promote maladaptive alcohol-seeking behavior and contribute to the development of AUD. Loss of cognitive control is a key feature in the transition from isolated events of drug use towards addiction. Including cognitive changes in AUD models expands upon previous research focusing on understanding immediate and rewarding effects of drug use (Barker and Taylor, 2014; Everitt et al., 2008). With this framework in mind, the present review aims to outline key components and experimental measurements of cognitive flexibility mediated by the PFC, and integrate that with research characterizing changes in flexible behavior associated with excessive alcohol use and alcohol-induced changes in the PFC.

2. Cognitive flexibility: relevance, characterization, and measurement

Diminished cognitive flexibility in particular may sit at the core of the transition to habitual-behavior and compulsive alcohol seeking that is associated with AUD. Cognitive flexibility (see Table 1 for relevant definitions) refers to the confluence of cognitive processes that are required to alter, adapt, and then update behavior according to changes in the environment (Uddin, 2021; Dajani and Uddin, 2015). This ability to adapt is important for generation of appropriate behavioral responses, and flexibility is associated with positive outcomes across one's lifespan (Highgate and Schenk, 2021; Genet and Siemer, 2011). Cognitive flexibility relies on multiple processes, including working memory, attention, response inhibition and conflict monitoring to assess the environment, and direct behavioral changes appropriately (Spellman et al., 2021; Bissonette et al., 2013; Abernathy et al., 2010). Changes in behavior resulting from applied cognitive flexibility can be described as flexible behavior or behavioral flexibility. Conversely, cognitive inflexibility is evidenced by perseverative or habitual behaviors (Ramakrishnan et al., 2022; McKim et al., 2016; Gillan et al., 2011).

In the context of the behavioral studies documented in this review, flexible behavior is a measure of the ability to effectively shift attention between environmental features or switch strategies driven by changes in stimulus-response-outcome relationships that guide behavior in order to achieve a goal. These behavioral changes inherently require suppression of previous behavior or attentional focus and a shift in attention or behavioral responses towards previously irrelevant stimuli. There are multiple experimental tasks designed to test flexibility including attentional set shifting tasks (ASSTs), strategy shifting tasks and reveral learning tasks. These tasks are linked conceptually wherein behavioral flexibility functions as a measure of underlying cognitive flexibility. In these tasks flexible behavior is measured by tracking correct and incorrect responses after a stimulus-response-outcome change as well as perseverative errors, where a subject continues with a previously reinforced stimulus or response. Additional metrics such as the number of trials to criterion, and response latencies all aim at measuring how well the animals can flexibly adapt to changing task related contingencies (Shnitko et al., 2017; Baxter and Gaffan, 2007)

This review focuses specifically on ASSTs and strategy shifting tasks (Fig. 1). We also consider flexibility evidenced through reversal learning, particularly within the context of ASST or strategy shifting tasks. Many variants of ASSTs and strategy shifting tasks have been used to investigate flexible behavior and several reviews detail how these methods vary across species (Uddin, 2021; Izquierdo et al., 2017; Dajani and Uddin, 2015; Brown and Tait, 2010). Important differences and commonalities between different flexibility tasks are documented in the next several sections and are summarized in Fig. 2. In this review we highlight how these common behavioral flexibility paradigms are prefrontal dependent, yet hold distinct task demands that differentially engage PFC subregions. Furthermore, we highlight an emerging number of studies that demonstrate relationships between excessive alcohol use and flexible behaviors, providing insight into the impacts of alcohol on PFC functions.

Attentional set shifting: ASSTs probe flexibility by rewarding responses based on the formation of an attentional set, followed by an uncued change in rewarded outcomes that challenges the established attentional set. An attentional set refers to the bias in attention toward a specific stimulus or stimulus dimension that guides behavior (Brown and Tait, 2010). ASSTs require flexible shifting of stimulus attention within or between perceptual domains. Analogous set shifting tasks across species allow impacts and mechanisms of alcohol related changes in cognitive flexibility to be investigated in humans, non-human primates (NHPs), and rodents, including in the context of AUD or AUD models (Fig. 1A–E). In all ASSTs subjects are presented with multidimensional compound stimulus sets and must attend to a particular stimulus dimension to reliably discriminate which stimulus predicts the availability of reward on a given trial (Birrell and Brown, 2000; Konishi et al., 1998). Correct discriminations are rewarded, and when an established criterion (e.g., 80% correct or 10 consecutively correct responses) is achieved, a shift is triggered. In order to demonstrate flexibility, the subject must identify the new reward-related outcome contingency by trial and error and shift their behavior accordingly to different stimulus features or modalities. Importantly as noted above, these tasks incorporate multiple shift types within and across dimensions to probe

Table 1
Terms and definitions used in the current review.

Key Terms	Definition
Cognitive flexibility	The ability to alter responses given changing environmental and internal demands.
Behavioral flexibility	The observable difference in behavior following a change in cognitive state, secondary to changes in environmental or internal demand.
Reversal	A change in response when stimuli remain the same, but the reward outcome contingencies within a given feature set/dimension are inverted
Attentional set	A stimulus feature dimension to which a subject attends in order to correctly perform a flexibility task, while ignoring other simultaneously presented stimulus features.
Strategy shift	A shift in response strategy when stimuli remain the same towards a previously unrewarded stimulus dimension, typically driven by experimenter-dictated rule changes in the relationship between response and outcome.
Attentional set shift	A shift of attention to a new stimulus feature/dimension, after presentation of new stimuli. Typically driven by experimenter-dictated changes in the relationship between stimulus identity and outcome.
Intradimensional shift (IDS)	An attentional set shift where the subject must learn new stimulus-outcome contingencies within the same stimulus dimension while continuing to ignore the irrelevant dimension (e.g. shifting to new exemplar color after previously attending to color)
Extradimensional shift (EDS)	A attentional or strategy based shift where the subject must attend to another stimulus dimension, and ignore the previously relevant stimulus dimension, to learn new stimulus-response-outcome contingencies that produce reward. (e.g. shifting to odor after previously attending to color)

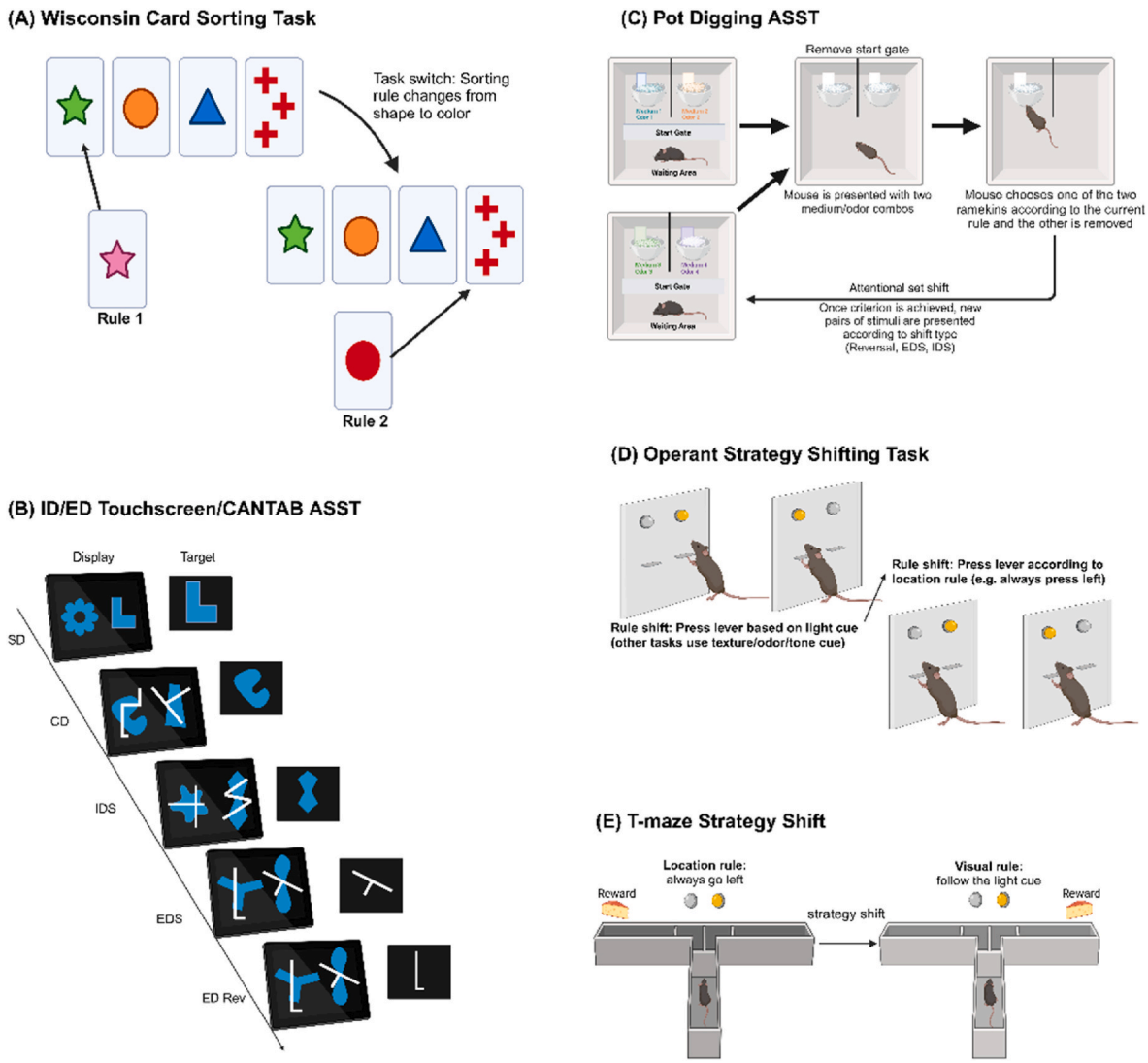

Fig. 1. Common experimental paradigms used to investigate behavioral flexibility. (A) Wisconsin card sorting (WCST) requires sorting by relevant features of the stimuli on the cards (e.g. shape). After an attentional set has been formed, there is an uncued shift in the sorting dimension (e.g. to color). This task is primarily used in human studies (B) Touchscreen/CANTAB set-shifting tasks use complex visual stimuli with multiple dimensions (e.g., shape, color and overlaid lines) to govern the formation of an attentional set before an uncued shift in the guiding feature. This method is often used in humans and non-human primates and less commonly in rodents. (C) The pot digging attentional set shifting task (ASST) pairs odors and textural dimensions to guide behaviors, again with uncued rule shifts that allow behavioral flexibility assessment in rodents. (D) Operant set-shifting uses one or more perceptual dimensions (e.g., odors, textures, lights, tones) and is a common way to evaluate flexibility in rodents. Operant paradigms can be used for attentional or strategy-based set-shifting tasks. Reward contingencies shift within and across dimensions. (E) Mazes can also be used to assess strategy shifting in rodents. Shifting occurs when rules are changed from being guided by visual cues to location rules or vice versa.

different aspects of cognitive flexibility (Ciampoli et al., 2021; Rikhye et al., 2018; Popik and Nikiforuk, 2015; Roberts et al., 1988).

Experimental task designs that enable an attentional shift are well illustrated by rodent ASSTs which usually begin with a single set of stimuli in one sensory dimension. In this, simple discrimination (SD), for example, responding to a green light is correct, and provides reward, but responding to a red light is incorrect. Once criterion is met the next stage overlays additional dimensions for compound stimulus discrimination. In a compound discrimination (CD), red and green lights still dictate presence or absence of reward, but now, e.g., peppermint and lemon odor are also presented and should not be attended to as they do not predict reward. Once subjects can perform CD, flexibility may be tested by an intradimensional shift (IDS), within a new stimulus set where now purple light is correct and yellow light is incorrect, for example, and two new odors presented are irrelevant. During these stages, reversals may be incorporated whereby the stimulus-outcome contingencies within a dimension are inverted (e.g., yellow light is rewarded, and purple is not). Finally, the most challenging test of flexible behavior during ASSTs is the extradimensional shift (EDS). For an EDS, a new stimulus set is presented but the relevant perceptual dimension has changed (e.g., odor identity now predicts reward instead of light identity). Each shift forces the development of a new attentional set based on novel stimulus-outcome contingencies and subsequent stages require that previous stimulus-response pairs are suppressed, leading to performance differences across stages (Scheggia and Papaleo, 2016; Heisler et al., 2015; Dajani and Uddin, 2015; Floresco and Jentsch, 2010; Birrell and Brown, 2000). In rodents, the pot- or bowl-digging ASST (Fig. 1C) has commonly been used to assess attentional set shifting ability (Heisler et al., 2015; Birrell and Brown, 2000). In these tasks, rodents make a choice between two bowls, each outfitted with a different textured media and odor. Subjects must correctly identify which stimulus (e.g., a specific odor or texture) predicts reward, which is buried in the media.

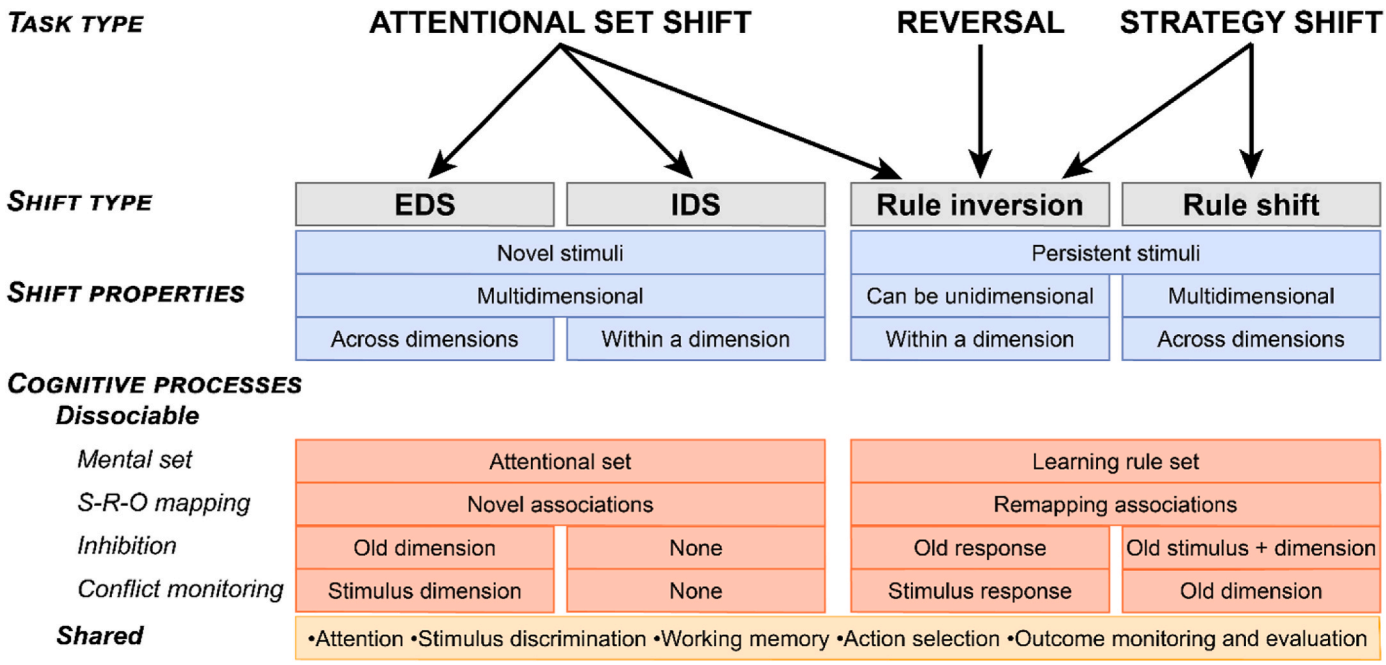

Fig. 2. Key differences and shared features across common flexibilty tasks. The experimental paradigms most commonly used to investigate cognitive flexibility fall into three major task types, ASST, reversal learning and strategy shifting. Each behavioral shift type within those tasks is highlighted in gray, extradimensional shifting (EDS), intradimensional shifting (IDS), rule inversions and rule shifts. Note that rule inversions can be employed within a single dimension in the context of an ASST or strategy shift task. Specific properties of each task shift distinguish one shift type from others (blue). It is the unique combination of these task properties in different behavioral shifts that engages a range of cognitive processes to enable flexibility, some of which are dissociable across shift types (orange), whereas others are similarly engaged across shift types (yellow).

The odors and textured media are replaced after criterion is reached, and the new correct stimulus is assigned based on shift type. Variants of this task use textured platforms as stimuli to be discriminated (Rodberg et al., 2017; Young and Shapiro, 2009).

Rodent ASSTs such as those outlined above are back translated variants of the human Wisconsin Card Sorting Task (WCST; Fig. 1A), one of the most common ASSTs used to assess flexibility (Grant and Berg, 1948). In a single session of WCST, subjects must sort novel multidimensional stimulus cards by an undeclared dimension, e.g., color, shape, or number of items with feedback on whether the sort was correct or incorrect. In sorting based on one dimension, the subject forms an attentional set, i.e., an attentional bias toward that dimension. Following an uncued, experimenter-dictated change, subjects must shift their attention across dimensions (EDS; e.g., a shift from color to shape), learning by trial and error. These shifts require inhibiting responses based on the previous attentional set and mapping new stimulus-outcome associations to form a new attentional set. In addition to the WCST, computerized ASST tasks for humans have been developed such as the intra-extra dimensional (ID/ED) set shift task for humans and NHPs as part of the Cambridge Neuropsychological Test Automated Battery (CANTAB). Although designed for, and predominantly used for, studies in humans and NHPs, several studies have applied CANTAB/touchscreen based tasks to assess behavioral flexibility within the visual domain in rodents (Piantadosi et al., 2019; Bussey et al., 2008; Dias et al., 1997; Roberts et al., 1988).

Key aspects of ASST designs differ between species. Rodent ASSTs often rely on stimulus sets that include multiple sensory modalities, as in the example described above, and shift across them e.g. visual to olfactory dimensions. The majority of human and NHP paradigms including WCST and the CANTAB ID/ED task, require dimensional shifting across multiple features of visual stimuli. Shape, color, orientation, patterning, numerosity, can be easily used by primates to distinguish between visual stimuli (Phillips et al., 2014). As such, set shifting in human and NHP tasks is extradimensional yet not extrasensory. This difference in stimulus choice for ASSTs reflects inherent sensory processing strengths across species (e.g., vision in humans and NHPs vs. olfaction/somatosensation in rodents) but may also relate to inherent cognitive differences as well (e.g., limited numerosity discrimination abilities in rodents). This key difference may highlight distinct cognitive processes and brain regions across tasks – e.g. those required to shift attention between sensory systems versus to shift to new features within the same sensory system. Despite differences in stimulus sensory features across species, all ASSTs leverage two key features. First, shifts are made between or within stimulus dimensions (stimulus features or sensory modalities). Second, trials involve presentation of novel stimulus sets or stimuli. Importantly, the combination of these two key features requires the subject to be able to generate an attentional set, and then following a shift, suppress attention to a previously attended set/dimension in the face of novel stimuli to assess flexibility, qualities that are unique to ASSTs.

Strategy shifting: Strategy-based shifting is another common task for assessing cognitive flexibility. Strategy shifting, sometimes termed task or rule switching, involves adaptive response strategies based on changes in response-outcome associations, despite persistent stimuli (Brady and Floresco, 2015). Strategy shifting tasks include maze-based tasks where rodents shift strategies between responding to visual cues or following location rules (Ragozzino et al.,1999, 2002). They also may include operant tasks in rodents or computerized task-switching paradigms in humans and NHPs (Brady and Floresco, 2015; Diamond, 2013; Floresco et al., 2008; Ragozzino et al., 2003). With all strategy shifting tasks, flexible behavior is evidenced by the ability to adapt to a new strategy or rule and avoid perseveration on previously relevant rules.

Strategy shifting is well exemplified by automated operant tasks where rodents are required to press a lever for reward based on visual cues, and then shift to a spatial rule regardless of the visual cue (Brady and Floresco, 2015). For example, in each trial a visual cue is displayed randomly over one of two levers (Fig. 1D). Initially, the rodent learns that pressing the lever below the visual cue is rewarded, i.e., a visual strategy must be employed, regardless of which lever the cue is over. After meeting criterion, a shift is deployed, visual cues continue to be

presented but now the lever location determines which lever press is rewarded, i.e., a spatial strategy is required. The rodent must employ a new task strategy and learn by trial and error that a new rule, lever location, is required to continue obtaining reward. Due to the use of stimuli across multiple dimensions, congruent trials can occur in which the old rule (visual cue) coincidentally overlaps with the new rule (lever location) facilitating opportunistic discovery of the new rule after a shift. As in the ASST above, reversals can be included (e.g., the rewarded lever switches from left to right).

In contrast to the ASST, identical stimuli are presented throughout the strategy shifting task. In the strategy shifting task, however, a novel behavioral response to these stimuli is required to achieve a favorable outcome. Because the stimuli are persistent, strategy shifting also requires the subject to explicitly ignore the previously reinforced stimuli after a shift in order to correctly engage a new strategy.

Reversal: Many studies focus on reversal learning as a measure of cognitive flexibility as a stand-alone task or within a shifting task. The basic principle of all reversal tasks is that a specific stimulus-outcome contingency is first learned before then being inverted (reversed). In rodents, reversal learning studies can use spatial tasks, such as the Barnes maze, Morris Water Maze, or T-maze (Fig. 1E). This typically involves habituation to the location of a platform, reward, or escape route followed by a spatial reversal test, requiring suppression of the previously correct response (Gawel et al., 2018). Other reversal learning paradigms employ operant responses in lever- or nose poke-based tasks or may use touchscreens or other technology (Palmer et al., 2021). Similar reversal paradigms, particularly computer and touchscreen-based tasks are used in humans and NHPs (Izquierdo et al., 2017). An example reversal paradigm would require a subject to discriminate between a left and right lever, where the one response (e.g., pressing the left lever) is rewarded and there is no outcome from pressing the other lever. After reaching discrimination criterion, the same stimuli remain but the contingencies switch, and the right lever is now rewarded whereas the left lever is not. Through trial and error, the subject must directly invert associations between lever positions and reward, by suppressing prior rewarded responses and exploring previously unrewarded actions. Distinct from strategy and attentional set shifting above, reversals only occur within a single dimension and not across dimensions. Like strategy shift tasks, all stimuli for reversals are consistent throughout the task. Reversal learning can be deterministic, where stimulus or response-outcome contingencies completely reverse from 0%/100%–100%/0%, or probabilistic, where the likelihood of outcome shifts from one stimulus or response to another (e.g., 70%/30%–30%/70%). There are interesting differences in the cognitive demands between these two tasks, which are described well elsewhere (Izquierdo et al., 2017). Although reversal learning can be assessed independently, it can also be integrated into ASSTs and strategy shifts, as noted above. To test reversal abilities in shifting tasks, after mastery of a given stimulus discrimination, stimulus-reward contingencies within one dimension of the existing stimuli is inverted. As with standalone reversal testing, reversals during shifting tasks are used in human, NHP, and rodent studies.

ASST, strategy shifting and reversal learning tasks described above exemplify the behavioral demonstration of cognitive flexibility and are the most common experimental methods used to explore flexibility across species, particularly in the context of alcohol and other substance abuse (Lim and Ersche, 2024). It is important to note however that these categories of tasks are only a subset of a wide range used to measure cognitive flexibility (Hohl and Dolcos, 2024; Uddin, 2021). Furthermore, the exploration of the neural substrates of cognitive flexibility, and the impact of alcohol on their function, benefits from a diversity of experimental paradigms.

Cognitive processes across flexibility tasks: Cognitive flexibility is considered a core executive function, yet flexibility is a product of multiple other cognitive processes as subcomponents (Braem and Egner, 2018; Diamond, 2013; Brown and Tait, 2010; Uddin, 2021; Dajani and Uddin, 2015). Each of the three tasks described above probes flexible behavior, yet each task engages a unique constellation of cognitive processes based on differences in task demands (Fig. 2). Understanding similarities and differences across tasks is useful in elucidating both the neural basis of as well as the impacts of alcohol on flexibility.

One particular factor that differentiates tasks and impacts the degree to which different cognitive processes are engaged is the range of stimuli used. Attentional set shifts employ novel stimuli upon each EDS/IDS shift, and those stimulus sets are always multidimensional, i.e., subjects are presented with stimuli encompassing more than one feature or sensory modality. Strategy shifting tests also present multidimensional stimulus sets, but in contrast with ASST, the same stimuli are used before and after rule shifts including EDS. For example, in an EDS in an ASST, new odors and textures are presented and the subject must shift from attending to one dimension (odor) to another (texture), whereas in an EDS in an operant strategy shifting task, the same stimuli are presented (lights and levers), but the subject must shift attention from light location to lever location, changing behavior accordingly. This incorporation of new stimuli is important for demonstrating the generalizability of an established attentional set in the ASST, but is less critical for strategy shifting in which the response rule shift is prioritized (Brown and Tait, 2010). Reversal tasks also use the same stimuli across trials, but in contrast with strategy shifting, stimuli used in reversals can be either unidimensional, in a stand-alone reversal task, or multidimensional, if the reversal is included in the context of a strategy or attentional set shifting task. These subtle differences across tasks result in potential differential recruitment of various cognitive processes such as working memory and response inhibition for optimal flexibility performance.

The composition of these tasks results in a spectrum of cognitive processes, such as stimulus discrimination, attention, response inhibition, working memory, action selection, and outcome evaluation. However, tasks differ in the degree to which specific cognitive processes must be employed, which is in part dictated by the task structure or properties, noted above. Three examples of how cognitive functions subserving flexibility are differentially challenged are described below. Consideration of the specific cognitive factors underlying each task is important for understanding both the neural substrates cognitive flexibility as a construct, as well as understanding the impact of alcohol, a topic considered further in the discussion below.

One cognitive process that differs within and across tasks is the nature of the attentional shift required for successful performance. In all shifts across tasks a previously ignored or unseen stimulus must be attended to. In the EDS of the ASST, subjects must redirect perceptual attention across stimulus features or domains to identify the stimulus that predicts the rewarded outcome. The IDS in the ASST similarly requires feature-based discrimination, although this is within, as opposed to across, dimensions. Thus, the EDS/IDS in the ASST are shifts in attention directed to sensory features. In strategy shifting tasks, the EDS can require a shift in attention to stimulus features (for example, in the operant version, shifting attention from the location of the light to the location of the lever), but the implementation of a rule shift goes beyond the redirection of attention, incorporating a shift in response as well. For example, in a maze-based strategy-shifting task, animals must switch from following a visual cue to direct correct choices (follow the light) to an egocentric direction-based strategy (always turn left). In these tasks, featural attention is certainly necessary, but the strategy EDS goes beyond selective filtering of sensory information and requires a change in response (Brown &Tait 2010; Ragozzino et al., 2002). Attentional processes in reversal tasks are similar to strategy shifting where behavioral responses must shift to stimuli that have always been present but previously unrewarded, however this occurs within a perceptual dimension as does IDS. These divisions are not absolute, as exactly what constitutes a change in action plan in strategy shifting vs. ASST vs. reversal is not clearly defined. As such the nature of attentional shifts across tasks is an interesting line of future research.

Another cognitive process that is differentially engaged across tasks

is the use of attentional and/or response inhibition to address conflicts between previously and currently rewarded stimuli and/or rules. All tasks involving a shift in behavior necessarily requires inhibition in that a previously reinforced stimulus or response must be ignored in order to use new information to guide behavior. As with attention regulation above, the extent and nature of inhibition in each of the three tasks described above varies somewhat. Inhibition is perhaps most clear during reversal trials as subjects must explicitly suppress a previously reinforced stimulus-response plan in the presence of the same previously rewarded stimuli, and redirect focus to the currently rewarded stimulus-behavior contingency. Similarly, in the EDS of strategy shifting, the same stimuli are presented across trials requiring inhibition of responding to a previously rewarded, but still-present stimulus. In the strategy shifting EDS, subjects must not only ignore a previously-rewarded stimulus, but must also inhibit a previously-rewarded behavioral strategy, potentially escalating the complexity of inhibition required. The EDS in an ASST is typically associated with presentation of novel stimuli, meaning that there is not conflict driven by the presence of previously-rewarded stimuli. However, this shift still presents a conflict whereby the previously attended-to dimension (e.g., texture) is still present and must be ignored in order to focus attention on the new dimension (e.g., odor). So even though novel stimuli are employed, the EDS in the ASST still exhibits an element of conflict. this element of conflict is a shared feature of reversals, strategy shifting, and EDS, but is absent from the IDS in ASSTs. For an IDS, novel stimuli are presented and, even though a second dimension is present, the subject has never been required to attend to the secondary dimension. Therefore, conflict monitoring and response inhibition are not required to complete an IDS. A potentially fascinating question that is raised by comparing tasks is the potential differential neural substrates of the different types of inhibition required – inhibition of attention to stimuli, inhibition of previously-rewarded strategies, and inhibition of categorical attention (e.g., to a particular sensory modality).

A third cognitive process that differs across tasks is working memory. Although all tasks require the maintenance of a stimulus-response-outcome association in working memory, the extent of working memory demanded across tasks varies. In reversal tasks in which stimulus sets are unidimensional, working memory is less challenged in that only a single item must be maintained to perform correctly. As noted above, working memory is challenged by the distraction of a persistent previously rewarded stimulus, but the scope of what must be maintained is relatively limited. In contrast, the ASST requires the use of hierarchical working memory maintenance, particularly during the EDS. Subjects must remember both the stimulus domain (e.g., olfactory vs. texture) as well as the identity of the specific stimulus leading to a reward. The shift across domains in the EDS likely presents unique challenges in that both levels of stimulus identity must be activated and maintained in working memory. In contrast, the IDS in an ASST does not require the stimulus domain to be maintained (as the other domain has not yet been identified as relevant) and, as such, working memory demands are similar to that seen in a reversal task. The EDS in the strategy shifting task presents additional challenges to working memory. This shift also requires updating of hierarchical memory - both rule category (e.g., use lever location not cue light location) and specific spatial or response rule memory (e.g., press the left lever, not the right lever). Intriguingly, the type of memory encoded may differ across ASST and the strategy shifting task, with the former being more sensory and the latter being more response-based. The strategy shifting EDS also exhibits working memory challenges similar to the reversal in that stimuli and potential rules persist across shifts, increasing distractions and requiring more effort to maintain working memory. Finally, strategy shifting presents a unique feature compared to other tasks which may further challenge working memory. After an EDS in strategy shifting tasks, there are some trials in which the previously rewarded and the currently-reward strategy are both correct. An example of the congruent trials is when the cue light (previously rewarded strategy) is present above the rewarded lever (currently-rewarded strategy). In some sense, congruent trials are facilitatory, in that there is no conflict between previous and current strategies. However, the periodic reappearance of the previously correct rule may also impede maintenance of a new rule in that the stability of the shift is challenged from trial to trial and the subject must actively compare the new rule to the old rule to accurately perform the task (Brown and Tait, 2010). This issue of congruency is not present in reversals (being unidimensional) or ASST shifts (as new stimuli are presented each shift). As with other cognitive processes, working memory is clearly necessary for performance of each type of task, but its engagement may vary across tasks. Given that working memory is driven in large part by frontal cortex function (Diamond, 2013; Funahashi, 2017; Lara and Wallis, 2015) and is impacted by alcohol use (Spinola et al., 2022; Day et al., 2015), a further understanding of the contributions of working memory, and other cognitive functions, to cognitive flexibility, is important.

In general, these cognitive subcomponents of flexibility tasks such as working memory, inhibitory control, and conflict monitoring, are differentially engaged depending on the specific task studied and, in some cases, vary on a trial-by-trial basis. This presents a rich platform for exploring the neural substrates of flexibility as a construct as well as of the underlying components that may differentiate different types of cognitive flexibility, its underlying neural processes, and associated clinical disorders, including AUD(Grant and Chamberlain, 2023). An important question, to be considered further in the discussion, is the degree to which the impact of alcohol on cognitive flexibility is via specific cognitive subcomponents or through an impact on the synthesis of these cognitive elements into the actual cognitive shifts that define flexibility.

3. Neural basis of cognitive flexibility in the PFC

The neural processing underlying cognitive flexibility has been a subject of intense investigation. The PFC has been repeatedly identified for its role in the generation of adaptive and flexible behaviors (Howland et al., 2022; Szczepanski and Knight, 2014; Willcocks and Mcnally, 2013). As noted above, the ability to switch between attentional sets and strategies requires a range of functions including working memory, attention to sensory stimuli, response inhibition, updating, and conflict monitoring (Abernathy et al., 2010; Bissonette et al., 2013). These executive functions, required for the emergence of flexible behavior, are regulated in large part by the PFC. The PFC receives high-level representations of sensory stimuli, integrates these representations, and directs outputs contingent on current and future demands (Euston et al., 2012). This integrative role of the PFC puts it at the seat of a wide rage of cogntive functions, including flexibility and its substrates.

The PFC comprises multiple subregions, several of which have been shown to play a critical role in cognitive flexibility. The majority of work referenced here pertains to neural correlates of set shifting, strategy shifting and reversal learning. However, it has been shown that these same key brain regions are involved in the balance between goal-directed and habitual, inflexible behavior more broadly (Gourley et al., 2010, 2016; Griffiths et al., 2014). Moreover, some frontal regions involved in flexible behavior are engaged by specific types of behavioral shifts while others are involved in shifting more broadly (Kim et al., 2012). Several other reviews provide a comprehensive account of the relationship between specific PFC subregions and neural processes underlying cognitive flexibility, as well as relevant differences across rodent versus NHP versus human frontal cortex/PFC (Howland et al., 2022; Cools and Arnsten, 2021; Laubach et al., 2018; Paneri and Gregoriou, 2017; Dajani and Uddin, 2015; Chudasama and Robbins, 2006). This review focuses on frontal regions underlying set shifting, reversal learning, and strategy shifting that have additionally been implicated in AUD or models of AUD, with a large focus on the rodent literature where a significant amount of work has been done, in order to emphasize this specific connection. Though contentious (Preuss and Wise, 2021), the

term medial prefrontal cortex (mPFC) is used in rodents here for consistency with previous literature and species distinctions are emphasized.

Neuroanatomical correlates of flexible behavior in humans and non-human primates: In humans, the prevailing frontal cortical areas shown to be involved in set shifting, strategy switching, and reversal tasks are the dorsolateral prefrontal cortex (dlPFC; Brodmann areas (BA) 9, 46), ventrolateral prefrontal cortex (vlPFC; BA 44 and 45) and orbitofrontal cortex (OFC; BA 10, 11 and 47), with some regional selectivity associated with task type (Uddin, 2021; Ezekiel et al., 2013; Dreher and Berman, 2002; Wilmsmeier et al., 2010). As mentioned previously, ASSTs often include reversal learning in addition to attentional set shifts, therefore, the studies in this section will include PFC regions underlying reversal learning particularly in the context of ASSTs or strategy shifts. The relationship between PFC and flexible behavior was demonstrated initially when human participants with surgical excisions of dlPFC (including BA 9 and 46) to treat epilepsy were shown to perform markedly worse on the WCST compared to all other excision locations (Milner, 1963). This was similarly found in patients with lesions in the frontal lobe (Owen et al., 1991). Early functional neuroimaging studies in humans demonstrated engagement of prefrontal regions during tasks requiring flexible responses, often the WCST and its analogs (Nakahara et al., 2002; Monchi et al., 2001; Omori et al., 1999; Konishi et al., 1998). In healthy human brains, reversal learning, intradimensional and extradimensional set shifting drove activation of specific prefrontal cortex regions (Rogers et al., 2000). For example, an EDS on the WCST increased activity in the dlPFC, an effect which was not shown with IDS or reversal learning. Functional MRI results of human subjects performing the WCST also identified dissociable PFC subregion activity during either set shifting (anterodorsal PFC/BA 46) or reversal switches (ventral PFC BA 11) (Nagahama et al., 2001). Other ASST variations which are able to distinguish between random errors and attentional set specific errors find that subjects with lateral PFC lesions (including dlPFC) have higher rates of perseverative errors, specific to attentional failures (Reindl et al., 2023; Barceló and Knight, 2002). These findings substantiate the involvement of dlPFC underlying the cognitive processes necessary for attentional set shifting specifically.

In human research, strategy shifting paradigms are often referred to as task-switching studies. Mirroring findings descibed above for ASST, strategy shifting is highly dependent on frontal cortical structures (Buchsbaum et al., 2005; Monsell, 2003). Early on, task switching investigations focused on determining if there were distinct networks and regions associated with performing different tasks simultaneously or subsequently. These studies identified that brain regions recruited for sequential task performance (i.e., task switching), relied on lateral PFC engagement (BA 9) (Dreher and Grafman, 2003; Sohn et al., 2000). Many studies have identified the dlPFC as critical for strategy switching in humans, however, a number of studies implicate greater involvement of vlPFC in strategy shifting, with less robust activity in dlPFC when compared to ASSTs (Smith et al., 2004; Braver et al., 2003; Rushworth et al., 2002; Dove et al., 2000; Myeong-Ho et al., 2000; Kimberg et al., 2000).

In addition to dlPFC and vlPFC, OFC is heavily implicated in cognitive flexibility, particularly reversal. Humans with OFC damage show particular reversal learning deficits in various paradigms outside the context of set shifting tasks (Berlin et al., 2004; Hornak et al., 2004; Rolls et al., 1994). This relationship between OFC and reversal learning has been confirmed through fMRI studies where lateral OFC shows strong activation during reversal learning (Rolls et al., 2020; O'Doherty et al., 2001).

Studies in NHPs show strong anatomical homology with humans to reinforce our understanding of the dlPFC as an essential node for flexible behavior through set shifting. A set of early lesion studies in NHPs identified the dlPFC as critical for extradimensional set shifting in parallel to confirming OFC as critical for reversal learning in the context of an ASST (Dias et al., 1996, 1997). Lesions to the dlPFC of NHPs have been shown repeatedly to impair performance on attentional set shifts, both intra- and extra-dimensional (Mansouri et al., 2020; Owen et al., 1991; Dias et al., 1996). Furthermore, electrophysiological recordings in NHP dlPFC during attentional set shifting tasks have corroborated the findings of imaging and lesioning studies, revealing single-neuron and population level encoding of task-relevant features during set shifting and reversals (Bartolo and Averbeck, 2020; Kamigaki et al., 2012). In parallel to human findings noted above, additional work in NHPs has corroborated the involvement of both the dlPFC and vlPFC in strategy shifting tasks, distinguishing the EDS within strategy shifting from that in ASSTs (Baxter et al., 2008). This evidence from both humans and NHPs, identifies potential dissociable neural substrates between ASST and strategy shifting, with the latter involving more ventral PFC regions, potentially associated with the higher demand for response inhibition due to persistent stimuli in strategy shifting.

Similar to dlPFC and vlPFC, the OFC in NHPs has been identified as critical for flexible behavior, mirroring results found in humans. OFC lesions were initially associated with explicit revesal learning deficits in NHP (Iversen and Mishkin, 1970). Since then, lesion studies across NHP species have identified the OFC as critical for explicit reversal learning and in the context of ASST tasks (Dias et al., 1996, 1997; Jones and Mishkin, 1972; Iversen and Mishkin, 1970). Other work in NHPs confirmed that bilateral excision of the OFC impairs reversal learning and results in desensitization to reward devaluation, a characteristic of inflexible behavior, mirroring results from human studies mentioned previously (Izquierdo et al., 2004). We note that the relationship between OFC and reversal, while well-established, has undergone some scrutiny as different techniques such as excitotoxic lesions have challenged an absolute relationship between OFC and reversal (Rudebeck and Murray, 2014; Rudebeck et al., 2013).

While the PFC is essential for cognitive flexibility in humans and NHP, these regions are heavily interconnected to other brain regions, recieving critical information from other areas, and targeting downstream regions that are equally crucial for executing flexible behavior. For example within the PFC, dlPFC projects to OFC, higlighting the collaborative role of PFC subregions in cognitive control and flexibility (Cools & Arnsten, 2022; Haber et al., 2021; Miller and Cohen, 2001). However, it is important to note that even these subregions are embedded in broader networks critical to flexible behavior. Human and NHP studies of set shifting, strategy shifting, and reversal learning have identified a range of areas outside of PFC/OFC regions that participate in these functions, including the anterior cingulate cortex (ACC; BA 24, 32 and 33), insula parietal cortex, dorsal and ventral striatum, and thalamus, to name a few (Dannenhoffer et al., 2021; Uddin, 2021; Izquierdo et al., 2017; Cools et al., 2004; Braver et al., 2003; Braver et al., 2001). The ACC in particular shows strong relevance for cognitive flexibility. Evidence from humans and NHPs supports the ACC as a critical node for tracking alternative strategies and selection of alternative responses when circumstances change (Tervo et al., 2021; Blanchard and Hayden, 2014; Hayden et al., 2011; Schuck et al., 2015). Lesions to the ACC alone are sufficient to impair EDS during ASSTs in NHP (Mansouri et al., 2020). ACC is well validated to subserve conflict monitoring, a cognitive process critical for flexibility (Botvinick et al., 1999, 2004; Allman et al., 2001; Braver et al., 2001)

The relationship between neural networks and the cognitive processes that allow flexible behavior in humans and NHP is an area that deserves additional attention, particulary in the context of flexibility disruptions by alcohol. The PFC is thought to orchestrate the coordinated communication of integrated sensory information, value, and response selection to these other brain regions that encode response outcomes for flexible behavior. For example, the dlPFC, vlPFC, OFC, and ACC all project to the striatum which has been shown to regulate flexible action plans (Suzuki and Nishimura, 2022; Dannenhoffer et al., 2021; Crews and Boettiger, 2009). These regions are thought to form a circuit that can encode and update response-outcome relationships to drive flexible behavior (Kőszeghy et al., 2023; Morris et al., 2014; Seo et al.,

2012; Tanaka et al., 2008). What needs to be established is whether alcohol may impact flexibility by disrupting relevant signaling in upstream PFC regions desribed above, downstream targets of those PFC regions or both, highlighting the need for comprehensive investigation of network functions after alcohol.

Neuroanatomical correlates of flexible behavior in rodents: In rodents, frontal cortical areas, particularly mPFC and OFC, are commonly associated with cognitive flexibility, similar to what is seen in primates with some evidence of anatomical specificity between tasks (Howland et al., 2022; Uddin, 2021; Birrell and Brown, 2000; de Bruin et al., 1994). Rodent mPFC can be broken down further into the anterior cingulate (ACC), prelimbic (PrL), and infralimbic (IL) cortices, from dorsal to ventral respectively (Anastasiades and Carter, 2021; Laubach et al., 2018; Seamans et al., 2008). Unlike human and NHP literature where ACC is tightly connected with but distinct from PFC, ACC in rodents is often included as a subregion of the mPFC with many flexibility studies containing lesions or inactivation ranges that include ACC (see van Heukelum et al., 2020 for anatomical considerations). In rodents, flexible behavior in ASST, strategy shifting tasks and reversals have been shown to heavily engage mPFC (including ACC) and OFC. Importantly, there is significant crosstalk between these PFC subregions, suggesting that information processing in one area can directly influence functioning of another to regulate cognitive flexibility (Gao et al., 2022; Howland et al., 2022).

Depite the fact that these areas are interconnected and are broadly associated with cognitive flexibility, there are notable differences in specific functions associated with subdivisions. Combined lesions to the ACC, PrL, and IL, i.e., the entire rodent mPFC, results in loss of ability to perform attentional set shifts, both intra- and extra-dimensional (Bissonette et al., 2008; Birrell and Brown, 2000). However, recent research highlights evidence suggesting that mPFC subregions may be differentially involved in attentional set and strategy shifting (Broschard et al., 2021; Spellman et al., 2021; Capuzzo and Floresco, 2020; Mukherjee and Caroni, 2018; Woon et al., 2020; Del Arco et al., 2017; Sharpe and Killcross, 2015). Most notably in rodent literature, the PrL cortex has been identified as essential for EDS. Inactivition of the PrL has been shown to impair EDS during ASST and strategy shifts as well as CD and IDS (Anderson et al., 2021; Mukherjee and Caroni, 2018; Oualian and Gisquet-Verrier, 2010). The PrL cortex may be specifically involved in updating attention to specific cues as well as exploring novel behavioral responses (Sharpe and Killcross, 2014; Marquis et al., 2007). Several studies investigating neural activity during ASSTs have shown strong task related representations within PrL underlying integration of trial feedback by representing both response and outcome features (Spellman et al., 2021; Del Arco et al., 2017). Within the PrL, unique neural ensembles reflect specific response-outcome rules during strategy shifting (Durstewitz et al., 2010). Following an EDS, successful acquisition of a new rule is associated with an abrupt transition to new and unique neural ensembles, indicating neural substrate for cognitive flexibility within the PrL. Not only do neurons within PrL identify specific rules, there is evidence that distinct populations of neurons in PrL emerge only during high conflict congruent trials during strategy shifting (Bissonette and Roesch, 2015). Thus evidence demonstrates that PrL neural activity reflects representations of task relevant stimulus-response-outcome associations which are updated upon trial feedback or a shift in the task. This positions PrL as critical in engaging and maintaining goal-directed strategies during set shifting, heavily supporting attention, stimulus discrimination and working memory processes needed for cognitive flexibility.

Fewer studies have characterized the specific role of IL in ASST or strategy shifting tasks (Mukherjee and Caroni, 2018; Oualian and Gisquet-Verrier, 2010) However, there is evidence that IL inactivation impairs reversal learning as well as the EDS stage of ASST with no impact on IDS (Mukherjee and Caroni, 2018). The synaptic plasticity marker egr-2 was increased in IL relative to other prefrontal regions after set shifting and reversals (DeSteno & Schmauss, 2008, 2009). This indicates that IL may serve a particular role in flexible behavior, where it is engaged at levels of high conflict (i.e., during reversals and EDS when there is a stimulus-based or categorical conflict). Collectively the role of IL in cognitive flexibility appears to subserve working memory processes to allow competing stumulus-response-outcome associations to persist in parallel before a new strategy is resolved, or by facilitating inhibition of prior responses in the presence of persistent conflicting stimuli. One common view characterizes PrL and IL as independently influencing flexible behavior through the use of opposing processes, with goal-directed behaviors being PrL mediated, and habitual, traditionally viewed as IL mediated (Gourley and Taylor, 2016; Smith et al., 2012; Coutureau and Killcross, 2003; Killcross and Coutureau, 2003). There certainly seem to be independent contributions of the PrL and IL cortices to flexible behavior; however, whether these regions are driving opposing processes remains unclear and is likely a more complex interaction (Moorman and Aston-Jones, 2015). For example, recent work suggests that PrL and IL regulate habitual and goal-directed behavior in an experience dependent manner, wherein the degree of training correlates with which subregion drives action selection (Shipman et al., 2018).

Aligned with human and NHP evidence described above, there is a particularly notable relationship between OFC and reversal learning in rodents. This close connection is supported by a large body of literature demonstrating that lesions and pharmacological inactivation of the OFC impairs reversal ability (Izquierdo et al., 2017; Brigman et al., 2013; Graybeal et al., 2011; Young and Shapiro, 2009; Bohn et al., 2003). As in other species, most of the work implicating OFC in behavioral flexibility, specifically reversal learning has been undertaken in pure reversal learning paradigms outside the context of set shifting. However, studies of reversals during attentional set and strategy set shifting further show that OFC is essential for reversal performance during set shifting (Bissonette et al., 2008; Ghods-Sharifi et al., 2008; Ragozzino, 2007). Critically, the rodent OFC seems to be primarily involved in reversal, but not other aspects of flexibility. For example, rats performing a maze-based strategy shifting task showed impaired ability to execute reversals, but not strategy shifts, following bupivacaine inactivation of OFC (Ghods--Sharifi et al., 2008). The role of OFC in shifting is supported by evidence for the primary functions of OFC in other tasks, particularly updating outcome values, a cognitive process necessary after inversion of a task rule during reversals (Klein-Flügge et al., 2022; Schoenbaum et al., 2009).

In addition to PrL, IL and OFC there is also some evidence from rodents that ACC is involved in flexible behavior, being implicated in both set and strategy shifting tasks (Proskurin et al., 2023; Sarafyazd and Jazayeri, 2019; Bissonette et al., 2013; Ragozzino and Rozman, 2007). Previous work has shown that ACC function regulates multiple cognitive processes required in flexibility tasks. For example, in a variant of an ASST, ACC encoded conflict through reward prediction errors, i.e., whether an outcome did or did not match expectation, and it was hypothesized that this signal may trigger updated representations of stimulus-response associations in working memory (Cole et al., 2024). These results build on previous theories that the ACC is involved in conflict monitoring more broadly (Botvinick et al., 2004) which, as noted above, is a key element of most tests of cognitive flexibility. Additional work has shown that ACC is recruited when shifting within an attentional domain, for example, during IDS (Ng et al., 2007). These, and other, results indicate that ACC is clearly involved during flexibility tests such as ASST and strategy shifting, but the specific contributions – perhaps driven by differential encoding across ACC microcircuitry – remain to be identified.

Altogether, these results highlight that frontal cortical subregions differentially regulate flexible behavior, potentially via implementation of different underlying cognitive processes such as attention, working memory, response inhibition and outcome monitoring. This is a crucial consideration when integrating the results of behavioral flexibility studies in the context of AUD-related manipulations that leverage these

complex tasks, discussed below. Many studies confirm and highlight the distinct contribution of the dlPFC/vlPFC in primates and mPFC in rodents, to set shifting and the OFC across species to reversal learning (Szczepanski and Knight, 2014; Gourley et al., 2010; Bissonette et al., 2008; Hornak et al., 2004; McAlonan and Brown, 2003; Schoenbaum et al., 2002, 2003). The key findings from each species have been replicated many times across testing paradigms providing robust validity between neural substrates of the PFC and the flexible behavioral processes they mediate (Uddin, 2021; Izquierdo et al., 2017; Bissonette et al., 2013; Ragozzino, 2007).

Neuromodulation of flexible behavior in the PFC: The PFC, particularly those regions noted above are heavily innervated by ascending neuromodulators, including dopamine (DA) and norepinephrine (NE), among others, and these neuromodulators can impact many PFC dependent functions, including cognitive and behavioral flexibility. Neuromodulatory influences are particularly relevant in the current context as their signaling is also altered by alcohol.

PFC regulation by catecholamines is known to exhibit Yerkes-Dodson (i.e., inverted U-shape) relationships capable of driving impairments in PFC-dependent cognition with too little or too much catecholaminergic tone, and this is also seen in behavioral flexibility tasks. Additionally, these neuromodulators fire tonically and in phasic bursts which may have differential impact of PFC targets (Cools and Arnsten, 2021; Nilsson et al., 2019; Prado et al., 2017; Floresco, 2013; Arnsten, 1998). Highlighting this unique type of relationship, both low and high rates of DA receptor D1 occupancy in the PFC are associated with poor performance on the WCST (Takahashi et al., 2008, 2012). Systemic DA receptor D2 agonists improved performance on a cued set-shifting task (i.e. a cue indicates a rule change) in humans, but this effect was only seen in individuals with genetic predisposition to lower levels of dopamine (van Holstein et al., 2011). These data indicate an influence of DA on flexibility in humans via multiple receptor subtypes.

Rodent studies have provided substantial evidence on how mesocortical DA dynamics regulate flexible behavior broadly by acting through PFC subregions (Ott and Nieder, 2019; Floresco and Magyar, 2006; Klanker et al., 2013). DA infusion into the IL cortex, but not PrL, promoted adaptive responding and flexible behavior during reward devaluation (Hitchcott et al., 2007). The mechanism appears to be D2-modulated, as locally enhancing D2 or inhibiting D1 signaling in IL was shown to promote flexible responses following previous development of a habitual response (Barker et al., 2013). In rodent strategy shifting tasks where PrL is critical for EDS, D1 and D2 antagonist and D4 agonist infusions in PrL impair flexibility (Floresco et al., 2005). Systemic D1-like agonists impaired deterministic reversal learning in mice (Izquierdo et al., 2006), and local D1 antagonists in rat OFC impaired probabilistic reversal learning by promoting perseverative behavior (Jenni et al., 2021). The role of DA on prefrontal targets may be to update values and stimulus-response associations via high affinity D2 receptors and D4 receptors to broadly promote flexibility across tasks. Given the clear relationship between DA and flexibility, further investigation of specific mechansisms after a history of alcohol use through the lens of DA impact on different subcomponent cognitive processes underlying flexible behavior, is warranted.

Flexible behavior, particularly measured by attentional set- and strategy-shifting tasks, has been tightly linked to NE projections specifically from the locus coeruleus (LC) to the PFC (Janitzky et al., 2015; McGaughy et al., 2008). LC neurons project widely throughout the PFC, with particularly strong innervation of critical PFC subregions including dlPFC, mPFC and OFC (Agster et al., 2013; Waterhouse and Chandler, 2012; Morrison et al., 1982). Evidence from human and studies using pulpillometry,a validated proxy for baseline LC activity, suggests that LC-NE activity increases in response to changes in stimulus-response contingencies during both WCST and ID/ED task. (Privitera et al., 2020; Liu et al., 2017; Pajkossy et al., 2017; Joshi et al., 2016; Reimer et al., 2016).

Preclinical studies provide more specific evidence of PFC subregions that utilize NE to engage in flexible behavior. Broad lesions of dorsal noradrenergic bundle, (DNAB) or targeted lesions of noradrenergic, but not cholinergic afferents, in rat PrL and IL cortex produced impairments of EDS ability using the pot-digging ASST (Tait et al., 2007, McGaughy et al., 2008). Pharmacologically enhancing LC-NE release can also significantly improve behavioral flexibility, especially EDS. ASST deficits after noradrenergic deafferentation of mPFC can be reversed by atomoxetine a NE reuptake inhibitor, which independently improves EDS in strategy shifting taks (Newman et al., 2008; Totah et al., 2015; Cain et al., 2011; Koda et al., 2010). Similar improvements have been shown with chronic treatment of NE reuptake blockers (Bondi et al., 2010; Nikiforuk et al., 2010; Lapiz et al., 2006). DREADD-mediated excitation of LC-NE terminals in PrL/IL also resulted in improved EDS performance during strategy shifting (Cope et al., 2019). Importantly, these results were not mirrored with global LC DREADD activation, indicating that NE specific to the PFC is critical for both strategy and attentional set shifting, refining prior evidence from dorsal noradrenergic bundle lesions (Tait et al., 2007). There is also evidence that NE tone is an important mediator of reversal learning and response inhibition. Early DNAB lesions showed impaired attention and reversal learning (Mason and Iversen, 1978). Reciprocally, pharmacological enhancement of NE tone improves revesal learning in both rodents and NHPs (Seu et al., 2009). Together, it appears that NE function underlies some aspect of many flexibility tasks, suggesting a primary role in flexibility in general or in some set of cognitive functions shared across tasks.

The specific receptor targets of LC-NE in the PFC that mediate cognitive flexibility are less explored but several studies show the importance of α-adrenoreceptors. Systemic α2-adrenergic receptor antagonist injection, to reduce adrenergic autoinhibition and promote NE release, improved EDS performance on the pot-digging ASST. This enhancement in performance was negated by microinjection of an α1-antagonist into PrL/IL region (Lapiz and Morilak, 2006). Intriguingly, activation of α2A receptors in NHPs, in the ventrolateral PFC where these receptors are also found postsynaptically, has been shown to improve ASST and reversal learning (Wang et al., 2004; Steere and Arnsten, 1997). One mechanism for α2A receptor activation may be to enhance outcome signaling during set shifting, as it has been shown to do in ACC but not dlPFC of NHPs (Hassani and Womelsdorf, 2023). Alpha NE receptors have also be implicated in mediating the noradrenergic influence over reversal learning in NHPs (Ridley et al., 1981). This range of studies further supports a role for NE in broadly mediating flexible behavior. Alpha NE receptors in particular may promote maintaince of goal-directed attention and flexible exploration of alternative options after a change in stimulus-response-outcome contingencies, potentially by facilitating response inhibition of prior behavioral responses.

Collectively both DA and NE play important roles in regulating flexibility as measured by tests such as the ASST, strategy shifting and reversal learning. The interaction between these, and potentially other, neuromodulatory systems, in the context of alcohol use disorder is a key research direction, both for understanding fundamental mechanisms of cognitive flexibility as well as for potentially developing treatments.

4. Alcohol impairs cognitive flexibility across species

A keystone feature of AUD is an inability to alter behavior to abstain from alcohol use despite negative outcomes associated with drinking (American Psychiatric Association, 2022). This exemplifies an impairment of higher-level executive functions, particularly cognitive flexibility, and loss of top-down cognitive control (Lim and Ersche, 2024; Dannenhoffer et al., 2021; Bagga et al., 2014; Ratti et al., 2002). As such, characterizing how acute, chronic, and binge-like alcohol exposure and withdrawal impacts cognitive flexibility and the PFC regions underlying flexibility has been an active area for research (see Table 2). Studies of humans with AUD have probed which specific executive functions are

Table 2
Alcohol impairs flexibility across species. Impaired flexibility as measured by strategy shifting, attentional set shifting (ASST), and reversal learning (nested within shifting) is consistently associated with excessive alcohol use across species and drinking paradigms. AUD = alcohol use disorder; AIE = adolescent intermittent ethanol; CIE = chronic intermittent ethanol, IAP = intermittent access protocol.

Species	Sex	Behavioral Ability	Drinking Paradigm	Citations
Humans	M & F	ASST ↓	Non abstinent/acute exposure	Lyvers and Maltzman (1991)
	M	ASST ↓	Abstinent AUD	Nweze et al. (2020)
				Gupta et al. (2018)
				Martelli et al. (2017)
				Banca et al. (2016)
				Czapla et al. (2016)
				Yen et al. (2015)
				Kopera et al. (2012)
				Chanraud et al. (2007)
				Bijl et al. (2005)
				Fama et al. (2004)
				Ratti et al. (2002)
	M & F			Kim et al. (2011)
				Loeber et al. (2009)
				Oscar-Berman et al. (2004)
				Beatty et al. (1995)
				Joyce and Robbins (1991)
Non-human primates	M	Enhanced discrimination ASST ↓	IAP	Shnitko et al. (2020)
		↓ Baseline ASST	Predictive of self-administration	Shnitko et al. (2019)
				Grant et al. (2021)
Rats	M	ASST ↓	AIE	Gass et al. (2014)
	M & F	Strategy shifting ↓ (males)	AIE	Varlinskaya et al. (2020)
	M	Reversal ↓	IAP	Charlton et al. (2019)
	M	↓ Baseline ASST	Predictive of self-administration	De Falco et al. (2021)
	M	Strategy shifting ↓	CIE	Trantham-Davidson et al. (2014)
Mice	M	ASST ↓	CIE	Rodberg et al. (2017)
				Kroener et al. (2012)
		Reversal ↓	CIE	Badanich et al. (2011)
	M & F	↓ Baseline ASST	Predictive of self-administration	Rodberg and Vazey (2022)

disrupted via batteries of cognitive tests such as the WCST, Stroop test, or digit cancellation test (Stephan et al., 2017; Brown and Tait, 2016; Stroop, 1935). These studies consistently demonstrate that individuals with AUD show disruptions in cognitive flexibility as well as executive deficits in several cognitive processes that underly flexibility including inhibitory control, attention, problem-solving, working memory, and decision-making (Maurage et al., 2014; Stautz and Cooper, 2013). The degree to which flexibility versus specific underlying cognitive functions are disrupted is discussed further below.

Broadly speaking, abstinent patients with AUD rely more heavily on habitual response strategies than goal-directed strategies, as measured in instrumental learning tasks (Sjoerds et al., 2013). This shift to habitual behavior can be driven by an inability to associate responses with outcomes, which is necessary for flexible behavior. The weakening of goal-directed behavior and increased reliance on habitual behavior after a history of alcohol use likely results from a complex interaction between multiple diminished cognitive processes that together impair cognitive flexibility. Abstinent humans with AUD show increased perseverative errors on the WCST (Joyce and Robbins, 1991). In a number of studies, abstinent and non-abstinent subjects with AUD completed fewer EDS shifts and showed increased total errors, higher error rate on the WCST or ID/ED flexibility tasks (Nweze et al., 2020; Yen et al., 2015; Kim et al., 2011; Loeber et al., 2009; Chanraud et al., 2007; Fama et al., 2004; Ratti et al., 2002; Beatty et al., 1995; Joyce and Robbins, 1991). These impairments on the WCST and the EDS portion of ID/ED test highlight a consistent impairment in EDS in humans with AUD as supported also by a meta-analysis of clinical studies (Stephan et al., 2017). In non-dependent human subjects acute ethanol, resulting in blood alcohol levels of 0.05%, also increased perseverative errors on the WCST during a social drinking experiment, similar to the deficits found with AUD (Lyvers and Maltzman, 1991).

Both binge drinkers and individuals with AUD show disrupted reversal learning, both deterministic and probabilistic, stemming from diminished sensitivity to trial outcomes during reversal that likely impairs their ability to update stimulus-response-outcome associations (Bağci et al., 2022; Yoo and Kim, 2016; Vanes et al., 2014). These findings highlight consistent and persistent cognitive flexibility deficits on EDS and reversal learning resulting from alcohol use in humans.

To investigate causality and explore relationships between alcohol consumption and cognitive flexibility, set shifting studies like those described above have been used in preclinical models of alcohol use, primarily in rodents and, to a lesser extent NHP. Prolonged drinking is used in NHPs and rodents, and chronic intermittent ethanol (CIE) paradigms are often used in rodents. CIE paradigms, subjects receive intoxicating doses of ethanol by vapor or other administration repeatedly, separated by withdrawal periods (Becker and Lopez, 2004). Repeated cycles of CIE drive physiological dependence, significantly escalate volitional alcohol intake, and can be used to translationally identify AUD risk factors via interactions with concomitant life experiences (e.g. stress) making this a useful model of AUD. CIE produces lasting increases in alcohol consumption after adolescent or adult ethanol exposure, across both sexes (den Hartog et al., 2020; Kimbrough et al., 2017; Anderson et al., 2016; Griffin et al., 2009).

Multiple studies using the CIE paradigm and its variants have demonstrated that alcohol-dependent rodents show signs of impaired flexible behavior that persist after alcohol exposure. For example, male mice who underwent three cycles of CIE and withdrawal showed impaired strategy shifting ability, but not reversal learning, on a maze based task (Kroener et al., 2012). Another study compared the combined and individual effects of a history of alcohol and stress on volitional alcohol drinking and flexible behavior. Using the two-dimensional pot digging ASST, this study demonstrated that mice who underwent cycles of CIE and stress exposure exhibited EDS impairments (Rodberg et al., 2017). Notably, this impairment was not seen in groups of mice who received only CIE or only stress exposure. However, in rats CIE alone leads to persistent deficits in EDS during strategy shifting (Trantham-Davidson et al., 2014). Additional work has shown that acute withdrawal in rodents following CIE results in deficits in reversal learning. After three consecutive cycles of CIE, mice tested during acute withdrawal (at 72 h) showed impaired flexibility on the pot-digging

ASST. These impairments were specific to the reversal learning levels of the task, resulting in more errors and requiring more trials to criterion. Uniquely, this study used repeated testing during prolonged withdrawal (10 days post-CIE), and found that reversal learning impairments returned to baseline, suggesting that there are mechanisms of recovery for alcohol-induced reversal deficits (Badanich et al., 2011). Shifting to a new attentional set was not impaired in these mice during acute or prolonged withdrawal, in contrast with other research in mice, rats and non-human primates (Rodberg et al., 2017; Shnitko et al., 2020; Kroener et al., 2012). This suggests that variations in ethanol or stress exposure, duration of withdrawal, or other factors can be important in the cognitive outcomes in models of AUD, as is similarly seen in humans with AUD (Maillard et al., 2020; Ghogare and Saboo, 2019). Outside the context of shifting tasks, it is well documented that CIE or binge like alcohol exposure leads to reversal learning deficits in both rats and mice across a range of reversal tasks that can also persist for extended periods beyond acute withdrawal (Badanich et al., 2016; Fernandez et al., 2017; Kuzmin et al., 2012; Obernier et al., 2002). Taken together, it is clear that a history of chronic alcohol can impair multiple aspects of flexibility as measured by multiple tasks across species. This implies that flexibility in itself may be sensitive to chronic alcohol, or that cognitive components underlying multiple flexibility tasks are impacted.

Among these studies of impaired flexibility, EDS and reversal learning in particular are consistently impaired across drinking paradigms and species. These deficits established in preclinical models show strong face validity with human evidence from AUD discussed above. Furthermore impairments in EDS and reversals are commonly documented cognitive outcomes of developmental exposure to excessive alcohol either prenatally or in adolescence (Dannenhoffer et al., 2021) identifying them as a nexus for the cognitive impacts of alcohol. The impact of alcohol on EDS and reversal learning could be a function of the cognitive effort required for the integration of cognitive processes. As mentioned previously, EDS and reversal learning have high levels of conflict: categorical conflict for EDS and stimulus conflict for reversal. This key difference could situate EDS and reversals as particularly challenging tests of flexible behavior, thus making them more vulnerable to the effects of alcohol.

Despite some differences in the specific cognitive flexibility impairments observed across these studies, they all provide strong evidence that a history of excessive alcohol exposure results in impairments in flexible behavior across species. Differences across studies may be be driven by total alcohol dose and/or timing of alcohol dosing and compounding factors such as stress. More research is needed for additional clarity regarding these intersecting relationships. Additional rodent and non-human primate models of AUD show deficits not only in flexibility but also in underlying cognitive processes such as working memory, response inhibition, and extinction learning (Barker et al., 2017; Gass et al., 2013, 2014, Barker and Taylor, 2014). These findings align with the idea that cognitive control and flexibility are particularly vulnerable in AUD and that animals models of alcohol use provide strong value in recapitulating many of the behavioral and cognitive changes observed in humans with AUD.

Recent studies in animal models have identified that low levels of cognitive flexibility are not only a consequence of excessive alcohol use but may also function as a predictive risk factor for excessive alcohol consumption. In several species, the degree of flexible behavior demonstrated before alcohol exposure differentiated animals that went on to become heavy alcohol drinkers from those with more modest consumption. In NHPs, baseline flexible performance on the ASST in alcohol naive animals was significantly worse in animals that went on to become heavy drinkers compared to those that later became low or binge drinkers (Grant et al., 2021; Shnitko et al., 2019a). This inverse relationship between flexible behavior and level of voluntary alcohol intake has been replicated in both mice and rats (Rodberg and Vazey, 2022; De Falco et al., 2021). In these studies, rodents were tested on the ASST prior to alcohol consumption highlighting the possibility that individual differences in underlying brain function may identify an endophenotype for those most at risk of excessive alcohol use. Thus, evidence supports a bidirectional relationship between behavioral flexibility and excessive alcohol use. The bidirectional relationship also supports a role for shared neurobiological vulnerabilities underlying AUD and cognitive flexibility.

Alcohol-induced changes of PFC circuits mediating cognitive flexibility: Given the strong, bidirectional relationship between alcohol and cognitive flexibility, it is important to consider which systems (i.e., neuromodulatory, network-level) that govern flexible behavior are particularly vulnerable to the effects of alcohol. This understanding will help guide the development of novel therapeutic targets to treat AUD, potentially by addressing its cognitive underpinnings. It is well established that humans with AUD exhibit structural and functional changes in the brain, particularly frontal regions (Staples and Mandyam, 2016; Schacht et al., 2013). Early studies showed that abstinent humans with AUD had significantly less gray and white matter volume in the cortex and a concomitant loss of neuronal density. The most pronounced reductions in frontal cortex regions have been observed in the OFC and medial frontal cortex and right hemisphere-lateral PFC including dlPFC (Suk et al., 2021; Cservenka and Brumback, 2017; Moorman, 2018; Fortier et al., 2014; Rando et al., 2011; Sullivan and Pfefferbaum, 2005; Kubota et al., 2001; Pfefferbaum et al., 1992, 1997; Jernigan et al., 1991). The extent of gray matter volume reduction in the medial frontal cortex was predictive of earlier return to relapse (Rando et al., 2011). These alcohol-induced brain volume and structural changes, particularly those originating in the frontal cortex, are associatied with the behavioral and cognitive deficits observed in AUD, particularly impulsivity, impaired decision-making and impaired cognitive flexibility (Zahr et al., 2017; Le Berre et al., 2014; Jansen et al., 2015; Zorlu et al., 2013). Chronic alcohol produces similar disruptions in frontal cortex structure in animal models, highlighting the universality of this phenomenon, and providing a powerful cross-species mechanism for translational studies (Shnitko et al., 2019b; McGuier et al., 2015; Coleman et al., 2011; Crews and Boettiger, 2009). These findings suggest that structural, and therefore functional, changes in this region may contribute to the feedforward cycle of alcohol addiction and relapse in a critical way.

Recent work revealed a relationship between functional neural connectivity and performance on the WCST in abstinent humans with AUD (Rice et al., 2024). In this study, there were no baseline differences in connectivity nor differences in WCST performance between those with AUD and age-matched control subjects. However, within the AUD group, the strength of functional connectivity in the frontoparietal network positively correlated with all measures of performance on the WCST. Only in the AUD group did weak functional connectivity in these networks associate with poor attentional set-shifting. Other studies have documented baseline functional connectivity differences between participants with AUD and age-matched controls, including those in frontal region networks critical for flexible behavior (Dai et al., 2023; Suk et al., 2021; Desmond et al., 2020; Weiland et al., 2014). Human neuroimaging studies have further shown that individuals with alcohol dependence rely more heavily on habitual response strategies and simultaneously demonstrated underlying changes in PFC activation that may be associated with impaired flexible behavior (Sjoerds et al., 2013). Many other studies have coroborated these functional and structural changes in AUD populations using a variety of imaging techniques (Fritz et al., 2022; Bühler and Mann, 2011).

Recent preclinical studies, primarily in rodents, have begun to elucidate the neurophysiological changes underlying these alcohol-induced deficits in flexible behavior. Multiple studies in rats and mice have shown hyperexcitability in the frontal cortex and other regions following a final withdrawal period after successive cycles of CIE (Smith et al., 2024; Alberto et al., 2023; Avchalumov et al., 2021; Gioia and Woodward, 2021; Nimitvilai et al., 2015, 2018; Pleil et al., 2015; Kroener et al., 2012; Tu et al., 2007). *Ex vivo* recordings have repeatedly

shown increased excitability in pyramidal neurons of the PrL, IL, and lateral OFC. For example, CIE induced hyperexcitability in the OFC of mice is associated with increased AMPA/NMDA ratio (Nimitvilai et al., 2015). A similar study showed the opposite effect in PrL/IL pyramidal neurons, highlighting region specific changes. CIE resulted in increased NMDA/AMPA current ratio in PrL and IL pyramidal neurons immediately and up to 1-week following the last exposure to alcohol (Kroener et al., 2012). These CIE mice also displayed impaired strategy shifting ability, with greater number of trials to criterion and increased error rate compared to controls. This hyperexcitability of the frontal cortex following chronic alcohol exposure appears in part due to altered excitatory and inhibitory balance between glutamatergic and GABAergic signaling. Other work in rodents has shown concomitant decreases in the excitability of GABAergic interneurons across layers of the PrL cortex following cycles of voluntary intermittent ethanol consumption (Dao et al., 2020). Hypoexcitability of interneuron subpopulations in the PrL cortex has been shown to recover in females, but not males, following a prolonged withdrawal period, suggesting there may be sex differences in the way that alcohol impacts in PFC microcircuitry, i.e., connections between and within PFC subregions or cell populations (Thompson et al., 2023). Downregulation of inhibitory neuron activity in the PFC may drive disinhibition of excitatory neurons and the overall shift towards increased excitability of the PFC following chronic alcohol exposure (Fish and Joffe, 2022; Dao et al., 2020; Hughes et al., 2020; Joffe et al., 2020; Trantham-Davidson et al., 2014; Trantham-Davidson et al., 2017). In contrast to studies showing hyperexcitability across the PFC/OFC, other work has documented CIE-induced reductions in OFC excitability accompanied by insensitivity to reward devaluation (Renteria et al., 2018). This contrarion study included both male and female mice and highlights the need for consideration of sex differences in rodent models of AUD to facilitate meaningful translation to our understanding of AUD in humans (see Discussion).Collectively these findings show lasting disruptions in frontal cortex signaling and that alcohol-induced neuroadaptations in glutamatergic and/or GABAergic transmission in multiple subregions of the PFC likely contribute to flexible behavior impairments observed in AUD, but that the impact may vary across subregion or projection target. Additionally, there may be multiple avenues by which the balance between excitatory and inhibitory signaling is altered by alcohol, as evidenced by the heterogenous results of excitability across PFC subregions and cell types.

As noted above catecholamines in the PFC are essential substrates for cognitive flexibility. It has long been acknowledged that prolonged alcohol use can lead to lasting changes in DA transmission (Banerjee, 2014). Neurons in the mPFC and OFC, directly and indirectly target dopaminergic neurons in the ventral tegmental area (VTA) and the substantia nigra pars compacta (SNc) and receive dopaminergic inputs from both regions (Hui and Beier, 2022; Barker et al., 2014; Lodge, 2011; Frankle et al., 2006; Sesack and Carr, 2002; Thierry et al., 1990; Goldman-Rakic et al., 1992; Watabe-Uchida et al., 2012). These reciprocal connections with the dopaminergic system are crucial for cognitive flexibility and they are also impacted by alcohol exposure (Trantham-Davidson et al., 2017; Wickens et al., 2007; Nelson and Killcross, 2006). Male rats that underwent CIE vapor cycles before strategy shifting paradigm required more trials to criterion and made more errors (Trantham-Davidson et al., 2014). *Ex vivo* recordings from PrL neurons in these rats showed loss of D2/D4 receptor inhibition following D2-agonist exposure. As noted above prefrontal D2 and D4 signaling has been implicated in flexible behavior in both rodents and humans. These results indicate that alcohol-induced functional differences in dopamine-sensitive neurons in medial frontal cortex, particularly those expressing D2 and D4 receptors, contribute to behavioral inflexibility following chronic alcohol use.

In addition to DA, NE transmission is dysregulated by alcohol use and may contribute to the development of AUD. Adreoreceptor function, particularly α adrenoreceptors in PFC are critical for flexibilty during EDS as described above. Inflexibility in AUD may in part result from alcohol-induced changes in NE receptor expression in the PFC. A recent study showed decreased α1 and β-receptor mRNA levels in the mPFC of alcohol-dependent mice along with impaired memory and increased anxiety-like behavior (Athanason et al., 2023). These findings support the hypothesis that alcohol-induced changes in LC-NE release in the PFC may be integral to the loss of flexible cognitive control and transition habitual, inflexible behavior.

5. General discussion and future directions

The investigations into cognitive flexibility described above show that the detrimental effects of alcohol are consistent across species, from mice and rats, to non-human primates, to humans with AUD, providing robust evidence supporting a relationship between alcohol, flexible cognition and behavior. Not only are the behavioral impacts seen across species, but the neural regions implicated across species are, in many cases, broadly congruent (e.g., OFC in rodents, NHPs, and humans is particularly implicated in reversal and perturbed by alcohol). However, despite significant advances in our understanding of the neural basis of cognitive flexibility and the impacts of alcohol on flexibility, there is still more work to be done. The field will benefit from a clearer understanding of the relationship between frontal cortex subregions, local circuits, and specific elements of behavioral flexibility in the context of alcohol use. More research is also needed on the influence of alcohol on frontal cortex extended circuitry. Projections from frontal cortex to striatum, and their regulation by catecholamines like DA and NE, are key to supporting flexible behavior (Latagliata et al., 2023; Oberto et al., 2023; Barker et al., 2015; Grant et al., 2022; Taylor et al., 2023). These findings, and others implicating extended frontal cortical circuitry in flexibility, highlight the collaborative involvement of parallel circuits and neuromodulation underlying flexible behavior and the need to investigate downstream frontal cortical targets in the context of AUD-impaired flexibility.

Behavioral flexibility impairments are seen across species, task types, and alcohol-use paradigms (Dannenhoffer et al., 2021), but there are still a number of key questions that remain largely unanswered. One important question relates to what, exactly, is alcohol impacting to disrupt flexibility. As mentioned previously, the variety of tasks used to demonstrate flexible behavior rely on the confluence and integration of many supporting cognitive processes (e.g., attention, response inhibition, and working memory). This raises the issue of whether alcohol dimishes behavioral flexibility by disrupting one or more of these supporting cognitive processes or whether it diminishes behavioral flexibility by disrupting integration of those processes, i.e., as cognitive flexibility arises from its component processes. As mentioned previously, EDS and reversal learning may be particularly vulnerable to the effects of alcohol, whereas other measures of flexibility like IDS, may be less sensitive. This discrepancy suggests that certain cognitive processes, which vary across tasks, may be especially sensitive to the effects of alcohol. So for example, reversals and EDS shifting require high levels of response inhibition to address conflict between stimuli (for reversal) or categories (for EDS), and these increased response inhibition demands may be more sensitive to alcohol. Alternatively, these tasks may require the confluence of more cognitive processes, and alcohol may impair flexible behavior at the convergence of these multiple cognitive processes, rather than impairing any one process independently. Another possible explanation is that these specific behavioral tasks require particularly high levels of cognitive effort, independent of the specific constellation of cognitive processes integrated, and that cognitive effort is particularly sensitive to disruption by alcohol. In general, we have a clear consensus that chronic alcohol is associated with impairments in cognitive flexibility, and there is considerable evidence that alcohol also impairs many of the cognitive processes that are required for strong cognitive flexibility and resulting flexible behavior. A major direction that needs investigation is this issue of where alcohol is exerting its detrimental effects. Future work should leverage the nuanced

differences between task-types in conjunction with measuring underlying cognitive processes to determine the level at which alcohol impairs flexible behavior. By identifying these specific targets, we have a better opportunity to identify specific neural systems that are impacted by alcohol that are critical for cognitive flexibility, which can ultimately be used to guide treatment.

Sex differences in the impact of alcohol and cognitive flexibility: There is also a critical need for the purposeful inclusion of both sexes in the study of how alcohol may alter prefrontal cortical function to impair flexible behavior. This need is driven by a number of highly salient factors. With respect to alcohol use differences, there is a higher prevalence of AUD in men than in women, but this gender gap is rapidly closing, as the proportion of women drinking at high levels has begun to match men (White, 2020). It is well established that female rodents drink alcohol at higher levels than males (Petersen et al., 2024; Li et al., 2019; Sneddon et al., 2019; Jury et al., 2017; Hwa et al., 2011; Strong et al., 2010; Vetter-O'Hagen et al., 2009; Cailhol and Mormède, 2002; Cailhol and Mormède, 2001; Grahame et al., 1999; Juárez and de Tomasi, 1999; Almeida et al., 1998; Lancaster et al., 1996; Lancaster and Spiegel, 1992; Eriksson and Pikkarainen, 1968). Thus there are clear sex differences in alcohol consumption which, given the evidence above supporting an impact of alcohol on cognitive flexibility, strongly suggests that variable levels of intake, driven in part by sex differences, will differentially influence cognitive function. Superimposed on these differences in alcohol use, there are also sex differences in flexible behavior. Recent work in NHPs and mice have shown baseline sex differences in flexible behavior, whereby females had lower levels of cognitive flexibility compared to males (Rodberg and Vazey, 2022; Workman et al., 2019). These baseline differences may be in part due to sex differences, shown in humans and NHPs, in resting state brain networks that modulate cognitive flexibility (Nephew et al., 2020; Weis et al., 2020; LaClair et al., 2019; Filippi et al., 2013). Beyond independent differences in alcohol consumption and flexible behavior, there may also be sex differences in how alcohol impairs flexible behavior, potentially resulting from differential impact of alcohol on PFC circuitry and cognition more broadly (Flores-Bonilla and Richardson, 2020; Fama et al., 2020). In one example, after CIE, male and female rodents combined demonstrated glutamatergic hypoactivity in OFC and reduced goal-directed behavior, opposing findings in previous research that identified hyperactivity and disinhibition in PFC after CIE in male rodents (Renteria et al., 2018). A majority of the evidence from rodent studies mentioned in this review report behavioral and physiological changes in males only. One reason cited for this was that CIE paradigms result in more varied escalation of voluntary consumption, or sometimes fail to induce escalation in females (Gioia and Woodward, 2021; Zamudio et al., 2021; Jury et al., 2017). Whether differences in alcohol-related changes in PFC function translate meaningfully to the differential experience, diagnosis, and treatment of humans with AUD is not yet understood. However, it is clear that neglecting sex differences in alcohol consumption and cognitive flexibility may blur our overall understanding of the effects of alcohol on flexible behavior. There are clearly multiple independent and interacting ways that sex differences can have an effect on the intersection between alcohol and cognitive flexibility: from sex differences in baseline cognitive and functional connectivity, to differences in alcohol intake, to a potentially differential impact of alcohol on neural circuits underlying cognitive function. Future studies need to take these variables into consideration in order to develop a complete model of the relationship of alcohol and flexible behavior. Furthermore, it is important to consider the degree to which sex differences impact cognitive flexibility directly, or whether they are more influential at the level of one or more cognitive processes underlying flexibility (e.g., response inhibition, working memory). Understanding which cognitive elements are influenced by sex with more precision, and how this intersects with alcohol use, may be highly informative for an understanding of neural systems underlying this relationship. Under the assumption that disrupted cognitive flexibility is a key determinent of AUD, disentangling these intersecting factors may provide valuable insight into treatments, particular through the lens of sex specific outcomes.

The impact of alcohol on cognitive flexibility across the lifespan: In addition to sex differences, another influential factor is the impact of age. There are a number of elements that demonstrate that age is a key component of relationship between alcohol use and cognitive flexibility. Frontal cortical systems that are critical for cognitive flexibility develop slowly, maturing throughout adolescence and into early adulthood (Schwarze et al., 2024; Dannenhoffer et al., 2021; Luna, 2009, Spear, 2013 Klune et al., 2021; Selemon, 2013; Best and Miller, 2010). This is reflected in substantial changes in cognitive flexibility, and executive function in general, over the course of development (Parr et al., 2024; Diamond, 2013; Somerville et al., 2011; Best and Miller, 2010; Crone et al., 2006; Davidson et al., 2006; Sowell et al., 2001). Alcohol use often starts during this time of frontal maturation (Tetteh-Quarshie and Risher, 2023; Squeglia et al., 2009, 2014), and there are well documented impacts of adolescent alcohol use on the development of frontal cortex circuits underlying flexibility that is potentially more profound than the impact seen in adulthood (Obray et al., 2022; Sicher et al., 2022; Dannenhoffer et al., 2021; Robinson et al., 2021; Varlinskaya et al., 2020; Crews et al., 2019; Centanni et al., 2017; Gass et al., 2014; Carpenter-Hyland and Chandler, 2007; Trantham-Davidson et al., 2017). Taken together, it is clear that, over the course of development, there are significant changes in frontal cortex structure and function, changes in executive function including cognitive flexibility, changes in alcohol use patterns, and changes on the impact of alcohol on neural systems in the frontal cortex (and elsewhere), all of which come together to produce a developmental window of particular sensitivity to cognitive disruption (Tousley et al., 2023; Dannenhoffer et al., 2021; Marquardt and Brigman, 2016; Skorput et al., 2015; Crews et al., 2007). Critically, this developmental window is quite wide, encompassing prenatal alcohol exposure through adolescence.

In addition to the effect of alcohol on flexibility circuits during adolescence, monitoring flexibility during adolescence may be a valuable predictor of future alcohol use. As described above, a number of studies have shown that cognitive flexibility performance pre-alcohol is negatively correlated with alcohol consumption. These studies have mainly been done in adult non-human animals (Rodberg et al., 2022; De Falco et al., 2021; Shnitko et al., 2019a) in which the timing of cognitive testing and alcohol use can be tightly controlled. However, there are a number of studies investigating cognitive and behavioral traits as well as frontal cortex structure and function in adolescence or young adulthood and correlating variations in these factors with alcohol use and other substances of abuse (Meque et al., 2019; Newton-Howes et al., 2019; Henges and Marczinski, 2012; López-Caneda et al., 2014; Norman et al., 2011; Nigg et al., 2006; Ernst et al., 2006). A better understanding of this predictive relationship has clear value for the possibility of prevention of AUD. Early intervention programs are associated with better future outcomes and have the potential to curb deaths associated with late diagnosis of AUD (Ebrahimi et al., 2023; Lees et al., 2021; Dunn et al., 2017). Machine learning algorithms have been used to predict AUD with a high accuracy (>90%) and help identify clinical factors useful for early detection of AUD (e.g. blood pressure, age, BMI). Integrating measures such as cognitive flexibility could strengthen predictive models and improve the clinician's toolkit for early AUD diagnosis, prevention, and subsequent treatment.

In addition to more work investigating the alcohol-flexibility relationship in early life, there is also a need to a better understanding of the impact of alcohol use on cogntive flexibility in older adults. Although there are numerous reports of impaired cognitive flexibility in older adults using the WCST (Amelchenko et al., 2023; Ferguson et al., 2023; Wasylyshyn et al., 2011; Weiler et al., 2008; Meiran et al., 2001; Ashendorf et al., 2008, De Luca et al., 2003), the specific details of impairment is still a subject of scrutiny. In particular, the question that has been raised multiple times in this review regarding the cognitive

underpinnings of flexibility is relevant to this line of work, with some studies finding that the ability to shift attention or behavior in and of itself is not impaired, but that other cognitive functions such as working memory that underlie flexibility may specifically be disrupted (Ferguson et al., 2023; Maldonado et al., 2020; Hartman et al., 2001). That said, there are clear disruptions of executive function in aging that include flexibility across species (Attalla et al., 2024; Lacreuse et al., 2020; Yang et al., 2019; Hara et al., 2012). This is particularly salient when considering diseases associated with aging such as Alzheimer's and other dementias. A number of studies have shown deficits in flexibility in patients with Alzheimer's, but intriguingly, there may be a more salient effect of task difficulty whereby patients are able to exhibit flexibile behavior on easier, but not more difficult variants of tasks such as the WCST (Guarino et al., 2019). These age-related changes in flexibility and its cognitive and neural underpinnings raise the important question of how alcohol impacts these aging-related changes in cognitive function (Seemiller et al., 2024). There is clearly an impact of excessive alcohol use on cognitive functioning in aged individuals, with alcohol both exacerbating and advancing the onset of aging-related dementias such as Alzheimer's disease (Listabarth et al., 2022; Koch et al., 2019; Schwarzinger et al., 2018; Sabia et al., 2014; Kim et al., 2012). Less work has been done specifically on the impact of chronic alcohol on flexibility in aged animal models, though some work in rodent models has shown that chronic alcohol expopsure in adolescence exacerbates reversal deficits in older animals (Matthews et al., 2022, 2023). Given the significant interaction between cognitive decline in aging and the impact of alcohol on cognitive function in both healthy aging and neurodengenerative populations, there is a clear need for a better understanding of how a history of alcohol impacts cognitive flexibility in aging populations, and the degree to which flexibility and/or its cognitive subcomponents are impaired.

Treatments for cognitive flexibility deficits in AUD: Given the impact of excessive alcohol use on cognitive flexibility, treatments designed to promote executive function and cognitive flexibility might provide a valuable option as therapeutic strategies for AUD. Current pharmacotherapeutics for individuals with AUD with the explicit intention to reduce alcohol intake are heavily underprescribed (Leggio et al., 2020; Ray et al., 2019; Flanagan et al., 2018). One possible new direction for AUD pharmacotherapy is the use of validated cognitive enhancers, i.e., therapeutics that promote executive function. These drugs, developed for a variety of mental disorders, appear to have positive impacts on cognitive flexibility, as well as other executive functions underlying flexibility, such as response inhibition and working memory (Malík and Tlustoš, 2022; Ricci, 2020; Maslen et al., 2014). Several treatments for attention-deficit hyperactivity disorder (ADHD) such as the stimulant methylphenidate, or the non-stimulant guanfacine, can improve flexibility and have been promoted as broad cognitive enhancers (Zhang et al., 2023). Interestingly, ADHD has a strong comorbidity with AUD and an ADHD diagnosis is a risk factor for poor AUD outcomes (Luderer et al., 2021). Methylphenidate, guanfacine and related compounds improve executive function, including behavioral flexibility, and have also been shown to improve cognitive processes that support flexibility such as working memory, response inhibition, and attention, through modulation of dopamine and/or norepinephrine in the PFC (Paolo Busardò et al., 2016). Repurposing cognitive enhancers to promote cognitive flexibility in the context of AUD may have significant therapeutic potential, not only for the cognitive disruption seen in AUD, but potentially even for reducing alcohol use (Gordon and Dunn, 2021). Whether cognitive enhancers have potential to reduce excessive alcohol intake, either directly or indirectly is largely unexplored. Guanfacine has been shown preclinically to selectively reduce excessive drinking (Fredriksson et al., 2014). Additionally, compounds that inhibit phosphodiesterase 4 (PDE-4) and are FDA approved for the treatment of psoriasis act as non-canonical, non-stimulant cognitive enhancers, promoting working memory and cognitive flexibility (Rodefer et al., 2012). Intriguingly, PDE-4 inhibitors have recently been shown to reduce alcohol intake across several models of excessive alcohol use and in humans with AUD (Grigsby et al., 2023). These two lines of research support cognitive enhancers as an underexplored therapeutic avenue to potentially provide relief from AUD by reducing excessive alcohol use and promoting cognitive flexibility. One major question that remains to be addressed is whether the impact of cognitive enhancing medication on alcohol use is dependent on or independent of its effects on cognition. Given the strong relationship between alcohol and cognitive flexibility, one argument might be made for an interaction whereby treatments that produce cognitive enhancement ameliorative effects on neural circuits disrupted by chronic alcohol, resulting in greater cognitive control over use. However, the fact that guanfacine and PDE-4 reduce drinking in animal models, where cognitive control is not required or challenged, suggests that these drugs may directly impact drinking in addition to their effect on cognitive functioning. These different outcomes raise a fascinating question about the independence of neural systems underlying motivation and cognitive control. It is possible, for example, that the targets of guanfacine for example (presumably primarily neural circuits expressing NE receptors) play a dual role in cognitive control and alcohol motivation, and finding the right treatment may simultaneoulsy support amelioration of both aspects of AUD, similar to how hypocretin/orexin antagonists have been proposed to treat both sleep disorders and substance use disorders, which are interconnected (Gyawali and James, 2023; Fragale et al., 2021; Mehr et al., 2021). Ultimately, however, this important topic needs more investigation to establish mechanistic functions to identify connections an/d or independence of outcomes related to improved cognitive enhancement and reductions in alcohol use.

Conclusions and future directions: In this review we have documented the robust evidence that the neural basis of cognitive flexibility in the frontal cortex across species is impaired by alcohol use. Furthermore, evidence is accumulating that variability in cognitive flexibility before alcohol use can be used as a predictive tool to identify individuals at risk of excessive alcohol intake. Although the impact of alcohol is widespread across the brain, disrupted structure and function in the frontal cortex broadly is very likely responsible for many of the reported alcohol-associated impairments in cognitive flexibility. We have also highlighted some major issues to be explored in future studies both in humans and in animal models. First, it is essential to dissect the construct of flexibility into its cognitive subcomponents. This is necessary both for understaning the neural basis of flexibility as a whole, but more saliently for identifying the specific impacts of alcohol use on the cogntive and neural substrates of flexibility. Second, as noted above, there is a bidirectional interaction between flexibility and alcohol use whereby variability in flexibility predicts alcohol use and alcohol use impairs flexibility. This relationship needs further investigation not only to design additional prevention-related assays prior to problematic alcohol use, but also to provide a better understanding of the impact of alcohol of cognitive function. Subjects who exhibit variable levels of cognitive flexibility prior to alcohol use may be differentially impacted by prolonged alcohol, necessitating a consideration of both cognitive and drinking history in evaluating outcomes. Third, more work needs to be done to disentangle the impact of sex on the intersection of alcohol and flexibility, as there are clear differences in both domains and their integration, arguing for potentially sex-specific neural substrates that must be considered. Fourth, the impact of age and development are key elements that need to be included in studies of this relationship. Significant work has been done to understand the impact of alcohol during development on flexibility and other cognitive functions (Dannenhoffer et al., 2021). This needs to be expanded further to better understand the precise neural adaptations during development that are most sensitive to alcohol (potentially in a sex-specific manner) so as to identify which specific neural systems are being impacted and when. Furthermore, more work needs to be done on the other end of the lifespan. It is clear that chronic alcohol impair cognitive function in older adults, potentially contributing to Alzheimer's and other dementias. A

comprehensive assessment of the impact of alcohol throughout the lifespan will provide a more comprehensive understanding of mechanisms relating alcohol use and cognitive function. The relationship between alcohol and cognitive flexibility (as well as other cognitive functions) is complex and requires multidimensional integration. However, continuing to integrate cognitive flexibility in future investigations of AUD and models of AUD has significant potential to improve our understanding of the neural basis of AUD. Furthermore, understanding this relationship has significant promise to identify effective new therapeutics, potentially through the lens of cognitive enhancement or the treatment of disrupted flexibility-related neural substrates, expanding the range of AUD treatments.

CRediT authorship contribution statement

Kathryn E. Nippert: Writing – review & editing, Writing – original draft, Visualization, Investigation, Funding acquisition, Conceptualization. **Courtney P. Rowland:** Writing – review & editing, Visualization. **Elena M. Vazey:** Writing – review & editing, Supervision, Resources, Funding acquisition, Conceptualization. **David E. Moorman:** Writing – review & editing, Supervision, Resources, Funding acquisition, Conceptualization.

Declaration of competing interest

None.

Data availability

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