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Impact of anxiety on prefrontal cortex encoding of cognitive flexibility

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Abstract

Anxiety often is studied as a stand-alone construct in laboratory models. But in the context of coping with real-life anxiety, its negative impacts extend beyond aversive feelings and involve disruptions in ongoing goal-directed behaviors and cognitive functioning. Critical examples of cognitive constructs affected by anxiety are cognitive flexibility and decision making. In particular, anxiety impedes the ability to shift flexibly between strategies in response to changes in task demands, as well as the ability to maintain a strategy in the presence of distractors. The brain region most critically involved in behavioral flexibility is the prefrontal cortex (PFC), but little is known about how anxiety impacts PFC encoding of internal and external events that are critical for flexible behavior. Here we review animal and human neurophysiological and neuroimaging studies implicating PFC neural processing in anxiety-induced deficits in cognitive flexibility. We then suggest experimental and analytical approaches for future studies to gain a better mechanistic understanding of impaired cognitive inflexibility in anxiety and related disorders.

Keywords

Behavioral flexibility; Prefrontal cortex; Anxiety; Decision making; Stress

Introduction

Anxiety can be an adaptive reaction to stressful and unpredictable life events. But depending on its duration and intensity, anxiety produces cognitive impairments including deficits in cognitive flexibility and decision making. Clinical studies have long established that individuals with anxiety disorders are impaired at shifting from a previously effective strategy to a currently valid strategy, and increased distractibility by task-irrelevant stimuli (Shin et al., 2001, Eysenck et al., 2007, Ansari et al., 2008, Bishop, 2009, Lyche et al., 2010). Similarly, animal behavioral studies have reported that increased anxiety, at least when causes by acute or chronic stress, impairs performance in tasks that assess behavioral flexibility such as extra-dimensional set-shifting (Bondi et al., 2008, Butts et al., 2013, George et al., 2015).

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The brain region most critically involved in behavioral flexibility is the prefrontal cortex (PFC). Specifically, a comprehensive literature has demonstrated that the functional integrity of PFC is essential for cognitive flexibility in rodents (Ragozzino et al., 2003, Stefani et al., 2003, Rich and Shapiro, 2009, Stefani and Moghaddam, 2010), primates (Dias et al., 1996, White and Wise, 1999, Wallis et al., 2001, Nakahara et al., 2002) and humans (Konishi et al., 1998, Nakahara et al., 2002, Nagano-Saito et al., 2008).

Here we posit that deficits in cognitive flexibility caused by anxiety may be attributed to neuronal processing anomalies in the PFC. We begin by reviewing recent neurophysiology and neuroimaging studies describing the PFC representation of cognitive flexibility. Then we discuss the neural substrates of anxiety-related disruptions in PFC and suggest future approaches for a better mechanistic understanding of how anxiety impacts cognitive flexibility.

I. PFC involvement in cognitive flexibility

i. Behavioral and lesion studies

Behavioral paradigms for cognitive flexibility test the ability to guide goal-directed actions based on two or more discriminative rules, and to shift from one rule to another on the basis of the feedback (i.e. response outcome). Among many versions of these tasks, the Wisconsin Card Sorting Task (WCST; Fig. 1A) has been used most commonly for rule-based flexible control of behavior in humans (Nyhus and Barcelo, 2009). In the WCST, participants are required to match the test cards with a sample card according to one of multiple possible rules (Fig. 1A; e.g. color rule, shape rule), with changes in the matching rule occurring without subjects' knowledge, thus requiring flexible adjustment of the sorting strategy based on the feedback. Studies have shown that, when performing the WCST, individuals with ventromedial PFC lesion fail to shift to a response strategy that is more advantageous in the long run (Bechara et al., 1996, Bechara et al., 2000). This is consistent with earlier work demonstrating that human subjects with frontal lobe injury show marked deficits in shifting from one mode of solution to another on a sorting task (Milner, 1963).

Animal studies have successfully used different version of the WCST (Fig. 1B–C) to investigate neural substrates of flexible rule-based decision making in rodents and primates. In these tasks, behavior is guided by the currently valid rule among two or more other rules on distinct perceptual dimensions. Rule shifting can occur between different perceptual dimensions (extra-dimensional shifting) or within a dimension (intra-dimensional shifting or reversal). Lesion or pharmacological manipulations of the rat medial PFC (mPFC) result in markedly impaired performance in these and other set-shifting tasks that assess behavioral flexibility (Birrell and Brown, 2000, Ragozzino et al., 2003, Stefani et al., 2003, Bissonette et al., 2008, Darrah et al., 2008, Floresco et al., 2008, Stefani and Moghaddam, 2010) (Fig. 2). This is similar to performance deficits observed after dorsolateral PFC lesion in non-human primates (Dias et al., 1996, 1997) and in humans with PFC damage (Anderson et al., 1999).

ii. Human neuroimaging studies

Cognitive flexibility involves multiple dynamic processes that monitor ongoing actions and action-outcome relationships, and then adjusts future actions based on outcome. This process can be subdivided into various constructs such as representations of the rule, performance errors, the conflict among different response tendencies, and the risk/uncertainty contingent on the action. Human and primate studies using functional magnetic resonance imaging (fMRI) have shown that different but overlapping subregions of the PFC are activated in correlation with these constructs using multiple tasks (Carter et al., 1998, Kerns et al., 2004, O'Doherty, 2004, Clark et al., 2008) (Egner and Hirsch, 2005). For example, fMRI studies have shown transient activation of PFC during rule shifting, (Konishi et al., 1998, Nakahara et al., 2002) and retrieval and maintenance of abstract rules for decision making (Bunge et al., 2003).

iii. Animal electrophysiological studies: individual neuronal coding

While human neuroimaging data have informed us about the general involvement of PFC subregions in cognitive-flexibility tasks, invasive electrophysiological recordings in laboratory animals have described the dynamic nature of neuronal encoding during these tasks. For example, studies in primates have revealed that PFC single neuron firing rates during different task states (baseline, cue, delay and response periods) vary as a function of the current task rule (Hoshi et al., 1998, White and Wise, 1999, Asaad et al., 2000, Fuster et al., 2000).

Electrophysiological studies in rodents have demonstrated that PFC subregions – including prelimbic PFC (PL), infralimbic PFC (IL), and orbitofrontal cortex (OFC) – are differentially involved in extra-dimensional set-shifting tasks. In an elegant study, Rich and Shapiro recorded from single neurons in rats navigating a plus maze with two alternating response strategies in egocentric path and spatial location (Fig. 1C; e.g. "go left" or "go west") dimensions (Rich and Shapiro, 2009). Subpopulations of PL and IL neurons encoded the strategy shift, even when neuronal activity during the two strategies was compared between trials with seemingly identical navigation. The PL encoding of a strategy shift temporally preceded both the behavioral shift and IL encoding, suggesting that dorsal rather than ventral medial PFC neurons drive the behavioral shift. Neurons in the OFC have been suggested to play a dissociable role that is more specialized for signaling outcome expectancy (Schoenbaum et al., 2009). This view is supported by behavioral studies showing the role of OFC in representation of outcome value and expectancy (Dias et al., 1996, 1997, McAlonan and Brown, 2003, Rudebeck et al., 2006, Bissonette et al., 2008, Burke et al., 2009). Neurophysiological studies suggest that OFC neurons signal outcome expectancy as well as reversal in cue-outcome association (Roesch and Olson, 2004, Morrison and Salzman, 2009, Bissonette et al., 2015, Simon et al., 2015).

iv. Animal electrophysiological studies: neural population coding

Recent neurophysiological studies have delved into PFC population-level codes that may underlie rule-based flexible control of behavior. Investigating the coordinated activity of neural populations is particularly important when examining the neural basis of rule-based behavior because such tasks require encoding of multiple task features to which individual

PFC neurons are dynamically tuned. Dynamic neuronal tuning properties have been illustrated in studies that investigated the population-level activity of PFC and other high-order cortical structures during flexible decision making (Karlsson et al., 2012, Mante et al., 2013, Rigotti et al., 2013, Ma et al., 2014, Raposo et al., 2014). The majority of PFC neurons have mixed selectivity: i.e., their responses are linearly or nonlinearly correlated with diverse combinations of the task-relevant features (such as the sensory stimuli, task rules or motor responses) rather than being purely selective for individual features (Fig. 3). Mixed selectivity is suggested to be the key computational property of PFC neurons that leverages the dimensionality of population-activity space related to the cognitive task performance (Rigotti et al., 2013). For example, Fusi and colleagues have recently demonstrated the advantages of PFC neuronal mixed selectivity by showing that the degree of dimensionality of the neuronal population activity space was correlated with actual choice behavior (Rigotti et al., 2010, Rigotti et al., 2013), suggesting that the high dimensionality of PFC population encoding is causally associated with decision-making capability.

Recent studies provide convincing evidence that some unique properties of PFC neuronal encoding may be exposed only when the ensemble-level activity is examined in a high-dimensional space. Seamans and colleagues experimentally addressed this by comparing the individual- and population-level neuronal discriminability of simultaneously recorded neurons in the anterior cingulate region of the PFC (ACC), and in the dorsal striatum (DS) (Ma et al., 2014). The individual neuronal discriminability of differential action sequences did not differ between the two regions, whereas the ACC outperformed the DS as an ensemble in all ensemble-based discriminability measures. This suggests that coordinated activity of PFC neurons leads to more information-rich ensembles as compared to the striatum.

Other studies have used trial-by-trial population trajectories to investigate the dynamic properties of PFC-neuronal representations of flexible decision making. Stokes et al. (2013), for example, analyzed PFC neural populations in monkeys performing a cue-target matching task with three possible cue-target pairs, requiring the choice of a target stimulus given the cue in the presence of distractors. By tracing population states in the high-dimensional space constructed by all neurons in the network, the authors found that the PFC population was dynamically tuned to represent momentary task demands – i.e., cue discrimination during the cue period and behavioral choice during the choice period – in a task-context dependent manner. This suggests that complex rule-based choices can be mapped onto high-dimensional PFC neural states that are tuned to reflect the current task requirement (Stokes et al., 2013). On a larger timescale, the PFC rule-learning process has been depicted as a rapid shift in the neuronal ensemble state, suggesting that the task-rule shift is represented by a sustained alteration in PFC population activity that occurs abruptly – an “a-ha” moment (Durstewitz et al., 2010).

v. Animal electrophysiological studies: local field potentials

Synchronization via coherent gamma oscillations (γ; 30~120 Hz) may subserve the formation and communication of functional ensembles in the PFC and other cortical brain regions (Fries, 2005, Sirota et al., 2008, Cardin et al., 2009, Sohal et al., 2009, Uhlhaas and

Singer, 2010, Buschman et al., 2012, Fries, 2015). During task-related processes, neuronal ensembles tend to engage in rhythmic synchronization that can temporally coordinate neuronal activity by creating a sequence of excitatory and inhibitory cycles (Fig. 4). Phase-locking of relevant ensembles into coherent excitation-inhibition sequences can facilitate communication between them while blocking 'noise' from incoherent ensembles. This may provide a mechanism for selecting ensembles that encode the currently relevant features of the task while deselecting the irrelevant ensembles.

Consistent with this model, distinctly synchronous PFC ensembles have been shown to be associated with different task rules suggesting that a rule-dependent emergence of synchronous ensembles may be a neural substrate of the cognitive flexibility (Buschman et al., 2012). An additional causal relationship has been suggested between task-relevant gamma oscillations and cognitive flexibility by Sohal and colleagues (Cho et al., 2015). The authors found that disruption of baseline and task-evoked gamma oscillations in a mouse model of deficient development of fast-spiking interneurons (FSINs) led to cognitive inflexibility. By optogenetically enhancing the activity of FSINs in these mice, the task-related gamma oscillations, as well as the rule-shifting behavior, could be rescued, suggesting a role of FSIN-mediated PFC gamma oscillations in cognitive flexibility. Collectively, these studies suggest that cognitive inflexibility may be associated with disruptions in baseline and/or task-evoked oscillations in the PFC.

II. Impact of anxiety on cognitive flexibility

i. Human studies

Human behavioral and neuroimaging studies have investigated the effects of anxiety on decision-making in healthy individuals and in patients with clinical anxiety (for a review, see Hartley and Phelps, 2012). For example, Bishop et al. have shown that PFC recruitment during the attentional control over the conflict elicited by distractors is reduced in individuals with high trait anxiety in correlation with impaired cognitive task performance (Bishop et al., 2004, Bishop, 2009). In addition, a series of human neuroimaging studies has used fear conditioning and extinction paradigms to model the perseverative conditioned fear response, revealing PFC involvement (Shin et al., 2001, Phelps et al., 2004, Pitman et al., 2012). In these studies, a neutral conditioned stimulus (CS) is paired with an aversive outcome during the conditioning session. This is then followed by an extinction session during which the CS is repeatedly presented without the aversive outcome. fMRI results show that successful extinction is correlated with increased activation of the ventromedial PFC (vmPFC) but reduced activation of the amygdala (for a review, see Pitman et al., 2012). This bidirectional modulation of the vmPFC-amygdala circuitry is impaired in PTSD patients with perseverative conditioned fear responses even after extinction (Phelps et al., 2004, Rauch et al., 2006, Pitman et al., 2012). Related neuroimaging studies have reported prefrontal dysregulation of subcortical neural activity in the population genetically vulnerable to developing anxiety disorders (Hariri et al., 2002, Hariri et al., 2003, Bertolino et al., 2005, Hariri et al., 2005, Pezawas et al., 2005, Meyer-Lindenberg et al., 2006).

Collectively, human studies suggest that anxiety biases information processing during flexible behavior. This can be manifested in at least two ways. First, anxiety biases attention

to threat-related stimuli. This is measured as faster response time detecting threat-related stimuli and as increased distractibility by these stimuli at the expense of attention to task-relevant stimuli (Mogg and Bradley, 1998, Bar-Haim et al., 2007, Cisler and Koster, 2010). Likewise, anxiety also results in heightened distractibility by non-threatening stimuli, as suggested by poor concentration and reduced multi-tasking capability in anxious individuals (Mineka et al., 1998, Eysenck et al., 2007). Second, anxious individuals favor negative interpretations of neutral or ambiguous stimuli. When presented with emotionally ambiguous stimuli, such as facial expressions or face-voice pairings, anxious individuals disproportionately interpret these stimuli as possessing negative valence (Richards et al., 2002, Koizumi et al., 2011). Anxiety also is associated with increased expectation of negative outcomes in decision making involving risk or ambiguity in the action-outcome relationship. On a variety of choice tasks, anxious individuals show heightened risk aversion and favor safe alternatives (Raghunathan and Pham, 1999, Anderson et al., 2012, Hartley and Phelps, 2012, Maner et al., 2012).

These anxiety-related behavioral biases most likely involve PFC-mediated cognitive processing. It is interesting that there is an association between disrupted PFC neural activity and anxiety-related behavioral phenotypes such as impulsivity and risk-averting in healthy individuals, although the association needs to be further examined in patients with clinical anxiety (Knoch et al., 2006, Li et al., 2009, Perugi et al., 2011, Giorgetta et al., 2012). In addition, studies of blood oxygenation level dependent (BOLD) signals during risk-based decision-making tasks, which may be associated with increased anxiety, show reduced activity in PFC subregions in contrast to increased activity in subcortical regions such as the amygdala and the ventral striatum (Knoch et al., 2006, Fecteau et al., 2007, Clark et al., 2008, Christopoulos et al., 2009). Along the same lines, economic decision-making studies also show that BOLD activity in the dorsolateral PFC is enhanced when the subject chooses the larger but more delayed reward during intertemporal choice, whereas an impulsive choice was associated with decreased BOLD signal (McClure et al., 2004, Kim and Lee, 2011).

An important area for future research is to elucidate how emotional and motivational factors interact with cognitive domains in anxiety. For example, is perseveration in fear extinction related to cognitive inflexibility and deficits in task strategy shifting caused by anxiety? More broadly, how are different anxiety-related cognitive and affective phenotypes related to each other? Do they share common prefrontal neural mechanisms? One way to answer these questions is to examine large populations with a spectrum of anxiety-related symptoms in the same behavioral framework, ideally with a neural activity measure. A recent study implemented this approach by sorting out the relationship between psychiatric symptoms and flexible control of goal-directed behavior. Gillan et al. (2016) had nearly 2,000 participants complete an online task of goal-directed behavior with questionnaires measuring symptoms of various mental health conditions. The authors found clustering of symptoms, and uncovered a specific association of the compulsivity cluster with difficulty in flexible control of goal-directed behavior. Using a similar approach, future studies may further unravel clustering of anxiety phenotypes in correlation with characteristic cognitive behavioral symptoms and patterns of PFC neural activity changes.

ii. Animal studies: current state of the field

Numerous studies have focused on PFC individual neuronal representations of fear and anxiety (Morgan and LeDoux, 1995, Baeg et al., 2001, Milad and Quirk, 2002, Davis, 2006, Quirk and Beer, 2006, Burgos-Robles et al., 2009). Findings from these studies have been corroborated by recent research that has further dissected the functional neuroanatomy of fear using state-of-the-art techniques of circuit manipulation, such as optogenetics (for a review, see Calhoon and Tye, 2015). These studies have confirmed that highly interlinked neural structures comprising the amygdala, the bed nucleus of the stria terminalis, the ventral hippocampus and the mPFC represent information about threats, defensive behavior, and constructs relevant to anxiety (Herry et al., 2008, Adhikari et al., 2010, Lesting et al., 2011, Felix-Ortiz et al., 2013, Kim et al., 2013, Duvarci and Pare, 2014, Likhtik et al., 2014, Namburi et al., 2015). In PFC, subpopulations of neurons respond preferentially to a conditioned stimulus associated with an aversive event, tracking alterations in the CS-US association – e.g. extinction (Baeg et al., 2001, Milad and Quirk, 2002, Burgos-Robles et al., 2009, Courtin et al., 2014). Moreover, the PFC interacts with other regions such as the amygdala and the ventral and dorsal hippocampus via pair-wise neuronal correlations and synchrony – particularly theta oscillations – to regulate conditioned fear responses and explorative behavior in anxiogenic environments such as the open field test and the elevated plus maze test (Adhikari et al., 2010, Lesting et al., 2011, Livneh and Paz, 2012, Kumar et al., 2014, Likhtik et al., 2014, Karalis et al., 2016).

While these studies have provided key information about how the PFC represents fear or anxiety *per se*, little is known about how anxiety affects ongoing PFC processing of cognitively relevant behavior. This includes a near-total lack of neurophysiological studies that have investigated the impact of anxiety on PFC neural correlates of cognitive flexibility. To this end, an important prerequisite for these studies is an appropriate experimental model of anxiety that mimics the physiological and behavioral phenotypes of anxiety while allowing animals to perform cognitive tasks. Fear conditioning paradigms are limited in two ways for this purpose: first, animals' fearful responses (freezing and/or avoidance) disrupt task performance. Second, a fearful state elicited by an imminent and concrete threat might be dissimilar to an anxious state, which is a temporally diffuse state often not associated with a specific event, and which may even be internally generated (Sylvers et al., 2011). Behavioral tests of anxiety based on explorative behavior – e.g. the open-field test and the elevated plus maze test – also are limited due to the lack of cognitive behavioral constructs in these assays.

iii. Animal studies: challenges for future research

In order to investigate the impact of anxiety on cognitive processing, experimental models that produce a sustained state of anxiety while allowing for cognitive task performance need to be designed and implemented. Only by using such models can we unravel anxiety-induced changes in cognitive flexibility at individual neuronal and neural population levels in the PFC on multiple timescales. Anxiety is a temporally diffuse emotional/motivational state and, therefore, it may be especially critical to assess the longer timescale, as measured by sustained changes in background firing rates and/or LFP oscillations. These types of

measures also have translational value because they are relevant to human imaging (fMRI, MEG and PET) data.

To this end, genetic mouse lines with anxiety-like behavioral phenotypes can be used to study anxiety-related alterations in PFC neuronal encoding of cognitive constructs (Shen et al., 2010, Soumier and Sibille, 2014, Lin and Sibille, 2015). Furthermore, the recent development of pharmacogenetic techniques such as DREADD provides conditional and cell-type specific loss of function related to anxiety (Soumier and Sibille, 2014). This may allow future studies to test for specific associations between anxiety-related cognitive deficits and neuronal activity changes. Another practical approach is to use anxiogenic compounds to produce a sustained state of anxiety during task performance. An example is the drug FG-7142, an inverse agonist of allosteric benzodiazepine binding sites in $GABA_A$ receptors, which produces anxiety in humans (Dorow, 1987) and laboratory animals (Pellow and File, 1986, Cole et al., 1995, Evans and Lowry, 2007), with cognitive deficits reported in rats and monkeys (Murphy et al., 1996a, Murphy et al., 1996b). In addition to behavioral indices of anxiety, it produces biochemical and neurochemical responses such as glucocorticoid release (Pellow and File, 1985) and increased release of dopamine (Moghaddam et al., 1990, Bradberry et al., 1991, Murphy et al., 1996a) and other catecholamines (Dazzi et al., 2002, Evans et al., 2006) specifically in the PFC. We have recently used this model to study the impact of anxiety on the PFC neuronal correlates of cognitive flexibility (Park et al., 2016). Systemic injection of FG-7142 produced anxiety-related alterations in set-shifting task performance in association with deficits in the prefrontal neuronal representation of the task rule.

Electrophysiological recordings using the anxiogenic FG-7142 model of anxiety showed suppressed spontaneously active PFC neurons (Park et al., 2016). This sustained response is consistent with stress changing firing rates of subpopulations of PFC neurons for 30–120 minutes after the stress exposure (Jackson and Moghaddam, 2006). In addition, this sustained change in PFC neural activity may be correlated with anxiety-related neurochemical changes, as exposure to the anxiogenic and/or stress protocols induces sustained increase of dopamine and norepinephrine in the PFC (Bradberry et al., 1991, Finlay et al., 1995, Butts et al., 2011, Arnsten, 2015). The relevance of PFC dopamine activation in anxiety was recently confirmed in studies using cell-type and projection-specific methods (Lammel et al., 2012, Gunaydin et al., 2014). Taken together, these findings so far suggest that anxiety engenders an aberrant state of spontaneous PFC neuronal activity on an extended timescale. A key question for future studies is how these changes in background PFC neuronal activity caused by anxiety influences PFC encoding of task-relevant events that may contribute to inflexible cognitive control of behavior.

Future studies addressing the impact of anxiety on PFC encoding of cognitive flexibility may need to consider the wide-spread mixed selectivity in PFC neurons. Similar to “normal” conditions (Rigotti et al., 2013), we posit that, during anxiety, the unique strengths of PFC ensembles in cognitive processing can be better understood by considering the neural population activity in a high-dimensional space on a trial-by-trial basis. This approach is especially useful for analysis of neural data during cognitive flexibility tasks because these experiments involve trial-to-trial changes in task variables. For example, these analyses can

allow statistical comparisons of how the population neural states or trajectories differ between trials of any task covariate combinations – e.g. correct trials under different rules, or correct vs. incorrect trials under the same rule.

Recent advances in dimensionality reduction methods (Cunningham and Yu, 2014) provide a useful tool to find the shared latent structure of neural population activity. Based on the shared covariance structure, the reduced high-dimensional space can be defined to extract trial-by-trial neural population trajectories. A growing number of studies on the neural basis of decision-making have fruitfully used a dimensionality reduction approach for neural population analysis (Briggman et al., 2005, Durstewitz et al., 2010, Harvey et al., 2012, Mante et al., 2013, Stokes et al., 2013). Future studies can use these analyses to answer important questions about the impact of anxiety on cognitive flexibility (Fig. 5). These include: 1) How does anxiety shift PFC population neuronal activity states? 2) How does anxiety affect the individual neuronal mixed selectivity and the high dimensionality that is characteristic of the prefrontal neural population? 3) How are the trial-to-trial population trajectories during different task events altered by anxiety? And finally 4) How are these anxiety-related changes in PFC neural population activity associated with behavioral changes during tasks that involve cognitive flexibility?

Concluding remarks

A debilitating aspect of anxiety is its impact on cognitive flexibility and decision making. The nature of these disrupted cognitive processes is consistent with aberrant PFC function in anxiety. Extensive research has so far advanced our understanding of how PFC neurons represent fear and potential future threats, and how they interact with upstream and downstream neural structures to generate fear- and anxiety-related responses. But the impact of anxiety on PFC ensembles, in correlation with cognitive deficits, is largely unknown. Newer experimental and analytical approaches suggested here may lead to a better understanding of how anxiety disrupts flexible cognitive control of behavior.

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Highlights

- Cognitive inflexibility is a hallmark deficit associated with anxiety.
- Growing evidence links cognitive inflexibility in anxiety to PFC dysfunction.
- Novel approaches are proposed to study PFC dysfunction in anxiety.

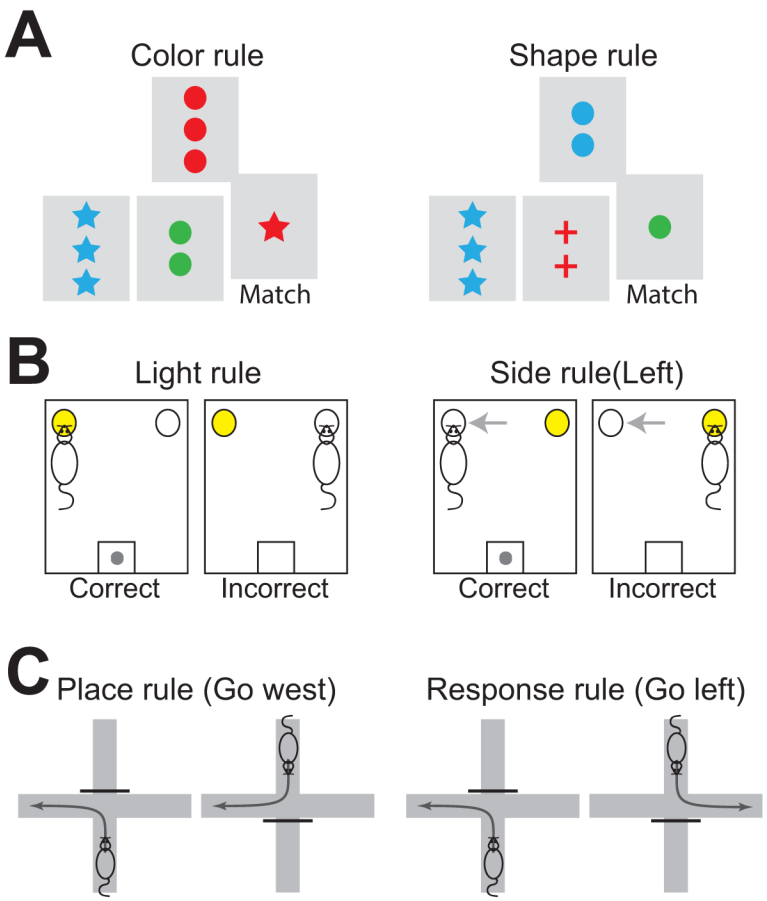

Figure 1.

Tasks measuring cognitive flexibility in humans and rodents. (A) Example trials in the WCST. The top card is the test card. The bottom three cards are the reference cards. During the matching period, the subject selects the reference card that matches the test card based on the currently valid sorting rule, e.g. matching based on the color or shape. Feedback is provided after each selection. An extra-dimensional set-shift occurs to another rule in a distinct perceptual dimension unbeknownst to the subject, who should respond to the shift according to task feedback. (B) A rodent version of a set-shifting task in the operant chamber. In this task, rats learn to guide their instrumental behavior based on two rules in distinct perceptual dimensions, and shift between them based on the task feedback (reward delivery or omission). In the “light rule,” a nose poke (or a lever press) to the illuminated port is correct, whereas in the “side rule,” a nose poke to the valid location (e.g. left port) is a correct response regardless of the illumination. The gray arrows indicate the current valid side (invisible to rats). (C) A rodent set-shifting task in the plus maze. In the place rule, rats are required to enter one goal arm (east or west) from both starting arms (north and south). In the response rule, one body turn response (right or left) should be made from either starting arm. Gray arrows indicate correct trajectories in either rule.

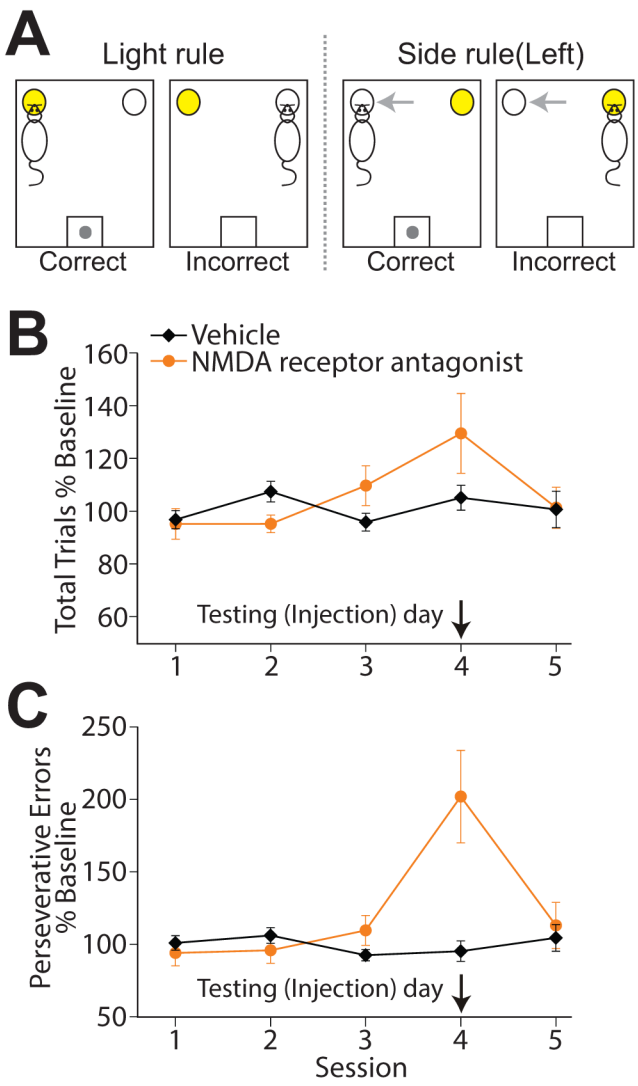

Figure 2.

Set-shifting task performance is impaired by intracranial microinjection of the NMDA receptor antagonist MK801 in mPFC. (A) The extra-dimensional set-shifting task used for this experiment. In each session, rats performed the operant task based on two alternating rules in distinct perceptual dimensions. Three extra-dimensional rule-shifts (i.e. total four sets with two light- and two side-rule sets interleaved in a pseudo-randomized order) had to be made to complete a session. (B) Rats underwent a total of five sessions with injections made only on the 4th session, indicated with an arrow below. MK801 significantly increased the number of total trials to complete the task, indicating impaired task performance. (C) The most pronounced drug effect was increased number of perseverative errors, scored when rats produced an error by making a choice based on the previously effective rule. This result indicates that the blockade of glutamatergic neurotransmission mediated by NMDA receptors in PFC leads to cognitive inflexibility. Figs. 2B-C were adapted from Darrah et al. (2008).

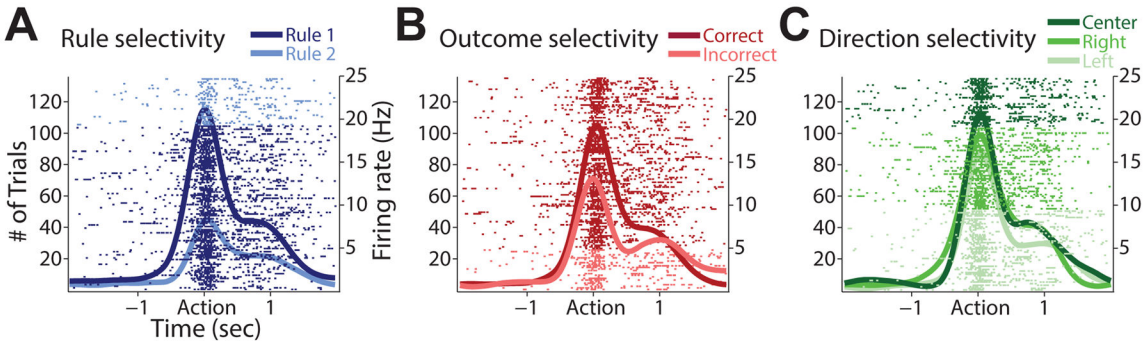

Figure 3.

Example of a PFC neuron with mixed selectivity for multiple task variables, recorded from a rat performing the extra-dimensional set-shifting task described in Fig. 1B & 2A. This neuron encoded three different task variable; the task rule (A), the response outcome (B), and the response direction (C), in overlapping or non-overlapping time bins around the time of the action, according to a multiple linear regression analysis (unpublished data).

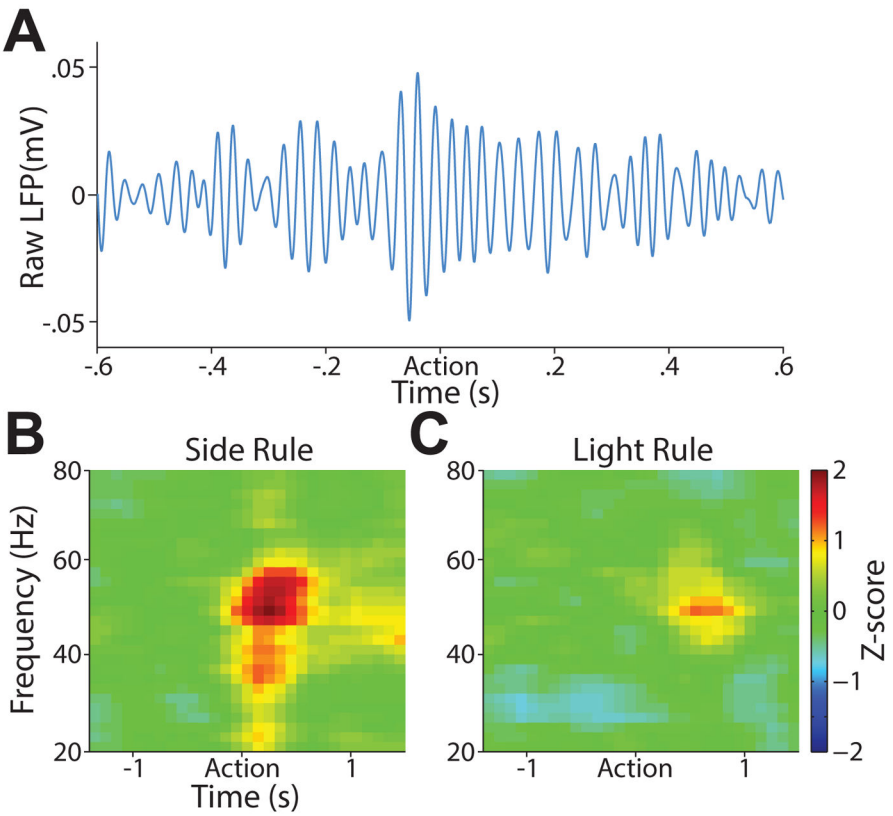

Figure 4.

A rule-based behavior is accompanied by an increase in prefrontal gamma oscillations specifically at the time of the action. (A) An example mPFC local field potential trace recorded from rats performing the extra-dimensional set-shifting task described in Figs. 1B & 2A. This example trace represents the enhanced gamma oscillatory power in the 30 to 60 Hz band, specifically at the peri-action window. (B–C) The z-score normalized power spectral densities show that the peri-action gamma oscillations were discriminative of the task rule, as a much more pronounced increase in gamma power was observed in the side-rule than light-rule trials.

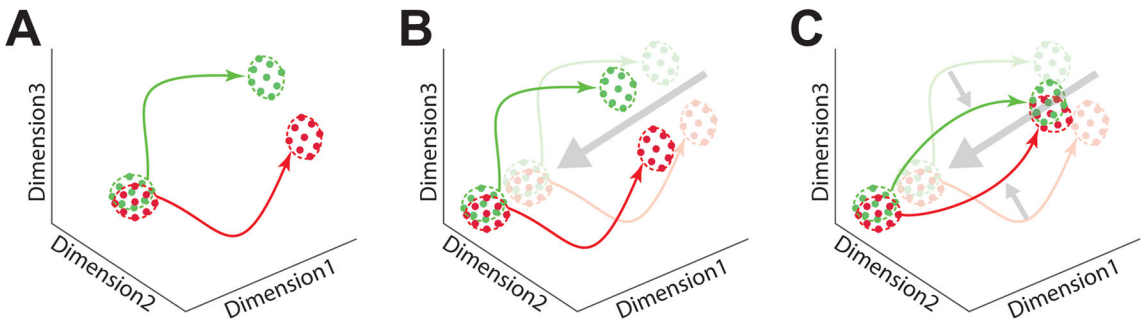

Figure 5.

Illustrations of trial-by-trial neural population activity represented in a reduced high dimensional space (hypothetical data), and research questions that can be more effectively investigated using this approach. (A) Trial-by-trial population neural trajectories can be extracted by dimensionality reduction methods. This approach enables visualization and comparisons across trial-to-trial neural trajectories, differentiated by numerous possible combinations of multiple task covariates of a complex cognitive task. For instance, a trajectory from one task rule (green) can be differentiated from that of another rule (red) in a cognitive decision-making task. Each line depicts a time-evolving neural population trajectory, and each dot represents the population state at the beginning and end of each trial. (B) Anxiety may induce sustained changes in ongoing PFC population activity (depicted with a gray arrow) that may lead to behavioral changes without affecting trial-by-trial neural trajectories during task events. (C) Alternatively, anxiety may also implicate changes in trial-by-trial neural trajectories (depicted with small gray arrows) in association with behavioral deficits, on top of the sustained change in the baseline population activity (depicted with a large gray arrow).