# The Neuroscience of Cognitive-Motivational Styles: Sign- and Goal-Trackers as Animal Models

**Martin Sarter** and
Department of Psychology and Neuroscience Program, University of Michigan

**Kyra B. Phillips**
Department of Psychology and Neuroscience Program, University of Michigan

## Abstract

Cognitive-motivational styles describe predominant patterns of processing or biases that broadly influence human cognition and performance. Here we focus on the impact of cognitive-motivational styles on the response to cues predicting the availability of food or addictive drugs. An individual may preferably conduct an analysis of the motivational significance of reward cues, with the result that such cues per se are perceived as rewarding and worth approaching and working for. Alternatively, a propensity for a "cold" analysis of the behavioral utility of a reward cue may yield search behavior for food or drugs but not involve cue approach. Animal models for studying the neuronal mechanisms mediating such styles have originated from research concerning behavioral indices that predict differential vulnerability to addiction-like behaviors. Rats classified as sign- or goal-trackers (STs, GTs) were found to have opposed attentional biases (bottom-up or cue-driven attention vs. top-down or goal-driven attentional control) that are mediated primarily via relatively unresponsive versus elevated levels of cholinergic neuromodulation in the cortex. The capacity for cholinergic neuromodulation in STs is limited by a neuronal choline transporter (CHT) that fails to support increases in cholinergic activity. Moreover, in contrast to STs, the frontal dopamine system in GTs does not respond to the presence of drug cues and, thus, biases against cue-oriented behavior. The opponent cognitive-motivational styles that are indexed by sign- and goal-tracking bestow different cognitive–behavioral vulnerabilities that may contribute to the manifestation of a wide range of neuropsychiatric disorders.

The search for vulnerability factors for neuropsychiatric disorders has increasingly focused on the impact of broadly defined, cognitive-motivational risk factors, or endophenotypes, such as a propensity for impulsive responding (Braver et al., 2014; Dickinson, Goldberg, Gold, Elvevåg, & Weinberger, 2011; Gur et al., 2007; Robbins, Gillan, Smith, de Wit, & Ersche, 2012). Endophenotypes are more conducive to the analysis of genetic risks than is

Correspondence concerning this article should be addressed to Martin Sarter, Department of Psychology and Neuroscience Program, University of Michigan, 530 Church Street, 4030 East Hall, Ann Arbor, MI 48109. msarter@umich.edu.

the case with diagnostic categories (Gur et al., 2007) and, in contrast to diagnostic categories such as psychosis, they can be reproduced in animals (Voon & Dalley, 2015).

The concept of cognitive-motivational styles is related to that of traits and endophenotypes but concerns the more comprehensive psychological impact of fundamental cognitive-perceptual preferences and biases (Sternberg & Zhang, 2001). Traits typically are revealed in relatively specialized contexts such as in tasks designed to specifically determine the presence or intensity of a trait. Cognitive-motivational styles contribute to the expression of traits, but they also influence cognition and performance in a more generalized fashion, impacting a range of psychological categories and task performances. Examples of such styles in humans include a persistently positively or negatively biased self-appraisal (Blatt, Quinlan, Chevron, McDonald, & Zuroff, 1982; Gormly, 1973; Kirby, Moore, & Schofield, 1988; White & Shah, 2011) or—the subject of this review—the cognitive-motivational biases that govern the response to reward-associated stimuli (Romens, Maccoon, Abramson, & Pollak, 2011). The conceptual breadth of cognitive-motivational styles led to earlier debates about their heuristic usefulness but more recent cognitive neuroscience research has demonstrated brain activity patterns associated with specific styles that can be used to predict the behavior of the individual (Kraemer, Rosenberg, & Thompson-Schill, 2009; Miller, Donovan, Bennett, Aminoff, & Mayer, 2012). Furthermore, cognitive-motivational styles have been shown to contribute to the risks for, and severity of, psychiatric and neurological disorders (Boosman, Visser-Meily, Post, Lindeman, & Van Heugten, 2012; Kleiman & Riskind, 2012; Stange et al., 2015).

Basic neuroscience research on cognitive-motivational styles has been lacking animal models that reproduce such broadly defined information processing biases. This review describes research on selected populations of rats which, at the extreme ends of the construct, exhibit a bias for bottom-up or cue-driven attention (sign-trackers, STs), or relatively high levels of top-down, goal-driven attentional control (goal-trackers, GTs). Below we will review the available evidence on the role of major neuromodulator systems in mediating these opponent cognitive styles (for reviews focusing primarily on the relevance of these rats in addiction research see Flagel, Akil, & Robinson, 2009; Flagel & Robinson, 2017; Robinson, Yager, Cogan, & Saunders, 2014).

## STs and GTs

STs and GTs are selected from outbred rat populations using a Pavlovian Conditioned Approach (PCA) test (Meyer et al., 2012; Tomie, Lincks, Nadarajah, Pohorecky, & Yu, 2012). Briefly, rats undergo five sessions of Pavlovian conditioning during which a lever (conditioned stimulus, CS) is inserted into a conditioning chamber for 8 s and upon retraction a banana-flavored pellet is delivered into an adjacent food cup. All rats reliably retrieve the pellet from the food cup. However, across these sessions, the animals' behavior in the presence of the lever evolves to form three distinct groups: (a) rats that approach and interact with the lever (STs), (b) rats that approach only the food cup (GTs), and (c) intermediates (INs) that exhibit no preference for either location, but often vacillate between the two (for reviews of the procedure and the reliability of this phentopye across rat strains

and vendors see Fitzpatrick et al., 2013; Flagel, Watson, Robinson, & Akil, 2007; Meyer et al., 2012; Robinson & Flagel, 2009; Robinson et al., 2014).

Consistent with the demonstration that ST-behavior is mediated via ventral striatal phasic dopamine (DA) responses (Flagel et al., 2011; Saunders & Robinson, 2012), sign-tracking has been interpreted as reflecting the attribution of incentive salience to the CS. Indeed, STs not only approach and interact with such cues but they will work to access such cues in the absence of food reward. That is, the lever-cue has enhanced conditioned reinforcing properties for STs relative to GTs. In addition, such cues instigate and energize instrumental action in STs (reviewed in Robinson et al., 2014). Because STs show a greater propensity for developing addiction-like behaviors and relapse, the psychological trait that is indexed by sign-tracking has been considered a drug and food addiction endophenotype in rodents (Flagel et al., 2007; Saunders & Robinson, 2010, 2011; Tunstall & Kearns, 2015) as well as humans (Versace, Kypriotakis, Basen-Engquist, & Schembre, 2015).

## Attention-Associated Levels of Cholinergic Neuromodulation in STs and GTs

Impaired or biased processing of drug-associated cues constitute a psychological trait in people with addiction disorders (Broos, Diergaarde, Schoffelmeer, Pattij, & De Vries, 2012; Ersche et al., 2011; Field & Cox, 2008; Pitchers, Wood, Skrzynski, Robinson, & Sarter, 2017; Tomasi et al., 2007). Given that STs have been demonstrated to be vulnerable for addiction-like behaviors (see also Kawa, Bentzley, & Robinson, 2016), our initial experiments on the attentional capacities of STs and GTs were guided by the hypothesis that STs exhibit a relatively weak degree of top-down attentional control when compared with GTs, and this relative "deficit" would render them to be inordinately attracted to drug-associated cues.

### Definition of Poor Attentional Control

The selection of stimuli to control behavior normally is strongly influenced by longer-term strategies and goals that bias our attention toward certain sources and types of stimuli and maintain relevant task-related instructions in working memory (Buschman & Miller, 2007; Connor, Egeth, & Yantis, 2004; Sarter, Gehring, & Kozak, 2006; Sarter, Givens, & Bruno, 2001). Poor attentional control is characterized by relatively unstable task performance, poor task compliance, and a limited capacity for restoring performance after exposure to distractors or other detrimental manipulations (Berry et al., 2014; Demeter & Woldorff, 2016; St. Peters, Demeter, Lustig, Bruno, & Sarter, 2011). Furthermore, a relatively automatic attraction to, or capture of attention by, salient environmental stimuli characterizes poor attentional control. In our research, the Sustained Attention Task (SAT) has been designed to tax attentional control mechanisms in rodents and humans (Demeter, Hernandez-Garcia, Sarter, & Lustig, 2011; Demeter, Sarter, & Lustig, 2008; St. Peters, Demeter, et al., 2011).

The SAT consists of a random sequence of signal (or cued) and nonsignal trials, with visual signals varying in duration or intensity, to minimize the development of a fixed detection

threshold and to present cues that are generally of relatively low saliency (McGaughy, Kaiser, & Sarter, 1996; McGaughy & Sarter, 1995). In the rat version of the task, two levers are extended following a signal or a nonsignal event, for a maximum of 4 s, and subjects report hits or misses, correct rejections or false alarms with hits and correct rejections yielding reward. Humans and mouse versions of the task have been established and cross-validated (Demeter et al., 2008; St. Peters, Cherian, Bradshaw, & Sarter, 2011). For the distractor condition of the rat version of the SAT, the chamber houselight typically flashes at 0.5 Hz. While the distractor is on, the performance of all subjects is nearly randomized and, thus, the efficacy of top-down control is revealed primarily by the rate and degree of postdistractor performance recovery. An attenuated or absent recovery of performance during the postdistractor period is indicative of poor attentional control.

### Poor Attentional Control in STs

We determined asymptotic SAT performance in STs and GTs, and then fully replicated this experiment using new groups of animals to determine the reliability of phenotype-based performance differences (Paolone, Angelakos, Meyer, Robinson, & Sarter, 2013). Across all signal durations, STs scored fewer hits than GTs. In STs, a greater degree of sign-tracking (high PCA scores) predicted lower hit rates. Furthermore, STs' performance was highly variable, fluctuating between levels of poor and good performance (illustrated in Paolone, Angelakos, et al., 2013). In contrast, the performance of GTs was more stable across sessions and at a higher level of response accuracy. Moreover, following the presentation of a distractor, GTs' attentional performance immediately improved and returned to predistractor baseline. In contrast, the performance of STs remained at distractor-associated chance levels throughout the postdistractor 16-min remainder of the test session (Kim, Rivet, Lustig, & Sarter, 2016). These findings in STs are hallmarks of poor top-down attentional control and likely involve weaknesses in both proactive and reactive control mechanisms (Braver, 2012). Poor attentional control is a component of the complex psychological trait that is indexed by sign-tracking.

### Low Cholinergic Modulation of SAT Performance in STs

In GTs, performance during the no-distractor SAT is mediated via increases in levels of cortical cholinergic activity. While absolute baseline acetylcholine (ACh) levels do not differ between STs and GTs (this issue will be addressed further below), SAT-associated increases in prefrontal extracellular ACh levels, measured by microdialysis during performance, were significantly lower in STs (Figure 1, taken from Paolone, Angelakos, et al., 2013). This finding is consistent with the hypothesis that in STs, SAT performance is based largely on bottom-up mechanisms and, thus, mediated via relatively low levels of cortical cholinergic neuromodulation.

### Potassium-Stimulation In Vivo Verifies Attenuated ACh Release Capacity in STs

As attentional performance-associated increases in ACh release were significantly lower in STs than in GTs, we hypothesized that a relatively straightforward method to evoke increases in ACh release—reverse dialysis of potassium—suffices to reveal the attenuated capacity of cholinergic neurons of STs to release ACh. As already noted, basal levels of cortical ACh release do not differ between the phenotypes. Potassium-stimulation-induced

ACh levels in GTs reached $201.81 \pm 27.28\%$ over baseline compared with $109.07 \pm 20.83\%$ in STs (Koshy Cherian et al., 2017). In contrast to ACh, GABA, glutamate, serotonin, dopamine, and norepinephrine levels were not differently stimulated in STs and GTs. It is important to emphasize that the nonselective depolarizing effects of potassium-stimulation merely served to reproduce a fundamental ACh release capacity limit in STs. Potassium-stimulation should not be thought of as a pharmacological model of the attention-associated release data as shown in Figure 1, in part because the degree of unspecific depolarization of all neurons in the perfusion area is unlikely to match the more selective, orchestrated activation of neuronal networks during attentional performance (e.g., Gill, Sarter, & Givens, 2000). However, the effects of potassium-stimulation confirm that STs exhibit an attenuated capacity for cortical ACh release.

## Unresponsive CHTs in STs

The neuronal high-affinity choline transporter (CHT; *SLC5A7*) is the rate-limiting step for the synthesis of ACh (Ennis & Blakely, 2016; Ferguson et al., 2004; Guyenet, Lefresne, Rossier, Beaujuan, & Glowinski, 1973; Haga, 2014; Parikh, St. Peters, Blakely, & Sarter, 2013; Sarter & Parikh, 2005; Simon, Atweh, & Kuhar, 1976). As such, the CHT is a major determinant of the capacity of cholinergic neurons to sustain elevated levels of cholinergic neuromodulation (Paolone, Angelakos, et al., 2013; Paolone, Mallory, et al., 2013). The capacity of the CHT to transport choline is largely controlled by translocation of intracellular CHTs into synaptosomal plasma membrane (Ferguson et al., 2003; Parikh et al., 2013; Pinthong et al., 2008; Ribeiro et al., 2003, 2006). Accordingly, we previously demonstrated in unscreened rats and mice that SAT performance increases CHT-mediated choline transport and that this increase was paralleled, and explained, by an increase in the density of CHTs in the synaptosomal plasma membrane (Apparsundaram, Ferguson, George, & Blakely, 2000; Parikh et al., 2013).

To begin revealing the mechanisms underlying the nearly unresponsive cholinergic neuromodulatory system in STs, we investigated CHT-mediated choline uptake and cellular CHT distribution following basal forebrain electrical stimulation (BF-ES) in vivo, using methods adopted from our studies on genetically imposed CHT capacity variants (Parikh et al., 2013). BF-ES stimulation parameters were selected from prior studies showing effects on sensory encoding and facilitation of cognitive processes (Edeline, Maho, Hars, & Hennevin, 1994; Goard & Dan, 2009; McLin, Miasnikov, & Weinberger, 2002) and were shown to increase choline uptake and CHT plasma membrane density (Parikh et al., 2013). The capacity of the CHT to support CHT-mediated choline transport and associated CHT subcellular distribution was assessed in cortical synaptosomes harvested following BF-ES. We found that BF-ES increased choline uptake in GTs but not STs.

To assess the cellular distribution of CHT, synaptosomes from separate groups of rats were further processed to separate a synaptosomal plasma membrane-rich fraction (LP1) from a fraction enriched with intracellular membranes (LP2). We then determined the total CHT protein in synaptosomes from frontal cortex in STs and GTs. Total CHT levels did not differ between the phenotypes. Likewise, at baseline (unstimulated), the density of CHTs in the synaptosomal plasma membrane did not differ between STs and GTs, consistent with the

absence of differences in basal ACh release. Stimulation was expected to increase CHT density in the plasma membrane-enriched LP1 fraction, reflecting mobilization from intracellular domains to synaptosomal plasma membrane. However, this was only the case for GTs, but not for STs (Koshy Cherian et al., 2017).

BF-ES-induced increases in CHT density in the plasma membrane are expected to be paralleled by removal of a proportion of CHTs from the intracellular LP2 fraction (Ferguson et al., 2003). BF-ES-induced reduction in LP2 CHT density occurred in both STs and GTs. Because, in STs, BF-ES did not increase synaptosomal plasma membrane density but removed a portion of LP2 CHTs, this portion of CHTs may have been moved to domains that were not captured by our subcellular fraction-based assays.

While these complications suggest the presence of multiple cellular domains involved in the trafficking of CHTs, the results from our experiments indicated that, in STs, BF-ES did not elevate choline transport and did not elevate synaptosomal plasma CHT density (see Figure 2 for illustration). The presence of a nearly unresponsive cellular CHT system may be responsible for, or at least contribute to, the limited capacity of the cholinergic system of STs to increase ACh release during attentional performance or in response to potassium-induced depolarization. In STs, ACh levels are not completely "frozen" at baseline because CHTs are present in the synaptosomal plasma membrane to support initial ACh release, as observed following the onset of potassium stimulation. However, in response to continued stimulation of cholinergic neurons, vesicular reloading and perhaps also the mobilization of secondary pools of vesicles likely are attenuated (Alabi & Tsien, 2012; Xue et al., 2013) and, thus, STs cannot sustain increases in ACh release. As we will discuss further below, the results of experiments on the effects of pharmacological inhibition of the CHT are consistent with the hypothesis that, mechanistically, attenuated CHT capacity mediates key aspects of sign-tracking behavior and, thus, represents at least one neuromolecular cause of the phenotype.

## Basal ACh Release and Basal CHT Distribution Do Not Differ Between STs and GTs

Basal cortical ACh release does not differ between STs and GTs. This finding corresponds with the observation that, at baseline, the density of CHTs in synaptosomal plasma membrane does not differ between the phenotypes (above). Thus, the cholinergic system in STs, when compared with GTs, is characterized by a reduced capacity to respond to stimulation, but likely not by fundamentally different synaptic mechanisms governing basal ACh release dynamics (Jahn & Fasshauer, 2012), or even by a relatively lower density of cholinergic terminals. This is an important observation as it supports a focus on CHT trafficking as a major mechanism underlying attenuated cholinergic neuromodulation in STs. Had we found lower levels of basal ACh release in STs we would have needed to be concerned about the presence of possible differences in the number of neurons or the density of terminals and, thus, the presence of potentially neuropathological mechanisms in STs. The absence of differences in basal ACh release further enhances the usefulness of STs for studying the functional implications of attenuated cholinergic release dynamics.

# CHT Inhibition Causes Sign-Tracking

## Poor Attentional Control, ACh, and Sign-Tracking

The evidence described thus far indicates a limited capacity of the cholinergic system of STs to increase levels of cholinergic neuromodulation for the mediation of enhanced attentional control. As a cellular cause, we demonstrated that in STs CHT outward trafficking is nearly unresponsive to stimulation. Although we typically determine the capacity for cholinergic neuromodulation by assessing attention task-associated levels of cholinergic activity, we hypothesized that a limited capacity for cholinergic neuromodulation in STs also impacts the very behavioral characteristic that provides the name for this phenotype—sign-tracking.

Sign-tracking behavior in the PCA test has been interpreted in terms of attribution of incentive properties to the CS (Flagel et al., 2009, 2007; Robinson et al., 2014; Saunders & Robinson, 2011). In the PCA screening test, the lever-CS is a salient Pavlovian cue predictive of reward. In addition to the motivational processes thought to govern sign-tracking, the attention of STs appears to be captured by the lever-CS that attain the ability to control their behavior (Koshy Cherian et al., 2017). As will be further defined and discussed below, these observations suggest, in STs, a bias for stimulus-driven (or bottom-up) attention and, conversely, a bias away from utilizing (top-down) attentional control to guide behavior. In contrast, GTs also learn about the cue, as indicated by orienting responses, but their cue-driven behavior is goal-directed, toward the location of impending pellet delivery. Poor attentional control and a propensity for attribution of incentive salience are hypothesized to be overlapping and complementary expressions of the cognitive-motivational styles that are indexed by "sign-tracking" (Koshy Cherian et al., 2017). In STs, orienting and approaching a CS initially may primarily be a result of the attentional bias but, over time, the power of the cue to control behavior and to serve as a conditioned reinforcer likely involves the attribution of incentive salience, rendering the CS attractive and magnetic.

## Attenuation of Elevated ACh Levels by VU6001221

We tested the hypothesis that sign-tracking behavior may also be mediated by relatively low levels of cholinergic activity by assessing the effects of a CHT inhibitor, VU6001221, on PCA performance. VU6001221 (Vanderbilt Center of Neuroscience Discovery) is a second-generation CHT inhibitor with improved CNS penetration and in vivo pharmacokinetic characteristics (Bertron et al., 2016). We first verified that the CHT inhibitor VU6001221 attenuates the capacity of cholinergic neurons to sustain elevated levels of neurotransmission. We used reverse dialysis of potassium as a means to upregulate cholinergic activity over a 15-min period. We conducted this experiment only in GTs because, in contrast to STs, they exhibit robust $K^+$-evoked increases in extracellular ACh levels. As expected, reverse dialysis of $K^+$ reliably increased prefrontal ACh levels by over 200%. Systemic administration of VU6001221 significantly attenuated the increases in extracellular ACh levels.

## Fostering Sign-Tracking

The first PCA session was conducted in the absence of drug to exclude all rats with PCA index scores >0 and, thus, were more likely to emerge as STs. Drug was then given before

Sessions 2–5 to determine whether, compared with the effects of vehicle, inhibition of the CHT yields a greater proportion of rats classified eventually as STs. By excluding early STs we favored the rejection of our hypothesis that administration of VU6001221 fosters sign-tracking. As expected, lever- and food cup-directed behavior (learning the conditioned response) evolved across sessions for all rats, irrespective of treatment. Furthermore, rats treated with vehicle or VU6001221 equally learned to discriminate between CS and non-CS periods as indicated by a decrease in non-CS food cup contacts across days of training. Administration of VU6001221 facilitated all aspects of lever-directed behavior (main effects of treatment on lever contact probability, number of lever contacts, and lever approach latency). With vehicle treatment, the final distribution was 10 STs, 6 GTs, and 8 rats with intermediate scores. In contrast, following the treatment with VU6001221, we obtained 19 STs, 2 GTs, and 4 INs, indicating a significantly greater proportion of STs in the drug-treated group (Koshy Cherian et al., 2017).

## Impact on Addiction: I. Cholinergic Processing of a Pavlovian Drug Cue in GTs, But Not STs

The low-capacity neuromodulatory system of STs is hypothesized to mediate poor attentional control, including a bias for bottom-up, or stimulus-driven attention or, conversely, a bias that disfavors goal-driven, top-down control. This bias of STs is hypothesized to extend to the control of Pavlovian drug cues: STs are expected to more readily exhibit drug-seeking behavior in the presence of such cues, reflecting that such cues readily capture their attention and, thus, control their behavior. Indeed, extensive evidence supports the view that cocaine or opiate cues control drug-taking and drug-seeking behavior to a greater extent in STs than GTs (Saunders & Robinson, 2010, 2011; Yager, Pitchers, Flagel, & Robinson, 2015; Yager & Robinson, 2013). Hypothesizing that GTs resist behavioral control by drug cues based on their relatively superior cholinergic top-down control capabilities, we measured the effects of presentation of a Pavlovian cue previously associated with intravenous injections of cocaine on the activity of two major neuromodulatory inputs to the prefrontal cortex, ACh and DA. We specifically hypothesized that STs would express their preference for cue-directed behavior and that increases in cortical extracellular DA levels would be associated with their bias for processing the motivational attributes of the cocaine cue, as has been described in cocaine addicts (Milella et al., 2016). In contrast, GTs were expected to exhibit less cue approach behavior, consistent with the very behavior that underlies their classification as GTs, and that the absence of cue approach would be associated primarily with increases in prefrontal ACh levels.

STs and GTs rats were randomly assigned to either paired (CS and US, unconditioned stimulus, presented together) or unpaired groups (US explicitly not paired with presentation of the CS). No action was required to initiate the cocaine infusion or the CS illumination (Pitchers, Kane, Kim, Robinson, & Sarter, 2017). As would be expected, STs approached the drug-associated CS more frequently than GTs. Indeed, the approach frequency of GTs was comparable with the low approach frequency seen in rats undergoing cocaine infusions

not paired with the CS. More important, STs and GTs oriented to the CS at similar rates, indicating that both learned the cue's predictive value.

Following a 10-day abstinence period, rats were exposed to the cue while cocaine was not available and four medial prefrontal 4-min dialysates (containing eight 5-s cue presentations each) were collected. The main results are summarized in Figure 3 (for statistical analyses, results from unpaired rats and results from additional control experiments see Pitchers, Kane, et al., 2017). STs approached the cue more frequently than GTs and their DA levels increased over levels measured during noncue periods. In STs, approaches and DA levels were significantly correlated. In contrast, in GTs, DA levels did not change from basal levels, and increases in ACh levels were not associated with any particular behavior, including locomotor activity during cue presentation periods.

The increases in prefrontal DA, but not ACh in STs together may have augmented their bias toward the processing of the Pavlovian drug cue. In other words, STs' behavior in the presence of a Pavlovian drug cue may be described as dopaminergically *and* noncholinergically mediated. In contrast, the behavior of GTs in the presence of the drug cue lacks dopaminergic mediation and, thus, the attentional-motivational processing of a salient and magnetic cue. More important, GTs oriented toward the cue at similar rates as STs, indicating that the informational value of the cue was not affected by phenotype. Increased extracellular levels of pre-frontal ACh may have contributed to an attenuated processing of the cue in GTs, reflecting that cocaine was unavailable during this phase of the experiment (extinction condition). Thus, cholinergic activity may support the "model-based" processing of cue information that integrates changes in context and accurate expectations of reward (Clark, Hollon, & Phillips, 2012; Flagel et al., 2009). This view also predicts that compared with STs, GTs favor the processing of contextual cues, or occasion setters, and that this requires basal forebrain cholinergic activity.

## Impact on Addiction: II. In GTs, Cholinergic Activity Is Necessary for Drug-Seeking in the Presence of a Contextual Cue

Thus far, we have focused on correlational and causal evidence indicating the impact of a low-capacity cholinergic neuromodulatory system on sign-tracking, attentional performance, and the behavioral control of drug cues. We saw that sign-tracking behavior emerges more likely as a result of inhibiting the choline transporter in potential goal-trackers, mimicking the attenuated CHT outward trafficking found in STs, that STs exhibit relatively poor attentional control that is associated with dampened levels of performance-associated prefrontal ACh, and that a Pavlovian cocaine cue controls their behavior, perhaps via enhanced frontal DA and nonresponsive ACh levels. An alternative approach to investigating the role of cholinergic systems in these opponent phenotypes is to test hypotheses about the role of the high-capacity cholinergic-attentional control system in GTs. GTs are considered to exhibit high levels of goal-directed attentional control that is indicated by the ability—during PCA screening—to avoid approaching Pavlovian food and cocaine cues and instead direct their behavior to the location of food delivery. While not approaching the cocaine cue (above), no explicit alternative behavioral response was available to GTs and, therefore, we

did not observe any systematic behavior in GTs in lieu of approaching the cue. Given this top-down processing bias in GTs, we predicted that they should be robustly more capable than STs in the processing of a complex contextual cue, or occasion setter (Bueno & Holland, 2008; Crombag, Bossert, Koya, & Shaham, 2008; Trask, Thrailkill, & Bouton, 2017) that indicates the availability of drug but, in contrast to a Pavlovian cue, does not merely precede the delivery of drug to an otherwise passive animal. Moreover, the processing of such a contextual cue by GTs should depend on cholinergic mechanisms.

To test these hypotheses, STs and GTs were trained to nose-poke to self-administer cocaine (no explicit cue given). Thereafter, these animals were moved to an intermittent self-administration regimen that is known to generate high levels of cocaine-seeking behavior (Zimmer, Oleson, & Roberts, 2012). Two spatially and spectrally different light cues indicated that drug was either available upon a nose-poke (DS$^+$) or not (DS$^-$). Thereafter, rats underwent extinction training (no cues and no cocaine upon nose-pokes) and removal of about ~50% of the cholinergic neurons in the basal forebrain, primarily in the nucleus basalis of Meynert, by infusions of the cholino-specific toxin 192 IgG saporin. Subsequently, rats were exposed again to the two cues while cocaine remained unavailable and nose-poking rates, indicative of drug-seeking behavior, were determined (for more details see Pitchers, Phillips, Jones, Robinson, & Sarter, 2017).

In the presence of the contextual cue (DS$^+$) that previously signaled the availability of cocaine, GTs exhibited more nose-pokes, indicating greater drug seeking, than STs (see Figure 4). Cholinergic losses in GTs reduced this behavior to levels seen in STs. Remarkably, cholinergic lesions had no effects on drug seeking behavior in STs. In GTs, the presence of the contextual stimulus may have generated a more cognitive expectation of drug than in STs, consistent with the general view that GTs are governed by goal-directed top-down biases. Secondary to expecting drug to be available in the presence of the cue, a state of heightened motivation or craving may have generated more nose pokes in GTs. Such an interpretation would also be consistent with the observation that craving for drug in humans is highest when drug availability is expected in the very near future (Dar, Rosen-Korakin, Shapira, Gottlieb, & Frenk, 2010). Accordingly, cholinergic lesions decreased the ability of such cues to elicit the expectation of drug availability and craving in GTs. This finding is consistent with prior studies that demonstrated that such lesions disrupt the processing of cues in attentional contexts and the integration of learning cues with motivational states (Leong, Radulescu, Daniel, DeWoskin, & Niv, 2017; Turchi & Sarter, 1997, 2000). In STs, the relatively low level of drug-seeking behavior elicited by such a contextual cue is thought to have been caused by their unresponsive cholinergic system and, thus, cholinergic lesions did not have any further effects on drug seeking in these rats.

## STs and GTs as Models for Research on Opponent Cognitive-Motivational Styles

The available evidence supports the role of the cholinergic system in mediating the opponent cognitive-motivational styles of STs and GTs, and the impact of these styles on addiction-like behaviors. This view is further supported, albeit more indirectly, by evidence from basic

research on cholinergic function and the impact of genetic CHT capacity variants on bottom-up versus top-down attentional styles.

## Support From Basic Research on Basal Forebrain Cholinergic Functions

Using diverse research approaches ranging from assessing effects of selective lesions, amperometric measures of the fast, phasic, or transient component of cholinergic neurotransmission, microdialysis measures of levels of cholinergic neuromodulation, neurophysiological recordings, and optogenetic generation and attenuation of fast cholinergic transients in performing rodents, the basal forebrain cholinergic projection system to the cortex has been shown to mediate, necessarily, the incorporation of cues into cortical circuitry, thereby allowing such cues to control behavior (Avery, Dutt, & Krichmar, 2014; Goard & Dan, 2009; Gritton et al., 2016; Howe et al., 2013; Howe et al., 2017; McGaughy et al., 1996; Parikh, Kozak, Martinez, & Sarter, 2007; Pinto et al., 2013; Runfeldt, Sadovsky, & MacLean, 2014; Sarter, Howe, & Gritton, 2015; Sarter, Lustig, Berry, et al., 2016; Sarter, Lustig, Howe, Gritton, & Berry, 2014). Furthermore, levels of cholinergic neuromodulation influence the likelihood and the amplitudes of cholinergic transients that cause the detection of cues in attentional contexts (for a circuitry model underlying this interaction see Hasselmo & Sarter, 2011). Relatively low levels of cholinergic neuromodulation—as is the case in STs—are predicted to cause relatively low and unstable hit rates in attention tasks (Paolone, Angelakos, et al., 2013), vulnerability to the effects of distractors, and a propensity to allow salient Pavlovian cues to control behavior. Conversely, high levels of cholinergic neuromodulation are predicted to support solid goal-directed performance, mediated in part by the generation of high-frequency oscillations in frontal regions (Howe et al., 2017), and to support the processing of complex contextual stimuli and their associated motivational states (Pitchers, Phillips, et al., 2017). Moreover, higher levels of cholinergic neuromodulation may also support the processing of erroneous outcomes and their consequences (Danielmeier et al., 2015), thereby further enhancing top-down cognitive control capacities (Fobbs & Mizumori, 2014). Together, the evidence from basic research is consistent with, and predictive of, the evidence on the impact of low-versus high-capacity cholinergic systems deduced from research in STs and GTs.

## Similarities of the Impact of Genetically Imposed Low CHT Capacity on Attentional Biases in Mice and Humans

The unresponsive CHT trafficking system and the resulting low-capacity neuromodulator system in STs resembles the impact of CHT heterozygosity (CHT$^{+/-}$) in mice. Stimulation of the cholinergic system of these mice, including by SAT performance, likewise fails to increase CHT-mediated choline uptake in the right frontal cortex, SAT-associated levels of extracellular ACh remain near basal levels, and SAT performance is unstable and vulnerable to behavioral and pharmacological manipulations (Paolone, Mallory, et al., 2013; Parikh et al., 2013).

Humans expressing the I89V single nucleotide polymorphism (SNP) of the CHT (Okuda, Okamura, Kaitsuka, Haga, & Gurwitz, 2002) may also model the impact of a low-capacity cholinergic neuromodulatory system. This SNP, when expressed in a human cell line,

reduced choline uptake by about 40% (Okuda et al., 2002) that, given the rate-limiting nature of the CHT for ACh synthesis and release, would be expected to limit elevations of cholinergic neuromodulation. We found that I89V humans self-report greater vulnerability for distractors and dramatically exhibit such vulnerability when tested in a continuous attention task in the presence of content-rich distractors, and they fail to activate right frontal regions in the presence of a distractor (Berry, Blakely, Sarter, & Lustig, 2015; Berry et al., 2014). As is the case in rats that are STs, the cognitive performance of humans expressing the I89V CHT subcapacity variant is consistent with a bias away from top-down attentional control and toward bottom-up, cue-driven performance (Sarter, Lustig, Blakely, & Koshy Cherian, 2016).

### Presence Versus Absence of Cue-Driven Dopaminergic Activity

As already discussed above, in STs, Pavlovian cocaine cues elicit increases in frontal DA, but not ACh, release while, in GTs, this pattern was precisely reversed (Pitchers, Kane, et al., 2017). We hypothesize that, in STs, the increases in frontal DA parallel the increases in ventral striatal DA levels that, in STs, support the behavioral significance of Pavlovian reward cues (Flagel et al., 2011) and cue-evoked drug-seeking behavior (Fraser & Janak, 2017; Saunders, Yager, & Robinson, 2013). Specifically, increases in cortical extracellular DA levels in STs may mediate their bias for processing of the motivational attributes of the cocaine cue, mirroring findings in cocaine addicts (Milella et al., 2016). Furthermore, in STs, cue-evoked increases in prefrontal DA levels may stabilize such cue-directed behavior (Ellwood et al., 2017). Cue-evoked increases in prefrontal and ventral striatal dopaminergic activity, and the absence of increases in cholinergic modulation, together may collaborate to support the cognitive-motivational style that governs the behavior of STs in the presence of Pavlovian reward and drug cues. Conversely, in GTs, the absence of increases in cue-evoked frontal DA levels, paralleling the absence of cue-evoked increases in ventral striatal DA signaling (Flagel et al., 2011) limits the potential deployment of processing biases that could compete with the predominance of their cholinergically mediated, "cold" analysis of the role of a conditioned reinforcer, resulting in the lack of cue-approach behavior and, therefore, also minimizing (Pavlovian) cue-induced drug-seeking.

Thus, elevations in frontal ACh versus DA levels appears to mediate opponent cognitive-motivational styles. Increases in cholinergic activity may directly limit elevations in frontal DA neurotransmission in GTs, thereby mediating their cold nonapproaching behavior. In contrast, in STs, the lack of increases in cholinergic neurotransmission may allow the elevation of DA levels and, thus, the approach to Pavlovian food or drug cues. It will be interesting to determine whether rats classified as intermediates exhibit parallel increases in both neuromodulators in the presence of drug cues, thereby preventing the expression of the two extreme styles that governs the behavior of STs and GTs.

## Hot and Cold Cognitive Styles and Risk for Neuropsychiatric Disorders

The evidence described herein suggests that STs have a propensity toward a relatively "hot" dopaminergic processing of the motivational significance of stimuli, to attend to salient cues and to attribute incentive value to such cues. GTs, in contrast, preferably apply a relatively

"cold" cholinergic processing of the utility of cues for goal-directed behavior while minimizing behavior directed to the cue per se.

The costs and benefits of individual cognitive styles depend strongly on situational variables and the nature of behaviorally significant cues. For example, compared with GTs, the behavior of STs appears to be generally controlled more effectively by Pavlovian reward cues. Conversely, contextual cues or occasion setters have significantly greater influence on the behavior of GTs than STs, including drug-seeking behavior (Pitchers, Phillips, et al., 2017). Thus, while much research is directed toward the hypothesis that a range of addiction disorders, including eating disorders, is associated with the motivational biases indexed by sign-tracking (for review see Flagel, 2014), the important role of contextual stimuli in the development and maintenance of these maladaptive behaviors in humans indicate a more complex relationship between these two phenotypes and vulnerability for addiction-like behaviors.

However, a relatively low capacity for cholinergic-attentional control, as represented in ST rats, in CHT$^{-/-}$ mice, and in humans expressing the I89V CHT subcapacity variant, may confer a relatively greater vulnerability for neuropsychiatric disorders that share relatively poor attentional control as a common cognitive style. These disorders include attention-deficit-hyperactivity disorder (ADHD), in which the low I89V subcapacity variant has already been found to be overrepresented (English et al., 2009), and schizophrenia in which low cholinergic-attentional control has been identified as a cognitive endophenotype (Luck, Ford, Sarter, & Lustig, 2012; Lustig, Kozak, Sarter, Young, & Robbins, 2013; Lustig & Sarter, 2015). The risks associated with the top-down cold cognitive biases of GTs are even less well understood but could be associated with deficient reward learning in situations in which Pavlovian cues control such learning, thereby potentially contributing to a wide range of psychiatric disorders (Bodi et al., 2009; Der-Avakian & Markou, 2012). Beyond their original role in addiction research, STs and GTs will assist in determining the disease risks associated with broad and fundamental biases toward the processing of behaviorally significant cues and the neuronal mechanisms mediating their opponent cognitive-motivational styles.

## Acknowledgments

## References

Alabi AA, Tsien RW. Synaptic vesicle pools and dynamics. Cold Spring Harbor Perspectives in Biology. 2012; 4:a013680. http://dx.doi.org/10.1101/cshperspect.a013680. [PubMed: 22745285]

Apparsundaram S, Ferguson SM, George AL Jr, Blakely RD. Molecular cloning of a human, hemicholinium-3-sensitive choline transporter. Biochemical and Biophysical Research Communications. 2000; 276:862–867. http://dx.doi.org/10.1006/bbrc.2000.3561. [PubMed: 11027560]

Avery MC, Dutt N, Krichmar JL. Mechanisms underlying the basal forebrain enhancement of top-down and bottom-up attention. European Journal of Neuroscience. 2014; 39:852–865. http://dx.doi.org/10.1111/ejn.12433. [PubMed: 24304003]

Berry AS, Blakely RD, Sarter M, Lustig C. Cholinergic capacity mediates prefrontal engagement during challenges to attention: Evidence from imaging genetics. NeuroImage. 2015; 108:386–395. http://dx.doi.org/10.1016/j.neuroimage.2014.12.036. [PubMed: 25536497]

Berry AS, Demeter E, Sabhapathy S, English BA, Blakely RD, Sarter M, Lustig C. Disposed to distraction: Genetic variation in the cholinergic system influences distractibility but not time-on-task effects. Journal of Cognitive Neuroscience. 2014; 26:1981–1991. http://dx.doi.org/10.1162/jocn_a_00607. [PubMed: 24666128]

Bertron JL, Ennis EA, Tarr CJ, Wright J, Dickerson JW, Locuson CW, Lindsley CW. Optimization of the choline transporter (CHT) inhibitor ML352: Development of VU6001221, an improved in vivo tool compound. Bioorganic & Medicinal Chemistry Letters. 2016; 26:4637–4640. http://dx.doi.org/10.1016/j.bmcl.2016.08.062. [PubMed: 27575469]

Blatt SJ, Quinlan DM, Chevron ES, McDonald C, Zuroff D. Dependency and self-criticism: Psychological dimensions of depression. Journal of Consulting and Clinical Psychology. 1982; 50:113–124. http://dx.doi.org/10.1037/0022-006X.50.1.113. [PubMed: 7056904]

Bódi N, Kéri S, Nagy H, Moustafa A, Myers CE, Daw N, Gluck MA. Reward-learning and the novelty-seeking personality: A between- and within-subjects study of the effects of dopamine agonists on young Parkinson's patients. Brain: A Journal of Neurology. 2009; 132:2385–2395. http://dx.doi.org/10.1093/brain/awp094. [PubMed: 19416950]

Boosman H, Visser-Meily JM, Post MW, Lindeman E, Van Heugten CM. Exploring the relation between learning style and cognitive impairment in patients with acquired brain injury. Neuropsychological Rehabilitation. 2012; 22:26–39. http://dx.doi.org/10.1080/09602011.2011.632907. [PubMed: 22176635]

Braver TS. The variable nature of cognitive control: A dual mechanisms framework. Trends in Cognitive Sciences. 2012; 16:106–113. http://dx.doi.org/10.1016/j.tics.2011.12.010. [PubMed: 22245618]

Braver TS, Krug MK, Chiew KS, Kool W, Westbrook JA, Clement NJ, the MOMCAI group. Mechanisms of motivation-cognition interaction: Challenges and opportunities. Cognitive, Affective & Behavioral Neuroscience. 2014; 14:443–472. http://dx.doi.org/10.3758/s13415-014-0300-0.

Broos N, Diergaarde L, Schoffelmeer AN, Pattij T, De Vries TJ. Trait impulsive choice predicts resistance to extinction and propensity to relapse to cocaine seeking: A bidirectional investigation. Neuropsychopharmacology. 2012; 37:1377–1386. http://dx.doi.org/10.1038/npp.2011.323. [PubMed: 22318198]

Bueno JL, Holland PC. Occasion setting in Pavlovian ambiguous target discriminations. Behavioural Processes. 2008; 79:132–147. http://dx.doi.org/10.1016/j.beproc.2008.07.001. [PubMed: 18657599]

Buschman TJ, Miller EK. Top-down versus bottom-up control of attention in the prefrontal and posterior parietal cortices. Science. 2007; 315:1860–1862. http://dx.doi.org/10.1126/science.1138071. [PubMed: 17395832]

Clark JJ, Hollon NG, Phillips PE. Pavlovian valuation systems in learning and decision making. Current Opinion in Neurobiology. 2012; 22:1054–1061. http://dx.doi.org/10.1016/j.conb.2012.06.004. [PubMed: 22749132]

Connor CE, Egeth HE, Yantis S. Visual attention: Bottom-up versus top-down. Current Biology. 2004; 14:R850–R852. http://dx.doi.org/10.1016/j.cub.2004.09.041. [PubMed: 15458666]

Crombag HS, Bossert JM, Koya E, Shaham Y. Context-induced relapse to drug seeking: A review. Philosophical Transactions of the Royal Society of London Series B, Biological Sciences. 2008; 363:3233–3243. http://dx.doi.org/10.1098/rstb.2008.0090. [PubMed: 18640922]

Danielmeier C, Allen EA, Jocham G, Onur OA, Eichele T, Ullsperger M. Acetylcholine mediates behavioral and neural post-error control. Current Biology. 2015; 25:1461–1468. http://dx.doi.org/10.1016/j.cub.2015.04.022. [PubMed: 25959965]

Dar R, Rosen-Korakin N, Shapira O, Gottlieb Y, Frenk H. The craving to smoke in flight attendants: Relations with smoking deprivation, anticipation of smoking, and actual smoking. Journal of Abnormal Psychology. 2010; 119:248–253. http://dx.doi.org/10.1037/a0017778. [PubMed: 20141262]

Demeter E, Hernandez-Garcia L, Sarter M, Lustig C. Challenges to attention: A continuous arterial spin labeling (ASL) study of the effects of distraction on sustained attention. NeuroImage. 2011; 54:1518–1529. http://dx.doi.org/10.1016/j.neuroimage.2010.09.026. [PubMed: 20851189]

Demeter E, Sarter M, Lustig C. Rats and humans paying attention: Cross-species task development for translational research. Neuropsychology. 2008; 22:787–799. http://dx.doi.org/10.1037/a0013712. [PubMed: 18999353]

Demeter E, Woldorff MG. Transient distraction and attentional control during a sustained selective attention task. Journal of Cognitive Neuroscience. 2016; 28:935–947. http://dx.doi.org/10.1162/jocn_a_00949. [PubMed: 26967946]

Der-Avakian A, Markou A. The neurobiology of anhedonia and other reward-related deficits. Trends in Neurosciences. 2012; 35:68–77. http://dx.doi.org/10.1016/j.tins.2011.11.005. [PubMed: 22177980]

Dickinson D, Goldberg TE, Gold JM, Elvevåg B, Weinberger DR. Cognitive factor structure and invariance in people with schizophrenia, their unaffected siblings, and controls. Schizophrenia Bulletin. 2011; 37:1157–1167. http://dx.doi.org/10.1093/schbul/sbq018. [PubMed: 20351040]

Edeline JM, Maho C, Hars B, Hennevin E. Non-awaking basal forebrain stimulation enhances auditory cortex responsiveness during slow-wave sleep. Brain Research. 1994; 636:333–337. http://dx.doi.org/10.1016/0006-8993(94)91033-2. [PubMed: 8012817]

Ellwood IT, Patel T, Wadia V, Lee AT, Liptak AT, Bender KJ, Sohal VS. Tonic or phasic stimulation of dopaminergic projections to prefrontal cortex causes mice to maintain or deviate from previously learned behavioral strategies. The Journal of Neuroscience: The Official Journal of the Society for Neuroscience. 2017; 37:8315–8329. [PubMed: 28739583]

English BA, Hahn MK, Gizer IR, Mazei-Robison M, Steele A, Kurnik DM, Blakely RD. Choline transporter gene variation is associated with attention-deficit hyperactivity disorder. Journal of Neurodevelopmental Disorders. 2009; 1:252–263. http://dx.doi.org/10.1007/s11689-009-9033-8. [PubMed: 21547719]

Ennis EA, Blakely RD. Choline on the move: Perspectives on the molecular physiology and pharmacology of the presynaptic choline transporter. Advances in Pharmacology. 2016; 76:175–213. [PubMed: 27288078]

Ersche KD, Barnes A, Jones PS, Morein-Zamir S, Robbins TW, Bullmore ET. Abnormal structure of frontostriatal brain systems is associated with aspects of impulsivity and compulsivity in cocaine dependence. Brain: A Journal of Neurology. 2011; 134:2013–2024. http://dx.doi.org/10.1093/brain/awr138. [PubMed: 21690575]

Ferguson SM, Bazalakova M, Savchenko V, Tapia JC, Wright J, Blakely RD. Lethal impairment of cholinergic neurotransmission in hemicholinium-3-sensitive choline transporter knockout mice. Proceedings of the National Academy of Sciences of the United States of America. 2004; 101:8762–8767. http://dx.doi.org/10.1073/pnas.0401667101. [PubMed: 15173594]

Ferguson SM, Savchenko V, Apparsundaram S, Zwick M, Wright J, Heilman CJ, Blakely RD. Vesicular localization and activity-dependent trafficking of presynaptic choline transporters. The Journal of Neuroscience: The Official Journal of the Society for Neuroscience. 2003; 23:9697–9709. [PubMed: 14585997]

Field M, Cox WM. Attentional bias in addictive behaviors: A review of its development, causes, and consequences. Drug and Alcohol Dependence. 2008; 97:1–20. http://dx.doi.org/10.1016/j.drugalcdep.2008.03.030. [PubMed: 18479844]

Fitzpatrick CJ, Gopalakrishnan S, Cogan ES, Yager LM, Meyer PJ, Lovic V, Morrow JD. Variation in the form of Pavlovian conditioned approach behavior among outbred male Sprague-Dawley rats from different vendors and colonies: Sign-tracking vs. goal-tracking. PLoS ONE. 2013; 8:e75042. http://dx.doi.org/10.1371/journal.pone.0075042. [PubMed: 24098363]

Flagel, SB. Sign-Tracking. In: Stolerman, IP., Price, LH., editors. Encyclopedia of Psychopharmacology. Springer, Berlin; Heidelberg: 2014.

Flagel SB, Akil H, Robinson TE. Individual differences in the attribution of incentive salience to reward-related cues: Implications for addiction. Neuropharmacology. 2009; 56(Suppl. 1):139–148. http://dx.doi.org/10.1016/j.neuropharm.2008.06.027. [PubMed: 18619474]

Flagel SB, Clark JJ, Robinson TE, Mayo L, Czuj A, Willuhn I, Akil H. A selective role for dopamine in stimulus-reward learning. Nature. 2011; 469:53–57. http://dx.doi.org/10.1038/nature09588. [PubMed: 21150898]

Flagel SB, Robinson TE. Neurobiological basis of individual variation in stimulus-reward learning. Current Opinion in Behavioral Sciences. 2017; 13:178–185. http://dx.doi.org/10.1016/j.cobeha. 2016.12.004. [PubMed: 28670608]

Flagel SB, Watson SJ, Robinson TE, Akil H. Individual differences in the propensity to approach signals vs goals promote different adaptations in the dopamine system of rats. Psychopharmacology. 2007; 191:599–607. http://dx.doi.org/10.1007/s00213-006-0535-8. [PubMed: 16972103]

Fobbs WC, Mizumori SJY. Cost-benefit decision circuitry: Proposed modulatory role for acetylcholine. Progress in Molecular Biology and Translational Science. 2014; 122:233–261. http://dx.doi.org/10.1016/B978-0-12-420170-5.00009-X. [PubMed: 24484704]

Fraser KM, Janak PH. Long-lasting contribution of dopamine in the nucleus accumbens core, but not dorsal lateral striatum, to sign-tracking. European Journal of Neuroscience. 2017; 46:2047–2055. http://dx.doi.org/10.1111/ejn.13642. [PubMed: 28699296]

Gill TM, Sarter M, Givens B. Sustained visual attention performance-associated prefrontal neuronal activity: Evidence for cholinergic modulation. The Journal of Neuroscience: The Official Journal of the Society for Neuroscience. 2000; 20:4745–4757. [PubMed: 10844044]

Goard M, Dan Y. Basal forebrain activation enhances cortical coding of natural scenes. Nature Neuroscience. 2009; 12:1444–1449. http://dx.doi.org/10.1038/nn.2402. [PubMed: 19801988]

Gormly J. Cognitive style as a dimension of personality. Journal of Personality Assessment. 1973; 37:574–578. http://dx.doi.org/10.1080/00223891.1973.10119925. [PubMed: 4766744]

Gritton HJ, Howe WM, Mallory CS, Hetrick VL, Berke JD, Sarter M. Cortical cholinergic signaling controls the detection of cues. Proceedings of the National Academy of Sciences of the United States of America. 2016; 113:E1089–E1097. http://dx.doi.org/10.1073/pnas.1516134113. [PubMed: 26787867]

Gur RE, Calkins ME, Gur RC, Horan WP, Nuechterlein KH, Seidman LJ, Stone WS. The Consortium on the Genetics of Schizophrenia: Neurocognitive endophenotypes. Schizophrenia Bulletin. 2007; 33:49–68. http://dx.doi.org/10.1093/schbul/sbl055. [PubMed: 17101692]

Guyenet P, Lefresne P, Rossier J, Beaujouan JC, Glowinski J. Inhibition by hemicholinium-3 of (14C)acetylcholine synthesis and (3H)choline high-affinity uptake in rat striatal synaptosomes. Molecular Pharmacology. 1973; 9:630–639. [PubMed: 4788157]

Haga T. Molecular properties of the high-affinity choline transporter CHT1. Journal of Biochemistry. 2014; 156:181–194. http://dx.doi.org/10.1093/jb/mvu047. [PubMed: 25073461]

Hasselmo ME, Sarter M. Modes and models of forebrain cholinergic neuromodulation of cognition. Neuropsychopharmacology. 2011; 36:52–73. http://dx.doi.org/10.1038/npp.2010.104. [PubMed: 20668433]

Howe WM, Berry AS, Francois J, Gilmour G, Carp JM, Tricklebank M, Sarter M. Prefrontal cholinergic mechanisms instigating shifts from monitoring for cues to cue-guided performance: Converging electrochemical and fMRI evidence from rats and humans. The Journal of Neuroscience: The Official Journal of the Society for Neuroscience. 2013; 33:8742–8752. http://dx.doi.org/10.1523/JNEUROSCI.5809-12.2013. [PubMed: 23678117]

Howe WM, Gritton HJ, Lusk NA, Roberts EA, Hetrick VL, Berke JD, Sarter M. Acetylcholine release in prefrontal cortex promotes gamma oscillations and theta-gamma coupling during cue detection. The Journal of Neuroscience: The Official Journal of the Society for Neuroscience. 2017; 37:3215–3230. http://dx.doi.org/10.1523/JNEUROSCI.2737-16.2017. [PubMed: 28213446]

Jahn R, Fasshauer D. Molecular machines governing exocytosis of synaptic vesicles. Nature. 2012; 490:201–207. http://dx.doi.org/10.1038/nature11320. [PubMed: 23060190]

Kawa AB, Bentzley BS, Robinson TE. Less is more: Prolonged intermittent access cocaine self-administration produces incentive-sensitization and addiction-like behavior. Psychopharmacology. 2016; 233:3587–3602. http://dx.doi.org/10.1007/s00213-016-4393-8. [PubMed: 27481050]

Kim, Y., Rivet, C., Lustig, C., Sarter, M. Poor attentional control as a trait in sign-tracking rats: Cortical cholinergic-GABAergic mechanisms; Paper presented at the Society for Neuroscience Annual Meeting; San Diego, CA. 2016.

Kirby JR, Moore PJ, Schofield NJ. Verbal and visual learning styles. Contemporary Educational Psychology. 1988; 13:169–184. http://dx.doi.org/10.1016/0361-476X(88)90017-3.

Kleiman EM, Riskind JH. Cognitive vulnerability to comorbidity: Looming cognitive style and depressive cognitive style as synergistic predictors of anxiety and depression symptoms. Journal of Behavior Therapy and Experimental Psychiatry. 2012; 43:1109–1114. http://dx.doi.org/10.1016/j.jbtep.2012.05.008. [PubMed: 22750469]

Koshy Cherian A, Kucinski A, Pitchers K, Yegla B, Parikh V, Kim Y, Sarter M. Unresponsive choline transporter as a trait neuromarker and a causal mediator of bottom-up attentional biases. The Journal of Neuroscience: The Official Journal of the Society for Neuroscience. 2017; 37:2947–2959. http://dx.doi.org/10.1523/JNEUROSCI.3499-16.2017. [PubMed: 28193693]

Kraemer DJ, Rosenberg LM, Thompson-Schill SL. The neural correlates of visual and verbal cognitive styles. The Journal of Neuroscience: The Official Journal of the Society for Neuroscience. 2009; 29:3792–3798. http://dx.doi.org/10.1523/JNEUROSCI.4635-08.2009. [PubMed: 19321775]

Leong YC, Radulescu A, Daniel R, DeWoskin V, Niv Y. Dynamic interaction between reinforcement learning and attention in multidimensional environments. Neuron. 2017; 93:451–463. http://dx.doi.org/10.1016/j.neuron.2016.12.040. [PubMed: 28103483]

Luck SJ, Ford JM, Sarter M, Lustig C. CNTRICS final biomarker selection: Control of attention. Schizophrenia Bulletin. 2012; 38:53–61. http://dx.doi.org/10.1093/schbul/sbr065. [PubMed: 21765166]

Lustig C, Kozak R, Sarter M, Young JW, Robbins TW. CNTRICS final animal model task selection: Control of attention. Neuroscience and Biobehavioral Reviews. 2013; 37:2099–2110. http://dx.doi.org/10.1016/j.neubiorev.2012.05.009. [PubMed: 22683929]

Lustig C, Sarter M. Attention and the cholinergic system: Relevance to schizophrenia. Current Topics in Behavioral Neurosciences. 2015; 28:327–362. http://dx.doi.org/10.1007/7854_2015_5009.

McGaughy J, Kaiser T, Sarter M. Behavioral vigilance following infusions of 192 IgG-saporin into the basal forebrain: Selectivity of the behavioral impairment and relation to cortical AChE-positive fiber density. Behavioral Neuroscience. 1996; 110:247–265. http://dx.doi.org/10.1037/0735-7044.110.2.247. [PubMed: 8731052]

McGaughy J, Sarter M. Behavioral vigilance in rats: Task validation and effects of age, amphetamine, and benzodiazepine receptor ligands. Psychopharmacology. 1995; 117:340–357. http://dx.doi.org/10.1007/BF02246109. [PubMed: 7770610]

McLin DE III, Miasnikov AA, Weinberger NM. Induction of behavioral associative memory by stimulation of the nucleus basalis. Proceedings of the National Academy of Sciences of the United States of America. 2002; 99:4002–4007. http://dx.doi.org/10.1073/pnas.062057099. [PubMed: 11904444]

Meyer PJ, Lovic V, Saunders BT, Yager LM, Flagel SB, Morrow JD, Robinson TE. Quantifying individual variation in the propensity to attribute incentive salience to reward cues. PLoS ONE. 2012; 7:e38987. http://dx.doi.org/10.1371/journal.pone.0038987. [PubMed: 22761718]

Milella MS, Fotros A, Gravel P, Casey KF, Larcher K, Verhaeghe JA, Leyton M. Cocaine cue-induced dopamine release in the human prefrontal cortex. Journal of Psychiatry & Neuroscience. 2016; 41:322–330. http://dx.doi.org/10.1503/jpn.150207. [PubMed: 26900792]

Miller MB, Donovan CL, Bennett CM, Aminoff EM, Mayer RE. Individual differences in cognitive style and strategy predict similarities in the patterns of brain activity between individuals. NeuroImage. 2012; 59:83–93. http://dx.doi.org/10.1016/j.neuroimage.2011.05.060. [PubMed: 21651986]

Okuda T, Okamura M, Kaitsuka C, Haga T, Gurwitz D. Single nucleotide polymorphism of the human high affinity choline transporter alters transport rate. The Journal of Biological Chemistry. 2002; 277:45315–45322. http://dx.doi.org/10.1074/jbc.M207742200. [PubMed: 12237312]

Paolone G, Angelakos CC, Meyer PJ, Robinson TE, Sarter M. Cholinergic control over attention in rats prone to attribute incentive salience to reward cues. The Journal of Neuroscience: The Official

Journal of the Society for Neuroscience. 2013; 33:8321–8335. http://dx.doi.org/10.1523/JNEUROSCI.0709-13.2013. [PubMed: 23658172]

Paolone G, Mallory CS, Cherian AK, Miller TR, Blakely RD, Sarter M. Monitoring cholinergic activity during attentional performance in mice heterozygous for the choline transporter: A model of cholinergic capacity limits. Neuropharmacology. 2013; 75:274–285. http://dx.doi.org/10.1016/j.neuropharm.2013.07.032. [PubMed: 23958450]

Parikh V, Kozak R, Martinez V, Sarter M. Prefrontal acetylcholine release controls cue detection on multiple timescales. Neuron. 2007; 56:141–154. http://dx.doi.org/10.1016/j.neuron.2007.08.025. [PubMed: 17920021]

Parikh V, St Peters M, Blakely RD, Sarter M. The presynaptic choline transporter imposes limits on sustained cortical acetylcholine release and attention. The Journal of Neuroscience: The Official Journal of the Society for Neuroscience. 2013; 33:2326–2337. http://dx.doi.org/10.1523/JNEUROSCI.4993-12.2013. [PubMed: 23392663]

Pinthong M, Black SAG, Ribeiro FM, Pholpramool C, Ferguson SSG, Rylett RJ. Activity and subcellular trafficking of the sodium-coupled choline transporter CHT is regulated acutely by peroxynitrite. Molecular Pharmacology. 2008; 73:801–812. http://dx.doi.org/10.1124/mol.107.040881. [PubMed: 17971421]

Pinto L, Goard MJ, Estandian D, Xu M, Kwan AC, Lee SH, Dan Y. Fast modulation of visual perception by basal forebrain cholinergic neurons. Nature Neuroscience. 2013; 16:1857–1863. http://dx.doi.org/10.1038/nn.3552. [PubMed: 24162654]

Pitchers KK, Kane LF, Kim Y, Robinson TE, Sarter M. 'Hot' vs. 'cold' behavioural-cognitive styles: Motivational-dopaminergic vs. cognitive-cholinergic processing of a Pavlovian cocaine cue in sign- and goal-tracking rats. The European Journal of Neuroscience. 2017; 46:2768–2781. http://dx.doi.org/10.1111/ejn.13741. [PubMed: 29044780]

Pitchers KK, Phillips KB, Jones JL, Robinson TE, Sarter M. Diverse roads to relapse: A discriminative cue signaling cocaine availability is more effective in renewing cocaine seeking in goal trackers than sign trackers and depends on basal forebrain cholinergic activity. The Journal of Neuroscience: The Official Journal of the Society for Neuroscience. 2017; 37:7198–7208. http://dx.doi.org/10.1523/JNEUROSCI.0990-17.2017. [PubMed: 28659281]

Pitchers KK, Wood TR, Skrzynski CJ, Robinson TE, Sarter M. The ability for cocaine and cocaine-associated cues to compete for attention. Behavioural Brain Research. 2017; 320:302–315. http://dx.doi.org/10.1016/j.bbr.2016.11.024. [PubMed: 27890441]

Ribeiro FM, Alves-Silva J, Volknandt W, Martins-Silva C, Mahmud H, Wilhelm A, Prado MAM. The hemicholinium-3 sensitive high affinity choline transporter is internalized by clathrin-mediated endocytosis and is present in endosomes and synaptic vesicles. Journal of Neurochemistry. 2003; 87:136–146. http://dx.doi.org/10.1046/j.1471-4159.2003.01974.x. [PubMed: 12969261]

Ribeiro FM, Black SA, Prado VF, Rylett RJ, Ferguson SS, Prado MA. The "ins" and "outs" of the high-affinity choline transporter CHT1. Journal of Neurochemistry. 2006; 97:1–12. http://dx.doi.org/10.1111/j.1471-4159.2006.03695.x.

Robbins TW, Gillan CM, Smith DG, de Wit S, Ersche KD. Neurocognitive endophenotypes of impulsivity and compulsivity: Towards dimensional psychiatry. Trends in Cognitive Sciences. 2012; 16:81–91. http://dx.doi.org/10.1016/j.tics.2011.11.009. [PubMed: 22155014]

Robinson TE, Flagel SB. Dissociating the predictive and incentive motivational properties of reward-related cues through the study of individual differences. Biological Psychiatry. 2009; 65:869–873. http://dx.doi.org/10.1016/j.biopsych.2008.09.006. [PubMed: 18930184]

Robinson TE, Yager LM, Cogan ES, Saunders BT. On the motivational properties of reward cues: Individual differences. Neuropharmacology. 2014; 76(Pt B):450–459. http://dx.doi.org/10.1016/j.neuropharm.2013.05.040. [PubMed: 23748094]

Romens SE, Maccoon DG, Abramson LY, Pollak SD. Cognitive style moderates attention to attribution-relevant stimuli. Cognitive Therapy and Research. 2011; 35:134–141. http://dx.doi.org/10.1007/s10608-010-9345-8. [PubMed: 21701701]

Runfeldt MJ, Sadovsky AJ, MacLean JN. Acetylcholine functionally reorganizes neocortical microcircuits. Journal of Neurophysiology. 2014; 112:1205–1216. http://dx.doi.org/10.1152/jn.00071.2014. [PubMed: 24872527]

Sarter M, Gehring WJ, Kozak R. More attention must be paid: The neurobiology of attentional effort. Brain Research Reviews. 2006; 51:145–160. http://dx.doi.org/10.1016/j.brainresrev.2005.11.002. [PubMed: 16530842]

Sarter M, Givens B, Bruno JP. The cognitive neuroscience of sustained attention: Where top-down meets bottom-up. Brain Research Reviews. 2001; 35:146–160. http://dx.doi.org/10.1016/S0165-0173(01)00044-3. [PubMed: 11336780]

Sarter, M., Howe, WM., Gritton, H. Cortical cholinergic transients for cue detection and attentional mode shifts. In: Wilson, G., Michael, A., editors. Compendium of in vivo monitoring in real-time molecular neuroscience. Vol. 1. Singapore: World Scientific; 2015. p. 27-44.http://dx.doi.org/10.1142/9789814619776_0002

Sarter M, Lustig C, Berry AS, Gritton H, Howe WM, Parikh V. What do phasic cholinergic signals do? Neurobiology of Learning and Memory. 2016; 130:135–141. http://dx.doi.org/10.1016/j.nlm.2016.02.008. [PubMed: 26911787]

Sarter M, Lustig C, Blakely RD, Koshy Cherian A. Cholinergic genetics of visual attention: Human and mouse choline transporter capacity variants influence distractibility. Journal of Physiology, Paris. 2016; 110:10–18. http://dx.doi.org/10.1016/j.jphysparis.2016.07.001.

Sarter M, Lustig C, Howe WM, Gritton H, Berry AS. Deterministic functions of cortical acetylcholine. European Journal of Neuroscience. 2014; 39:1912–1920. http://dx.doi.org/10.1111/ejn.12515. [PubMed: 24593677]

Sarter M, Parikh V. Choline transporters, cholinergic transmission and cognition. Nature Reviews Neuroscience. 2005; 6:48–56. http://dx.doi.org/10.1038/nrn1588. [PubMed: 15611726]

Saunders BT, Robinson TE. A cocaine cue acts as an incentive stimulus in some but not others: Implications for addiction. Biological Psychiatry. 2010; 67:730–736. http://dx.doi.org/10.1016/j.biopsych.2009.11.015. [PubMed: 20045508]

Saunders BT, Robinson TE. Individual variation in the motivational properties of cocaine. Neuropsychopharmacology. 2011; 36:1668–1676. http://dx.doi.org/10.1038/npp.2011.48. [PubMed: 21471956]

Saunders BT, Robinson TE. The role of dopamine in the accumbens core in the expression of Pavlovian-conditioned responses. European Journal of Neuroscience. 2012; 36:2521–2532. http://dx.doi.org/10.1111/j.1460-9568.2012.08217.x. [PubMed: 22780554]

Saunders BT, Yager LM, Robinson TE. Cue-evoked cocaine "craving": Role of dopamine in the accumbens core. The Journal of Neuroscience: The Official Journal of the Society for Neuroscience. 2013; 33:13989–14000. http://dx.doi.org/10.1523/JNEUROSCI.0450-13.2013. [PubMed: 23986236]

Simon JR, Atweh S, Kuhar MJ. Sodium-dependent high affinity choline uptake: A regulatory step in the synthesis of acetylcholine. Journal of Neurochemistry. 1976; 26:909–922. http://dx.doi.org/10.1111/j.1471-4159.1976.tb06472.x. [PubMed: 1271069]

Stange JP, Hamilton JL, Burke TA, Kleiman EM, O'Garro-Moore JK, Seligman ND, Alloy LB. Negative cognitive styles synergistically predict suicidal ideation in bipolar spectrum disorders: A 3-year prospective study. Psychiatry Research. 2015; 226:162–168. http://dx.doi.org/10.1016/j.psychres.2014.12.042. [PubMed: 25660736]

Sternberg, RJ., Zhang, L-f. Perspectives on thinking, learning, and cognitive styles. Mahwah, NJ: L. Erlbaum Associates; 2001.

St Peters M, Cherian AK, Bradshaw M, Sarter M. Sustained attention in mice: Expanding the translational utility of the SAT by incorporating the Michigan Controlled Access Response Port (MICARP). Behavioural Brain Research. 2011; 225:574–583. http://dx.doi.org/10.1016/j.bbr.2011.08.025. [PubMed: 21888929]

St Peters M, Demeter E, Lustig C, Bruno JP, Sarter M. Enhanced control of attention by stimulating mesolimbic-corticopetal cholinergic circuitry. The Journal of Neuroscience: The Official Journal of the Society for Neuroscience. 2011; 31:9760–9771. http://dx.doi.org/10.1523/JNEUROSCI.1902-11.2011. [PubMed: 21715641]

Tomasi D, Goldstein RZ, Telang F, Maloney T, Alia-Klein N, Caparelli EC, Volkow ND. Thalamo-cortical dysfunction in cocaine abusers: Implications in attention and perception. Psychiatry

Research. 2007; 155:189–201. http://dx.doi.org/10.1016/j.pscychresns.2007.03.002. [PubMed: 17582746]

Tomie A, Lincks M, Nadarajah SD, Pohorecky LA, Yu L. Pairings of lever and food induce Pavlovian conditioned approach of sign-tracking and goal-tracking in C57BL/6 mice. Behavioural Brain Research. 2012; 226:571–578. http://dx.doi.org/10.1016/j.bbr.2011.10.021. [PubMed: 22026925]

Trask S, Thrailkill EA, Bouton ME. Occasion setting, inhibition, and the contextual control of extinction in Pavlovian and instrumental (operant) learning. Behavioural Processes. 2017; 137:64–72. http://dx.doi.org/10.1016/j.beproc.2016.10.003. [PubMed: 27720958]

Tunstall BJ, Kearns DN. Sign-tracking predicts increased choice of cocaine over food in rats. Behavioural Brain Research. 2015; 281:222–228. http://dx.doi.org/10.1016/j.bbr.2014.12.034. [PubMed: 25541036]

Turchi J, Sarter M. Cortical acetylcholine and processing capacity: Effects of cortical cholinergic deafferentation on crossmodal divided attention in rats. Cognitive Brain Research. 1997; 6:147–158. http://dx.doi.org/10.1016/S0926-6410(97)00027-X. [PubMed: 9450608]

Turchi J, Sarter M. Cortical cholinergic inputs mediate processing capacity: Effects of 192 IgG-saporin-induced lesions on olfactory span performance. European Journal of Neuroscience. 2000; 12:4505–4514. [PubMed: 11122361]

Versace F, Kypriotakis G, Basen-Engquist K, Schembre SM. Heterogeneity in brain reactivity to pleasant and food cues: Evidence of sign-tracking in humans. Social Cognitive and Affective Neuroscience. 2015; 11:604–611. [PubMed: 26609106]

Voon V, Dalley JW. Translatable and back-translatable measurement of impulsivity and compulsivity: Convergent and divergent processes. Current Topics in Behavioral Neurosciences. 2015; 28:53–91. http://dx.doi.org/10.1007/7854_2015_5013.

White HA, Shah P. Creative style and achievement in adults with attention-deficit/hyperactivity disorder. Personality and Individual Differences. 2011; 50:673–677. http://dx.doi.org/10.1016/j.paid.2010.12.015.

Xue L, Sheng J, Wu XS, Wu W, Luo F, Shin W, Wu LG. Most vesicles in a central nerve terminal participate in recycling. The Journal of Neuroscience: The Official Journal of the Society for Neuroscience. 2013; 33:8820–8826. http://dx.doi.org/10.1523/JNEUROSCI.4029-12.2013. [PubMed: 23678124]

Yager LM, Pitchers KK, Flagel SB, Robinson TE. Individual variation in the motivational and neurobiological effects of an opioid cue. Neuropsychopharmacology. 2015; 40:1269–1277. http://dx.doi.org/10.1038/npp.2014.314. [PubMed: 25425322]

Yager LM, Robinson TE. A classically conditioned cocaine cue acquires greater control over motivated behavior in rats prone to attribute incentive salience to a food cue. Psychopharmacology. 2013; 226:217–228. http://dx.doi.org/10.1007/s00213-012-2890-y. [PubMed: 23093382]

Zimmer BA, Oleson EB, Roberts DC. The motivation to self-administer is increased after a history of spiking brain levels of cocaine. Neuropsychopharmacology. 2012; 37:1901–1910. http://dx.doi.org/10.1038/npp.2012.37. [PubMed: 22453139]
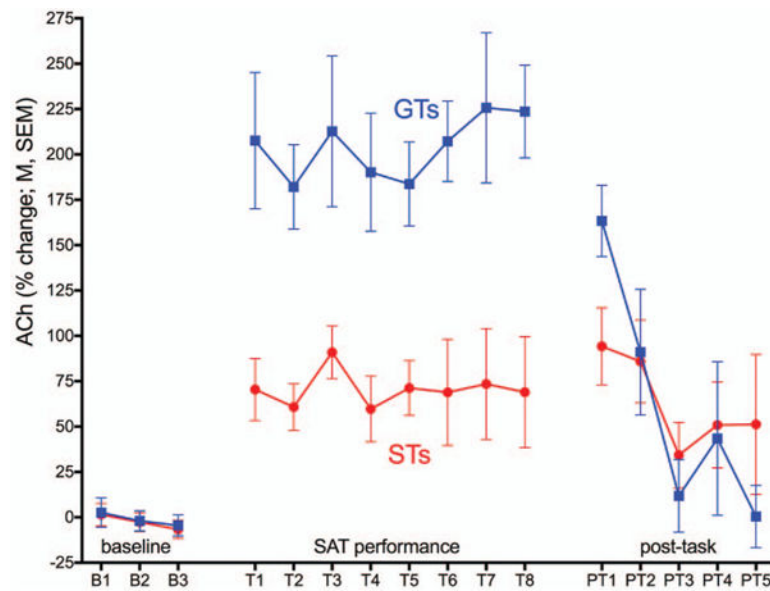
**Figure 1.**
Sustained Attention Task (SAT) performance-associated increases in extracellular acetylcholine (ACh) levels in the medial prefrontal cortex of goal-trackers (GTs) and sign-trackers (STs; B1-B3, pretask baseline; T1-T8: during SAT; PT1-PT5: posttask levels). Absolute basal ACh release levels did not differ between the groups. The relatively poor and unstable attentional performance of STs was associated with strikingly attenuated right prefrontal extracellular ACh levels when compared with GTs (from Paolone et al., 2013, reprinted with permission). See the online article for the color version of this figure.
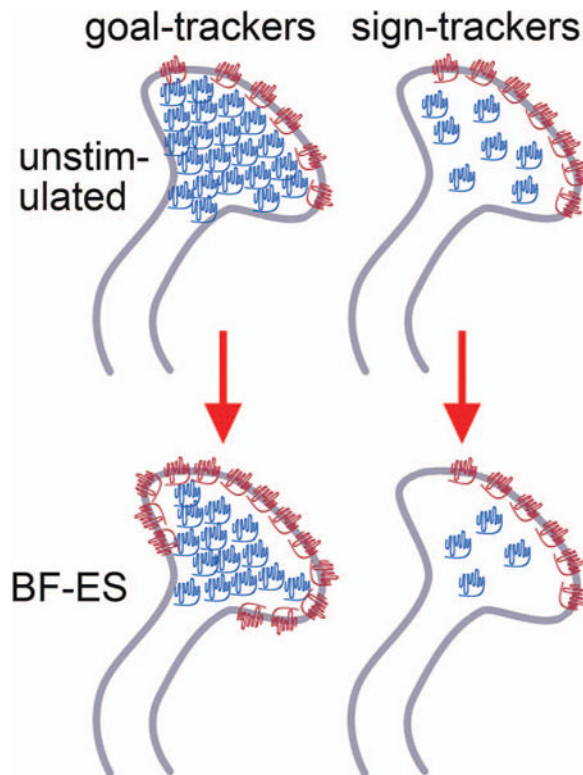
**Figure 2.**

In synaptosomes from sham-stimulated (unstimulated) animals, the density of choline transporters (CHTs) in the synaptosomal plasma membrane (indicated by red protein symbols in membrane) did not differ between sign-trackers (STs) and goal-trackers (GTs), consistent with the absence of differences in basal, absolute levels of acetylcholine (ACh) release as measured by microdialysis. However, while total synaptosomal CHT protein did not differ between the phenotypes, the density of CHTs in the intracellular LP2 fraction (blue protein symbols) was lower in STs than in GTs, suggesting that a portion of CHTs in STs are on domains not captured by our fractionation methods. Following basal forebrain electrical stimulation (BF-ES), in GTs, CHT density in the synaptosomal plasma membrane increased and this was reciprocated by losses in the LP2 fraction, consistent with an upregulation of the capacity of cholinergic neurons of GTs to increase levels of neuromodulation. In STs, BF-ES failed to increase synaptosomal plasma CHT density. Moreover, intracellular CHT density also decreased in STs following BF-ES, suggesting again that CHT trafficking in STs involves additional subcellular domains hosting CHTs. The absence of increases in CHT density in synaptosomal plasma membrane in STs is hypothesized to be the primary mechanism responsible for the limited capacity of cholinergic neurons of STs to support increases in levels of cholinergic neuromodulation (for details see Koshy Cherian et al., 2017). See the online article for the color version of this figure.
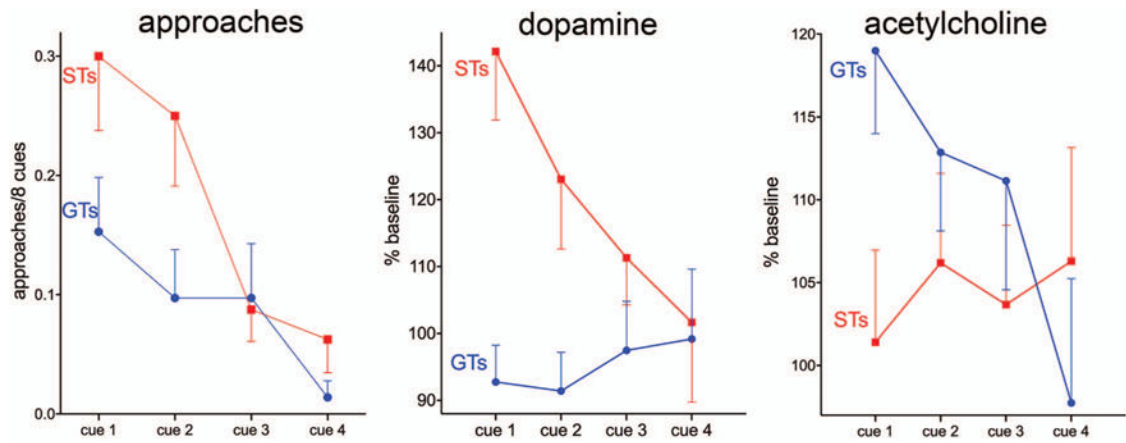
**Figure 3.**

Number of approaches to the Pavlovian drug cue and extracellular dopamine (DA) and acetylcholine (ACh) levels in sign-trackers (STs) and goal-trackers (GTs) during 4-min blocks during which the cue was presented eight times for 5 s every 30 s (cocaine was unavailable). STs significantly approached the cue more frequently than GTs, exhibited increased prefrontal DA levels and, in contrast to GTs, did not exhibit increases in ACh release. Unpaired rats did not approach the cue and did not exhibit significant changes in DA or ACh levels. In STs, the number of approaches and DA levels were significantly correlated (Pitchers, Kane, et al., 2017). See the online article for the color version of this figure.
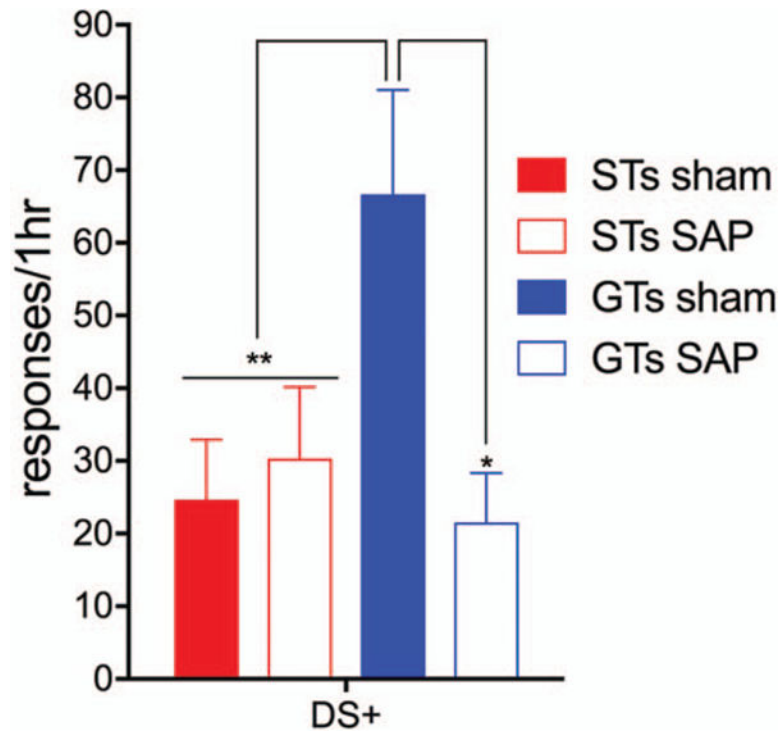
**Figure 4.**
Number of responses previously yielding cocaine infusions in the presence of the DS+ by
sham-operated goal-trackers (GTs) and sign-trackers (STs) and rats with 192 IgG saporin-
induced (SAP) losses of the BF cholinergic system. Sham-operated GTs generated
significantly more nose-pokes than STs. Loss of about 50% of the cholinergic neurons in the
basal forebrain reduced cocaine-seeking behavior in GTs to the level seen in sham-operated
STs. The lesions had no effects on cocaine-seeking in STs (reproduced with permission from
Pitchers, Phillips, et al., 2017). See the online article for the color version of this figure.