

Attention and the Cholinergic System: Relevance to Schizophrenia

Cindy Lustig and Martin Sarter

Abstract Traditional methods of drug discovery often rely on a unidirectional, “bottom-up” approach: A search for molecular compounds that target a particular neurobiological substrate (e.g., a receptor type), the refinement of those compounds, testing in animal models using high-throughput behavioral screening methods, and then human testing for safety and effectiveness. Many attempts have found the “effectiveness” criterion to be a major stumbling block, and we and others have suggested that success may be improved by an alternative approach that considers the neural circuits mediating the effects of genetic and molecular manipulations on behavior and cognition. We describe our efforts to understand the cholinergic system’s role in attention using parallel approaches to test main hypotheses in both rodents and humans as well as generating converging evidence using methods and levels of analysis tailored to each species. The close back-and-forth between these methods has enhanced our understanding of the cholinergic system’s role in attention both “bottom-up” and “top-down”—that is, the basic neuroscience identifies potential neuronal circuit-based mechanisms of clinical symptoms, and the patient and genetic populations serve as natural experiments to test and refine hypotheses about its contribution to specific processes. Together, these studies have identified (at least) two major and potentially independent contributions of the cholinergic system to attention: a neuromodulatory component that influences cognitive control in response to challenges from distractors that either make detection more difficult or draw attention away from the distractor, and a phasic or transient cholinergic signal that instigates a shift from ongoing behavior and the activation of cue-associated response. Right prefrontal cortex appears to play a particularly important role in the neuromodulatory component integrating motivational and cognitive influences for top-down control across populations, whereas the transient cholinergic signal involves orbitofrontal regions associated with shifts between internal and external attention. Understanding how these two modes of

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cholinergic function interact and are perturbed in schizophrenia will be an important prerequisite for developing effective treatments.

Keywords Schizophrenia · Acetylcholine · Attentional effort · Right prefrontal cortex · Cross-species

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Deficits in controlled attention are a primary cognitive symptom of schizophrenia. They are present before the first psychotic episode and in putatively healthy relatives, are not well-treated by standard dopaminergic medications, and persist even in remission states (Cornblatt and Keilp 1994; Nuechterlein and Dawson 1984; Wohlberg and Kornetsky 1973; see Lesh et al. 2011 for a recent review). These deficits are critical to address, as in both cross-sectional and longitudinal studies, impairments in controlled attention and closely-related executive functions are among the strongest predictors of real-world outcomes including social functioning and work skills (e.g., Bowie et al. 2008; Green 1996; Torgalesboen et al. 2014, 2015). The cholinergic system is an attractive target for potential pharmaceutical interventions because it plays a critical role in attention (see Hasselmo and Sarter 2011; Sarter et al. 2014; Sahakian et al. 1989, 1993) and is disrupted in schizophrenia. Here, we review some of the difficulties in developing such interventions, emerging approaches and results that may help overcome those difficulties, and promising avenues for future research.

Despite strong a priori reasons to believe that cholinergic treatments should benefit cognition in schizophrenia, attempts to develop them have been largely disappointing (see reviews by Foster et al. 2014; Money et al. 2010; Rowe et al. 2015; but see Meltzer 2015 for a more optimistic view). Several factors play into this. One is that in contrast to most antipsychotics, where drug development has

relied heavily on “me too” variations of early discoveries, there is a lack of initial effective agents to serve as a starting point (Young et al. 2010). Another, common to almost all areas of psychiatric drug research, is the paucity of well-validated paradigms that allow preclinical research in animal models to translate to effectiveness in treating human neuropathology (Markou et al. 2009; Wong et al. 2010). A third is that most existing drugs are based on theoretical models that treat the cholinergic system primarily as a diffuse neuromodulator (e.g., Briand et al. 2007; Dani and Bertrand 2007; Picciotto et al. 2012). Burgeoning evidence points to both regionally and temporally specific cholinergic functions that interact with each other but are independent and dissociable (Hasselmo and Sarter 2011; Sarter et al. 2009b).

With those factors in mind, the limited success of cholinergic procognitive treatments is understandable. However, the more positive news is that the field has become acutely aware of these issues and is working to address them. In particular, the MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia) and CNTRICS (Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia) initiatives have specifically targeted the goal of producing standardized, reliable assessments that can be used in both preclinical and clinical research to assess specific aspects of neurocognitive function. In addition, there is an increasing recognition that there are multiple neurobiological pathways to the same behavioral outcome, and that understanding and targeting the correct pathways will be a critical link between manipulations of cellular mechanisms and successful behavioral change. Taking things a step further, if the ultimate target is improved cognitive function that will generalize to real-world behavior, then one also has to establish the degree to which the behavioral test measures that function. That is, it is not enough for a test to translate from animal model to patient, it also has to translate from the lab or clinic into everyday life.

In discussing these issues and the problems plaguing psychiatric drug discovery more generally, Sarter and Tricklebank (2012) suggested that most drug discovery efforts leap from genetic and molecular targets to changes in behavior in standardized, even reified preclinical behavioral paradigms (e.g., Morris water maze measures spatial learning/memory; Y-maze measures anxiety) without much consideration of the neural circuits that mediate such behaviors, or the cognitive operations that they reflect. They suggested that a more integrated consideration of the neural circuits level would likely lead to better success (Fig. 1).

Others have reviewed the genetic and cellular mechanisms of cholinergic function and their effects on neural circuits (e.g., Bentley et al. 2011; Bloem et al. 2014a, b; Hasselmo and Sarter 2011; Rowe et al. 2015; Riedel et al. 2015; Sarter 2015; Thiele 2013) as well as what is known about schizophrenia-related dysfunction at these levels of analysis (e.g., Gagne et al. 2015; Nikolaus et al. 2014; Seo et al. 2014). Here we begin by describing some of the deficits in attention performance observed in schizophrenia and their neuroimaging correlates in humans. Next, we describe the evidence for cholinergic modulation of neural circuits contributing to those neuroimaging and behavioral findings. Together, these guide hypotheses about the cognitive operations reflected by behavior, how they may be disrupted in schizophrenia and other conditions, and potential avenues for treatment.

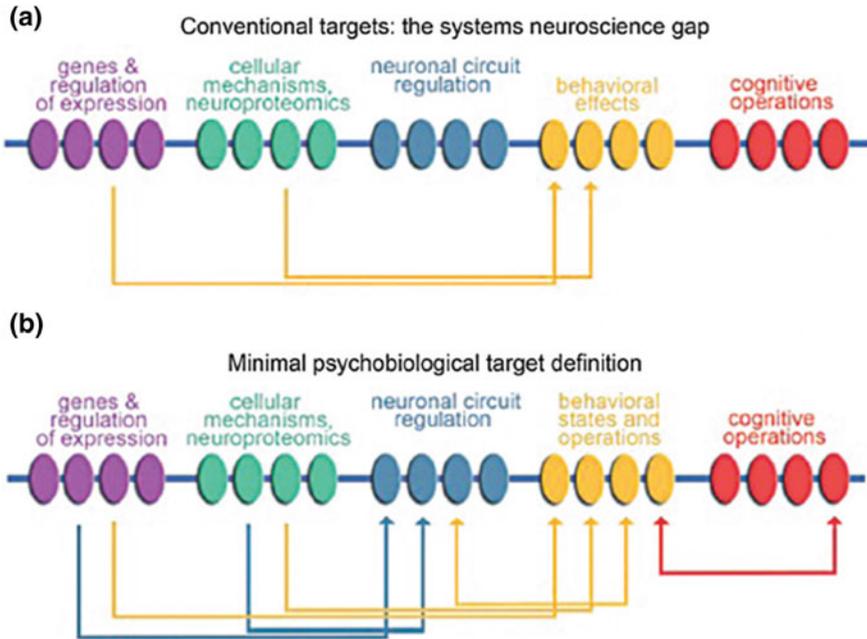


Fig. 1 Conventional and psychobiological target definition (from Sarter and Tricklebank 2012). **a** Current efforts at drug development have defined targets based on the findings that manipulation of genetic or cellular mechanisms influence behavior, but often fail to consider how neural circuits mediate those influences. As behavior is multiply determined, this is a likely contributor to the low success rate of pharmaceutical development. **b** A recommended approach is to establish whether an intervention affects the activity of neural circuits, and then in turn whether those circuits mediate the behavior in question. Further, consideration of the cognitive operations driving behavior is required to avoid misinterpretation of the behavior [e.g., does failure to respond to a signal represent a failure to see it (perceptual), a failure to activate the task set and responses associated with the signal (cognitive), or a lack of interest or motivation (motivational/emotional)] and facilitate generalization. The present review focuses on cholinergic regulation of frontoparietal circuits involved in attention and the consequences for behavior and cognition in schizophrenia (reproduced with permission)

1 Attentional CRUNCH points in Schizophrenia: A Special Role for Right PFC?

Attention is a very broad-based concept, and the use of this single term to describe what in all likelihood is a wide range of cognitive abilities and processes can lead to significant confusion. Recognizing this, CNTRICS recommended restricting its use in the context of schizophrenia to selective attention, and specifically to the “input selection” function. The related concept of “rule selection” was assigned to executive function. However, the distinction is somewhat arbitrary and made primarily to allow a more manageable grouping of different tasks within the CNTRICS framework (Luck et al. 2012). For example, one might consider selecting a target

out of an array of distractors as an example of input selection, but of course rules are required to determine what constitutes the target. At the other extreme, choosing the correct sorting rule in the Wisconsin Card Sort would be an example of rule selection, but the process of subsequently keeping attention on the correct dimension (color, shape, or number) might be considered input selection.

Input selection is defined as restricting processing to a subset of inputs, and determining which inputs are sent to memory and/or response systems (Luck et al. 2012). For example, as you are reading this, you are receiving various other sensory inputs, such as ambient noise from the environment or the pressure from your chair on your back and legs. Well-functioning input selection processes ensure that the words on this page are selected for further processing, rather than those irrelevant inputs. The construct of input selection can be subdivided into those processes responsible for controlling attention versus those involved in implementing that control by increasing the strength of the relevant signal and/or decreasing the strength of irrelevant inputs. (See Box 1 for a description of human and animal paradigms selected by CNTRICS as relevant to input control.)

Patients are thought to have impaired top-down control, but relatively preserved implementation. For example, they are impaired if there is a conflict inherent in a cue [e.g., in anti-saccade tasks, where the task is to attend in the opposite direction of the cue; Fukushima et al. (1990)] or if the cue itself is nonspecific [e.g., identifies several potential target locations that must be simultaneously monitored; Hahn et al. (2012)]. In contrast, if the cue is simple (as in a prosaccade task), patients and controls typically show equivalent benefits to response time and accuracy—that is, they are equally able to implement the modulation of attention in response to that cue. Furthermore, even though sustaining attention over time is typically considered a controlled-attention or executive process, patients do not typically show exaggerated time-on-task declines unless the task that is to be maintained over time puts high demands on input selection (e.g., Demeter et al. 2013; Egeland et al. 2003 c.f., Hahn et al. 2012 for an example with high input-selection demands).

However, equivalent performance at the behavioral level does not necessarily imply equivalence at either the neural circuit or cognitive operations levels. Patients have dysfunctional sensory processing starting at very early stages, and both that dysfunction and attempts to compensate for it lead to widespread, interactive effects. Several studies have shown that patients with schizophrenia have reduced retinal nerve fiber thickness compared to controls, and it is speculated that dopamine-glutamate dysregulation may further affect the processing of remaining cells, e.g., by altering ganglionic receptive fields (see review by Gracitelli et al. 2015). Contrast sensitivity deficits are frequently associated with schizophrenia, although there is some controversy as to whether the magno- and parvo-cellular systems are affected equally or if not, which one is affected more. The answer to this question may differ depending on whether one is considering first-episode versus chronic patients, and on medication status (Shoshina et al. 2014).

Furthermore, adaptations that are beneficial in some circumstances can be detrimental in others. For example, Leonard et al. (2014) found that despite presumed impairments in magnocellular pathways, patients were more vulnerable to

distractors designed to activate the magnocellular system than those designed to selectively activate the parvocellular system, whereas healthy controls showed the opposite pattern. The authors speculate that this may occur if later-stage top-down processing attempts to compensate for degraded magnocellular pathways by giving more weight to their inputs. Although this may aid the processing of relevant magnocellular inputs, it has the side effect of also increasing vulnerability to distractors with components (e.g., movement or flickering, contrast rather than hue differences from background) that stimulate this system.

Regardless of their source, such reductions in sensory processing add noise to the inputs that are to be selected among, creating an increased burden on input-selection processes. In addition, modulatory feedback from top-down attention systems affects processing even at these early stages (Laycock et al. 2007; Skottun and Skoyles 2007). In other words, patients may suffer from a “triple-hit”: (1) their bottom-up sensory inputs are impaired starting at very early (e.g., retinal) stages, (2) impaired top-down control systems are inefficient at modulating these sensory inputs (e.g., Dima et al. 2010; Silverstein et al. 1996; see discussion by Robinson et al. 2011; Sarter et al. 2005), (3) both of these combine to result in noisier representations that further tax already-impaired top-down control, including input selection. (See Lustig and Jantz 2015 for a parallel argument applied to aging.)

The increased demands on an already-impaired top-down attentional system in schizophrenia may help explain what at first appear to be contradictory findings regarding schizophrenia-related abnormal activation patterns in the frontoparietal regions thought to support top-down control. That is, abnormalities in both structural and functional neuroimaging measures of these regions are typically found in both patients and their putatively healthy relatives, but some activation studies find that patients and their relatives show more activation in these regions than do controls, whereas others find the opposite (see meta-analyses by Gogarhi 2011; Minzenberg et al. 2009; Scognamiglio and Houenou 2014). Thus, there is general agreement that prefrontal processing is abnormal in schizophrenia, but apparent contradiction across studies as to the direction of that abnormality.

Manoach (2003) suggested that these contradictions might be resolved by considering load-performance interactions. This hypothesis suggests that at low loads, patients will show equivalent performance but increased frontoparietal activation (i.e., hyperactivation) compared to controls. As load increases, both patients and controls increase activation in response, but patients may reach a functional ceiling at lower loads than controls. Once that ceiling is reached, patients will show lower performance and activation (i.e., hypoactivation) compared to controls. After that point, activation may decline not just relative to controls but absolutely, as patients become demotivated or disorganized due to poor performance at the highest loads, or perhaps try alternative strategies. Controls are hypothesized to show a similar performance x activation function, but shifted to the right (Fig. 2).

Although it appears to have been missed in the Manoach (2003) review, an early PET study by Fletcher et al. (1998) provides what is to our knowledge the most direct evidence supporting this hypothesis. Healthy controls and patients with either

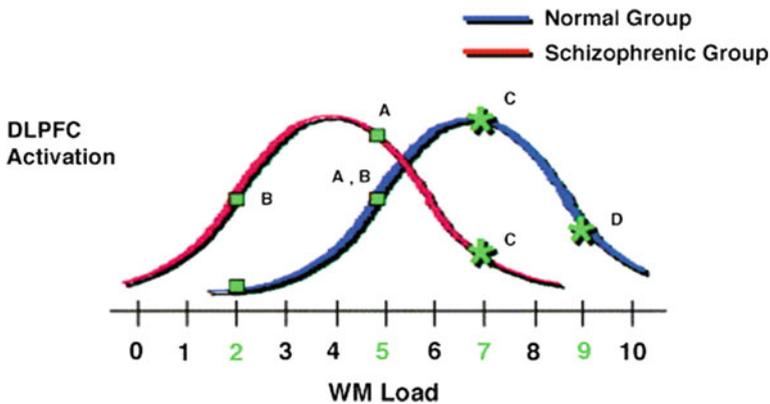


Fig. 2 CRUNCH in schizophrenia? Idealized relationship between working memory load and dorsolateral prefrontal (DLPFC) activation in schizophrenia (Figure from Manoach 2003; squares indicate empirical data points, asterisks indicate hypothesized results). As load increases, so does DLPFC activation, until load supersedes ability and both performance and activation decline. This pattern occurs for both patients and healthy controls, but the curve for patients is shifted left, so that at low objective loads (2 items) patients exhibit higher activation and similar performance as controls. At high loads (7 items) patients are expected to show decrease in activation and performance, whereas healthy controls continue to activate DLPFC to meet with the increased demand. This pattern has also been observed when comparing healthy older adults to young adults, where it is described under the CRUNCH (Compensation Related Utilization of Neural Circuits Hypothesis) framework (Reuter-Lorenz and Lustig 2005; Reuter-Lorenz and Cappell 2008)

high or low degrees of memory impairment heard and then attempted to retrieve word lists of 1–12 items. All groups showed an initial increase in prefrontal activation up to about 7 items. After this point, activation levels for high-impairment patients leveled off and began to drop, with activation at 12 items being roughly the same as at 4 items; for less-impaired patients this function was shifted right, with increasing activation up to about 9 items. Controls did not show a downturn, but this may have been because the task was not sufficiently demanding (and they may have switched to long-term rather than short-term memory retrieval), as their performance remained relatively stable following an initial drop at the introduction of supra-span lists.

Subsequent studies by other groups (e.g., Cairo et al. 2004; Manoach et al. 1999, 2000) likewise found that patients showed comparative hyperactivation at low working memory loads and hypoactivation at higher ones, but did not test even higher loads that might have allowed observation of the absolute downturn. Similar results were reported in a meta-analysis by Van Snellenberg et al. (2006). A later empirical study from this group failed to find shifted functions for patients compared to controls in a procedure previously shown to produce an inverted-U function in healthy adults, but interpretation is complicated by a failure to observe an effect of memory load in any brain regions in patients, suggesting they may have approached the task very differently (Van Snellenberg et al. 2013, 2015).

Notably, the shifted inverted-U pattern hypothesized for schizophrenia has been observed in several studies of healthy older adults, suggesting a common mechanism. The CRUNCH (Compensation Related Utilization of Neural Circuits Hypothesis) framework similarly suggests that older adults will show preserved performance but higher prefrontal activation at low loads, and that as load increases, individuals reach a “CRUNCHpoint” or functional ceiling, after which performance and activation decline (Reuter-Lorenz and Lustig 2005; Reuter-Lorenz and Cappell 2008). As in schizophrenia, most tests of this hypothesis have used working memory tasks, since load is easy to manipulate, but at least one study also found support for the hypothesis when manipulating executive-attention demands (Sebastian et al. 2013). Several of the studies in aging have found the hypothesized downturn in activation at high levels of demand, suggesting that these paradigms may be useful for rigorous tests of the hypothesis in schizophrenia.

Further supporting the hypothesis of a common pathway potentially supporting compensation in patients with schizophrenia and older adults, and possibly other populations including multiple sclerosis (e.g., Cader et al. 2006; Parry et al. 2003), right dorsolateral prefrontal cortex along middle and inferior frontal gyrus appears to be a common locus for the inverted U-curve with load in healthy adults, the CRUNCH pattern in older adults, and abnormality in schizophrenia (Fig. 3). As we will describe in the next section, parallel rodent–human studies suggest that the cholinergic system plays a critical role in modulating this region’s response to demand, and may also provide insight into associated cognitive operations.

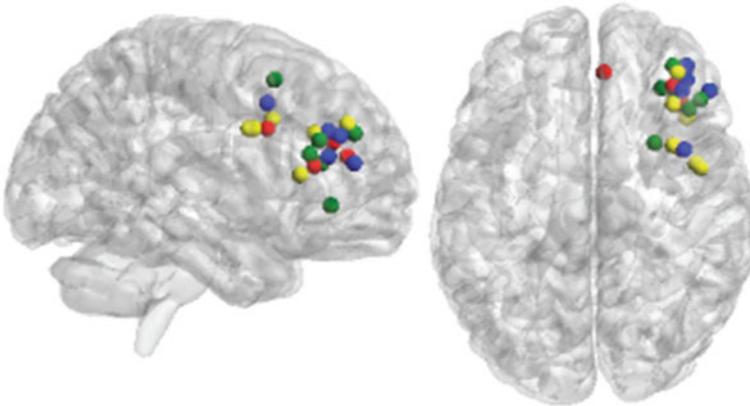


Fig. 3 Overlap between CRUNCH, schizophrenia, and dSAT. Right middle and frontal gyrus is a common site for activation peaks reported in studies of U-shaped demand-activation curves in young adults (*green*; Callicott et al. 1999; Van Snellenberg et al. 2015), shifted U-curves (the CRUNCH pattern) in older adults (*blue*; Cappell et al. 2010; Mattay et al. 2006; Schneider-Garces et al. 2010; Sebastian et al. 2013); schizophrenia-related abnormalities in working memory tasks (*red*; Fletcher et al. 1998 PET study cited in text; Minzenberg et al. 2009 meta-analysis), and distractor-related activation in the dSAT (*yellow*; Berry et al. 2014; Demeter et al. 2011)

2 Cholinergic-Attentional Control Deficits: Anatomical Foundations and Evidence from Rodent Studies

The neuronal circuitry-based foundations of the attentional impairments in schizophrenia remain largely unclear. However, the considerable evidence for the influence of basal forebrain cholinergic innervation on the frontoparietal networks that support attention and cognitive control suggests that abnormalities in this system likely play a major role. Below we briefly describe key aspects of the functional anatomy of the basal forebrain cholinergic system, including the main cortical effects of cholinergic neurotransmission and the influence of cortical feedback to the basal forebrain and, indirectly, via mesolimbic regions. The potential contributions of cholinergic abnormalities to attention problems in schizophrenia are discussed in light of our current understanding of abnormalities in the development and regulation of forebrain circuitry schizophrenia.

2.1 Cortical Cholinergic Projections: Anatomical Aspects Consistent with Top-down Functions

The basal forebrain cholinergic projections to the cortex historically have been considered a component of the brain's ascending systems. The attribution of broad, undefined functions, such as enhancing arousal, wakefulness, and gating the cortical processing of stimuli has been characteristic of such traditional hypotheses (e.g., Castro-Alamancos and Gulati 2014). Consistent with its largely ascending projections to telencephalic regions, such conventional conceptualizations of the cholinergic system are strictly bottom-up, meaning that cholinergic activation has been considered stimulus-driven or under the control of circadian mechanisms. In other words, cholinergically-induced cortical states have been viewed as secondary to the presence of a stimulus or endogenous clocks.

Our alternative view of the cholinergic system conceptualizes these ascending projections as a major arm of the brain's top-down machinery. In other words, we describe the recruitment of cholinergic neurons as occurring in the service of cognitive control functions such as task maintenance, particularly maintaining rules "on-line" for responding flexibly to changing stimulus (or cue) configurations, sustaining attention to defined cue sources and cue probabilities, integrating levels of motivation with performance, and with the last function possibly the calculation of the value of continued performance over alternative action.

Importantly, recent analyses of the anatomical organization of cholinergic projections to cortical regions increasingly reject the conventional notion of a "diffusely organized" or "reticular" projection system. Instead, they document evidence for a highly topographic, cluster-based organization of cholinergic neurons in the basal forebrain, with associated projection patterns that dissociate cortical subregions, columns, and even patches coinciding with other afferent cortical projection

systems (Zaborszky et al. 2005, 2008, 2012, 2015a, b; Bloem et al. 2014a, b; Ji et al. 2015). Although there is still much debate about the extent of the cortical terminal field of individual cholinergic projections and clusters of basal forebrain cholinergic neurons (Mechawar et al. 2000; Umbriaco et al. 1994; Muñoz and Rudy 2014), recordings of acetylcholine (ACh) release in behaving animals increasingly demonstrate that cholinergic activity is at least in part highly localized and supports defined behavioral/cognitive operations (below), consistent with the contemporary description of basal forebrain cholinergic projections as a highly topographic, clusterized projection system (see also Xiang et al. 1998).

Understanding the cortical cholinergic input system as a main branch of the brain's top-down machinery begins with evidence indicating that, in primates and rodents, prefrontal regions are the only cortical regions that project directly to the cholinergic basal forebrain (Gaykema et al. 1991; Zaborszky et al. 1997). Second, mesolimbic regions, including the nucleus accumbens and the ventral tegmentum target cholinergic neurons in the basal forebrain (Smiley et al. 1999; Zaborszky and Cullinan 1996). Prefrontal regions directly influence these mesolimbic dopaminergic activity (Carr and Sesack 2000; Brady and O'Donnell 2004; Belujon and Grace 2008), and thus the activation of cholinergic neurons as a function of demands on attention (below) likewise constitutes a prefrontally-supervised function.

Third, prefrontal circuitry can influence and even control cholinergic activity via projections that, directly and indirectly, target cholinergic terminals. Specifically, the generation of phasic cholinergic signaling has been hypothesized to be based primarily on cortical circuitry controlling cholinergic terminals. That is, the cortex integrates cholinergic terminals into its circuitry based on heteroreceptors expressed at cholinergic terminals. Such terminal regulation adds a tremendous degree of functional specification of cholinergic function as local cortical circuitry can control the release of ACh and thus specify cholinergic function regardless of the (disputed) degree of terminal arborization space and the "diffuseness" of the cortical cholinergic projection system (Sarter et al. 2014).

In addition to these three anatomical sources of top-down control of cholinergic activity, cholinergic activity in prefrontal regions per se influences, top-down, cholinergic activity elsewhere in the cortex, but the reverse does not occur (Nelson et al. 2005). These prefrontal efferent effects require the stimulation of muscarinic acetylcholine receptors (mAChRs), consistent with the general view that this group of receptors mediates the flow of information within and between cortical circuits (Hasselmo et al. 1992; Disney and Aoki 2008). Cholinergic stimulation of mAChRs in the frontal cortex generates high-frequency oscillatory activity (Sarter et al. 2015), considered an indication of cross-regional coordination of cortical processes (Bauer et al. 2012). Thus, in prefrontal cortex, cholinergic activity may foster the orchestration of cognitive mechanisms that support, top-down, the sustaining of attention, particularly in the presence of distractors. Cholinergic activity in parietal and other cortical regions serves as a component mediating these top-down effects, as it is controlled via prefrontal projections to basal forebrain and mesolimbic regions and, via one or multiple synapses, to cholinergic terminals in sensory and sensory-association regions.

2.2 Multiple Time Scales of Cholinergic Signaling Mediate Distinct Attentional Processing Steps

Recent evidence indicates that in addition to the spatial specificity described above, cholinergic activity is also temporally specific. At least three timescales have been observed in rodent prefrontal cortex. The first appears to operate in the seconds - to-minutes range, and is represented by the increases in prefrontal acetylcholine (ACh) levels seen as the animal moves from baseline to task performance, with further increases in response to the distractor condition or other challenges (Himmelheber et al. 2000; Kozak et al. 2006, 2007; St. Peters et al. 2011). This neuromodulatory component of cholinergic activity interacts with mesolimbic systems: Stimulation of the nucleus accumbens shell reduces distractor-related performance impairments, reflecting enhanced or compensatory mesolimbic recruitment of cholinergic-attentional mechanisms. Consistent with this hypothesis, the benefits of accumbens stimulation are eliminated by removing either prefrontal or parietal cholinergic inputs (St. Peters et al. 2011).

Recent technological developments allowed the identification of a second “transient” response system, operating at the seconds timescale (Parikh et al. 2007, 2010). Thus far, cholinergic transients have been observed in response to signals that occur either with a long temporal delay between trials (Parikh et al. 2007) or when a signal trial is preceded by a perceived nonsignal (i.e., correct rejection or miss) trial (Howe et al. 2010). Cholinergic transients are initiated by a signal-evoked thalamic glutamatergic response that is itself modulated by the longer timescale subsystem described above. Notably, this thalamic signal is required but not sufficient to initiate the cholinergic response, as indicated by the absence of such transients during consecutive trials requiring cue-oriented responses. The thalamic signal occurs for every detected signal, but the cholinergic transient is governed by the temporal and/or sequence constraints described above. This suggests that the cholinergic response is involved in cognitive rather than sensory processing, a supposition further supported by the finding that the cholinergic transients are more closely associated in time with cue-triggered response initiation than with the cue per se.

Parikh et al. (2007) also found evidence for cholinergic functions at a third, intermediate timescale. Gradual decreases in cholinergic activity over the 20 s before signal presentation were associated with correct signal detection (hits), whereas gradual increases were associated with failures to detect the signal (misses). We have not further explored this subsystem, although one distinguishing feature is that these more gradual increases and decreases are seen in both PFC and motor cortex, whereas the transients described above are only seen in PFC. Although further testing using different interstimulus intervals is needed to determine if the 20 s value is meaningful or coincidental (that is, would similar drifts occur at longer or shorter interstimulus intervals?), there are some intriguing parallels at this timescale in the human cognitive neuroscience literature. Fluctuations in response-time variability, though to reflect fluctuations in attention, occur in about 20 s cycles in the Ericksen flanker task, and this pattern is exaggerated in

subjects with ADHD (Castellanos et al. 2005). In another attention task, O'Connell et al. (2009) observed that increases in EEG measures of alpha activity occurred about 20 s before a missed target, a pattern very reminiscent of the increases in cholinergic activity before a miss observed by Parikh et al. (2007). The idea that these phenomena may be related is reinforced by the fact that alpha oscillations are cholinergically modulated. For example, in a spatial attention paradigm, physostigmine reduced alpha activity in the hemisphere contralateral to stimulus presentation and improved performance (Bauer et al. 2012).

3 Cholinergic Dysregulation in Schizophrenia: Possible Causes and Consequences

Understanding of how neuronal circuitry is structurally abnormal and functionally dysregulated in schizophrenia remains quite limited, and further complicated by the likelihood of multiple subtypes of the disorder that may manifest different neuropathologies. For example, in a *post mortem* study, Scarr et al. (2009) found that about 25 % of patients had especially marked deficiencies in a PET marker of muscarinic binding sites in middle and inferior frontal gyrus sites, and might constitute a separate genetic and behavioral subgroup. The hypothesis of cholinergic dysfunction in schizophrenia is indirectly supported by several lines of evidence including genetics, neuroimaging, and high rates of nicotine use that suggest attempts at self-medication, but the nature of that dysfunction has been difficult to define. This difficulty accrues from the lack of suitable *in vivo* methods for monitoring cholinergic activity in patients, the limited insights afforded by post-mortem analysis of cholinergic enzyme levels that are not rate-limiting steps in the synthesis or metabolism of ACh, the challenges associated with the interpretation of changes in receptor levels measured in *in vivo* studies, and the scarcity of pharmacological tools to assess defined and selective aspects of cholinergic function (for detailed discussion of evidence on cholinergic function in schizophrenia and related pharmacological issues see Sarter et al. 2012; Sarter et al. 2009a; Hasselmo and Sarter 2011).

Current theories of schizophrenia focus on the development of cortical microcircuitry, in particular the wiring of inhibitory interneurons and abnormal functions of amino acid receptors and cytoskeletal proteins. Establishing relationships between such mechanisms and hypotheses about circuit-based neuronal aberrations has remained a difficult objective (see also Higley and Picciotto 2014). However, there is wide agreement that the clear neurotransmitter-related hallmark of schizophrenia, the hyperdopaminergic functions during active disease states (e.g., Howes and Kapur 2009; Kapur and Mamo 2003), eventually may be understood as a consequence of the diverse, largely telencephalic, developmental, and cellular abnormalities that all yield schizophrenia. Similarly, abnormal interneuronal contacts, GABAergic, and glutamatergic receptor function all may contribute to the low levels of cholinergic neuromodulation and cholinergic transient dysregulation that

are candidate hypotheses for explaining the attentional control issues in these patients. Specifically, we hypothesize that GABAergic functions are essential for suppressing cholinergic transients in noncued trials and we demonstrated that glutamatergic synapses of thalamic afferents are necessary, but not sufficient, for the generation of cholinergic transients (reviewed in Sarter et al. 2014; Sarter 2015). Thus, dysregulation in front-parietal GABA and glutamatergic functions may readily disrupt the generation of cholinergic transients and yield ill-timed transients, failures to generate transients, or transients with temporal dynamics that are sufficient altered to cause nonadaptive and even invalid cue detection operations.

Furthermore, abnormal mesolimbic dopaminergic activity has been conceptualized as a consequence of abnormal frontal cortical circuitry (e.g., Brady and O'Donnell 2004; Sesack and Grace 2010). Mesolimbic activity is necessary for cholinergic activation and associated performance (Neigh et al. 2004) and abnormal mesolimbic dopaminergic activity therefore is likely to alter cholinergic function and thus attentional control and cue detection. These mesolimbic–cholinergic interactions are key to understanding the integration of motivational with attentional functions (Small et al. 2005; Krebs et al. 2012; Mendelsohn et al. 2014; Hungya et al. 2015). Thus, abnormal dopaminergic functions in schizophrenia may greatly impact cholinergic neuromodulation and the generation of cholinergic transients. Consistent with this view, animals with sensitized mesolimbic dopaminergic functions—which may model an acute disease state—exhibit cholinergic systems that remain “frozen” at baseline and unable to support attentional performance (Kozak et al. 2007). We know much less about the reactivity of the dopaminergic system outside active disease states but it would be expected that it is dysregulated. Thus, the cholinergic abnormalities deduced from experiments in rodents may be present in schizophrenia and secondary to frontoparietal dysmorphogenesis, altered amino acid receptor function, and mesolimbic dysregulation. Dysregulated cholinergic neurotransmission in the cortex likely further escalates dysregulation in distributed cortical-mesolimbic-basal forebrain circuitry (Zaborszky et al. 1997; Zaborszky and Cullinan 1992), rendering the identification of a primary “causal culprit” a difficult objective. Finally, we cannot exclude the possibility of a primary abnormality in the regulation of cholinergic neurons in the disease, akin to the choline transporter (CHT) regulation abnormalities found in sign-tracking rats (see below).

4 Parallel Rodent–Human Studies Implicating Right PFC ACh Dysfunction in Impaired Schizophrenia Responses to Attentional Challenge

Of the three components described above, the relatively long timescale neuromodulatory component has been the most extensively studied, and is the most potentially relevant to the CRUNCH pattern observed in aging and hypothesized in schizophrenia. As noted earlier, microdialysis studies indicate that right PFC

acetylcholine increases as the animal moves from baseline to task performance, and further in the face of a distractor or other attentional challenge (e.g., St. Peters et al. 2011). These increases in prefrontal ACh are more closely related to demands on attention than to performance levels, and thus often occur when performance is impaired by the distractor or other challenge (e.g., Kozak et al. 2006; Sarter et al. 2006; St. Peters et al. 2011). On the other hand, cholinergic lesions reduce performance, especially in conditions of attentional challenge, indicating that these increases play an important if not sufficient role in supporting performance (e.g., Kucinski et al. 2013; McGaughy and Sarter 1999).

Prefrontal ACh increases associated with attentional performance and in response to the distractor appear to be largely right-lateralized (Apparsundaram et al. 2005; Martinez and Sarter 2004; Parikh et al. 2013). Human fMRI studies of the dSAT likewise indicate a special role for right PFC. Across several studies, baseline task performance without the distractor typically elicits bilateral PFC activation, but the response to the distractor is right lateralized (Berry et al. in prep., 2014; Demeter et al. 2011). Again paralleling the rodent studies, greater right PFC activation is associated with greater vulnerability to the distractor (Berry et al. in prep.; Demeter et al. 2011). As illustrated in Fig. 3, distractor-related increases and correlations with performance are prominent in right middle and frontal gyrus, near locations associated with the CRUNCH pattern in aging and disruption in schizophrenia.

Definitive evidence that the right PFC ACh increases observed in rodents contribute to the right PFC activation increases observed in fMRI is difficult to obtain because of the restrictions on what studies can be ethically performed in humans. Indirect support derives in part from humans with a genetic polymorphism (Ile89Val variant of the CHT gene SLC5A7, rs1013940) that, when expressed in cells, reduces the capacity of cholinergic synapses to sustain ACh release. These individuals fail to show the typical distractor-related increase in right PFC activation (Berry et al. 2014). Likewise, mice with a heterozygous deletion of the choline transporter gene show normal basal ACh release but greatly reduced prefrontal ACh responses to either direct basal forebrain stimulation or task demands on attention (Paolone et al. 2013b; Parikh et al. 2013). While this evidence is indirect, the parallels between right PFC activation and genetic limits on cholinergic capacity in humans and right PFC ACh increases and genetic limits on cholinergic capacity in mice make a cholinergic contribution to the fMRI findings the most parsimonious explanation.

Whether patients show an abnormal right PFC response to the dSAT, and what the cholinergic contribution to any such abnormality might be, has not yet been established. However, behavioral studies in patients and measurements of right PFC ACh in a rodent model of the disorder are so far consistent with these ideas. Although patients show some deficits even in signal detection in the basic, no-distractor SAT—possibly due to perceptual difficulties with the brief, low-contrast stimulus used as the “signal”—they show a specific, differential vulnerability to the distractor condition (Demeter et al. 2013). Their distractor vulnerability does not reflect a generalized performance impairment in the face of all forms of attentional demand, as they were able to sustain performance over time

just as well as controls. This contrasts with the results from children (age 8–11 yrs), who showed less distractor vulnerability than patients but greater time-on-task declines. Together with previous findings separately implicating right middle and inferior frontal gyrus in responses to the distractor and abnormalities in schizophrenia, these data predict that patients would show right PFC abnormalities in the dSAT.

This prediction is also supported by findings from a rodent model of attention deficits in both the acute and chronic states of the disease. Rats with sensitized mesolimbic dopaminergic functions tested under amphetamine challenge—thought to model an acute disease state—exhibit cholinergic systems that remain “frozen” at baseline, unable to support attentional performance (Kozak et al. 2007). When these animals are tested without acute dopaminergic challenge, conditions thought to model the remission state as in the patients tested by Demeter et al. (2013), they are able to perform normally in the baseline, no-distractor SAT but with much greater increases in right PFC ACh than those observed in control animals. This exaggeration of the right PFC ACh response suggests that these animals required increased attentional effort and top-down control. The distractor condition was not tested in these animals, but is predicted to result in greater performance impairments than seen in controls—similar to the greater distractor-related performance impairments exhibited by the patients in Demeter et al. (2013)—and a drop in right PFC ACh levels, similar to the right PFC CRUNCH pattern described above. The corresponding prediction for schizophrenia patients would be exaggerated right middle/inferior frontal gyrus in the baseline SAT, and performance deficits and reduced right middle/inferior frontal gyrus activation in response to the distractor challenge.

5 Cholinergic and Dopaminergic Interactions with Right PFC: Integrating Attention and Motivation?

These parallel rodent–human studies build a strong if still circumstantial case that cholinergic dysregulation makes an important contribution to the right PFC abnormalities consistently observed in schizophrenia (e.g., Minzenberg et al. 2009). However, they leave somewhat ambiguous what that contribution might be in terms of cognitive operations. The findings of increased right PFC ACh in rodents and increased right PFC activation in humans, and that lesions or blockade of the cholinergic system impair performance, suggest an important role in increasing top-down control. On the other hand, that suggestion is seemingly contradicted by the negative relationship between performance and right PFC ACh or activation across conditions or individuals. Further complicating matters, although mice genetically modified to have reduced cholinergic function and humans with a genetic polymorphism thought to reduce cholinergic function fail to show dSAT-related increases in right PFC ACh or activation, they show relatively preserved performance (Berry et al. 2015; Paolone et al. 2013b; Parikh et al. 2013).

One proposed explanation for these complex findings is that right PFC ACh and/or activation should be thought of in terms of “attentional effort” (Sarter et al. 2006; see also Raizada and Poldrack 2007). That is, rather the specific attentional processes or mechanisms needed to respond to the requirements of a particular task (e.g., target selection, inhibition, or shifting attention), right PFC activity may reflect the motivated recruitment of those mechanisms.

Put in terms of cognitive operations, by this view right PFC would be described as translating error, conflict, or uncertainty signals from anterior cingulate that indicate a need for increased attentional control into the recruitment of motivation and attention to meet those demands. Conceptualizing the role of right PFC as a critical hub for integrating demand signals, motivation, and attentional control (Watanabe and Sakagami 2007) may explain why it is so often the locus of the “inverted U” activation-demand function in healthy young adults (e.g., Callicott et al. 1999; Van Snellenberg et al. 2015), the observed shift of that function in aging (e.g., Reuter-Lorenz and Cappell 2008), and the hypothesized shift and observed dysregulation in schizophrenia (Fletcher et al. 1998; Manoach 2003; Minzenberg et al. 2009). That is, as demand increases, there is increased recruitment of motivated attention until the “crunchpoint”, after which it falls. It is not yet clear whether the drop in activation (and performance) at the end of the demand curve reflects a loss of motivation, the abandonment of current task-goal representations to try alternative strategies, including shifts from top-down to bottom-up attention, or some combination.

Abnormalities in right PFC in schizophrenia may thus be related to the disorder’s “amotivational” aspects and negative symptoms (e.g., Wolkin et al. 1992). Many discussions of reward processing and abnormalities in schizophrenia focus on orbitofrontal cortex (see Young and Markou 2015 for a recent review of translational animal paradigms). Orbitofrontal cortex appears to play an important role in representing reward value (hedonics) and updating stimulus-reward associations. Anterior cingulate and dorsolateral prefrontal cortex may be more involved in using that information to guide behavior. Anterior cingulate has been implicated in demand signals (including both error or conflict and the amount of effort needed to overcome it), and dorsolateral prefrontal cortex is associated with the translation of reward-value and performance information to task-goal representations and top-down control (see discussion by Barch and Dowd 2010). Evidence from both healthy populations and patients points to an especially prominent role for right middle and inferior frontal gyrus in this translation, and its impairment in schizophrenia.

For example, whereas other regions show sensitivity to incentive valence (reward/loss) or arousal, right middle frontal gyrus is specifically responsive to unexpected changes in reward or loss that may signal a need to shift task sets (Akitsuki et al. 2003). Jimura et al. (2010) found that the tendency to deploy this region proactively or reactively was related to reward sensitivity as assessed by an independent personality test: In a working memory task where some task blocks

presented a mix of rewarded and unrewarded trials, individuals with high reward sensitivity showed sustained right middle frontal gyrus activity throughout the rewarded blocks, suggesting sustained top-down control that benefitted even non-rewarded trials within the block. In addition, they showed strong transient activity at the early stages of rewarded trials, suggesting proactive control. In contrast, low reward sensitivity was associated with low sustained activity and a larger late transient, suggesting a reactive control strategy. Such findings indicate that right middle frontal gyrus is not involved in the evaluation of incentive per se, but rather in the mobilization of control in response to incentive. Likewise, right PFC abnormalities in schizophrenia are associated with evaluation of reward outcomes, especially unexpected outcomes that may require top-down control to re-evaluate and possibly change task set (e.g., Koch et al. 2009; Nielsen et al. 2012).

While dopaminergic contributions are heuristically linked to reward and motivation, we suggest that cholinergic contributions can be thought of in terms of activating and maintaining task set representations. Specifically, neuromodulatory activity in right PFC may help to stabilize task-goal representations and protect them from competing influences. Multisynaptic projections from PFC, including through basal forebrain, to posterior parietal and somatosensory cortex, then act to optimize input processing in accordance with those goals. Inputs that are relevant to task goals (e.g., the central target in the dSAT or color information in Stroop) will be enhanced, whereas those that are irrelevant (e.g., the changing background in dSAT or word information in Stroop) will be suppressed.

Conceptualizing cholinergic neuromodulatory function in terms of stabilizing internal task representations may at first seem inconsistent with widely accepted computational models proposing that “acetylcholine enhances the response to afferent sensory input while decreasing the internal processing based on previously formed cortical representations” (Hasselmo and McGaughy 2004, p. 207; Hasselmo et al. 1992). However, such inconsistencies are largely superficial. These models (as well as empirical data) also support ACh’s role in self-sustained persistent firing to support continued representation in memory and attention—what is suppressed is the spread of activation or associational processing (see discussion by Deco and Thiele 2011; Newman et al. 2012; Hasselmo and Sarter 2011).

Low-cholinergic neuromodulation would thus be predicted to engender increased processing of irrelevant inputs, a greater tendency to make inappropriate associations and less-specific representations of context, and increased intraindividual performance variability related to fluctuation of the task set and its control over behavior—all prominent cognitive symptoms of schizophrenia. These predictions play out in rats exhibiting stable individual differences in sign-tracking (ST) versus goal tracking (GT). Sign-trackers are screened from outbred populations using a Pavlovian approach procedure, and are distinguished by their strong tendency to approach and manipulate the reward-predicting cue or “sign” (e.g., pressing a lever whose appearance predicts reward delivery, even if lever pressing

is not required for reward). In contrast, GTs orient behavior toward the reward delivery system (e.g., the food cup where reward will be delivered). STs are thought to attribute incentive salience to the cue while GTs' behavior is more controlled by "cold" goal-directed cognition (Flagel et al. 2009; Meyer et al. 2012). ST (but not GT) is strongly dependent on nucleus accumbens core dopaminergic function, reflecting its role in incentive salience (Flagel et al. 2011; Saunders and Robinson 2012).

In addition to the dopaminergic contributions to incentive salience, the increased processing of the irrelevant cue and tendency to inappropriately associate the cue with incentive salience could also reflect low cholinergic function. To test this hypothesis, STs and GTs were tested on the SAT (Paolone et al. 2013a). Compared to GTs, STs had lower task-related increases in right PFC ACh, and their performance showed a high degree of fluctuation between performance and chance levels. Importantly, however, STs exhibited bouts of high levels of performance that matched those seen in GTs, and did not omit more trials than GTs. In other words, rather than a fundamental inability or low motivation to perform, their performance was unstable, indicating a fluctuation of control rather than its absence. STs' attentional control dysregulation also manifests in impairments in executing complex movements across dynamic surfaces (Kucinski and Sarter 2015). Furthermore, the reduced task-related increase in right PFC cholinergic activity is associated with attenuated choline transporter (CHT) capacity to support synaptic ACh synthesis and release (Kucinski et al. 2015).

To our knowledge, it is not yet established whether patients with schizophrenia have differential tendencies toward sign- or goal-tracking. However, behavioral tests to assess variations in reinforcement learning have been recommended by CNTRICS for preclinical studies (Markou et al. 2013). It has also been hypothesized that inappropriate learning of associations to irrelevant stimuli may contribute to delusional symptoms (e.g., Jensen et al. 2008; see recent review by Deserno et al. 2013; Gilmour et al. 2015), and dysregulated associational learning in schizophrenia is associated with abnormal right middle frontal gyrus activation (e.g., Koch et al. 2010). More transparently related to the attention-control deficits seen in STs, schizophrenia is associated with exaggerated intraindividual performance variability in many laboratory tasks (e.g., Cole et al. 2011; Kaiser et al. 2008; Roche et al. 2015; see reviews by MacDonald et al. 2006; Matthyse et al. 1999).

To summarize, substantial evidence from rodent models, healthy young adults, older adults, and patients with schizophrenia point to right PFC, especially right middle and inferior frontal gyrus, as an important site for the integration of motivation and top-down control. In particular, dopaminergic interactions with nucleus accumbens shell and cholinergic neuromodulatory influences are hypothesized to support cognitive-behavioral vigor for staying on task, and the stable representation of which task to stay on, respectively (e.g., Floresco 2015). Both of these aspects may be impaired in schizophrenia, leading to both low motivational tone and distractible, erratic performance even when behavior is activated.

6 Cholinergic Transients: Spared, Impaired, or Overactive?

Although sustained cholinergic neuromodulation of right PFC is important for maintaining goal-directed behavior in challenging conditions, it has become increasingly clear both that alternative compensatory pathways can support performance under at least some conditions, and that cholinergic innervation acts on more than one timescale. In particular, although mice heterozygous for a deletion in the choline high affinity transporter gene (CHT \pm) and humans with a genetic polymorphism thought to reduce the efficiency of the CHT (I89 V allele; rs1013940 of SLC5A7) fail to show task-related increases in right PFC Ach and dSAT-related increases in right PFC activation, respectively, they show relatively preserved performance (Berry et al. 2015; Paolone et al. 2013b). However, data from the mouse model indicates that performance remains cholinergically dependent, demonstrated by a compensatory increase in nicotinic acetylcholine receptors (nAChRs) and larger performance declines in response to nAChR blockade by mecamylamine.

This apparent paradox can be resolved by noting that reduced CHT function would be expected to primarily affect the sustained, neuromodulatory component of cholinergic function. That is, low CHT efficiency limits the rate at which choline can be transported into the cell for the production of ACh. It therefore does not affect basal, pre-task levels, only the degree to which elevated neurotransmission can be sustained over time (Paolone et al. 2013b; Parikh et al. Parikh et al. 2013). Although it has not been directly tested, it might also be expected that intermittent transient responses might be less impaired (as long as sufficient time passed between them for the system to “restock”, even if more slowly), and that these more minor reductions might be compensated for by the increase in nAChRs.

As described above, cholinergic transients appear to support orienting toward salient signals and activating the response sets associated with them. Thus, if transients are relatively intact in low-CHT groups, they may take a “reactive”, bottom-up approach, relying on signal salience to drive performance, rather than top-down, proactive cognitive control (c.f., Braver 2012). Supporting this hypothesis, although humans with the Ile89V polymorphism thought to reduce cholinergic function fail to show right PFC responses to the dSAT, they show differential activation of regions associated with bottom-up signal salience and emotional-motivational processing (Berry et al. 2015; see also Gorke et al. 2014). Furthermore, in a behavioral paradigm where the target had very low bottom-up salience (slight duration changes from a standard) and the distractor had high salience (videos playing alongside the main task computer), Ile89V participants had normal no-distractor performance and ability to sustain performance over time, but showed a specific vulnerability to the distractor (Berry et al. 2014). Together, these findings suggest that although transients can support the detection of signals and the

activation of their associated task sets, top-down control from the neuromodulatory component is required in situations with multiple salient stimuli to prevent transients and false alarms to nontargets.

The same trial sequences that yield transient cholinergic responses in rodents lead to transient right PFC fMRI activations in humans. The inference of a cholinergic contribution to this transient fMRI BOLD activation is supported by “back translation” using tissue-oxygen measures thought to parallel BOLD in rodents performing the task and under direct cholinergic stimulation (Howe et al. 2013). Notably, the activation site for these transient responses is not in middle or inferior frontal gyrus, but instead in a lateral orbitofrontal region hypothesized to serve as a “gateway” between externally-directed perceptual processing and internally-directed reflective processing (e.g., Burgess et al. 2007; Chun and Johnson 2011). Thus, the timescale, location, and associated cognitive processes of transients indicate their independence from the right PFC neuromodulatory effects.

Although neuromodulatory and transient cholinergic responses are dissociable, the neuromodulatory component influences the occurrence and sharpness of transients by stimulating $\alpha 4\beta 2^*$ nAChRs expressed by glutamatergic terminals. Reduced cholinergic neuromodulation in patients would thus be predicted to show two abnormalities in the transient response when attentional demand is increased. First, patients would show attenuated neuromodulatory enhancement of transients compared to controls. Second, reduced top-down control would result in inappropriate transients to nontarget distractors.

As of this writing, neither cholinergic transients nor the putatively parallel fMRI response have been assessed in schizophrenic patients. Indirect evidence comes from the literature on event-related potentials (ERPs) in schizophrenia. The rare-target design of the SAT is similar to the “oddball” paradigms used to elicit the P300 response in ERP research, and preliminary evidence (Berry et al. in prep.; Demeter et al. 2015) indicates that target detection and specifically switch-hits elicit a P300 response. In traditional oddball paradigms, the P300 response is strongly influenced by cholinergic manipulations, and has been suggested as a biomarker for neuropsychiatric disorders involving cholinergic disruptions (Javitt et al. 2008; see discussion by Weinberger and Harrison 2011). Compared to controls, patients and first-order relatives generally show a reduced amplitude of P300 to targets, and a relatively exaggerated P300 amplitude to distractors (e.g., Grillon et al. 1990; Kogoj et al. 2005). Interestingly, it has been suggested that the apparent schizophrenia-related reduction in P300 amplitude to targets may be an artifact of increased variability in latency (Donchin et al. 1970; Callaway et al. 1970; Roth et al. 2007; Ford et al. 1994; Roschke et al. 1996). As described above, increases in variability may reflect fluctuations in top-down control, further supporting the hypothesis that transient responses are affected by longer timescale neuromodulation.

7 Implications for Treatment Development and Translational Research

As reviewed here and elsewhere, there is considerable evidence to suggest *that* the cholinergic system is involved in the cognitive deficits of schizophrenia. Still lacking however, is a detailed knowledge of *how* this system is disrupted, and how it interacts with other (also likely disordered) neuromodulatory systems. This is especially the case since most of the evidence for specific receptor deficits comes from post-mortem studies, and there is increasing appreciation that there are important individual differences in the course of the disease, most likely with a genetic component (see discussions by Jablensky 2015; Ross et al. 2010). This may include subgroups with specific patterns of muscarinic deficits (e.g., Seo et al. 2014). In light of these factors, it seems premature to recommend any specific targets; readers interested in recent efforts are referred to Rowe et al. (2015) for nicotinic targets, Kruse et al. (2013) for muscarinic receptor ligands, and Money et al. (2010) for a general overview.

Despite these difficulties, there is considerable interest in the possibility of cholinergic treatments for cognitive deficits in schizophrenia because of the evidence for cholinergic dysfunction, limited efficacy of antipsychotics in treating cognitive deficits, and extensive evidence for cholinergic modulation of the neural circuitry supporting the cognitive-behavioral functions that are impaired by the disease. Below we describe what the major findings covered in this review suggest are promising directions and methods of research.

First, cholinergic influences are pervasive, with effects from early levels of sensory processing at the retina through high levels of executive control, but also regionally and temporally specific. Understanding specific cholinergic subsystems and how they interact—for example, how reduced top-down control and filtering lead to noisier sensory representations, and the burden that these noisier representations create for later control operations such as discriminating targets from distractors—will be essential for improving cognition in schizophrenia and other conditions, including normal aging. One hypothesis is that relatively long timescale muscarinic signaling supports PFC top-down control of sensory and response systems (Hasselmo et al. 1992; Disney and Aoki 2008), whereas within the basal forebrain-PFC circuit, cholinergic neuromodulation influences the cortical circuitry that generates cholinergic transients primarily via stimulating $\alpha 4\beta 2^*$ nicotinic acetylcholine receptors (nAChR) that are expressed at glutamatergic terminals of thalamic afferents (Lambe et al. 2003; Parikh et al. 2008, 2010).

This suggests that interventions targeting muscarinic receptors could improve task-set stability as well as the quality of sensory representations, whereas those impacting nicotinic receptors, especially $\alpha 4\beta 2^*$ nAChRs, could improve cue detection, especially the activation of the cue-appropriate response set. In rodents, a selective $\alpha 4\beta 2^*$ nAChR agonist has been shown to enhance transients in attentional challenge conditions (Howe et al. 2010). Notably, neither nicotine nor a $\alpha 7$ nAChR agonist had these beneficial effects; in fact, blocking nicotine from stimulating $\alpha 7$

nAChR receptors amplified its pro-attentional effects. To our knowledge, $\alpha 4\beta 2^*$ nAChR agonists have not been tested in schizophrenia, although they have had some success in adult attention deficit disorder (Apostol et al. 2012; Bain et al. 2013).

Second, the value of cross-species research using parallel tasks is illustrated in part by the human data demonstrating the regional specificity of right PFC responses to attentional demand (right middle and inferior frontal gyrus) versus transients (right orbitofrontal cortex). The human data reveal this distinction, which would not have been obvious from the animal studies. Furthermore, the human neuroimaging data began to link the cognitive processes associated with each region to observe structural, functional, and behavioral abnormalities in schizophrenia, as well as other conditions. The animal data indicate the likely neurotransmitter influences on activation and behavior, with genetic populations and pharmacologic manipulations helping to establish (or potentially disconfirm) the hypothesized cholinergic contributions.

This brings us to two more subtle points: Although parallel paradigms can be very powerful, it is important to remember that apparently parallel behavior between species or even between individuals does not necessarily entail the same neurocognitive processes. Rodents of course have much less-developed frontoparietal control systems than do humans, and even the simple signal detection task of the SAT likely places a greater proportional demand on rodents' top-down control. Even within human populations, the perceptual difficulties associated with schizophrenia may increase the attentional demands of the task relative to healthy controls. Furthermore, as discussed previously, low-cholinergic populations may be more likely to adopt a reactive, bottom-up approach as opposed to the proactive, top-down attention engaged by healthy controls. Thus, parametric manipulations of attentional challenge and other task variables, as well as converging evidence from other tasks testing-related constructs, are critical for establishing parallels and testing their limits.

In addition, parametric manipulations are important for revealing cholinergic effects. In many cases described above, drug and genetic manipulations have little or no effect on behavior, ACh release, or fMRI activation patterns in baseline conditions; the differences only become apparent with increases in demand. This pattern is consistent with ACh's putative role in responding to attentional demands, but means that assessments without such manipulations may miss important differences between different animal models, treatment conditions or between patients and controls. Thus, it is critical to test any potential treatments in the context of behavior, and if possible, with parametric manipulation of demand on the targeted cognitive process. Some have recommended that any potential pharmacologic treatment be administered in combination with cognitive training (other methods, such as transcranial stimulation, may have similar effects); to do otherwise has been described as giving protein powder without exercise and expecting muscle growth (Keefe et al. 2011).

Third, any potential interventions also need to be evaluated in the context of a disordered system, not just in healthy subjects, and in consideration of potential

interactions with other drugs such as antipsychotics and nicotine. Furthermore, while cholinergic mechanisms may be established in rodent studies using local administration of different agents to the brain structures of interest, most treatments are administered systemically, and interactions throughout the brain and entire body must be taken into account when considering both efficacy and side effects. New technologies may ultimately help to address the last point, including potential nanoparticle delivery to targeted regions (see discussion by Money et al. 2010).

As one example of such new technologies, transcranial stimulation may provide an interesting method to stimulate or mimic cholinergic activity in specific regions, either in isolation or in combination with cholinergic drugs. For example, Reinhart et al. (2015) recently reported that direct-current stimulation of medial PFC, including anterior cingulate, normalized theta-band coherence between medial and dorsolateral prefrontal cortex in patients, and improved their performance on a measure of top-down control so that it was equivalent to healthy controls at baseline. Furthermore, the degree of change in theta correlated with performance improvements. These findings are remarkable in that the initially disorganized theta coherence found in patients is consistent with the idea that fluctuations in the coordination of anterior cingulate—dorsolateral prefrontal (including right middle and inferior frontal gyrus) contributes to fluctuations in top-down control and performance. Further, muscarinic ACh receptor-signaling exerts a strong influence over theta oscillations (Blatow et al. 2003; Lukatch and MacIver 1997). Although Reinhart et al. did not speculate on the neurotransmitter changes underlying their effects, this suggests that modulation of cholinergic activity plays a role. Their findings obviously occurred under highly artificial conditions, but long-term one might imagine that combining such stimulation with training and biofeedback to teach patients to regulate such activity more autonomously, perhaps in combination with pharmacologic agents to enhance the “raw materials” in terms of cholinergic availability and receptor sensitivity, could provide a powerful intervention with real-world effects.

8 Conclusions

Although it is widely agreed that cholinergic disruptions play an important role in cognitive impairments in schizophrenia, our understanding of exactly what those disruptions and their consequences might remain at a rudimentary stage. This is not surprising, as understanding of the basic function of the cholinergic system and its contribution to attention and other cognitive functions is also quite incomplete. However, there have been recent major advances in understanding the wired, regionally localized aspects of cholinergic neurotransmission as opposed to unspecified volume transmission effects, and in the recognition that it acts on multiple, likely interacting, timescales.

We have suggested here that cholinergic abnormalities in schizophrenia begin at the earliest sensory stages, and contribute to a vicious cycle in which reduced top-down control contributes to noisier perceptual processing, which in turn creates

an increased burden for later controlled attention processes such as target selection. In rodent studies of PFC ACh release and human neuroimaging studies, this may lead to a “shifted U”, where patients and animal models of the disorder exhibit higher levels of PFC activation and/or ACh release compared to controls in order to maintain performance at relatively lower levels of demand, but hit a functional ceiling at high levels of demand, so that activation/ACh levels are lower than healthy controls and may even show absolute declines. Right middle and inferior frontal gyrus appears to be an important locus for these effects and for the integration of dopaminergic (motivational) and cholinergic (cognitive) influences for a number of populations (older adults, ADHD, and even healthy controls), suggesting a fundamental neurocognitive component. Interventions that improve cholinergic function here, hypothesized to stabilize the task-set representations that guide sensorimotor and attentional processing, could thus have widespread cognitive effects, not just in schizophrenia.

There is less basis for speculation regarding potential schizophrenia-related disruptions in the more recently-identified cholinergic transient system. To the degree that P300 ERP responses to oddball stimuli may reflect such transients, they suggest blunted responses to targets, a failure to downregulate responses to distractors, and an overall increase in variability that may reflect aberrant interactions with the cholinergic system’s longer timescale neuromodulatory top-down control functions. However, these hypothesized connections require more direct tests.

Throughout, the integration of data across species, methods, and levels of analysis helps to constrain hypotheses and interpretations within each level. The complexity of the cholinergic system and its disruption in schizophrenia makes it a challenging target for translational research. However, given the central importance of cognitive symptoms to disease prognosis and real-world function, it remains a critically important one. Recent advances in our understanding of this system’s modes of function as well as new methods of analysis and potential intervention hold promise for more targeted and ultimately more successful intervention.

Box 1. CNTRICS control of attention tasks.

The goal of the CNTRICS initiative is to develop measurement approaches from different areas of neuroscience so that they can be refined, assessed for psychometric quality and sensitivity to schizophrenia-related impairments in the construct of interest, and ultimately implemented for treatment research. Different meetings focused on defining the constructs and choosing biomarkers, human tasks, or animal tasks.

One important construct identified at the first meeting was the control of attention (Luck and Gold 2008). All of the tasks used for this construct focused on the “input selection” function of attention, or the ability to restrict processing to relevant inputs. (see text) Human tasks selected at the next meeting (Nuechterlein et al. 2009) were the Guided Search task (Gold et al. 2007), and the human version of the distractor condition Sustained Attention Task (dSAT; Demeter et al. 2008; McGaughy and Sarter 1995). The Guided

Search task requires searching for a target (e.g., a red square with a gap at the top) among a set of distractors (red and blue squares with gaps on different sides). The dSAT is a simple detection task in which a centrally-presented signal (small low-contrast gray square on computer screen for humans, illumination of center panel light for rodents) does or does not occur with 50 % probability on each trial; at the end of the trial, participants are to report whether or not a signal occurred. Uncertainty is added by varying the duration of both the signal and the monitoring period. In the distractor (dSAT) condition, the background rapidly changes (flashing computer screen for humans, flashing houselight for rodents), increasing attentional challenge.

The dSAT was also selected as a potential task for imaging biomarkers related to the control of attention (Luck et al. 2012), along with the attentional singleton task (Theeuwes 1992) and attentional cueing paradigms (e.g., Giesbrecht et al. 2003). In the attentional singleton task, the target is an item with a unique shape, but on some trials a highly-salient distractor of a different color is also presented along with other, same-colored distractors. Attentional cueing paradigms present a cue indicating the likely location of an upcoming target, neural activation between the cue and the target is thought to represent maintenance of the goal to move attention to that location.

The fourth meeting focused on the selection of animal paradigms with promise for preclinical research (Lustig et al. 2013). The dSAT was again chosen as a potential measure of input control, along with the 5-choice serial reaction time task (see Robbins 2002 for a review) and the 5-choice continuous performance task (Young et al. 2009). The 5-choice serial reaction time task is based off of a sustained attention task previously developed for humans and is part of the CANTAB battery used with both healthy and clinical populations (Alexander et al. 2005; Sahakain et al. 1993; Cambridge Cognition, camcog.com). The task is to detect a brief visual target presented briefly in a 5-choice array. The 5-choice continuous performance task is very similar, except that it adds nontargets to which the subject must inhibit responding.

A common theme throughout these tasks (with the attentional cueing paradigms perhaps being somewhat of an outlier) is the requirement to detect and respond to a target signal in the face of attentional challenge. The paradigms vary in how that challenge is implemented—the global distractor of the dSAT, competing options in the 5-choice tasks, and similar but incorrect competitors in the guided search and attentional singleton tasks, the latter of which also adds a high degree of saliency to the distractor. An important question going forward is the degree to which the neural circuitry for responding to these different types of attentional demand is overlapping versus distinct, and how those components are affected by schizophrenia.

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