UNIVERSITY OF MICHIGAN

PSYCHOLOGY

exploring the mind

Control of Attention

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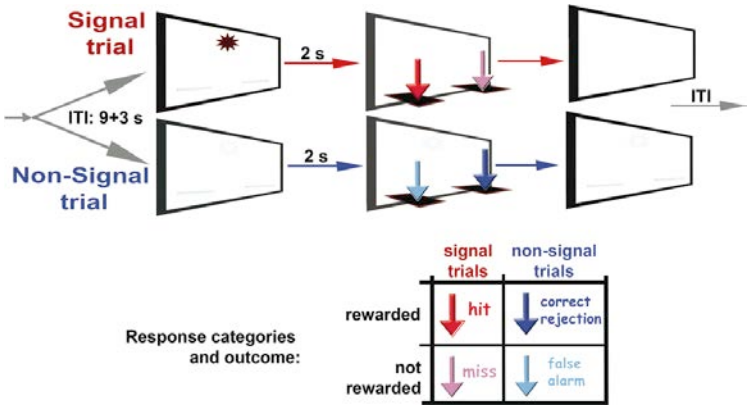
Sustained attention and top-down control of attention: key elements of the cognitive construct

working memory and executive control processes. Furthermore, given recent studies which suggest that impairment in control but not implementation of input selection is deficient in schizophrenia,[25,28,29] the CNTRICS group decided to emphasize control of attention as the core attention construct in its evaluation of promising cognitive paradigms. Control of attention was defined as "the ability to guide and/or change the focus of attention in response to internal representations." Luck and Gold[21]

Nuechterlein, Luck, Lustig & Sarter 2009

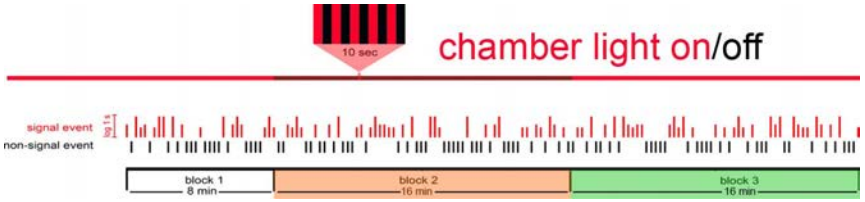
Sustained attention and top-down control of attention

Sustained Attention Task (SAT)



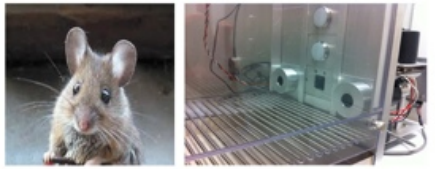
- signal trials require **cue detection** (*...the entry of information concerning the presence of a signal into a system that allows the subject to report the existence of the signal by an arbitrary response indicated by the experimenter*"; Posner et al., 1980)
- detection largely abolished by removal of cortical cholinergic inputs (McGaughy et al. 1996)
- involves blank trials (not requiring cue detection); unaffected by cholinergic lesions
- involves switches between response modes governing non-signal versus signal trials

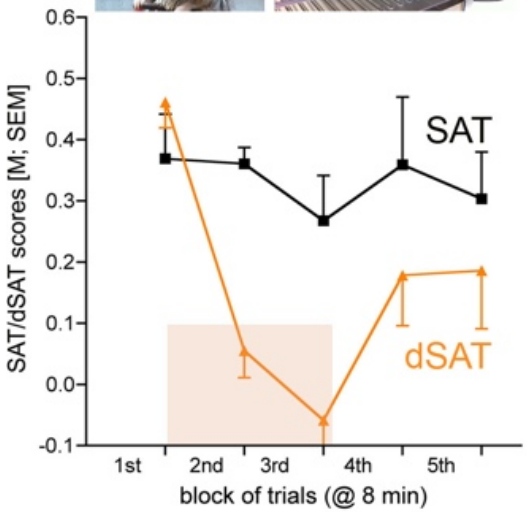
distractor condition Sustained Attention Task (dSAT)



- amplification of signal processing and distractor filtering
- distractor-evoked neuronal activity in cortex mediated by ACh (e.g., Gill et al., 2000; Broussard et al. 2009)
- acute effects and recovery: reflects the motivated activation of attention system, to stabilize and recover attentional performance
- top-down control via direct projections to the basal forebrain and via mesolimbic (accumbens) circuitry (St. Peters et al. 2011)

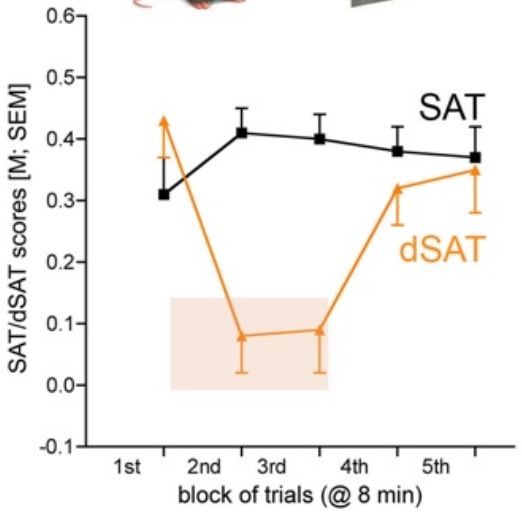
SAT and dSAT performance in mice, rats and humans





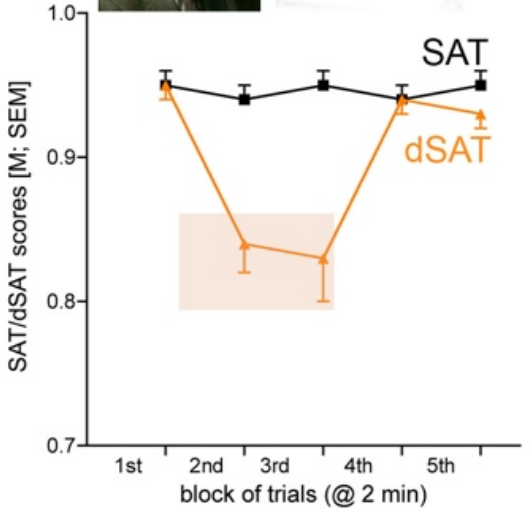
ITI: 9±3 sec
Signals: 500, 50, 25 msec
Response triger: poker out & opening
Response window: 4 sec

St. Peters, Bradshaw & Sarter, in prep.



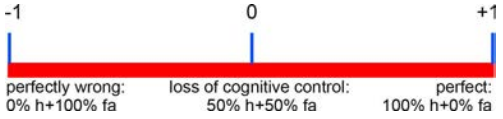
ITI: 9±3 sec
Signals: 500, 50, 25 msec
Response triger: lever extension
Response window: 4 sec

McGaughy & Sarter, 1995



ITI: 2±1 sec
Signals: 50, 29, 17 msec
Response triger: 75 msec low frequ buzz
Response window: 1.5 sec

Demeter, Sarter & Lustig, 2008



SAT/dSAT score

- humans: higher levels of performance, distractor effects less severe, reflecting overall superior top-down control
- dSAT: humans adopt a more conservative, rats & mice adopt a riskier criterion
- overlaps and differences allow for informed translational research

dSAT in humans

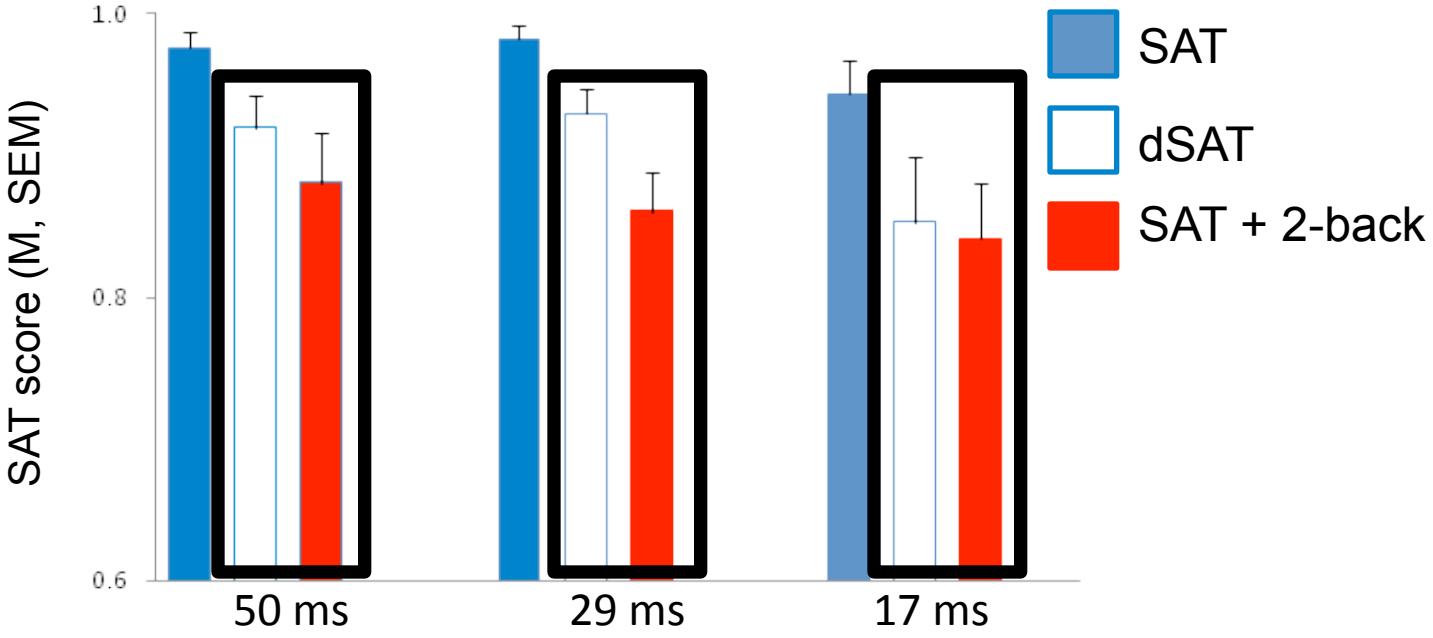
High Internal Reliability

Group	n	SAT	dSAT
Rats	11	.83	.24
College students (no penalty)	16	.93	.88
College students (penalize misses)	32	.86	.93
Schizophrenia patients	10(+)	.99	.95
Matched controls	10(+)	.92	.84
Matched controls, variable location	10(+)	.92	.84
Children	15(+)	.97	.93

+ : data collection is ongoing

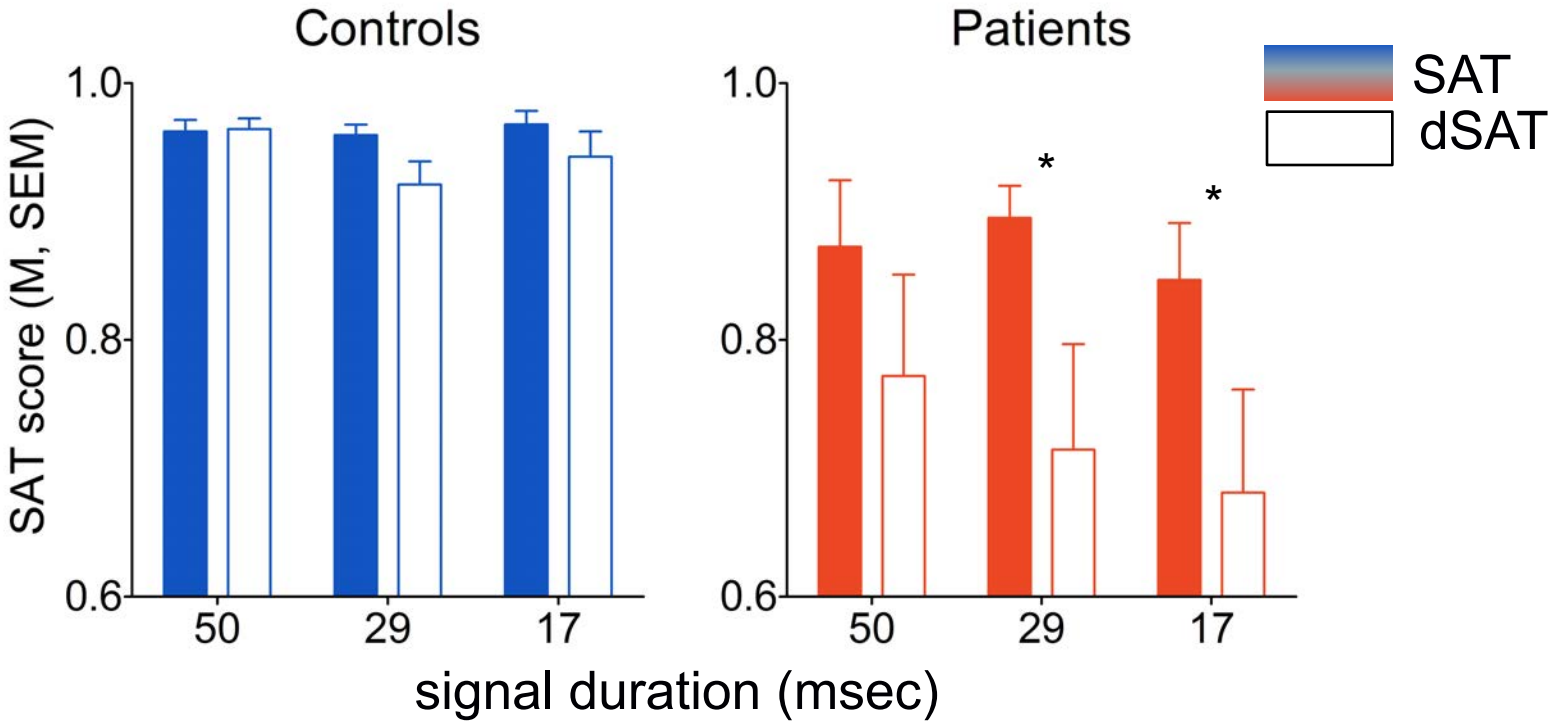
Perceptual Confounds? Probably not.

- All groups (except rats at short signal durations) have d' > 2.0 in dSAT
- Cognitive "distractors" have same effect as flashing screen distractor.
- Experiments with different distractor formats ongoing.



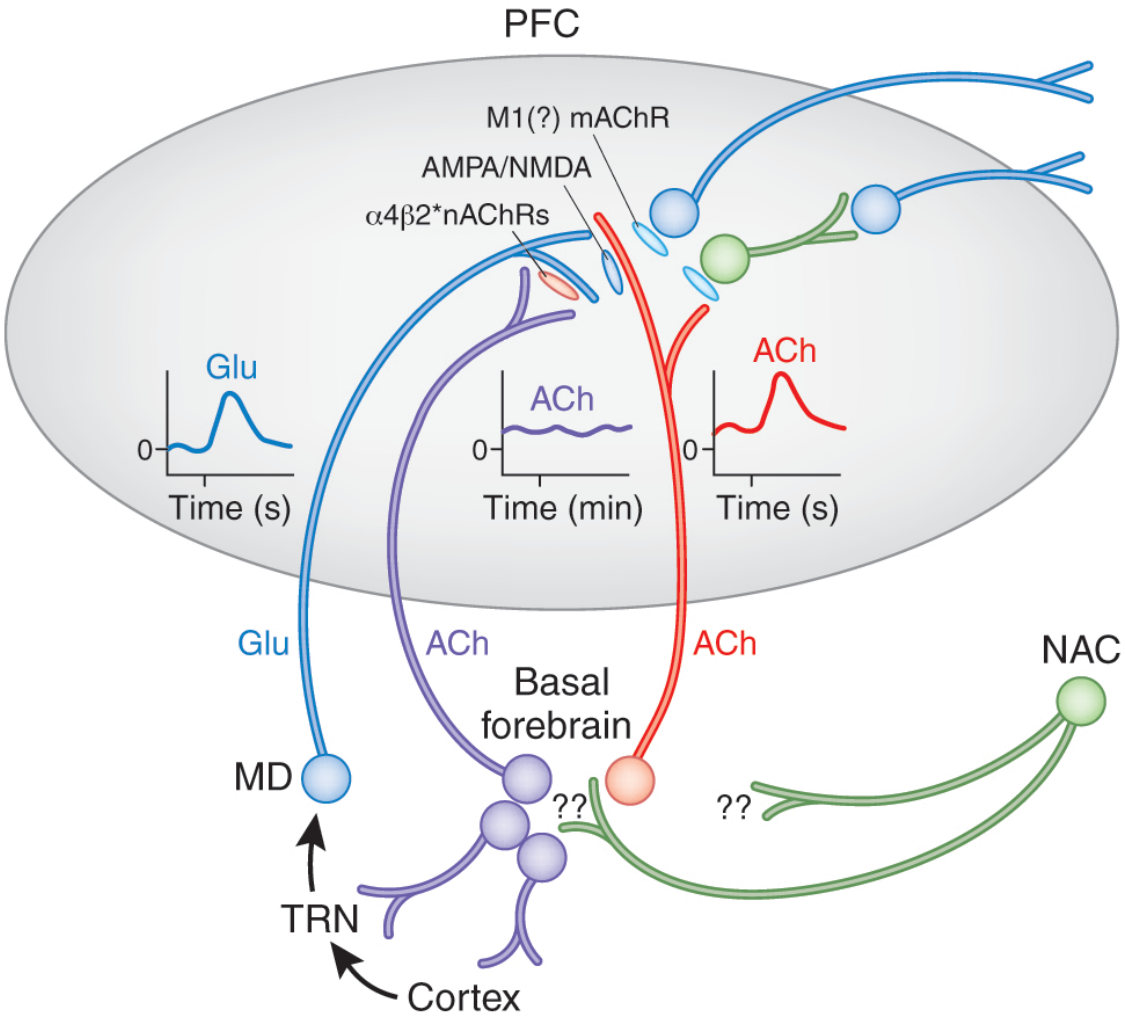
SAT and dSAT performance in patients with schizophrenia

- stable, medicated outpatients (n=17), age- and gender-matched controls (n=15)
- 15.2 versus 18.3 years of education
- All patients on antipsychotic treatments (mostly risperidone, haloperidol)
- Brief Psychiatric Rating Scale: 30.4 ± 1.7 (“mildly to moderately ill”)
- Hamilton Score: 7.7 ± 1.1 (healthy range)
- Scale for Assessment of Negative Symptoms (SANS): 20.5 ± 2.7 (mild)
- Patients’ SAT performance impaired and more severely affected by distraction than controls.



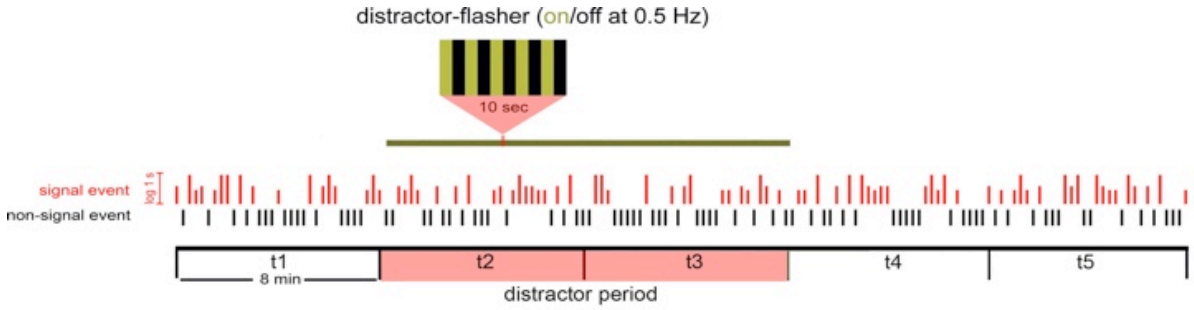
Demeter, Guthrie, Taylor, Sarter & Lustig, 2011

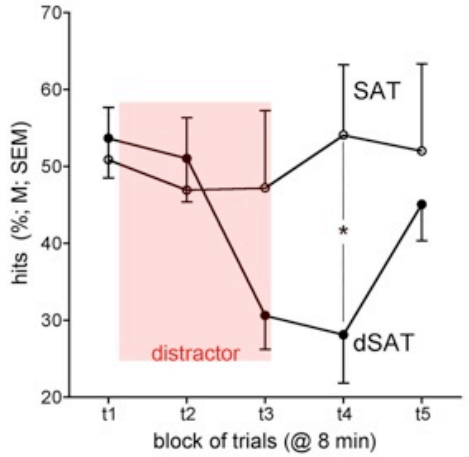
Tonic ACh modulates prefrontal cue detection circuity.
Phasic ACh mediates detection & processing mode shifts.

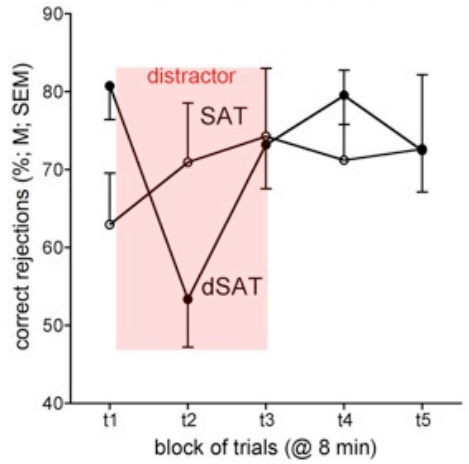


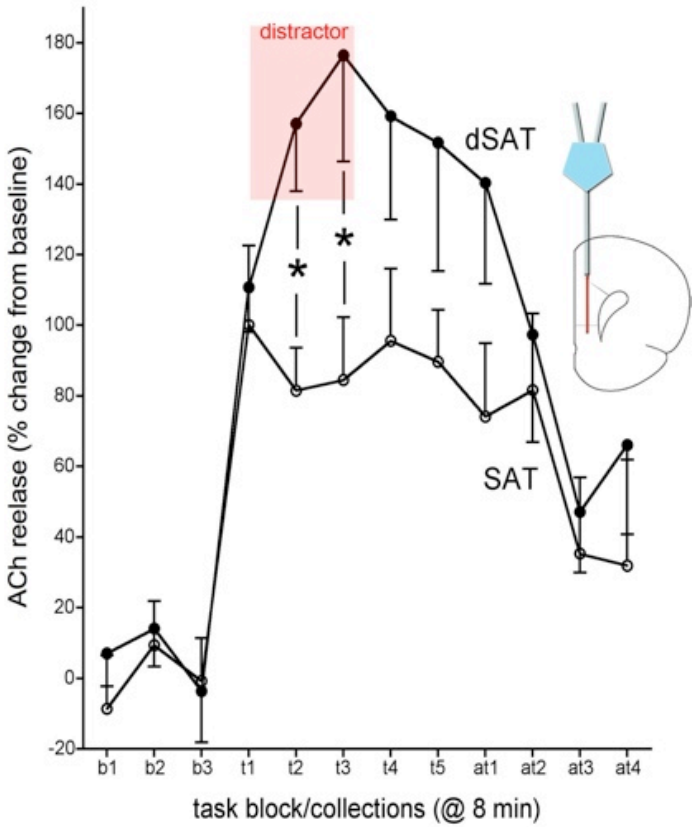
Hasselmo & Sarter NPP 2011

Attentional demand-dependent increases in cortical ACh release







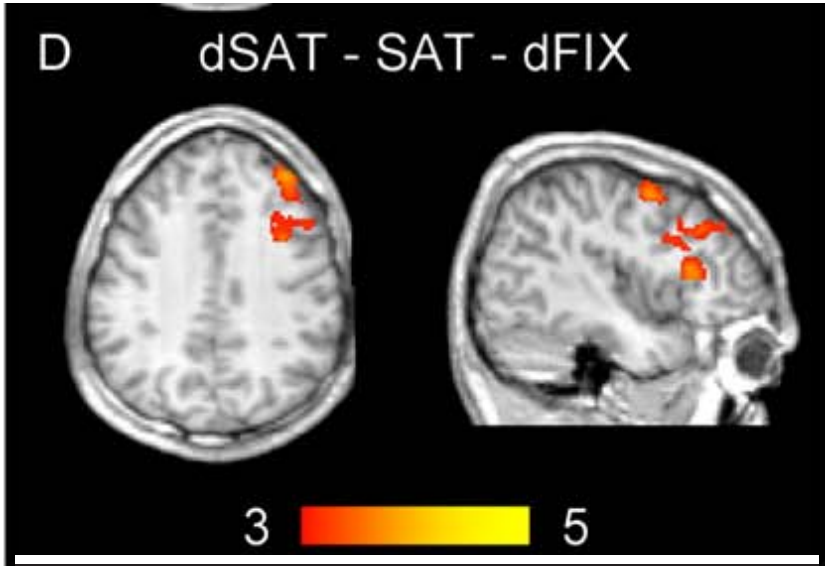


- SAT-performance-associated increases in cortical ACh release not observed during control procedures devoid of demands on attention.
- distractor-SAT (dSAT): increased demands on attention further increase prefrontal ACh release.
- Cholinergic modulation of prefrontal circuitry acts **top-down** to enhance cue detection and distractor filtering.

St. Peters et al., 2011

Demands on attention: ASL and BOLD fMRI reveal BA9

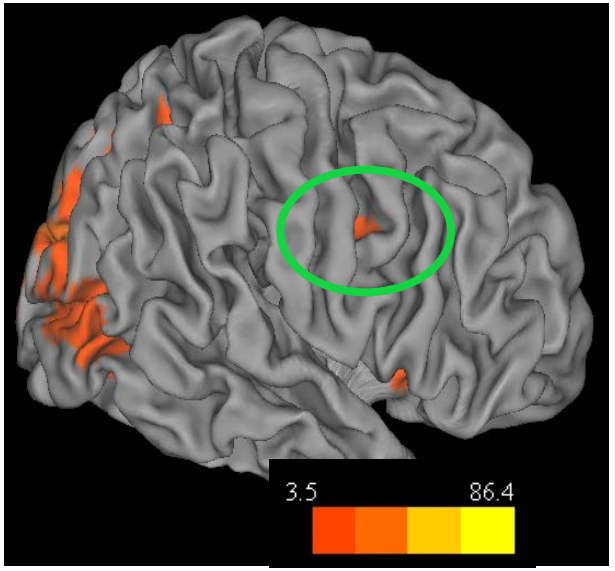
ASL-fMRI

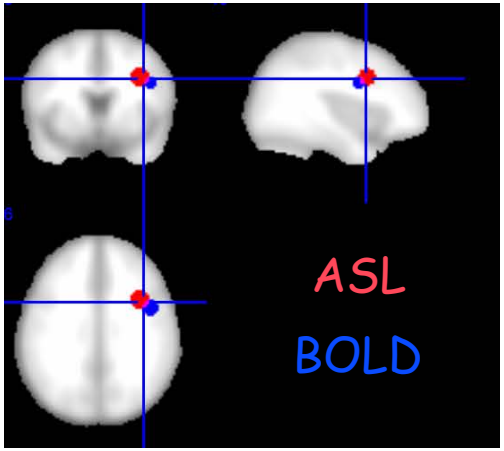


Size (Voxels)	Anatomical Label	BA	MNI coordinates			Z score
			x	*y*	*z*	
Contrast: distractor condition Sustained Attention Task (dSAT) versus Sustained Attention Task (SAT) and distractor fixation (dFIX)						
1661	R. middle frontal gyrus	9	38	42	32	4.69
	R. insula/inferior frontal gyrus	45	42	22	10	4.27
	R. middle frontal gyrus	9	36	10	34	4.12
	R. middle frontal gyrus	9	36	28	28	4.08
	R. precentral gyrus	6	44	0	52	4.08

Demeter et al. 2011

BOLD-fMRI

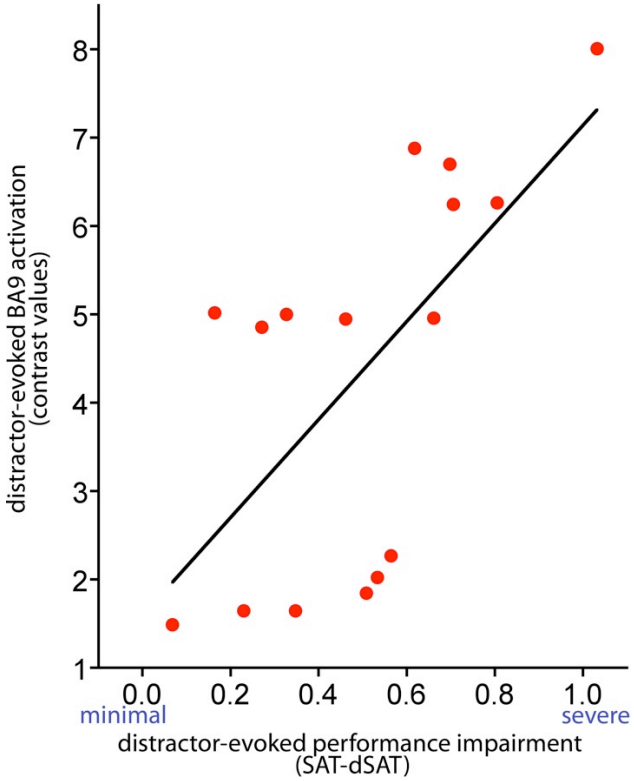




Berry et al. in prep.

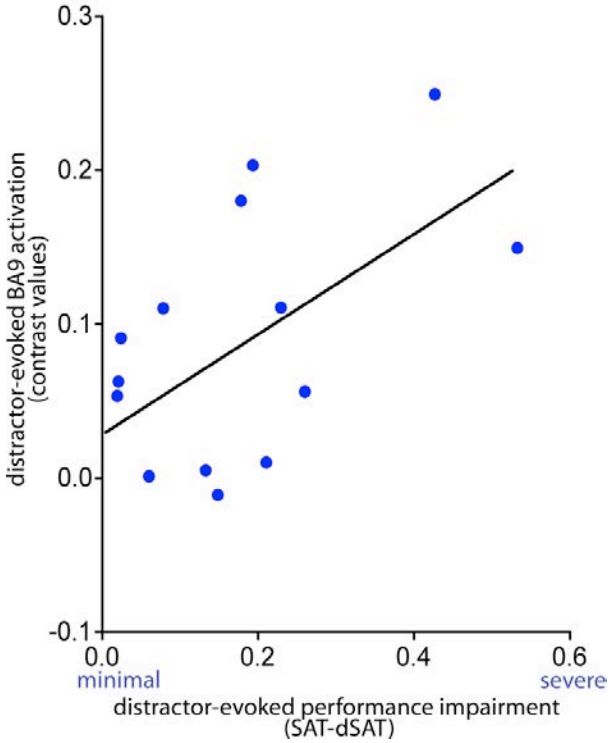
Higher prefrontal activity but **lower** cholinergic activity correlated with more severe distractor effects

ASL-fMRI

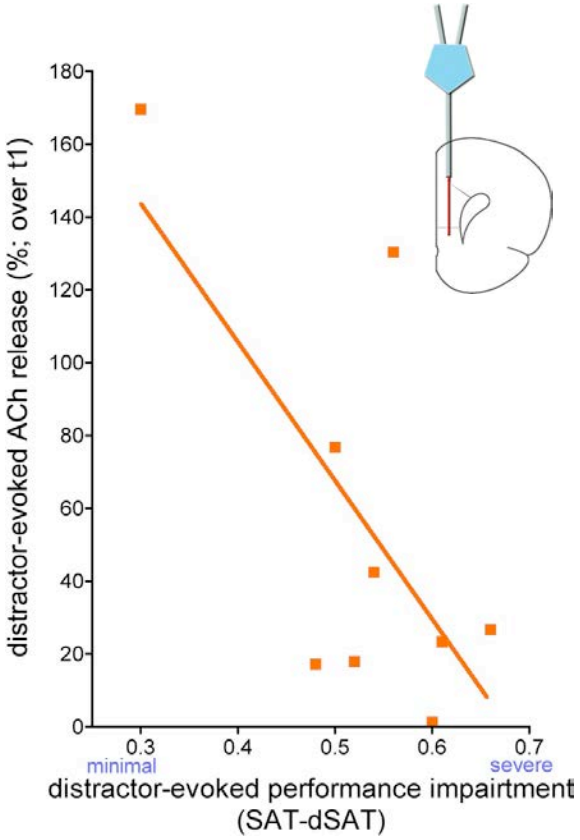


Demeter et al., 2010

BOLD-fMRI

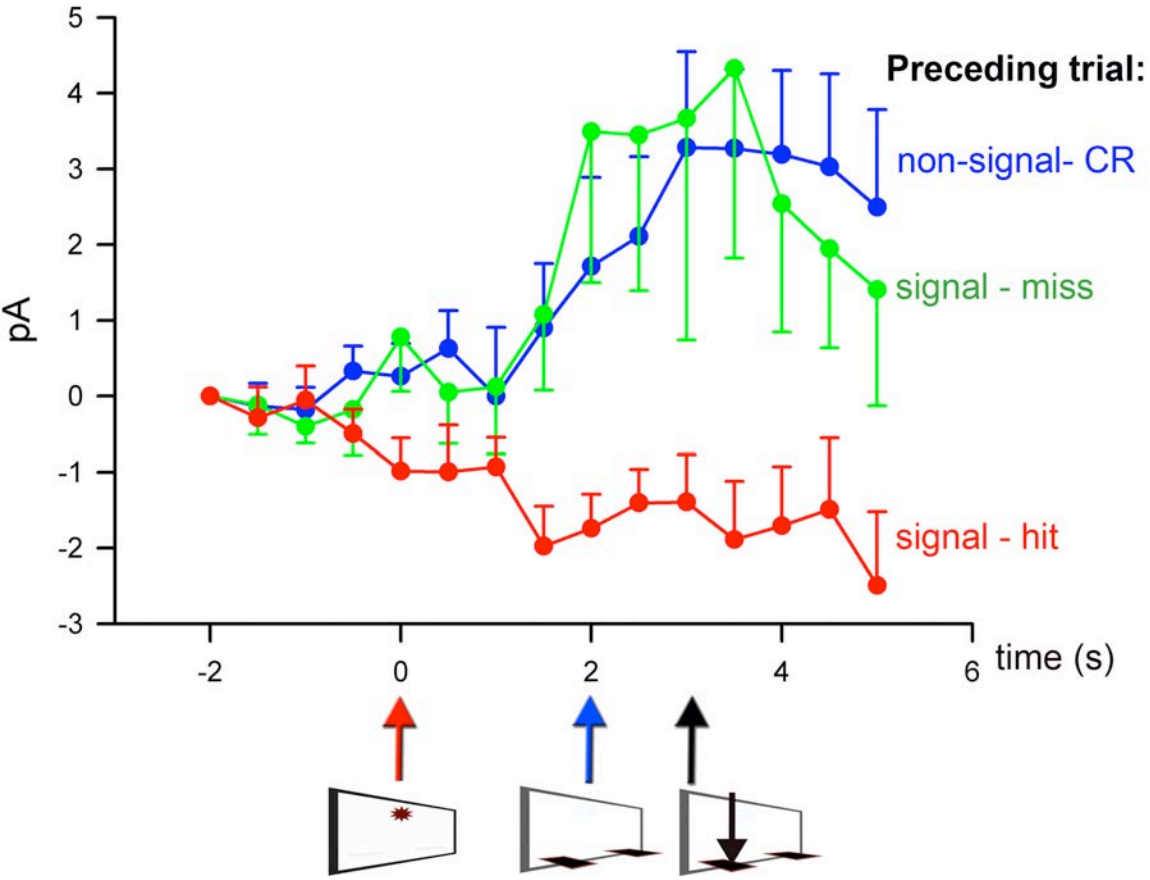


Berry et al., in prep



St. Peters et al., 2011

Cholinergic transients mediate attentional orienting and processing mode switches

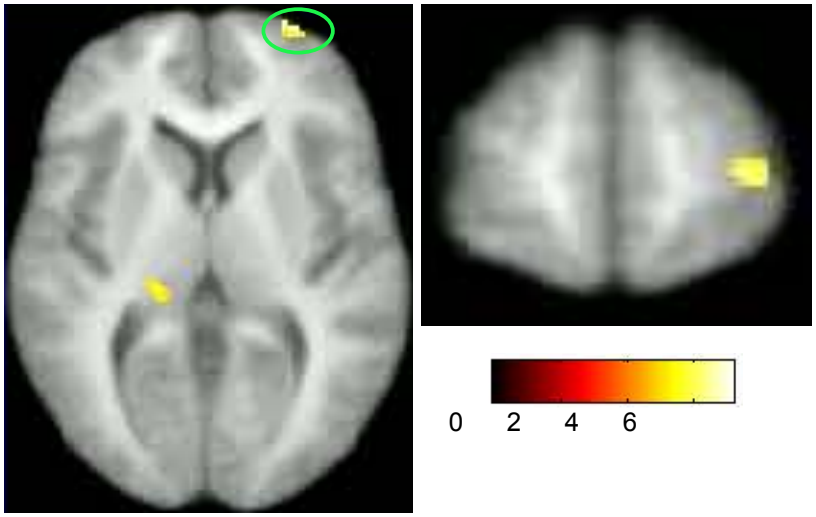


- Non-signal to signal: requires re-aligning of attention to source of input?
- Orienting: *"mental process designed to align attention with the source of sensory input"* (Posner). Attentional orienting, wether overtly or covertly, fosters detection but is neither sufficient nor necessary for detection.
- Hit-hit: no such alignment is necessary, thus no transient.
- Alternatively: Transients foster shift from default to detection mode.

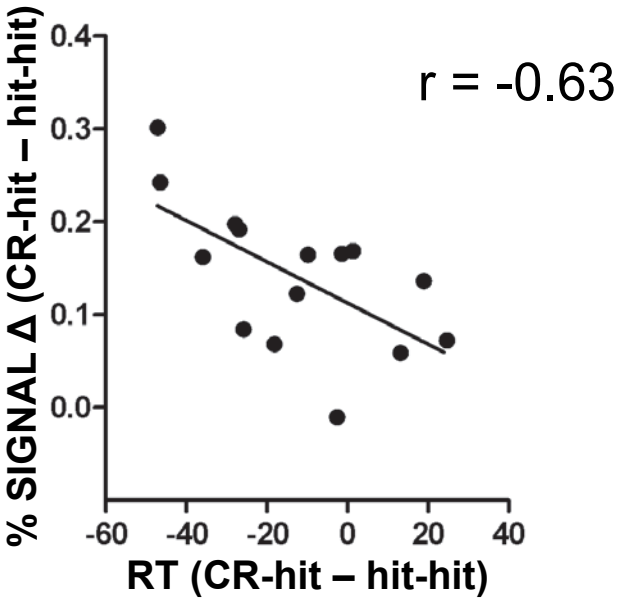
Howe et al., in prep

Right BA10 selectively activated by switch from default to detection mode

CR - hit > hit - hit



FDR corrected p < 0.05, 20 voxel threshold.

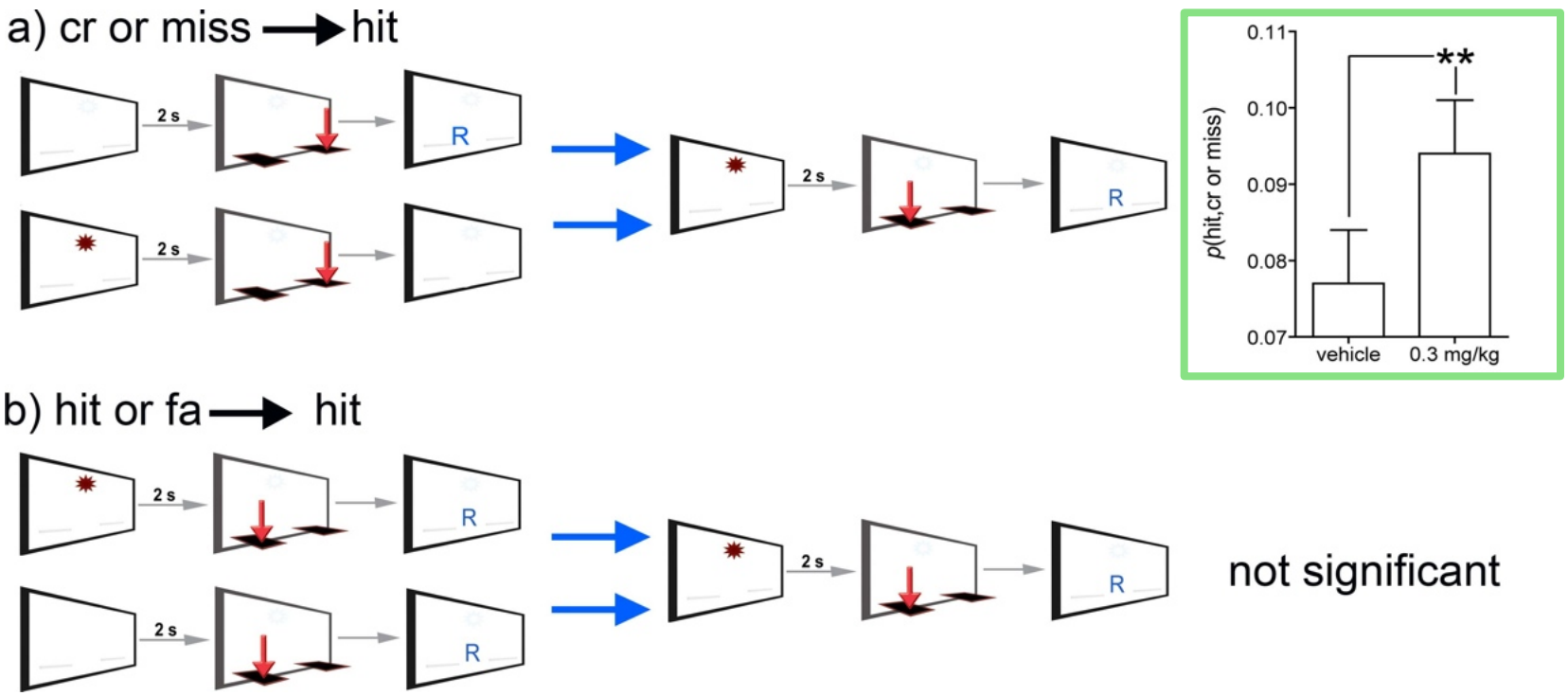


BA 10: gateway for switching attention between internal and external representations (Burgess et al., 2007).

More BA10 activity is correlated with faster response latencies for incongruent relative to congruent trial sequences

Berry et al., in prep.

S38232 enhances hits if involving switch to detection mode

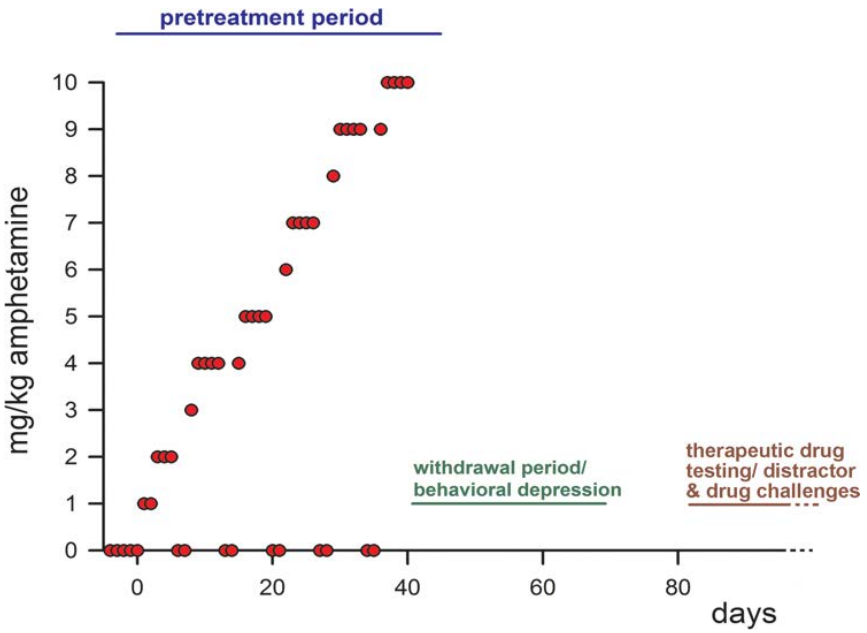


- post-distractor performance: hit rate significantly increased by S 38232
- S 38232 enhanced detection rate specifically in signal trials that followed factual or perceived non-signal trials
- Enhanced attentional re-orientation/mode switching

Howe et al., Neuropsychopharmacology 2010

Animal models of schizophrenia-related attentional impairments

- prior exposure to escalating doses of amphetamine in SAT-performing animals; persistent vulnerabilities to performance challenges;
- SAT performance fails to properly activate tonic cholinergic activity;
- performance moderately improved by effects of chronic low-dose haloperidol or clozapine (reviewed in Sarter et al., 2009)



➡ neonatal (TTX-infusion-evoked) disruption of ventral hippocampal circuitry

➡ accumbens-recruitment of cholinergic system completely attenuated

➡ cholinergic transients attenuated

➡ impairments in monitoring and consolidating changes in attentional performance outcome

Conclusions

1. SAT and dSAT in mice, rats, humans, patients.
2. Construct validity has expanded to incorporate attentional re-orienting or processing mode shifts.
3. Treatment effects on incongruent trial sequences consistent with current understanding of the neurobiological mechanisms mediating task performance and drug effects.
4. Next: characterization of animal models of the cognitive symptoms of schizophrenia
5. Next: treatment effects on BA10 activity in healthy humans; a4beta 2* nAChR agonists as adjunct treatment in patients.