

Increased distractor vulnerability but preserved vigilance in patients with schizophrenia: Evidence from a translational sustained attention task

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Running title: Control of Attention in Schizophrenia

Word count: Abstract 207; Main text 3,577

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Abstract

Objective: Attentional deficits represent a core cognitive impairment in schizophrenia. The distractor condition Sustained Attention Task (dSAT) has been identified by the Cognitive Neuroscience Treatment to Improve Cognition in Schizophrenia (CNTRICS) initiative as a promising translational task for assessing schizophrenia-related deficits in attentional selection-control, identifying neuroimaging biomarkers of such deficits, and for preclinical animal research on potential pro-cognitive treatments. Here, we examined whether patients would show specific difficulties in selection-control and in avoiding distraction in the dSAT.

Method: Selection-control deficits are measured by comparing attentional performance in the Sustained Attention Task (SAT) without distraction to performance on the task when distraction is present (dSAT). The baseline SAT condition can also be used to assess time-on-task or vigilance effects. Patients with schizophrenia, age- and gender- matched healthy controls and, as an additional control, school-aged children were tested on both the SAT and dSAT.

Results: Compared to healthy controls, patients had reduced performance overall and were differentially vulnerable to distraction. In contrast, patients but not children had preserved vigilance over time.

Conclusion: These results demonstrate specific input-selection control impairments in schizophrenia and suggest that patients' distraction-related impairments can be distinguished from general performance impairments and from deficits in other attentional processes (e.g., sustaining attention) evident in other groups.

Keywords: schizophrenia, CNTRICS, attentional control, sustained attention, distraction

1.0 Introduction

Attentional impairments are among the core cognitive deficits in schizophrenia (Heinrichs and Zakzanis, 1998; Nuechterlein et al., 2004), persisting across periods of psychosis and remission (Asarnow and Maccrimmon, 1978; Nuechterlein et al., 1992; Wohlberg and Kornetsky, 1973). These impairments have a significant relationship to functional outcomes, including the acquisition of basic life skills and social problem solving (Green et al., 2000). The success of attempts to develop pro-cognitive treatments has been limited (Hill et al., 2010; Sarter et al., 2012; Tandon et al., 2010), in part because it is not well-understood how different aspects of attentional function may be differentially spared or impaired by the disease. Another factor is the paucity of translational research connecting preclinical drug-development studies in rodents, cognitive neuroscience studies of healthy humans, and clinical research in patients (Sarter, 2006). The present study attempts to address these gaps by testing patients and several control groups on a task that a) allows simultaneous assessment of multiple aspects of attentional control, b) has been used extensively in animal studies of the basal forebrain cholinergic system's role in attention (McGaughy and Sarter, 1995; St. Peters et al., 2011a,b), and c) has been recently extended to human behavioral and neuroimaging studies (Demeter et al., 2008, 2011). The results may help illuminate which aspects of attentional function are especially impaired in schizophrenia and point to potential pathways for treatment.

To better define the cognitive deficits accompanying schizophrenia, the CNTRICS (Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia) initiative proposed a set of operational definitions based on findings from cognitive and behavioral neuroscience (Carter & Barch, 2007). The attentional functions involved in input selection (selecting task-relevant inputs for further processing) are distinguished from rule selection (selecting context-appropriate rules to govern processing). Input selection can be further divided into the control of selection (mediated primarily by prefrontal and parietal regions) and the implementation of selection (usually occurring within sensory regions). The control of selection

is thought to be impaired in schizophrenia, whereas implementation may be spared (see Luck and Gold, 2008 for a discussion of these constructs in the CNTRICS framework). The present study tested the hypothesis of specific deficits in selection control in schizophrenia, over and above general attention or performance deficits.

To this end, we tested patients and controls in the distractor condition sustained attention task (dSAT), selected by CNTRICS as a candidate for the behavioral assessment of selection-control deficits (Nuechterlein et al., 2009), identification of biomarkers of reduced selection control (Luck et al., 2012), and drug development in animal models (Lustig et al., 2012). Other tasks associated with selection control include the guided search task (Gold et al., 2007; Nuechterlein et al., 2009), attentional cueing paradigms (Luck et al., 2012), the distractor singleton paradigm (Luck et al., 2012; Theeuwes, 1994), and the five-choice serial reaction time and continuous performance tasks (Lustig et al., 2012; Robbins, 2002; Young et al., 2009). These other tasks measure participants' ability to direct attention in response to cues indicating a target's likely color or location, or to discriminate a target from similar lures. The dSAT operationalizes input selection somewhat differently, requiring participants to report the presence or absence of a centrally-presented but weak (small size, low contrast, and short duration) target input in the face of salient, broad-based distracting input (rapidly-changing background illumination).

Specific deficits in selection control can be assessed by comparing the distractor condition with the base sustained attention task (SAT). The SAT is identical to the dSAT but minimizes demands on selection-control by using a constant (rather than flashing) background. However, it still requires signal detection and thus top-down attention related to executive control and rule selection, especially to maintain performance over time and cope with the unpredictability of signal occurrence and duration (see discussion by Sarter and McGaughy, 1998). Likewise, both the SAT and dSAT may be influenced by bottom-up factors, including signal salience and activation effects associated with performing the motor response. The SAT

condition therefore provides a general measure of attentional performance, whereas contrasts between the SAT and dSAT conditions isolate problems with input selection. In fMRI studies (Demeter et al., 2011; Berry et al., in prep.), this contrast yields activation in right middle frontal gyrus (approximating Brodmann Area (BA) 9) that correlates with distractor vulnerability. Right BA 9 is frequently associated with cognitive control deficits in patients and high-risk relatives (Bhojraj et al., 2011; Holmes et al., 2005; see meta-analysis by Minzenberg et al., 2009), further motivating our hypothesis of a specific distraction-related deficit in schizophrenia.

In addition to serving as a control for the dSAT, the SAT condition may help address the controversial issue of whether schizophrenia impairs the ability to sustain attention (related to the CNTRICS working memory/goal maintenance construct). Deficits in sustained attention are described as a hallmark of schizophrenia (e.g., Nuechterlein, 2004), but most papers cited in support of this view assess overall performance on continuous performance tests (CPTs) that place high demands on input selection by requiring detection of a target amid a rapid input stream, rather than time-on-task effects related to sustaining attention *per se*. The few studies that have examined time-on-task effects have yielded mixed results. Schizophrenia-related deficits in sustaining attention over time are most often found when the task uses degraded stimuli that place additional demands on input selection (e.g., Mass et al., 2000; Hilti et al., 2010), but even with degraded stimuli there are examples of patients with schizophrenia showing preserved performance over time, whereas other patient populations decline (e.g., Egeland et al., 2003). Hahn et al. (2012) took a different approach to increasing input-selection demands by requiring simultaneous monitoring of 11 continuously changing stimuli. Even in this demanding divided-attention situation, the initial time-related performance declines were equivalent for patients and controls; the difference was that controls were better able to recover performance on subsequent blocks. This suggests that patients may have had deficits in recovery processes or in learning and practice effects that may counteract sustained-attention declines, rather than in sustained attention *per se*.

The SAT's low input-selection demand leads to the hypothesis that although patients may show reduced performance overall, they should not show greater time-on-task performance declines even in an extended (12 minutes) version of the task. To further differentiate schizophrenia-related performance deficits related to selection control from those related to other cognitive-control deficits, we also compared patients' performance to that of children (8-11 yrs old). Like patients, children were hypothesized to have general deficits in controlled attention because their brains, particularly the prefrontal regions involved in attentional control, are not fully developed (e.g., Asato et al., 2010). The ability to sustain attention over time is also not yet fully developed at this age (McKay et al., 1994; Betts et al., 2006). Therefore, we predicted that although both patients and children would show general performance deficits relative to healthy adults, children would show a specific deficit in sustained attention whereas patients would show a specific deficit in distractor vulnerability. Finally, in keeping with the CNTRICS mission we provide psychometric internal reliability data and suggestions for future task optimization.

2.0 Materials and Methods

2.1 Participants

Participants consisted of 1) stable, medicated outpatients meeting DSM-IV criteria for schizophrenia or schizoaffective disorder established by a Structured Clinical Interview for Diagnosis (First et al., 1995), 2) age- and gender-matched controls run on the same task versions as patients, 3) age- and gender matched controls run on a version with greater attention demands (VSL controls; see below), and 4) children age 8-11 years. See Table 1 for demographics. Participants were recruited from the community through local advertisements and via participant databases maintained by the investigators and approved by the University of Michigan's Institutional Review Board (IRB). All adult participants gave informed consent to participate in the study. Children's parents provided informed consent for their child to

participate and children provided written assent. The University of Michigan's IRB approved the study protocol and consent forms.

2.2 Procedure

Testing generally followed procedures reported in Demeter et al. (2008); see Figure 1. Each trial required participants to report the presence or absence of a variable-duration (17, 29, or 50 ms) 3.5 mm² grey square (the "signal") presented in the center of the screen. The signal occurred unpredictably on 50% of trials, and the time required to monitor for the presence or absence of the signal also varied (1000, 2000, or 3000 ms). In the SAT condition the background was a static grey; in the dSAT condition it alternated (10 Hz) between grey and black. Signals were always presented against a grey background so the signal-background contrast was constant across conditions. A 430 ms low-frequency buzzer indicated the end of the monitoring period; participants then had up to 1500 ms to make a keypress response indicating whether or not the signal had been presented on that trial. A 500 ms high-frequency tone followed correct responses, and participants received cumulative feedback at the end of each run (1 "point" for each % correct). Children earned one ticket for each point. Tickets were redeemed at the end of the session for small toys; more tickets allowed access to more attractive toys.

As noted above, one set of healthy adult controls was tested using a version with increased attention demands to make their SAT (non-distractor condition) performance levels closer to patients'. For this Variable Signal Location (VSL) group, the signal's vertical location varied randomly across three positions (25%, 50%, or 75% from the top of the screen). An additional signal duration (150 ms) was also added to further increase uncertainty but was not included in data analysis. All other aspects of procedure were the same as for the other groups.

Participants were first trained on the SAT and dSAT for 30 s each. If necessary, SAT practice was repeated until accuracy was over 70%. Participants then completed two 8-minute runs that contained both the SAT and dSAT conditions, and two 12-minute runs consisting only

of the SAT. The 8-minute runs began with a 2-minute block of the SAT condition, followed by two 2-minute blocks of the dSAT condition, and ending with a final 2-minute block of the SAT condition. The 12-minute runs containing only the SAT condition were subdivided into six 2-minute blocks and used to examine potential declines in vigilance. Eight- and 12-minute runs were interleaved, with the order counterbalanced across participants in a group.

2.3 Data Analysis

Responses were recorded as hits, misses, correct rejections, false alarms and omissions. Our primary dependent measure was the SAT score, a measure of performance across both signal and nonsignal trials typically used in rodent studies of the SAT and dSAT, including studies using a rodent model of schizophrenia (see Sarter et al., 2009) as well as our previous studies with humans (Demeter et al., 2008, 2011). The SAT score is preferred to signal-detection indices such as d' because it does not make the same assumptions about equal variance of positive and negative responses, which are often violated (see discussion by Frey & Colliver, 1973). In this regard the SAT score is similar to the nonparametric similarity index (SI) but unlike SI it is not confounded by errors of omission. It was calculated for each condition (SAT, dSAT) and signal duration using the formula $\text{SAT score} = (\text{hits} - \text{false alarms}) / [2(\text{hits} + \text{false alarms}) - (\text{hits} + \text{false alarms})^2]$. SAT score varies from +1.0 to -1.0, with +1 indicating all responses were hits or correct rejections and -1 indicating all responses were misses or false alarms.

Our analyses focused on hypothesis-guided comparisons of patients versus other groups on distractor vulnerability and time-on-task effects. To assess the effects of distraction, data from the two 8-min runs were combined within the SAT and dSAT conditions and analyzed using repeated-measures ANOVAs with the factors of Group (patients, age-matched controls, VSL controls, children), Distraction (absent, present), and Duration (50, 29, 17). Our primary theoretical interest was in Group x Distraction interactions. Signal duration is primarily manipulated to increase uncertainty and cognitive load and is not of central theoretical interest.

However, it is included as a factor because our previous studies with rodents and healthy young adults have revealed Duration x Distraction interactions, suggesting that distraction effects may be greatest when signal durations are short enough to be challenging but not so short as to lead to floor effects. Here, we expected Group x Duration x Distraction interactions if patients are more sensitive to distraction than controls. Although monitoring period was also manipulated as a task variable, it does not typically have strong effects or interactions with distraction and is not included as an analysis factor as it is not relevant to the conceptual questions.

Finally, to assess how the groups performed over time, data from the two 12-minute runs containing only the SAT condition were analyzed using repeated-measures ANOVAs with the factors of Block (six, 2 minute-long task blocks), Duration (50, 29, 17), and Group. We expected to see interactions between Block and Group if any group showed greater declines in vigilance than the other groups.

3.0 Results

Primary results for the distraction and time-on-task effects are shown in Figures 2 and 3. Full ANOVA tables for these results and additional analyses of the data in accordance with signal detection theory (Swets et al., 1961) and can be found in the Supplemental Data section. In keeping with the CNTRICS mission, we also analyzed the internal reliability of the SAT and dSAT and found all groups had high internal consistency on both conditions (see Supplemental Data section for results).

Patients are especially vulnerable to distraction. Patients performed worse than the first group of adult controls in both the SAT ($F(1,38) = 6.60, p = 0.01, \eta^2_G = 0.13$) and dSAT ($F(1,38) = 9.16, p = 0.004, \eta^2_G = 0.18$) conditions, but the critical Group x Distraction interaction indicated the distractor effect was larger for patients, ($F(1,38) = 6.12, p = 0.02, \eta^2_G = 0.03$). Although this interaction was not significantly modulated by signal duration, follow-up analyses indicated that controls only showed significant distraction effects at the shortest duration, ($t(19) = 2.25, p =$

0.04, $d = 0.50$), whereas patients showed significant effects at all durations, all $p < 0.05$, $d > 0.47$.

Controls' SAT performance was statistically off-ceiling for all durations (one-sample t -tests versus 1, all $p < 0.005$), but was very high, raising concerns that the apparent Group x Distraction interaction was an artifact of ceiling performance. We therefore compared patients to controls tested in the VSL condition, where additional uncertainty as to signal location and duration reduced performance, and to children who, because of incomplete frontal-parietal development, were expected to have reduced attentional control. Both VSL controls and children showed off-ceiling performance in the SAT (all $p < 0.0001$, $d > 1.0$). In addition, while VSL controls and children had numerically higher SAT performance than patients (average scores: VSL controls, 0.93; children, 0.88; patients, 0.87), this difference was not significant for either group (VSL controls, $F(1,38) = 2.50$, $p = 0.12$, $\eta^2_G = 0.05$; children, ($F(1,36) = 0.11$, $p = 0.74$, $\eta^2_G = 0.003$).

Comparisons between the VSL controls and patients revealed a significant Group x Distraction x Duration interaction ($F(2,76) = 3.68$, $p = 0.03$, $\eta^2_G = 0.004$). Analyses within each duration found patients showed a greater distraction impairment on the 29 ms duration than the VSL controls (Distraction x Group, $F(1,38) = 4.72$, $p = 0.04$, $\eta^2_G = 0.04$). This effect was not significant for the other durations (both $p > 0.29$, $\eta^2_G < 0.007$). Within the VSL group, performance dropped significantly with distraction at the shortest signal duration (paired t -test, $t(19) = 2.64$, $p = 0.02$, $d = 0.59$) and numerically but not significantly at the other durations (both $p > 0.15$). As noted earlier, patients showed distractor effects at all durations, all $p < 0.05$, $d > 0.47$.

Comparisons between children and patients likewise revealed a Group x Distraction x Duration interaction ($F(2,72) = 3.38$, $p = 0.04$, $\eta^2_G = 0.003$). Unlike either adult control group, children showed significant distraction effects for all signal durations, with the largest drop observed for the shortest duration (all $t(17) > 2.37$, $p < 0.03$, Cohen's $d > 0.56$). Analyses within

each duration showed patients were more impaired than children by distraction on the 29 ms duration (Group x Distraction, $F(1,36) = 4.05$, $p = 0.04$, $\eta^2_G = 0.03$), but not the 17 or 50 ms durations, both $p > 0.33$, $\eta^2_G < 0.003$.

Overall, the data suggest schizophrenia is associated with general performance deficits but also a specific vulnerability to distraction. Healthy individuals' performance also decreased during distraction, especially for the shortest signal duration, but patients showed large declines for all durations. Patients' distractor impairments were especially pronounced for the middle signal duration, where their distractor effects exceeded that of any other group.

Patients but not children sustain attention over time. We also compared the groups' ability to maintain performance across the 12-minute SAT runs, which might require different aspects of attentional control than those needed to overcome distraction. The critical Group x Block interaction was significant ($F(15,370) = 1.93$, $p = 0.02$, $\eta^2_G = 0.01$, Figure 3), and there were also main effects of Group ($F(3,74) = 4.01$, $p = 0.01$, $\eta^2_G = 0.09$) and Duration ($F(2,148) = 13.50$, $p < 0.001$, $\eta^2_G = 0.01$), replicating the findings for the SAT blocks in the 8-minute runs.

To probe the Group x Block interaction, repeated-measures ANOVAs were run within each group using the factors of Block and Duration. Only children showed a main effect of Block ($F(5,85) = 3.19$, $p = 0.02$, $\eta^2_G = 0.04$). The block effect did not approach significance for the other groups, all $p > 0.15$. Of particular importance, patients did not show a decrease in performance or an increase in omissions over the blocks, both $F < 1$.

4.0 Discussion

Our results suggest that in addition to a general deficit in attentional performance, schizophrenia is associated with a specific vulnerability to distraction consistent with the CNTRICS input selection construct. Further, this is not a case of patients simply showing greater sensitivity to any increase in cognitive demand: Patients but not children sustained performance over time. The identification of a deficit in a particular aspect of attentional control,

especially in a task with high internal reliability (see Supplemental Data) and ties to behavioral and cognitive neuroscience, may ultimately help guide the development and testing of treatments for its remediation.

As noted earlier, in healthy adults the distraction effect correlates with activation in right MFG, a region previously linked to cognitive-control disruptions in schizophrenia (e.g., Demeter et al., 2011; Minzenberg et al., 2009). An obvious next question is whether patients will over- or under-activate this region in response to distraction. Our hypotheses in this regard are guided by evidence from an animal model of schizophrenia: Rats pre-treated with amphetamine over several weeks and then allowed to recover from withdrawal serve as a model of remission (Kozak et al., 2007; Sarter et al., 2009). These animals maintained performance on the SAT, but had higher levels of right-prefrontal acetylcholine release than did saline-treated controls. When faced with the distractor, pretreated animals failed to activate the cholinergic system and had corresponding performance deficits. This leads to the prediction that in humans, patients will over-activate right MFG in the SAT condition but fail to show additional activation increases in response to the distractor. If such a pattern is found, the cholinergic link established in animals suggests a treatment strategy for remediating deficits in distractor-related activation and performance (see Sarter et al., 2012).

The patients' vulnerability to distraction contrasts with their relatively spared sustained attention. As noted earlier, many previous studies purporting to show sustained-attention deficits did not assess performance changes over time and used tasks with high input-selection demands. Although the SAT is sensitive to group differences in sustaining attention, as shown by differential time-on-task declines in children, its low input-selection demands may have allowed patients to maintain performance. However, formal parametric studies manipulating input-selection demands and other factors may be necessary to determine when schizophrenia-related deficits in sustained attention do and do not occur.

The present study has important limitations. One caveat is that patients were medicated. However, secondary analyses within the patient group did not reveal any effects of medication type or dosage; furthermore, attentional deficits are known to exist in the absence of medication (Asarnow and MacCrimmon, 1978; Nuechterlein et al., 1992), and antipsychotic medication has little effect on cognitive control (Barch and Ceaser, 2012). Another concern is the difference in baseline (SAT) performance between patients and matched controls performing the same version of the task. These differences would be less relevant for clinical trials assessing improvement within patient groups, but could limit the ability to assess how closely an intervention brings patients to normal function. They may also raise questions about the relative contribution of attentional factors versus perceptual factors, given schizophrenia-related deficits in contrast sensitivity (Butler et al., 2005). For questions where it is important to match baseline performance, future studies may consider titrating the signal duration or contrast until performance is equalized in the SAT, allowing a more precise estimate of differences due to distraction.

In summary, the present results demonstrate both impaired and spared aspects of attention in schizophrenia. Although further development is needed to fully understand the nature of patients' increased vulnerability to distraction, the dSAT's ties to behavioral and cognitive neuroscience research guide specific hypotheses about the neural systems that may underlie them and suggest potential avenues for treatment.

Role of funding source

The study was funded by a grant to SKG from the University of Michigan Tobacco Research Network and The American Legacy Foundation, as well as start-up funds to CL. These funding sources had no further role in study design, collection, analysis and interpretation of data, in the writing of the report or to submit the final paper for publication.

Contributors

ED, SKG, SFT, MS and CL designed and planned the study. ED collected the data. ED, SKG, SFT and CL were responsible for project and data management. ED carried out the statistical analyses and wrote the first draft of the manuscript. All authors contributed substantively to the editing of the manuscript and approved the final version prior to submission.

Conflict of interest

All authors declare that they have no conflict of interest.

Acknowledgements

We thank Jessica Oakley for her help with data collection. ED was supported by an NSF Graduate Research Fellowship. MS was supported by NIH Grant KO2 MH10172.

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Figure Legends:

Figure 1. Sustained Attention Task (SAT). Each trial of the SAT consists of a variable interval (1000, 2000 or 3000 ms) followed by the presentation of a signal or nonsignal event. The signal is a 3.5 mm² grey square on a silver background and varies in duration (17, 29 or 50 ms). Signal and nonsignal events are randomized and equally presented over the course of each 2-minute task block. One hundred milliseconds after a signal appears or does not appear, participants hear a low frequency buzzer cuing them to respond. Participants respond on a keyboard using one index finger for signal trials and their other index finger for nonsignal trial (left-right key assignment counterbalanced across participants). Participants have up to 1500 ms to respond before the initiation of the next trial. Correct responses are followed by a high frequency feedback tone; incorrect responses or omissions do not result in feedback. The SAT thus has several features that add to the attentional load of the task, including the variable time participants are required to monitor for a signal, the variable signal duration and the competing response rules. For the healthy adult controls in the variable signal location (VSL) condition, the attentional load was further increased by presenting the signal in one of three locations on the screen and by adding a fourth signal duration (150 ms). The distractor condition Sustained Attention Task (dSAT) adds to the attentional control demands of the task by adding in a global, continuous distractor. This distractor consists of the computer screen flashing continuously from gray to black at a rate of 10 Hz while participants perform the task.

Figure 2. Effects of distraction on SAT scores for healthy adult controls, patients with schizophrenia, and school-age children. Data shown are from the averaged dSAT run, collapsed by whether distraction was absent (SAT condition, black bars) or present (dSAT condition, white bars). Bars represent the mean and standard error of the mean. (a) Healthy adult control participants show high levels of attentional performance, dropping only slightly

when distraction is present. (b) Healthy adults run on a version of the task with variable signal locations and an additional duration to increase uncertainty (VSL condition, see Methods) showed SAT scores without distraction that were off of ceiling and significant distraction effects at the shortest signal duration (paired t -test between SAT and dSAT, 17 ms condition, $p < 0.05$). (c) In contrast, while patients and children performed equivalently without distraction, patients' SAT scores were disproportionately affected by the presence of distraction, declining further than the drop seen in healthy controls. (d) Healthy school-age children were even further off of ceiling in SAT scores without distraction, but did not show as great of impairment with distraction as patients with schizophrenia. Collectively, these results indicate that patients with schizophrenia show deficits in attentional performance on this task that are amplified in the presence of distraction.

Figure 3. SAT scores decline over time in school-age children. Data are SAT scores (mean and standard error around the mean) for the 50 ms, 29 ms, and 17 ms durations from the average of the two SAT runs. Each run consisted of six 2 minute blocks. Performance of healthy adult controls (a) and healthy adults performing a more challenging version (VSL condition) of the SAT (b) did not vary significantly between blocks. (c) Patients with schizophrenia also showed relatively stable attentional performance levels over time. In contrast, school-age children's (d) SAT scores declined over time, with their lowest levels of performance coming at the end of the run.

Table 1. Demographic and clinical characteristics of subjects. Both adult control groups were age- and gender- matched to the patients. The mean socio-economic status (SES) of the three adult groups did not differ ($p = 0.85$). SES information was unavailable for the children. Within the patient group, five patients' primary diagnosis was schizoaffective disorder and the rest had schizophrenia as a primary diagnosis. All were stably-medicated, with 4 individuals on typical antipsychotics (3 haloperidol, 1 trifluoperazine) and the remaining on atypical antipsychotics (9 risperidone, 3 clozapine, and 1 each on ziprasidone, paliperidone, aripiprazole, and quetiapine).

Mean \pm SE	Patients ($n = 20$)	Controls ($n = 20$)	VSL controls ($n = 20$)	Children ($n = 18$)
<i>Demographics</i>				
Age (y)	45.8 \pm 2.5	46.1 \pm 2.4	46.9 \pm 2.4	9.4 \pm 0.3
Males/females	13/7	13/7	13/7	15/3
Education (y)	14.9 \pm 0.5	17.3 \pm 0.9	15.4 \pm 0.6	3.4 \pm 0.3
Socio-economic status	2.8 \pm 0.2	2.7 \pm 0.2	2.7 \pm 0.2	--
<i>Clinical measures</i>				
BPRS total	31.2 \pm 2.0			
SANS global sum	19.3 \pm 2.9			
HAM-D-17	7.2 \pm 1.1			

Abbreviations: BPRS: Brief Psychiatric Rating Scale (Overall and Gorham, 1962); SANS: Scale for the Assessment of Negative Symptoms (Andreasen, 1983), HAM-D-17: Hamilton Scale for Depression, 17 items (Hamilton, 1960).

Figure 1.

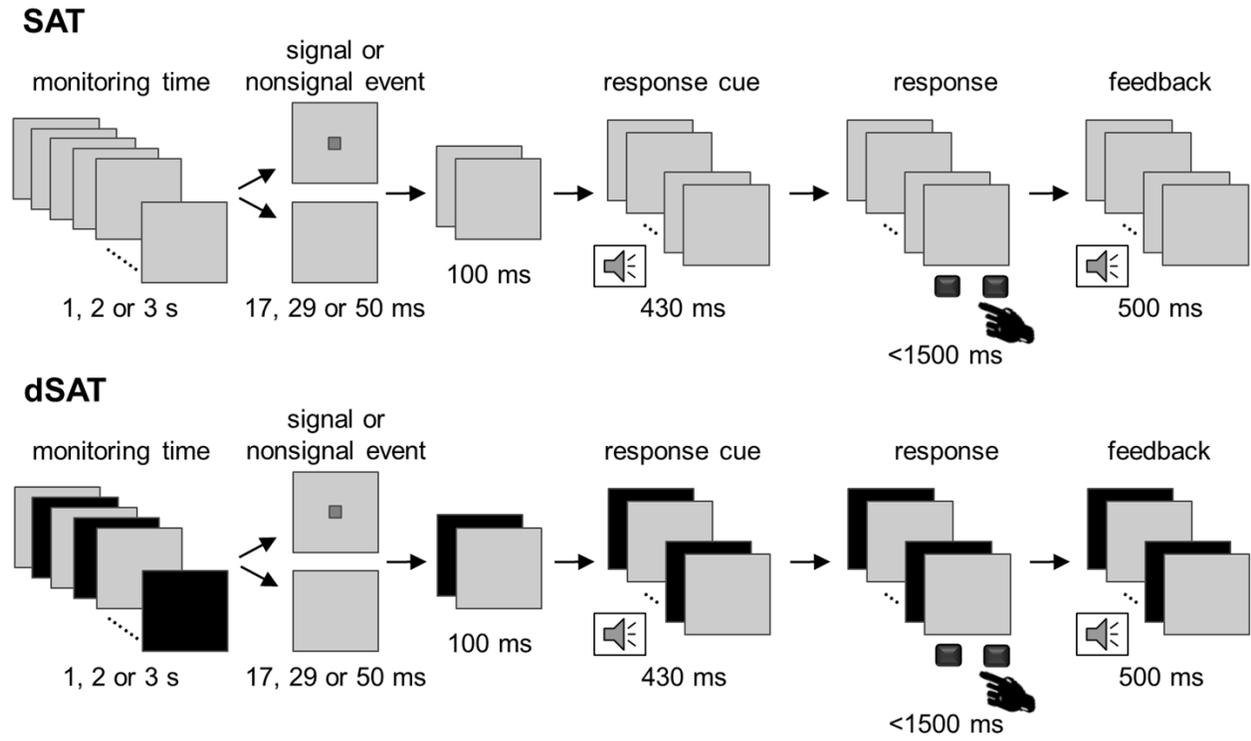


Figure 2.

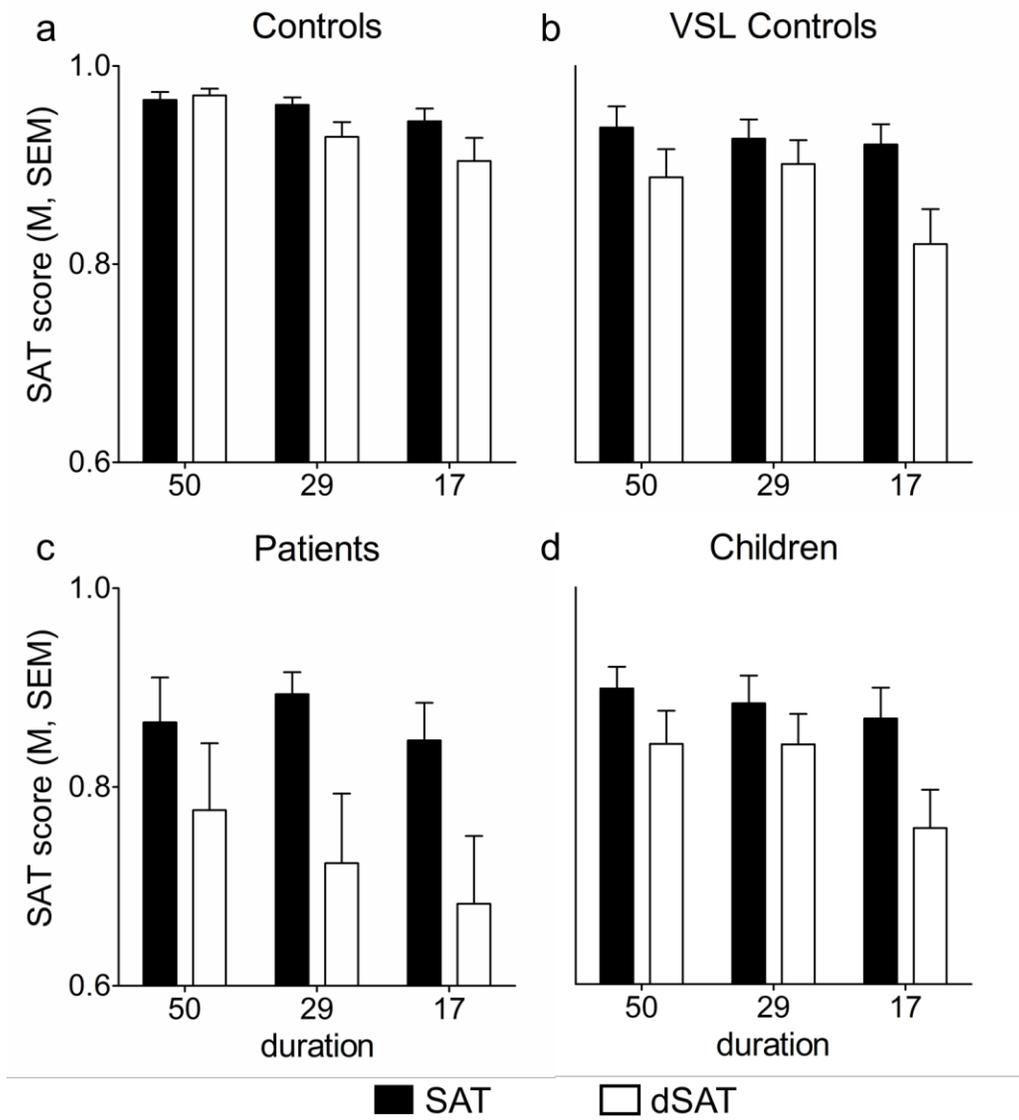
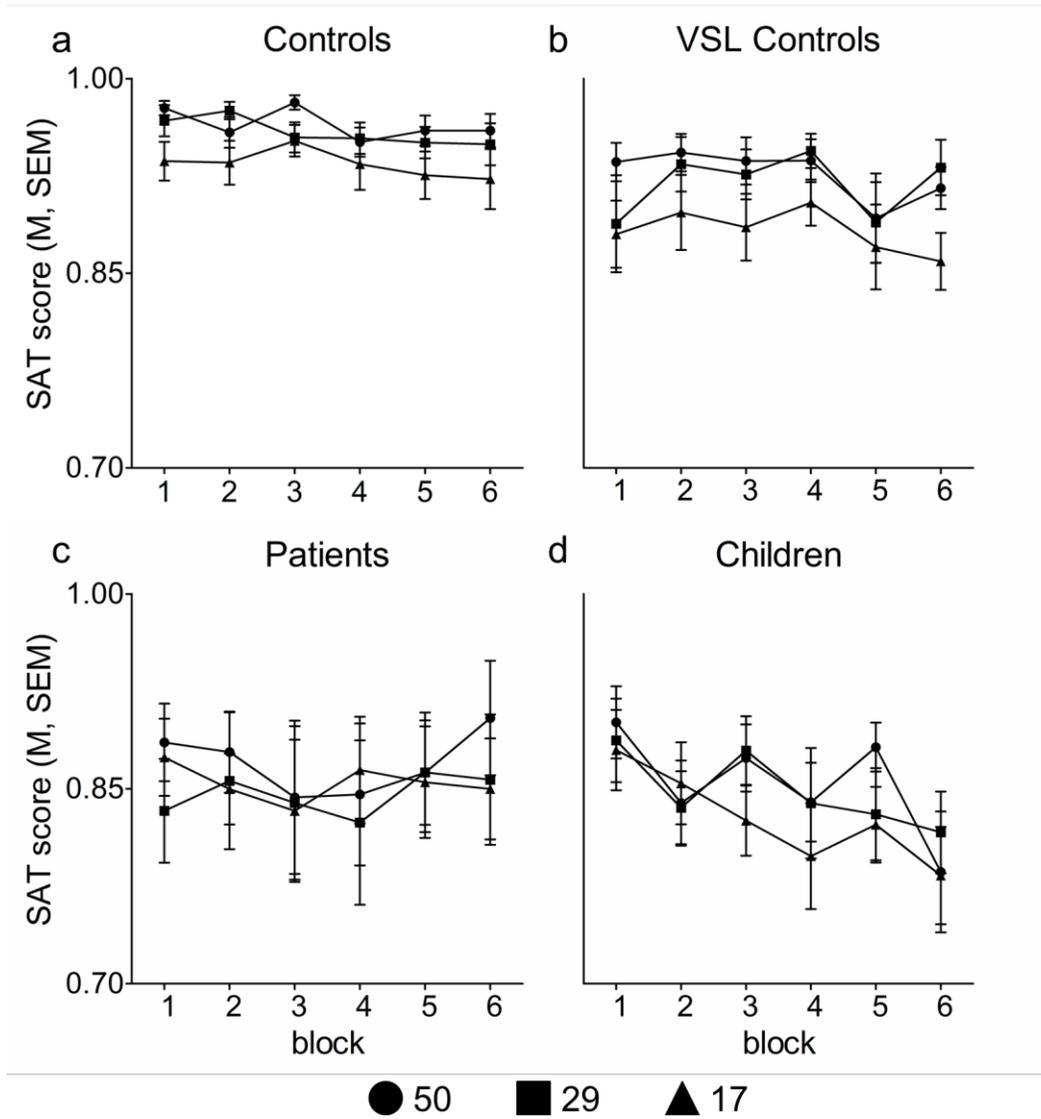


Figure 3.



Acknowledgements

We thank Jessica Oakley for her help with data collection. ED was supported by an NSF Graduate Research Fellowship. MS was supported by NIH Grant KO2 MH10172.

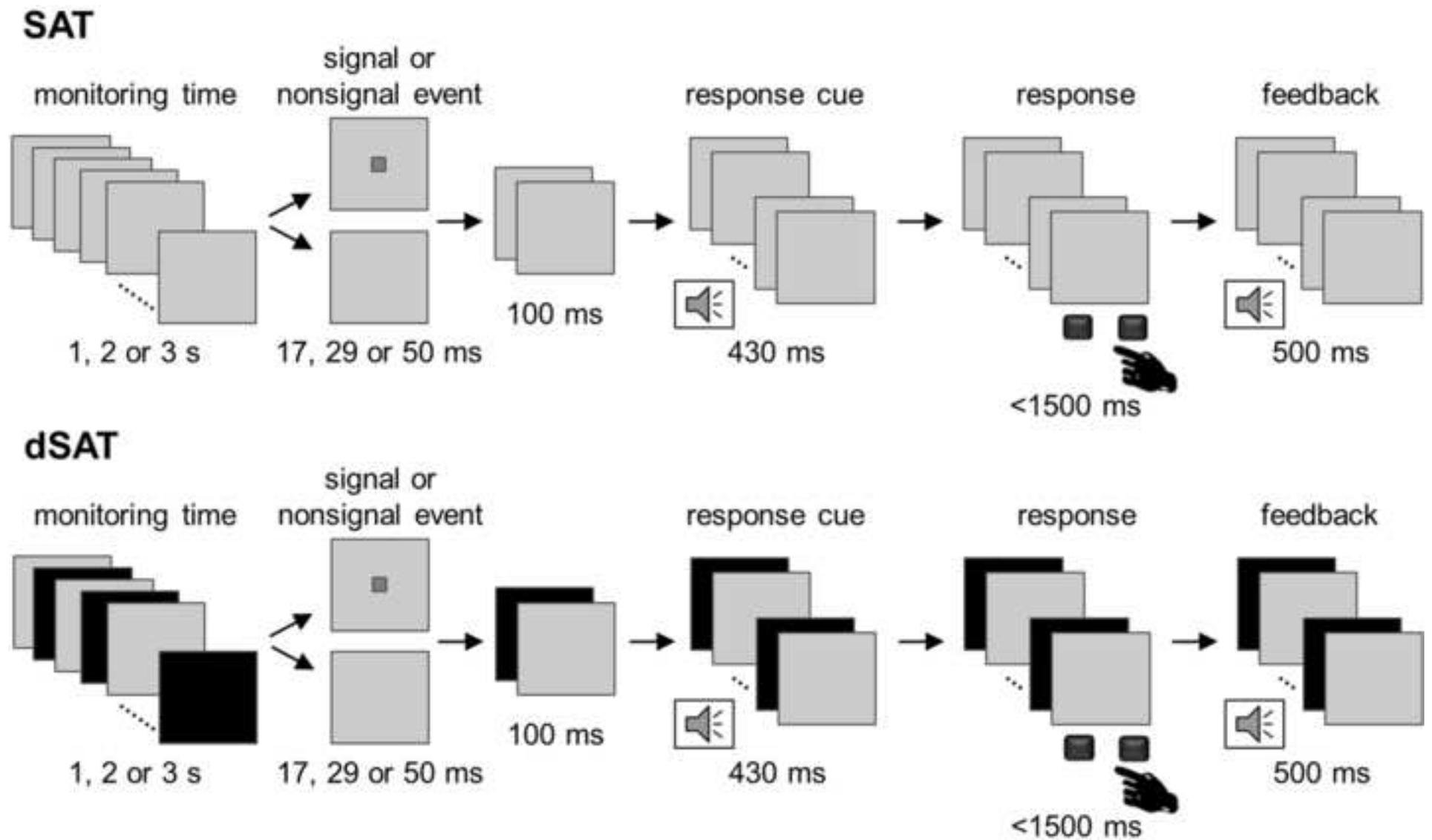
Conflict of interest

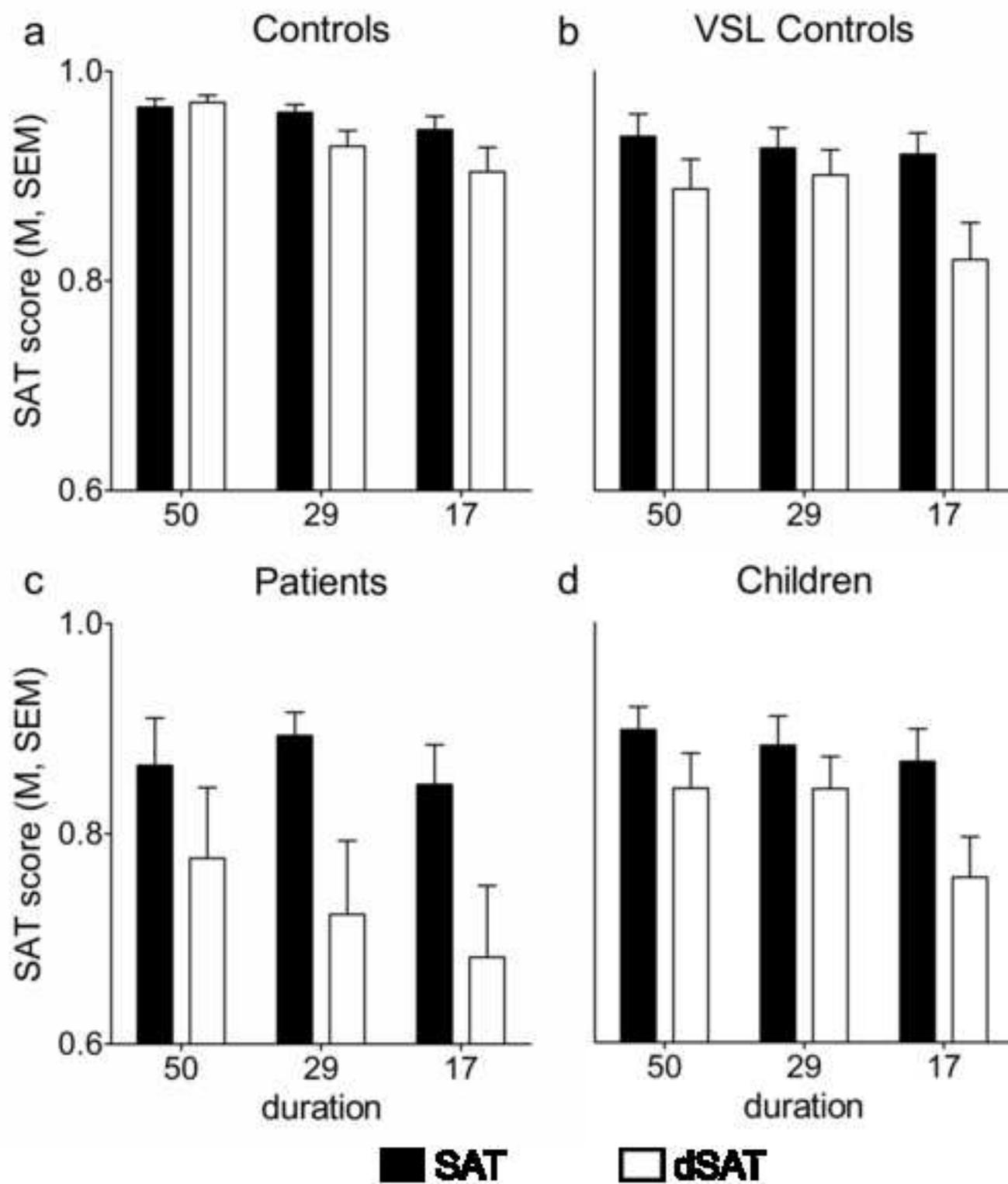
All authors declare that they have no conflict of interest.

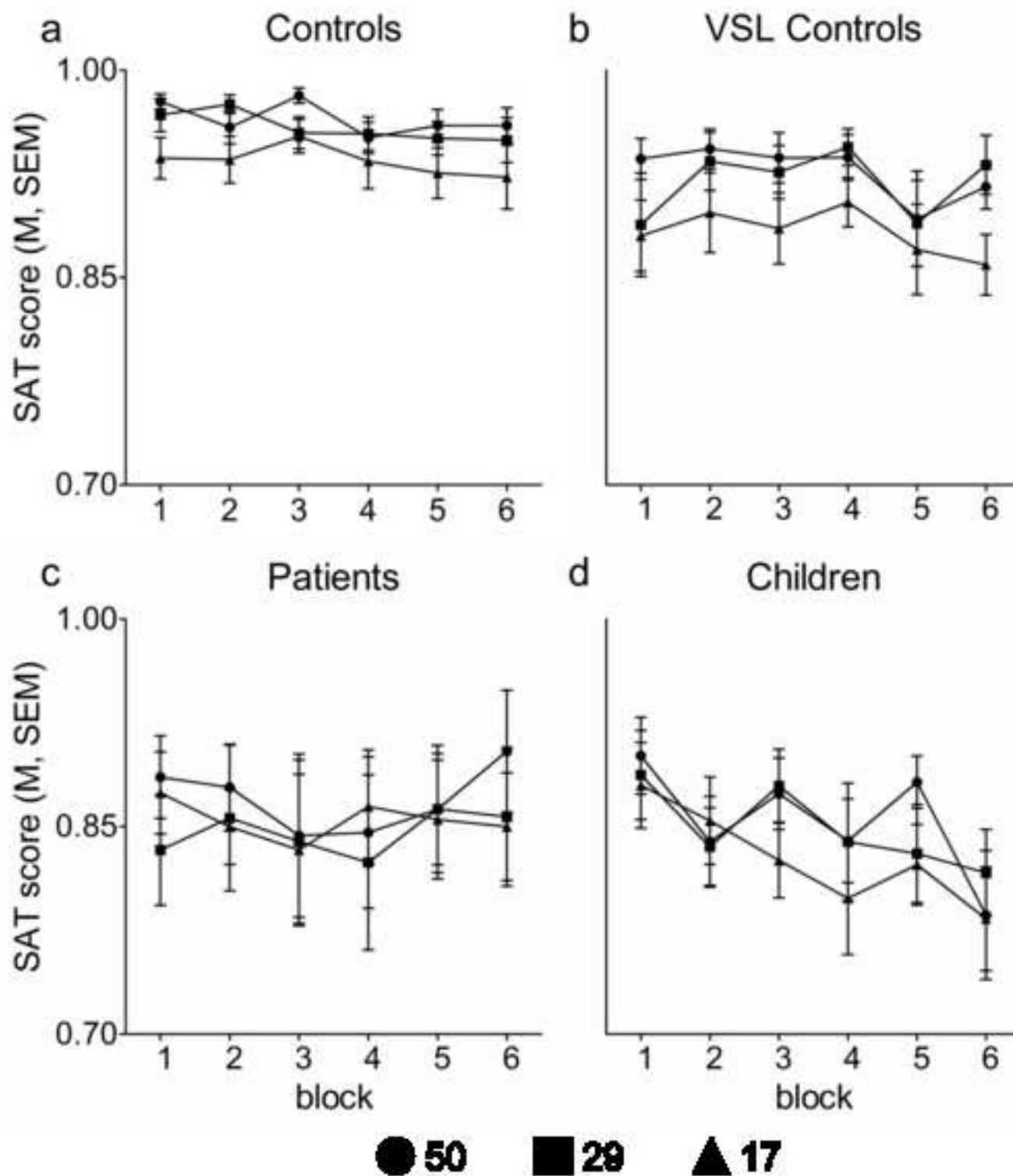
Contributors

ED, SKG, SFT, MS and CL designed and planned the study. ED collected the data. ED, SKG, SFT and CL were responsible for project and data management. ED carried out the statistical analyses and wrote the first draft of the manuscript. All authors contributed substantively to the editing of the manuscript and approved the final version prior to submission.

Figure(s)
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Role of funding source

The study was funded by a grant to SKG from the University of Michigan Tobacco Research Network and The American Legacy Foundation, as well as start-up funds to CL. These funding sources had no further role in study design, collection, analysis and interpretation of data, in the writing of the report or to submit the final paper for publication.

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