Research Article

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Higher-Order Clicker Questions Engage Students and Prepare Them for Higher-Order Thinking Activities

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Previous research has shown that the use of clickers in the classroom enhances student engagement. However, few studies have investigated how the type of clicker question may influence learning outcomes. To explore this, we compared the effects of lower-order cognitive skill (LOCS) and higher-order cognitive skill (HOCS) clicker questions on later exam performance in a biology course. During class time, students were presented with clicker questions directly related to unit content. Half of the content units were taught with LOCS, the other half with HOCS. To ensure that type of content did not influence results, the cognitive level of the clicker questions was counterbalanced across two semesters. The exams included a mix of LOCS and HOCS for each content unit. We also investigated the possible moderating effects of student perceptions on the relationship between type of clicker question and exam performance using student surveys. We found that using HOCS clicker questions significantly affects student learning. Practice with HOCS clicker questions improved performance on LOCS exam questions but not on HOCS exam questions. Students ranked lecture with clickers as a preferred and most helpful teaching methodology. Overall, these results suggest that practice with HOCS questions is engaging and gives students practice recalling content to "solve" a problem, thereby encoding low-level information and preparing them for higher-order thinking activities.

KEYWORDS higher-order thinking, clickers, human biology, undergraduate

INTRODUCTION

Fostering the development of higher-order cognition skills, including problem-solving and critical reasoning skills, is a common goal for many college courses and one that is particularly emphasized in the biological sciences (1–5). Given their value to our students, it is therefore incumbent on researchers to examine the pedagogical methods and tools that can be used to promote these skills. For example, some research has shown that providing students with regular practice addressing problem-solving questions as part of coursework and assessments may promote the development of higher-order cognition skills (6–9). Of course, students need a foundation of content knowledge and many hours of deliberate practice to master the skill of critical thinking (1, 10). Thus, it is important to identify and examine methods and tools for solidifying a more basic understanding of concepts in the classroom as well.

One possible tool for building basic knowledge and higher-order cognition skills is clicker technology. Combining clicker technology with other questioning methods and peer discussion in the classroom can significantly improve student learning in biology courses (4, 11–16). For one thing, the use of clickers has been shown to promote student engagement during lectures (11, 17–20), which fosters meaningful student learning (21–23). Potentially as a result, students perform better on exams following the use of clicker questions in class. For example, Crossgrove and Curran (24) found that student performance was higher on exam questions covering content reviewed with clickers than on exam questions not reviewed in this way. Relatedly, in some studies frequency of clicker use was positively associated with exam scores (25, 26; but see also reference 4) and final course grades (27, 28).

While several studies have considered the utility of clicker questions in the classroom (see reference 29 for a meta-analysis), few studies to date have investigated how the type of clicker question may influence learning outcomes. In the present research, we were interested in how clicker questions that differed with regard to cognitive skill may influence later exam performance. Questions that are considered "lower-order cognitive skill" (LOCS) focus on semantic knowledge (e.g., definitions of terms) and basic comprehension of a concept, whereas questions considered "higher-order cognitive skill" (HOCS) focus on analysis of concepts, synthesis across concepts, and/or evaluation of ways in which concepts may be applied (7).

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Existing guidelines for writing effective clicker questions (30–33) recommend designing questions that focus on the qualitative or application level, that is, HOCS clicker questions. Indeed, a small body of evidence suggests that asking HOCS questions leads to greater student learning than does asking LOCS recall questions (34, 35). Another study (36) found that HOCS questioning during the learning process specifically improved performance on HOCS exam questions but, interestingly, had no effect on LOCS exam questions.

Student learning and performance are also potentially influenced by students' perceptions of the learning environment and the utility of teaching methods in a given class (37–40). In other words, the effectiveness of clicker questions as a review tool may depend partly on whether students believe they are helpful. In past studies, DeBourgh (41) and Russell et al. (42) reported that students found the use of clickers helpful for developing deep understanding and problem-solving skills in the context of a course. In particular, students recognized that the clicker questions at the application or synthesis level (i.e., HOCS) were the most helpful types of questions (42, 43). In the present research, we therefore also gathered information on student perceptions of the utility of clicker questions, compared with other traditional elements of a course—the textbook and standard lecture/discussion.

Hypotheses

We sought to better understand the influence of the type of clicker question on student learning by comparing the effects of LOCS and HOCS clicker questions on later exam performance in a biology course. We also considered the possible moderating effects of student perceptions on the relationship between type of clicker question and exam performance. Given the existing literature, we hypothesized that LOCS clicker questions would enhance performance on LOCS exam questions but that they would not significantly improve performance on more challenging HOCS exam questions. Similarly, given the findings of Slain et al. (36), we expected that HOCS clicker questions would improve performance on HOCS exam questions, without significantly affecting LOCS exam question performance. Finally, given the value of understanding student perceptions of our pedagogical tools, we also explored whether students would perceive clicker questions as being as helpful as their textbook and standard lecture/discussion. We hypothesized that LOCS and HOCS clicker questions would be perceived as equally helpful.

METHODS

Course background and participants

Clickers were used in a 1-semester, 100-level nonmajors' Human Biology course. This course satisfies a natural sciences general education requirement at St. Norbert College. The class met (in person) three times per week for a 70-min lecture/discussion and once per week for a 2-h laboratory experience. This research was completed over the course of 2 semesters (semester 1 [fall 2010] and semester 2 [fall 2012]). In semester 1, 28 participants (68% female) were enrolled in the course, and 25 participants were enrolled during semester 2 (88% female).

Study design

The study began in the 4th week of the respective semesters, after the first exam, allowing students to become familiar with the clicker technology, the instructor, and course expectations. Human Biology is traditionally taught using a series of content units that correspond to various human body organ systems. Eleven different content units were used in the study, each with clicker questions as part of the learning process. The Blooming Biology Tool of Crowe et al. (6) was used to develop and score low- and high-cognitive-level (LCL and HCL, respectively) clicker questions and exam questions. Specifically, LOCS questions focused on knowledge and comprehension, whereas HOCS questions focused on analysis, synthesis, and evaluation (an example of each type of question is provided in Chart S1 in the supplemental material). All clicker questions were presented in a multiple-choice (MC) format, and exam questions included a mix of multiple-choice and short-answer questions. All questions were written and categorized by the lead author, who has had formal training in writing multiple-choice questions for standardized exams such as the Medical College Admission Test (MCAT). In addition, two colleagues each provided a secondary rating for a set of 92 questions, indicating whether each was either an LOCS or an HOCS question; interrater reliability between these secondary raters and the lead investigator was strong ($k = 0.836$).

(i) Clicker questions during learning

During class time, students were presented with clicker questions throughout all 11 content units. Approximately half of the content units involved LOCS clicker questions, while the other content units involved HOCS clicker questions. To ensure that type of content did not influence results, the cognitive level of the clicker questions was counterbalanced across the two semesters (Table 1). In other words, if the skeleton was taught using all LOCS clicker questions in semester 1, the skeleton was taught using all HOCS clicker questions in semester 2.

Students completed 5 to 6 clicker questions interspersed throughout each lecture. Specifically, after a main point was made (usually within a 15- to 20-min lecture segment), students responded to a clicker question designed to assess their knowledge, comprehension, etc., of information relevant to the topic. When fewer than 75% of students selected the correct answer, they were encouraged to interact in a think-pair-share methodology, followed by a second

TABLE 1
Summary of research design

Exam	Content unit	Yr 1				Yr 2			
		Cognitive level of clicker questions	No. of exam questions by cognitive level		Student survey	Cognitive level of clicker questions	No. of exam questions by cognitive level		Student survey
			Low	High			Low	High	
II	Skeletal system	Low	9	5		High	11	5	
	Muscle anatomy and physiology	High	10	3		Low	10	6	
	Digestive system	Low	12	4		High	12	5	
	Respiratory system	High	12	4	Yes	Low	14	5	Yes
III	Cardiovascular system	Low	11	6		High	14	6	
	Genetics	High	10	4		Low	9	6	
	Cancer	Low	12	3	Yes	High	14	5	Yes
IV	Urinary system	High	19	4	Yes	Low	20	9	
	AIDS/HIV	Low	11	2		High	11	5	
	Immune system	High	12	5		Low	16	7	
	Nervous system	Low	9	2		High	16	5	Yes
Total		Low	64	22		Low	69	33	
		High	63	20		High	78	31	

round of responses to the original question. Histograms showing student responses were revealed to the class only after the readministration of the clicker question. If a majority of student responses were still incorrect after the second administration, the instructor provided feedback on the concept from a different perspective. An additional clicker question for that concept was then used to reassess student understanding.

(ii) Exam questions

On each of the three exams relevant to this study (exams II to IV), students were asked both LOCS and HOCS questions. Importantly, both LOCS and HOCS exam questions were used for each of the 11 content units in both semesters (Table 1). Across these exams, four scores were computed for each student. First, for units that used LOCS questions during learning, we computed the percentage of correct responses to LOCS exam questions across all units (Low-Low%Correct) and to HOCS questions across those same units (Low-High%Correct). Next, for units that used HOCS questions during learning, we computed the percentage of correct responses to HOCS exam questions across all units (High-High%Correct) and to LOCS questions across those same units (High-Low%Correct). The means for these four scores, combining data across both semesters, are depicted in Fig. 1.

(iii) Student perceptions survey

All students were asked to complete a self-report survey prior to each exam. The survey (Fig. S2) was designed for the purposes of the study, asking students about their understanding of and interest in a portion of the recently covered content (Table 1). They were also asked about how effective three pedagogical features were in facilitating learning: the clicker questions, the textbook, and the standard lecture/discussion. For each of the two semesters, students were surveyed about one topic that used LOCS questions during learning and about two topics that used HOCS questions during learning. To ensure confidentiality of students' surveys, all responses were compiled by an assistant, and all identifying information was removed from the data file before it was provided to the investigators. For each semester separately, three scores were computed to reflect the perceived helpfulness of the three pedagogical features, respectively.

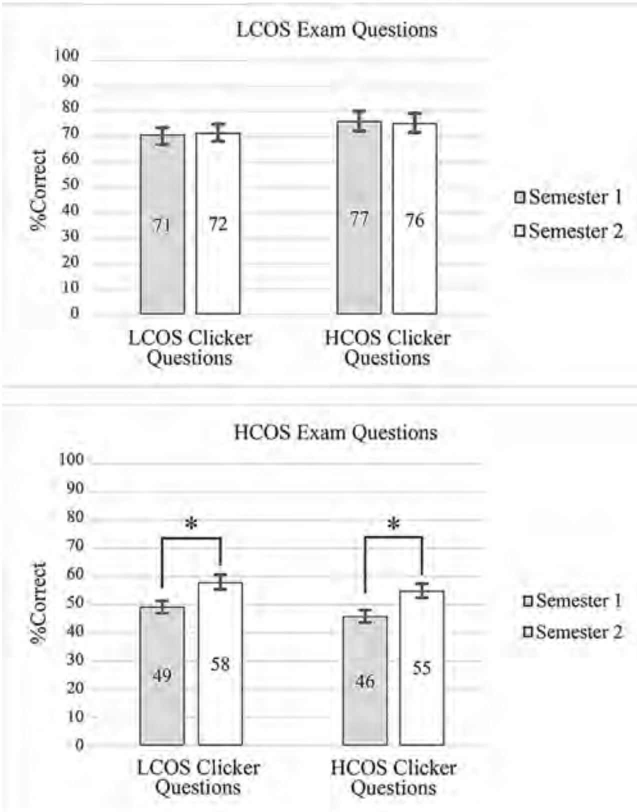

FIG 1. Comparison of student performance on low- and high-cognitive-skill (LCOS and HCOS, respectively) exam questions when low- and high-cognitive-level clicker questions were used in class. Each bar represents the average number of correct answers on all of the indicated exam questions taken from three exams for 53 students. Error bars, 95% confidence interval. *, $P < 0.001$.

Institutional review

All study methods and procedures were reviewed and approved by the Institutional Review Board (IRB) at St. Norbert College (IRB no. 10-09-0001).

Data analytic plan

First, to test our hypotheses regarding whether LOCS or HOCS clicker questions improved student performance on these two types of exam questions, respectively, we ran a 2 (type of clicker question: LOCS or HOCS) × 2 (type of exam question: LOCS or HOCS) × 2 (semester 1 or semester 2) mixed analysis of variance (ANOVA). Second, we examined student perceptions of the utility of clicker questions during learning, compared with the utility of the textbook and standard lecture/discussion, by running a 3 (pedagogical feature: clicker questions, textbook, or standard lecture/discussion) × 2 (type of clicker question: LOCS or HOCS) × 2 (semester 1 or semester 2) mixed ANOVA to further analyze student perceptions. All statistical analyses were performed using SPSS version 27.0 (44).

RESULTS

Exam performance

We hypothesized that LOCS clicker questions during the learning process would enhance student performance on LOCS exam questions related to the same content. Similarly, we hypothesized that HOCS clicker questions during the learning process would enhance student performance on HOCS exam questions. To test these hypotheses, we ran a 2 (type of clicker question: LOCS or HOCS) × 2 (type of exam question: LOCS or HOCS) × 2 (semester 1 or semester 2) mixed analysis of variance (ANOVA).

As shown in Table 2, the main effect for type of clicker question was nonsignificant (NS), whereas the main effect for type of exam question was significant. In other words, on the one hand, overall performance on clicker-related exam questions was not significantly influenced by whether the information had been reviewed using LOCS versus HOCS clicker questions. On the other hand, performance on LOCS exam questions was overall significantly better than performance on HOCS exam questions, as indicated by a large effect size. Additionally, the main effect for semester was statistically significant, with a medium effect size; students in semester 2 performed better than students in semester 1 overall.

However, these main effects should be interpreted in light of the significant interactive effects found in our analysis. First, the interaction between type of exam question and semester was significant, with a large effect size. To interpret this interaction, we ran a set of independent-sample *t* tests (Fig. 1). Results indicated that there were no important differences between semester 1 and semester 2 students with regard to their performance on LOCS exam questions, whether they had been reviewed using LOCS clicker questions ($t[51] = 0.51$, $P =$ NS) or HOCS clicker questions ($t[51] = 0.32$, $P =$ NS). However, semester 2 students outperformed semester 1 students on HOCS exam questions, both when reviewed using LOCS clicker questions ($t[51] = 3.10$, $P = 0.003$, Cohen's $d = 0.79$) and when reviewed using HOCS clicker questions ($t[51] = 2.52$, $P = 0.015$, Cohen's $d = 0.67$). These would be considered medium-to-large effect sizes (45).

Additionally, the interaction between type of exam question and type of clicker question was statistically significant, with a large effect size, when looking at all students across both semesters. Follow-up paired-sample *t* tests were used to interpret this interaction, with results contrary to our predictions. Looking at the two semesters combined, HOCS clicker questions contributed to better performance on LOCS exam questions than did LOCS clicker questions (M_{LCL} = 72% versus M_{HCL} = 76%; $t[52] = 4.25$, $P < 0.001$, Cohen's $d = 0.47$), with a small-to-medium effect size. Also contrary to hypotheses, performance on HOCS exam questions was not better when HOCS clicker questions were used during the learning process; HOCS and LOCS clicker questions led to similar exam

TABLE 2
Effects of clicker question type, exam question type, and semester on exam performance

Variable(s)	Wilks' Λ	*F*	Hypothesis *df*	Error *df*	*P*	Partial η^{2a}
Main effects						
Clicker questions	0.98	0.84	1	50	NS	0.02
Exam questions	0.10	453.48	1	50	<0.001	0.90
Semester		4.86	1	50	0.032	0.09
Two-way interactions						
Clicker questions × semester	0.99	0.47	1	50	NS	0.01
Exam questions × semester	0.73	18.63	1	50	<0.001	0.27
Clicker questions × exam questions	0.85	9.14	1	50	0.004	0.16
Three-way interaction						
Clicker questions × exam questions × semester	1.00	0.03	1	50	NS	0.00

[a]Partial η^2 of >0.06 is considered a medium effect; partial η^2 of >0.14 is considered a large effect (45).

performance (M_{LCL} = 53% versus M_{HCL} = 51%; $t[52] = 1.26$, P = NS).

Student perceptions

We also explored student perceptions of the utility of clicker questions in their learning process, compared with the utility of the textbook and standard lecture/discussion. We ran a 3 (pedagogical feature: clicker questions, textbook, or standard lecture/discussion) × 2 (type of clicker question: LOCS or HOCS) × 2 (semester 1 or semester 2) mixed ANOVA to further analyze student perceptions.

As shown in Table 3 and depicted in Fig. 2, there was no significant main effect for type of clicker question. However, significant main effects were found for both pedagogical feature and semester. Paired-sample *t* tests revealed that across the two semesters combined, students rated the textbook as less effective than both clicker questions ($t[48] = 4.74$, $P < 0.001$, Cohen's $d = 0.70$) and standard lecture/discussion ($t[48] = 6.51$, $P < 0.001$, Cohen's $d = 0.80$), with medium-to-large effect sizes. There was no significant difference in perceptions of clicker questions and standard lecture/discussion in the combined sample. Moreover, students in semester 1 reported more positive perceptions of the utility of all three pedagogical features, combined, than did students in semester 2 ($t[47] = 8.80$, $P < 0.001$, Cohen's $d = 1.56$), with a large-effect-sized difference.

There were also notable interactive effects. The two-way interaction between pedagogical feature and semester was statistically significant and was further explored with a series of independent-sample *t* tests. Semester 1 students reported more positive perceptions of all three pedagogical features: clicker questions ($t[47] = 5.13$, $P < 0.001$, Cohen's $d = 1.19$), textbook ($t[47] = 4.11$, $P < 0.001$, Cohen's $d = 1.04$), and standard lecture/discussion ($t[47] = 10.80$, $P < 0.001$, Cohen's $d = 1.68$), all with large effect sizes.

Although they did not meet traditional standards for statistical significance (i.e., $P < 0.05$), the two-way interaction between pedagogical feature and type of clicker question and the three-way interaction between these two variables and semester were both of medium effect size (Table 3). We therefore conducted a set of follow-up paired-sample

TABLE 3
Effects of pedagogical feature, type of clicker question, and semester on student perceptions

Variable(s)	Wilks' Λ	*F*	Hypothesis *df*	Error *df*	*P*	Partial η^{2a}
Main effects						
Pedagogical features	0.50	22.82	1	46	<0.001	0.50
Clicker questions	0.98	1.1	1	46	NS	0.02
Semester		77.41	1	46	<0.001	0.62
Two-way interactions						
Pedagogical features × semester	0.85	3.95	1	46	0.026	0.15
Clicker questions × semester	0.99	0.29	1	46	NS	0.01
Pedagogical features × clicker questions	0.94	1.46	1	46	NS	0.06
Three-way interaction						
Pedagogical features × clicker questions × semester	0.94	1.59	1	46	NS	0.07

[a]Partial η^2 of >0.06 is considered a medium effect; partial η^2 of >0.14 is considered a large effect (44).

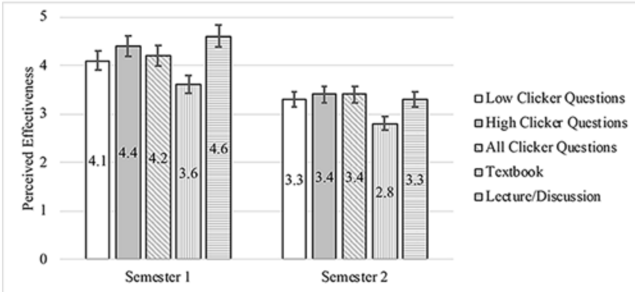

FIG 2. Students' ratings of three learning resources by cognitive skill level of clicker question. Error bars, 95% confidence interval.

t tests examining the interaction between pedagogical features and type of clicker question, running these analyses in the two semester-based subsamples separately. Students in both semesters reported that the textbook was less helpful than both LOCS and HOCS clicker questions. More interestingly, whereas students in semester 1 viewed the LOCS clicker questions as less helpful than standard lecture/discussion ($t[22] = 2.86$, $P = 0.009$, Cohen's $d = 0.74$) with a medium effect size, semester 2 students found LOCS clicker questions to be equally as helpful as lecture/discussion ($t[25] = 0.32$, $P =$ NS).

DISCUSSION

Clicker questions and exam performance

Our results suggest that the cognitive level of clicker questions significantly affects student learning. We showed that the use of high-cognitive-level clicker questions led to increased student performance on low-cognitive-level exam questions for students in Human Biology (Fig. 1). These findings are compatible with those of Barnett and Francis (46) and McDaniel et al. (47) and McDermott et al. (48), who found that students who practiced with higher-order thinking quizzes performed better on low-cognitive-level exam questions than students who were not exposed to such quizzes. If students practice retrieving knowledge (via clicker questions and/or quizzes), they are better able to recall it on exams (46–48). Higher-order questions require students to review and practice recalling factual material in order to "solve" the problem, thereby encoding low-level information. Mastery of this foundational or declarative knowledge, as demonstrated by the higher score on LOCS exam questions, is consistent with the Bloom taxonomy principle that higher-cognitive-level processes subsume lower-level processes (49).

The findings also suggest that reviewing course content with clicker questions is likely not the best tool for developing higher-order cognitive skills. We expected that in-class practice of higher-level reasoning by peer discussion of HOCS clicker questions would encourage students to study course material more deeply, as assessed by HOCS exam questions. However, practice with HOCS clicker questions did not improve performance on HOCS exam questions. One possible explanation for this finding is that the exam format signaled that multiple choice (MC) is important; over 95% of the exam questions were MC rather than constructed response (CR; i.e., short-answer or essay) questions. Student expectations about exam format strongly influence their study habits (50). The expectation of a primarily MC exam format may have encouraged students to study at a surface level (37), devoting little time to using more cognitively active learning behaviors such as self-testing, asking questions, comparing and contrasting, and practicing retrieval of information (51).

Changing the exam format to include more CR questions may encourage students to engage in more cognitively active study behaviors (50). However, a change in exam format alone is not likely to significantly improve students' critical thinking skills. The development of critical thinking skills requires deliberate practice with solving problems and learning how to apply knowledge in a new context (1, 52). Our results suggest that even purposefully and carefully created HOCS clicker questions do not achieve this goal. Instead, examples of activities that enhance critical thinking skills for course-specific content include giving students higher-order question assignments related to course material (53), retrieval practice with a variety of testing formats (54, 55), practice transferring acquired knowledge to a new situation (1), and effective questioning (52). Such activities would therefore be recommended, when possible. These activities can be incorporated into the classroom as described or tailored to complement an existing course activity. For specific, novel implementation suggestions, see the work of Brame and Biel (56).

Student perceptions of clicker questions

Our survey questions probing students' impression of the helpfulness of using clicker questions revealed that students tended to find them to be more helpful than the textbook (Fig. 2). These results are consistent with those of a recent study which reported learning preferences for Generation Z students (57). Students ranked lecture with clickers as a preferred and most helpful teaching methodology, whereas assigned textbook reading was the least preferred method. This is not surprising given that a textbook can be less engaging than answering questions and/or participating in class discussions. In addition, many students view the textbook as a source of factual information, which may or may not be organized in a way that is compatible with class material.

Students perceived low- and high-level clicker questions to be equally effective, which is inconsistent with the exam performance data. The HOCS clicker questions were significantly more helpful in preparing students for LOCS exam questions (Fig. 2). In contrast, DeBourgh (41) and Russell et al. (42) reported that students discriminated between type of clicker question and helpfulness. These studies revealed that students found the use of clickers helpful for developing deep understanding and problem-solving skills in the context of the course. In particular, students believed that the case study or conceptual (application/synthesis-level) clicker questions were the most helpful types of questions (42, 43). The reason that the students in this study did not discriminate between helpfulness of the low- and of the high-level clicker questions may be due to the study design. Students experienced either high- or low-level clicker questions for a particular topic, not a mix. It is likely that because students found clicker questions in general helpful, they were not considering how the different levels of questions for a particular topic might affect their learning.

Students performed better on LOCS exam questions overall. This is not surprising given that students had practice with LOCS clicker questions and likely practiced recalling factual content as a first step to solve the higher-order thinking questions. In general, performance on LOCS exam questions was about the same for the semester 1 and 2 cohorts, no matter what type of clicker question (high or low cognitive level) was used. We found other notable interactive effects when comparing pedagogical feature, type of clicker question, and semester. These were not statistically significant but evoke potential topics to consider in future investigations.

In summary, the first and second original hypotheses are unsupported by the data. Practice with LOCS/HOCS clicker questions does not enhance performance on LOCS/HOCS exam questions. However, practice with HOCS clicker questions did contribute to better performance on LOCS exam questions. The most likely explanation is that when students are answering HOCS questions, they are practicing retrieval of factual material to solve the problem posed. This retrieval practice enhances their ability to recall factual knowledge during the exam. Students perceived LOCS and HOCS clicker questions as equally effective in facilitating learning, which supports the third hypothesis. However, the results of the study indicate that the two types of clicker questions are not equally effective based on exam performance. The HOCS clicker questions were significantly more helpful in preparing students for LOCS exam questions.

Limitations and future directions

One limitation of the present research is that there is a significant difference between the semester 1 and semester 2 cohorts with regard to performance on HOCS exam questions. Semester 2 students outperformed semester 1 students when lecture material was reviewed with low- or high-cognitive-level clicker questions. On the other hand, semester 1 students reported higher scores for perceived effectiveness of pedagogical features overall, and they demonstrated a nonsignificant preference for lecture over LOCS clicker questions. One possible explanation is that the semester 2 cohort had a higher aptitude overall. In support of this, semester 2 students reported less-positive perceptions of all three pedagogical features than did the semester 1 cohort. Higher-aptitude students may be more confident in their abilities and thus less likely to attribute their success to the review questions and lecture/discussion. Another possibility is that the instructor's teaching strategy was significantly more effective during semester 2. However, this explanation is less likely given that the course was taught a dozen times by the same instructor prior to this study. To further explore the differences in the overall performance of the two classes, a future iteration of this study would include more information on the students. For example, student class standing and prior biology courses may have contributed to differences in overall performance of the two classes.

Another limitation to be addressed in future studies is that it is not possible to explore correlations between students' perceptions and their grades and/or exam scores. These data may have provided more insight about the disconnect between student perception of the effectiveness of practice with LOCS versus HOCS and student exam performance.

Building on the finding that higher-level clicker questions did not help students when answering higher-level exam questions, it would be worthwhile to compare exam question modality. There could be something about practicing in an MC format that does not transfer to short-answer exam questions.

Conclusions and practical implications

Although practicing HOCS questions in class does not enhance performance on higher-cognitive-level exam questions, the higher-order questions are potentially valuable for reviewing factual content in preparation for higher-order thinking activities. And there is much evidence to support the fact that students find the use of clickers engaging. A recommended strategy would be to combine HOCS clicker questions with other pedagogical techniques known to augment critical thinking skills (e.g., pretesting, assigning higher-order questions to supplement reading, and teaching students about metacognition). Building on the metacognition piece, the more that instructors can share about teaching and learning strategies, the more power and motivation students will have to become independent learners.

SUPPLEMENTAL MATERIAL

Supplemental material is available online only.

SUPPLEMENTAL FILE 1, PDF file, 0.1 MB.

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We declare we have no conflicts of interest.

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