PERSPECTIVE
Devising a Method to Study if Wernicke's Aphasia Patients are Aware That They Do Not Comprehend Language or Speak It Understandably

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Wernicke's Aphasia (WA) is characterized by an individual speaking fluent gibberish without the ability to understand anything that is said to them or anything they attempt to read. It is caused by damage to the left posterior temporoparietal cortex, also known as Wernicke's area. An additional intriguing symptom of WA patients is their apparent obliviousness to their own lack of understanding despite their intact reasoning or other cognitive abilities. Their only deficit seems to be in the basic rules of language that define word meaning, also known as phonology. Growing out of a project in an undergraduate class, we devised a phonology-free approach to communicating with WA patients that attempts to answer the questions of whether WA patients know that they do not understand what is said to them, that others do not understand what they have said, and if these patients are distressed by this lack of communication. We here describe the process and the resulting method.

Key words: Wernicke's Aphasia (WA), anosognosia

CONTEXT
One of the most difficult skills to teach students is the process and performance of research (Cajal, 1999 [1916]). Typically, this is taught in an independent study setting/format. Along with the inherent difficulties in the endeavor, other challenges in trying to teach research to a class include limited time, a fixed schedule full of other obligations, and different levels and background knowledge and skills of students. As a part of a class on major breakthroughs in biomedicine and biotechnology, we thought it would be educational and fun for the students in the class to work together on a specific research topic. We wanted the students to have a novel, challenging and thought-provoking experience with the exciting motivation that their project might actively be used in a clinical setting. There was strong interest in the class in neuroscience, and since language is also a topic of general interest, we enlisted the students to help design tests to answer remaining, fundamental questions about Wernicke's aphasia, and neuroscience in general, that originate from Wernicke's original report (1874).

BACKGROUND: WERNICKE'S APHASIA
Aphasia is one of the most interesting aspects of neuroscience for students, as it leads one to explore and try to understand the many different kinds of deficits that can follow stroke or other brain lesions (Heilman, 2006). Also, study of aphasia causes one to think anew about the multiple aspects of language in healthy individuals. In the 1860's, Broca described patients with lesions to the left frontal lobe who had intact understanding of language but the inability to produce coherent speech (Broca, 1861).

In 1874, Carl Wernicke (Wernicke, 1874) described an entirely different form of aphasia in patients with a lesion to the left temporoparietal cortex (Robson et al., 2014). Wernicke's patients, unlike Broca's, spoke fluently, but the speech/language that came out was often mere gibberish. In addition, Wernicke's patients were unable to understand what was said to them or to read. Wernicke's patients had a third curious issue: They seemed to be surprisingly unaware, indeed oblivious to, their language problems and were not upset by their difficulties (Wernicke, 1874). As a project in an undergraduate class taught by one of us (ELA), the class' help was enlisted to design stimuli to test if Wernicke aphasia (WA) patients do or do not have agnosia for their language deficits. The undergraduates enjoyed the opportunity to participate in scientific research, not just learn about it, and also to interact with medical students who were also working on the project. The method and stimuli we devised is described below. At the end we discuss issues that warrant further research in the future.

Research by others and ourselves has shown that WA patients do not have deficits in thinking or reasoning. The overriding deficit is a loss of phonology—the ability to translate sounds to the meaning of words (Zangwill, 1969; Baker et al., 1975; Gardner et al., 1976; Heilman, 2006; Altschuler et al., 2006). Despite this relatively isolated deficit, efforts to rehabilitate WA patients and to improve communication, including group therapy (Simmons-Mackie and Elman, 2011), transcranial magnetic stimulation (Ren et al., 2014), language therapies, and pharmacotherapy (Allen et al., 2012) have been unsuccessful.

There have been many efforts to study comprehension in WA patients. In 2011, Robson et al. compared patients with WA to patients with semantic dementia (SD) and semantic aphasia (SA) to further differentiate the causes of these comprehension impairments. Robson found that WA patients' performance was most affected by the input modality of the test, specifically with auditory-verbal performance. This supported the theory that impairment in WA was secondary to "a dual breakdown in both acoustic-phonological analysis and semantic cognition" (Robson, 2011). In other words, Robson found that patients cannot understand language spoken to them or think and produce organized language internally. In a further study, WA patients were tested for semantic association judgment and performed significantly more accurately for pictures than written words (Robson et al., 2014). Robson also found that when performing these pictorial semantic tasks, the patients recruited brain areas similar to those areas that healthy control patients recruited when performing under challenging conditions. This demonstrated an "enhancement or over activity" rather than recruitment of new neural components (Robson et al., 2014). While these findings demonstrate sites of comprehension impairment in WA patients, they also confirm that pictorial tasks can be learned and accomplished. A 2006 study by us also showed that WA patients maintain their cognitive function in other non-verbal tasks, including becoming upset when intentional illegal chess moves were made by investigators (Altschuler et al. 2006). Their distress at illegal chess moves demonstrated their ability to understand and apply a complex set of logical rules despite their language deficits, a finding that is greatly encouraging for future success for communicating with WA patients.

To begin the class project, the instructor (ELA) initially presented four questions to the class:

1. Do WA patients understand that they do not understand what is said to them? These patients certainly do not understand what is said to them. Indeed, if you give a simple command such as "raise your arm," they do not.
2. If the WA patients do understand that they do not understand what is said to them, is this bothersome?

And two more parallel questions:

3. Do WA patients understand that others do not understand what they say?
4. If they understand that others do not understand them, is this bothersome?

From experience seeing patients with WA, they seem to have no problems interpreting pictures or even cues given as pictures, e.g., WA patients will walk into the correct bathroom based on the picture of a male vs. female outside the bathrooms. Thus, we thought that pictures provide a "language" with which to communicate with WA patients to answer the questions 1-4 above. For example, if one showed a WA patient a picture of a bone and gave them a "choice" of a picture of a dog or cat, they would choose the dog. Conversely, if you showed the WA the word 'bone' and gave them a choice of 'dog' or 'cat,' they wouldn't know which one to choose.

LEARNING OBJECTIVES

- Students will participate in the process of developing a novel method to test an important neuroscience question.
- Students will learn about the process of refining the method and preparing stimuli used to test the question.
- Students will understand what an internal positive control experiment is.
- Students will learn basic Bernoulli trial statistics, and learn to use Bernoulli trials in experimental design and analysis.

CLASSROOM MANAGEMENT OVERVIEW

As time permitted, a portion of class was spent on developing our class testing method. This was done partly in "lab meeting" style with the faculty presenting and the "floor" open for students to question or comment, and partly in Socratic style led by the faculty. Occasionally homework was assigned to think about an issue that came up in class or to develop stimuli. Students were offered the chance to participate in publication of a manuscript, dependent on contribution, and also, class credit was given for particularly good ideas or insights. Further, students were informed that general points about the process of making a scientific discovery could be "fair game" to appear on the final exam.

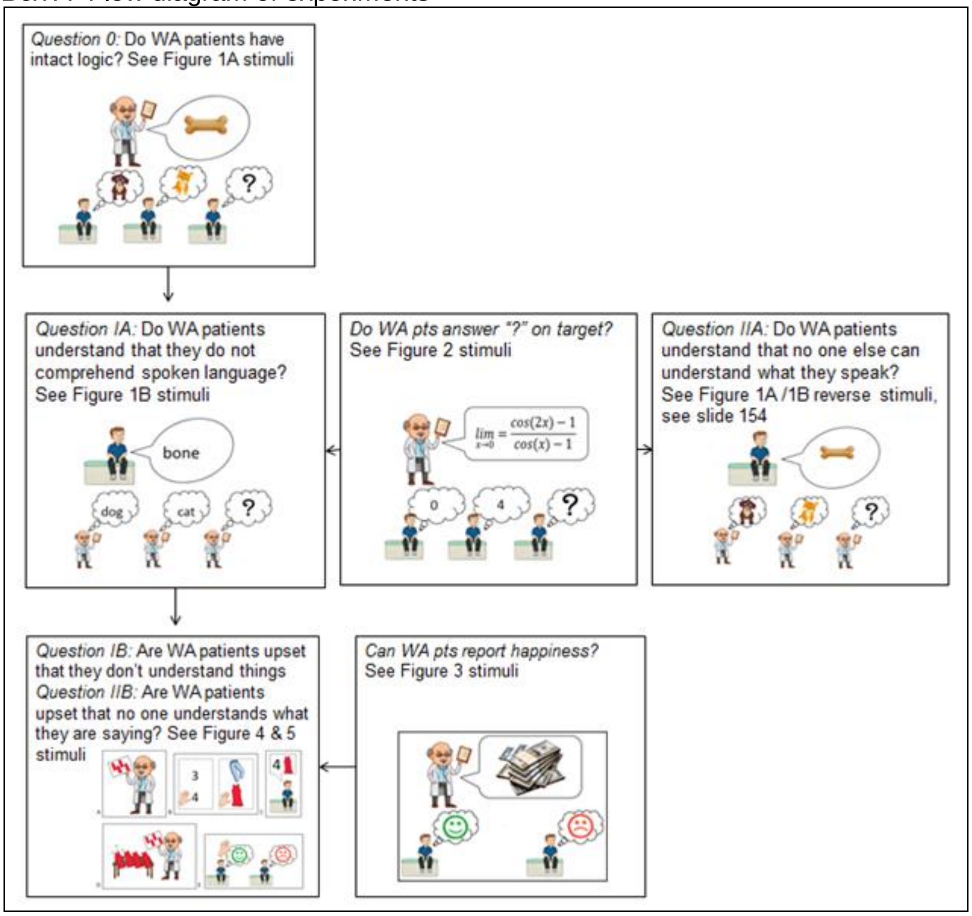
DEVELOPING A METHOD TO TEST WA PATIENTS

The first issue was figuring out how to turn the apparent difference for WA patients in understanding cues presented as pictures compared with words, into a practical testing approach. Question 1 seemed the most important and basic. After a number of class discussions and homework assignments, we decided to represent the interlocutor with the WA patient as a picture of physician or professor and use a cartoon "mouth bubble" to show what the questioner was asking, and a cartoon "thought bubble" to represent what the WA was thinking the questioner was asking (e.g., as in Fig. 1A). Crucially, we then hit upon the idea of having the questions asked with pictures being "spoken" out of the questioner's mouth (Fig. 1A), and similarly for the questions asked with words (Fig. 1B). The class then discussed how this method of "talking" begs the question of what it means to "speak" in pictures, but we felt that neurologically intact individuals would get the point of the figure, and that WA should as well, since their logic appears to be intact.

The next question was how to specifically show whether or not the WA understood they did not understand questions asked in words. We thought the best way to do this was to include '?' as an answer choice.

Then the faculty noted to the class: (1) the ability of WA patients to answer questions asked in pictures would establish that they possessed both normal logical thinking and the ability to understand the specific testing paradigm—an internal positive control; (2) with the testing paradigm established one could then start to address question 1; (3) when questions were asked as words, if WA patients DID understand that they did not understand what was said to them, they would answer '?', but if they did not understand that they did not understand what was said to them, they would randomly pick one of the two choices or '?'; (4) patients might randomly occasionally not respond as per the dichotomy in (3) so that statistics would need to

Box A Flow diagram of experiments



be used to properly answer question 1 above; (5) finally, that the four questions above fell into two natural and parallel groups, and that establishing WA understanding of the testing paradigm was a "question 0" which was necessary to proceed to answer the other questions:

(0) Do WA patients have intact logic?

(IA) Do WA patients understand that they do not comprehend spoken language?

(IB) Are WA patients upset that they don't understand things?

(IIA) Do WA patients understand that no one else can understand what they say?

(IIB) Are WA patients upset that no one understands what they are saying?

See Box A for hierarchy of dependence of these questions and summary of experiments and stimuli needed to answer these questions.

REFINING METHOD TO TEST WA PATIENTS

Answering Question 0 -- Do Wernicke's Patients Have Intact Logic?

We start by describing the method we developed to determine whether patients with Wernicke's aphasia are aware that they do not comprehend when language is spoken to them or written for them. In Fig. 1A, the WA patient sees a picture of a bone coming out of a doctor's mouth—that is, the doctor is "saying" the bone. At the bottom of the figure the patient is presented with three images coming out of a patient's head via a thought bubble, a dog, a cat, or a question mark. The patient must then choose which image is associated with the picture of a bone. The target answer to this question is the dog because cats are not associated with bones. If the patient is consistently able to answer these types of questions correctly by choosing the correct association, we know that the patient has maintained logical thought processes. If the patient chooses incorrect association, we cannot assume that he or she has maintained logical thought processes.

To fully test their thought process, the patient will be asked 20 such pictorial questions. If the patient answers with the correct target answer 15 or more times, we can assume this is not random guessing with the correct association only chosen by chance: To show this, we calculated the likelihood that a patient could choose correctly 15 times solely by random guessing. (See Box B for explanation and relevant examples of Bernoulli statistics.) In Fig. 1A, of the three choices, there are two "active choices" and one question mark. Even with two choices (i.e., the "active choices"), we would expect that, using a Bernoulli trial model with $p=0.5$, $q=0.5$, $N=20$, if guessing, a patient would get on average 10/20 questions correct ($\mu=p*N=(.5*20)=10$) with a standard deviation of 2.24 ($\sigma=\sqrt{(Npq)}=\sqrt{(20*.5*.5)}$). Thus, there is less than 5% chance of even getting 15 correct if a patient is

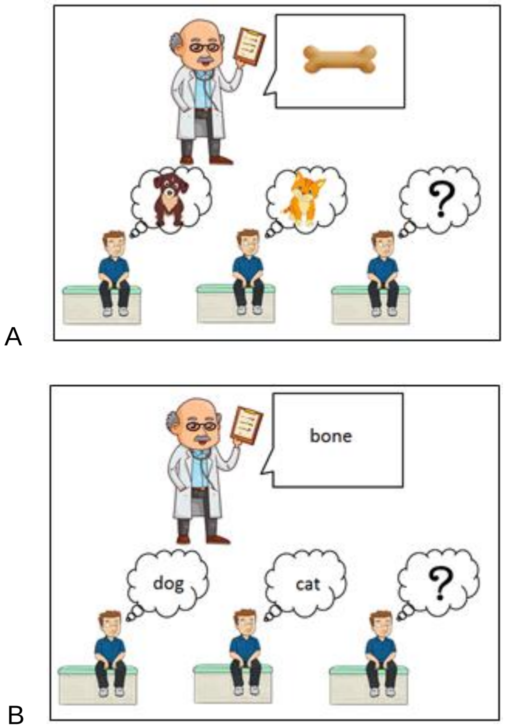


Figure 1. Method to test if patients know they do not understand language. *A.* Example of stimulus where the question and the answers are presented as pictures. If the patient's logical thinking is intact, and the patient understands the task, then the patient should be able to answer all or most of these questions correctly. *B.* The same question as in (A) but now the question and the answers are presented as words. If the patient does not appreciate that he does not understand language, then the patient should randomly pick an answer. If the patient does appreciate that he does not understand language, then '?' should be answer chosen.

guessing (95% confidence interval is μ ± 2σ = 10 ± 2*2.24). (See Box B.) If we consider all three answer choices to be viable – the question marks also as a viable choice – then the chance of even getting 11 correct (p=.33, q=.67, n=20, μ =p*N=(.33*20)=6.6; σ= √ (Npq)= √ (20*.33*.67)=2.1) is less than 5% if the patient is guessing (95% confidence interval is μ ± 2σ = 6.6±2*2.1) (Box B). The task requires strong thought and logic, and if the target answer is selected 15 or more times, we can infer that the patient understands the task and that logic and thinking are intact—an internal positive control for logic (Zangwill, 1969; Baker et al, 1975; Gardner et al, 1976; Heilman, 2006). This is informative of whether or not the patient has intact thought and logic and whether the patient understands the task (internal positive control). From the hypothesis that WA patients have intact thought and reasoning, and only lack phonology, we predict that they should be able to answer questions which are represented as pictures at a level significantly better than chance.

Answering Question IA? – Are Wernicke's Patients Aware That They do not Understand Written Language?

In Fig. 1B, we have the same question and answers

Box B Basic Bernoulli trial statistics and examples

Key
μ: mean | σ: standard deviation | N: number of trials
p: probability of correct answer | q: probability of incorrect answer(s)

$Sample\ mean\ (\mu) = p \cdot N$ | $Std\ deviation\ (\sigma) = \sqrt{N \cdot p \cdot q}$ | $q = 1 - p$

Example (N=20 with two answer choices)
$p = 0.5; q = 0.5; N = 20$
$(\mu) = p \cdot N = (0.5) \cdot (20)$
$(\mu) = 10$

$(\sigma) = \sqrt{N \cdot p \cdot q} = \sqrt{(20) \cdot (0.5) \cdot (0.5)}$
$(\sigma) = 2.24$

95% confidence interval = $\mu \pm 2\sigma = 10 \pm 2(2.24) = 5.52 - 14.48$

Example (N=20 with three answer choices)
$p = 0.33; q = 0.67; N = 20$
$(\mu) = p \cdot N = (0.33) \cdot (20)$
$(\mu) = 6.6$

$(\sigma) = \sqrt{N \cdot p \cdot q} = \sqrt{(20) \cdot (0.33) \cdot (0.67)}$
$(\sigma) = 2.1$

95% confidence interval = $\mu \pm 2\sigma = 6.6 \pm 2(2.1) = 2.4 - 10.8$

associating a dog and a bone. However, now the questions and answers are spelled out in words. Clearly, in order to correctly answer this question with the choice of 'dog,' a patient would need to understand phonology in written language. However, a WA patient without phonology will need to either answer with a random guess or with the accurate statement "I don't know," represented by "?". In this case, though 'dog' would be the correct association for a healthy patient, a WA patient is most correct by choosing "?", thereby showing that they recognize their deficit in understanding written language. To fully test if the patient understands their deficit, the patient is asked 20 such word questions, and if the patient answers with the target answer ("?") more frequently than would be expected by chance, we have confirmed that the patient is aware of their deficit in understanding written words. If the patient selects answers at random, e.g., answer distribution of 7-6-7, then we know that the patient either is (a) unaware of their deficit and instead thinks that they know the answer to each individual question or (b) does not understand the meaning of the "?" response choice, and therefore, does not consistently choose it. If the patient does consistently choose the "?" response, this is informative as to whether or not the patient knows that he/she does not understand words. Supplementary slides 3-22 and 33-52 can be used to test Questions 0 and IA. (https://drive.google.com/drive/folders/0Byx0QUleeLpzR01 0WDBKVVRjeU0?usp=sharing). See Appendix for Table of Contents of supplementary slides located on page E12.) Supplementary slides 23-32 and 53-62 can be used for practice or demonstration.

Now, before starting testing for questions 0 and IA, it is necessary to establish that WA patients will answer with a "?" ("I don't know") when this is the correct target answer (Box A). We devised a number of sets of stimuli to establish whether WA patients can select the target answer of "?" when appropriate. In the process of devising stimuli, we also noticed that the "space" of questions whose target answer is "I don't know" is rather extensive and diverse. We illustrate a number of questions whose target answer is "?" in Figure 2 where four classes of "I don't know" questions were created:

1. Questions regarding real-life situations where we truly are ignorant of the answer – for example identifying the dog that makes the paw prints (Fig. 2A) with the parallel real-life control question presented in the same format where there is a definitive target answer (Fig. 2B)
2. Mathematics questions of sufficient difficulty that the answer is "I don't know" (Fig. 2C) with a parallel mathematics question where the answer is simple and we can assume a patient can determine the answer (Fig. 2D)
3. Questions with absurd pictorial situations, in which none of the answer choices make sense (Fig. 2E) with parallel control questions asking the patient to recognize non-absurd pictorial patterns (Fig. 2F)

We believe WA patients will be able to complete easy (single digit) math questions but will have difficulty with more complex (limits, tangents) math questions. To fully test the patient's understanding of when to appropriately respond with "?", we will ask 20 such questions in each of the four categories presented in random order and interspersed with parallel control questions that do have definitive answers. As per our previous calculations, if the patient answers at least 11/20 correct for the subset of questions with a definitive answer, it proves that the patient understands the task and has the reasoning ability to correctly identify the target answer. Similarly, if the patient correctly chooses "?" for at least 11/20 of the questions for which there is no definitive answer, we know that the patient understands when to use the "?" response. (See Box B.) If these standards are met by the patient, then we have answered the question of whether the patient knows when to answer "I don't know." The following slides can be used to test the patients: 64-123 (doctor asks question with unknown answer), 186-215 (easy math), 217-246 (hard math), 279-308 (absurd pictorial situation), 248-277 (non-absurd pictorial situation). Supplementary slides are included (See Appendix) and can be used for practice or demonstration.

Answering Question IIA: Do WA patients know that others cannot understand them?

Question IIA is a parallel to question IA and the same pictographic and word-based stimuli can be used, with the patient speaking the question and the doctor having to give the answer. (See Box A rightmost panel.) Similarly, as in the statistical analysis for Question IA, in a subset of 20 questions where the patient asks the questions and the doctor gives the answers in the form of a picture, if the patient gets 15/20 correct, the patient certainly understands the task as well as the reasoning involved to complete the task at a rate significantly higher than chance. This once again will confirm comprehension of the test and intact logic. In the subset of questions where the questions and answers are presented as words, at least

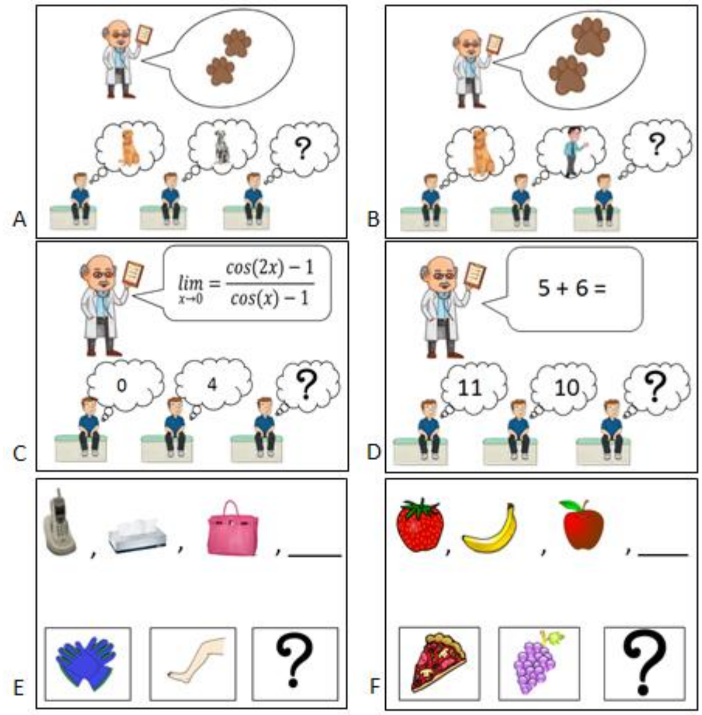


Figure 2. Do WA patients answer "?" on target. See text for discussion. *A.* Example of stimulus where the target answer is '?.' It is not known if the yellow dog or spotted dog made paw prints. *B.* This question is parallel to *A*, but here there is a definite target answer (dog makes paw prints). *C.* A very difficult math question where the target answer is '?' for anyone—WAP or neurologically healthy individual—because the question is so difficult. *D.* A simple math question with target answer 11. *E.* The target answer here is '?' because no other answer makes sense. *F.* This question is parallel to *E* but here grapes make sense as the answer in a list of fruits.

11/20 answers of "?" by the patient indicates that they understand that other people are not understanding what they are saying and that they understand when to use the "?" response. Fewer selections of "?" would indicate that they likely do not appreciate that people do not understand what they are saying. Slides 125-144 and 155-174 can be used to test Question IIA. Supplementary slides 145-154 and 175-184 can be used for practice or demonstration (See Appendix).

Answering Question IB and IIB: do patients care that they are not communicating and cannot understand?

As a prerequisite to answer question IB (Box A), we first have to establish that patients will be on target when answering with the happy or sad pictures. To fully test this, we produced a number of slides that convey either a happy or a sad situation and ask the patient to choose a happy or sad picture. An example of this is shown in Fig. 3. Patients will be presented with 20 such questions, and if they choose the target emotion for greater than 15/20, we can statistically assume that he or she understands the purpose of the pictures. Slides 310 – 329 can be used for testing. Supplementary slides (330 – 369) are also included and can be used for practice or demonstration (See Appendix).

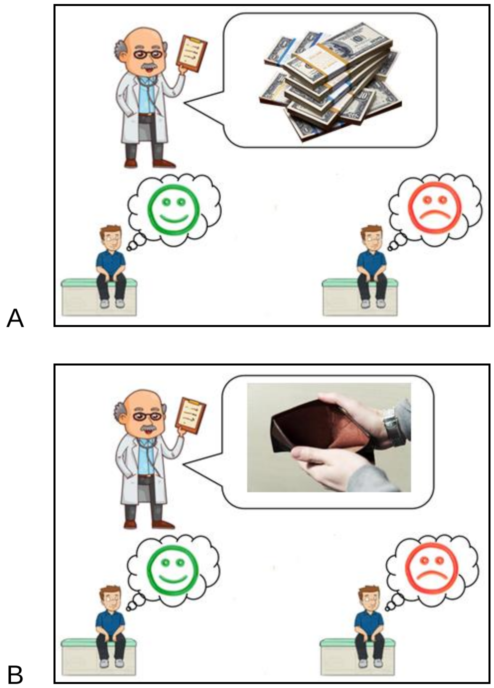


Figure 3. Do WA patients on target identify happy and sad situations? In order to determine that a Wernicke's patient will "correctly" (i.e., target answer) feel happy when a healthy person would, stimuli presented in the form of a picture, as shown above, will be utilized. *(A)* The target answer should be a happy face (stacks of money), while for *(B)* the target answer should be a sad face (empty wallet). The patient is asked 20 such questions.

To answer questions IB we designed related but different stimuli (see Fig. 4). In our experience we find that WA patients can often do one-digit arithmetic or counting. In Fig. 4A, the patient is shown a picture of several objects by the physician. In the next slide, the patient is then presented with several options from which he or she must select the object they saw in the previous slide and the number of those objects (Fig. 4B). The next slide shows the imaginary patient correctly choosing the object type and number (Fig. 4C). After this, we see the patient's choice compared with the original picture of the objects from slide 4a, indicating the patient's success in choosing the correct object and number (4D-not clear). After viewing this series of slides indicating successful communication and choice, the real patient is given the option of choosing a happy face or a sad face (4E). In this example, the patient has selected the happy face because the imaginary patient was successful. This indicates whether our patients find successful communication and choice something to be happy about, providing us with a control when determining if failure in communication is frustrating or upsetting. Slides 371-498 can be used. Supplementary slides are included and can be used for practice or demonstration. Ideally patients should be asked 20 questions such as Figure 4A.

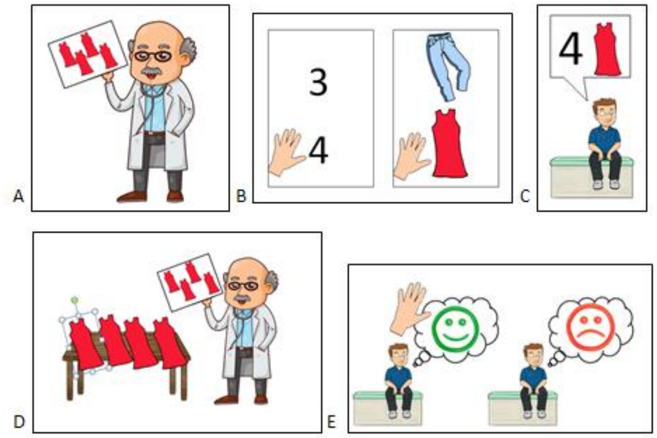


Figure 4. Are WA patients happy when they get the correct answer? *A.* The patient is shown the target answer by the physician ("four red dresses"). *B.* The patient is presented with the answer choices (3 vs 4, and blue pants vs red dress). *C.* The patient selects his answers, and is given what he selects. *D.* The patient's choice is then compared with the target answer by the physician. *E.* the patient is asked to identify whether he is happy or sad. In this example, the patient has selected the happy face, illustrating that in this case the WAP both understands the task and give the target answer for having fulfilled the task correctly.

Our next task will be to determine if unsuccessful choice and communication in a parallel task prompts a patient to choose the unhappy face. For a WA patient, replacing the pictures of the previous task with words will ensure failure. Figure 5 illustrates a situation where the patient has to give his choices in words. The patient's incorrect choice is then compared with the target answer by the physician (Fig. 5D), and the patient is asked to identify whether he is happy or sad about this failure of communication (Fig. 5E). To fully test the patient's emotional response to failures in communication, we will have a series of 20 such questions for each patient. This will be informative as to the question of whether or not Wernicke's patients are upset when they do not communicate effectively.

Minimum testing regimen

To test if a patient does or does not understand that they do not understand what is said to them, Question IA would need about 100 slides: 10 or less practice/preliminary slides for the "life situation" "I don't know" questions (Fig. 2) + 40 (=20 with definitive target answers (Fig. 2A) + 20 without definitive target answers randomized (Fig. 2B) + 10 practice/preliminary slides for understanding questions (Fig. 1) + 40 (=20 questions asked to the patient in pictures (Fig. 1A) + 20 asked to the patient in words (Fig. 1B) randomized). Another 50 slides are needed to test if patients know or do not know that others do not understand what they say—Question IIA—these are 10 practice and testing slides taken from Supplementary slides 125-184. Another 50 slides or so are needed to test Question IB: 10 practice "happy/sad" slides, then 20 slides to test that this is on target, then 10 scenarios as in Figure 4 and a parallel 10 as in Figure 5.

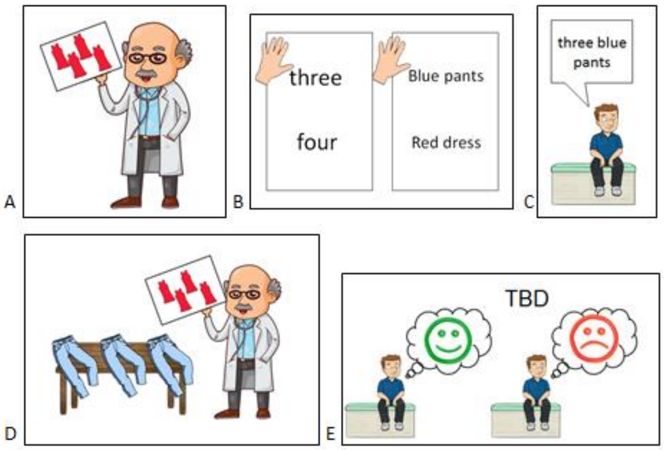


Figure 5. Making selections using words. As in Figure 4, a similar approach is used – but with words replacing pictures. *A.* The patient is again shown the target answer by the physician ("four red dresses"). *B.* The patient is presented with the answer choices (three vs four, and blue pants vs red dress). *C.* The patient selects his answers and is given what he selects. *D.* The patient's choice is then compared with the target answer by the physician. *E.* The patient is asked to identify whether he is happy or sad. In this example, the patient has selected the happy face, illustrating that WAPs do not understand words, and therefore, are not upset by the outcome of the experiment**.**

DISCUSSION

We describe a method devised to answer the century and a half old questions of whether or not a patient with WA knows that she/he does not understand what is said to her, that others do not understand what she says and if this lack of understanding is upsetting to the patient. The stimuli we have made also allow testing of the proposition that WA patients have intact non-verbal reasoning and logic. In preparing testing stimuli we have also appreciated that the "space" of "I don't know" questions is rather large and diverse.

After the semester ended, three students continued to work with medical students to make and refine the stimuli presented here. The undergraduate students enjoyed working with and interacting with medical students.

Devising slides to test Question IIB—the parallel of IB—is left as a future project for students. A much more interesting and important question for study for students, and their teachers, is devising a way to test the method given here. The issue is that patients with WA cannot give informed consent. But in the interim, the stimuli developed here may have important clinical use: If it is important to ask a WA patient a question, for example about symptoms or medical history, a subset of the stimuli developed here can be used to establish that, when queried by pictures, the WA is giving on target answers. Then the desired novel question can be asked in picture form, and there can be confidence in the answer the WA patient gives.

PROJECT EVALUATION

The objectives were met: Ipso facto undergraduate students participated in designing a method to answer the question of whether or not WA patients understand that they do not understand what is said to them. Some of these students in the class also participated at a higher level with medical students in the process of refining the method and complete the stimuli needed. Students in the class understood the concept of an internal positive control and were able to utilize this concept in analyzing other topics and studies discussed in class. A question on the course final exam tested Bernoulli trial statistics as used in the case, and more than 85% of the students in the class solved that problem correctly or nearly so. The students enjoyed the opportunity to work on design of a scientific study that could have future clinical use. We suggest that student designs of other clinical protocols for neuroscience related medical conditions could be exciting vehicles to teach experimental design principles and fundamental neuroscience concepts through group problem solving.

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APPENDIX

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