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14. ABSTRACT

We have been testing the hypothesis that relatively implicit measures of cognitive processing (eye movements, pupillary dilation monitoring, and the N400 component of event-related potentials) will prove sensitive to receptive vocabulary knowledge, even in the absence of more traditional behavioral responses. To date, we have sought to first demonstrate the use of these measures in two populations in whom behavioral responses are expected to be reliable: normal adults and normally developing children. In both groups, the implicit measures differentiated known from unknown words: eye movements were faster to a named picture for known words; pupillary dilation from baseline was greater in the unknown condition; and an N400 congruency effect was observed for known (but not unknown) words. Our initial results suggest that these measures similarly differentiate known from unknown words in individuals with autism, even in the absence of a behavioral response. These results suggest that these measures may be used as valid measures of comprehension, even in nonverbal, non-responding individuals.

15. SUBJECT TERMS

event-related potentials; eye movements; pupillary dilation; implicit knowledge

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INTRODUCTION

Approximately 50% of individuals affected by autism fail to develop useful speech, and many of these individuals never learn to communicate in any functional way. An important scientific as well as practical question about such individuals, as well as in those with other diagnoses and a similar inability to express themselves, is whether this lack of expressive ability is necessarily accompanied by an equally severe deficit in knowledge of receptive language. Little rigorous research has been directed at this possibility, both because of the difficulty of working with such low-functioning subjects, and because of the lack of sensitivity of most traditional behavioral methodologies. Recently, however, several experimental methodologies have been developed and refined to the point that they may prove sensitive enough to provide reliable evidence of comprehension, even in the absence of more traditional behavioral responses such as speech and gesturing, and even at the individual subject level. We have been developing the use of three such research methods to attempt to detect receptive vocabulary knowledge – eye movement recording, pupillary dilation monitoring, and event-related brain potentials. We have been testing whether these relatively implicit measures of comprehension actually do reflect single-word comprehension in participants in whom we expect reliable behavioral responses to serve as comparison measures (normal adults, normally developing children, and high-functioning individuals with autism), as well as in low-functioning, nonverbal individuals with autism, for whom overt behavioral responses might be unreliable or even impossible.

BODY

Experiment 1: Validating the use of the eye movement monitoring (EM), pupillary dilation monitoring (PD), and event-related potential (ERP) techniques for the measurement of receptive vocabulary knowledge – normal adults

Our first experiment was designed to validate the use of the three implicit methodologies for the detection of receptive vocabulary knowledge in normal adults, a participant population in whom overt behavioral responses would be expected to be reliable (and thus capable of serving as a measure of comparison).

Fifty-five right-handed, native English-speaking participants were recruited from the Johns Hopkins University community. All were screened to have no history of cognitive or learning disability or neurological trauma or deficit, and no current use of medications that might affect the functioning of the brain. All had self-reported normal or corrected-to-normal vision and hearing. All were tested on the Peabody Picture Vocabulary Test (PPVT;[1]) and the Vocabulary, Similarities, and Information subtests of the Wechsler Adult Intelligence Scale (WAIS; [7]).

All participants were asked to engage in two separate tasks using the same set of 160 words and pictures. Eighty of the words were very high frequency and were expected to be very familiar to all of the adults; these included words such as *airplane* and *camera*. The remaining 80 words were low frequency, relatively unfamiliar words that were not expected to be known by many of the participants (as confirmed by prior pre-testing). Examples of words in this set included *agouti* and *cainito*. All words were concrete and highly imageable. High-resolution, color digital pictures were selected to represent each word. In the *forced-choice recognition task*, participants were asked to use the mouse to select one of four pictures presented simultaneously on a computer screen after hearing one of the objects named. We simultaneously collected eye movement and pupillary dilation data, using an ASL Model 504 eye-tracking system. In the *congruity task*, a picture was presented on the computer screen, accompanied by the auditory presentation of a single word, which either matched (congruous condition) or did not match (incongruous condition) the pictured item. Participants were asked to push a button to indicate whether the auditory word and the picture matched. Simultaneously, ERPs were recorded using Electrical Geodesics Inc.'s 256-channel Hydrocel Geodesic Sensor Nets.

Finally, normal adult participants were asked to participate in a word familiarity posttest, in which they were asked to rate their familiarity with the 160 words used in the experiment, on a scale from 1 (very unfamiliar) to 9 (extremely familiar), with an additional option of 0 (no familiarity whatsoever).

Of the 55 normal adult participants recruited, 20 participants supplied a complete set of "useable" data from the three implicit measures. Reasons for data exclusion have included participant attrition; inadequate screening procedures, which have since been modified; difficulty with eye-tracker calibration, which usually results from excessive participant movement; and/or loss of ERP data due to difficulty lowering scalp impedances, excessive motion artifact, or excessive eye movements/blinks.

Behaviorally, participants were faster and more accurate at both the forced-choice task and the congruity task for known words than for unknown words. Our results for the normal adults were also as predicted for all three of the implicit measures (See Figure 1). Specifically, eye movements to the picture that matched the auditory word were faster for known than for

unknown words. End-of-trial fixations were also on the named picture more frequently for known words. Pupillary dilation from baseline was greater in the unknown condition (evidencing the greater engagement of cognitive resources when the word is unknown). Additionally, an N400 congruency effect was observed in the event-related potentials for known words, but not for unknown words. Thus, all three implicit measures (EM, PD, and ERPs) were able to distinguish the processing of known from unknown words in this participant population.
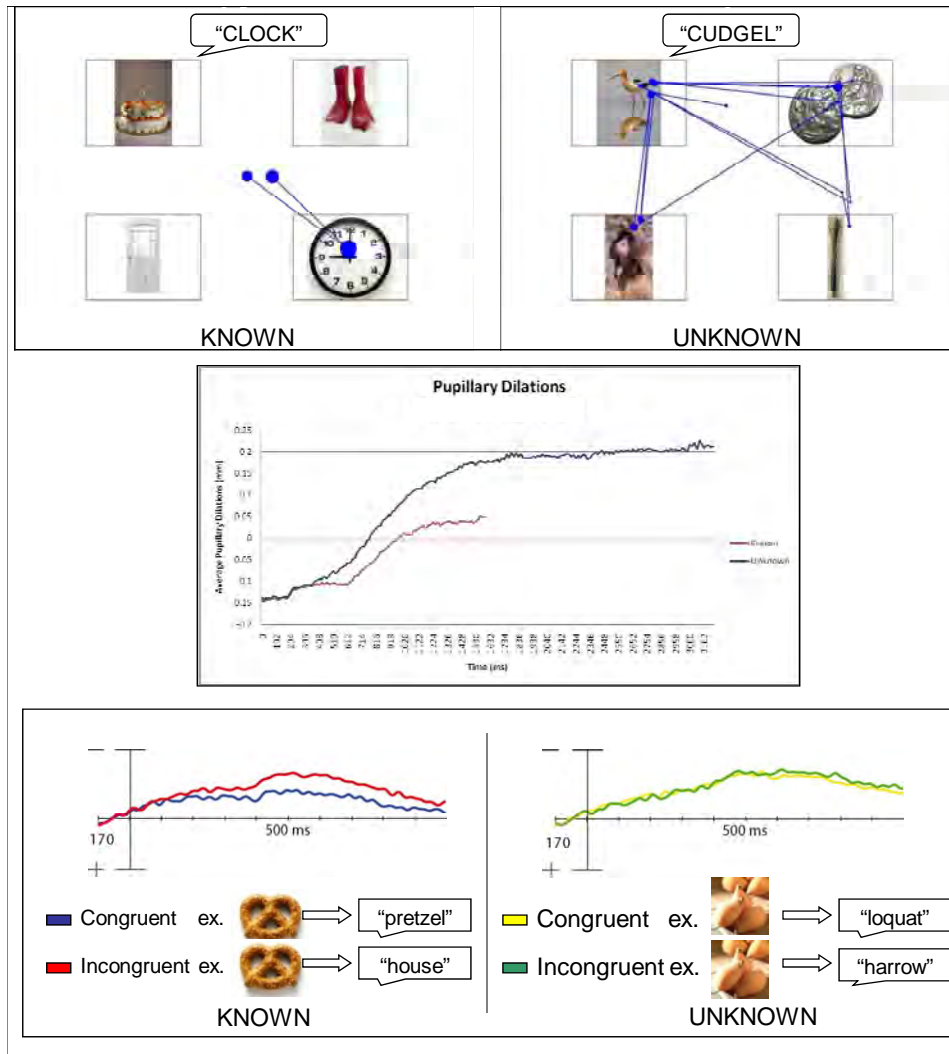

Figure 1. EM, PD, and ERP results from the group of 20 normal adult participants. Top panel: Sample EM results (from one participant) to known (left) and unknown (right) words. Size of the dot indicates the length of the fixation. Middle panel: Average PD results for known and unknown trials. Bottom panel: Grand-average ERPs for congruent vs. congruent trials for known (right) and unknown (left) words.

We have spent additional time during this year trying to refine our data analysis techniques (and thus the data analysis phase of this experiment has taken longer than predicted in our original Statement of Work). First, we have refined the artifact rejection techniques that we are using in our analysis of the event-related potential data. This has allowed us to retain a greater number of trials, while at the same time increasing our confidence that our data reflects

true processing differences, not changes due to artifacts (such as eye movements or muscle activity). These refinements will be especially important when it comes to analyzing data from the other three participant populations (in whom such artifacts are more difficult to prevent). Second, we have been trying to develop a metric by which we can pool the known and unknown words on an individual basis for each participant. Most of our analyses have been done using *a priori* classifications of whether a word is "known" or "unknown;" that is, we grouped the items in our analyses based on our prior determinations (and pre-testing, as described previously). However, especially for the group of normal adult participants, it is possible that some participants may be familiar with some of the words that we have estimated to be generally "unknown." In other words, it would not be surprising if some adults have idiosyncratic knowledge of the less familiar words. To the extent that this is the case, the effects that we have observed will be muted (due to the inclusion of what are truly known items in our analyses of "unknown" words). It is therefore to our benefit to try to base the classification of "known" and "unknown" items on what truly is known or unknown to each individual participant. To this end, we have been working to develop a way of incorporating the various behavioral responses that we have collected from each participant into a metric that would estimate the likelihood that each item known to that participant. These behavioral responses include accuracy on the forced choice; accuracy on the congruity task; and the participant's rating on the familiarity post-test. Based on these calculations, we then re-categorize the experimental items for each participant into new groups of "known" and "unknown" items, and re-analyze the data accordingly. We are now at the point of completing this re-analysis.

One this re-analysis is complete, we will complete the drafting of the manuscript based on the data from our normal adult participants, and submit the manuscript for review; we expect to submit the manuscript by the end of August 2011.

Experiment 2: Validating the use of the EM, PD, and ERP techniques for the measurement of receptive vocabulary knowledge – normally developing children

Our second experiment was designed to validate the use of the three implicit methodologies for the detection of receptive vocabulary knowledge in normally developing children, another participant population in whom overt behavioral responses would be expected to be reliable (and thus capable of serving as a measure of comparison).

Sixty-eight right-handed, native English-speaking child participants (ages 5-17) were recruited from the Johns Hopkins University community. All were screened to have no history of cognitive or learning disability or neurological trauma or deficit, and no current use of medications that might affect the functioning of the brain. All had self- or parent-reported normal or corrected-to-normal vision and hearing. All were tested on the Peabody Picture Vocabulary Test (PPVT; [1]), the Kaufman Brief Intelligence Test (KBIT; [4]) and the Autism Spectrum Screening Questionnaire (ASSQ; [2]), the latter of which was used to ensure that none of the normally developing children exhibited excessive behaviors associated with autism.

All of the children were asked to complete the forced-choice recognition task and the congruity task described above. Older children (those old enough to understand and properly perform the task; generally those ages 10 and above) were also asked to complete the familiarity post-test described above.

Of the 68 normally developing child participants recruited, 20 participants supplied a complete set of "useable" data from the three implicit measures. Reasons for data exclusion were similar to those described above for the normal adults, but in all cases were more pronounced for the child participants.

Data analysis for the normally developing children is on-going (we have concentrated primarily on individual analyses, not group analyses), but our analyses so far suggest that the results for the child participants were very similar to those observed for the normal adults (see Figure 2). Behaviorally, children were faster and more accurate at both the forced-choice task and the congruity task for known words than for unknown words. Eye movements to the picture that matched the auditory word were faster for known than for unknown words. End-of-trial fixations were also on the named picture more frequently for known words. Pupillary dilation from baseline was greater in the unknown condition. Additionally, an N400 congruency effect was observed in the event-related potentials for known words, but not for unknown words. Thus, all three implicit measures (EM, PD, and ERPs) were able to distinguish the processing of known from unknown words for the normally developing children that we have tested. We continue to analyze these data, further refining our artifact rejection techniques as described above for the normal adults. We are also attempting to apply the familiarity metric developed for the adults to the children's data (at least to that of those children old enough to complete the familiarity post-test).
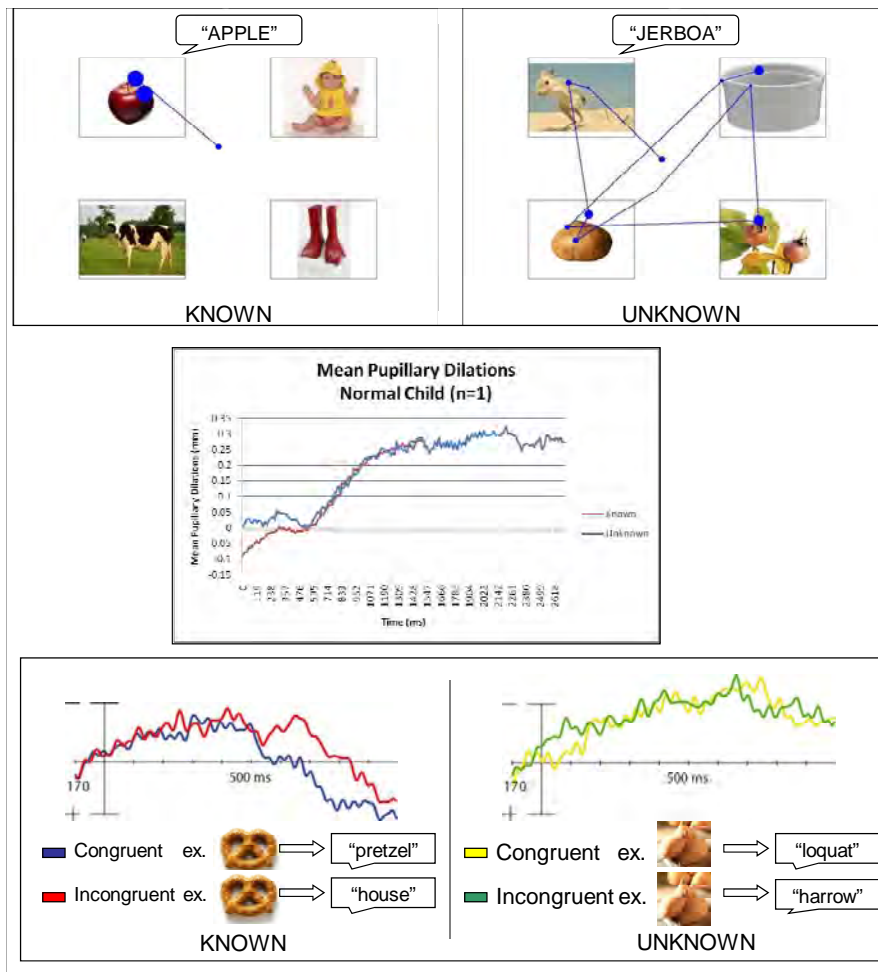
Figure 2. EM, PD, and ERP results from one normally developing child participant. Top panel: Sample EM results to known (left) and unknown (right) words. Size of the dot indicates the length of the fixation. Middle panel: Average PD results for known and unknown trials. (Unlike most normally developing child participants, this one does not show a difference between the two conditions.) Bottom panel: Average ERPs for congruent vs. congruent trials for known (right) and unknown (left) words.

We are completing data analysis, and beginning the drafting of the manuscript to report the results for the normally developing children, much as we had anticipated in our original Statement of Work. The testing of normally developing children was somewhat slower than anticipated due to challenges with recruitment; however, we have overcome this by trying as much as possible to analyze data as it comes in, so that for the most part, testing and analysis happen concurrently.

Experiment 3: Validating the use of the EM, PD, and ERP techniques for the measurement of receptive vocabulary knowledge – high-functioning individuals with autism

Our third experiment was designed to validate the use of the three implicit methodologies for the detection of receptive vocabulary knowledge in high-functioning individuals with autism, another participant population in whom overt behavioral responses would be expected to be reliable (and thus capable of serving as a measure of comparison), but which also offers a more closely-matched comparison group to the low-functioning individuals with autism.

Twenty-four participants with autism (ages 8-29) were recruited from the Johns Hopkins University community. All responded to advertisements asking for volunteer participants with autism who would be interested in participating in language experiments. Participants were administered the Kaufman Brief Intelligence Test (KBIT; [4]), the Autism Diagnostic Observation Schedule (ADOS; [5]), and the Autism Diagnostic Interview – Revised (ADI-R; [6]) to confirm diagnosis and to determine level of functioning/verbal ability. Of the 24 participants recruited, seven are currently scheduled for initial screening, or are currently at some stage in the initial screening process.

Of the remaining 17 participants recruited, 7 were determined to be higher-functioning. These participants were asked to complete the forced-choice recognition task and the congruity task described above. Of the 7 higher-functioning individuals with autism recruited, 4 participants supplied a complete set of "useable" data from the three implicit measures. Reasons for data exclusion were similar to those described above for the normal adults, but again were more pronounced for the autism participants.

Data analysis for the high-functioning individuals with autism is on-going (we have concentrated primarily on individual analyses, not group analyses). To date, there is a fair amount of individual variability amongst the results of the high-functioning individuals with autism. Generally, the EM and PD results of these individuals have looked similar to those of the normal adults and normally developing children. Some high-functioning individuals with autism also show a similar N400 congruency effect in their ERPs as was observed for the normal adult and normally developing child groups (see Figure 3). However, for others, the difference between the congruent and incongruent known conditions was much smaller than that seen for the other groups, if it was observed at all. More data is needed before strong conclusions can be drawn about the results from this group.
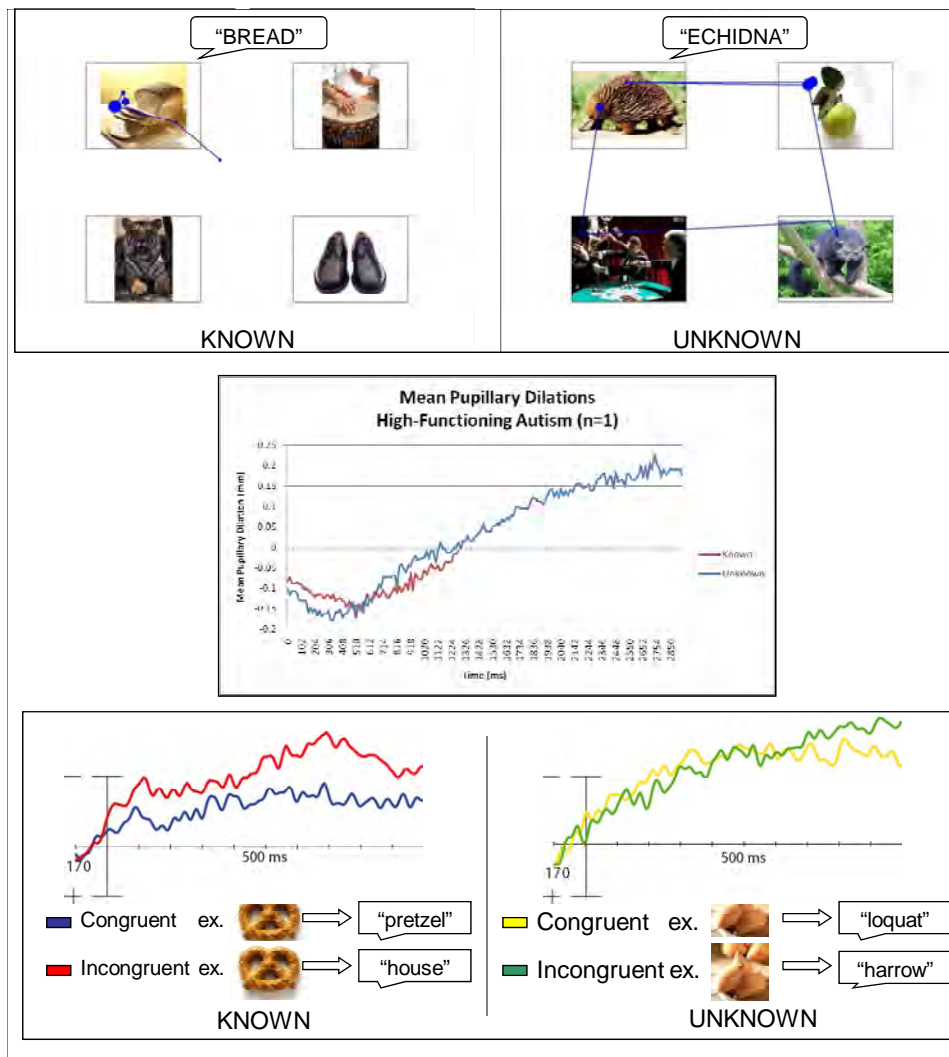
Figure 3. EM, PD, and ERP results from one high-functioning individual with autism. Top panel: Sample EM results to known (left) and unknown (right) words. Size of the dot indicates the length of the fixation. Middle panel: Average PD results for known and unknown trials. Bottom panel: Average ERPs for congruent vs. congruent trials for known (right) and unknown (left) words.

The greatest challenge in the progress of Experiment 3 has been the recruitment of participants with autism. Our initial recruitment efforts yielded only a low number of participants. We have since been working to expand these efforts, to include advertisements in different venues; a greater distribution of flyers; working with medical professionals who might be willing to share information about our study with their patients and their families; and working with schools and other community organizations to increase awareness of our study. We have already seen gains in our recruitment due to these heightened efforts. Another challenge in the conduct of this study is participant retainment; because participants are asked to attend multiple sessions for testing (as many as five different sessions, some lasting more than two hours), it can be difficult to schedule times that are convenient for participants and their families, and to maintain their motivation to participate after the first few sessions. We have also

developed strategies for overcoming this obstacle: we try to do as much of the testing (especially the screening evaluations) at the individual's home, to make it more convenient; we go to greater lengths to warn the participants and their families about the time commitment necessary before testing begins, so they know what they are getting into; and we try to foster personal relationships with the participants and their families, so that there is a social benefit to their continued participation. We also go to great lengths to let the participants and their families know how grateful we are for their time and their participation; for instance, our research assistants are trying to set up the means to take the participants and their families out for lunch on their final day of participation to show our gratitude.

Experiment 4: Extending the use of the EM, PD, and ERP techniques for the assessment of receptive vocabulary knowledge to low-functioning individuals with autism

Our fourth experiment was designed to extend the use of the three implicit methodologies for the detection of receptive vocabulary knowledge to a population in whom behavioral responses are generally less reliable (or absent altogether) – low-functioning, low- or non-verbal individuals with autism.

As described above for Experiment 3, 24 participants with autism (ages 8-29) were recruited from the Johns Hopkins University community. All responded to advertisements asking for volunteer participants with autism who would be interested in participating in language experiments. Participants were administered the Kaufman Brief Intelligence Test (KBIT; [4]), the Autism Diagnostic Observation Schedule (ADOS; [5]), and the Autism Diagnostic Interview – Revised (ADI-R; [6]) to confirm diagnosis and to determine level of functioning/verbal ability. Of the 24 participants recruited, seven are currently scheduled for initial screening, or are currently at some stage in the initial screening process.

Of the remaining 17 participants recruited, 10 were determined to be low-functioning. All were minimally verbal to nonverbal. Stimuli for the low-functioning group were drawn from the larger pool of 160 words and pictures, but were individualized for each participant based on parental/caregiver report of items that were expected to be known receptively by the child. Parents/caregivers were asked to complete the MacArthur-Bates Communicative Development Inventory – Words and Gestures ([3]), plus a similar experiment-specific inventory that covered those words from our set of 160 that were not included on the MacArthur-Bates. These measures thus provided information about what words were likely to be known (and unknown) receptively by the child. The number of stimuli tested were determined for each individual to maximize signal-to-noise ratio while minimizing experiment length. For some individuals, for whom the pool of known words was small, repetition of items within a testing session, or the repeated testing across multiple testing sessions, was necessary to adequately assess their receptive knowledge.

In addition to the assessments provided by the ADOS and the ADI-R, each low-functioning participant received a series of behavioral assessments designed to evaluate his/her ability to successfully participate in our language testing. We assessed potential participants on things such as their ability to sit still for extended periods of time; their ability to look at the computer screen; their ability to tolerate the eye tracking and ERP equipment; and their likelihood to exhibit adverse behaviors (such as hitting, biting, or other aggressive behaviors). Based on these assessments, an individual determination was made as to the appropriateness of

participation and the need for further individualized training to acclimate the participant to the eye-tracking and ERP equipment and experiment procedures. Such training was then conducted as needed over a period of days or weeks, sometimes in our testing space, and often at the participant's home.

After training, participants completed the same forced-choice and congruity tasks as described for Experiments 1-3. However, they were not required to make any overt behavioral response (using the mouse or pressing a button). (Some low-functioning individuals with autism are very familiar with computer programs of the type used in our experiments, and would like to engage in some kind of task during the experiment. For these participants, we allow them to make responses as they wish. However, importantly, the successful analysis of the implicit measure data in this experiment does not depend upon the behavioral completion of these tasks.)

Of the 10 higher-functioning individuals with autism recruited, 3 participants supplied a complete set of "useable" data from the three implicit measures. Reasons for data exclusion were similar to those described above for the normal adults. Additionally, even with acclimation training, low-functioning participants have a much harder time engaging in the tasks for extended periods of time, and therefore all of the eye-tracking and ERP artifacts for this group are very pronounced. The behavior of individuals in this population is quite variable, so that on some days, they are unwilling to participate at all. Also, participant attrition is a problem, given the large time commitment required of the participants and their families for successful acclimation training and testing.

Data analysis for the low-functioning individuals with autism is on-going (we have concentrated primarily on individual analyses, not group analyses). To date, there is a fair amount of individual variability amongst the results of the low-functioning individuals with autism. Each low-functioning individual with autism has shown results on at least one of the three measures that were similar to those of the normal adults and the normally developing children (see Figure 4). More data is needed before strong conclusions can be drawn about the results from this group; however, we are very optimistic that our the use of these implicit measures can be extended to assess receptive vocabulary knowledge in low-functioning individuals with autism.
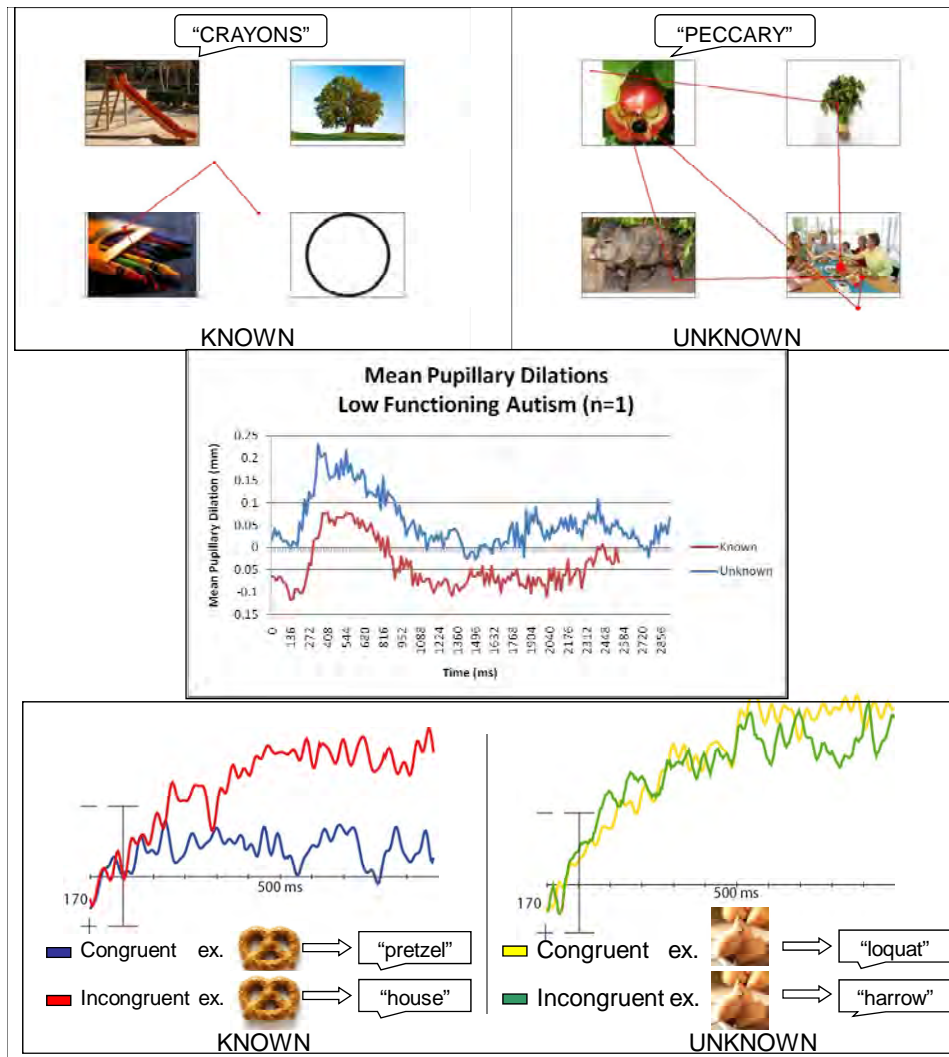
Figure 4. EM, PD, and ERP results from one low-functioning individual with autism. Top panel: Sample EM results to known (left) and unknown (right) words. Size of the dot indicates the length of the fixation. Middle panel: Average PD results for known and unknown trials. Bottom panel: Average ERPs for congruent vs. congruent trials for known (right) and unknown (left) words.

Experiment 5: Using the EM, PD, and ERP techniques to study new word learning in low-functioning individuals with autism

Our fifth experiment was designed to examine changes in EM, PD, and ERP measures in nonverbal, low-functioning individuals with autism that accompany repetitive exposure to new words during a learning period.

To date, we have identified two low-functioning individuals with autism who we believe will be suitable candidates for our fifth experiment. Both of them participated in the fourth experiment successfully, and are available for a long-term training study. Based on our analysis of their data from Experiment 4, we have recently begun to determine the appropriate exposure

and non-exposure sets for these two individuals. Our autism specialist and our speech-language pathologist have also been working together to determine the best training method to try to ensure maximal learning of the exposure items over a relatively short period of time (4-8 weeks). We have also been working to train personnel on the administration of the training sessions.

KEY RESEARCH ACCOMPLISHMENTS

- Completion of normal adult testing
- Completion of first-pass of normal adult data analysis
- Refinement of artifact rejection techniques
- Development of familiarity metric for re-classification of stimuli as "known" and "unknown"
- Preliminary draft of normal adult data
- Completion of normally developing child testing
- Development of improved child and autism recruitment methods
- Implementation of improved autism retention approaches
- Presentation of data at A Brain Research Meeting: The Emerging Neuroscience of Autism Spectrum Disorders, November 2010; submission of abstract to present at the Neurobiology of Language Conference, November 2011

REPORTABLE OUTCOMES

Ledoux, K., Pickett, E.J., Van Droof, L.V., Buz, E., Billings, N.M., & Gordon, B. (2010, November). <u>Receptive Vocabulary Knowledge in Individuals with Autism as Assessed by Eye Movements, Pupillary Dilation, and Event-Related Potentials</u>. Poster presented at A Brain Research Meeting: The Emerging Neuroscience of Autism Spectrum Disorders, San Diego, CA.

Gangopadhyay, I., Ledoux, K., Bosley, L., & Gordon, B. (2011). <u>The Use of Implicit Measures to Assess Receptive Vocabulary Knowledge in Individuals with Autism.</u> Abstract submitted for presentation at the Neurobiology of Language Conference 201, November 2011.

CONCLUSION

In all three populations capable of reliable behavioral responses (normal adults, normally developing children, and high-functioning children with autism), our results indicate that the implicit techniques provide valid measures of receptive knowledge. All three measures (eye movement monitoring, pupillary dilation monitoring, and ERPs) appear capable of differentiating known from unknown words, as compared to the criterion of behavioral responses. Specifically, eye movements were faster to, and eyes fixated longer on, the matching picture in the forced-choice task for known words relative to unknown words; pupillary dilation was greater from baseline for unknown words, relative to known words; and the N400 congruency effect was observed for known words, but not for unknown words. Thus, these data support the validity of these techniques and our experimental design.

Our preliminary testing of low-functioning participants with autism also suggests that these implicit techniques provide valid measures of receptive knowledge even in the absence of behavioral responses. All three appear capable of differentiating known from unknown words within this group, in that the preliminary results for low-functioning individuals with autism were remarkably similar to those observed for normal adults, normally-developing children, and a high-functioning individual with autism.

The demonstration of receptive abilities in nonverbal individuals would lay a foundation upon which we might better understand their baseline abilities for communication and for comprehension. Knowing that an individual can understand language even when he or she does not speak might support the development of more intensive speech and language therapies, using a broader range of modalities, to capitalize on that individual's functional preferences or strengths. We believe that our results provide an initial demonstration of such abilities in a group in which such knowledge has traditionally been difficult to assess, and which has been severely under-represented in the studies of cognitive processing and abilities.

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