Video Article

A Semantic Priming Event-related Potential (ERP) Task to Study Lexico-semantic and Visuo-semantic Processing in Autism Spectrum Disorder

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Abstract

Individuals with autism spectrum disorder (ASD) have characteristic deficits in understanding the meaning of language, or semantic processing. However, some evidence indicates that semantic processing of non-linguistic stimuli is intact, suggesting that semantic deficits may be language-specific. To appropriately characterize semantic processing deficits in individuals with ASD, comparison of within-modality linguistic (*e.g.,* written words) and non-linguistic (*e.g.,* pictures) stimuli is required. This paper describes such a methodology that makes use of a semantic priming paradigm during concurrent recording of electroencephalographic (EEG) data. EEG provides a dynamic measure of brain activity that is well-suited to characterize subtle differences in semantic processing that may not be observable at the behavioral level. The semantic priming paradigm presents a prime picture or word (*e.g.,* dog) followed by a target picture or word that is either related (*e.g.,* cat) or unrelated (*e.g.,* pencil) to the prime. This paradigm can thus be used to evaluate semantic processing across different modalities, and to compare lexico-semantic and visuo-semantic processing abilities in individuals with ASD and how they might differ from TD individuals. The specific steps involved in creating the stimuli, performing the EEG testing, and analyzing the EEG data are discussed. Representative results illustrate how the N400 component of the event-related potential (ERP) is reduced following semantically-related prime-target pairs compared to unrelated pairs. Comparisons of the N400 between conditions, modalities, and groups can provide estimates of the success of semantic processing, and can thereby be used to characterize semantic deficits in individuals with ASD or other clinical populations.

Video Link

The video component of this article can be found at https://www.jove.com/video/57217/

Introduction

Researchers in cognitive psychology have long been interested in how people understand the meaning of language. Language processing involves a sequence of steps of increasing complexity, from letter and word recognition, to semantic processing, to syntactic parsing. Semantic processing refers to accessing the meaning of a stimulus, be it a word, picture, or sound. Following early steps of initial word recognition, access of a word's meaning, or semantics, is a crucial step in language processing. Semantic integration refers to the process of integrating the meaning of stimuli to understand their relationships, and is crucial for higher-level language processing such as understanding sentences. Not only does the meaning of each word in a sentence need to be accessed, but the meanings of each individual word need to be integrated to form a coherent understanding of sentence meaning, or "gist".

Individuals with autism spectrum disorder (ASD) often have significant deficits in language comprehension[1]. There is some evidence suggesting that these difficulties stem from deficits in semantic processing and integration[2,3,4]. However, other studies have suggested that individuals with ASD do not show semantic processing deficits when materials are presented in non-linguistic (*e.g.,* visual or auditory) modalities[3,5,6]. Such findings suggest that semantic processing deficits in ASD may be restricted to linguistic (*i.e.,* written or spoken) modalities. As such, approaches that contrast different modalities may provide insight into the extent to which semantic processing deficits are domain-specific or indicative of a pervasive processing style. The purpose of this paper is to describe a methodology for comparing semantic processing between different modalities using a semantic priming task during concurrent electrophysiological recording.

The semantic priming paradigm has a long history in research investigating how semantic processing influences lower-level word recognition[7,8]. In traditional semantic priming tasks, a prime word is presented (*e.g.,* cat) followed by a target word that is either semantically related (*e.g.,* dog) or unrelated (*e.g.,* book) to the prime. Such a task is often done in the context of a lexical decision task, such that participants are asked to determine whether the target word is a real word or not. Other paradigms may have participants perform a semantic categorization task on the target word, or judge whether the two stimuli are related or not. Regardless of the specific task, decades of evidence have established that reaction times (RTs) are faster to target words that are semantically related to the prime compared to those that are unrelated.

This "semantic priming effect" has been attributed to a number of mechanisms in theoretical accounts[7,8]. One is that the priming effect is due to automatic spreading activation through the semantic network, such that the retrieval of the prime word's meaning activates the meaning of other semantically related words, including the target word. This then reduces the time needed for semantic activation of the target word. A second theoretical mechanism is that of expectancy, which posits that upon seeing the prime word, participants generate an expected set of potential targets. Target words that are included in this set are then recognized more quickly. Finally, others have postulated the existence of a post-lexical mechanism of semantic matching, which establishes the existence of a semantic relationship between the prime and target word. Regardless of the specific mechanism underlying the effect, semantic priming can be a useful index of semantic processing and integration. This paradigm is also not limited to lexical stimuli, and can also be used to investigate semantic priming of non-language stimuli like pictures[9] as well as cross-modal semantic priming (*e.g.,* between words and pictures)[3].

Semantic priming effects have been well-studied in the psycholinguistic literature, and have been investigated with regards to the type of prime-target relations, the timing of prime and target presentation, and many other manipulations[8]. The electrophysiological correlates of this effect have also been well-characterized[10]. Electroencephalography (EEG) is a method of recording neural activity via changes in electrical activity measured at the scalp. EEG is a useful choice of methodology for a semantic priming paradigm because it has very good temporal resolution (on the order of milliseconds, ms) and can thereby provide subtle differences in semantic processing between conditions or groups even in the absence of behavioral effects or responses.

Event-related potentials (ERPs) are time-locked changes in the EEG that arise in response to a specific stimulus or behavior. Depending on the timing and polarity of the response, different components of the ERP are reflective of different aspects of cognitive processing. The N400 component is a well-established marker of semantic processing and semantic integration[11,12] (although several other interpretations exist[10,13]). The N400 amplitude is reduced when semantic integration is easier (such as when the prime and target in a semantic priming paradigm are semantically related) compared to when semantic integration is more difficult (such as when two words are unrelated). Importantly, the amplitude difference between related and unrelated conditions (*i.e.,* the "N400 effect") is not specific to language. N400 effects are also observed in non-language modalities, such as in response to pairs of semantically-related and unrelated pictures or environmental sounds[14,15,16,17]. The N400 is thus a useful ERP component for the purposes of the current paradigm because it can be used as a modality-independent estimate of semantic processing and integration abilities.

Individuals with ASD show reduced or absent semantic priming effects and N400 effects in response to language stimuli[2,3,4], suggesting impairments in semantic processing. Such effects have been found in response to visuo-semantic and audio-semantic stimuli[3,5,6], lending support to the claim that semantic processing is selectively impaired for language stimuli. However, most previous studies comparing modalities have used cross-modal priming, such that the prime-target pair contains a lexical stimulus. Given the proposal that individuals with ASD have deficits in semantic processing of language stimuli, such cross-modal stimuli may have affected results. To truly investigate whether semantic processing of language is selectively impaired in individuals with ASD, within-modality pairs of lexical and non-lexical stimuli must be used. In a recent study, Coderre *et al.*[6] provided the first direct comparison of within-modality word and picture semantic priming to investigate semantic processing deficits in adults (ages 18-68) with ASD. Participants with ASD and typically-developing (TD) participants viewed pairs of pictures and words and were asked to judge whether the stimuli were related or not. During this semantic priming task, their brain activity was recorded using EEG. By comparing N400 effects between groups and modalities, this paradigm provided insight into the nature of semantic processing in individuals with ASD.

The purpose of this paper is to describe the semantic priming ERP methodology employed by Coderre *et al.*[6]. Although this paradigm was initially implemented to study semantic processing in adults with ASD, it may prove useful for any experimenters wishing to explore the neural correlates of lexico-semantic and visuo-semantic processing, either in TD individuals or in specific clinical populations.

Protocol

All methods described here were approved by the Institutional Review Board of Johns Hopkins University, where the original study[6] was performed.

1.Creating Stimuli

1. **Create an initial list of concrete nouns from which prime-target pairs will be made.**
    1. From a selected corpus such as Subtlex[19], select approximately 500 concrete nouns and obtain variables of interest (*e.g.,* frequency, length, concreteness, imageability, *etc.*) for each word.
    NOTE: Other corpuses, such as the Medical Research Council (MRC) Psycholinguistic Database[18] or Corpus of Contemporary American English[20], can also be used. Subtlex was used in the original study because this database is just a large Excel file and thereby easily allows for searching for stimulus generation. Other corpuses have different graphical interfaces and may require the user to input a specific text string into an input box and check the variables of interest being requested.
2. **Perform latent semantic analysis (LSA) between stimuli to establish semantic relatedness**
    1. Select LSA method or tool. A useful online tool is provided by Colorado University Boulder (http://lsa.colorado.edu/).
        1. From the main landing site, click on Matrix Comparison.
        2. Enter individual words to compare, separated by a blank line.
        3. Click Submit Texts.
    2. Using a spreadsheet, create a matrix of LSA values between each word and every other.
3. **Divide stimuli into related and unrelated conditions based on LSA (Figure 1A).**
    1. Manually select 200 word pairs with high LSA values (approximately 0.5 or higher)for the "related" condition.
    2. Manually select 200 word pairs with low LSA values (approximately 0.1 or lower) for the "unrelated" condition.
    NOTE: The experimenter may need to manually inspect word pairs to ensure that the semantic relation makes sense for the category. Some word pairs may have high LSA ratings but the semantic relatedness may not be immediately apparent to participants. Similarly, some may have low LSA ratings but may be semantically related in other ways.

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3. When creating related and unrelated pairs, manually match words on frequency, length, and any other variables that have been noted to be relevant in the literature (*e.g.,* direction of association[7,8]) or that are of interest for the specific study. Match words as closely as possible on the variables of interest (*e.g.,* within 1-2log10 frequency units; within 1-2 letters or syllables).

4. **Divide stimuli into word and picture modalities (Figure 1A).**
   1. Within the stimulus file in the spreadsheet, add another column of "condition".
   2. In the "condition" column, label 100 of the related pairs and 100 of the unrelated pairs as "picture" condition. Label the other remaining stimuli as "word" condition.

5. **Obtain picture stimuli.**
   NOTE: Picture stimuli may be obtained from online sources (*e.g.,* Google image searches) or from other sources available to the experimenter.
   1. Select 2–3 pictures to represent each word.
   2. Perform initial pilot testing by having one or more independent raters (*e.g.,* students, research assistants who have not been involved in stimulus development) decide which picture best represents the concept.
      1. Open all potential picture files at once using a photo viewer program, then read the word aloud and ask the rater to choose the most representative picture. Record each rater's responses for every word.
      2. For each word, identify the picture that the majority of raters selected as best representing the concept, and use this file as the stimulus for that word. If no majority exists, select a different array of pictures and repeat step 1.5.
   3. Using GIMP (or another photo editing program of choice), scale pictures to all be the same size (approximately 400 pixels or 3–5 inches height or width).
      NOTE: The precise size of the pictures may differ depending on the size of the monitor stimuli will be presented on. Horizontal and visual angle of the stimuli should be between 7 and 13°.

6. **Perform pilot testing**
   1. Pilot test word and picture pairs by asking 3–4 independent raters (*e.g.,* students, research assistants who have not been involved in stimulus development) to rate each pair as related or unrelated.
      1. Program the experiment in E-Prime (or other stimulus presentation program of choice) to present both words on the screen at once, either one above the other or side by side. Ask participants to rate the words as related or unrelated by pressing a button (*e.g.,* 1 for related, 2 for unrelated). See the E-Prime manual[21] for details on how to program an experiment in this software package.
         NOTE: Pilot testing can take place in the lab where the experimental testing will take place, or at any computer running the stimulus presentation program. No special room is required.
      2. Repeat pilot testing (with new independent raters who have not seen the stimuli) until a set of words and pictures is obtained with reliable ratings of related and unrelated. Obtain a total of 100 related word pairs, 100 unrelated word pairs, 100 related picture pairs, and 100 unrelated picture pairs.
         NOTE: It has been suggested that investigators using the N400 component to investigate cognition in clinical populations collect a minimum of 40 usable trials per trial type to elicit a reliable effect[22]. Anticipating that some trials will be lost during the data cleaning process, the number of trials included in the paradigm should be increased. In prior work using this specific paradigm [6], 100 trials per trial type was more than enough to ensure robust N400 effects on both an individual and group basis. Because the N400 component is similar between words and pictures[10], this estimated number of trial types is recommended to be kept consistent between modalities.
      3. Retain an additional 8 pairs (4 words, 4 pictures) for a practice session (see step 2.2.1below)

2. Task Programming

1. **Create stimuli lists.**
   1. From the final set of stimuli, sort stimuli into 8 blocks. Modality (picture/word) should be blocked (4 blocks each).
   2. Within each block, ensure an equal number of related and unrelated stimuli.
   3. Manually pseudo-randomize presentation lists within each block such that there are no more than 5 related or unrelated stimuli in a row, and pairs next to each other are not semantically related. Avoid trials such as "carrot-broccoli", "apple-pear" immediately next to each other.

2. **Program the task using E-Prime, or other stimulus presentation software of choice.**
   NOTE: Steps described here are specific to E-Prime and NetStation, and will differ if another stimulus presentation software or EEG acquisition software is used. Please see the E-Prime manual[21] and the E-Prime Extensions for NetStation tutorial[23] for more specific details on how to program an EEG experiment in this software package and how to enable communication between E-Prime and NetStation.
   1. Program two practice sessions for the picture and word blocks (4 pairs each), to be performed before the experimental testing begins.
   2. Program an instruction screen at the beginning of the practice session to read: "You will see two words presented on the screen one after the other. Please try to sit as still as possible and do not blink while the words are being presented. After the pair is presented, you will see a black cross on the screen. When you see the black cross, please indicate if the words were related or not. Press button 1 if the words ARE related. Press button 2 if the words are NOT related. Press any key to start the practice session."
   3. For each of the word stimuli, double-click on the TextDisplay icons in the experiment structure. Click the Properties icon at the top left. Under the Font tab, select Courier New font size 28. Under the General tab, select ForeColor as black and BackColor as white to present the words in black font on a white background.
      NOTE: The specific font size may need to be amended depending on the size and resolution of the monitor used for presentation. Horizontal visual angle of the words should be between 1 and 6°.

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4. For each of the picture stimuli, double-click on the Slide icons in the experiment structure. Click the Properties icon at the top left. Under the General tab, select BackColor as white to present pictures on a white background.
5. Program each trial to present the following stimuli in this order: a red pre-trial fixation cross (400 ms); stimulus 1 (1,000 ms); interstimulus interval (blank white screen; 300 ms); stimulus 2 (1,000 ms); blank screen (400 ms); intertrial interval (black fixation cross; randomly jittered between 1,000–1,400 ms in 100 ms intervals, average 1200 ms); see **Figure 1B**. To set durations, double-click the TextDisplay or Slide icons in the experiment structure and hit the Properties button on the top-left of the window. Set the duration under the Duration/Input tab.
NOTE: The blank screen is included before the intertrial interval to provide a visual break between the second stimulus and the black cross, and to provide a subtle prompt for the upcoming semantic relatedness judgment.
6. Program a TextDisplay object called "Break" after each block is completed saying "End of block, please take a break"

3. **Include parameters for communication between E-Prime and NetStation. See the E-Prime Extensions for NetStation manual[23] for specific instructions on how to include this information.**
    1. For each "word1" or "word2" Text Display object, select the object in the Experiment structure. Under the "Properties" window, set the Tag as "WRD1" or "WRD2", respectively.
    2. For each "picture1" or "picture2" Slide object, set the Tag as "PIC1" or "PIC2", respectively.
    3. Under "Unreferenced E-Objects", create a new List called "CellList". Enter the cell numbers as: 1 = picture related; 2 = picture unrelated; 3 = word related; 4 = word unrelated. Within the trial list for each block, include a column called "CellNumber" and enter the corresponding cell numbers for each trial according to condition and modality.

3. EEG Testing

NOTE: The specific procedures described here are for an EGI system. Procedures may differ if other systems are used.

1. **Prepare for EEG testing.**
    1. Mix 2 teaspoons (10 g) of potassium chloride with 1 quart (1 L) of water and 1 tablespoon (15 mL) of baby shampoo in a clear plastic bucket to create electrolyte solution
    2. Measure circumference of participant's head, passing through the inion and nasion, to determine appropriate net size. Select the appropriate sized net according to the participant's head circumference.
    3. Immerse the electrodes in the electrolyte solution, ensuring that all sponges are fully submerged, and let soak for at least 5 minutes.

2. **Apply EEG net.**
    1. Have participant sit comfortably in a chair, facing the experimenter. Explain to the participant that you will be putting the net on now, then will adjust it and check the signal before beginning the test.
    2. Place towels around participant's shoulders. Instruct participant close their eyes, then apply net to participant's head. Adjust the net and tighten ties to ensure a snug fit to participant's head.
    3. Work through all electrodes to seat them against the scalp. Use a sweeping motion with the electrode to move hair away. Rewet sponges using a pipette if necessary.
    4. Once all electrodes have been seated, check impedances. Reseat or rewet any electrodes with impedances above 50 kiloohms (kΩ).

3. **Run semantic priming experiment during EEG recording.**
    1. Once the net is applied, impedances have been checked, and the participant is ready to begin, start the semantic priming task.
    2. Reiterate the instructions to participants before testing. Instruct participants to judge whether the word or picture stimuli are related or unrelated by pressing a button on a keyboard or button-box. To avoid motor artifacts confounding the EEG signal, instruct participants to wait to make their response until the second stimulus has disappeared from the screen and the black cross has appeared.
    3. Run the practice session at least once to ensure that participants understand the task.
    4. After every 2 blocks, during the break, rewet electrodes and recheck impedances.

4. EEG Preprocessing

1. **Open NetStation Tools.**
NOTE: The steps described here are specific to preprocessing in NetStation 5. See the NetStation 5 User Manual[24] for more details on how to use NetStation Tools. Other preprocessing packages may include EEGlab, ERPlab, FieldTrip, or other software of the experimenter's choice. Note that preferred order of preprocessing steps may differ between software packages. Observation of an N400 effect should not differ based on choice of analysis package.
2. **Filter the data.**
    1. At the bottom of the NetStation Tools window, create a new filtering tool by selecting "Filtering" in the 'Create' drop-down menu. Rename the tool appropriately.
    2. Set the highpass filter to 0.1 Hertz (Hz) and the lowpass filter to 50 Hz.
    NOTE: The highpass filter can be lower than 0.1 Hz but it is not advised to exceed this cutoff, to avoid risk of introducing spurious effects[25]. A lowpass filter as low as 30 Hz can be used.
    3. Save the tool, then drag the original EEG recording file into the "Input Files" box at the top left of the window and hit "Run".

3. **Segment the data into trials.**
    1. Create a new "Segmentation" tool and name it appropriately.
    2. Under "Categories to create", hit the plus sign to create a new category and rename it "picture related". Drag the "Code" icon into the "Create category based on criteria" box and set it as "Code is PIC1" to time-lock to the presentation of stimulus 1. Drag the "Key Code" icon into the "Create category" box and set it as "Key Code cel# is 1".

1. To include only correct trials, drag another "Key Code" icon into the "Create category" box and set it as "Key Code eval is 1".

3. At the bottom of the window, set the segment length to "Extend segment 100 ms before and 2,300 ms after".
NOTE: Segments may be time-locked to the onset of either the first or second stimulus. If locked to the first stimulus, segments should extend 100 ms before to 2300 ms after (to include presentation duration of both stimuli (1,000 ms each) plus inter-stimulus interval (ISI) time (300 ms)). If locked to the second stimulus, segments should extend 100 ms before to 1,000 ms after.
4. Clone the category by hitting the "Clone" button and rename it "picture unrelated". Set the Code to PIC1 and the Key Code cel# to 2.
5. Clone the category and rename it "word related". Set the Code to WRD1 and the Key Code cel# to 3.
6. Clone the category and rename it "word unrelated". Set the Code to WRD1 and the Key Code cel# to 4.
7. Save the tool, then drag the most recent preprocessed file into the "Input Files" box at the top left of the window and hit "Run".

4. **Perform artifact detection.**
   1. Create a new "Artifact Detection" tool and name it appropriately.
   2. Under "Artifact Detection Settings", hit the plus sign at the bottom of the window to add a new setting. Select "Bad Channels" from the dropdown menu under "Operation". Leave all of the default settings (max-min > 200 microvolts (μV); Entire segment; Moving average of 80 ms).
   3. Add a new setting and select "Eye Blink" from the "Operation" dropdown menu. Leave all of the default settings (max-min > 140 μV; window size 640 ms; moving average of 80 ms).
   4. Add a new setting and select "Eye Movement" from the "Operation" dropdown menu. Leave all of the default settings (max-min > 55 μV; window size 640 ms; moving average of 80 ms).
   5. Save the tool, then drag the most recent preprocessed file into the "Input Files" box at the top left of the window and hit "Run".
   6. Open the resulting file in NetStation Review and scroll through every trial by hitting the arrow buttons under the "Categories" menu on the right side-bar. Mark trials as good or bad by hitting the green or red circles, respectively. When done, close the file to save the results.

5. **Perform bad channel replacement.**
   1. Create a new "Bad Channel Replacement" tool and name it appropriately. No parameters need to be set by the user for this tool, so save the tool, then drag the most recent preprocessed file into the "Input Files" box at the top left of the window and hit "Run".

6. **Perform single-subject averaging to collapse over trials.**
   1. Create a new "Averaging" tool and name it appropriately. Under "Averaging Settings", select "Handle source files: Together" and "Handle subjects: Separately".
   2. Save the tool, then drag the most recent preprocessed file into the "Input Files" box at the top left of the window and hit "Run".

7. **Reference data to the average reference[26].**
NOTE: The average reference is used here because EGI provides dense-array EEG (128 and 256 channels). It has been suggested that an average reference be used with dense-array recording systems[26]; other semantic priming ERP studies using 128-channel or 256-channel nets have used the average reference[6,27,28]. Other reference choices include the average of the right and left mastoids, the nose, or the earlobe[29]. There is no optimal choice of reference electrode, and the experimenter should note that choice of the reference electrode may affect the resulting ERP waveforms[26,29].
   1. Create a new "Montage Operations" tool and name it appropriately.
   2. Select the appropriate net from the dropdown menu under "List Montages for Sensor Layout". Select "Average Reference" and make sure the "Exclude bad channels from reference" box is selected. Save the tool, then drag the most recent preprocessed file into the "Input Files" box at the top left of the window and hit "Run".

8. **Perform baseline correction using the first 100 ms of the segment[10,28].**
NOTE: A baseline period of 200 ms can also be used[29].
   1. Create a new "Baseline Correction" tool and name it appropriately.
   2. Under "Baseline Correction Settings", select "Select baseline from portion of segment", "Select baseline with respect to segment time = 0", and "Baseline begins 100 ms before time zero and is 100 ms long".
   3. Save the tool, then drag the most recent preprocessed file into the "Input Files" box at the top left of the window and hit "Run".

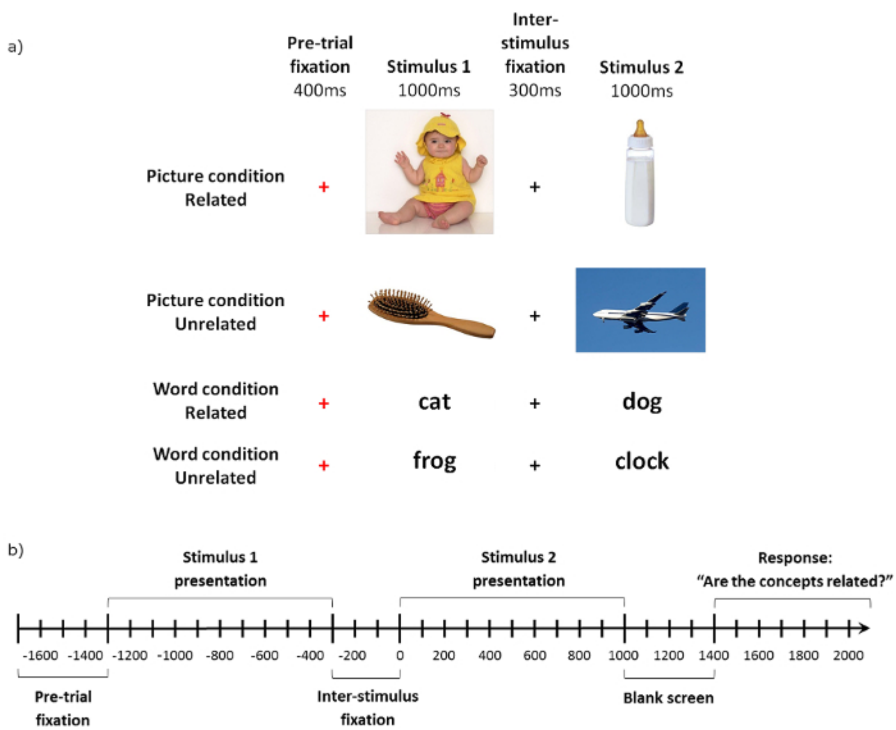

Figure 1: Experimental examples and timeline. (**A**) Examples of picture and word stimuli. (**B**) Timeline of stimulus presentation. This figure has been reprinted with permission from Coderre *et al.*[6] Please click here to view a larger version of this figure.

Representative Results

If stimuli have been appropriately sorted into related and unrelated conditions, an N400 effect should be observed for both word and picture stimuli (**Figure 2**). This is identifiable as a greater negative amplitude in unrelated conditions compared to related conditions. For word stimuli, the effect should occur from 300–500 ms over central or centro-parietal scalp[6,10]. For picture stimuli, the effect may be slightly earlier or more frontally distributed[9,15,16].

Statistical analyses may test the significance of the N400 effect by comparing the average amplitude between related and unrelated conditions. This may be performed at a single electrode or over multiple electrodes. The spatial extent of the effect may be evaluated by including electrode site and/or laterality in statistical models. Mass univariate statistics (see for example Groppe *et al.*[30] for details) may be used to evaluate the precise timing of the effect or to establish time windows of interest for further analyses. (Note that if multiple analyses are performed, results will need to be adjusted to correct for multiple comparisons. The mass univariate statistical method described by Groppe *et al.*[30] includes several options for such corrections.)

For investigators using this semantic priming ERP paradigm to study semantic processing in clinical populations, it is important to also collect data from a TD control group. The control group should show the described N400 effects for both picture and word conditions. However, clinical populations may show reduced or absent N400 effects to one or both conditions (**Figure 3**). To determine whether the magnitude of the N400 effect differs between controls and clinical populations, group can be included as a between-subjects factor in the statistical models. A significantly smaller N400 effect in a clinical population would indicate difficulties with semantic processing. Differences in the timing or scalp distribution of the effect may also indicate processing differences between groups.

Although the representative results described above are at the group level, in keeping with the majority of research on the N400 effect, this component is quite robust and can often be observed on a single-subject level[31,32]. Especially for clinical populations such as individuals with ASD, information about a single individual's semantic processing abilities might be highly desirable. Investigators should be aware, however, that individuals with ASD may have inherently noisier EEG data than TD individuals[33] (although see reference[34]), which may preclude reliable single-subject effects in certain participants. For investigators interested in evaluating single-subject effects, permutation tests can be performed to assess statistical significance of effects within a single individual. Briefly, in such a method one would perform many (*e.g.,* 5,000) iterations in which condition labels (related/unrelated) are permuted between individual trials. For each permutation, the conditions are then statistically compared. The statistics from each permutation are used to create a null distribution of test statistics, against which the observed test statistic is compared to derive a significance result.

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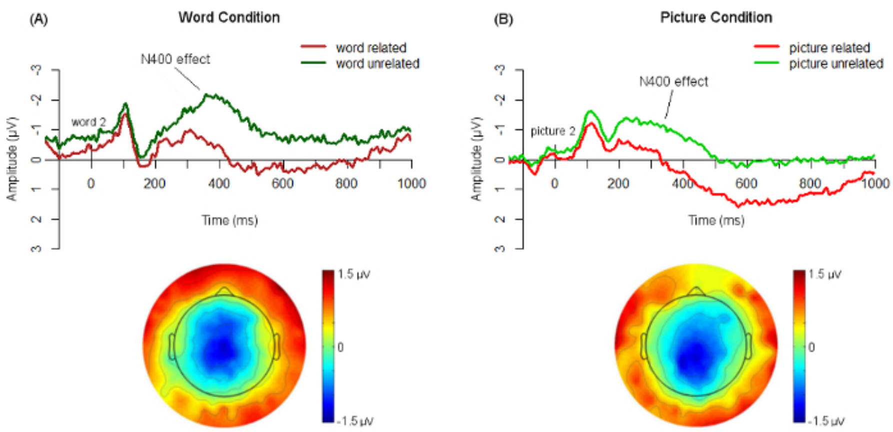

Figure 2: Representative N400 effects in response to the second stimulus in each pair for (**A**) word conditions and (**B**) picture conditions. Data is averaged over a group of 20 TD adults (data taken from Coderre *et al.*[6]). Preprocessing was performed using an average reference. Top panels: Representative ERP waveforms at electrode Cz showing a larger amplitude to unrelated conditions compared to related conditions at approximately 400 ms (negative is plotted up). Bottom panels: Topographic plots of the unrelated-related difference, averaged over a window from 400–500 ms (precise distribution may change with choice of reference). For topographic plots, the top of the figure indicates the front of the head. Please click here to view a larger version of this figure.

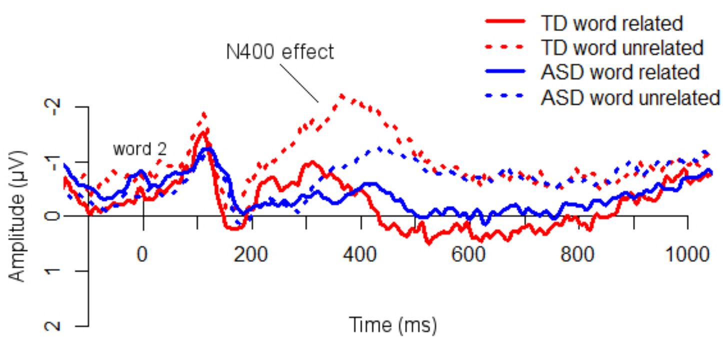

Figure 3: Representative group differences in N400 effects for word conditions at electrode Cz. Data is averaged over a group of 20 TD adults and 20 adults with ASD (data taken from Coderre *et al.*[6]). Preprocessing was performed using an average reference. Clinical groups, such as individuals with ASD, may show a smaller N400 effect in response to words, which suggests difficulties with lexico-semantic processing.

Discussion

The present paper has reported critical steps in developing a semantic priming ERP paradigm with picture and word stimuli for exploring semantic processing deficits in individuals with ASD. Major steps include creating the stimuli, programming the task, and performing EEG testing and analyses. The most time-consuming part of this procedure is likely to be the creation of stimuli, as this requires careful matching both between and within stimulus pairs, conditions, and modalities on variables such as length, frequency, and semantic relatedness. As such, a significant amount of pilot testing will likely be needed to ensure that the final stimulus set is appropriate.

Although the suggestions included here, and the prior work that this method is based off of[6], tested adults with and without ASD (ages 18–68), this paradigm could easily be extended to child or adolescent populations. Indeed, other studies have used similar semantic priming EEG paradigms in children with and without ASD to compare semantic processing across modalities[3]. Several considerations would need to be taken into account when modifying for different ages and developmental stages. For example, the stimulus set could be restricted to higher-frequency words to ensure that all children know the meanings of all stimuli (see next paragraph). Other modifications could also be done to the testing paradigm to ensure adequate data quality from child or adolescent participants, such as including more breaks, offering incentives, or showing brief videos upon completion of a block of stimuli.

Several factors regarding the method described here and the previous work are important to note. First, the prior work[6] was performed in a group of adults who had average to above-average language and intellectual functions. One limitation of this paradigm is that it can only be used with individuals who are familiar with the words or pictures being presented. Prior work has shown that N400 effects do not occur if the lexical item is outside the individual's vocabulary range[32,35]. Therefore it is important that participants either have average to above-average verbal and reading abilities, or that care is taken to ensure that all stimuli used in the experiment fall within the vocabulary range of the individual. In the latter case, this could involve administering a vocabulary test following the EEG session testing the individual's knowledge of all of the words used in the experiment. In the case of words that the individual does not know, these trials could be removed from further analysis. Unfortunately, because intellectual disability and impaired language skills are a common co-occurrence in individuals with ASD[1,36], these requirements for language and reading abilities will mean that individuals who also have intellectual disability or below-average language abilities will not be able to participate. Further modifications to the paradigm that will allow for testing of these more severely-affected individuals should be considered in the future.

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It is important to note that the method described here does not consider different types of semantic relationships between the prime and target. Some studies have found that the magnitude of the semantic priming effect is modulated by the type of relationship (*e.g.,* associative vs. "pure", forward vs. backward, mediated vs. direct)[8]. In the current methodology, these various types of prime-target relationships are not considered. However, for researchers interested in exploring their effects, this may be an additional step in stimulus creation.

It is also notable that the method described here instructs participants to make a semantic relatedness judgment during the task. The explicit nature of this task may induce strategies that could affect results. For instance, asking participants to pay attention to the semantic relationships between stimuli could mitigate group effects[6]. Future research using this paradigm will modify it to include an implicit semantic processing design, for example in which participants press a button each time an animal word is presented or simply watch the words and pictures appearing on the screen. Semantic priming N400 effects have been observed in the absence of explicit tasks[3], so this type of manipulation should still yield observable effects and may also reveal group differences in implicit semantic priming.

Decades of research have established the semantic priming paradigm as a valuable way of studying semantic processing. The reliability of this task across different modalities makes it particularly valuable for studying how lexico-semantic and visuo-semantic processing may differ. Such a between-modality comparison is particularly useful in certain clinical populations such as ASD, in which semantic priming deficits may be restricted to language domains. By comparing and contrasting semantic priming effects and N400 effects between groups and modalities, investigators can establish whether the purported deficits in semantic processing in ASD are restricted to the linguistic domain or are representative of a more global semantic dysfunction.

The extension of the semantic priming paradigm to EEG also provides valuable insight into the neural mechanisms underlying semantic processing and can provide additional information that behavioral responses cannot capture. Due to the volume of spatial and temporal information that is obtained with EEG, this method may reveal more subtle differences in semantic processing than would be observed with behavioral responses. For instance, in the previous study using this paradigm, Coderre *et al.*[6] found that an N400 effect did occur in the ASD group in response to word stimuli, in contrast to previous literature; however, subtle differences in the timing and topography of the effect suggested that the two groups were using different cognitive mechanisms for semantic processing. In sum, a semantic priming ERP task with words and pictures can be useful for studying domain-general semantic processing, both in TD individuals and in clinical populations.

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The author has nothing to disclose.

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