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Electroencephalography (EEG) and Event-Related Potentials (ERP's) with Human Participants

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Abstract

Understanding the basic neural processes that underlie complex higher-order cognitive operations and functional domains is a fundamental goal of cognitive neuroscience. Electroencephalography (EEG) is a non-invasive and relatively inexpensive method for assessing neurophysiological function that can be used to achieve this goal. EEG measures the electrical activity of large, synchronously firing populations of neurons in the brain with electrodes placed on the scalp. This unit outlines the basics of setting up an EEG experiment with human participants, including equipment, and a step-by-step guide to applying and preparing an electrode cap. Also included are support protocols for two event-related potential (ERP) paradigms, P50 suppression and mismatch negativity (MMN), which are measures of early sensory processing. These paradigms can be used to assess the integrity of early sensory processing in normal individuals and clinical populations, such as individuals with schizophrenia.

Keywords

Electroencephalography (EEG); Sensory Gating; P50 Suppression; Mismatch Negativity (MMN); Schizophrenia

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Understanding the basic neural processes that underlie complex higher-order cognitive operations and functional domains is a fundamental goal of cognitive neuroscience. Electroencephalography (EEG) is a non-invasive and relatively inexpensive method for assessing neurophysiological function that can be used to achieve this goal. EEG measures the electrical activity of large, synchronously firing, populations of neurons in the brain with electrodes placed on the scalp. Many EEG researchers utilize an event-related potential (ERP) experimental design, in which a large number of time-locked experimental trials are averaged together, allowing the investigator to probe sensory, perceptual, and cognitive processing with millisecond precision. This high temporal resolution lends itself well to the study of the earliest stages of information processing and the subsequent transitions from sensory-based perceptual processing to the higher cognitive operations that are necessary to successfully navigate through the complex stimulus-laden environment of everyday life.

Basic Protocol 1 details the set-up for an EEG study participant. Additional Support Protocols provide outlines for conducting two specific ERP study designs: P50 suppression -

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an operational measure of sensory gating, and mismatch negativity (MMN) – an early measure of auditory change detection, both of which are known to be impaired in individuals with schizophrenia. All research involving human participants must be approved by the institutions' Institutional Review Board prior to study initiation.

BASIC PROTOCOL: Preparation of human subjects for EEG studies

Electroencephalography (EEG) provides a temporally precise measure of neurophysiological function during different tasks and conditions. The applications of this method are extremely wide-reaching, as they allow investigators to explore a nearly infinite number of domains where it is of interest to understand the relative timing of neural events. To collect EEG data, electrodes are placed on the scalp and face, and scrubbed with a conducting gel to facilitate measurement of the electrical activity of populations of neurons (scalp electrodes) and muscle activity (face electrodes). The basic methods for preparing a human participant for EEG data collection will serve as a foundation for the two Alternate protocols, which detail specific event-related potential (ERP) paradigms.

Materials List

- EEG acquisition software (e.g. Neuroscan, BioSemi, or equivalent)
- Digital EEG Amplifier (e.g. Neuroscan NuAmps, BioSemi, or equivalent)
- 2 computers: Check EEG acquisition program documentation for system requirements
- Stimulus Generator (e.g. EMG-SR/SR-HLAB System Stimulus Module or equivalent)
- Stimulus generation software (e.g. E-Prime, Presentation, or equivalent)
- Electrically sheltered room/chamber (if available, suggested but not required)
- Gauss Meter with sensitivity to electrical frequency for your location (usually 50-60 HZ; e.g. EMF, Allied Products, or equivalent).
- Electrode Tester (UFI Checktrode or equivalent)
- Electrode Cap (Easycap or equivalent)
- Forty Ag/AgCl sintered ring electrodes (Suggested vendor: Easycap, see Suppliers Index for contact information)
- 10 Electrode Adaptors of appropriate size for electrodes (Suggested vendor: Easycap, see Suppliers Index for contact information)
- Electrode Washers of appropriate size for electrodes (Suggested vendor: Easycap, see Suppliers Index for contact information)
- Abrasive electrolyte gel (Abralyt or equivalent)
- Four 20-ml customary syringes (without needle)
- Several cotton swabs with a free wooden end
- Foam insert earphones (E.A.R or equivalent. Suggested vendor: 3M, see Suppliers Index for contact information)
- Flexible tape measure
- Tissues or towel

- Towel or cape to cover participant's clothes
- Facilities and supplies for participants to wash hair after experiment – Large sink, spray attachment for faucet, shampoo, conditioner, combs, towels, hair dryer, hand mirror (recommended by not required; participants can wash hair at home if not available)
- Human participants – If possible, participants should arrive with their hair washed without using additives like conditioner or hair styling products as this helps significantly to achieve low impedances essential to EEG recording.

Figure 1 is a schematic of the equipment configuration used for these experiments. The use of an EMG-SR amplifier (now called SR-HLAB) allows for the collection of both electromyographic (EMG) data, as in the prepulse inhibition paradigm (PPI – PROTOCOL IN PREP[*Editor: refers to a separate manuscript being prepared by the same authors]), and EEG data in the same experimental session with human participants (Light and Braff, 2001) and animal subjects (Swerdlow et al., 2006). It is difficult to estimate the necessary computer parameters for individual experiments as the processing load increases with the number of channels collected, sampling rate, and acquisition rate. Check the reference materials for the particular EEG acquisition software being used for recommended system requirements, and increase disk speed as necessary.

1. Ambient electrical noise can be problematic for EEG recordings. When setting up a laboratory, and periodically throughout the course of data collection, it is useful to check noise levels using a handheld gauss meter that is sensitive to the electrical noise frequency range emitted by power lines, computers, and other electrical appliances. In the USA this frequency range is 60 HZ, other parts of world such as the United Kingdom it can be 50 HZ.

One method for reducing the influence of this electrical noise is to collect EEG data in an electrically shielded room or chamber. If such a chamber or room is not readily available, and checking with a gauss meter indicates the presence of electrical noise, often one can simply move the offending equipment a short distance away from electrodes and electrode wires to reduce the impact of noise on recordings. A ground electrode, usually placed on the forehead, is used when collecting EEG data to ground the system (discussion of placement of ground electrode is found in Step 9 of the Basic Protocol). Reducing the impedance of this ground electrode can also substantially reduce electrical noise (discussion of reducing electrode impedance is found in Steps 12 and 13 of the Basic Protocol).

2. Switch on stimulus generation and data collection equipment at least 30 minutes prior to starting data collection to allow it to warm up and stabilize.

> The temperature of the recording room and/or chamber should be maintained in a comfortable range for participants. Specifically, if participants are perspiring, this can create problems in the recording of EEG data.

3. When the study participant arrives at the lab, explain the study and have them sign an informed consent form that has been approved by the institutions' Institutional Review Board.

4. Select the correct cap size. Measure the head circumference in cm (hat size) of the participant around the widest point on the head using a flexible tape measure. Cap sizes range from 52 to 60 cm in increments of 2 cm. Most labs have 54, 56, 58, and 60 cm sizes as part of a standard EEG set-up. If the measurement is between sizes try on the next cap size up. The fit of the cap should be snug. It is very important to ensure a cap is fitted correctly, as a cap that is too large may reduce quality of EEG recordings, or make preparation of electrodes and lowering of impedances much more difficult. To check the fit of the cap, ask

participants to nod head up and down, and turn head side to side. If the cap shifts, it is too big, and a smaller size should be used. Also, when cap is on the participant's head, gently press down on one of the electrode adaptors towards the scalp. If the adaptor bounces back, there may be too much space between electrode adaptor and scalp, and a smaller cap size should be tried. Once correct cap size is determined, remove the cap from head and snap in the electrodes.

> Some EEG caps come prepopulated with electrodes; that is, the electrodes are permanently attached to the cap. One advantage to these caps is their ease in application, as electrodes do not need to be snapped in for each participant. However, these caps are harder to clean than caps with removable electrodes, and if one of the electrodes fails, it can be difficult to replace. In comparison, caps with removable electrodes can be easily cleaned and disinfected, and individual electrodes are easy to replace.
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> If the EEG cap is prepopulated, skip to Step 6 below.. If the cap has removable electrodes, it may be necessary to label electrode adaptor locations on cap according to manufacturer instructions. For connecting electrodes to cap see Step 5 below.

5. Snap electrodes into white plastic adaptors on the cap. Let the leadwire point toward the narrow side of the adapter and be sure not to bend or break the leadwire where it leaves the electrode. Use a narrow tool such as the wooden end of a cotton swab to snap electrodes into the adaptors (Figure 2). Insert ring electrodes into all desired adaptors on electrode cap.

6. Plug the electrodes into the EEG Amplifier in the appropriate locations (Figure 3). Refer to EEG acquisition software materials for instructions on how to designate channels. Depending on the setup and equipment, it may be necessary to label the channels on the amplifier (e.g. Ground, FP1, CZ, REOG, LEOG).

Mount the cap on the participant—7. Before placing the cap on the participants head, roughly measure the distance between the participants' nasion (bridge of the nose) and inion (bump on lower base of skull: to find inion place hand in middle of neck and slide upwards) using your hands. The FPz electrode should be placed about 10% of this distance above the nasion in the middle of the forehead. Place front of cap on participant's forehead with FPz in this position, ask the participant to hold cap in place, and then pull cap over the head. Next, adjust the position of the CZ electrode so it lies half way between the nasion and the inion.

> In order to check that CZ is in the correct position, measure the distance from nasion-to-inion and the preauricular-to-preauricular; CZ should be centered between these points. A "quick and dirty" method for locating these midpoints is to place the small finger of one hand on the participant's inion and the small finger of the other hand on the participant's nasion. Bring thumbs toward one another on the top of the participant's head. CZ should be centered between thumbs. If CZ is not located there, adjust the cap until CZ is centered.
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> When cap is positioned correctly, the frontopolar electrodes Fp1/Fp2 should lie directly above the eyebrows, and the inion electrode should lie directly on top of the inion. If these electrodes are not positioned correctly choose another cap size. Also check that CZ is right-left centered as well, and that lateral electrode positions are symmetrical. Finally, make sure that the center line of electrodes is centered on the participant's head.

8. Next, secure the cap with chin strap. If using a cap with large ear holes, make sure that the participant's ears are completely showing through the ear holes. The ears should be pulled out of the slits completely to allow the cap to fit snugly onto the skin behind the ears, that is,

on the mastoid positions. With some caps, however, this is not appropriate as ear slits are too small to allow ears to comfortably fit. Please refer to materials enclosed with specific cap used to determine appropriate procedure. When using the chin belt, attach in such a way that the soft, flat, side points towards the skin. The chin belt requires only minimal tension; however, minimizing conversation can lessen any uncomfortable pressure on the larynx.

9. Attach desired additional electrodes, including electro-oculographic electrodes (EOGs) to monitor vertical (e.g., blinks) and horizontal eye movements, as well as reference and ground electrodes. When applying additional electrodes outside of the cap, use an electrode adapter. Snap an electrode into an adapter and attach it to an electrode washer. This firmly attaches the electrode and is suitable for monitoring eye movements, ground and/or reference electrodes outside the cap, or even for electro-myographic (EMG) electrodes to monitor movements of arms or legs. Good impedance is achieved more easily with these electrodes due to direct contact with the skin (see Step 10 below). After additional electrodes have been applied, plug them into appropriate locations on EEG amplifier.

A typical set up includes an EOG electrode for monitoring eye movements approximately 2 cm:

- Above left eye
- Below left eye
- Directly to the side of left eye
- Directly to the side of right eye

A ground electrode is needed to serve as a common reference point for all voltages in the system. The ground electrode can be placed almost anywhere, but a forehead or ear location is often used.

All EEG recordings are bipolar; that is, they represent the difference in potential between the active electrode of interest, and a reference electrode that is treated as relatively electrically inactive. There is no consensus in the field as to the best location for the reference electrode(s), but common options include the tip of the nose, single mastoids or linked mastoids (the average signal of electrodes placed on both mastoid bones), and single or linked earlobes. An excellent reference for critical discussion of the reference electrode is Nunez and Srinivasan (2006). One important point made in this text is that the use of any linked reference (mastoid or earlobe) can be problematic for some components and analyses; for the MMN paradigm described in Alternate Protocol 2, it is not appropriate to use a linked mastoid reference (further discussion of the reference choice for MMN paradigm can be found in Alternate Protocol 2, Step 2). Another alternative to the use of a physical reference electrode it to take the average output of all channels and use this as the reference for each individual electrode of interest.

10. Minimize impedance of electrical connection between electrode and scalp by applying abrasive electrolyte gel. This gel conducts electrical activity from the scalp to the electrodes themselves. Supply sufficient illumination. Place the wooden end of the cotton swab through the opening of the electrode and push the hair aside until the skin is clearly visible (Figure 4). Push the hair aside in one direction. When hair is long, lift up the adapter a little bit when moving hair to one side. However, be sure to let the adaptor back down again while moving back the swab to grab a new bunch of hair, as this will prevent already-moved hair from slipping back.

Before proceeding, check that the adapter is not located above a mole, scar, blemish or any break in the skin. The following application of abrasive paste could cause

inflammation. If needed, move the adapter a little bit to the side to avoid these features.

11. Fill 4-5 20-ml syringes with abrasive electrolyte gel.

12. Reduce impedances using one of the following two methods:

a. Fill 4-5 electrodes with gel using a syringe (make sure the plastic tip of the syringe touches the scalp) and then begin to gently scrub on the scalp through the electrode opening by twirling the cotton end of the cotton swab between thumb and index finger.

b. Dip the cotton swab into a small amount of electrolyte gel (use a small container to hold gel and discard extra gel after use) and gently scrub the scalp a bit first before filling electrodes.

Impedances for all electrodes are compared to both the ground and reference electrodes during data analysis. Therefore, if there are poor impedances (e.g. above 5 kΩ) on either of these electrodes, good impedances will not be possible on any other electrodes. Thus, the ground and reference electrodes should be prepared and checked first before moving on to other electrodes. Some EEG acquisition programs do not allow for impedance checks on reference and ground electrodes. If this is the case, check these electrodes with a hand-held electrode checker BEFORE preparing scalp electrodes. Make sure impedance values for ground and reference electrodes are between 1 and 5 kΩ before proceeding.

13. To lower impedances, continue to twist Q-tip on the scalp. It may be necessary to apply more gel using syringe. If the gel in one syringe runs out, use a new, pre-filled one. Do not use excessive pressure as it may cause abrasions. Do not refill an emptied syringe until it has been washed and sterilized.

This process allows for a thorough connection between skin and electrolyte gel. If a participant has long and/or thick hair that is pushed back behind the ear when cap is applied, this may make it difficult to minimize impedances for electrodes TP9/TP10. If this is the case, these electrodes may be individually attached in the same manner as EOG electrodes (Step 9).

14. After an impedance value between 1 and 5 kΩ for a particular electrode is achieved, use the syringe of electrode gel to completely fill the space from skin to electrode. When electrodes are closely spaced, while filling space with gel concurrently draw back the plastic tip of the syringe from the scalp to prevent electrolyte gel from swelling underneath the adapter rim and bridging two adjacent electrodes. Never return used gel from syringes to the original gel storage container as it is no longer sterile.

Many EEG acquisition programs will allow real-time online monitoring of electrode array impedances, which is especially useful for minimizing these values. If this is the case, open your software package and check impedances for all electrodes. If the available software does not have this feature, check impedances with handheld electrode checker.

15. Optional: Insert earphones. This is only necessary for paradigms that use auditory stimuli.

In paradigms that measure neural responses to auditory stimuli it is necessary to test participants' hearing prior to study inclusion to ensure they can detect stimuli being presented. Standardized testing usually includes a variety of tone frequencies, such as 500, 1000, and 6000 Hz in each ear using a staircase method. Depending on the paradigm and

stimulation settings (e.g., duration MMN, Support Protocol 2, uses 1000-Hz tones), it may be desirable to tailor exclusion criteria for maximal performance on the particular task. For example, for studies presenting 1000-Hz tones, it is common to exclude subjects who are unable to detect 1000-Hz tones at <40 dB (mean of both ears; test each ear separately and average). If subjects have gross abnormalities or asymmetries in their hearing thresholds, they may also be excluded. This testing should be done after the participant has signed an informed consent form.

For EEG studies, foam insert earphones are preferred to external (over the ears) headphones for a number of reasons: 1) If external headphones are seated on or near electrodes, this may cause stimulus artifacts in the EEG data. 2) External headphones are more likely to shift during the data collection session, resulting in inconsistent levels of stimulation throughout the session. 3) The insert earphones reduce ambient noise to minimize interfering auditory stimulation.

To insert, roll foam earphone into a narrow cylinder as shown in Figure 5A. It is important that the earphone be sufficiently compressed to be inserted deep into the ear canal, as a deep insertion is essential for complete stimulus delivery. Proper insertion of earphones is easier if the ear canal is straightened and enlarged by gently pulling the outer ear (pinna) outward and upward during insertion (see Figure 5B). Pull the pinna gently but firmly, usually in the direction the ear extends from the head. Don't just press it flat against the skull. After insertion, it may be necessary to hold the plug in place with a fingertip for a few moments until it begins to expand and block external noise. A properly inserted earphone may be uncomfortable at first, but as the foam expands, the earphone will retract slightly from ear. As such, wait about 30 seconds after insertion for discomfort to subside. If earphone is still too uncomfortable, withdraw it slightly. A properly inserted earphone will be entirely inside the ear canal (Figure 5C); if the foam is visible (Figure 5D) the insertion is too shallow and should be removed and reinserted.

Begin data collection—16. Open the EEG acquisition software and load the experiment file. Observe the resting activity of all the electrodes, and make sure there are no "bad" channels; that is, electrodes that produce flat line signals, or show a lot of activity while the participant is resting. If any bad channels are suspected, it may be necessary to apply more electrode gel and scrub to minimize impedances, or replace the electrode. Tell the participant to avoid eye blinks, and tensing muscles in their forehead or jaw, as this will introduce noise into the EEG data.

After giving these instructions to participants, allow them to view a computer screen with the active EEG signals. Ask participants to blink eyes, and then observe the effect on EEG signal. Emphasize that these large changes in the signal make it hard to understand the information that is collected, and so it is important to avoid blinking whenever possible. Repeat procedure with participant raising eyebrows, clenching jaw, and tightening forehead muscles.

Once all the electrode signals look acceptable, begin recording and start the experiment file. If collecting data for an ERP experiment, or other design in which time of stimulus presentation is important for signal processing, observe the first few trials carefully to ensure that the stimulus presentation software is sending "trigger" markers for stimulus presentation. If timing markers are not being sent, data can not be processed using stimulus presentation as a reference point, which is essential for ERP designs.

Save the continuous data file and monitor throughout recording (see **Troubleshooting** for more details of specific things to watch for).

If collecting data for an ERP experiment, in addition to the continuous data file, it may be desirable to view an average data file as trials are run. If both files are being recorded and monitored, be sure to save both files.

17. After data collection is complete carefully remove cap and electrodes from participant. It is desirable to have access to a large sink with a sprayer attachment for the faucet, as well as equipment for hair washing, drying and styling. If such facilities are available, guide participant to sink area and assist with hair and face washing and drying as necessary. If this is not available, participants may use a nearby restroom to clean off some of the gel, and may shower and wash their hair after they return home.

Clean equipment—18. Push the electrodes out of the adapters on cap with the wooden end of a cotton swab. Take care not to bend or damage the leadwire. If the sensor element of the electrodes comes in contact with greasy material (e.g., sweaty fingers), degrease with alcohol prior to washing. Clean caps and electrodes after each use in a mild detergent (e.g., children's shampoo) with a toothbrush. After gently scrubbing with a toothbrush to remove all traces of electrode gel, rinse the cap with water and the electrodes with distilled water. Disinfect caps, electrodes, and combs after each use by soaking in Barbicide disinfectant solution, obtained from a beauty supply shop, for 15 minutes. After soaking in Barbicide, gently rinse with cool water. Remove excess moisture from cap by wrapping in a towel and squeezing gently, and then lay to air dry. Store the electrodes in a dark and dry place.

It is important that EEG equipment be properly and promptly cleaned after each participant. In addition, proper storage is essential for extending the life and preserving the quality of the equipment.

A children's shampoo is good choice of cleanser as dishwashing detergents often leave a film.

The leadwires are made for moderate tension stress, so avoid tangling and contusing whenever possible. With careful handling, a cap system will be serviceable for several years. The life span of chinstraps is extended if they are cleaned separately only when necessary. The electrode manufacturer explicitly warns not to soak electrodes in saline solution or bleach them, as corrosion of connections will result. Do not to autoclave or use other hot sterilization methods as the wire insulation can be damaged

When electrodes are not cleaned sufficiently or are not used for a long time a brown oxidation coating may occur. This coating can be removed by grinding the sensor pellet (electrode) with abrasive paste or sanding paper. The sinter pellet (black part of electrode) is massive and 1 mm thick, so this surface renewal can be repeated several times. Afterwards, clean the electrodes as described above. Sintered electrodes are not really suited for use in a supersonic cleaner. This procedure should be employed as seldom as possible.

ALTERNATE PROTOCOL 1: P50 SUPPRESSION, A MEASURE OF SENSORY GATING

P50 suppression is assessed by measuring EEG responses to repeated pairs of 50-msec auditory clicks separated by about 500 msec, typically presented with inter-pair intervals of about 10 seconds (Adler et al., 1982a). The percentage reduction in the amplitude of the P50 response from the first to the second click is the dependent variable, called "P50 suppression" (see example data Figure 6). This P50 suppression is thought to be a sensory gating mechanism, by which redundant stimuli cause reduced neural activity. One clinical population that does not show this typical response is individuals with schizophrenia. A lack

of P50 suppression in this population has been interpreted as a lack of appropriate “sensory gating” of redundant stimulation, which may contribute to their psychotic symptoms (Braff and Light, 2005).

Additional Materials

Program to deliver clicks as detailed above. These can be programmed in SDI itself, in the EEG acquisition program, or an external program such as E-Prime (Psychology Software Tools, Inc.)

NOTE: For all paradigms that involve the presentation of auditory stimuli, such as P50 or mismatch negativity (Alternate Protocol 2) it is important to perform regular (monthly) calibration of stimuli to ensure no drift in sound intensities over time. Calibration often requires the use of artificial ears or special couplers for accurate and reproducible measurement of sound intensity. These accessories may need to be special ordered to fit the custom application (e.g., ear inserts vs. external headphones). It is acceptable to use headphones to calibrate auditory stimulation system intensity even when using insert earphones.

1. P50 suppression is typically measured at the CZ electrode; as such, the minimum electrode array to collect these data are CZ, a reference electrode, a ground electrode, and external electrodes to monitor eye movements. However, individual differences in anatomy can lead to variation in the scalp maximum for P50, and some labs have made use of this to measure P50 at sites other than CZ. For this paradigm, as well as all EEG experiments, the choice of electrode array and density is a complicated issue, related to where the scalp maximum lies, additional information obtainable from off-midline sites (such as hemispheric asymmetries), and whether the investigator is interested in performing data transformations such as source localization, current-source density transformations, principal components analysis, or independent components analysis. All of these methods require or benefit from multi-electrode scalp arrays, and even for P50, there are examples in the literature of investigators making use of such arrays and data transformations. Refer to published experimental papers to assess what density of electrode array is most appropriate for the type of analyses planned for the P50 data that are collected.

Apply electrodes, insert foam earphones, and load program as detailed in steps 1 - 15 of Basic Protocol 1. Digitize signals at a rate of 1 kHz with system acquisition filter settings at 0.5-100 Hz.

2. Tell participants that during the session they will hear some clicks through the headphones. Ask participants to stay still, awake, and alert. As with all EEG studies, participants should relax their face, and avoid blinking while clicks are playing; instruct participants to try to wait to blink in periods between click pairs. Monitor signal quality during data collection, and make sure to acquire at least 120 trials free of gross artifacts (±50 μV across the 0 to 512 msec following stimuli) before terminating data collection. As many as 200 presentations may be needed to obtain 120 artifact-free trials.

3. After data collection is finished, remove electrode cap and clean equipment as detailed in Steps 16 and 17 of Basic Protocol 1.

Analyze P50 data—4. Analyze P50 suppression at the CZ electrode. Do not score P50s until there are a minimum of 120 artifact-free trials. A trial consists of one click-pair sequence. The 120 trials do not have to be collected sequentially, simply remove trials with artifacts as necessary. Monitor waveforms carefully during testing to ensure that each event-related potential waveform has a P50 component present. Correct continuous data files to

remove eye movements. Eye-blink and eye-movement artifacts in the EEG can either be removed by omitting trials that show evidence of such activity in the HEOG and VEOG electrode channels or by statistical correction of the EEG data using a number of possible algorithms. One common correction is the Semlitsch method implemented in the Neuroscan package, other commonly used methods are the Gratton method, Singular Value Decomposition (Neuroscan), BESA, or independent components analysis. There are many ways to deal with eye-movements and blinks, and there is not a consensus in the field as to which approach is best. Begin to make this decision by exploring the correction options available within the EEG software package used and modify as necessary.

Epoch files −100 to 923 msec relative to the first click. This will ensure that the EEG responses to both the 1st and the 2nd stimuli will be included in the epoch for simultaneous evaluation for artifact and averaging. Also, reject trials with other artifacts such as muscle tension or clipping (see Troubleshooting). Subsequently, the continuous data should be digitally low-pass filtered at 100 Hz before artifact screening to eliminate any residual electrical noise. The artifact-free epochs can then be averaged and digitally bandpass-filtered (10 to 50 Hz) in the frequency domain to prevent temporal aliasing.

Temporal aliasing occurs when the reconstructed signal has a component at a correct frequency, but the amplitude and phase of that component do not match the original continuous signal. For practical considerations, to prevent or reduce aliasing two options are available. First, as is suggested in Alternate Protocol 1 and Alternate Protocol 2, the sampled signal may be bandlimited such that frequency components at or above half of the sampling frequency can be neglected by means of a suitable low-pass filter. Second, the sampling rate may be increased, to above twice the frequencies that are aliasing.

A P50 peak is the maximum positive-going amplitude in the 40-80 msec range following each click. Be sure to check the +/− values on the y-axis because sometimes positive is up-facing and sometimes positive is down-facing, depending on the EEG system. There will be a P50 peak between 40 and 80 msec (P50 to Click 1) and between 540 and 580 msec (P50 to Click 2) relative to presentation of the first click stimulus.

The latency of each P50 peak with respect to its eliciting click must be within 10 ms or else the P50 response to the second click stimulus is considered absent, “gated,” or totally “suppressed.” Some researchers score these suppressed trials as 0.001 μV to avoid divide by zero values if data are exported to a spreadsheet program. Otherwise, these trials can be excluded.

P50 amplitude is the difference between the P50 wave and the preceding negativity. The preceding negativity is located between 30 and 60 msec following each of the clicks. If the negativity that precedes P50 is earlier than 30 msec, then use the amplitude at 30 msec in calculations.

5. Calculate the amplitude of P50 waveform to each click for individual trials:

1st P50 amplitude = 1st P50 peak (μV) minus 1st preceding negativity (μV)

2nd P50 amplitude = 2nd P50 peak (μV) minus 2nd preceding negativity (μV)

Then calculate P50 suppression, which is either the difference between the P50 amplitude to Click 1 and P50 amplitude to Click 2 (P50 Click 1 – P50 Click 2), or the amplitude of the P50 wave to Click 2 divided by the P50 amplitude to Click 1, which gives a suppression ratio. For discussion of the advantages and disadvantages of choosing a difference score or ratio calculation please see Commentary, Background Information, *P50 suppression*; some

studies perform both analyses and compare results to verify findings are consistent with both methods.

Figure 7 shows an ideal waveform. Usually the P50 waveform is between 1-4 μV in amplitude (difference between preceding negativity and P50 peak).

ALTERNATE PROTOCOL 2: MISMATCH NEGATIVTY (MMN), A MEASURE OF EARLY AUDITORY CHANGE DETECTION

Mismatch negativity (MMN) is an event-related potential (ERP) component that reflects a largely automatic and preattentive form of sensory processing. The MMN wave is automatically generated when a sequence of “standard” repetitive stimuli is interrupted by infrequent “deviant” stimuli (e.g., stimuli that differ in duration or pitch from the more frequently presented “standard” stimuli). A “standard” tone might be presented on 90% of trials, with the deviant tone on 10% of trials. The MMN response onset occurs as early as 50 msec following deviant stimuli and peaks after an additional 100-150 msec.

At frontocentral electrodes, the MMN wave is sometimes followed by a positive-going ERP component that peaks 250-300 msec after deviant stimulus presentation. In the paradigm described below, based on (Michie, 2001) that has been used to investigate MMN deficits in patients with schizophrenia (Light and Braff, 2005a; Light and Braff, 2005b) this “P3a” component is present in the MMN difference waveforms. The presence of P3a in a MMN paradigm depends on the ability of the deviant stimuli to covertly capture attention. P3a is thought to reflect an automatic re-orienting or shifting of attention. Typically, the P3a is elicited in response to occasional “distracter” stimuli when the subject is actively trying to detect infrequent target stimuli (e.g., of a different pitch) embedded in a stream of frequently presented standard stimuli (Dien et al., 2004; Grillon et al., 1990; Naatanen, 1992; Polich and Criado, 2006; Squires et al., 1975; Turetsky et al., 1998).

Additional Materials

Program to present standard and deviant stimuli spaced about 500 msec apart. See Additional Materials, Alternate Protocol 1 above for program suggestions.

Computer or TV screen to present distracter task; specific equipment needed depends on task employed, more details in Step 1 of Alternate Protocol 2 below.

NOTE: For all paradigms that involve the presentation of auditory stimuli it is important to perform regular (monthly) calibration of stimuli. See beginning of Alternate Protocol 1 for more details.

1. Most MMN paradigms employ some kind of “distracter” task to engage participants’ attention away from the noises presented in the auditory stream. In the literature, these tasks range from relatively passive tasks, such as watching a silent video (Light and Braff, 2005a; Light and Braff, 2005b; Light et al., 2007) to more complex tasks such as reading (Sams et al., 1985), visual discrimination tasks (Muller-Gass et al., 2006), or playing a video game (Woods et al., 1992). The specific parameters described in this protocol had used viewing a silent video as the distracter task (Light and Braff, 2005a; Light and Braff, 2005b; Light et al., 2007)

2. As for all EEG studies, the choice of electrode array depends on the nature of the study questions and the type of analysis conducted. For most MMN studies, it is important to collect data from at least FZ electrode as well as mastoids. Adding more electrodes will allow for source localization and for principle or independent components analyses. A

suggested array is listed below, but refer to published experimental papers that have performed the planned analyses to ensure sufficient electrode placement.

Prepare and apply the following electrodes: FP1, FP2, FZ, F3, F4, F7, F8, FC1, FC2, FC5, FC6, CZ, C3, C4, CP1, CP2, CP5, CP6, Pz, P3, P4, P7, P8, O1, O2, PO9, PO10, Iz, T1, T2, T7, T8, TP9, and TP10 as directed in Steps 1 – 13 of Basic Protocol 1.

The choice of a reference electrode is especially important for MMN paradigms, as there is another ERP component, the N2b, which can be elicited under similar experimental circumstances and may contaminate MMN measurements. One important difference between the MMN and the N2b is that the MMN waveform will flip in polarity (that is, switch from a negative wave to a positive wave) at the mastoids, whereas the N2b does not. As such, this is an essential check to ensure one is really measuring the MMN component.

To do this, it is important to collect data from the mastoid sites. Is it also important to not use these mastoid sites as the reference electrode so this check can be performed. As such, the nose is recommended as the reference electrode for MMN paradigms, which preserves the mastoid signals for these analyses.

3. Insert foam earphones into participants' ear and load program as directed in Steps 15 and 16 of Basic Protocol 1. Set up necessary equipment for presentation of distracter task.

4. Instruct participants that during the session they will hear some noises coming through the headphones. Tell them they do not need to pay attention to the noises, but rather to focus on the other task presented (e.g. watching a silent video, or a more complex task, depending on study design). Explain instructions for distracter tasks as needed. Ask participants to stay still, awake, and alert. As with all EEG studies participants should relax their face and avoid excessive blinking during data collection as much as possible.

Analyze MMN data—5. Do not score MMN data until a sufficient number of artifact-free responses to deviant stimuli have been obtained. Correct continuous data files for eye movements and epoch data relative to the onset of stimuli (−100 to 500 msec), centered at the mean of the prestimulus baseline. Reject epochs containing > ±50 μV in frontal recording sites.

There is no clearly established method for determining the optimal number of responses to obtain as it will depend upon the participant population, deviant probability, and how distinct the deviant stimulus is from the standard in terms of its physical properties. Consult published literature using the specific MMN paradigm of interest for estimates of the number of deviant trials required. In one example using duration-deviant stimuli designed for schizophrenia research applications (Light and Braff, 2005a; Light and Braff, 2005b), a minimum of 225 artifact-free trials in response to the deviant tones were collected at data acquisition (see Figure 8 for schematic of paradigm).

6. Average EEG responses to standard and deviant stimuli separately to create a standard ERP and a deviant ERP.

7. To generate MMN waveforms, subtract the ERPs in response to standard tones from the ERPs generated in response to the deviant tones. Low-pass filter MMN waves at 20 Hz (0-phase shift and 24-dB/octave roll-off) to remove any residual high-frequency artifact. The precise time window in which to examine MMN will depend on the characteristics of the deviant stimulus as well individual variability within participant samples. For a paradigm similar to that of Michie et al. (Michie, 2001)(also used in (Light and Braff, 2005a; Light

and Braff, 2005b), one can determine the MMN amplitude as the mean voltage from 135 to 205 milliseconds, and calculate the peak latencies and mean amplitudes of MMN across the 135-205 ms range. However, a more sophisticated method of analysis which may be preferable for some studies is find MMN peaks in the difference waveforms for individual participants and use either the amplitude and latency of that peak itself, or calculate the area approximately +/− 25 ms around that peak.

As can be seen in Figure 8, using the specific MMN parameters above allows for the detection of a P3a component in the difference waveform. However, for some MMN paradigms, in which the deviant stimuli may not be as salient, P3a will not be present in difference waveforms. Indeed, most studies that are interested in P3a components in isolation do not employ a subtraction method (deviant - standard) to detect the component, but rather directly compare ERP responses to standard stimuli to those of deviant/oddball stimuli (Polich and Criado, 2006;Turetsky et al., 1998;Mathalon et al., 2000).

COMMENTARY

Background Information

Electroencephalography (EEG) is an index of neurophysiological activity that measures the electrical activity of large, synchronously firing populations of neurons at the scalp level. The major advantage of EEG compared to other methods is the excellent temporal resolution, allowing for investigation of neural activity at the level of milliseconds, which best approximates the timing of neural events. EEG is also a non-invasive method which poses no risks and minimal discomfort to experimental participants. From a practical standpoint, there is a large, initial investment in setting up an EEG laboratory. However, maintenance and upkeep costs are relatively minimal compared to other methods like functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) which may cost several hundred dollars per hour of imaging.

The following limitations should be considered before beginning an EEG study.

1. Determining the neural generators of EEG signals is a computation-heavy process with limited inferential power, as any observed pattern of EEG activity could possibly be caused by an infinite number of neural generator combinations (the so-called “inverse problem”)
2. EEG has relatively poor spatial resolution compared to other neuroimaging methods, like fMRI.
3. Due to the physical properties of how neuronal signals are picked up by the EEG electrodes, this method is most sensitive to activity of populations of neurons on gyri, versus sulci.
4. As EEG measures electrical activity at the scalp, the neural signal is “smeared” by the meninges, cerebrospinal fluid, and the skull.

P50 Suppression—Schizophrenia is conceptualized as a disorder with functional deficits in many areas, including the interrelated domains of attention, cognition, and information processing. Various measures have been used to identify and assess the core cognitive and attentional deficits present in schizophrenia patients. One such indicator is P50 suppression, an operational measure of sensory gating. The P50 is a small-amplitude, positive event-related potential that occurs about 50 msec after an auditory stimulus. P50 suppression is assessed by measuring electroencephalographic (EEG) responses to repeated pairs of clicks separated by about 500 msec, typically presented with inter-pair intervals of about 10 sec (Adler et al., 1982b).

There has been much debate in the P50 literature regarding the optimal means of scoring and interpreting P50 data obtained from the traditional paired-click "gating" paradigm, including whether quantifying P50 suppression using a ratio or as difference score is more appropriate. Traditionally, P50 suppression has been measured as suppression ratio of P50 to Click 2/ P50 to Click 1. One advantage to a ratio calculation is that this method may be more robust to an apparent decrease in P50 amplitudes to the first click over the last 20 years (Light and Braff, 1998), particularly for between group comparisons. However, several additional factors argue in favor of quantifying P50 suppression the difference between Click 1 and Click 2, including higher test-retest reliability (Rentzsch et al., 2008) and higher heritability (Greenwood et al., 2007).

In the P50 suppression paradigm, most normal individuals exhibit robust suppression whereas patients with schizophrenia exhibit significantly less suppression (Adler et al., 1982b). This lack of P50 suppression has been interpreted as a lack of appropriate "sensory gating" of redundant stimulation. Deficient P50 suppression in schizophrenia patients has been confirmed repeatedly (e.g., (Boutros et al., 1991; Braff and Geyer, 1990; Clementz et al., 1998; Griffith et al., 1998). The deficient P50 suppression observed in schizophrenia participants has prompted further studies to clarify the clinical and neural substrates of this finding. Poor P50 suppression also occurs among nonpsychotic family members of patients with schizophrenia (e.g., (Cadenhead et al., 2005; Freedman et al., 1997), indicating that these deficits are not sufficient to produce the syndrome of schizophrenia but may reflect an intermediate phenotypic marker. Furthermore, while this issue remains controversial, it has been suggested that schizophrenia patients and unaffected family members have large effect size deficits in their P50 ERP responses to the initial (S1) stimuli, substantially contributing to their deficits in the relative "gating" of S2 responses (Adler et al., 1982a; Turetsky et al., 2007).

Mismatch Negativity—Mismatch negativity (MMN) is an ERP component that reflects a largely automatic and preattentive form of sensory processing. The MMN wave is automatically generated when a sequence of "standard" repetitive stimuli (e.g., 90% of trials) is interrupted by infrequent (e.g., 10% of trials), "deviant" stimuli (e.g., stimuli that differ in duration, pitch, or some other feature from the more frequently presented "standard" stimuli). The MMN response onset occurs as early as 50 msec following deviant stimuli and peaks after an additional 100-150 msec.

Physiologically, MMN is the first measurable brain response that differentiates deviant vs. standard stimuli (Naatanen et al., 1989). MMN is not under participant control, requires no overt behavioral responses, can be elicited while participants perform other mental activities in parallel without apparent interaction or interference and is to a large extent unaffected by top-down information processing (Naatanen, 1992; Rinne et al., 2001; Sussman et al., 2003). Indeed, the mismatch response is evoked regardless of whether participants are even remotely aware of subtle, task-irrelevant deviant stimuli in the environment. In this context, it is striking that well-defined MMN waveforms can be obtained from sleeping infants (Cheour-Luhtanen et al., 1996) and adults (Nashida et al., 2000) and even comatose individuals who ultimately regain consciousness (Fischer et al., 1999). Since MMN occurs even in the absence of conscious and effortful attention, it appears to index a preattentive form of sensory memory (Naatanen, 1992) that may "govern" some higher order physiological and behavioral cognitive operations in normal participants (Tiitinen et al., 1994). A variety of complex MMN paradigms have also been developed to assess higher cognitive processes beyond simple auditory change detection (e.g., discrimination of abstract sound patterns, sorting of multi-channel input into sources, temporal grouping, anticipation of sounds; cf., (Naatanen et al., 2001).

MMN has many uses for basic cognitive neuroscience and clinical science (Michie, 2001). First, MMN can be rapidly assessed and is highly stable over time (Light and Braff, 2005a; Light and Braff, 2005b; Pekkonen et al., 1995). Second, since the mismatch response appears to reflect a predominantly automatic process, it allows investigators to interrogate the earliest stages of information processing free of attentional and motivational artifacts that may confound the assessment of some higher cognitive operations in clinical populations such as schizophrenia patients (Braff and Light, 2004).

At frontocentral electrodes, the MMN wave is often followed by a positive-going ERP component that peaks 250-300 msec. This "P3a" component is thought to reflect an automatic re-orienting or shifting of attention. Typically, the P3a is elicited in response to occasional "distracter" stimuli when the subject is actively trying to detect infrequent target stimuli (e.g., of a different pitch) embedded in a stream of frequently presented standard stimuli (e.g., (Dien et al., 2004; Grillon et al., 1990; Turetsky et al., 2007). Unfortunately, the corresponding cognitive process associated with the P3a waveform is not as well understood in the context of a traditional, passive MMN experiment where attention is commonly directed away to some other task such as watching a silent video.

Many studies have convincingly demonstrated that patients with schizophrenia have robust deficits in MMN (cf. Michie, 2001; Turetsky et al., 2007; Umbricht and Krljes, 2005) and P3a (e.g., Turetsky et al., 1998; Mathalon et al., 2000; Griffith et al., 1998); such that patients show a reduction in the amplitude of both components compared to normal individuals (see Figure 9). MMN deficits appear to be specific to schizophrenia relative to many other severe and persistent mental illnesses such as bipolar, major depressive, (Catts et al., 1995) and obsessive-compulsive disorders (Oades et al., 1997). Remarkably, MMN deficits in schizophrenia patients are highly associated with patients' impairments in daily functioning, level of independence in their community living situation, and functional outcome (Light and Braff, 2005a; Light and Braff, 2005b; Kawakubo and Kasai, 2006). Across studies, schizophrenia patients with more severe functional impairments had relatively smaller (i.e., less negative) MMNs than higher functioning patients.

Specifically, the authors of this unit recently (Light and Braff, 2005a) reported that tone-duration MMN deficits in schizophrenia patients were highly associated (r=−0.65) with clinician ratings of global daily functioning in 25 chronic schizophrenia patients. This correlation between MMN and functioning followed the same frontocentral topographic distribution as MMN deficits in schizophrenia patients, further indicating an overlap in the neural bases of these factors. In a related study of patients longitudinally assessed over a 15-month interval (Light and Braff, 2005b), it was confirmed that the MMN deficits in schizophrenia were highly associated with ratings of functional status at both the first (r= −0.63) and second (r=−0.68) test session, indicating that the MMN-functioning relationship is stable even across relatively long time intervals. This association of MMN and functional deficits in schizophrenia patients has been replicated and extended by an independent research group, where a relationship was observed between functional deficits and MMN in response to a duration-change of Japanese speech sounds (r=−0.53; Kawakubo and Kasai, 2006). Other studies of schizophrenia patients have found relationships between MMN and verbal memory deficits (Baldeweg et al., 2004; Kawakubo et al., 2006).

It has also recently been shown that MMN amplitude is associated with higher-order cognitive and psychosocial functioning in normal adults, as indexed by performance on a standardized memory task, and overall ratings of psychosocial functioning (Light et al., 2007), indicating that the cognitive implications of MMN may not be limited to special populations. These data indicate that early CNS information processing in clinically normal individuals is strongly associated with cognitive and real-world psychosocial functioning.

Despite relatively intact MNN amplitudes in this sample, the participants still exhibited enough variation in performance and functional variables to reveal robust associations among disparate measures (i.e., EEG, cognitive, and functional).

Thus, MMN and P3a reflect processes that both contribute to inter-individual variance in normal populations, and are sensitive to neurobiological disturbances linked to schizophrenia (cf., Braff and Light, 2005). Finer parsing of domains of functioning may reveal that measures of early information processing are associated with distinct aspects of normal function in healthy subjects (e.g., work satisfaction) versus more pathological components of functioning in schizophrenia patients (e.g., inability to tolerate interactions with others). This finer parsing of function is currently being investigated to assess the contribution of early information processing abnormalities to the cognitive and functional impairments of patients with schizophrenia.

P50, MMN, and P3a can also be used as endophenotypes to probe the genetic substrates of early automatic sensory processing in normal and clinical populations. In addition, these measures are being used increasingly in a variety of drug development applications including: “proof-of-concept” studies designed to determine if a drug has an effect on brain functions, as a test of normalization of aberrant levels of sensory processing following acute drug administration, as a predictor of long-term treatment-related outcomes, or as outcome measures themselves (Braff and Light, 2005; Braff and Light, 2004; Kawakubo and Kasai, 2006; Braff et al., 2008; Kawakubo et al., 2007).

Critical Parameters

Essential to the collection of good EEG data is achieving low impedances (between 1 and 5 kΩ) on all electrodes, especially the reference and the ground. Proper insertion of foam ear plugs is important to ensure that only the experimentally delivered auditory stimuli are represented in the EEG trace. During data collection, it is important to monitor and remind participants to relax their facial muscles, and avoid blinks during critical parts of data collection to maximize usable data for analysis

Troubleshooting

Eye blinks—Blinks can affect the EEG data. In Figure 10 for example, the large deviations in the SEOG channel is an eye blink. If the blinks occur between stimuli they do not affect the data and the trial can be used. If blinks are interfering with collecting clean data, pause data collection and remind the participant to relax their eyes.

Muscle Tension—EEG data can also be affected by muscle tension. Figure 11 shows both muscle tension and blinks. If this happens frequently during the experimental session, pause data collection and remind the participant to relax their forehead and jaw.

Clipping—Another common problem is amplifier saturation, often referred to as “clipping”. Clipping will appear in the EEG trace as a flat line at a given electrode (at SEOG in Figure 12). Occasional clipping can be minimized by ensuring low impedance is achieved for each electrode prior to beginning data collection. Usually the amplifiers will come back online within several seconds and clipping will terminate on its own. There is no good method to stop this occasional clipping as it occurs, and these segments of data will be excluded from analysis. If possible, within the experimental session, increase data collection to account for this data loss. If clipping occurs regularly, however, this may indicate that the gain of the amplifier is set too high, so that measured voltages often exceed the available range. This can be corrected by lowering the gain so that measured voltages fill the available range without exceeding the upper limits.

Anticipated Results

For the P50 paradigm in a population of normal individuals, suppression ratios within the range of 50%–70% are expected for most participants. Low suppression ratios have been interpreted as a lack of appropriate sensory gating (see Background Information, *P50* for more information).

For the MMN paradigm in a population of normal individuals, difference waves between the standard and deviant ERPs are expected to show a negativity in the range of 135-205 ms (the MMN) and a positivity in the range of 250-300 ms (the P3a). This paradigm often reveals deficits in neuropsychiatric and neurodevelopmental populations. MMN and P3a can be elicited with auditory stimuli that are deviant along a variety of dimensions, for example pitch, duration, intensity, speech sounds, and spatial location.

The presence of an MMN/P3a complex is considered indicative of intact early auditory change detection mechanisms. Differences in the peak amplitude and latency of the MMN and P3a components, between participant populations, or experimental conditions, are indicative of variations in this early processing. Lower peak amplitudes of these waveforms are often interpreted as reduced resource availability for these preattentive processes, or reduced neural efficiency at distinct stages of processing (i.e., MMN vs. P3a vs. later components). A later latency (onset) of these components is often interpreted as reduced speed of processing. For example, individuals with schizophrenia show reduced MMN amplitudes compared to normal individuals, which is interpreted as a deficit of early auditory change detection in this population, which may have downstream effects on cognition and function (for more details see Background Information, MMN).

Time Considerations

The EEG capping procedure usually takes 25-35 minutes to complete. Data collection sessions vary widely, depending on the number of trials, and the ability of participants to relax muscles, refrain from blinking, and stay alert during the session. Typical EEG experiments have between 16 and 20 participants per group or condition of interest, though the number of participants needed will vary based on number of trials collected per participant, and the size of the effect that is being tested. Power calculations should be performed during the experimental design phase to determine the necessary number of trials and number of participants. A review of the literature relevant to the question of interest will also provide an idea of the number of trails/participants that should be included.

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Appendix

SUPPLIERS INDEX

EEG Equipment:

EASYCAP GmbH

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Phone 011 49 8152 3722-24

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Web: http://www.easycap.de/easycap/

info@easycap.de

Insert Earphones:

3M

http://www.aearo.com/ - Select E.A.R link

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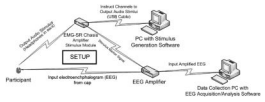

Figure 1.
Schematic overview of EEG setup. Stimulus generation computer outputs stimuli (in this example auditory) to the participant via the stimulus amplifier. EEG data collected by electrode cap on participant's head is relayed to EEG amplifier and integrated with information about timing of stimulus presentation. Amplified EEG data with stimulus markers is then relayed to acquisition computer for data analysis.

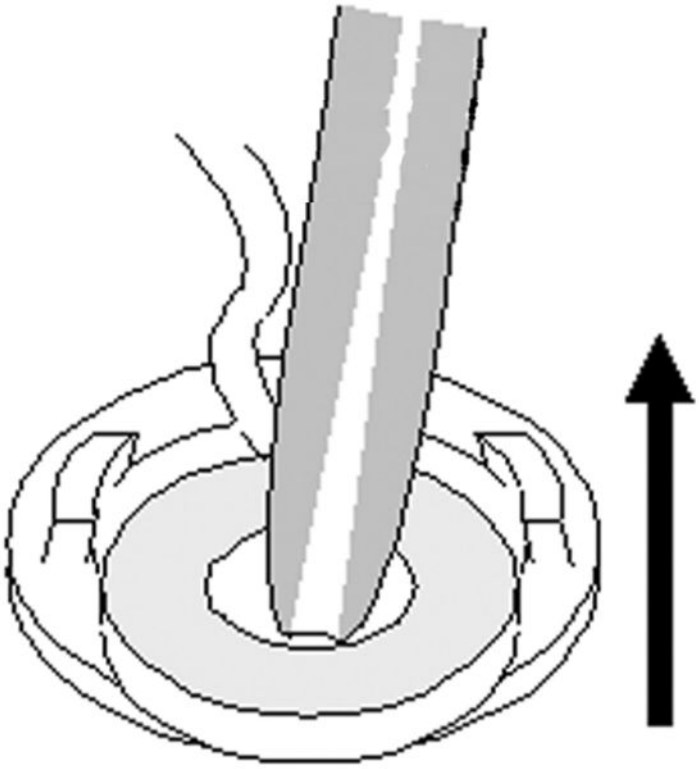

Figure 2.
Snapping in electrode. Place electrode over white plastic adaptors on electrode cap, with leadwire placed in the narrow opening between raised plastic ridges. Use a narrow tool such as the wooden end of a cotton swab or an old ink pen to firmly snap electrodes into electrode collar, pushing towards narrow side of adaptor as indicated by arrow. Figure used with permission from Easycap GmbH.

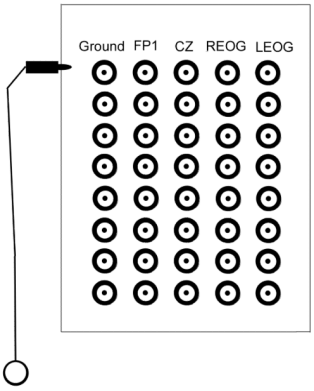

Figure 3.
Schematic of EEG amplifier. Specifics will vary according to manufacturer, but will include plugs for EEG channels to be measured. Plug the electrode from the corresponding channel position on EEG cap into the appropriate plug. Some amplifiers will come with channels already labeled, some may need to be labeled by hand. In this diagram the top row of plugs are labeled as an illustration, with the plugs for the Ground, FP1, CZ, REOG and LEOG channels.

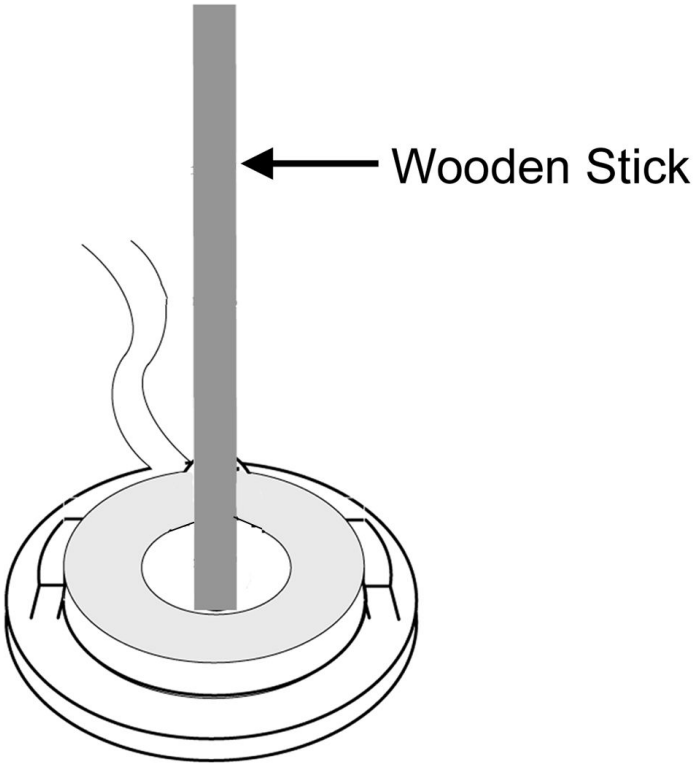

Figure 4.
Minimizing impedances. Insert wooden end of a cotton swab into center of electrode and gently push hair to one side. You may need to lift electrode and adaptor away from scalp a bit to ensure that scalp is clearly visible. Figure used with permission from Easycap GmbH.

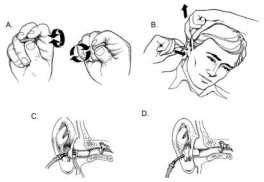

Figure 5.
Insertion of foam eartips. A. Roll eartips between fingers to form narrow cylinder prior to insertion. B. Proper insertion of eartips is easier if the ear canal is straightened and enlarged by gently pulling the outer ear (pinna) outward and upward during insertion. Pull the pinna gently but firmly, usually in the direction the ear extends from the head. C. An example of a well inserted eartip, with no foam visible outside of ear. D. An example of an eartip with a shallow insertion. Figures A and B represent insertion of foam eartips and are provided by 3M, Indianapolis, IN. Figures C and D represent E-A-RLink©, a trademark licensed to, and a product manufactured by 3M Occupational Health and Environmental Safety Division, Indianapolis, IN.

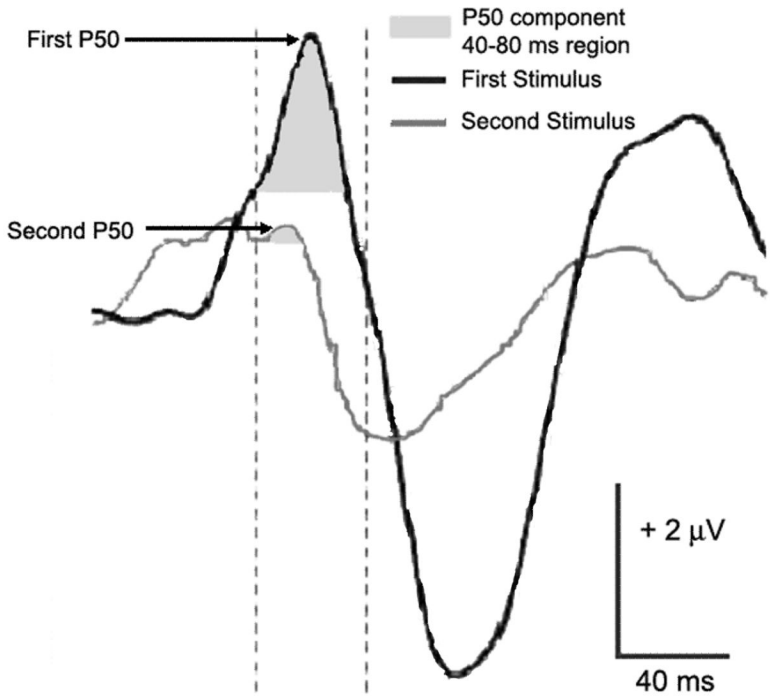

Figure 6.

Example P50 waveforms. Overlay of neural responses to first click stimulus (black line - First P50) and second click stimulus (grey line - Second P50). Shaded area indicates range of P50 component. This example shows robust suppression of the P50 wave from the first P50 to second P50.

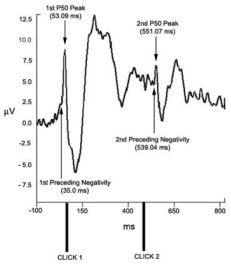

Figure 7.

Example EEG trace generated in response to 2 auditory clicks (50 ms duration), one at 0 ms, and the other at 500 ms. Time points relevant to computing P50 suppression ratio are labeled. For 1st peak, point of maximum amplitude between 40 and 80 ms following presentation of first click (at 53.09 ms), and amplitude of negative-going portion of EEG trace immediately prior to that peak (at 35.0 ms). For 2nd peak, point of maximum amplitude between 540 and 580 ms following presentation of first click (at 551.07 ms), and amplitude of negative-going portion of EEG trace immediately prior to that peak (at 539.04 ms).

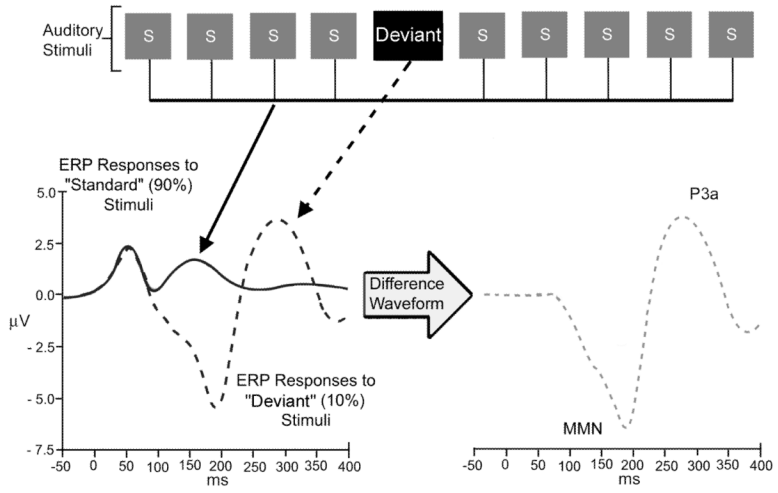

Figure 8.

Schematic for mismatch negativity (MMN) ERP design. Participants are presented with stimuli consisting of primarily “standard” stimuli (90% of trails; grey box labeled “S” in figure) with rare, “deviant” trials interspersed on 10% of trials. ERP waves to Standard (solid black line) and Deviant (dashed black line) are calculated by averaging EEG responses to each stimulus type. Subtracting the Standard ERP from the Deviant ERP yields the MMN-P3a waveform (dashed grey line).

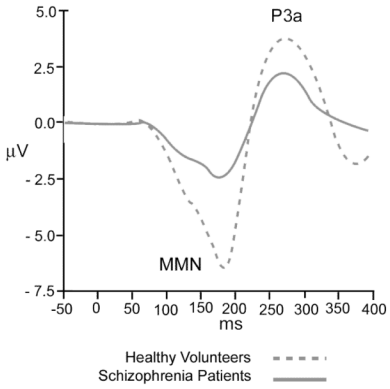

Figure 9.

MMN/P3a waveforms for healthy volunteer participants (dashed grey line) and schizophrenia patients (solid grey line). Compared to healthy individuals, schizophrenia patients have reduced amplitude of the MMN and P3a waveforms. This difference is though to be indicative of disrupted early auditory processing in this population.

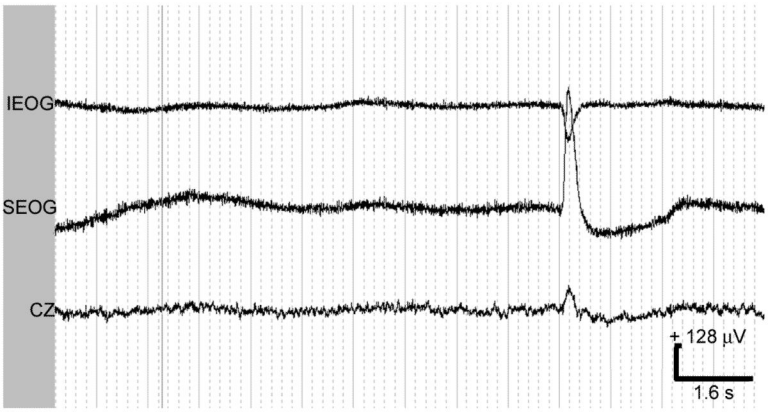

Figure 10.
Example of EEG waveforms when participant has blinked eyes. Sharp spike in activity at SEOG electrode is an eye blink.

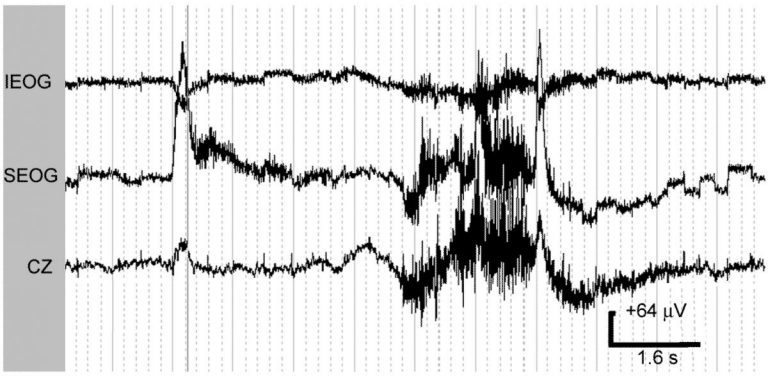

Figure 11.
EEG trace with blinks and muscle tension. Sharp spikes in activity at SEOG electrode are blinks, and thick black traces at all electrodes shown (though most prominent at SEOG and CA) are periods of muscle tension.

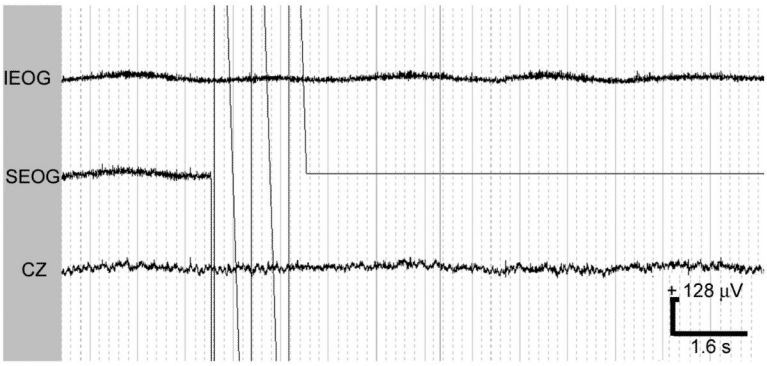

Figure 12.
EEG trace with clipping. Flat line at SEOG electrode is an example of electrode clipping.