Event-related potentials in clinical research: Guidelines for eliciting, recording, and quantifying mismatch negativity, P300, and N400

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Abstract
This paper describes recommended methods for the use of event-related brain potentials (ERPs) in clinical research and reviews applications to a variety of psychiatric and neurological disorders. Techniques are presented for eliciting, recording, and quantifying three major cognitive components with confirmed clinical utility: mismatch negativity (MMN), P300, and N400. Also highlighted are applications of each of the components as methods of investigating central nervous system pathology. The guidelines are intended to assist investigators who use ERPs in clinical research, in an effort to provide clear and concise recommendations and thereby to standardize methodology and facilitate comparability of data across laboratories.

Keywords

Event-related potentials; Mismatch negativity; MMN; P300; N400; Guidelines; Clinical investigations

1. Introduction

1.1 Event-related potentials defined

Event-related potentials (ERPs) are one of the most informative and dynamic methods of monitoring the information stream in the living brain. The voltage deflections comprising the ERP reflect the reception and processing of sensory information as well as higher level processing that involves selective attention, memory updating, semantic comprehension, and other types of cognitive activity. ERPs are linked in time with a physical or mental event, and are typically extracted from the scalp-recorded electroencephalogram (EEG) by means of signal averaging. An ERP component is defined by its positive or negative polarity,[1] its latency, its scalp distribution, and its relation to experimental variables. ERPs provide a noninvasive method of studying, with exceptional temporal resolution, cognitive processes in the normal human brain, and can therefore also provide a means of assessing pathological states.

The sequence and latencies of ERP components track the time course of processing activity in milliseconds, whereas their amplitudes indicate the extent of allocation of neural resources to specific cognitive processes. ERPs are sensitive to variables related to information processing (e.g., auditory discrimination acuity, expectancy, semantic processing) and complement traditional and limited performance measures, such as the accuracy and speed of behavioral responses. The cognitive operations reflected in ERP components are supported by specific brain systems, which, in some cases, have been delineated (e.g., Giard et al., 1995; Pineda, 1995; Nieuwenhuis et al., 2005). Deviations in components can therefore lead to inferences about the nature and locus of brain dysfunction. The brain structures and systems that generate long-latency components are more complex than those underlying shorter latency, sensory components. Nevertheless, as the neural generators of these cognitive components are characterized with greater specificity, abnormalities in their amplitude, latency, or scalp distribution will provide useful diagnostic information. Indeed, ERPs have recently shown promise as measures of injury severity, and have value in predicting recovery from stroke and other brain trauma as well (e.g., Fischer et al., 1999, 2000, 2004, 2006).

1.2 ERPs in clinical research

Notwithstanding the utility of this highly informative assay, the methods and procedures for applying cognitive ERPs in investigations of clinical disorders have not been standardized as systematically as those for sensory evoked potentials (Chiappa, 1997). The Executive Board of the International Federation of Clinical Neurophysiology (IFCN) therefore requested that we develop guidelines for using cognitive ERPs to evaluate brain function in clinical populations.

Our focus is on three major cognitive components with established clinical utility: mismatch negativity (MMN), P300, and N400. Each of these ERP components has been well characterized in terms of eliciting stimuli, technical recording methods, and quantification. Moreover, each component has been operationally related to the neurocognitive process it reflects. Basic research on these components has led to their application to investigation of clinical disorders, where they have demonstrated significant promise. Although other cognitive ERPs have also been applied to address clinical issues (e.g., contingent negative variation, error- related negativity), the clinical

[1] *i.e., voltage difference between the recording and reference electrodes.*

databases for those components are not as well developed as they are for the components outlined here, and the methodologies used are considerably more variable.

In addition to reviewing recommended procedures for recording each of these components, examples are provided to illustrate their application to investigations of normal functioning, normal development, and neurobehavioral pathology. The choice of exemplar disorders is intended to illustrate how these cognitive components can be used in research. An exhaustive review of all clinical applications was avoided as exceeding the present goals. However, apposite entry points into the relevant literature are provided with references to review papers. Methodological recommendations in the context of clinical applications are also provided. There is an art to collecting ERPs from uncooperative or disturbed patients, children, uncommunicative individuals, etc. Just as the clinical sensory evoked potential laboratory develops methods, procedures, and normative values, the clinical researcher using cognitive ERPs needs to establish effective paradigms to ensure that high-quality ERP data are acquired. This information comes with a firm grounding in the basics of the technique in conjunction with patient experience. The present report provides an outline; the reader must supply the text.

2. Mismatch negativity

2.1. Overview

The mismatch negativity (MMN; Näätänen et al., 1978; for reviews, see Näätänen and Winkler, 1999; Näätänen et al., 2007) and its magnetoencephalographic equivalent, MMNm, are elicited by any discriminable change in auditory stimulation. This component is thought to reflect an automatic process that detects a difference between an incoming stimulus and the sensory memory trace of preceding stimuli. MMN can be elicited even in the absence of the participant's attention, which makes it useful in the assessment of very young or impaired participants. Common procedure in MMN studies involves presentation of a series of identical stimuli with occasional mismatching stimuli. The mismatching stimuli can differ on any discriminable auditory dimension such as pitch, duration, intensity, or location. Hence, one of the stimuli ("standard") occurs frequently (e.g., p = .80), and the other ("deviant") occurs infrequently (p = .20). The two stimuli are usually presented at relatively short interstimulus intervals (ISI), such as 500 ms to 1 s. Table 1 summarizes recommended stimulus attributes.

MMN is typically seen as a fronto-central negativity of approximately 0.5–5 IV in amplitude, occurring in the latency range of 100–250 ms. It exhibits a phase reversal (i.e., positive polarity) over mastoid and other lateral posterior sites over the same latency range when a nose reference is used. The peak latency thus occurs well after the sensory N100 component. MMN amplitude should be quantified after the N100 latency window to avoid contamination of MMN measures by possible differences in the N100 elicited by standards and deviants. As the magnitude of the difference increases between the standard and deviant stimuli, the peak latency of MMN becomes progressively shorter and its peak amplitude larger (see Fig. 1). However, a small MMN can be elicited by even threshold-level differences. MMN can, therefore, be used to evaluate discrimination acuity; it provides what may be the best objective measure available for this purpose.

MMN is generated from the auditory cortices bilaterally, but there may also be a contribution from the right frontal cortex (Giard et al., 1990). The biological function represented by this ERP component is to monitor and detect any change in ongoing auditory stimulation, irrespective of where attention is directed. The MMN subcomponent generated in supratemporal areas is an auditory-cortex marker of a change that occurs automatically (and preperceptually). The frontal MMN subcomponent is a sign that the frontal cortical mechanisms implicated in the recruitment of attention (involuntary attention switching) have been activated in response to a

change in auditory stimulation (Näätänen and Michie, 1979; Giard et al., 1990; Escera et al., 1998, 2001; Rinne et al., 2000).

2.2. Methodology

A typical MMN paradigm comprises a rapidly presented sequence of repeated standard sounds, occasionally interrupted by a rare deviant sound. In clinical applications, the probability of the deviant sound ranges from 0.05 to 0.20. As MMN is a small component, it is highly recommended that the stimulus series be of sufficient duration to achieve an adequate signal-to-noise level. Thus, it is important that the stimulus sequence continues until at least 150 deviant stimuli of each type have been presented. The duration of trial blocks is thus on the order of 6–12 min depending upon the ISI and preferred number of deviant types.

For most purposes, it is sufficient to use 5–10 active electrodes to record MMN, which always include Fz, Cz, C3, C4, and mastoid locations. The preferred reference is the nose, as this method allows both frontal negative and mastoid positive aspects of the signal to be visualized and measured. A recording bandpass of 0.1– 30 Hz is recommended (at least for the awake state), along with a digitization rate of no less than 200 Hz. Further digital filtering of the data may be required to produce a bandpass of 1–20 Hz. MMN is typically extracted in a difference waveform obtained by subtracting the average ERP to the standard stimulus from the average ERP to the deviant stimulus.

The optimal MMN recording conditions are those in which the participant ignores the auditory stimuli – a technique that eliminates other cognitive components elicited during active attention, such as N200 (for a review, see Näätänen and Gaillard, 1983) and P300. A visual distraction task is most commonly used, such as a simple visual discrimination task, watching a movie (with low or no sound levels), or reading a book. Watching an engaging movie with no sound is a frequently used distracter task in clinical studies, as it is well tolerated by most participants.

Recent efforts have been devoted to simplifying and standardizing the MMN recording and analysis methodology. In order for MMN to become a useful tool for clinical practice, it needs to be reliably measurable in individual patients (McGee et al., 1997; Ponton et al., 1997; Ha et al., 2003; Marco-Pallarés et al., 2005). Näätänen et al. (2004) have developed an "optimal" MMN paradigm that yields a multifaceted profile of auditory discrimination abilities with a recording time of approximately 15 min (see also Pakarinen et al., 2007). The deviant tones differ from the standard tones on one of five possible attributes: duration, frequency, spatial location, intensity, or by having a sound gap in the middle of the tone (see Table 1 for stimulus details). Each of the deviants ($p = .10$ each) is presented in the same series with standard tones ($p = .50$), so that a standard alternates with one or the other of the five deviants. The advantage of such a paradigm is that it permits evaluation of specific MMN alterations in a variety of clinical conditions in a manner and amount of time that is feasible for clinical work.

2.3. Clinical applications

A selection of the most studied and most promising clinical applications of MMN will be described.

2.3.1. Coma

To date, the most promising and advanced field of MMN application is in coma monitoring and outcome prediction, in which reappearance of the MMN is a valid predictor of recovery from coma. The capacity of MMN to predict awakening from coma has been investigated in five cohort studies in which MMN and N100 have reliably reflected the functional status of comatose patients (for a review, see Daltrozzo et al., 2007). MMN can be useful in efforts to ascertain perceptual

capabilities of the comatose patient as well as the likelihood of awakening from coma. The presence of MMN recorded during the comatose state is the best predictor of awakening within a 12-month period (Fischer et al., 1999). A positive predictive value for awakening has been reported in 100% of cases in a recent study (Fischer et al., 2006), whereas absence of MMN was predictive of non-awakening in 84% of cases. In predicting awakening, MMN was superior to auditory N100, early somatosensory evoked potentials, N20 and P40, middle latency auditory ERPs, auditory brain stem potentials, and pupillary light reflex. In a decision tree-based analysis to determine the hierarchy of different predictors for awakening and non-awakening, the first predictor to emerge was MMN: Presence of MMN was strongly associated with awakening. The additional observation of absent pupillary reflex or abolished somatosensory N20 and P40s improved the prediction of non-awakening from coma at 12 months. MMN can also be used to predict the outcome and the extent of recovery of patients in a vegetative state (Wijnen et al., 2007).

2.3.2. Schizophrenia

A second clinical disorder studied extensively with MMN is schizophrenia (for a review, see Michie, 2001). A decrease in the amplitude of MMN in patients with schizophrenia is a robust and consistent finding in biological psychiatry. In a recent meta-analysis, out of a total of 62 published studies, 32 met criteria for inclusion (Umbricht and Krljes, 2005). The overall effect size of the difference in MMN amplitude between patients and healthy controls was 0.99[2] (95% confidence interval, range = 0.79–1.29) for frequency or duration deviants. MMN to duration deviants produced a larger effect size than MMN to frequency deviants, suggesting that processing of duration deviants is more impaired than that to frequency deviants (see Michie et al., 2000), although this difference in effect size was not statistically significant. However, frequency MMN was related to length of disorder, whereas duration MMN was not. Recent evidence (Todd et al., 2008) suggests that duration MMN is reduced early in the course of the illness and in younger patients; however, a reduction in frequency MMN, not evident at this early stage, emerges with a longer duration of illness and increasing age of the patients. MMN to intensity deviants showed a similar pattern to duration deviants (see Fig. 2).

In a recent study (Salisbury et al., 2007; see also Salisbury et al., 2002), schizophrenia patients at initial hospitalization, bipolar disorder patients, and healthy controls did not differ from each other in the amplitude of frequency-change MMN. At a follow-up evaluation 18 months later, only the patients with schizophrenia showed smaller MMN amplitude; this was highly correlated with a reduction in left-hemisphere Heschl Gyrus volume. This finding suggests that MMN could have major theoretical and clinical implications for understanding and treating schizophrenia (van der Stelt and Belger, 2007).

The reduction in amplitude of MMN in patients with schizophrenia has been attributed to the impaired functional condition of the NMDA[3] -receptor system (Javitt et al., 1996; Umbricht et al., 2003) involved in auditory memory-trace formation. A defect in this mechanism may also account in part for the impaired central auditory processing in these patients. Furthermore, MMN amplitude reduction could also reflect impairment of the frontal-cortical mechanism implicated in switching involuntary attention (Baldeweg et al., 2002). This weakening of the appropriate attention-switching response may contribute to the social withdrawal exhibited by patients with

[2] It should be noted that the effect size was reduced (0.65) when potential publication bias was addressed.
[3] The NMDA receptor (NMDAR) is an ionotropic receptor for glutamate. NMDA (Nmethyl d-aspartate) is a name of its selective specific agonist. Activation of NMDA receptors results in the opening of an ion channel that is nonselective to cations. This allows the flow of Na+ and K+ ions, and small amounts of Ca2+. Calcium flux through NMDARs is thought to play a critical role in synaptic plasticity, a cellular mechanism for learning and memory.

schizophrenia: Ordinary social interaction requires adaptive switches of attention, depending on context; patients with schizophrenia are unable to switch adaptively and may ultimately withdraw from social interactions.

In their seminal paper, Light and Braff (2005) demonstrated a close association between attenuation of duration MMN amplitude and functional outcome as assessed with the scale for the Global Assessment of Functioning. This scale, one of the multiaxial ratings in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV, 1994), assesses patients' overall level of functioning, combining psychological, social, and occupational domains. Overall, MMN amplitude at fronto-central sites accounted for approximately 42% of the variance in scores on the Global Assessment of Function. Hence, a significant contribution of MMN to schizophrenia research and treatment lies in its ability to predict patients' functional outcomes and to provide an endophenotype for genetic studies (however, see Bramon et al., 2004). Moreover, there is evidence of a reduction in MMN amplitude in first-degree relatives of patients with schizophrenia (Michie et al., 2002; Jessen et al., 2001) or those with 22q11.2 deletion syndrome. Such persons are at increased risk of schizophrenia (Baker et al., 2005). This outcome suggests that small MMN may also reflect genetic vulnerability to schizophrenia.

2.3.3. Cognitive decline

MMN can also serve as an index of cognitive deterioration in other clinical disorders, such as multiple sclerosis. MMN is reduced in patients with multiple sclerosis, and reductions are more evident in patients with cognitive impairments than in those without cognitive impairments. The amplitude of MMN is thus correlated with cognitive disturbances in patients with multiple sclerosis (Jung et al., 2006).

In studies of aging, MMN has been used to assess the duration of auditory sensory-memory traces (Pekkonen et al., 1996). The duration of the trace, which in young adults is on the order of 5–10 s, decreases gradually over the course of aging. This outcome is thought to reflect a general age-related decrease in brain plasticity, and appears to be accelerated in cases of chronic alcoholism (Polo et al., 1999). Moreover, this decline is notable in degenerative brain disorders such as Alzheimer's disease (Pekkonen et al., 1994).

MMN has also been used to monitor symptomatic changes in recovery from aphasia following left-hemisphere stroke (Ilvonen et al., 2003). In stroke patients, MMN allows a determination of the specific types of auditory discrimination that are affected, such as tonal frequency or speech sounds (Aaltonen et al., 1993).

2.3.4. Childhood disorders

Another important clinical application of MMN involves dyslexia. In children with dyslexia, the amplitude of MMN elicited by a change in tone frequency is reduced considerably. Moreover, the magnitude of this reduction is correlated with the severity of dyslexia (Baldeweg et al., 1999). MMN can also be employed to assess the effectiveness of dyslexia rehabilitation programs (see Kujala et al., 2001).

As MMN can be recorded in infants and young children, it has been used to assess central auditory processing abilities in these groups (Ceponiene et al., 2002). Recent studies (Draganova et al., 2005; Huotilainen, 2005) demonstrate that MMNm can also be recorded from a fetus (through the mother's abdominal wall). In addition, it has been utilized to evaluate the improvement of auditory discrimination after installation of a cochlear implant (Ponton et al., 2000; Lonka et al., 2004).

3. P300

3.1. Overview

The P300 (also known as P3 or P3b) is a large, broad, positive component in the ERP that typically peaks 300 ms or more after onset of a rare, task-relevant stimulus. The P300 has a centro-parietal scalp distribution that is maximal over midline scalp sites. A rare event that is not task-relevant may also elicit a positive-going ERP component that has been labeled "P3a." P3a can be distinguished from P300 on the basis of an earlier peak latency of 250–300 ms and a scalp distribution with a midline fronto-central maximum (Squires et al., 1975). The relation between P3a and P300 has not been fully explicated, and has been the focus of theoretical debate (see Polich, 2007).

The P300, first reported by Sutton et al. (1965), is perhaps the most studied ERP component. It is commonly elicited in the oddball paradigm, in which a random sequence of stimuli is presented. The stimuli can be classified into one of two categories, and the task is to classify the stimuli, either by counting or by pressing a button to members of one category. If stimuli in one of the categories occur infrequently ("oddballs"), they will elicit a P300. As shown in Fig. 3, it is well established that the lower the probability of an attended stimulus, the larger the amplitude of P300 (DuncanJohnson and Donchin, 1977).

However, the time between stimuli also affects P300 amplitude: P300s elicited with shorter ISIs have smaller amplitudes than those obtained with longer ISIs (Picton and Stuss, 1980; Woods and Courchesne, 1986). ISI and the interval between successive target stimuli interact with probability in determining P300 amplitude: When the ISI is 6 s or longer, the influence of stimulus probability wanes considerably (Polich, 1990a,b). When the interval between successive target stimuli is 6–8 s, probability effects are eliminated (Gonsalvez and Polich, 2002).

In addition to global and temporal probability, P300 amplitude is affected by expectancies generated by the sequence of stimuli preceding the eliciting stimulus. For instance, Squires et al. (1976) observed that successive repetitions of stimuli are associated with decreases in P300 amplitude. When the repetition pattern was disrupted, the amplitude of P300 to the immediately following stimulus was shown to vary directly with the length of the preceding run. Moreover, an alternating sequence also generated an expectancy to continue and elicited a larger P300 when the pattern was broken. Target stimuli, i.e., those that require a response, generally elicit larger P300s than nontargets even when they are equal in probability (Duncan-Johnson and Donchin, 1977; see Fig. 3). P300 amplitude is also sensitive to the salience of the eliciting stimulus, that is, its reward value or affective significance (Keil et al., 2002; Yeung and Sanfey, 2004). Finally, subjective probability and salience are modulated by the amount of attentional resources allocated to the stimulus (Isreal et al., 1980b; Kramer et al., 1985; Johnson, 1993; Johnson et al., 2004).

Stimuli that would normally elicit a P300 fail to do so when they are ignored or when attention is directed away from them (e.g., Hillyard et al., 1973; Duncan-Johnson and Donchin, 1977; Johnson and Donchin, 1978) (see Fig. 3). Moreover, in a dual-task paradigm, the P300 to a primary task stimulus varies according to the perceptual demands of the secondary task (Kramer et al., 1983). However, the motor requirements of the secondary task have little or no effect on P300 amplitude (Isreal et al., 1980a). Thus, perceptual and attentional variables influence P300 amplitude, whereas the physical features of the stimuli, or factors affecting response production, have little or no effect.

The inverse relation between stimulus probability and P300 amplitude even for meaningful stimuli (such as male and female names) implies that P300 is elicited only after the stimulus has been evaluated and categorized. Stimuli that are more difficult to categorize (e.g., two tones that differ by only a few Hz) elicit longer latency P300 components. The more complex the stimulus processing required by the task, the longer the latency of P300, which can vary from approximately 250–1000 ms. Whereas P300 latency is sensitive to variables involved in stimulus

evaluation (e.g., Kutas et al., 1977; Squires et al., 1977; Duncan-Johnson, 1981; Duncan-Johnson and Donchin, 1982), it is relatively unaffected by variables that affect response selection and execution (McCarthy and Donchin, 1981; Magliero et al., 1984). P300 latency can therefore be used to decompose the variance in reaction time into the portion associated with stimulus evaluation and the portion associated with response production (Duncan-Johnson and Kopell, 1981; Verleger, 1997; Spencer et al., 2000).

3.1.1. Neural generators of P300

Numerous investigations have attempted to identify the cerebral generators of P300. These studies have involved intracranial or scalp recordings in patients undergoing neurosurgery (Halgren et al., 1980; McCarthy et al., 1989; Smith et al., 1990) and scalp recordings in individuals with well-characterized brain lesions (Knight et al., 1989; Johnson, 1988a,b; Yamaguchi and Knight, 1991, 1992; Polich and Squire, 1993). The fact that P300 is seen simultaneously, with uniform latency, over widespread areas of the scalp (Soltani and Knight, 2000) has suggested either that it is produced by multiple, relatively independent generators or that it is a reflection of a central integrated system with widespread connections and impact throughout the brain (Pineda et al., 1989; Duncan, 2003; Nieuwenhuis et al., 2005).

Consistent with either view is the fact that P300 can be recorded from several cortical and subcortical locations. There appear to be major foci of P300-generating cerebral tissue in the hippocampus, superior temporal sulcus, the ventrolateral prefrontal cortex, and, probably, the intraparietal sulcus (Kiss et al., 1989; Smith et al., 1990; Halgren et al., 1995, 1998). Lesions in the temporal-parietal region have been reported to be associated with reduced P300s to rare, task-relevant stimuli (Knight et al., 1989; Yamaguchi and Knight, 1991, 1992; Verleger et al., 1994). P300 can be recorded from multiple brain regions, including the hippocampus, amygdala, and thalamus. However, unlike the structures within the temporal-parietal junction, lesions in these areas do not alter P300 (Stapleton et al., 1987; Johnson, 1988a,b; Polich and Squire, 1993). Converging evidence suggests that provided part of this complex cortical and subcortical brain system remains intact, the capacity to generate P300 still exists (Halgren et al., 1980; Johnson, 1988a,b; McCarthy et al., 1989; Nieuwenhuis et al., 2005).

3.1.2. Biological factors affecting P300

P300 is affected by naturally occurring alterations in arousal, whether tonic or phasic (Kok, 1990, 1997); variability arising from these sources should be considered, especially when clinical and healthy groups are compared. These biological determinants of P300 may occur spontaneously, be induced by environmental variables, or may stem from individual differences (Polich and Kok, 1995). Some of the determinants affecting P300 amplitude and latency include circadian and other seasonal cycles (Deldin et al., 1994), exercise and fatigue (Yagi et al., 1999), commonly used drugs, age, IQ, handedness, and gender, as well as some personality variables (Polich and Kok, 1995). Moreover, differences related to attentional capacity need to be considered (Kujala and Näätänen, 2003; Näätänen, 1995; Orlebeke et al., 1989; Pelosi et al., 1992a,b; Colet et al., 1993; Stelmack and Houlihan, 1994).

3.1.3. Genetic contributions to P300

Spectral characteristics of the EEG are highly similar for identical twins (Lykken et al., 1974; Stassen et al., 1987), with strong similarities also observed for biologically-related family members (Vogel et al., 1979a,b; Eischen et al., 1995). It is therefore not surprising that P300 characteristics have been found to be strikingly similar between pairs of monozygotic as compared to dyzygotic twins or unrelated controls (Polich and Burns, 1987; O'Connor et al., 1994; Katsanis et al., 1997). Meta-analyses of twin studies (van Beijsterveldt and van Baal,

2002) estimated P300 amplitude heritability to be 60%, with a more recent twin study (Hall et al., 2006) yielding a somewhat higher estimate of 69%. P300 heritability is also reflected in biologically-related family members, who demonstrate significant inter-family member correlations for P300 measures elicited by both auditory and visual stimuli (Eischen and Polich, 1994; Polich and Bloom, 1999). Given these genetic influences, P300 may eventually contribute to understanding the etiology of certain disease endophenotypes (e.g., Porjesz and Begleiter, 1996; Bharath et al., 2000).

3.2. Methodology

Table 2 summarizes recommended parameters for eliciting and recording P300.

3.2.1. Stimuli and tasks

As an index of information processing, P300 is well suited to investigating conditions in which cognition is impaired. The oddball paradigm has been used most frequently in clinical research, because it elicits robust P300s and there is a large database of prior studies. Whereas the oddball task reveals information about how the brain discriminates stimuli and processes probability, its relation to models of cognitive processing is rather general.

The best paradigms are those for which well-developed models of information processing are available. To use P300 as an index of a particular cognitive process, ERPs should be recorded when that process is active. It is advisable, therefore, to devise paradigms in which P300 is recorded when the presumed cognitive process is invoked, as evidenced by behavioral measures. The beginning investigator should take advantage of previous work rather than inventing new paradigms. In particular, when gathering data on previously unstudied populations, the use of an established P300 paradigm is recommended.

In clinical studies, it is essential to adjust the demands of the task to the ability level of the participants, whether children, elderly adults, or persons with a clinical disorder. If the participant is unable to perform the task, no inference about an absence of P300 is possible. In situations in which an active discrimination task cannot be performed, a passive oddball or single stimulus task can be used to elicit a P3a or P300 component (Polich, 1989; Mertens and Polich, 1997). There is converging evidence that P3a is an index of an automatic process involved in orienting to infrequent novel or salient stimuli (Polich, 2007), and is generated by a network of brain regions in the frontal lobes and temporo-parietal cortex (Baudena et al., 1995; Halgren et al., 1995).

3.2.2. Data acquisition

3.2.2.1. Recording and reference sites.

A montage for recording P300 should include the Fz, Cz, and Pz scalp locations, with more extensive electrode arrays recommended to obtain information on scalp distribution: These data are useful in distinguishing P300 from the earlier and more fronto-centrally distributed P3a. The most common reference is the earlobe or the mastoid process. Physically linking the two earlobes (or mastoids) is not recommended because the shunting of current between electrode sites may distort the distribution of voltage over the scalp (Miller et al., 1991). It is recommended instead that electrical signals from the two earlobe electrodes be recorded separately (using one earlobe as reference for EEG channels as well as for the other earlobe) and mathematically combined offline to yield an average earlobes reference derivation. Additional channels are necessary to monitor the horizontal electro-oculogram and vertical electro-oculogram for eye movements and blinks. To obtain reliable measures of P300, a minimum of 36 usable trials (after artifact rejection or correction) in each stimulus category is recommended, although there is evidence that 20 trials may suffice (Cohen and Polich, 1997). Repetition of tasks can also be helpful in identifying stability of P300. 3.2.2.2. Bandpass. Because P300 is a slow potential, a high-pass setting of

0.01 Hz is optimal, although up to 0.1 is acceptable. (Duncan-Johnson and Donchin, 1979). The low-pass setting depends on the other components of interest, as well as the analog-to-digital (A/D) conversion rate (approximately 1=4 A/D rate[4] ; Picton et al., 2000). A setting of 100 Hz is recommended. If necessary, additional filtering can be done offline using digital filtering techniques (e.g., 0.01–20 Hz). A digitization rate of at least 200 Hz is recommended. A typical epoch has a prestimulus baseline of 100–150 and 800– 1000 ms post stimulus. It is essential that the recording epoch is long enough to allow P300 activity to return to baseline.

3.2.3. Measurement

P300 is typically measured as the peak amplitude and latency within a specified latency range. Area or mean amplitude within a selected interval is another common method of quantifying P300. Both measures are derived relative to a prestimulus baseline. However, neither peak nor area measures take into account overlapping components in the ERP waveform (Donchin and Heffley, 1978). Principal components analysis can be useful in disentangling components that overlap in time (Spencer et al., 2001).

The scalp location where P300 is of maximum amplitude is typically used to measure latency. If the scalp distribution of P300 is of interest, measures of amplitude should be taken at this latency for every electrode site. To do otherwise risks the introduction of noise and/or contributions from other, overlapping ERP components (Picton et al., 2000). Dien et al. (2004) have presented a new method for calculating P300 latency that uses a centroid measurement.

3.3. Clinical applications

An early indication that P300 might be useful in assessing cognitive function came from studies of dementing illness: The peak latency of P300 from patients with dementia was prolonged compared to that of aged-matched, healthy controls (Goodin et al., 1978). Subsequent clinical studies confirmed that the amplitude of P300 is reduced, and its latency increased, in the presence of cognitive impairment (e.g., Polich et al., 1986; O'Donnell et al., 1992; Potter and Barrett, 1999).

P300 may serve overlapping functions in research on cognitive dysfunction: One is as a clinical assay of a disease-associated marker. Polich and Herbst (2000) have shown that measures of P300 are comparable to standard clinical laboratory procedures in terms of measurement variability. Another function of P300 is to provide information useful for discriminating among subtypes of disorders or among pathophysiological mechanisms. Each of these functions can be extracted from P300 measures by relating patient data to normative values and careful comparison of disease subtypes. Such information could be helpful in making a differential diagnosis and in planning interventions.

Impaired attention may be the most ubiquitous clinical symptom of neuropsychiatric disorder (Mirsky and Duncan, 2001), and P300 is a sensitive measure of the capacity to allocate attentional resources (Johnson et al., 2004). Altered P300 may not be specific to a particular neuropsychiatric disorder; nevertheless, its sensitivity to impaired attention and its ease of elicitation make it a potentially useful clinical research tool. In addition to studies of basic information processing, P300 has been used extensively in investigations of psychiatric and neurological disorders as well as of normal and abnormal development. A comprehensive review of this body of literature is beyond the scope of this paper. We present here examples of clinical applications of P300 to illustrate the kinds of information that this metric can provide in relation to the pathophysiology of brain disorders, as well as to normal functioning and development.

[4] The low-pass (also called high cutoff) filter setting should be low enough to prevent inducing artifactual low frequencies in the digitized data (called aliasing). See Picton et al. (2000) for further information on analog filtering.

Recent studies have confirmed the utility of ERPs as prognostic indicators in patients with severe brain injuries of different etiologies and consciousness levels. Fischer et al. (2006) found that MMN can be used in this capacity. In a recent meta-analysis, Daltrozzo et al. (2007) concluded that prognostic assessment of low responsive patients with auditory ERPs should take into account both MMN and P300. In the longer perspective, P300, together with other ERP measures, holds promise for monitoring cognitive function in communication-impaired individuals (D'Arcy et al., 2000). P300 may also serve as a mediating response, allowing brain control of prosthetic devices (Donchin et al., 2000; Sellers and Donchin, 2006; Nijboer et al., 2008).

3.3.1. Schizophrenia

Alterations in P300 latency and amplitude appear to reflect deficits in cognitive processing present in varying degrees across clinical groups. A classic example is the reduced P300 amplitude in patients with schizophrenia, which was first reported 35 years ago and has been replicated many times (e.g., Ford, 1999; Duncan et al., 1987b). This finding may be consistent with an observed fronto-temporal atrophy seen in many patients with schizophrenia and their impairment in sustained attention (Kornetsky and Orzack, 1978; Nuechterlein et al., 2006; Seidman et al., 1998). Further investigation found that P300 amplitude was reduced in patients with schizophrenia, but that the difference was significant for auditory but not visual stimuli (Duncan et al., 1987a). The decrement in auditory P300 is apparent even when patients are least symptomatic (Michie et al., 1990). The amplitude of auditory, and possibly visual, P300 tracks fluctuations in clinical state; however, only auditory P300 amplitude appears to be a trait marker of schizophrenia (Duncan, 1988; Ford et al., 1999; Mathalon et al., 2000). Analysis of abnormal P300 modulation in relation to ISI (Mathalon and Ford, 2002) may help to illuminate aspects of deviant cognition in the disorder. Jeon and Polich (2003) conducted a comprehensive meta-analysis that characterized a variety of factors in schizophrenia.

Fig. 4 presents grand averages from a large family study of schizophrenia (Price et al., 2006). Findings from 60 patients, 53 unaffected family members, and 44 healthy controls provide additional support for auditory P300 as a trait marker of the disorder. As compared with the healthy controls, the amplitude of auditory P300 was reduced in both the probands and the unaffected family members. Moreover, the latter two groups did not differ on this measure. Other studies of the unaffected siblings of patients have also reported changes in auditory P300, with reduced amplitude at temporo-parietal sites and increased amplitude at frontal P300 sites (Roxborough et al., 1993; Weisbrod et al., 1999). These variables may be quantitative endophenotypes associated with increased genetic risk for schizophrenia, and may be useful in genetic studies of schizophrenia (Price et al., 2006; Winterer et al., 2003).

3.3.2. Mood disorders

Findings of deviant P300 are less consistent in mood disorders than in schizophrenia and may be related to patient subtypes or to the severity of depression (Bruder et al., 1998; Kaustio et al., 2002). Bruder noted that approximately half of the studies using an oddball task did not report a smaller P300 in depressed participants, most likely because the task was not sufficiently demanding to reveal a decrement in performance or P300. The variable results may also be related to co-morbid factors such as anxiety (Bruder et al., 2002). Patients with bipolar disorder seem to show more consistent P300 deviations in both latency and amplitude than those with unipolar disorder (Vandoolaeghe et al., 1998). Whereas the magnitude of P300 abnormalities in bipolar disorder may be equal to those seen in schizophrenia (O'Donnell et al., 2004), differences in scalp topography may indicate differences in the affected neural generators (Salisbury et al., 1999).

3.3.3. Alcohol dependence

P300 amplitude is small in individuals with alcoholism, and not as a consequence of the deleterious effects of alcohol on the brain. After abstinence, many of the clinical and electrographic signs characteristic of alcohol dependence may return to normal; nevertheless, the P300 amplitude reduction persists. The utility of a decrement in P300 amplitude as a potential endophenotypic marker was strengthened by studies suggesting that the degree of reduction in P300 observed in alcoholics was highly correlated with the number of alcohol-dependent individuals in the family (Pfefferbaum et al., 1991). Linkage analyses of highly heritable electrophysiological endophenotypes (including P300) were conducted on a large sample of families with a high density of alcohol dependence as part of the Collaborative Study on the Genetics of Alcoholism. The results have begun to provide evidence on the loci and role of the affected genes (Begleiter et al., 1998; Porjesz et al., 2002, 2005). The findings suggest a disinhibitory syndrome common to substance abuse and psychiatric conditions involving reduced impulse control (Porjesz et al., 2005).

3.3.4. Dementia

ERP measures have distinguished between subcortical and cortical dementias (Rosenberg et al., 1985; Goodin and Aminoff, 1986), and P300 latency can help to distinguish individuals with dementia from those with depression-associated pseudodementia. The latter group shows only the delay in latency associated with normal aging (Brown et al., 1982; Patterson et al., 1988). Discrimination between patients with early Alzheimer's disease and healthy individuals has also been reported (Holt et al., 1995; Polich et al., 1990a), with simple tasks yielding the largest P300 difference between groups (Polich and Corey-Bloom, 2005). More sophisticated cognitive paradigms have been applied to these populations with some success, but no bioelectric disease markers have yet been established (Golob et al., 2007).

3.3.5. Traumatic brain injury

P300 has also been used in investigations of head-injury survivors (Campbell and de Lugt, 1995). A reduction in the amplitude of visual P300 in survivors of traumatic brain injury has been observed in approximately half of these studies. Moreover, in a number of studies in which visual P300 amplitude was not significantly attenuated, there was a trend toward a reduction in survivors as compared with healthy controls (Heinze et al., 1992; Cremona Meteyard and Geffen, 1994; Bernstein, 2002; Potter et al., 2002; Duncan et al., 2003).

The most frequently reported effect of traumatic brain injury on ERPs is a reduction in the amplitude of auditory P300 (for a review, see Duncan et al., 2005). Early auditory processing deficits (see section on MMN) may affect perceptual ability and thereby indirectly affect auditory P300. It should be noted, however, that a number of investigations of brain injury have not reported significant attenuation of P300 amplitude. In a recent investigation (Duncan et al., 2005), it was shown that P300 is low in amplitude in head-injury survivors only when the task is sufficiently demanding (Fig. 5). This finding underscores the need to titrate the task difficulty to the cognitive capacity of the clinical group. Hence, simple oddball tasks that are sensitive to Alzheimer's disease may not be sensitive to mild traumatic brain injuries. Differences in the nature or difficulty of the task could account for the variability in reported results. When task demands exceed the available processing resources, performance declines and is accompanied by reductions in P300 amplitude.

3.4. P300 in healthy children and childhood disorders

The application of P300 to development lies in two domains. One concerns the description of normal cognition, including the maturation of various cognitive capacities and identification of

their neural origins. The other domain is directed at understanding disordered cognition, which seeks to identify disturbances in cognitive function in childhood disorders and to predict which individuals will develop the disorder within vulnerable groups. Studies in this domain rely on an understanding of normal cognition and are directed at more targeted remedial efforts, as well as interventions that could forestall the onset or mitigate the severity of childhood disorders. Cross-sectional studies can contribute to both domains, but longitudinal studies provide invaluable information on normal developmental trajectories. Indeed, when applied to "high-risk" groups, a longitudinal design is uniquely informative but requires a commitment of many years and substantial resources.

3.4.1. Normal development

It is not known whether ERP components that have been identified in adults have exact counterparts in children. Early investigations showed that rare nontarget stimuli elicit different ERP components in children and adults, while equally rare, target stimuli elicit similar components in children and adults (Courchesne, 1977). It was found that a broad frontal negativity, known as the NC component, decreases with age (Courchesne, 1978), but P300 increases in amplitude and decreases in latency with age (Polich et al., 1990b). There is evidence that the developmental trajectory of P300 differs when elicited by auditory as opposed to visual stimuli. Auditory P300 has a centro-parietal distribution that increases in amplitude and decreases in latency (Martin et al., 1988; Ladish and Polich, 1989) steadily from age 5 to age 19. This pattern is observed for both active and passive oddball tasks (from 1 to 21 years: Fuchigami et al., 1995). In contrast, both the amplitude and latency of visual P300 appear to decrease from age 10 to age 21 (Katsanis et al., 1996; but see Ridderinkhof and van der Stelt, 2000).

Developmental changes in ERPs have been studied using paradigms other than the standard oddball, and the data have been useful in describing age-related changes in key cognitive operations. Using a three-stimulus oddball (frequent standard, rare target, rare nontarget novel), Oades et al. (1997) reported that frontal P3a amplitude elicited by rare novel stimuli tends to increase between the ages of 8 and 20 years. Moreover, P300 to rare target stimuli was observed to become more centro-parietally localized over this time period. Määttä et al. (2005) also used a three-stimulus oddball task, with very rare novel stimuli, in 8- and 9-year-old children. As compared with adults, the P3a in the children was larger and more frontally distributed. Although it appears that the processing of novel acoustic stimuli is basically the same in adults and children, the larger P3a in children is consistent with a developmental change in frontal brain regions. This conclusion is supported by findings that show that structural maturation of the frontal cortex continues until late adolescence (Määttä et al., 2005). It should be noted, however, that their findings of a larger P3a in children than in adults is not consistent with other reports in the literature (e.g., Oades et al., 1997).

Jonkman et al. (2003) examined age effects in ERPs elicted in a visual warned go/no-go task, the Continuous Performance Test (CPT-AX), in which letters are presented one at a time. The participants were instructed to press a button when the letter X appeared, but only when it was preceded by the letter A (AX sequence). Children 9–10 years of age did not show the fronto-central no-go P3 seen in adults. Jonkman (2006) studied an additional group of 6- to 7-year-olds and observed that the no-go P3 component was absent in the youngest group, although it was beginning to appear in the 9- to 10-year-olds. The P300 elicited by the warning cue also increased in amplitude but decreased in latency as a function of age. Johnstone et al. (2007) examined both stop-signal and go/no-go P300 in 7- to 12-year-olds. In the stop-signal task, participants are required to make a choice response to a series of visual stimuli. On an unpredictable subset of trials, the go stimulus is followed by an auditory stop signal, and participants are instructed to withhold their response on these trials. The P300 elicited by visual

go signals and the stop P3 elicited on successful auditory stop signals increased in amplitude with age. However, in an auditory go/no-go task, the latency of the central no-go P3 decreased with age. Taken together, these data suggest that age effects on visual P300, P3a, and no-go P3[5] vary substantially between tasks. These findings add to the complexity of assessing ERP abnormalities in childhood disorders and underscore the need for comprehensive normative data.

For routine initial examination, the passive oddball may be the most useful task across a wide age range. In auditory tasks, the use of headphones provides reliable and consistent stimulus delivery; care must be taken to ensure that the child perceives stimuli in other modalities. Stationing the experimenter in the same room as the child, rather than isolating the child in an experimental cubicle, may facilitate participation as well as reduce the child's anxiety.

3.4.2. Childhood disorders

When diagnosing disorders in children, all sources of information should be evaluated, preferably with independently-derived agreement among clinicians. Equally important is the composition of control groups, which should be matched as closely as possible on a child-by-child basis in terms of age, gender, and other relevant variables (James and Barry, 1981).

3.4.2.1. Attention-deficit/hyperactivity disorder.

Studies of P300 in childhood disorders such as attention-deficit/hyperactivity disorder (AD/HD) have suggested that children with this diagnosis may have small P300 amplitudes to both auditory and visual stimuli. This may be seen in a variety of paradigms. In contrast, the latency of P300 in the oddball task is generally not altered in AD/HD (for a review, see Barry et al., 2003).

In their seminal studies of P300 in boys with AD/HD, Klorman and co-workers used a CPT under passive and active conditions (Klorman et al., 1979, 1983). They found that P300 was smaller in boys with AD/HD but only in the active condition ("respond quickly to the letter X"). In a replication and extension of this study (Michael et al., 1981), using the more complex "A" version of the CPT, a P300 decrement was found for AD/HD children. Furthermore, methylphenidate increased the amplitude of P300, suggesting normalization. P300 has been used to track medication effects in children with AD/HD in other studies as well. For example, Lawrence et al. (2005) recorded the P300 elicited by target stimuli in a visual CPT. A frontal shift in P300 observed in children with AD/HD was found to normalize following administration of methylphenidate.

In children with AD/HD, a decrement in P300 at posterior electrode sites has been reported in conjunction with an augmentation at frontal sites (Johnstone and Barry, 1996; Johnstone et al., 2001). This finding suggests a shift in source activity of P300 in AD/HD (i.e., different brain regions or different activity in those regions may be involved as compared with healthy children). Analysis of topographic variation is therefore critical in ERP assessment of disorders in children. This result was observed more consistently in children with the combined type of AD/HD as compared with the inattentive type, and in childhood than adolescent AD/HD. The inference of unusual P300 source activity in AD/HD has been con- firmed and extended using an inter-modality oddball task (Brown et al., 2005; Barry et al., 2006), a stop-signal task (e.g., Dimoska et al., 2003), a go/no-go task (e.g., Smith et al., 2004), and a CPT (e.g., Banaschewski et al., 2003, 2004).

[5] There is no consensus at this time as to whether P3a and no-go P3 are distinct components (e.g., Barry and Rushby, 2006; Polich, 2007).

3.4.2.2. Autistic disorder.

Children with autism display a reduced ability to process certain types of information, typically showing greater impairment in processing auditory and verbal information than visual information. Specifically, autistic children may have a limited ability to process novel information (Courchesne et al., 1985). They have smaller and later P300s than healthy children. Oades et al. (1988) reported that the P300 elicited by targets in an auditory choice reaction time task was smaller in amplitude and more anterior in distribution in autistic children than in healthy controls. However, P3a to rare nontargets was not reduced. Kemner et al. (1995) reviewed a number of studies with similar P300 results, and also found that in comparison to healthy, dyslexic, and AD/HD control groups, autistic children had larger P300s to rare stimuli in an active condition. Ferri et al. (2003) examined a group of 6- to 19-year-olds with autism. They reported that in comparison to controls, younger children with autism had larger P3as, whereas the reverse was found in older children. Kemner et al. (1999) reported that children with autism had smaller P300s than children with pervasive developmental disorder (PDD); and Courchesne et al. (1989) reported that autistic children had smaller than normal P300s, with Nc either small or absent.

Hoeksma et al. (2004) reported that the P3a elicited by visual probe stimuli in auditory tasks of two levels of difficulty was smaller in tasks with difficult (as compared to easy) discriminations in adolescents with PDD, as well as in the controls. This reduction was not apparent in younger participants with PDD, consistent with their developmental delay. This inference is supported by a later study by Hoeksma et al. (2006), in which normal visual and auditory P300s were seen in adolescents but not younger children with the diagnosis of PDD. Nevertheless, an ERP signature for the autism spectrum disorders has not been identified. It may be productive, in future studies, to use more syndrome-relevant stimuli in simple paradigms, such as emotional face stimuli in an oddball task.

3.4.2.3. Other disorders of childhood.

P300 differences have been reported in a variety of other childhood disorders. For example, Jirsa and Clontz (1990) found that a group of children with central auditory processing difficulties either failed to generate ERPs or had substantially increased latencies and smaller amplitudes of auditory P300. However, some of the children had normal ERPs, suggesting a variety of etiologies in children with impaired central auditory processing. In children with specific language impairment, Ors et al. (2002) found increased P300 latency to both tone and speech stimuli, but low P300 amplitude only to speech stimuli. Schulte-Körne et al. (2004) noted that children with dyslexia have normal P300 on a word-recognition task, although a subsequent late positive component was small. Using a go/no-go task, Baving et al. (2004) found no difference in the P300s of children with anxiety disorders as compared to controls. In 11-year-old children with oppositional-defiant disorder, Baving et al. (2005) found smaller P300 amplitudes to both cues and targets in a CPT. Rich et al. (2005) investigated the performance of children diagnosed with bipolar disorder in a spatial-cueing task. Both normal feedback and rigged feedback were used, intended to induce frustration. These manipulations led to impaired performance and smaller P300s in the patients as compared with the healthy controls.

3.4.2.4. High-risk studies.

P300 has been used to assess children at familial risk for disorders that develop later in life. Begleiter et al. (1984) used a visual mental rotation task and found that P300 amplitude was smaller for young boys at high- compared to low risk for alcoholism – an outcome similar to their previous data on individuals with alcohol dependence. Because in alcoholics the diminution persisted despite abstinence, it suggested that small P300 amplitude might be a risk marker for alcohol abuse. Lower P300 amplitudes also were observed in the pre-adolescent sons (who were

naïve to alcohol or illicit drugs) of alcoholic men (Porjesz and Begleiter, 1985). However, a meta-analysis of available studies indicated that not all ERP studies found reliable effects; the greatest effects were obtained using difficult visual discrimination tasks (Polich et al., 1994). Using fMRI and a visual oddball task, Rangaswamy et al. (2004) observed under activation of a frontoparietal circuit and suggested that it may be the basis for smaller P300s in high-risk individuals.

Hill et al. (1995) reported an 8-year follow-up study of 11 children at high risk and 9 children at low risk for alcoholism, with a mean age at first assessment of 10.7 years. A modified two-tone oddball task with tones presented at three levels of conditional probability was used. Small P300s were obtained in the high-risk children, and P300 amplitude decreased as stimulus probability increased. The group difference remained across the 8-year period. It is of interest that four of the high-risk children met criteria for alcohol dependence at retest, and these four evinced smaller P300 amplitudes in the low-probability condition than the other 16 children. Hill et al. (1999) reported a second study of 156 children and adolescents with multiple assessments using both auditory and visual ERP tasks. Growth-curve analyses confirmed the occurrence of small P300s in high-risk children in both modalities. Whereas this pattern was clearly evident in boys, girls demonstrated small P300 components only in the presence of a diagnosed childhood disorder. These results were confirmed in a larger study by Hill and Shen (2002).

Reductions in P300 are observed in a variety of paradigms. Van der Stelt (1999) reported that both young children and adolescents whose parents had alcoholism showed small P300 amplitudes to target and novel stimuli. Moreover, the expected enhancement of P300 in a visual selective attention task was smaller in these at-risk children than in low-risk matched controls. However, recent studies have suggested that instead of an association between P300 amplitude and risk for alcoholism, small P300 may be associated with a general vulnerability to externalizing disorders, including antisocial disorders and alcohol and other substance abuse (Porjesz et al., 2005; Patrick et al., 2006; Hicks et al., 2007).

3.4.2.5. Future studies.

The alterations in ERP components observed in the various childhood disorders provide a guidepost for future research. They also pose a challenge. Investigators have only occasionally deviated from the initial description of deficits, and are just beginning to use P300 to study putative etiological mechanisms and seek disorder-specific processing deficits. This development has occurred to some extent in studies of AD/HD, with the change in focus from the oddball to theoretically-based paradigms such as inhibitory processing in the stop-signal task (Johnstone et al., 2007), error processing in discrimination tasks (Burgio-Murphy et al., 2007), and interference produced in the flanker task (Johnstone et al., 2008). This shift in focus can serve as a model for research in other childhood disorders. Future work will thus be able to test predictions from emerging theories regarding function and etiology and, eventually, to develop useful, targeted interventions.

4. N400

4.1. Overview

The label N400 refers to a negative-going component in the average ERP that reaches its peak amplitude approximately 400 ms after stimulus onset. N400 has a broad scalp distribution, with maximal amplitudes at midline central or parietal sites and noticeably smaller amplitudes at prefrontal and lateral frontal sites. This component was first reported by Kutas and Hillyard (1980a,b,c) in a comparison of sentence-final words that formed predictable completions and

those that were semantically incongruent. Whereas predictable endings elicited a broad positive waveform from 200 to 600 ms, the incongruent words elicited a large negative wave in this latency range.

It soon became clear that neither anomalous endings nor full sentences were required to observe contextual modulation of N400 amplitude. Smaller N400s were also elicited by the second words of semantically-related (e.g., hot/cold) compared to semantically-unrelated (e.g., hot/noise) pairs (Boddy, 1981; Bentin et al., 1985; Rugg, 1985; see Fig. 6). Moreover, intermediate words of sentences presented one word at a time elicited large N400s for the first open-class words, while N400 became progressively smaller for subsequent words as the developing sentence context provided semantic constraints (Van Petten and Kutas, 1990, 1991; Van Petten, 1993).

The semantic context effect is evident in printed, spoken, and signed language (Kutas et al., 1987; Holcomb and Neville, 1990, 1991; Connolly et al., 1990, 1992; Neville et al., 1992). N400 amplitude is also sensitive to several lexical characteristics in addition to contextual factors. Low frequency (less commonly used) words elicit larger N400s than high frequency words (Van Petten and Luka, 2006). In reading, words with more orthographic neighbors (other words that can be formed by changing one letter) elicit larger N400s than words with fewer neighbors (Holcomb et al., 2002). Concrete words elicit larger N400s than abstract words (West and Holcomb, 2000). Finally, words used metaphorically elicit larger N400s than words used literally (Coulson and Van Petten, 2002, 2007). Overall, the data suggest that N400 amplitude is a general index of the difficulty of retrieving stored conceptual knowledge associated with a word. This outcome depends on both the stored representation itself and the retrieval cues provided by the preceding context (Kutas and Federmeier, 2000; Kutas et al., 2006).

N400-like potentials are also evident in response to other meaningful nonlinguistic stimuli such as line drawings, photos, and environmental sounds. These potentials are also smaller in amplitude when nonlinguistic stimuli are preceded by conceptually-related stimuli (Holcomb and McPherson, 1994; Van Petten and Rheinfelder, 1995; Ganis et al., 1996; Plante et al., 2000). These potentials are characterized as "N400-like" because they resemble the verbal N400 in wave shape and timing, but have slightly different distributions across the scalp. Conceptual context for pictorial materials has shown a more anterior maximum than the analogous effect for printed words, and the effect for meaningful nonlinguistic sounds has a small lateral asymmetry opposite to that for spoken words. These data suggest that verbal and nonverbal N400s reflect similar cortical computations occurring in different, but overlapping, populations of neurons.

The neural substrates of the scalp-recorded N400 have been examined only for verbal stimuli, using a variety of methods that include intracranial recordings in patients undergoing evaluation for neurosurgery, magnetoencephalographic recordings, and scalp recordings in patients with well-characterized lesions. Converging evidence from these studies indicates that the N400 is generated within the left temporal lobe with a smaller and more individually variable contribution from the right temporal lobe (see Van Petten and Luka, 2006).

4.2. Methodology

Recommended recording parameters for N400 are summarized in Table 3.

4.2.1. Matching clinical and control groups

Because the amplitude of N400 semantic context effects declines continuously from childhood onward (Holcomb et al., 1992; Kutas and Iragui, 1998), age matching clinical and control groups is critical. Also, the scalp distribution of the N400 in very young children appears to be more frontal than that in adults, emphasizing further the need for very close age matching when recording from infants and toddlers (Friedrich and Friederici, 2004; Mills et al., 2005).

Some aspects of verbal ability – particularly working memory capacity – have also been correlated with amplitudes and/or latencies of sentence-level N400s (Gunter et al., 1995; Van Petten et al., 1997; D'Arcy et al., 2005). Thus, it is also advisable to match groups on level of formal education. Finally, hemispheric asymmetries are reliably related to not only the handedness of the participants, but also the presence of left-handers in the immediate family (Kutas et al., 1988). Information about personal and familial handedness should be considered in comparing asymmetries between patients and controls.

4.2.2. Stimuli

Stimuli should not be repeated for a given participant unless memory is the research focus, because N400 amplitude is reliably reduced by stimulus repetition (Van Petten et al., 1991; Olichney et al., 2000). The sensitivity of the N400 to multiple lexical variables (see above) also mandates that stimuli should be matched on variables not of experimental interest (for useful lexical statistics for matching stimuli, see Kiss et al., 1973; Coltheart, 1981; Baayen et al., 1995; Balota et al., 2002).

If some words are designated as incongruent with the preceding sentence context, it is important to note whether the incongruity of the critical word is immediately apparent, or if the sentence might continue plausibly. For example, although "big" is a poor final word for "He always runs at least a ... ," the sentence might plausibly continue as "...big loop around his campus." Thus, participants may not immediately realize that "big" will not be followed by additional words. Words in sentences exhibit a continuum of semantic plausibility and expectedness given prior context. It is prudent to quantify the fit of particular words in sentences by asking a normative group of participants to complete or continue the sentence frames and evaluate the predictability of particular words (a cloze probability procedure; see Coulson et al., 2005).

The required number of stimuli per condition depends on the particular experimental manipulations. The maximal N400 difference is observed between highly predictable and wholly incongruent sentence-terminal words, and as few as 20 trials per condition have been used (Kutas and Hillyard, 1980a). Other N400 amplitude effects are smaller and require more trials (e.g., the difference between related and unrelated words in pairs). In general, 40–120 trials per condition should suffice, depending on the size of the anticipated effect. A larger number of trials will be required when onset latencies are of particular interest; reduced waveform noise levels provide greater accuracy in identifying when the developing response separates from the "ambient" noise inherent in an average ERP. Onset latency is often calculated as the time at which a difference between conditions reaches a given percentage of its peak amplitude (e.g., 10%). Thus, the lower the noise level, the more accurate the measure of onset latency.

4.2.3. Stimulus presentation

To minimize contamination of the EEG by electro-oculographic artifacts, visual sentences are conventionally presented one word at a time, with sufficient time between words to reduce temporal overlap between sequentially-presented words. Typical timing parameters for healthy young adults are 200-ms word durations, and a 500-ms stimulus onset asynchrony. An inter-trial interval (i.e., the time between sentences) of 3–5 s is recommended to allow the participant to blink without contaminating the recording epoch. Some clinical populations may require longer stimulus durations and intervals, but these may encourage scanning eye movements and more electro-oculographic artifacts. Pilot work can assist in optimizing timing parameters. Auditory stimuli (typically digitized natural speech) are frequently more comfortable for older adults and patients, who may experience eyestrain or difficulty in restricting eye movements to the intervals

between trials. ERP recordings should always be made with eyes open and fixated due to the excessive eye movements associated with eyes-closed conditions.

4.2.4. Task assignment

In the initial N400 report (Kutas and Hillyard, 1980a), participants were instructed to read for comprehension without overt response requirements. Subsequent work has confirmed that as long as the stimuli are attended (Bentin et al., 1993; McCarthy and Nobre, 1993), a task with an overt response is not necessary to elicit robust N400 effects (Connolly et al., 1990). In long recording sessions, or with participants whose attention may fluctuate, it is advisable to use a task requiring an overt response. In order to avoid component overlap (e.g., by a task-related P300), tasks should be used in which both decision-making and response preparation cannot begin until after N400 effects are expected to appear and resolve (e.g., Kutas and Hillyard, 1989; Van Petten and Kutas, 1990; Coulson and Van Petten, 2002). The use of paradigms expected to elicit overlapping P300s and N400s may lead to erroneous conclusions; the amplitude and latency of the P300 may also differ between clinical and control groups, making it difficult to evaluate the nature of an apparent difference in N400 activity.

4.2.5. Data acquisition

4.2.5.1. Bandpass.

N400 effects between conditions may last 300 ms for lexical manipulations such as word frequency, but can be even longer in sentence contexts (~700 ms). Hence, filter settings can vary depending on the experimental manipulations. However, given the extended duration of N400 effects in many paradigms, a low high-pass filter setting is advisable (e.g., 0.01 Hz is optimal). A low-pass setting of 30 Hz is unlikely to attenuate N400 amplitude; thus, the low-pass filter setting depends on which higher-frequency ERP components are of interest. In comparisons of patients with controls, it may be useful to evaluate earlier components of the ERP as well (e.g., auditory N100, visual N180), which require a low-pass setting in the range of 100 Hz.

4.2.5.2. Recording and reference sites.

A minimal set of recording sites would comprise four to five midline locations (Fpz, Fz, Cz, Pz, Oz) and two lateral pairs over the anterior and posterior temporal lobes (e.g., T3, T4, T5, T6). In addition, horizontal and vertical electro-oculographic activity should be recorded (e.g., an electrode below one eye to identify blinks and vertical eye movements when compared with Fpz, and a pair of electrodes at the external canthi of the two eyes to detect horizontal eye movements). Additional electrode sites will provide more information regarding the scalp distribution of N400 and thus may increase the chance of detecting group differences in distribution. A 32-channel recording montage is generally considered adequate. Few studies have compared directly the scalp distribution of the N400 using different reference sites (see Van Petten and Kutas, 1988), or between conventional ear or mastoid references and average-reference methods. Given that the majority of previous studies have used average-mastoid or earlobe references, including these sites in the recording montage will allow offline recalculation of different equivalent references (Picton et al., 2000) and facilitate comparisons to prior work.

4.2.6. Measurement

N400 effects are of long duration and do not always appear as a single clearly defined peak in individual-subject averages. Mean amplitude within a latency range (as compared to a prestimulus baseline) is most often used to quantify N400 amplitude. For healthy young adults, a latency range of 300–700 ms is typical for visually-presented material, with earlier latencies evident for continuous speech (Holcomb and Neville, 1991). Long-duration effects are sometimes

subdivided into shorter analysis epochs (e.g., 100-ms windows, or 300–500 and 500–700 ms). Given the broad scalp distribution of the N400, it is not necessary or advisable to select single electrode sites for measurement or analysis. It is preferable instead to evaluate scalp distribution by examining interactions between experimental conditions and scalp sites, which can be defined by anterior–posterior location, or, for lateral sites, left versus right and distance from the midline.

4.3. N400 in clinical populations

N400 has been applied to patients with a variety of developmental, neurological, and psychiatric disorders. Many studies have also used N400 paradigms to examine normal language development and changes with advancing age. A comprehensive review of this work is beyond the scope of this paper. Therefore, a number of studies will be described to illustrate applications of N400 paradigms in accordance with four objectives: clinical assessments performed to plan or evaluate treatment (Section 4.3.1), diagnostic differentiation (Section 4.3.2), analysis of complex symptoms in terms of underlying processing deficits (Section 4.3.3), and elucidation of the neural substrates of language (Section 4.3.4) We conclude with a brief description of research on developmental disorders (Section 4.3.5), for which all four objectives are relevant.

4.3.1. Clinical assessment

Decrements in amplitude and delayed latencies of N400 elicited by semantic incongruities are observed in patients who have suffered strokes in the left temporal lobe or temporo-parietal junction. Damage to these same regions leads to an aphasic syndrome marked by a semantic comprehension deficit (Hagoort et al., 1996; Swaab et al., 1997; Friederici et al., 1998). This relationship offers the possibility of using the N400 as a quantitative tool to assess the presence and severity of comprehension deficits (Connolly and D'Arcy, 2000; Marchand et al., 2002). In stroke patients, D'Arcy et al. (2003) used Form M of the Peabody Picture Vocabulary Test-Revised (PPVT-R) to elicit ERPs. This computer adapted version comprises 25–40 trials of picture-word pairings at three levels of vocabulary difficulty. Each trial begins with the presentation of a picture taken from the original test accompanied by a single spoken word that is semantically congruent or incongruent with the picture (e.g., a picture of a ball accompanied by the spoken word ball or cat). In a study using healthy volunteers, a distinct N400 was elicited by spoken words that were semantically incongruent with the picture (Connolly et al., 1995; see Fig. 7a). In addition to N400, a marked phonological mapping negativity (PMN), which reflects phonological processing of speech stimuli (Connolly and Phillips, 1994; Steinhauer and Connolly, 2008), was also observed to incongruent word pairs. In left-sided stroke patients with varying degrees of semantic impairment, there was a high correlation between scores on the standard version of the PPVT-R (Form L) and N400 amplitudes in the adapted version (up to $r = .86$, Fig. 7b). Kojima and Kaga (2003) reported a similarly high correlation between N400 context effects and a standardized aphasia measure in Japanese-speaking patients. These results suggest that ERP measures can be used to assess comprehension in patients with severe language deficits (receptive or productive) that preclude testing with the traditional version of the PPVT-R.

The presence of N400 as an indicator of semantic comprehension and possible awareness was used to evaluate a survivor of a traumatic brain injury who appeared to be in a vegetative state (Connolly et al., 1999). The patient exhibited N400 activity that showed conditional sensitivities found in healthy controls. These findings were used to justify a therapeutic program that otherwise would have been withheld due to the patient's diagnosis. The program was successful and led to the patient's return to a productive life. Use of computer-adapted neuropsychological tests to elicit cognitive ERP components has been implemented in a number of language (Connolly et al., 2006), memory (Marchand et al., 2006), and forensic (Lefebvre et al., 2007) contexts.

Focal seizure disorders often involve abnormal tissue in the temporal lobe; evaluations of language comprehension and verbal memory are therefore important for decisions about surgery and assessment of treatment effects. In a group of patients with left temporal lobe epilepsy, Miyamoto et al. (2000) used a task that required overt decisions about semantic relatedness, leading to larger decision-related P300s for related than for unrelated items. Whereas the N400 semantic context effect was reduced in seizure patients as compared with healthy controls, the differences in P300 and reaction time between related and unrelated items were equivalent for the two groups. The findings suggest that the observed N400 effects could serve as a specific and sensitive index of left temporal dysfunction.

N400 amplitude is smaller for repeated words than for initial presentations, at least for lags of fewer than six to twelve intervening words (the maximum retention interval has not been characterized precisely). Moreover, the amplitude of a slightly later positive component is also sensitive to repetition. The positive component – referred to as the "parietal old/new effect" or simply "late positive component" (LPC) by different authors – is thought to provide a sensitive index of retrieval from episodic memory. These N400 and LPC repetition effects are often difficult to distinguish (Van Petten et al., 1991). However, in a paradigm involving both semantic congruity and repetition, Olichney et al. (2000) observed that the N400 repetition effect was intact in patients with amnesia, but the LPC was reduced in proportion to the severity of the amnesic disorder. This dissociation was interpreted as reflecting a division between generators of N400 in lateral neocortex, which serve relatively short-term verbal memory, and a medial temporal lobe system that supports long-term episodic memory and the LPC.

This separation of function is also seen in data from intracranial recordings (Elger et al., 1997; Helmstaedter et al., 1997). Using scalp recordings, Olichney et al. (2002b) reported that a group of patients with right temporal lobe epilepsy had normal N400 semantic context effects as well as normal N400 and LPC repetition effects. In contrast, patients with left-sided lesions had severe reductions in all three effects, suggesting dysfunction of both medial and lateral cortex. This ERP paradigm has not yet been applied to patients who have undergone surgical excision of epileptic tissue, but pre- and post-tests might serve as a useful means of evaluating treatment effects on both comprehension and verbal memory.

4.3.2. Diagnostic classification

Perhaps the most prevalent disorder affecting the temporal lobe is Alzheimer's disease, for which any sort of early intervention depends on early diagnosis. There have been a number of reports of smaller and later effects of semantic context on N400 in Alzheimer's patients than in healthy controls (see Fig. 8). There is, however, substantial variability in the magnitude of the group difference, depending on the strength of the semantic context. Patients may show nearly normal effects with a strong semantic context, but abnormally small effects with weaker semantic relationships (Hamberger et al., 1995; Ford et al., 1996, 2001; Iragui et al., 1996; Schwartz et al., 1996, 2003; Ostrosky-Solis et al., 1998; Revonsuo et al., 1998).

Another source of variability in the magnitude of the N400 semantic context effect in Alzheimer's disease is likely to stem from the stage of the disease. The disease typically begins in the medial temporal lobe before spreading to neocortex. Current evidence suggests that both semantic processing and the generators of the scalp-recorded N400 are located primarily in neocortical areas of the temporal lobe (Van Petten and Luka, 2006). Thus, N400 deficits might be expected only if Alzheimer's disease has advanced to these brain regions. In contrast, deficits in episodic (as opposed to semantic) memory processes that are critically dependent on the medial temporal lobe are generally considered to be the earliest symptoms of Alzheimer's dementia. ERP paradigms that evaluate episodic memory are thus likely to be of greater utility in this disorder than those that emphasize semantic processing. In a task manipulating semantic congruity and

word repetition, Olichney et al. (2002a) reported that the LPC portion of the repetition effect – rather than the N400 portion – identified individuals with mild cognitive impairment who developed Alzheimer's disease within one to three years. Despite these promising lines of research, ERPs are not at this point capable of making clinical diagnoses; nor do substantial between-group differences necessarily allow prediction of differences among individuals.

4.3.3. Neurocognitive analyses of complex symptoms

Disorganized speech is a fundamental clinical symptom of schizophrenia. This symptom has spurred numerous ERP studies examining N400 semantic context effects in patients with this disorder. With word pairs or simple sentence materials, results have been inconsistent. Some studies have shown either normal or reduced N400 effects, with or without group differences in raw N400 amplitudes (see Kuperberg et al., 2006; Ditman and Kuperberg, 2007). Other studies, however, have presented a more coherent picture of preserved semantic access to individual word meanings, combined with difficulty building or maintaining a semantic representation based on longer sequences of words. Salisbury et al. (2002) found that schizophrenic patients fail to use context to disambiguate homographic words, but instead persist with the more frequent word meaning. Depending on the experimental stimuli, this deficit can lead to an N400 effect that is larger or smaller than in controls. For example, while reading, "The toast was sincere," patients exhibited an abnormally large N400 at "sincere" due to persistence of the dominant meaning of "toast" (bread). In contrast, over-reliance on the dominant meaning of a homograph will lead to an abnormally small N400 when encountering a word that is related to that dominant meaning but implausible in the larger sentence context (e.g., "The guests played bridge because the river..") (Sitnikova et al., 2002; critical words are italicized only for clarity). Behavioral studies in healthy individuals have indicated that those with lower working memory capacity are also prone to premature interpretation of ambiguous words in favor of their more frequent meaning, whereas those with higher scores on working memory tests are thought to maintain both possible meanings until there is a reason to select one over the other (Miyake et al., 1994).

A study by Kuperberg et al. (2006) provides support for the idea that semantic deficits in schizophrenia stem from impairments of working memory. Patients and controls generated equivalent N400 effects in a comparison of congruent and incongruent words in sentences such as, "For breakfast the boys would only eat ..." and "For breakfast the boys would only bury..." Note, however, that the difference between these sentences need not rely on representations of the full sentences, but may boil down to word pairs: breakfast-eat versus breakfast-bury. In a third condition, word-pair relationships were not sufficient to indicate the incongruity: "For breakfast the eggs would only eat ..." In this third condition, control participants generated large late positive potentials (latencies in the 600-ms range) rather than N400s, as, observed in other laboratories (Kolk and Chwilla, 2007). Patients with schizophrenia generated only very small late positivities, suggesting that they processed only the relationships among individual words (breakfast-eggs-eat), without creating a higher-level representation of the complete sentence. This pattern of results presents an intriguing parallel to that observed in healthy participants, in which those with high and low working memory capacity were equally sensitive to word-pair relationships within sentences, but the ERPs of low-capacity individuals showed little sign of sentence-level congruity effects (Van Petten et al., 1997).

An important conclusion from the schizophrenia studies is that it is not appropriate to assume that the only possible outcomes are that a particular ERP component will prove to be normal or abnormal in a particular disorder. The examples cited above indicate that the brains of patients with schizophrenia are fully capable of generating N400s, but may or may not do so depending on the demands of the material. With sophisticated experimental designs, the N400

as well as other components of the ERP can be used as noninvasive tools to gain insight into the specific nature of a cognitive disorder.

4.3.4. Elucidating the neural substrates of language

In many of the examples discussed above, experimental manipulations led to modulations of ERP components other than the N400. Patterns of normal versus abnormal amplitude across multiple ERP components may offer greater insight into both normal and disordered cognition than N400 measures alone. However, variation in more than one component can also pose measurement difficulties unless the components can be separated by their latencies or scalp distributions, which can be difficult to achieve. A powerful design is one in which different pairs of conditions are used to isolate different components, and patients are shown to differ from controls on one component but not another. Identifying intact versus reduced cognitive ERP components in patients has been useful for understanding the anatomical substrates of normal language processing. In contrast to the substantial impact of left temporal and inferior parietal damage on the N400, patients with damage restricted to the frontal lobe have typically shown normal semantic context effects (Swick et al., 1998; Swick, 2004). In a group of patients with lesions confined to the inferior frontal gyrus, anterior insula, and basal ganglia, typical N400 differences were observed between semantically congruent and incongruent sentence completions (Friederici et al., 1999). These results suggest that although these areas of the frontal lobe may be involved in some aspects of semantic processing, they are not critical for the initial access to semantic memory reflected in the N400.

Friederici et al. (1999) found that patients with inferior frontal or insular damage failed to show another ERP effect – the early left anterior negativity (ELAN), elicited by an illegal preposition-verb sequence. Those with lesions restricted to the basal ganglia showed an intact ELAN to the grammatical error, as did patients with Parkinson's disease (Friederici et al., 2003). These results suggest that anterior cortex (frontal or insular) is engaged during early analysis of syntactic structure, but that the basal ganglia are not. Invasive intracranial recordings in patients being evaluated for neurosurgery as well as scalp recordings from patients with well characterized lesions continue to play an important role in linking the knowledge gained from healthy participants to the anatomical structures that support language.

4.3.5. Developmental learning disabilities

According to the DSM-IV (1994), approximately 5% of students in public schools in the United States have been identified as having a specific learning disability. The definition of this disorder includes a deficit in one or more of the components of language – listening, speaking, reading, and writing – in the absence of another handicapping condition such as frank sensory or motor disorder or mental retardation. When multiple language skills are assessed, individuals with a developmental language disorder differ substantially from one another in areas of strength and weakness. However, there is no general agreement on the number or nature of distinct disorders or subtypes of developmental language disorder (Bishop, 1997; Démonet et al., 2004; Plante and Beeson, 2007). Thus, "dyslexia" in one laboratory may be "specifically language impaired" in another laboratory.[6] The goals of ERP research in this area thus include at least three of the objectives enumerated above: diagnostic differentiation, identification of processing deficits that underlie complex symptoms, and greater understanding of the neural substrates of language.

Because semantic processing is contingent on adequate decoding of a sensory input, one

[6] *We use the group labels provided by the authors when referring to individual studies, but the inclusive term learning disabled when referring to multiple studies.*

would predict that semantic manipulations should produce smaller or later N400 effects in learning disabled samples than in controls. This should be true regardless of whether the primary problem lies in lower-level visual/auditory processing, orthographic/phonological processing, or semantic processing per se. This has largely been confirmed. In comparisons of ERPs or magnetic fields elicited by predictable versus incongruent sentence endings, four studies report lower amplitudes for the N400 difference between conditions in learning-disabled subjects (Helenius et al., 1999; Sabisch et al., 2006b; Meng et al., 2007; Schulz et al., 2008); and two report latency delays without amplitude decrements (Helenius et al., 2002; Robichon et al., 2002). However, variability among the subjects sampled in different laboratories (and even within a laboratory) is evident from Sabisch et al.'s (2006a) report of no difference in the N400s of subjects with and without specific language impairments, and Neville et al.'s (1993) report of a larger sentence congruity effect in the former group. An additional four studies have examined responses to words preceded by single items that were semantically related or unrelated. Similar to the sentence congruity results, three of these studies obtained smaller N400 effects in children with developmental learning disabilities (Stelmack and Miles, 1990; Miles and Stelmack, 1994; Plante et al., 2000); whereas one reported no difference between dyslexic and control subjects (Rüsseler et al., 2007).

Overall, small or delayed N400 effects in learning-disabled subjects comprise some three-quarters of published reports using a semantic context manipulation. In nearly all of these experiments, the participants with learning disability have been able to discriminate related/congruent words from unrelated/incongruent words with high accuracy. This indicates that the N400 measures are extremely sensitive to the underlying pathophysiology, even when the abnormal neural processes were sufficient to support a binary judgment. In contrast, the absence of group differences (or reversed group differences) in a sizable minority of published reports could be viewed as indicative of low reliability or low sensitivity of the ERP measures. Discrepant outcomes among well-executed experiments are likely attributable to variability across individual subjects in different samples, and that variability can lead to new clinical insights. For instance, individuals with relatively preserved versus absent N400 effects could prove to benefit from different sorts of training programs, but the relationships between ERP measures and clinical interventions for developmental disorders have barely begun to be explored (cf. Stevens et al., 2008 for a step in this direction using attention-sensitive ERP components). A second potential application of N400 semantic-context effects is the identification of children with developmental learning disorders who may benefit from early intervention. Friedrich and Friederici (2006) reported a promising step in this direction in that abnormally small N400 context effects at 19 months of age were predictive of poor expressive language skills at 30 months.

An abnormality in the N400 effect to a semantic manipulation is not especially informative about the nature of a language deficit, which may lie in stages of processing that precede access (or attempted access) to a word's meaning. For example, Bergmann et al. (2005) found that subjects with dyslexia lacked the normal N400 differentiation between real words and unpronounceable strings of consonants. This result may indicate impaired access to the meanings of the actual words – a semantic problem – or difficulty in an earlier stage of identifying orthographically-legal letter sequences that could possibly bear meaning. One experiment showing both normal and abnormal N400 effects in the same participants supports the hypothesis of pre-semantic deficits. Plante et al. (2000) observed a small and nonsignificant N400 effect when learning-disabled subjects heard spoken words preceded by related or unrelated visual words. The same participants generated N400 effects that were as large as the control group when hearing environmental sounds preceded by related or unrelated drawings (e.g., the sound of breaking glass preceded by a drawing of a broken window versus a drawing of a piano). This

dissociation suggests a deficit not in semantic processing, but in orthographic or phonological processes that distinguish words from other varieties of meaningful stimuli.

Other investigators have tested the hypothesis that impaired readers are deficient in converting letter strings to sound patterns, by asking for judgments about the phonological similarity between printed words. Rhyming influences the amplitude of a negative ERP component that strongly resembles the semantic N400 (Praamstra et al., 1994; Grossi et al., 2001; Radeau et al., 1998). For visual words, the rhyme effect is dependent on engagement in an overt rhyme-judgment task, in contrast to the fairly task-independent nature of the N400's sensitivity to semantic context (Perrin and Garcia-Larrea, 2003). McPherson et al. (1998) observed a smaller than-normal rhyme effect in poor readers classified as "dysphonetic" when printed words served as the stimuli, but a normal effect when the stimuli were auditory words that did not require conversion from orthography to phonology. Ackerman et al. (1994) also observed, in subjects with dyslexia, a small rhyme effect when judging printed word pairs, but paradoxically, a normal rhyme effect when judging pseudo word pairs. Only Rüsseler et al. (2007) used both semantic and rhyme manipulations in the same participants: They observed no amplitude differences between dyslexic and control groups, but a slight latency delay in the former group for the rhyme effect only. Clarification of the relationship between rhyme and semantic N400 effects in individuals with learning disabilities requires further research. Similarly, the MMN paradigm has been informative in studies of developmental language disorders. However, to our knowledge, no studies have examined the relationship between auditory/phonological processing deficits evident in MMN measures and comprehension as evident in N400 measures.

5. Concluding remarks

The goal of this paper is to promote the most reliable and useful methods for eliciting, recording, and measuring three cognitive ERP components in investigations of clinical disorders. The usefulness of cognitive ERPs in providing information about central nervous system function was illustrated with specific clinical applications of these cognitive components.

Participants in clinical studies should be selected according to clear diagnostic criteria; and, because clinical science is continually evolving, patients should be chosen on the basis of current criteria. Moreover, samples should be as homogeneous as possible (Picton et al., 2000). To the extent feasible, controls should differ from the clinical group on only the variable of interest. Moreover, medications taken by participants must be documented. Even when these guidelines are followed, because neuropsychiatric diagnoses are based on clinical symptoms and not on specific etiologies and pathophysiologies, the search for ERP markers will be difficult. Robust, highly significant, and replicable differences between a patient group and a control group may not allow accurate classification of individual patients. The diagnostic utility of ERP alterations in clinical disorders is therefore limited.

Another methodological issue concerns the importance of minimizing eye movements. Signal-to-noise ratios are often lower in patients than in healthy controls because many patients have more eye movement and muscle artifacts, as well as lower ERP amplitudes. The loss of trials due to artifact and the smaller amplitudes of certain components seen in some clinical populations may require collecting more trials to be averaged than would be necessary in studies using healthy adults. Although a number of methods have been developed to remove activity recorded from electro-oculographic electrodes from the EEG (e.g., Gratton et al., 1983; Woestenburg et al., 1983; Semlitsch et al., 1986; Berg and Scherg, 1994), most rely on estimates of EEG not contaminated by eye movements and blinks. An alternative method not requiring uncontaminated EEG is the revised artifact-aligned average electrooculogram correction method (Croft et al., 2005). This method can be used with an additional calibration run in which eye movements are

generated. Removal of ocular artifacts using independent components analysis (e.g., Makeig et al., 1996) does not require uncontaminated EEG or a calibration procedure but has not been widely used. It is essential that minimizing eye movement artifacts be borne in mind in designing the experiment as well as during data acquisition.

Another issue concerns the measurement of components. Näätänen and Picton (1987) defined an ERP component as "the contribution to the recorded waveform of a particular generator process, such as the activation of a localized area of cerebral cortex by a specific pattern of input. Whereas the peaks and deflections of an EP [evoked potential] can be directly measured from the average waveform, the components contributing to these peaks can usually be inferred only from the results of the experimental manipulation" (p. 376). The data recorded at a given time point in the ERP epoch can be affected by multiple components, which makes it problematic to identify peaks in selected latency windows as specific components. Furthermore, identifying ERP components in clinical studies is complex, because there can be differences between groups in more than one component (Johnson, 1993).

Components can be disentangled by means of experimental manipulations if they are differentially sensitive in amplitude or latency to different manipulations (Donchin et al., 1978). In addition to its response to experimental manipulations, an ERP component is characterized by its polarity, latency, and scalp distribution. Subtraction methods (subtracting an ERP waveform elicited in one condition from that of another condition) can be used to reveal an underlying ERP component; MMN and N400 are routinely quantified using this technique. Moreover, statistical methods such as principal components analysis are useful in identifying overlapping ERP components (Donchin and Heffley, 1978; Glaser and Ruchkin, 1984), a technique that has been used to disentangle P3a and P300 (e.g., Spencer et al., 2001; McDonald et al., in press).

A final methodological issue concerns the polarity convention of the ERP waveform. This refers to whether upward deflections indicate positive or negative potentials at the scalp electrodes relative to the reference electrode(s). Both conventions are used in the literature, and there is a lack of consensus as to which is preferable (Picton et al., 2000). Plotting ERP waveforms with upward deflections indicating negative potentials is the tradition from clinical neurophysiology: This tradition likely dates from the early days of EEG, when epileptic spikes were found to be negative in polarity and to be easier to visualize when plotted up (see Hallett, 2006). However, this is clearly an arbitrary convention. As Hallett noted, "Having conventions for display of waveforms makes sense in the clinic. It aids recognition of normal and abnormal patterns and helps prevent medical errors" (p. 1167). It is thus recommended that recordings of cognitive ERPs in clinical contexts be plotted using the negative-up convention to assist in pattern recognition, thereby avoiding medical errors and promoting effective clinical case management. In the basic research context, however, either polarity convention is acceptable.

The guidelines we have proposed are intended to inform the researcher as to possible clinical applications of ERPs and methods to acquire data that are accurate, reliable, and valid. The reader is also referred to the report by Picton et al. (2000), which presents detailed recommendations for recording ERPs and criteria for publishing the results. Whereas guidelines provide a good starting point, the most effective way to acquire skill in the application of these methods is to learn them in a laboratory where they are being used on a regular basis and in accordance with the highest standards of the field.

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Table 1
Recommended recording conditions for MMN.

Parameter	Comment
I. Stimulus factors	
A. Single deviant paradigm	One frequent standard tone, one rare deviant tone
Standard	
Duration	50–150 ms (fixed), 5 ms rise/fall
Frequency	Sinusoidal tones (500–1000 Hz [fixed])
Spectrally rich sounds can be used	
Intensity	80 dB SPL
Interstimulus interval	500–1000 ms (fixed)
Location	Midline (binaural)
Deviant	10% increment or decrement in frequency or intensity. Duration deviants usually shorter than standards (e.g., 30-ms deviants for 75-ms standards, 100-ms deviants for 150-ms standards). Location deviants usually located 90° to the left or right of midline. MMN increases in amplitude and decreases in latency with increasing stimulus change from frequent to rare tone.
Probabilities	Deviant is 0.10–0.20, standard at complementary probability. At least 2 standards are presented before each deviant.
B. Optimal paradigma	One frequent standard, five rare deviant tones
Standard	Harmonic stimulus comprising 3 sinusoidal partials of 500, 1000, and 1500 Hz, with intensity of second and third partials 3 and 6 dB lower than the first partial
Duration	75 ms, 5 ms rise/fall
Intensity	60 dB above individual's threshold
Interstimulus interval	500 ms (fixed)
Location	Midline (binaural)
Deviants	
Duration	25 ms, 5 ms rise/fall
Frequency	Half of frequency deviants are 10% higher partials, half are 10% lower partials.
Intensity	Half of intensity deviants are 10 dB higher, half are 10 dB lower.
Location	Half of location deviants are perceived as having a spatial location 90° to the right and half 90° to the left of the midline by introducing an interaural time difference of 800 μs.
Gap	Silent gap of 7 ms (including 1 ms rise/fall) in the middle of a 75-ms stimulus
Probabilities	.50 (standard), .10 (each of the deviants), one standard between each deviant
II. Participant and task	
Position	Seated or lying down
Eyes	Open
Active or passive task	Optimal task for an awake, alert participant is performing an interesting visual task, e.g., watching a video.
III. Electrophysiological recording	

Electrode sites	Minimal configuration is Fz, Cz, C3, C4, and mastoid electrodes.
Reference	Nose – with algebraic re-referencing to average of the mastoids to increase signal-to-noise ratio (if necessary)
Ground	AFz
Bandpass of amplifiers	0.1–30 Hz
Digitization rate	200 Hz as a minimum
Epoch length	500 ms, with 50-ms prestimulus baseline
Artifact reduction	EOG rejection or correction; ±100 μV for all EEG channels
Minimum # trials	150 of each deviant
Digital filtering	1–20 Hz
IV. Quantification	
Average ERPs	Average ERP waveforms and difference waveforms must be presented for each group and condition.
Difference waveform	Deviant average ERP minus standard average ERP
Latency	150–250 ms; decreases as magnitude of change increases
Amplitude	Peak amplitude in a latency window in difference waveforms
Scalp distribution	Maximal at Cz and Fz; polarity reverses over mastoid sites

[a] Näätänen et al. (2004)

Table 2
Recommended recording conditions for P300 in an oddball task.[a]

Parameter	Comment
I. Stimulus factors	Two categories of stimuli, one rare, one frequent
Auditory	Tones, environmental sounds, spoken words
Frequencies	1000 Hz (target), 500 Hz (standard)
Duration	50–150 ms duration, 5 ms rise/fall
Intensity	70 dB SPL
Visual	Colors, shapes, words, pictures
Duration	50–150 ms; stimuli should be perceptible
Interstimulus interval	1–2 s (fixed or variable), longer if categorization task is difficult
Dimensions of change	Physical attributes of stimuli; meaning of stimuli. Stimuli must comprise two categories (high vs. low tone; female vs. male names).
Probabilities	.10–.20 (target), .80–.90 (standard)
II. Participant and task	
Position	Seated
Eyes	Open

Sensory/health factors	Document integrity of sensory function and relevant health factors (e.g., history of central nervous system disorder or injury, medications affecting CNS).
Active or passive[b] task	Attention to stimuli required; concurrent behavioral task with measurable performance (e.g., button press to target stimulus) is necessary.
III. Electrophysiological recording	
Electrode sites	Minimal configuration is Fz, Cz, Pz, VEOG; additional electrode sites recommended to obtain information on scalp distribution.
Reference	Nose or one earlobe used as online reference, with offline averaging with the other earlobe.
Ground	AFz
Bandpass of amplifiers	0.01–100 Hz
Digitization rate	200 Hz minimum (4× low-pass filter setting)
Epoch length	1000 ms, with a prestimulus baseline of 100–150 ms; longer epoch for difficult categorizations
Artifact reduction	EOG rejection or correction, and rejection of trials with voltages ±100 μV in any EEG channel
Minimum # trials	36 artifact-free
Digital filtering	Not recommended for ERPs prior to quantification; low-pass filtering at 12 Hz is acceptable for ERPs to be displayed.
IV. Quantification	
Average ERPs	Average ERP waveforms, excluding trials with incorrect behavioral responses, must be presented for each group and condition.
Latency	Typically peaks in the 300–400 ms range but varies according to the difficulty of categorizing the stimuli, age, and clinical status.
Amplitude	Peak amplitude in a latency window (e.g., 280–420 ms) relative to prestimulus baseline; mean amplitude in a latency window relative to prestimulus baseline also acceptable; PCA/ICA
Scalp distribution	Parieto-central in adults, becomes more equipotential in elderly.

[a] Other paradigms that elicit P300 include the 3-stimulus oddball task, the Continuous Performance Test or CPT, the Eriksen flanker task, the Stroop test, etc.
[b] A "passive" task means that no response, overt or covert, is required of the participant.

Table 3
Recommended recording conditions for N400.

Parameter	Comment
I. Stimulus factors	
Congruity	Words (printed, spoken, signed) or pictures after sentence or discourse contexts that are semantically congruent or incongruent
Semantic relationships	Meaningful stimulus (word, picture, environmental sound) following a single conceptually-related or unrelated item
Lexical factors	
Word frequency	High versus low frequency of usage in the language

Concreteness	Concrete versus abstract words
Orthographic neighborhoods	Words with many versus few orthographic neighbors
Probabilities	Probability of occurrence is not considered a significant variable, but equal probability of congruous and incongruous items is typical.
Memory/learning	Initial presentation versus repetition
Duration	Not considered relevant, as long as stimuli are perceptible
Interstimulus interval	Visual: faster than normal reading speed is not recommended, longer intervals of 400–600 ms allow separation of ERPs to consecutive words
	Auditory: continuous speech, or speech with a temporal break before critical word
Stimuli should be matched on all factors not of experimental interest.	
II. Participant and task	
Position	Typically seated
	Lying down possible but can affect recordings from posterior sites due to pressure of head on electrodes
Eyes	Open
Handedness measure	Determined using standardized test (e.g., Edinburgh Handedness Questionnaire, Oldfield (1971)); important to determine handedness of immediate family members as well
Sensory/health factors	Integrity of sensory function and relevant personal health factors (e.g., history of central nervous system disorder, concurrent medications affecting CNS); self-report sufficient for healthy controls
Active or passive task	Attention to stimuli is required; concurrent or delayed behavioral task ensures this.
III. Electrophysiological recording	
Electrode sites	Minimal configuration is Fz, Cz, Pz, F3/T3, F4/T4, P3/T7, P4/T8 and bilateral mastoid/earlobe electrodes.
Reference	Offline averaging of left and right mastoids or earlobes avoids possibility of hemispheric asymmetry in reference.
Ground	AFz
Bandpass of amplifiers	0.01–100 Hz
Digitization rate	250 Hz
Epoch length	100–200 ms prestimulus baseline, at least 900 ms following stimulus onset
Artifact reduction	EOG rejection or correction, and rejection of trials with voltages ±70 μV in any EEG channel
	Minimize artifacts by fixation of gaze and avoiding tongue/jaw movements during overt speech or speech preparation.
Minimum # trials	Paradigm dependent but typically 40 or more
Digital filtering	Not recommended prior to quantification of ERPs; low-pass filtering at 15 Hz is acceptable for ERPs to be displayed.
IV. Quantification	
Average ERPs	Average ERP waveforms, excluding trials with incorrect behavioral responses, must be presented for each group and condition.

Difference waveform	Incongruous average ERP minus congruous average ERP (useful for determining onset latency)
Latency	Typically peaks in the 350–550 ms range but varies by paradigm and clinical status.
Amplitude	Difference between the prestimulus baseline and mean integrated voltage within a specified latency window(s) (e.g., 300–500 and 500–700 ms).
Scalp distribution	Centro-parietal with word stimuli, more anterior with pictures or increased memory load; slight right asymmetry in highly dextral individuals

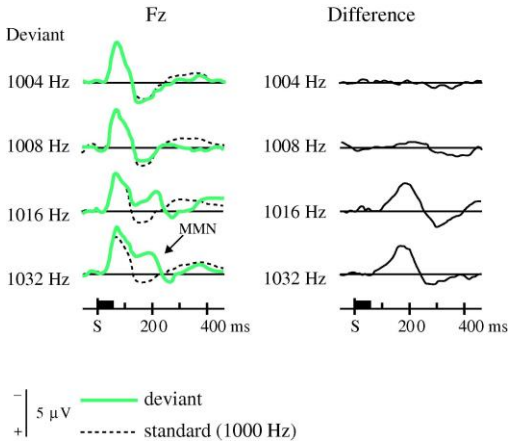

Fig. 1

ERPs at Fz, elicited by tones deviant (p = .20) in frequency from standards (p = .80). The difference waveforms (deviant–standard) are also displayed. As the magnitude of the frequency difference increased between the deviant and standard stimuli, the peak latency of MMN became progressively shorter and its peak amplitude larger. In this and all subsequent figures, negativity is plotted as an upward deflection.

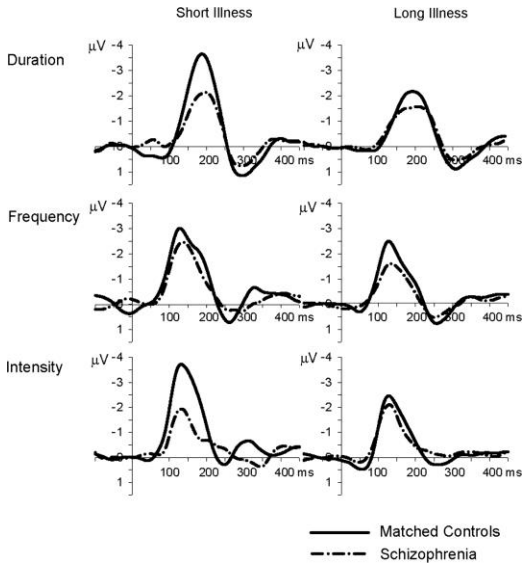

Fig. 2

The MMN at Fz, elicited by tones deviant from the standard in duration, frequency, or intensity. Difference waveforms are shown for two groups of patients with schizophrenia, one early in the course of illness (short illness), and the other with a longer duration of illness (long illness). Data from healthy matched controls are also shown. Note that duration and intensity MMNs were reduced early in the course of illness, whereas a reduction in frequency MMN was evident only after a longer duration of illness.

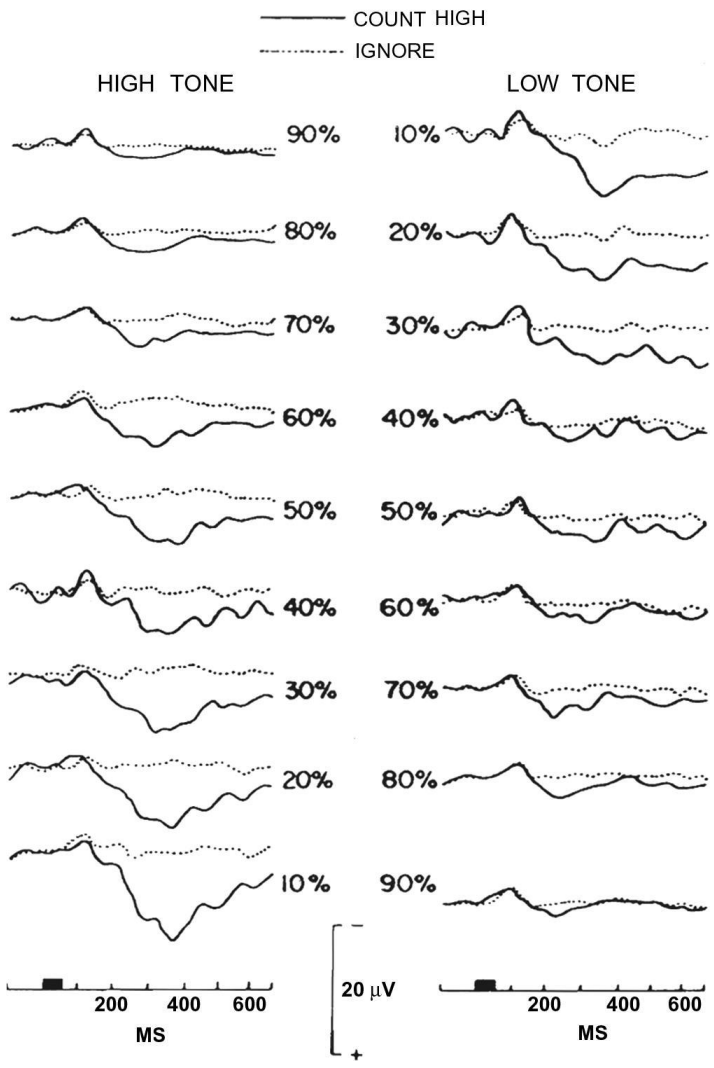

Fig. 3

Grand-average ERPs at Pz, elicited by high (1500 Hz) and low (1000 Hz) tones at nine levels of stimulus probability in an oddball task. The data collected in the Count high and Ignore (word puzzle) tasks are superimposed at each level of probability. The amplitude of P300 elicited by high and low tones depended on the probability of the stimuli. Moreover, the P300 to the counted tones (targets) was slightly larger than that to the uncounted tones at the same level of probability. When the tones were not task-relevant (Ignore), P300 was not elicited by stimuli at any probability.

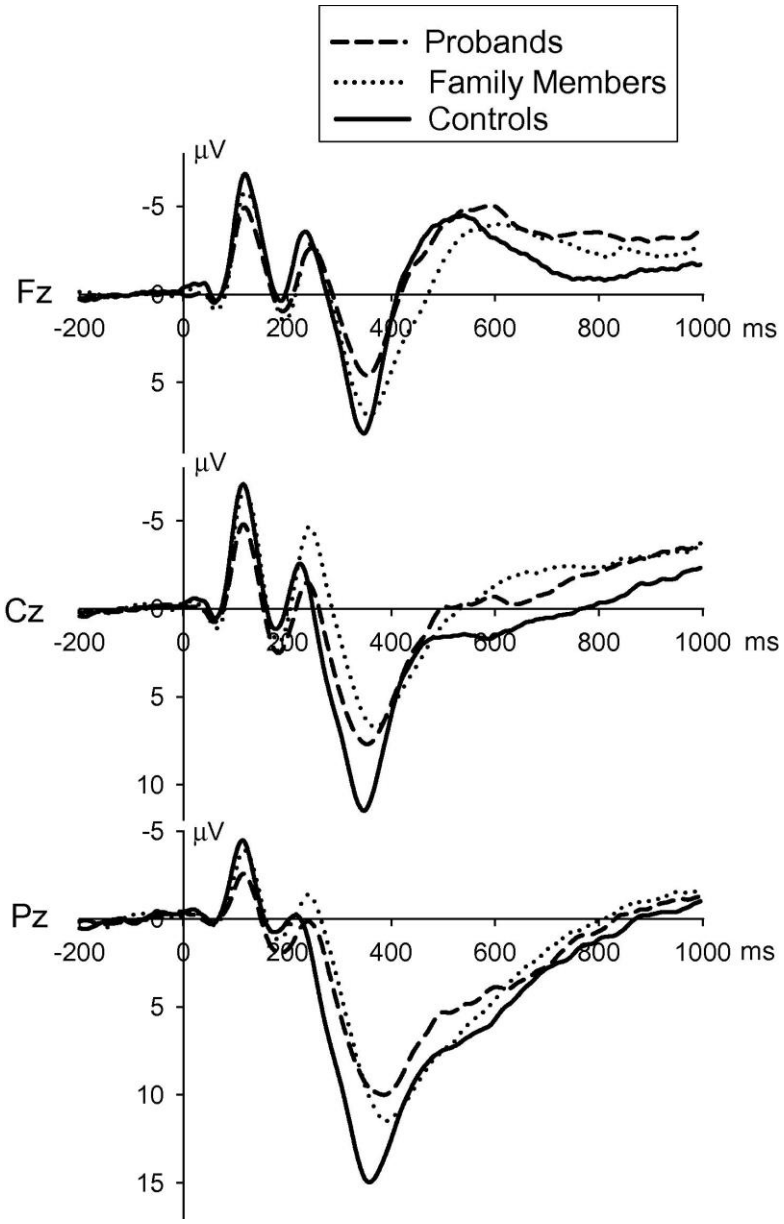

Fig. 4

Grand-average ERPs at three midline electrode sites (Fz, Cz, Pz), elicited by correctly detected auditory targets (1500 Hz, $p = .10$) interspersed at random between standards (1000 Hz, $p = .90$). The waveforms for three groups are superimposed: patients with schizophrenia (probands), first-degree unaffected relatives, and healthy controls. As compared with the controls, the amplitude of P300 was smaller in the probands and the unaffected relatives, who did not differ from one another.

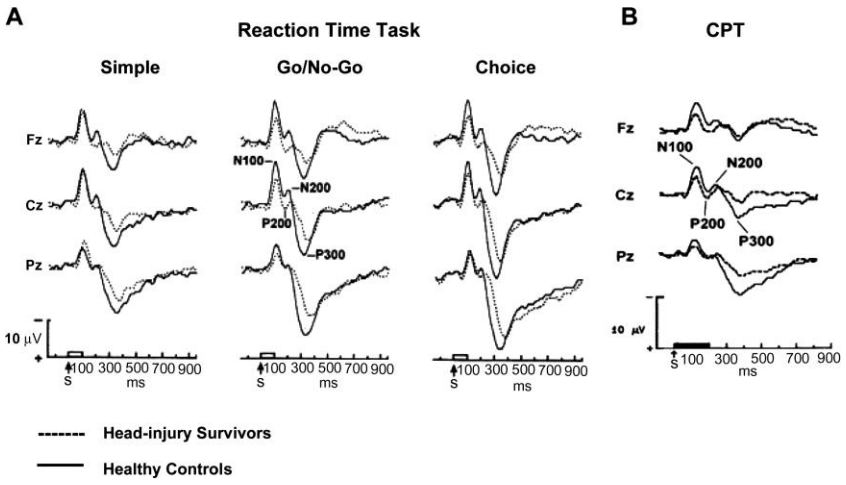

Fig. 5

(A) Grand-average ERPs elicited by rare tones (1500 Hz, p = .10) in simple, go/no-go, and choice two-stimulus reaction time tasks. The ERPs for head-injury survivors and healthy controls are superimposed at three midline electrode sites (Fz, Cz, Pz). As compared with the controls, N100 and N200 amplitudes were attenuated, and N200 and P300 latencies were delayed, in the survivors. The differences between groups in N200 and P300 latency were reflected in a significant difference in response speed. (B) Grand-average ERPs elicted by target stimuli (1500 Hz, p = .25) in a three-tone auditory Continuous Performance Test (CPT). The ERPs for the head-injury survivors and the healthy controls are superimposed at three midline electrode sites (Fz, Cz, Pz). The amplitudes of N100, N200, and P300 were reduced in the survivors as compared to the controls. The smaller amplitudes in the survivors corresponded to fewer detected targets on the CPT

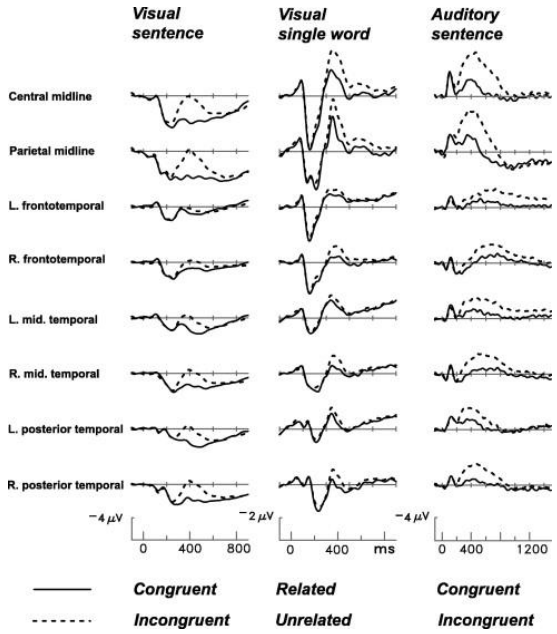

Fig. 6

Three examples of N400 amplitude modulations in healthy young adults. All ERPs were elicited by single words after semantic contexts comprising either sentence frames or single words. Left column: grand-average ERPs to the final words of printed sentences (data from Van Petten, 1993). Middle column: grand-average ERPs to the second words of related and unrelated visual word pairs (data from Luka and Van Petten, 2005). Right column: grand-average ERPs to the final words of auditory sentences (data from Van Petten et al., 1999). Comparison of the word-pair and sentence data shows that the related words elicited larger N400s than the congruent sentence completions. This is because a strong sentence context can make the final word very predictable, whereas any single word is related to many other words. The general morphology of the waveforms differs between stimuli presented in the two modalities, with the auditory ERPs being predominantly negative and the visual ERPs being predominantly positive with respect to the baseline. In both modalities, N400 context effects are maximal at central and parietal midline scalp sites. Note that the context effect is somewhat larger over right than left scalp sites in the visual modality. This asymmetry is less evident in the auditory modality.

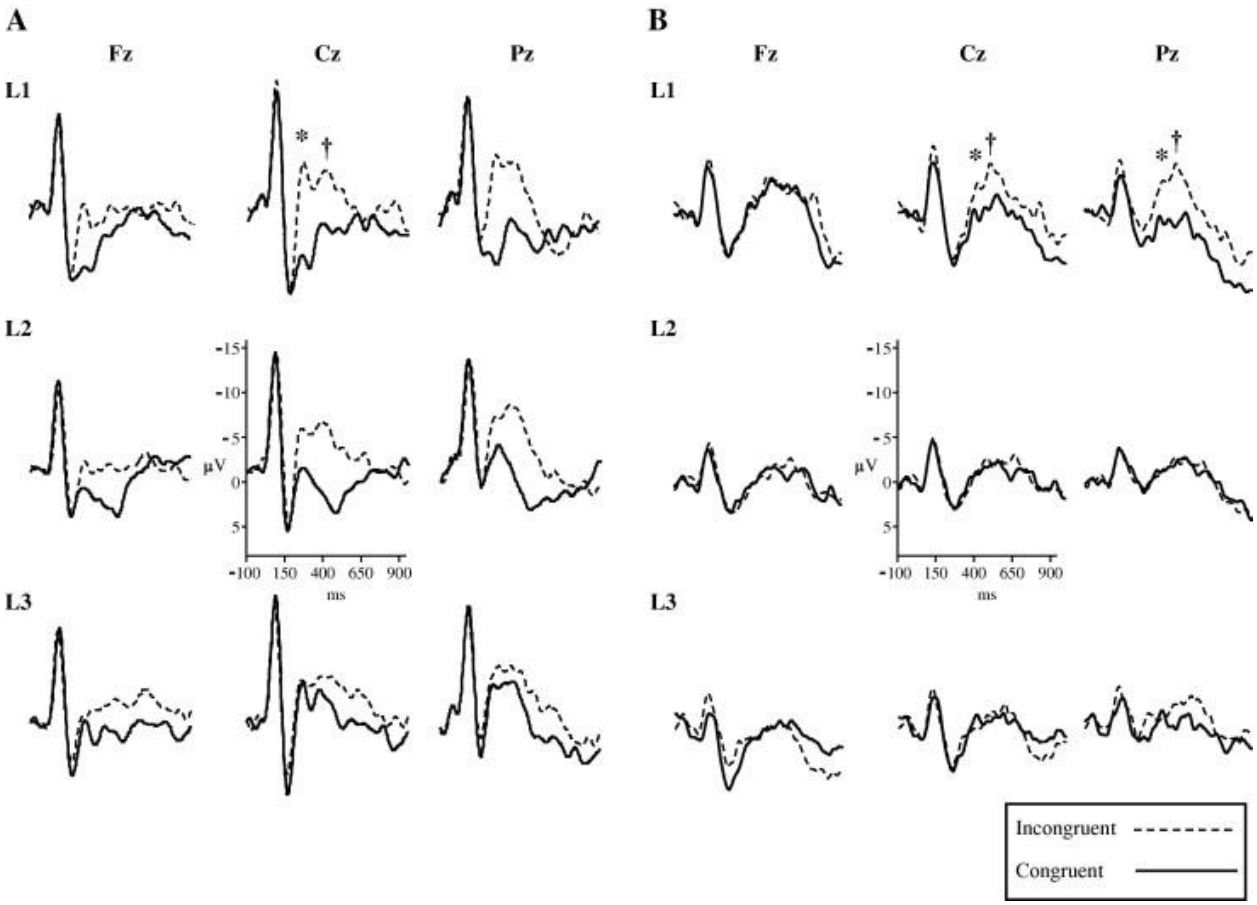

Fig. 7

(A) Grand-average ERPs at three midline electrode sites (Fz, Cz, Pz) recorded from a group of healthy young volunteers. A computerized version of the Peabody Picture Vocabulary Test-Revised (PPVT-R), adapted for simultaneous ERP recording, was administered at three levels of vocabulary difficulty (L 1 = preschool; L 2 = child; L 3 = adult). In each trial of the PPVT-R, a picture (e.g., a car) is presented, followed by a digitized spoken word that is either semantically congruent ("car") or incongruent ("lamp") with the picture. Note that the amplitudes of two components, the phonological mapping negativity (PMN, designated by *) and the N400 (designated by †), were enhanced to incongruent relative to congruent spoken words. The effect of incongruity was reduced or (statistically) absent when the vocabulary level of the words exceeded participants' knowledge levels (see L 3, where PMN and N400 were elicited by congruent as well as incongruent words). (B) Grand-average ERPs from a group of left-hemisphere stroke patients tested with the computerized PPVT-R. The N400 components of the patients were smaller in amplitude generally, and the difference between incongruent and congruent words was reduced, beginning at L 2. The correlation between patients' performance on the standard PPVT-R and an ERP measure (Marchand et al., 2002) was 0.87, demonstrating the capability of ERPs to function as a neuropsychological assessment tool.

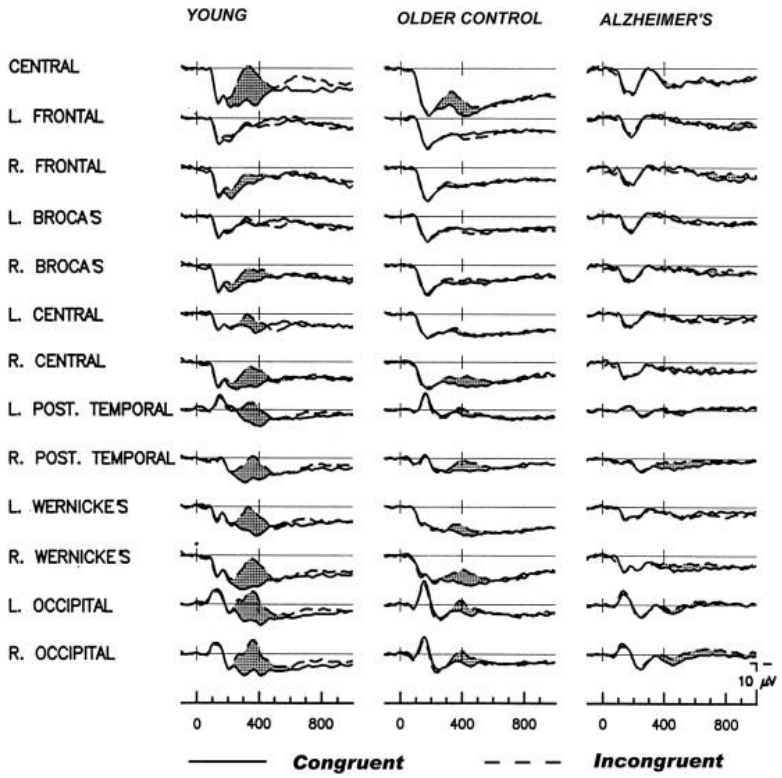

Fig. 8

Grand-average ERPs recorded from groups of healthy young adults, healthy old adults, and patients with Alzheimer's disease. On each trial, a spoken phrase was followed by a picture; the task was to indicate whether or not the target word was appropriate give the sense of the preceding phrase. For example, congruent: "The opposite of good" followed by "bad"; incongruent: "The opposite of give" followed by "center." The ERPs elicited by congruent and incongruent targets are superimposed at each electrode site. The N400 effect was delayed and smaller in the elderly controls relative to the younger controls and was further reduced in amplitude and delayed in latency in the patients with Alzheimer's disease. Shading reflects the congruity effect.