Part I

Neuropsychology of Language: Methods and Paradigms

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Potentials and Paradigms: Event-Related Brain Potentials and Neuropsychology

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Introduction

In the past few decades, researchers in neuropsychology have applied a wealth of new scientific techniques to investigate brain mechanisms underlying cognitive (dys)function. Here, we focus on how one such technique – scalp-recorded electroencephalographic (EEG) event-related brain potentials (ERPs) – has impacted our understanding of normal cognitive processes (including language) and which thus has great potential for investigating their disruption by disease states. Given what is now known about certain ERP effects in particular paradigms, combining the ERP method with neuropsychology is an excellent marriage of two specialized techniques.

In ERP studies, the EEG is recorded from participants, typically via surface electrodes affixed to the scalp (or embedded in a cap), as experimental stimuli are presented and sometimes, albeit not necessarily, require a (manual, vocal, or silent) response. In this context, the cognitive "events" of interest may include a particular class of stimulus, the absence of an (expected) stimulus (omitted stimulus paradigm), a correct or incorrect response, among many other possibilities, as long as a distinct time point for ERP time-locking can be defined; speech, environmental sounds, sign language, gestures, short videos, and the like also can be used. Segments of the EEG, each encompassing a fixed period of time before and/or after each instance (or "trial") of an event, can then be averaged to yield an average ERP. Averaging over multiple trials eliminates unrelated background activity that theoretically is random with respect to the stimulus and thus averages to zero, given enough trials. The resultant ERP reveals neocortical activity that is related, and synchronized in time and phase, to the stimulus (there are other analytic methods

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for extracting information from the background EEG that can complement ERP findings, but these will not be covered herein). The average ERP thus provides a picture of a significant subset (albeit not necessarily all) of the electrical brain activity involved in processing the event of interest. This traditional averaging method has, for the past 50 years or so, enabled ERP researchers to fruitfully examine brain activity associated with specific cognitive operations (see, e.g., Coles & Rugg, 1995; Kutas, van Petten, & Kluender, 2006; Münte, Urbach, Duezel, & Kutas, 2000, for reviews).

ERP recordings are one of the oldest neuroimaging techniques – although initially the "neuro" part of its character was downplayed, absent the one-to-one mapping between the distribution of electrical potentials at the scalp and their neural generators. Indeed, this inverse problem led many cognitive ERPers to argue that to the extent that ERP parameters are systematically related to perceptual, cognitive, or response processes, they would be psychologically informative even if generated in the big toe. Although true, this does a disservice to the technique for not only are ERPs neurally generated, but unlike indirect measures of neural activity such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), ERPs are a direct, instantaneous reflection of summed postsynaptic potentials primarily from neocortical pyramidal cells. And, although the use of many more recording channels over the past decade has not resolved the in principle unsolvable inverse problem, it has led to more attempts to delimit the neural loci of scalp ERPs and development of high resolution EEG (see Handy, 2005).

The precision of ERPs as a real-time index of neocortical neural activity makes them an apt tool for identifying when, and how, the information processing stream is affected – sometimes disrupted – in various neuropsychological disorders. ERPs from neuropsychological patients also serve a localizing function (for review see Swick, 2005); that use is not our focus here. Since ERPs can be elicited even without any overt response requirement, they are particularly suitable for work with communicatively impaired individuals (e.g., those with aphasia, motor deficits, or coma).

Despite these benefits, there are a number of special challenges in designing, conducting, and interpreting ERP experiments in clinical populations. For instance, structural brain pathology could affect volume conduction of electrical activity, altering the size or topography of scalp ERPs. To confirm that observed ERP differences in patients vs. controls reflect functional abnormalities, and are not due to structural lesions, it helps to ascertain that they are component-specific (see Swaab, 1998, for discussion). Furthermore, patients' and demographically matched controls' endurance and ability to understand and perform complex experimental tasks may not equal that of university students – the typical "normal" participant, and this may practically limit the range of paradigms that can be translated to patient studies (see Luck & Gold, 2008, for discussion). Limitations notwithstanding, careful patient ERP studies are essential to improving our understanding of neuropsychological disorders.

Although ERPs could be recorded in response to any stimuli/events in any type of experimental paradigm, using a new paradigm with a patient group is asking for trouble. It is challenging enough to "read" or to functionally link ERP patterns to perceptual, cognitive, and affective processes in typical subjects. We thus suggest using "tried and true" or well-established paradigms, where ERP sensitivities to different stimulus and task parameters have been well delineated through years of painstaking work. The more that is known about the normal ERP and its parameters in a particular paradigm, the more definitive the conclusions that one can make about how the corresponding processing is affected in the disease condition, even if with each new use, we may also learn more about the ERP per se.

Before applying the paradigm to an experimental patient group, replicate with a control group – personally producing known effects with your equipment and your stimuli. Failure to replicate effects in the normal group makes it pointless to extend the paradigm to a patient group, prompting instead a search for explanation(s), e.g., unusual characteristics of the "normal" sample, or confounds in the experimental set-up, design, or stimuli.

Only test the patient group when all is as it should be with controls. However, if task parameters need to be modified to meet patient abilities, do so, but examine their consequences within controls. Whenever feasible, designing experiments to yield large effect sizes in the controls is advantageous, because it increases statistical power to detect differences with the patient group, in whom a number of factors – including heterogeneity of disease effects; difficulty inhibiting sources of artifacts such as eye movements, blinking, and other muscle activity; possibly increased noise in the EEG itself (Winterer et al., 2004) and decreased tolerance for a high number of experimental trials (typically used to increase the signal-to-noise ratio) – often decrease such power by increasing within- and between-subject variability. Of course, effect sizes (and the experimental conditions under which these are likely to be largest) can more easily be estimated from published work.

In actuality, there exist a limited set of well-studied paradigms with known ERP effects that can be applied to investigate when and how various cognitive processes are affected in clinical populations. These paradigms (sometimes a thoughtful systematic series of them) allow inferences about a wide range of cognitive processes, e.g., inattentive auditory processing, selective attention, stimulus evaluation, working memory updating, movement preparation and inhibition, error processing, memory, language processing, and face processing, among others. Next we focus on a few of these.

Importantly, we believe that it would be a disservice to language processing researchers to restrict either the choice of paradigms or the ERP effects of interest to those traditionally linked to language (e.g., the ELAN, LAN, N400, PMMN, P600). Language processing is no longer considered an encapsulated mental module fundamentally separate from other cognitive functions. The early stages of visual processing in the brain do not distinguish linguistic from nonlinguistic stimuli; nor should we (e.g., Schendan, Ganis, & Kutas, 1998). Moreover, the beauty of the ERP technique is that it reflects a time series of neural processing from the moment the stimulus impinges upon the retina until it is but a fading memory, leaving a visible trace of sensory processing in the primary sensory cortex even if our primary interest, for instance, is in the modulation of a later segment of the ERP by semantic priming.

This exquisite temporal record of brain activity during stimulus processing is both a boon and a bane; though we can track stimulus processing as it traverses (to and fro) the brain, we must carefully control and/or match all aspects of our stimuli, conditions, and tasks to avoid introducing confounds or missing small effects that might go unnoticed by other measures. In short, the choice of paradigm (and componentry) should be driven by the question under study, not by the linguistic nature of the stimuli. Different paradigms are useful for answering questions about selective attention, mental chronometry, stimulus evaluation, response preparation, error monitoring, semantic analysis, etc., and it makes good scientific sense to capitalize on lessons learned by cognitive ERPers over decades. For these reasons, here we focus on some standard paradigms with well-established ERP effects that are not necessarily, if at all, specific to language. We sidestep debates regarding whether or not there exist any language-specific ERPs, because if a component answers a processing question, its language specificity is irrelevant. The N400, for example, has customarily been considered “language-related,” although it has more to do with semantic processing and contextual relations than with language per se. By contrast, other unarguably nonlanguage-specific ERP measures, like the mismatch negativity (MMN) and lateralized readiness potential (LRP) have nonetheless effectively been employed to address critical questions about language acquisition and production, respectively.

A final comment before we begin our review. It may be tempting to apply some ERP paradigm to a patient population “to see what will happen” to the known ERP effects, because something will. The union of ERP paradigms and clinical population is likely to be most valuable, however, in light of specific hypotheses and predictions for the patient group. Whereas it is not essential to predict the exact ERP patterns in patients, it is critical for anything but a posteriori interpretation to have some good reason(s) to think that the putative mental representation(s) or operation(s) linked to the dependent ERP measure are indeed affected in this group.

Oddball Paradigm, Mismatch Negativity, and Sensory Discrimination

Perhaps the most well-known ERP paradigm is the “oddball” paradigm (Donchin, 1981). In an “oddball” paradigm, there are two classes of stimuli/events – typically, infrequent (“oddball” or “target”) events that are randomly interspersed within a sequence of more frequent (“standard”) events. In the most typical task participants respond to the target (via button press or silent count), although in some variants all stimuli require some response. The ERP response to the “oddball” event is a P3 complex – comprising an N200 (whose distribution varies with modality) followed by a centroparietal positivity (P3), and a later frontally-negative posteriorly-positive slow wave (SW). These different subcomponents of the ERP response to the oddball are differentially sensitive to experimental manipulations.

Most researchers focus on the robust positivity variously called P3, P300, P3b, parietal P3, oddball P3, target P3, classical P3. Large and reliable P3b's are elicited by subjectively improbable events when attended. Although there is no consensus on exactly which cognitive operation (e.g., working memory updating, event categorization) the P3 indexes, much is known about its behavior in the oddball paradigm. For example, a low probability "oddball" event in an attended sequence will reliably elicit a large P3, allowing the inference that the event was categorized and encoded into working memory. Moreover, P3 peak latency provides an upper bound on the time by which enough information about the event accrued to support categorization. The oddball paradigm thus has proven particularly useful for investigating timing of stimulus-evaluation processes (vs. response-related processes), event categorization, and attentional allocation in dual-task situations, among others (e.g., Donchin, 1981; Kok, 2001). Can a patient group differentiate this class of items from another, and, if so, can they do it at normal speeds? Can irrelevant features of a stimulus be ignored while another feature is used as a basis for decision? An oddball P3 paradigm can provide an answer for such questions.

A similar positivity (P3b) also is seen in guessing paradigms (Sutton, Braren, Zubin, & John, 1965) where its amplitude is modulated by its probability of occurrence (bigger for low probability) and correctness (larger for correct than incorrect guesses with probability held constant), similarly in both the visual and auditory modalities, and its timing is modulated by the moment when the uncertainty of what the stimulus will be and when it will occur is resolved; gambling tasks are current-day versions of guessing paradigms (e.g., Gehring & Willoughby, 2002).

The parietal P3b contrasts with an earlier, frontal, P3a also elicited by an "oddball," whether or not the event sequence is attended. However, the P3a is best seen (not swamped by the P3b) when this sequence is unattended, such as when it is played auditorily while the participants reads a book or watches a silent video. In that case, the oddball event is more accurately referred to as a deviant. The P3a in the traditional oddball paradigm, or in a 3-stimulus paradigm which includes probable standard stimuli, improbable target stimuli, and equally improbable deviant stimuli, is excellent for investigations of processing outside the focus of attention, or novelty processing when each deviant is unique.

The unattended oddball paradigm in the auditory modality also reliably elicits a mismatch negativity (MMN) – a negative-going ERP over the frontocentral scalp whose peak occurs approximately 100–300 ms after the onset of deviant stimuli, lasting for ~150 ms (Näätänen, Gaillard, & Mäntysalo, 1978). Typically, MMN measurements are taken from point-by-point subtractions between the deviant ERP and the standard ERP. Deviants differing from a string of repetitive stimuli (the standards) on any physical parameter (e.g., pitch/frequency, intensity/loudness, duration) elicit an MMN if the brain (human or otherwise) is sensitive to the deviation.

Complex patterns of feature combinations also elicit MMNs, making this an excellent dependent measure for examining all sorts of auditory pattern sequences including temporal parameters. For instance, repeating a tone in a sequence of steadily descending tones elicits an MMN (Tervaniemi, Maury, & Näätänen, 1994), suggesting that the sensory memory trace (or echo) incorporates features not only of individual stimuli but also of their sequences. Although often larger with attention, MMNs do not require active attention and have even been observed in individuals in stage-2 and REM sleep, as well as in patients in a coma or persistent vegetative state (reviewed by Cheour, Leppanen, & Kraus, 2000). The MMN thus is an unparalleled index of auditory sensory memory in individuals with limited behavioral responses – such as infants, aphasics, those with dementia, etc.

On the dominant view, the MMN reflects a pre-attentive change detection mechanism, and indexes a mismatch between the deviant stimulus and a sensory trace of the preceding standard stimuli in echoic memory (~10 s; Näätänen et al., 1978). The MMN is smaller in amplitude and occurs later when the physical difference between deviants and standards is less pronounced (Aaltonen, Niemi, Nyrke, & Tuhkanen, 1987; Näätänen, Paavilainen, Alho, Reinikainen, & Sams, 1989), presumably reflecting greater difficulty of mismatch detection. Thus, both size and timing of the MMN effect are informative: amplitude reflects the perceived difference between standard and deviant, and latency reflects the speed of deviance detection. MMN scalp topography varies with the acoustic parameter differentiating deviants and standards (pitch, intensity, duration), in a manner implicating nonidentical neural populations within auditory cortex (Giard et al., 1995). Multiple sources of evidence pinpoint MMN generators near primary auditory cortex. Source localization studies also have more arguably implicated additional frontal generators (Doeller et al., 2003; Opitz, Rinne, Mecklinger, von Cramon, & Schroger, 2002), perhaps reflecting subliminal attentional switching (Giard et al., 1995).

The MMN has been used to investigate categorical perception in typical populations. As an exquisite index of auditory sensory memory, the MMN is a perfect ERP tool for studying any abnormalities at this level of auditory processing. The MMN also has been investigated as a prognostic indicator in brain disorders. In coma and persistent vegetative state, auditory MMN amplitude is smaller than normal, and predictive of eventual recovery of consciousness and overall functional outcome (Luaute et al., 2005; Wijnen, van Boxtel, Eilander, & de Gelder, 2007). Thus, among brain-damaged patients larger MMNs likely reflect a residual level of stimulus discrimination necessary to support recovery of higher cognitive function.

Schizophrenia patients also exhibit auditory MMN amplitude deficits, correlated with their deficits in a range of attention-dependent cognitive functions including verbal memory and figurative language comprehension (Kawakubo et al., 2007; Kiang et al., 2007); and with their degree of impairment in social and occupational function (Light & Braff, 2005). Although the mechanism underlying these correlations remains unclear, MMN deficits may reflect impairment in lower-level brain functions, such as pre-attentional stimulus discrimination or cognitive resource allocation, that may, in turn, be instrumental for higher cognitive operations (Braff

& Light, 2004; Javitt, Doneshka, Grochowski, & Ritter, 1995). Alternatively MMNs and these higher functions may both rely on fundamental neurochemical processes affected in schizophrenia, explaining the observed correlations. An important question for future research is whether MMN has prognostic utility for predicting long-term functional outcome in patients in the early stages of schizophrenia.

A well-designed patient study should include not only conditions with abnormal MMNs due to the hypothesized disorder, but also conditions with similar MMNs in controls and patients for unaffected stimulus processing. For example, Schulte-Koerne et al. (1998) investigated their dyslexic adolescent sample for a specific phonological deficit vs. a general auditory processing deficit. To that end, they used both speech (syllables /da/ vs. /ba/) and nonspeech (sine wave tones) to elicit MMNs, and found that MMNs for the tones were the same in the two groups whereas the syllable MMNs were smaller in the dyslexics, contra any general auditory processing deficit. To be fair, there are many more MMN studies of this type with mixed results as many factors differentiate speech and nonspeech and these need to be teased apart (Bishop, 2007; Näätänen, 2003). Nonetheless, the methodological point remains: as in neuropsychological studies with other dependent measures, dissociations rule!

The MMN paradigm has been an especially powerful research tool because it is also sensitive to long-term perceptual learning. MMNs have been found to track participants' discrimination abilities: initial inability to discriminate two frequencies was reflected in the absence of any reliable MMN which, however, emerged during and after learning, as the participant learned to distinguish them. Accordingly, the MMN has become a tool of choice for investigators of language acquisition and language learning.

Cheour et al. (1998), for example, used an MMN-eliciting paradigm to track changes in infants' abilities to discriminate phonemes. The standard /e/ and the deviants /ö/ and /õ/ were played to Finnish infants at age 6 months, and again at age 12 months. The standard and the deviant /ö/ are both naturally occurring phonemes in Finnish, whereas deviant /õ/ is not. Acoustically, /õ/ differs from /e/ more than does /ö/. In 6-month-old Finnish infants, presumably with only limited preferential exposure to the language, MMN amplitude is driven by the acoustic difference: the MMN was *larger* to the /õ/ than the /ö/ deviant. In contrast, in older (12-month-old) Finnish infants, presumably with more exposure to the Finnish phoneme /ö/ but not to /õ/, the MMN pattern reversed such that phonemic not acoustic deviance drove MMN amplitudes: MMNs were *smaller* to /õ/ than to /ö/. Statistical analyses showed that this change from 6 to 12 months of age reflected an increase in MMN amplitude to /ö/, and a decrease in MMN amplitude to /õ/. In contrast, in a comparison control group of 12-month-old Estonian infants, whose mother tongue includes both /õ/ and /ö/ as phonemes, the MMN was, as expected, larger to /õ/ than to /ö/.

Would amnesic patients of various types exhibit perceptual learning of this type? How about individuals with word deafness or patients with amnesia? Do individuals with specific language impairment have a specific problem with auditory signals with certain temporal parameters, only? Answers to such questions will not only tell us more about the nature of the MMN but also about the disorders themselves.

Go/No-Go Paradigm, No-Go N200 Effect, Lateralized Readiness Potential, and Mental Chronometry

Cognitive scientists and psycholinguists are interested in questions of timing; they routinely deal with issues of mental chronometry – the timing of mental operations – such as the relative temporal availability of different types of linguistic information. For many years, N200/P3b latencies were *the* ERP measures for inferring the timing of stimulus evaluation processes (e.g., Friedman, Simson, Ritter, & Rapin, 1975; Magliero, Bashore, Coles, & Donchin, 1984). However, with the adaptation of the go/no-go paradigm to ERP research, researchers have modified it to investigate timing during language production and cognition. In a simple go/no-go paradigm, participants respond to one class of stimuli and withhold their responses to another class. From one perspective the go/no-go paradigm is just another variant of an oddball paradigm, where one class of stimuli requires a response and the other does not; in many cases, the no-go event is low probability and elicits a large P300. However, even when oddball (no-go) and standard (go) events are equiprobable, the oddball also elicits a frontocentral negativity known as the no-go N200. The no-go N200 effect (point-by-point subtraction of the go ERP from the no-go ERP) is taken to reflect response inhibition. This hypothesis is supported by the finding that in monkeys if an experimenter stimulates the frontal cortex on go trials at the time an N200 typically would have occurred on a no-go trial, their overt response is suppressed (Sasaki, Gemba, & Tsujimoto, 1989). In humans, if the timing of the information on which the go/no-go decision is based is varied, the latency of the N200 effect can be used to infer when the specific information was extracted.

Another ERP measure routinely examined in the go/no-go paradigm is the lateralized readiness potential (LRP), a derived measure based on the asymmetric portion of the readiness potential (RP), a gradually increasing negativity beginning ~500–1000 ms before the onset of voluntary movements (Deecke, Scheid, & Kornhuber, 1969). The RP is also present on at least some if not all trials in stimulus-locked ERP averages in the interval between a warning stimulus and an imperative stimulus requiring a response (i.e., foreperiod) in a chronometric paradigm, and can be extracted (Kutas & Donchin, 1980) and used to compute the LRP via subtractions under the right set of conditions. The RP is largest at scalp sites over the central sulcus; its latter half (last ~500 ms) is larger over contralateral motor cortex, where it is generated, albeit contingent on integrity of the cerebellar-thalamo-cortical loop (Vaughan, Costa, & Ritter, 1968).

In an experiment in which some trials call for a right-hand response and others a left-hand response, this lateralized activity can be visualized by calculating the LRP either via a double subtraction or subtraction averaging method, where subtractions are performed with reference to the hand that should be used to execute the correct response on that trial (De Jong, Wierda, Mulder, & Mulder, 1988; Gratton, Coles, Sirevaag, Eriksen, & Donchin, 1988). On the subtraction averaging procedure: (1) for each hand, subtract the ERP at the ipsilateral central site from that at the contralateral central site (i.e., for right-hand responses, subtract the ERP at a right central site from the ERP at the corresponding left central site, and for left-hand responses, subtract the ERP at the left central site from the ERP right central site); and (2) average these two difference ERPs. This derivation eliminates any ERP activity that is the same for both left- and right-hand responses, leaving a measure reflecting differential activation of one responding hand relative to the other. The presence and polarity of the LRP thus are taken to index preferential response activation, its amplitude to index the degree of preferential response activation, and its latency when a response is preferentially activated.

Researchers have used both the latency of the no-go N200 and aspects of the LRP in the go/no-go paradigm to better characterize relative timing of the availability of different types of linguistic information (phonological, semantic, syntactic, etc.) during production (specifically, picture naming). One useful variant of the paradigm requires a stimulus with multiple attributes, with values of one attribute telling the subject which hand to respond with (right or left) and the other telling the subject whether or not to respond (go vs. no-go). For example, given the letters S and T, with letter identity (S vs. T) as one stimulus attribute and size (large S T or small s t) as the other, in one condition, the responding hand is contingent on letter identity, and the go/no-go decision is contingent on letter size, whereas in the other condition, these mappings are reversed (responding hand based on letter size and go/no-go based on letter identity). As already noted, the experimental design requires that across all trials, right hand be the correct response as often as left hand, and also that across all conditions both stimulus attributes be mapped onto each response variable (i.e., responding hand and go/no-go). It is only from the ERP patterns across the two conditions that inferences are warranted.

Schmitt, Münte and Kutas (2000) employed this type of go/no-go paradigm designed by van Turennout et al. (1997) to visualize the time course of speech planning processes – specifically, to determine whether semantic or phonological information is accessed first during tacit picture naming. Their participants viewed pictures of animals or inanimate objects. In one condition the go/no-go decision was contingent on a semantic attribute (whether stimulus depicted an animal or an inanimate object), and response hand was contingent on a phonological attribute of the stimulus (whether stimulus name began with a consonant or vowel). In the other condition, the decision mappings were reversed: the go/no-go decision was contingent on phonology, and the response hand on semantics.

As already noted, if semantic information is available before phonological information, then in the *go/no-go = phonology; hand = semantics* condition, individuals would use the semantic information as soon as it became available to differentially prepare a response with the appropriate hand – as seen in an LRP. Critically, this LRP would be evident not only on go but also on no-go trials, until the later incoming phonological information indicates no response be made. This no-go pattern would not be seen with the reverse mapping because the semantic information indicating that no response is needed would precede the phonological information triggering differential hand preparation. For the no-go N200 effect, the comparisons are the same, but the critical measure is its relative timing: the earlier no-go N200 effect indexes which of the two attributes is available for encoding first.

The results were clear: there was an LRP on no-go trials in the *go/no-go = phonology; hand = semantics* condition, but not in the *go/no-go = semantics; hand = phonology* condition – suggesting that semantic information in the stimulus was available ~80 ms before phonological information. The concurrently recorded no-go N200 data likewise implied an ~80–90 ms precedence of semantic encoding relative to phonological encoding. The potential utility of this paradigm for investigating neuropsychological disorders has been virtually unexplored thus far. The go/no-go paradigm as well as other paradigms allowing LRP calculation are also excellent for studying errors and their consequences. Peaking ~80–100 ms after a person commits an error there is a frontal negativity in the response-locked average, thought to be generated in the anterior cingulate cortex. This response is variously called the error-related negativity (ERN) or Ne (in contrast with a positivity – Pe – also seen following errors). The ERN is seen whether or not the person is aware of having erred (Falkenstein, Hoormann, Christ, & Hohnsbein, 2000; Gehring, Goss, Coles, Meyer, & Donchin, 1993). A similar negativity (fERN vs. rERN) is also seen to stimuli providing participants performance feedback, in this case, time-locked to the feedback stimulus (Holroyd, Nieuwenhuis, Yeung, & Cohen, 2003). This paradigm and associated component provide an excellent means of investigating error-related processes and feedback in all sorts of patient populations with language and nonlanguage materials and decisions.

Semantic Anomaly Paradigm, Semantic Priming Paradigm, and the N400

We have seen how researchers might shed light on the neuropsychology of language by using ERP paradigms that are more customarily associated with the study of other cognitive, nonlanguage domains. We now turn to two paradigms which are most commonly associated with language but which likewise have been extended to nonlinguistic stimulus processing and to questions that are not all about language.

In the late seventies, Kutas and Hillyard (1980) used a language "oddball" paradigm in which the final word of 25% of the sentences participants read (word by word) were semantically anomalous and the remaining 75% were semantically congruent (*He spread the warm bread with socks* vs. *He spread the warm bread with butter*, respectively). The ERP to the semantically anomalous ending, relative to the congruent ending, was characterized by a large centroparietal negativity between 200 and 500 ms, peaking around 400 ms in young adults (N400). Unlike for the

P300, a large N400 was elicited even when half the experimental trials included a semantic anomaly. Across many studies it became clear that the N400 is not a response to an oddball but rather the default response to potentially meaningful items, including written or spoken words, pseudowords, acronyms, pictures, signs in a sign language, environmental sounds, line drawings, scenes, video frames, gestures, etc. Moreover, years of research have revealed that many different factors (attention, word frequency, word repetition, orthographic neighborhood size, word typicality, and, perhaps especially, a word's offline cloze probability – i.e., the percentage of individuals who would continue a sentence context with that word) all influence N400 amplitude (for reviews see Kutas & Federmeier, 2000; Kutas et al., 2006). Many interesting psycholinguistic questions about all language levels (semantic, syntactic, phonological, discourse, prosodic, information structure) have and can be asked using the sentence violation paradigm. In fact, although not covered here, there are other potentials besides the N400 elicited in sentence violation paradigms where the violations are more syntactic in nature (e.g., the P600) that have made significant contributions to psycholinguistics (see van Berkum, 2008, for review).

As neither the P600 nor N400 in written (presented visually one word at a time) or naturally spoken sentences requires outright violations, it is possible for neuropsychologists to investigate a whole host of language processes without introducing any violations, and to do so under conditions in which participants have no task besides reading or listening and on some occasions answering comprehension questions. This is an extremely powerful paradigm, although when applied to new sentential structures, results may be easier to interpret when there are control materials and comparisons (e.g., a low cloze vs. high cloze word comparison) known to yield an N400 effect (difference between high and low cloze).

Another important finding with practical experimental consequences for studies of cognition is that N400 elicitation is not contingent on sentence materials. N400 amplitude modulations are seen in semantic priming paradigms – where stimuli are presented in pairs, a prime followed by a target – that are somehow related to each other (vs. not). N400 amplitudes to target stimuli are smaller (sometimes even positive) when a prior stimulus (prime) is semantically related to it (e.g., *cat* has a smaller N400 when preceded by *dog* than by *chair*). Many different types of prime–target relations have led to N400 priming effects including identity, morphological, phonological, functional, and affective, among others (Bentin, McCarthy, & Wood, 1985; Kellenbach, Wijers, & Mulder, 2000; Zhang, Lawson, Guo, & Jiang, 2006). The stronger the association between the prime–target pair, the greater the N400 reduction (e.g., Harbin, Marsh, & Harvey, 1984; Kutas & Hillyard, 1989). Critically, the N400 priming effect is seen not only for spoken and written words, but nonverbal stimuli (environmental sounds, pictures, gestures) as well, with slightly different latencies and/or scalp distributions. Critically, whether N400s appear in a semantic priming paradigm, a sentence, or even a discourse, their timing and qualitative characteristics are very similar. Moreover, N400 word-level priming effects interact with higher-level contexts. These sorts of findings have had important ramifications for theories that suggested a linear progression of analysis from the word, to sentences, to discourse as well as for theories wherein lexical and sentential processes are encapsulated in separate modules. It appears then that both the sentence violation and the semantic priming paradigms with N400 as the dependent measure are well suited for investigating questions about the role of context on (non)object or (non)word processing in normal and abnormal populations as well as about the functional (dis)organization of and access to knowledge about the world (semantic memory).

Indeed, the N400 in these paradigms has proven particularly useful in studies of how the functional organization of semantic memory is affected by normal and abnormal aging. While a host of behavioral studies have revealed that performance of the elderly on many verbal measures, such as vocabulary (Verhaeghen, 2003) and ability to generate normative word associations (Burke & Peters, 1986) matches (or even exceeds) that of younger individuals, others have noted that aging leads to slower response times in tasks such as picture naming, word reading, and word categorization (Feyereisen, Demaeght, & Samson, 1998), suggesting changes in semantic processing with age. Federmeier and Kutas (2005) used the N400 to investigate whether the young and the elderly make differential use of context in accessing semantic memory. They found that, in strongly constraining sentence contexts (with high-cloze completions) such as *He didn't worry about burglars because he kept two fierce <u>dogs</u>,* elderly compared to younger individuals exhibited larger N400 amplitudes to the final word, although both groups showed similar N400 amplitudes to these words in weakly constraining contexts (*They both have jobs, but they get some extra income by raising <u>dogs</u>.*) These results suggest that aging decreases the ability to make use of strongly constraining contexts to guide semantic processing.

N400 paradigms also have been used to examine abnormal aging as in Alzheimer's disease (AD), a common cause of dementia in the elderly. AD is a neurodegenerative disorder whose symptoms include problems with memory and attention in addition to language and visuospatial deficits. AD patients show impaired performance on tasks relying on semantic memory (e.g., category fluency, object naming). Schwartz et al. (2003) investigated the cause of this impairment by comparing N400s elicited by semantically associated vs. unassociated word pairs (lexical context effect) embedded within congruous vs. anomalous spoken sentences (sentential context effect), in AD patients and age-matched normal control participants. The following are examples of the sentence stimuli, with associated and unassociated word pairs underlined:

Congruent and associated: *After taking his wallet they waved a <u>gun</u> and threatened to <u>shoot</u> him if he reported it.*

Anomalous and associated: *After trying his Chinese they irritated a <u>gun</u> and expected to <u>shoot</u> him if he clipped it.*

Congruent and unassociated: *The mill worker caught his hand in a piece of <u>machinery</u> and was <u>rushed</u> to the hospital.*

Anomalous and unassociated: *The young shoes took their promotion in a discussion of machinery and were rushed to the aliens.*

If AD patients are characterized by a breakdown in semantic memory, then N400 amplitudes to target words should show less than normal reductions when preceded by related lexical and/or sentential context, given the degraded associative links between the stimulus and contextual concepts. By contrast, if AD patients' representations in semantic memory remain relatively intact, but retrieval of this information is impaired, then related lexical and/or sentential context should lead to normal N400 reductions, reflecting its supportive effect on retrieval. Schwartz et al. found that AD patients exhibited normal N400s to unassociated words in anomalous sentences, along with a normal degree of N400 amplitude reduction with related lexical or sentential context. However, this amplitude reduction occurred much later than normal, raising the possibility that this slowed access to relatively intact or only partially impaired semantic memory precludes normal language function.

Schizophrenia is another disorder in which some symptoms appear to reflect abnormal processing of relationships between concepts in semantic memory. One of these symptoms is disorganized speech, which includes words or phrases unrelated to their context. Another such symptom is delusions (fixed false beliefs), which often involve "an abnormal view of relationships between events" (Hemsley, 2005). For example, patients may attribute special significance to the co-occurrence of two unrelated events. Conversely, an object or event occurring in its normal context may be experienced as being out of place and hence unusual or suspicious. Thus, researchers have used the N400 to probe for abnormalities in how meaningful context facilitates processing of subsequent stimuli in schizophrenia with mixed results, possibly due to subpopulation or experimental task differences. Overall, however, results suggest that, over a very short interval, stimuli that are relatively weakly related to context may be facilitated more than normally (as reflected in smaller than normal N400s); whereas, over longer intervals, there appears to be a deficiency in the use of context to facilitate related concepts in general (as reflected in larger than normal N400s; reviewed in Kiang, Kutas, Light, & Braff, 2008; Kreher, Holcomb, & Kuperberg, 2006; Salisbury, 2008). The latter deficiency may also account for N400 evidence that schizophrenia patients fail to normally suppress generically dominant associations when they are not context-appropriate, such as associates (e.g., *river*) of the dominant meaning of a homograph (*bridge*) being used in its subordinate sense (a card game) in a sentence context (see Kuperberg, 2008). Elucidating how each of these abnormalities might be related to specific clinical symptoms is a focus of ongoing research.

Not surprisingly N400 priming paradigms also have been applied to the study of language disorders in aphasia to assess residual capacities. For example, Hagoort et al. (1996) used an N400 semantic priming paradigm to examine the integrity of semantic-lexical representations and their use by elderly controls, various types of aphasic patients, and nonaphasic patients with right hemisphere lesions. All groups listened to pairs of spoken words that were associatively related, semantically related, or unrelated. The elderly controls showed the normal N400 priming effect with reduced N400s for both types of related targets relative to unrelated target words, as did aphasics with minor comprehension deficits. Right hemisphere patients also exhibited normal N400 priming effects for associatively related pairs, but only a smaller priming effect for the semantically related pairs. By contrast, aphasic individuals with severe comprehension deficits showed no reliable N400 priming effects for either relation. In fact, the size of the N400 priming effect was negatively correlated with the degree of the comprehension deficit in the aphasic patients, regardless of their specific diagnosis. The authors concluded that the aphasic patients' word representations were largely intact, but that those patients with severe comprehension deficits were unable to integrate them into a context – and all this inferred from a passive priming task with patients merely listening and experimenters listening in via electrical brain recordings!

Summary, Conclusion, and the Future

We have introduced a number of different paradigms (oddball, chronometric and go/no-go, semantic anomaly, and semantic priming) and the ERP components reliably elicited within them (P3b, P3a, MMN, no-go N200, LRP, ERN, N400). We reviewed many (although not all) of the factors that influence parameters (amplitude, latency, distribution) of these components and/or effects (comparisons shown as difference ERPs) and provided a few examples of how they have been applied to neuropsychological populations. And, in some cases, we raised some unanswered questions that were ripe for the asking with a particular paradigm/ERP combination. Our review is selective, not comprehensive; for instance, we do not discuss attentional paradigms (e.g., visual or auditory selective attention) and related P1, N1, Nd, PN components; visual search paradigm and N2PC effect; a whole host of grammatical violations, and various related components such as LAN or P600; or face processing and the N170, among others. All of these are potentially applicable to address questions about the nature of language processing (normal or deficient) in a variety of patient populations.

Via the right combination of paradigms and associated ERP effects, we can tease apart different stages and/or subprocesses of analysis, and gain a deeper understanding of what goes on in the mind/brain of an individual, be their brain intact and typical or somehow atypical or compromised. If we have succeeded, then we have convinced our readers that under the appropriate experimental conditions, different aspects of the ERP waveform can be analyzed to determine *whether* and *when* certain neural/mental operations take place. To complete what has already been mentioned, (1) early sensory potentials (e.g., the occipital P1 and the N1) index whether a stimulus is sensed and perceived, (2) potentials between 200 and 550 ms or so post-stimulus (the time region of the N400) over posterior scalp sites index whether, once perceived, a particular event is analyzed at a semantic/conceptual level, and (3) late posterior positivities between 400 and 800 ms (the P3b) index whether the event was identified, categorized, and consolidated in working memory. There is obviously more to know about information flow through the central nervous system and its relation to mental processes, but whatever clever use of basic ERP effects can tell us is quite powerful. We conclude with a specific example of how ERPs have been used to isolate the temporal locus of the attentional blink (AB) phenomenon.

The AB is a brief period (300 to 600 ms) after the detection of a target item embedded in a stream of rapidly presented stimuli during which a subsequent target is missed (Raymond, Shapiro, & Arnell, 1992). For instance, shown rapidly flashing characters (e.g. B T D A 3 N P **Z** F R K M) at a rate of 10/s or less, and asked to report on two targets (e.g., a number and a letter in a contrasting color – in this example the number 3 and the letter **Z**), participants can accurately report whether the first target (T1) is odd or even, but are less accurate at reporting whether the second target (T2, at lag 3) is a vowel or a consonant. This impairment occurs when T2 falls within 300–600 ms interval after the first target (the AB), but not immediately after T1 (lag 1) or later (at lag 7). The question is: What accounts for this pattern of effects? Is T2 not detected, or is the problem somewhere after initial detection but before identification or consolidation into working memory? These questions are amenable to ERP analysis as beautifully demonstrated by Vogel and his colleagues.

To establish which of these processes is the likely culprit, Vogel et al. (1998) recorded ERPs during a modified AB paradigm. Their first study tested the hypothesis that the AB is due to suppression of sensory processing, using two early (~100 ms or less) sensory visual ERPs – the P1 and N1 components, known to be sensitive to physical sensory parameters (e.g., intensity) as well as visuospatial selective attention – as dependent measures. They modified the typical AB paradigm to maximize ERP inferences. In any given trial participants saw 19 letters and 1 digit per stream, 88 ms per character. Two items in the stream were targets (T): T1 was a blue digit, and T2 was a red letter, occurring at one of three lags (1, 3, or 7); all nontarget letters were also blue; participants were asked to report whether T1 was even or odd and whether T2 was a vowel or a consonant. ERPs were recorded to a task-irrelevant white square flashed behind T2 on 50% of the trials and not on the other half. The dependent measure in this irrelevant probe flash technique was the difference ERP between flash and nonflash trials, thereby avoiding the interpretive problems arising from fast presentation rates when ERPs to individual items massively overlap. The pattern of T2 report accuracy across the 3 lags – with and without the flash – showed a clear AB effect at lag 3; this was important to show because the flash may have unwittingly altered the behavioral phenomenon. The difference ERPs to the flash (that appeared concurrently with T2) were characterized by P1 and N1 components, which were statistically indistinguishable at all 3 lags. Thus, it does not appear that AB reflects the suppression of information at a perceptual stage. Rather, AB is post-perceptual. But where?

In another experiment Vogel et al. used the centroparietal P3b elicited by stimuli that have been encoded into working memory as a dependent variable. The question was whether a target in the AB period did or did not elicit a P3b: if it did, then AB occurs after information reaches working memory, if not, the AB occurs at that stage of processing or before. In this version, T1 was a black digit embedded among black nontarget letters; T2 was a white letter. However, given that the largest P3b's are elicited by infrequent stimuli plus the need to avoid component overlap, T2 was a white E on 15% of the trials (response required) and some other white letter on 85% of the remaining trials (no response required). The dependent ERP measure was the difference between the oddball T2 and the standard T2 – a P3b effect. The results were clear: the P3b effect was large at lags 1 and 7 and nonexistent within the AB at lag 3, leading to the conclusion that AB operates before or during the process of forming a stable representation of the stimulus in working memory.

In yet another version of the AB paradigm modified for ERP recording (in this case an N400 effect), participants were presented with a context word at the beginning of each trial (e.g., *shoe*), followed by a stream of consonant strings presented at a rate of one every 83 ms. Within this rapid stream there were two critical target items: T1 was a string of numbers (e.g., 8888888) and T2 – occurring at one of 3 lags – was a word either related to the context word (e.g., *foot*) or unrelated to it (e.g., *pickle*). T2 was always followed by additional consonant strings plus a 1 second delay, after which participants reported on the targets. In the dual-target (vs. control single-target) condition, instructions were to make forced choice responses at the end of each trial on both T1 (odd or even) and T2 (related or unrelated to the context word). The dependent ERP measure was the difference between the ERP to the T2 semantically related vs. unrelated to the context word. The results in the dual-target conditions indicated that participants were accurate at reporting whether T2 was semantically related to the context word at lags 1 and 7, but not at lag 3. From this result one might have concluded that blinked items were not analyzed to a semantic/conceptual level. However, the ERP pattern revealed a large, similarly sized N400 semantic relatedness effect at all three lags. So although participants could neither identify nor classify words falling in the AB zone in terms of their relation to the meaning of the context word, these words nonetheless exhibited a reliable N400 semantic priming effect, indicating that the blinked words had been analyzed to a semantic/conceptual level. This result is but one of many that point to the value of recording ERPs and behavior for they are different measures taken at different times that are only sometimes redundant in what they reveal about the workings of the human mind/brain. There are more experiments in this series examining the role of consolidation of information in working memory in the AB phenomenon, as well as others using known ERP effects in a similar fashion to explain other behavioral phenomena.

Properly and wisely used, ERP components are not only handy tools for capturing specific computational processes in action and for functionally demarcating and dissecting the human cognitive (including language) architecture, but at times one of the few available tools to do so, in all human brains – young or old, intact or compromised, compliant, defiant, or simply incapable.

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