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Chapter 2.5

Cognitive event-related potentials

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General description of the method and its use and pertinent terminology

Long latency event-related potentials (ERPs) have been shown to vary as a function of a multitude of cognitive factors such as attention, memory, and language among others. For research purposes the questions that can be addressed with cognitive potentials are countless, leading to a proliferation of different paradigms and stimulation schemes. On the other hand, clinical applications of cognitive potentials have been less successful for the following reasons.

- Many paradigms are too complicated for application in patient populations.
- The overlap between normal and cognitively impaired populations is considerable, therefore limiting the diagnostic utility of cognitive potentials.
- Many of the paradigms used in research are very time consuming, prohibiting their use in clinical practice.
- The psychological constructs associated with a certain component are sometimes ill defined.

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These points notwithstanding, cognitive potentials have been used to address a number of clinical questions, most notably in the area of dementia. Here, the auditory oddball paradigm giving rise to a prominent P3 (P300, LPC) component, has proven to be useful. We will first address the recording of the P3 component in the auditory oddball paradigm followed by the discussion of other components with potential clinical use.

P3 in the auditory oddball paradigm

The P3 component has a large supramodal portion and can therefore be obtained in the auditory as well as visual and somatosensory modalities and in many different experimental situations. The latency of the P3 ranges from about 300 ms in simple auditory classification tasks to more than 700 ms in complex visual tasks. Owing to its simplicity, the auditory oddball-paradigm has been most widely used in clinical populations and should therefore be the focus here.

Physiological background

Long latency cognitive ERPs originate predominantly from cortical structures and intracranial

recordings have revealed multiple generators including sites in the hippocampus, and the temporal, parietal and frontal lobes. As the different cortical structures involved are likely subserving different functions, this suggests that the P3 is probably not a unitary phenomenon.

In terms of P3 latency, it has been suggested that it reflects stimulus evaluation time rather than response selection time even though this has been the subject of criticism. P3 amplitude has been found to vary as a function of stimulus probability (both objective and subjective), certainty of the subject about the response, the amount of information transmitted by a stimulus, among others (Johnson 1986).

Technical requirements

While for research purposes recording arrays of 32 and more electrodes are standard, for clinical P3 studies a reduced set of 4 recording channels is often sufficient. These should include electrodes Fz, Cz and Pz of the international 10/20 system referenced to the mastoid processes (preferably algebraically rereferenced to the mean activity at the two mastoid processes) and a montage (e.g. infraorbital electrode vs. the mastoid processes) to monitor eye movements for rejection.

A time-constant of 1 s (better 3 s, exceptionally 0.3 s) and low-pass filter settings at 30–100 Hz are required for recordings with minimum distortion. Recording epochs should include a pre-stimulus baseline of 100 ms and should include 700–1000 ms post-stimulus. AD conversion should be performed with a resolution of 4 ms or better.

Averages should be obtained after artifact rejection (for example by using an amplitude criterion on the eye-channel) and should include at least 50 stimuli per condition. Recording should be repeated at least twice to judge the constancy of the response.

The auditory oddball-paradigm entails the presentation of frequent (~80%) tones (e.g. 65 dB HL, 1000 Hz, 50 ms duration, 10 ms rise and fall time) with randomly interspersed rare tones (~20%, e.g. 65 dB HL, 2000 Hz, 50 ms duration, 10 ms rise and fall times). The interstimulus interval should be randomized and should be approximately 1500 ms. To ensure the subjects' attention, they can either be asked to mentally count the rare tones or to press a button held in their dominant hand for each rare (target) tone.

Factors affecting the quality of the investigation

Their unique sensitivity to cognitive factors makes the cognitive potentials also very vulnerable to general changes in attention and vigilance sometimes rendering an examination uninterpretable as no discernible P3 peak emerges. Potentials from subjects who did not perform the task properly should therefore not be evaluated.

Eye-blinks, especially when they occur time-locked to target tones, can sometimes preclude the examination of a patient. Sometimes an increase of the total number of stimuli delivered can remedy this problem. Also, several approaches have been proposed for the mathematical correction of eye-blinks, but these procedures are time -consuming and not available for most clinical routine laboratories.

Waveform description

A typical example for the P3 component is depicted in Fig. 1. The first discernible peak is a negativity around 80 ms (N1) with a frontocentral maximum present for both rare and frequent tones. For the targets this is followed by a second negative peak around 250 ms (N2) and a positive peak (P3) peaking between 300 and 370 ms in a middle aged normal population. The P3 is maximum at Cz and Pz sites. Sometimes a double-peak is observed in the P3 range, with the first peak (P3a) usually showing a more frontal maximum than the second peak (P3b). In these cases the second peak should be used for the determination of the peak latency. Normal values can be determined from Table 1. They show that age is a very important variable and clinical results should only be reported with regard to age-matched normal controls. It is customary to compute an age latency regression line together with standard errors. Clinical experi-

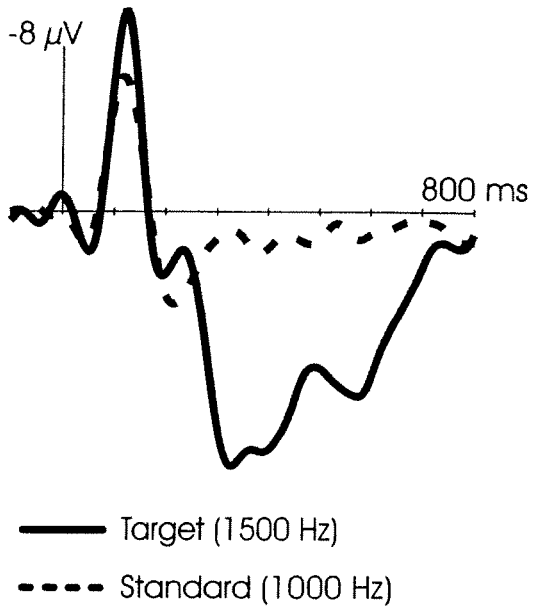

Fig. 1. Typical waveforms obtained in a normal 60 year old subject in an auditory oddball paradigm. After an initial negative peak that is present for both stimulus categories a broad positivity (P300) is observed for the targets. Task: Button press for targets. Montage: Cz referred to averaged mastoids. Average of 50 target and 200 standard stimuli.

ence suggests to define 2 standard errors away from the regression line as the upper limit of P3 latency.

Typical application for clinical pratice

The principal clinical application of the P3 in the oddball paradigm has been in the area of diagnosis of dementia. Here, a number of papers has reported a delay of P3 latency with regard to age-matched control populations. However, the specificity and sensitivity of P3 latency are still a matter of discussion, with sensitivity in real mixed clinical populations around 70%. As P3 latency indicates cognitive slowing, the specificity with regard to diagnosis is naturally low.

The clinical usefulness might be high, however, in specific situations such as the distinction between depressive pseudo-dementia and dementia (Polich 1998).

TABLE 1
TYPICAL NORMAL LIMITS OF P300 LATENCY[a]

Age (years)	Latency (ms)	
	Mean	Upper limit
20	320	360
40	350	390
60	390	425
80	420	460

[a] These values vary depending on specific stimulation (rate, modality, task) and recording techniques.

Mismatch negativity in clinical situations

Physically deviant auditory stimuli occurring among frequent ('standard') stimuli (e.g., tones or phonetic stimuli) elicit the mismatch negativity (MMN), a component occurring with an onset latency of about 130 ms and lasting to about 250/300 ms (Näätänen 1995). The MMN is presumably generated by a mismatch process between the sensory input from a deviant stimulus and a neural sensory-memory trace representing the physical features of the standard stimulus. This process, as well as sensory analysis of auditory input and its encoding into the memory trace, appear to be automatic since the MMN is elicited even by changes in unattended auditory stimuli. Therefore the MMN opens the unique possibility of an objective measure of the central representation of a sound. It appears possible to assess discriminative capabilities in individuals whose auditory capacities are difficult to determine, including infants, young children and those with severe cognitive impairment.

An optional situation for the recording of the MMN entails the presentation of repetitive sounds (e.g. 65 dB HL, 75 ms duration, 10 ms rise and fall time, 1000 Hz) with an occasional deviating sound (e.g. 25 ms, probability ~10 %) while the subject is attending elsewhere (e.g. reading a book, performing a visual task). In principle, other types of mismatch (loudness, spatial location, rhythm, complex auditory features) are possible (Fig. 2). MMN is best observed in frontal and central channels and for clinical purposes 5 channels (Fz, Cz, F3, F4 referenced to linked/averaged mastoid processes or the tip of the nose) are sufficient. Bandpass should be 0.1 (0.3) Hz to 30 (100) Hz.

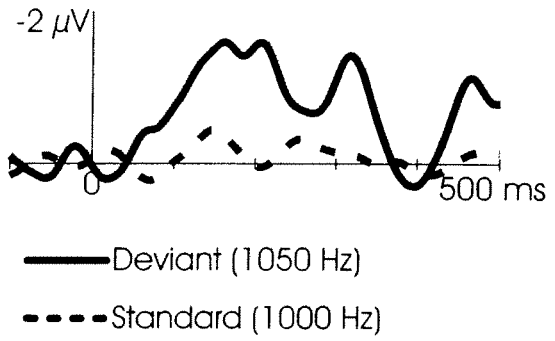

Fig. 2. Typical waveforms obtained in a passive listening task while the 60 year old subject was reading a book. Occasional (10%) deviant stimuli produce a negativity relative to the frequent standard stimuli (average of 60 deviant stimuli). Montage: Cz referred to averaged mastoids.

Averages should be obtained for at least 500 ms after stimulus onset (AD resolution 4 ms or better). For a reliable estimate, at least 200 deviants should be recorded. For clinical purposes at least one replication should be done.

Electro- and magnetoencephalographic dipole mapping studies have localized the generators of MMN to supratemporal auditory cortex in the vicinity of Heschl's gyrus, probably reflecting preattentive stimulus change.

Extensive normative values similar to P3 latency have not been published for the MMN. However, the response can be obtained over the entire lifespan including newborn infants. As the MMN typically is used as a marker of preattentive auditory processing, for clinical purposes its presence or its absence is most important.

N400 in clinical situations

Another component with potential clinical use is the N400, a negative going deflection that can be obtained in language tasks (Hagoort and Kutas 1995). A typical situation for the reliable elicitation of the N400 entails the presentation of words that either match or do not match a preceding context which can be either a sentence or a single word (e.g. Sentences: I drink my coffee with cream and sugar/mud; Words: boat, ship/crater). Words that do not match the context give rise to a more negative waveform starting approximately 250 ms after stimulus onset and peaking at about 400 ms. The effect is widespread, has a centroparietal maximum and is slightly bigger over the right scalp. N400 responses can be obtained to auditory and visual stimuli with the auditory modality being more feasible for patient populations. At least 50 stimuli (better 80) per category (match/mismatch) should be recorded. Each critical stimulus should be different as repetition diminishes the N400 response and the critical stimuli should be matched in terms of word frequency, length and word-class between the two conditions (Fig. 3).

A bandpass of 0.1–30 (100) Hz should be used for recording and the AD resolution should be 4 ms or better. Recording epochs should include at least 800 ms after the onset of the stimulus.

N400 has been used in the investigation of dementia, head trauma, schizophrenia and aphasia. It has been demonstrated that it can give an index for the receptive vocabulary in a severe case of cerebral palsy, thus suggesting that single case studies using N400 are viable. Also, in a number of group studies, aphasics' N400 has been shown to be delayed indicating a temporal problem.

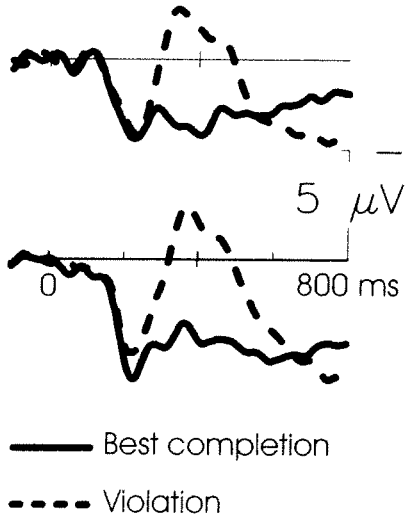

Fig. 3. Example of an N400 experiment. The subject's task was to read for comprehension. Half of the 160 sentences ended with a violation (I drink my coffee with cream and mud), while the other half ended with the best completion (...sugar). The violations produce a monophasic negativity with a peak around 400 ms. Montage: P3 (upper panel) and P4 (lower panel) referred to averaged mastoids.

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