The learning-oddball paradigm: Data of 24 separate individuals illustrate its potential usefulness as a new clinical tool

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**Abstract**

Objective: In a previous article reporting group data, we presented event-related potentials (ERPs), which were evoked by randomly presented target stimuli in a ‘learning-oddball’ task. These ERPs contained a large N2-P3 complex that decreased and a Contingent Negative Variation (CNV) that increased when the targets were presented in a regular fashion. Using the learning-oddball paradigm, the aim of the present paper was to determine ERP effects of introducing regularity in individual participants.

Methods: The data from the previous study were re-analyzed at the level of the individual participant, extracting individual sigmoid curves by means of wavelet-denoising and focusing on RTs, and CNV, N2, and P3 ERP components.

Results: Most participants displayed significant sigmoid curves with respect to the P3 component (22 of the 24 participants – 22/24), the N2 component (20/24), and/or the CNV (19/24) component. In contrast, reaction times (RTs) appeared less sensitive to incidental learning (15/24). Modest correlations were observed between RTs and N2 component amplitudes.

Conclusions: It is possible to extract significant ERP changes to introducing regularity in individual participants.

Significance: Tracking ERP changes within the learning-oddball paradigm might be a useful tool to assess pattern detection capacities in individual patients.

**Highlights**

- An ERP study using a learning-oddball paradigm was employed to assess pattern detection in individual participants.
- ERP changes across learning trials corresponded to sigmoid curves that could be established in each individual participant.
- The ERP/learning-oddball paradigm implicates a potential tool for assessing pattern detection capacities in individuals.

1. Introduction

1.1. Clinical applications of event-related potentials

Event-related potentials (ERPs) are time-locked voltage fluctuations in the EEG resulting from sensory, cognitive, or motor-evoked neural activity (Rugg and Coles, 1995). ERP components are typically divided into two types, based on their latency. Components with latencies of up to 100 ms after stimulus onset are assumed to be primarily determined by the physical characteristics of the stimulus presented, and are, therefore, referred to as exogenous components. The later occurring endogenous components (>100 ms after a stimulus or event onset) are assumed to be determined by cognitive aspects of information processing (Gaillard, 1988).

ERPs have been examined as a potentially useful clinical tool in a number of previous studies. For example, Halliday et al. (1973),
examining visually evoked potentials, found that a large proportion of patients suffering from multiple sclerosis (MS) displayed increased latencies in early exogenous components compared to healthy controls. This delayed response can be used as a biomarker for the diagnosis of MS in individual patients. More generally, such electrophysiological tests of sensory function have proven to be of considerable assistance in the diagnosis of a variety of neurological disorders (Barrett, 2000).

Within an oddball task, a common target detection task, target stimuli typically elicit a large ERP P3 component. The P3 component (also referred to as P300 or P3b) is a positive wave that peaks between 300 and 600 ms after target presentation, and has maximum amplitude over the central posterior region of the brain (Polich, 2007; Pritchard, 1981). It has been well established that on a group level schizophrenic patients display a decreased P3 amplitude compared to healthy controls (Brenner et al., 2009; Jeon and Polich, 2003; Rosburg et al., 2008) and that AD patients display an increased P3 latency (Rossini et al., 2007). However, when evaluating these abnormalities as a means to differentiate between healthy controls and AD patients, Patterson et al. (1988) concluded that the oddball paradigm is useful in describing group differences, but is not sufficiently sensitive to differentiate individual AD patients from healthy individuals. This lack of sensitivity has been attributed to the nature of the task. The oddball is a relatively simple target detection task, and it was suggested that a more demanding task, which measures more specific cognitive functions that are affected by the disorder (e.g. [working] memory), might be more effective.

1.2. The ‘learning-oddball’ paradigm

In a previous study, we employed a ‘learning-oddball’ paradigm (Jongsma et al., 2006). This paradigm enables the tracking of the dynamic processes that underlie auditory pattern learning. The ‘learning-oddball’ paradigm has been developed as a variant of the classic auditory oddball paradigm. In a typical oddball experiment, frequent background stimuli are occasionally replaced (at random intervals) by infrequently occurring deviant stimuli – the ‘oddball’ or target stimuli. These deviant stimuli typically elicit a P3 ERP component. In addition to the P3 component, unexpected stimuli also give rise to an N2 component (also referred to as N200 or ‘N2b’), a centrally distributed negative wave that peaks at approximately 200 ms after stimulus presentation and often precedes the P3 (Folstein and van Petten, 2008). Also, when expecting a target stimulus, a slow negative shift in the ERP waveform appears – the ‘Contingent Negative Variation,’ or ‘CNV’ (Birbaumer et al., 1990; Walter et al., 1964) – starting about 300 ms before target presentation. The key modification in the learning-oddball paradigm is that in a block of trials with 16 target presentations, the first 8 target stimuli are presented at (pseudo) random positions, whereas the remaining 8 target stimuli are presented at the same intervals, thus leading to the introduction of a regular pattern of non-target/target presentations (see Fig. 1). With this paradigm it has been shown that at a group level (N = 24) the amplitudes of the ERP N2-P3 complex, the CNV, and reaction times (RT) in response to the 16 consecutive target stimuli (8 random, 8 regular) could be fitted by sigmoid curves that correlated with the thus introduced regularity (Jongsma et al., 2006). Moreover, when all 6 blocks of irregular–regular targets where analysed at the level of single-trials, a higher order effect was observed, such that the regularity effects reflected by the sigmoid curves appeared more rapidly after regularity onset with each consecutive block. We thus proposed that with respect to the introduced regularity within the oddball paradigm, implicit learning occurred (Jongsma et al., 2006).

1.3. Aim of the study

In the current study, we developed a procedure to analyse the data at the level of the individual participant. With the learning-oddball paradigm, sigmoid curves accompanying pattern learning can be established at a group level (Jongsma et al., 2006). However, if similar curves can also be established for each individual participant, the learning-oddball paradigm could lead to a useful clinical tool to test if individual patients are capable of detecting temporal regularities. Because oddball stimuli were presented at 8 random and 8 regular positions respectively, with the use of the wavelet denoising technique (Quian Quiroga and Garcia, 2003), gradual changes in the ERP amplitudes may be determined on a trial-by-trial basis within each participant. Such dynamic tracking of ERP waveforms within an individual could potentially give more insight into the cognitive functions of individual patients suffering from subtle cognitive deficits affecting temporal pattern detection. In sum, we argue that measuring ERP changes within the “learning-oddball paradigm” at the level of individual participants could open the door to a new technique that can be of value as a clinical, diagnostic tool.

2. Materials and methods

2.1. Participants

Twenty-four participants (13 females, 11 males), with a mean age of 27.4 (±4.9) years, took part in the experiment. Only right-handed healthy adults, not using medication and without a neurological or psychiatric history, were accepted. All participants signed a written statement of informed consent. The participants sat comfortably in a recliner during the experiment, were instructed to keep their eyes closed, and to sit as still as possible. Participants were tested in an electrically shielded, sound-attenuated, dark cubicle (inside dimensions: 2 × 2.2 × 2 m). A computer mouse was placed under the participant’s dominant hand to collect responses.

2.2. Experimental design

A graphical representation of the ‘learning-oddball’ paradigm is depicted in Fig. 1. Within the learning-oddball paradigm, targets (n = 96) with a 12.5% probability, interspersed within a train of background stimuli (SOA 800 ms), were presented in an eyes-closed situation. Within a session, six blocks of 16 consecutive targets occurred as one continuous, ongoing train of stimuli (of 96 targets and 672 background tones). The first eight targets of each block were presented at a random position (preceded by a semi-random (2–6 or 8–12) number of background tones), whereas the following eight targets were located at a fixed position (all preceded by seven background tones). Thus, targets located at fixed positions became predictable. The program E-Prime was used for stimulus presentation and behavioral response collection. The participant’s task was to respond after the first standard tone following a target stimulus. This delayed response task was chosen in order to avoid motor activity that is closely locked to the responses upon target presentations.

2.3. EEG recordings

EEG (band-pass: DC – 100 Hz, sampling rate: 500 Hz) was recorded from 27 electrodes mounted in an elastic cap (EASICAP, FMS, Breitenbrunn, GER) at placements based on the International 10–20 recording system (American Encephalographic Society, 1994), referenced to linked mastoids and stored on disk for offline
analyses. Vertical and horizontal eye movements were recorded by two additional bipolar channels placed above and below the right eye and on the outer canthi of each eye. Impedances of all electrodes were kept below 10 kΩ. After segmentation, epochs (−2048 ms−2048 ms around stimulus onset) were de-trended and baseline corrected over the full 4.096 s length of each epoch (Jongsma et al., 2006). EEG epochs were subsequently subjected to an independent component analysis, as implemented in EEGLAB (Delorme and Makeig, 2004), running in the MATLAB environment (The Mathworks, Inc., Natick, MA). Variance-components with activity attributable to artefacts, such as eye-movement, fronto-temporal muscle activity, and mains noise were removed. Only waveforms from FCz and CPz where submitted to further processing and were denoised by means of a wavelet transform analysis method (Quian Quiroga and Garcia, 2003). The accuracy of this method in smoothing ERPs has been demonstrated with simulated data, and with visual and auditory ERP data (Atienza et al., 2005; Jongsma et al., 2004; Quian Quiroga and Garcia, 2003; Quian Quiroga and van Luijtenaar, 2002; Sambeth et al., 2003; Talnov et al., 2003). Subaverages of six repetitions for all the 16 consecutive targets were constructed for each individual and waveforms were additionally smoothed using a 3-point moving average across adjacent epochs. For denoising, we applied the same procedure as in our previous study (Jongsma et al., 2006). Briefly, denoising parameters were the same for all participants but separately determined at FCz (to extract the Contingent Negative Variation (CNV)) and at CPz (to extract the N2 and P3 components) based on initial group averages. For each participant, the CNV amplitudes were determined as the average amplitude on the 300 ms preceding stimulus onset; the N2 amplitudes were determined as the minimum values (average amplitudes of ±10 ms surrounding the peak values) between 180 and 280 ms; and the P3 amplitudes as the maximum values (average amplitudes of ±10 ms surrounding the peak values) between 280 and 480 ms. Also for each participant separately, the peak latencies for each component were determined from an average of the first 4 irregular targets for each block of trials (i.e. without temporal regularity being present).

2.4. Data analyses

A priori defined hypotheses were tested by non-linear regression analysis of the CNV, N2, and P3 ERP components, and of RTs,
using the program GraphPad Prism 4. F-tests for goodness of fit were obtained comparing:

- H0: There is no effect of introducing target regularity; modelled by a straight line with slope = zero. Y = Intercept + Slope * X;
- H1: ‘Pattern detection’ occurs after switching from random to regular target presentation: modelled by a sigmoid-curve. Y = Bottom + (Top–Bottom)/(1 + 10^(Tn50–X)); X is the target in the sequence (1–16). Y is the response; Y starts at Bottom and goes to Top with a sigmoid shape. The learning effect here is quantified as the Tn50: the target (between 0 and 16) where 50% of the maximal response has occurred (or the Tn50).

Fits were obtained for each separate individual (N = 24). In addition, correlations between RTs and ERP components were determined.

3. Results

3.1. Sigmoid curves

Group effects of the learning-oddball paradigm have already been reported previously for Fz, Cz, and Pz electrodes separately (Jongsma et al., 2006). Because in the current article FCz and PCz data are reported, new constructed group data at FCz and CPz electrodes are briefly presented in the current paper for the sake of consistency. With curve-fitting, we tested whether a sigmoid curve describes the data better than a straight line (slope = 0), for the CNV (at FCz), the N2 (at PCz), and the P3 (at PCz) ERP components, as well as for the RTs.

The group grand average ERPs to all 16 consecutive targets. Sigmoid curves with respect to the CNV (Fig. 2b), the N2 (Fig. 2c), the P3 (Fig. 2d), and the RTs (Fig. 2e) are depicted at the right. Target regularity gave rise to a CNV component (F = 45.34, p < .0001), and diminished both the N2 and P3 component amplitudes (F = 52.57, p < .0001; and F = 45.06, p < .0001 respectively). All these effects could best be described by sigmoid curves. Group data revealed that introducing target regularity resulted in a tendency to decreased RTs (F(2, 381) = 2.40, p < .1).

3.2. Individual results

As an example, ERP waveforms of one individual participant and corresponding sigmoid curves are depicted in Fig. 3. Supplementary Fig. S1 shows the wavelet denoising of the first 10 single trials of participant 01. Using the same format, the ERP waveforms and fitted sigmoid curves for each of the remaining 23 participants are depicted in Supplementary Fig. S2. p-Values of the goodness of fit tests for the sigmoid curves are listed in Table 1 for the CNV, N2, P3, and RT for all 24 individual participants. To give an estimation of the variability observed for the different participants, the Supplementary Table S1 lists all individual variances of sigmoid curves per dependent variable (ERP CNV, N2, and P3 components and RTs), including the absolute difference between top and bottom values with concurrent lower and upper 95% Confidence Intervals (CI’s) and Standard Error (SE) of the sigmoid curves per participant (Pp), the Tn50s of the sigmoid curve with concurrent lower and upper 95% Confidence Intervals (CI’s) and Standard Error (SE) per participant and test results of curve estimates on 6 cycles (16 per cycle) of single-trial ERPs (p < .05).

All 24 participants showed significant, or a trend towards significance, learning effects on either 1 (2 participants), 2 (8 participants), or all 3 (14 participants) ERP components. The P3 appeared to be the most sensitive component with respect to detecting the target regularity; the effect size (in µV) was largest...
Fig. 3. ERPs of an individual participant. ERPs of participant 01 at CPz are depicted in figure. ERPs to all 16 targets are plotted with the ERPs to the 8 irregular targets followed by the ERPs to the 8 regular targets from bottom to top (a), averaged over the 6 cycles. The panels on the right show results (means ± SEM) with respect to the CNV (b), the N2 (c), the P3 (d), and the RTs (e). Sigmoid “learning” curves were determined on individual data and tested against a straight line with slope = 0. Appropriate p-values are included in the panels. In addition, Supplementary Fig. S1a shows the raw EEG epochs of the first 10 trials before wavelet denoising of participant 01. Supplementary Fig. S1b shows the same single-trial ERP epochs after wavelet denoising of participant 01. For a complete overview of all other participants (2–24), see the Supplementary Fig. S2.

Table 1

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<th>CNV (FCz)</th>
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<td>Pp 24</td>
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<td>20/24</td>
<td>22/24</td>
<td>15/24</td>
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* p < .05.
** p < .001.
*** p < .0001.
† p < .1.

With respect to the Reaction Times (RTs): for some individuals 1 outlying value was excluded, this has been marked with a † behind the level of significane.

Fig. 4. Correlations. Correlation between the N2 amplitude (µV) and RTs (ms) are depicted in (a); correlations between the effect size (difference between top and bottom of the sigmoid curve) of the N2 amplitude (µV) and RTs (ms) are shown in (b).
for this component and for most participants (22 out of 24) could be fitted by a sigmoid curve. With respect to the amplitudes of the N2 ERP component, 20 out of 24 participants showed significant sigmoid curves, whereas for the CNV this was the case for 19 out of 24 participants. The RTs exhibited significant regularity effects, or trends towards significance, in 15 out of 24 participants.

3.3. Descriptive statistics

With respect to the RTs and ERP components, a negative correlation ($p < .05$) was observed between average RT speed and N2 amplitude (see Fig. 4a). In addition, we observed a positive correlation between the effect sizes of target regularity of RTs with the ERP N2 component (see Fig. 4b).

4. Discussion

4.1. Summary of the results

In this study, by separately analysing data of 24 individuals, it was investigated whether trial-to-trial changes of ERPs that are elicited in a previously described incidental learning task (Jongsma et al., 2006), could be measured at an individual level. Such an approach could lead to the application of long-latency ERP components as a clinical tool. We tracked changes accompanying the detection of pattern regularity by measuring amplitudes of the CNV, N2, and P3 components, as well as RTs to consecutive targets. All individuals showed sigmoid curves on one or more ERP components. Out of 24 participants, 22 individuals showed sigmoid curves on the P3, 20 on the N2, 19 on the CNV, and only 15 individuals showed sigmoid curves on RTs. However, RT data were based on a delayed response. This means that all targets, both random and regularly presented, allowed the individual to prepare a response for at least 800 ms. It can thus be argued that RTs were less sensitive because the delay might have introduced a floor effect. However, despite this effect, a negative correlation between the RT and N2 amplitude was still observed, in addition to a positive correlation between the effect size of the RT and the effect size of the N2. This suggests a relation between the N2 component and the preparation of the overt response. Together, these results illustrate the possibility of measuring incidental learning within individual participants.

4.2. Possible advantages of the ‘learning-oddball’ as a clinical tool

Differences in ERP waveforms between healthy participants and patients with a disorder or a disease (e.g., Parkinson’s disease) have already been reliably established at a group level (Brenner et al., 2009; Jeon and Polich, 2003; Rosburg et al., 2008; Rossini et al., 2001). In a sequence learning paradigm, a series of successive stimuli follows a repeating pattern without participants being aware of such a pattern. Reaction times tend to decrease progressively with repetition but increase again when the repeating pattern is modified. This is in line with our previous findings of decreased RTs with target regularity but without conscious awareness of the pattern (Jongsma et al., 2006). An additional advantage of the learning-oddball paradigm concerns the robust ERP results without the need of a clear motor response (Jongsma et al., 2006). This makes the learning-oddball paradigm suitable when studying certain pathologies that affect motor behaviour that might interfere with gathering reaction time data (e.g., Parkinson’s disease).

The learning-oddball paradigm has also some methodological advantages compared to the classical oddball paradigm. For example, one reason why deviations in ERP responses between an individual patient and a healthy control group are difficult to interpret is because of the large inter-individual variability in ERP morphology (van Beijsterveldt and van Baal, 2002; van Beijsterveldt and Boomsma, 1992). Individual variance in ERP morphology, and especially the P3 component, is understood to be genetically determined, (Eischen and Polich, 1994; Hansell et al., 2005). This genetic variability leads to a decreased specificity and, thus, to an increased incidence of both false-negative and false positive diagnoses (Kurtzberg et al., 1995). Moreover, patients often use medication, which may have a profound effect on the background EEG (Blume, 2006), and consequently on the ERP waveform (Jongsma et al., 2000). More trivial factors, such as recency of food intake, fatigue, handedness, and age, additionally influence the shape of the ERP waveforms (Polich and Herbst, 2000). Ideally, all these factors have to be standardized when comparing an individual patient with a healthy control group. However, within the learning-oddball paradigm, the absolute ERP component amplitudes are not taken into consideration, but rather the gradual changes of these components over 16 target stimuli, 8 of which cannot be predicted, and 8 that are presented in a regular fashion and are predictable. Thus, the initial morphology of an individual’s ERP is not of much importance here, but its gradual changes during the task at hand. By comparing the gradual changes in the 16 consecutive ERPs, sigmoid curves can be fitted and it can be assessed whether or not the introduced regularity has been noted. This approach has the advantage that the variability due to different EEG and ERP levels of different participants is largely reduced. Also, because of the wavelet de-noising technique, a few stimulus presentations (i.e. 6 blocks of 16 targets) are already sufficient to construct a reliable ERP component. Besides these advantages of the learning-oddball paradigm, there is still some variability across participants, as described in the Supplementary Table S1. It is not possible to establish at this stage how small or large this variability is, as for a clinical application such an assessment will depend on how much the values found in different pathologies differ from the distribution (and variability) found for normal participants. In spite of this fact, it is, however, encouraging at this stage that sigmoid curves could be fitted for all participants at least for one (and in most cases for all) ERP components. The lack of such a result would have clearly limited the applicability of this technique as a clinical tool.

In addition, brain imaging studies have found that both the striatum and medial temporal lobes are involved in sequence learning (Rauch et al., 1997; Schendan et al., 2003), and individual differences in the involvement of these areas may thus be related to the variability of individual performances. As noted above, sequence learning is understood to be a type of implicit learning, and several brain imaging studies have reported that implicit and explicit learning involve different neural systems (Doyon et al., 1997; Schendan et al., 2003). Involvement of the dorsolateral pre-
frontal cortex has been observed in explicit learning, whereas in implicit learning activation of both the striatum and medial temporal lobes are commonly observed (Melrose and Stern, 2003; Rauch et al., 1997; Schendan et al., 2003). These differences in involved brain structures might explain why in Alzheimer’s Disease (AD) implicit learning seems to be relatively intact while explicit learning is affected. Indeed, with AD, cortical thickness declines in the dorsolateral prefrontal cortex, the temporal and parietal regions (Lerch et al., 2005). In contrast, implicit learning seems to be diminished in Parkinson’s Disease (PD). Indeed, PD is, amongst other pathological findings, associated with volume reduction of the basal ganglia (Doyon et al., 1997; Geng et al., 2006).

4.3. Possible future applications

The CNV, N2, and P3 ERP component amplitudes resulted in clear sigmoid curves that appeared to be more robust than sigmoid curves based on the behaviourally collected RT data. In general, ERP components directly measure the responses of the neural substrate involved in the task at hand without the need of a verbal response. The learning-oddball paradigm could contribute to determine to what degree cognitive functions of patients are still intact and to test patients suspected of having a decreased ability of implicit pattern recognition, such as might be the case for individuals suffering from Parkinson’s Disease (Siegert et al., 2006) or schizophrenia (Siegert et al., 2008). Because the learning-oddball paradigm involves an incidental sequence learning task, patients do not intentionally have to take part, which makes it rather unique for cognitive testing. In theory, the patient only has to be connected to the EEG equipment, the stimuli have to be presented and the ERP responses analyzed. This procedure is non-invasive and relatively quick to apply.

5. Conclusions

In a previous study, we found a decrease in RTs and in the N2-P3 ERP complex amplitude, accompanied by an emerging CNV in response to the learning-oddball paradigm (Jongsma et al., 2006). The current study shows that similar changes can be discerned at the level of individual participants. Because of these results and the nature of the paradigm, this paradigm could be used as a clinical tool to assess cognitive functions involved in temporal pattern recognition. Since the ERP components appeared to be good predictors of detecting target regularity, this task might be especially useful in patients with speech and/or motor disabilities.

Acknowledgement

All data were collected at the lab facilities of the Department of Biological and Medical Psychology, Division of Cognitive Neuroscience, University of Bergen, Norway, with the help of G. Solhaug, H. Brendalsmo, and L. Sørensen.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.clinph.2012.09.009.

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