LOCALIZATION OF THE EVENT-RELATED POTENTIAL NOVELTY RESPONSE AS DEFINED BY PRINCIPAL COMPONENTS ANALYSIS

Joseph Dien[12], Kevin M. Spencer[13], and Emanuel Donchin[14]

[1]Department of Psychology

University of Illinois, Urbana-Champaign

[2]Department of Psychology

Tulane University

[3]Department of Psychiatry

Harvard Medical School/VA Boston Healthcare System

[4]Department of Psychology

University of Southern Florida, Tampa

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Address for correspondence: Joseph Dien, Department of Psychology, 2007 Percival Stern Hall, Tulane University, New Orleans, Louisiana 70118. Phone: 504-862-3300. Fax: 504-862-8744. E-mail: jdien@tulane.edu. URL: http://www.tulane.edu/~jdien/Dien.html.

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Abstract

Recent research indicates that novel stimuli elicit at least two distinct components, the Novelty P3 and the P300. The P300 is thought to be elicited when a context updating mechanism is activated by a wide class of deviant events. The functional significance of the Novelty P3 is uncertain. Identification of the generator sources of the two components could provide additional information about their functional significance.

Previous localization efforts have yielded conflicting results. The present report demonstrates that the use of principal components analysis (PCA) results in better convergence with knowledge about functional neuroanatomy than did previous localization efforts. The results are also more convincing than that obtained by two alternative methods, MUSIC-RAP and the Minimum Norm.

Source modeling on 129-channel data with BESA and BrainVoyager suggests the P300 has sources in the temporal-parietal junction whereas the Novelty P3 has sources in the anterior cingulate.

1. INTRODUCTION

When a person unexpectedly hears an unusual sound, or sees an unusual image, event-related potentials (ERPs), the electroencephalographic activity time locked to the event of interest, register a burst of activity termed the Novelty P3, peaking at about 300 msec. after the stimulus. This response has been observed to both novel environmental sounds [41] and to novel colored squiggles [15]. Even simple stimuli can produce a Novelty P3 if they are quite different from the task relevant ones [14,31,38,75]. This response occurs to all rare sounds, regardless of whether they are targets, as long as they are quite different from the frequent standards [28,67].

The Novelty P3 is of especial interest because its scalp distribution suggests a source in the frontal cortex. Findings concerning the Novelty P3 could be informative for neuroscientists investigating the frontal lobe. For example, studies have suggested it may throw light on working memory deficits in the elderly [25]. Such efforts would benefit from better knowledge of the neural generators of the Novelty P3, since the frontal cortex is quite heterogeneous.

A critical issue for source localization analysis of a component such as the novelty response is whether it is unitary in nature [3,76]. A powerful method for determining the componential structure of ERPs is principal components analysis or PCA [21]. Although a report that PCA can misallocate variance [74] has often been cited as a weakness of PCA, this finding was little more than a statement that PCA does not produce perfect results. Such a finding is not specific to PCA; indeed, Wood and McCarthy took pains to state that misallocation is a concern for all ERP analysis techniques, such as windowed ANOVAs, and that it is a strength, not a weakness, of PCA that it makes this issue explicit.

Efforts to address misallocation issues for PCA (and other techniques) are ongoing. Simulation studies indicate that accuracy of PCA solutions can be substantially improved by using an oblique rotation [17]. Such oblique rotations allow the resulting factors to be correlated with each other, which may allow the ERP components to be more accurately characterized if they are indeed correlated. Promax was chosen because of its popularity as an algorithm that gives good simple structure quickly and easily [32], for much the reasons that Varimax is a popular orthogonal rotation. Furthermore, researchers have varied in whether they use correlation [i.e., 63] or covariance matrices [i.e., 66]. Simulation analyses indicate improvements can be achieved by the use of a covariance matrix rather than a correlation matrix (Dien, Beal, & Berg, submitted). In this latter simulation study which utilized real background EEG, 64 simulated electrodes, and two P300-like positivities centered on Pz and Cz, the combination of a covariance matrix and a Promax rotation reproduced the original point dipoles within 4 mm of the original locations. This is comparable to estimates of average spatial resolution of 7-8 mm based on a phantom skull model [45]. While it is likely that the use of simplified spherical head models inflated the performance of the PCA procedure, it has been reported that more realistic boundary element models do not notably change results [45]. These results indicate that PCA can be an effective method for isolating ERP components for source localization.

Further refinements of PCA are also possible. An innovative two-step spatiotemporal PCA process was used to clarify the componential composition of the response to deviant events [66,67]. In the first step, a spatial PCA [17] was utilized in which the variables are the individual electrodes, yielding factors that correspond to scalp patterns in the dataset. Spatial factors do not necessarily have a one-to-one correspondence with specific ERP components since a spatial factor will amalgamate all components with similar scalp patterns but with disparate temporal foci. Thus, for example, the P300 and the posterior Slow Wave component share a scalp distribution but

the Slow Wave follows the P300 and is sensitive to different experimental variables [59,67]. The data are therefore subjected to a second "temporal" PCA in which the variables are the time points. This second step separates the spatial factors into components with different time courses. While this procedure could be accomplished in a single step using a three-mode PCA [1,20,51,72,73]. We choose not to do so since rotation techniques for three-mode PCA have not yet been fully developed, let alone evaluated, and there is no reason in principle to think that unrotated solutions will relate to the underlying components as anything other than uninterpretable linear combinations of these components.

Using this procedure, we demonstrated that the ERP response to novel stimuli (in the typical oddball paradigm) consists of both the frontal Novelty P3 and the posterior P300 (Spencer et al., 1999)[1]. The P300 is thought to be elicited when an updating of a representation of the environment is called for [19,22]. Efforts to characterize the novelty response, both functional and neuroanatomical, must therefore distinguish between the frontal and posterior processes. The next logical step is to use this information to identify the separate sources of these two components.

Investigations of the oddball task and the P300 have yielded a number of potential generators [35]. Although this observation sometimes leads researchers to opine that the P300 must therefore have multiple distributed sources that would be difficult or impossible to localize with point equivalent dipoles [34], we suggest this conclusion may be unnecessarily pessimistic. Analyses of the scalp-recorded ERPs in the oddball task [66,67] reveal multiple components aside from the P300 that could account for at least some of these regions. The principle of parsimony indicates that one should first evaluate the simplest possibility of a single primary P300 generator site before considering more complex arrangements.

Following this logic, there is a general consensus that the temporal-parietal junction (TPJ) is a major source for the P300. It has been implicated by intracranial electrode studies [65]. Although a wide variety of areas have been shown to be activated by rare targets in the oddball paradigm, the only region that is consistently activated across studies is the TPJ [6,23,39,40,46,48,50]. A study that found a different pattern of results [68] examined non-target changes in a non-attended stimulus; a situation that does not normally elicit a P300 [26]. Furthermore, lesions of the temporal-parietal junction have been found to reduce the amplitude of the P300 [16,43,75]. Activation of the TPJ, along with the anterior cingulate, was correlated with the amplitude of the P300 in a co-registered ERP/SPECT study [24].

In contrast, efforts to localize the generator source of the Novelty P3 (auditory stimuli for the most part) with a variety of methods have yielded conflicting results. Lesion studies have demonstrated that the process resulting in the Novelty P3 is dependent on a distributed network since lesions in a variety of regions including prefrontal cortex [16,41] and the hippocampus [42] disrupt it. Such lesions do not necessarily indicate the generator site itself. For example, since unilateral prefrontal lesions reduce the Novelty P3 bilaterally, Knight [41] suggested the Novelty P3 is not generated in prefrontal cortex.

Efforts to identify the generator site itself have tended to fall into two groups. The first group has pointed toward the auditory cortex of the superior temporal plane. An initial effort [4] using magnetoencephalography (MEG) found a magnetic equivalent to the Novelty P3 that source modeling fit to a superior temporal plane point equivalent dipole. A more directly relevant finding [55] was reported using a 3T functional magnetic resonance imaging (fMRI) scanner and a high-density 128-channel EEG montage. They reported an fMRI activation in the superior temporal plane that was

stronger to the novel stimuli; moreover, when this location was used to seed an equivalent point dipole it explained more than 90% of the variance of the novelty effect.

Another group of findings has focused on the frontal cortex. Intracranial recordings suggest several generator sources for the Novelty P3, including the inferior frontal cortex and the anterior cingulate [7]. These findings are constrained by limited recording sites since electrodes can only be placed where medically necessary. Moreover, there is no guarantee that an intracranial potential corresponds to scalp recordings. A co-registered SPECT/ERP study found that the anterior cingulate activity positively correlated with the amplitude of the Novelty P3 [24]; however, SPECT cannot readily record from the superior temporal plane so it is unknown whether there was correlated activity there as well.

An initial dipole modeling effort of the Novelty P3, comparing the ERPs elicited by novel and target stimuli, yielded a point equivalent dipole solution in the rostral anterior cingulate [49]. As the authors noted, this study was limited by the use of a sparse montage of only 30 electrodes. Nonetheless, the result seems to converge with one of the regions indicated by the intracranial recordings.

A final pair of studies[2] [39,40] used event-related fMRI and found a variety of areas responding to novel stimuli compared to target stimuli, including the anterior cingulate, inferior frontal gyrus, insula, inferior parietal lobule, and inferior, middle, and superior temporal gyri. This plethora of findings is exciting but rather complicates the picture. Recent data suggests that the BOLD signal registered by fMRI reflects the same aspect of neural activity as that recorded by ERP methods [47]. It is therefore possible that some or all of these sites contribute to the scalp-recorded potentials. On the other hand, fMRI provides very limited temporal resolution so it is possible that most of these activations occur during other time points. Furthermore, many of the studies cited above treated as one component the multiple components that we now know to be elicited by

deviant events. When the Novelty P3, the P300 and the P3a are not parsed the measurements applied to the combination may yield confusing results. The Spatiotemporal PCA provides precisely the decomposition required as a step preceding source localization. We therefore set out to examine in detail the possible intracranial sources of these components.

In the present report, we utilize a previously reported dataset [66,67] to localize the Novelty P3 generators. ERPs were obtained with a high-density electrode array (128 channels), and the spatiotemporal PCA approach was used to dissociate the Novelty P3 from the P300 and other late ERP components. As a further refinement, the Promax rotation [37] was utilized which allows factors to be correlated, removing a possible source of distortion in the factor results [17]. The resulting factors are then submitted to source analysis and then related to previous Novelty P3 localization reports. We also improve on previous BESA modeling efforts by using it in conjunction with BrainVoyager to more meaningfully communicate solution coordinates (while acknowledging inherent limits to resolution). BrainVoyager, a software package written by Brain Innovation, is able to import BESA results, translate them into stereotactic coordinates, and directly render them into MRI images.

For comparison's sake, analyses were also conducted directly on the grand averages using two alternative methods, MUSIC-RAP [53] and Minimum Norm [36]. The former essentially acts as a PCA constrained by a simultaneous source localization analysis. The latter is a distributed source solution that models the data using broad regions of activation rather than point dipoles. Since some intracranial ERP researchers take an opposing position that the P300 and the Novelty P3 have broadly distributed sources that cannot be analyzed with point dipoles [34] the minimum norm is especially appropriate as a complementary analysis.

2. METHODS

The electroencephalogram (EEG) was recorded from fifteen students at the University of Illinois at Urbana-Champaign using a 129-electrode Geodesic Sensor Net [71], with 12-bit digitizing at 250 Hz, as previously described [66]. Each electrode was referenced to the Cz site. Amplifier bandpass was 0.1-50 Hz. The continuous EEG recordings were divided into slightly overlapping 1008 ms single trial epochs with a 200 ms pre-stimulus period.

For the purposes of source localization we use the data recorded in the novelty oddball reported in [66]. 300 trials were presented with an interstimulus interval of 1000 msec. The auditory stimuli were generously provided by Fabiani and Friedman [25]. Two tones (350 and 500 Hz, 336 ms duration, 10 ms rise and fall times) served as the rare (12%) and frequent (76%) events, interspersed (12%) with novel sounds (e.g., a bird call, a laugh). The novels' duration did not exceed 400 msec. All stimuli were presented binaurally at 65 dB.

Participants were told to press a button in response to the rare tones as quickly as possible while still being accurate. Both response hand and rare/frequent tones were counterbalanced across subjects separately. Subjects were not told that the novel sounds would be presented, following standard practice. Note that no response was required to the novel sounds. As far as the subject's task was concerned these tones were functionally similar to the frequent tones.

The EEG channels were corrected for vertical and horizontal eye movements [33]. The averages were digitally filtered (0-20 Hz) and baseline-corrected. The data presented has been re-referenced to a mean mastoid reference.

PCAs were conducted using the PCA Toolbox, a set of Matlab routines that are freely available from the first author upon request. A covariance matrix was used so that the solutions would be most influenced by more active variables (channels for a spatial

PCA and time points for a temporal PCA). A promax rotation (without the Kaiser correction option) was used to rotate the results to simple structure [17,37]. The PCA Toolbox (version 1.3) has three differences from the PCA procedure used in the prior reports, which are not expected to have notable impact on the present source analyses: 1) it variance corrects the factor scores but does not mean correct them, preserving mean differences in the factor scores. 2) it turns off the Kaiser correction, which has the undesirable effect of equalizing the contribution of the variables. 3) it directly rotates the factor scores, which makes it possible to apply separate temporal PCAs to each spatial factor (which will not affect the source localization results since they are solely dependent on the results of the initial spatial PCA).

Source localization can be conducted on the factors by first reconstructing the portion of the grand average accounted for by the factor. For a conventional PCA, one multiplies the factor loadings by the mean of the appropriate factor scores and the standard deviation for each variable [18]. For an oblique rotation, the factor pattern matrix is most appropriate since the factor structure matrix includes influences from correlated factors. In a spatiotemporal PCA, the spatial factor scores are rearranged such that the scores for each time point are positioned as the variables for the temporal PCA (with subjects and conditions constituting the observations). To reconstruct the data, one must first multiply the factor scores of the temporal factor by the spatial factor loadings and by the standard deviations of the variables of the temporal step (the factor scores positioned as time points). This multiplication reconstitutes the portion of the spatial factor scores accounted for by the temporal PCA factor of interest. This is then multiplied by the spatial factor loading and by the standard deviations of the spatial variables (the channels). The full equation to generate the microvolt value for a specific time point t and channel c for a spatiotemporal PCA is: L1 * V1 * L2 * S2 * V2 (where L1 is the spatial PCA factor loading for c, V1 is the standard deviation of c, L2 is the

temporal PCA factor loading for t, S2 is the mean factor scores for the temporal factor, and V2 is the standard deviation of the spatial factor scores at t.

All dipole analyses were conducted with BESA2000 (4.2) using a four-shell elliptical head model and the following constraints [for a review of dipole localization principles, see 60,61]. The dipole pairs were constrained to have symmetrical mirror locations but free orientations. In addition, the energy criterion was turned on to minimize interaction between dipoles and the minimum-distance criterion was activated to avoid solutions with closely spaced dipoles. The seven periocular channels were dropped to minimize the effect of ocular artifacts. An iterative algorithm was utilized in which the program automatically shifted the position of the dipoles until it found a position of maximum fit. To maintain uniformity, all reported solutions are based on a central starting position. To guard against local minima, each source analysis was conducted with anterior and posterior starting locations as well and the same results were obtained. Since the direction of the BESA dipoles is arbitrary (a negative wave oriented in one direction is equivalent to a positive wave oriented in the opposite condition), when the final orientation of the two members of a pair pointed in opposite directions, one was manually flipped (signs reversed for all three coordinates) for clarity's sake. Since the flipped solution is mathematically equivalent, this had no effect on the RV.

The resulting dipole solutions were converted to a Talairach coordinate system [69] and rendered using Brain Voyager 2000 (4.4). The Brodmann areas derived from the Talairach Atlas are only approximations since they are based on a single brain and since the present dataset may not be wholly comparable either anatomically or cytoarchitectonically. The Atlas is utilized since it represents the only currently available standard and provides a reference point across studies. Likewise, the MRI used for rendering is provided as an aid to interpretation but is not derived from the subject sample.

The MUSIC-RAP solution was conducted using BESA using the SBSI modification. Since this procedure operates upon a single grand average waveform, it was not possible to carry it out in the same manner as the PCA. In order to isolate the P300 before modeling the result, the difference wave between the rare target and the frequent standard was utilized. Moreover, only the period between 250 and 350 msec. was examined. Three dimensions were specified (two more than the one expected component dimension, following published guidelines). Since the activity was expected to be bilateral, a 2 topography solution was specified, with a 90% correlation threshold. Other constraints for the MUSIC-RAP algorithm, as instantiated in BESA, were not modifiable. Information regarding the inherent constraints in the MUSIC-RAP algorithm are available elsewhere [52,53].

The minimum norm solution, which used the MUSIC algorithm to define the subspaces, was applied to the same data as the MUSIC localization using depth weighting, spatio-temporal weighting by single source scan, subspace correlation with 24 dimensions, and individual channel weighting.

3. RESULTS

For comparison's sake, a conventional source analysis was conducted on the grand average data first. A 2-dipole model was first fit to the rare-frequent difference wave to model the P300 in the 252-452 msec window. The residual variance (RV) was 5.15%, indicating that this pair of dipoles was largely sufficient to model the difference wave. As observed in a previous report [49], the dipole pair was clustered on the midline, corresponding to the corpus callosum: (-8, -28, 18) and (9, -28, 17). The prior authors had speculated this was due to their relatively sparse montage (30 electrodes) but the current result with 129-electrodes indicates this is not the case. Given depth

indeterminacy, this solution could correspond to a widespread cortical activation centered in the temporal-parietal junction. Figure 1 is presented as BESA glass brains so that readers can directly compare the results to the Mecklinger and Ullsperger figure. If the reader obtains a copy of both articles and compares the two figures, it will be seen that the current solution is places the foci at a somewhat higher location but is otherwise quite similar. The present analysis has thus replicated the Mecklinger and Ullsperger results and we are in agreement with their evaluation of this result as being unconvincing since it places the source in white matter, which cannot generate ERPs.

We then proceeded to determine if the present analysis would replicate the remainder of the source solution. Because it is known that the novel condition contains the same P300 plus at least one additional Novelty P3 component, a logical procedure for adding the Novelty P3 to the source solution is to utilize the novel-rare difference wave. Since it is known that the P300 does not have the same amplitude in the two conditions [66,67], the difference wave should still have a P300 in it, albeit to a lesser extent. The P300 solution was fit to the novel-rare difference wave to account for the P300 variance, resulting in an RV of 34.19%.

Keeping these dipoles fixed, an additional pair was added, resulting in an RV of 17.83%. These dipoles were located in medial BA9 (translation to Talairach coordinates by BrainVoyager places it somewhat higher in the frontal cortex than that seen in the less precise BESA glass brain): (-6, 47, 14) and (12, 47, 14). Since a substantial residual variance remained, an additional pair was added, keeping the previous pairs fixed, lowering the RV to only 10.90%. These dipoles fell into BA6, supplementary motor area: (-1, -6, 71) and (7, -6, 71). This same six-dipole solution applied to the full novelty grand average was 3.65% (the RV is better because the signal to noise ratio is lower for a difference wave since such an operation subtracts signal but adds as much noise as it removes). As can be seen in Figure 1, the dipole pair corresponding to the Novelty P3 (in

BA6) is virtually identical to the Mecklinger and Ullsperger report. The remaining pair of dipoles in BA9 accounts for a frontal negativity described by Spencer et al. [67]. This pair of dipoles is similar to the third dipole pair reported by Mecklinger & Ullsperger, albeit much more anteriorly situated. The present analysis has therefore substantially replicated their findings. It can therefore be concluded that the problem was not due to their use of a sparse montage (30 channels) since the same results were produced with a high-density 129-channel montage.

A spatial PCA was then conducted on the full epoch, ranging from a 152 ms baseline to 756 ms after the stimulus onset. Based on a scree test [10], twelve factors, representing 92% of the variance, were retained. A separate temporal PCA was conducted on each set of spatial factor scores. For simplicity's sake, the same number of temporal factors was retained across all twelve spatial factors. Scree tests indicated that retaining four temporal factors would be sufficient for all the spatial factors. For continuity's sake with the previous reports, the two PCA steps were first conducted with a Varimax rotation and then with the Promax rotation. In this manner, it may be ascertained whether the adoption of an oblique rotation makes a noticeable difference to the ultimate source analysis.

Analysis was *a priori* restricted to the three spatial factors with the same Pz, Fz, and Fpz maximums of the P300, Novelty P3, and frontal negativity respectively. Likewise, only the temporal factors with the relevant latencies were *a priori* analyzed. The Pz spatial factor accounted for 37.08% of the variance. The Fz spatial factor accounted for 2.48% of the variance. The Fpz spatial factor accounted for 1.22% of the variance. As seen in Figure 2, for the Varimax solution, the first temporal factor of the first spatial factor (S1T1) appears to reflect the P300, with a parietal-central positive focus and a peak at 360 ms. S1T1 has greater amplitude for both rare targets and rare novels: cell, $F(2,14)=19.2$, $p = .0001$. The p value for this and all subsequent ANOVAs has been

adjusted for sphericity using the Greenhouse-Geisser epsilon correction factor [29]. Figure 3 shows that the second temporal factor of the second spatial factor (S2T2) appears to reflect the Novelty P3, with a frontal positive focus and a peak at 304 ms. This positivity is largest in the novel condition: cell, $F(2,14)=9.7$, $p=.002$. The third factor of interest (S3T1) corresponds to a frontal negativity previously noted in this dataset [67]. This factor has a negative focus in the vicinity of Fpz, peaks at 488 ms, and has a tendency to be larger for both targets and novels: cell, $F(2,14)=2.44$, $p=.13$. This component appears to be different from the Reorienting negativity, which has a less frontal scalp distribution centered on Fz [9].

For the Promax solution, the results are quite similar and hence have little consequence for the conventional analyses. S1T1 has a similar topography, a peak at 364 ms and is larger for rare targets and novels: cell, $F(2,14)=14.5$, $p=.0001$. S2T2 has a frontal positive focus, a peak at 300 ms, and is larger for novel stimuli: cell, $F(2,14)=6.5$, $p=.0065$. Finally S3T1 has a very frontal focus, a peak at 488 ms, and a tendency to be larger for targets and novels: cell, $F(2,14)=2.1$, $p=.157$. If anything, the results are modestly less significant. Although the oblique rotation permits a closer fit to the components by permitting correlated factors, it appears it also results in a modestly higher noise level.

Figure 4 presents the results of the BESA dipole localization analyses of the PCA factors. Talairach coordinates of EEG data should be treated as rough estimates with an accuracy in the vicinity of 5 to 10 mm according to published studies [13,45]. Furthermore, due to depth indeterminacy, the BESA solutions are representative of a range of possible solutions. The larger the extent of the generator region, the more superficial the actual source location [cf, 60]. To properly interpret the results, readers should interpolate between the given point and the cortical surface to generate the full range of possible solutions. Finally, identification of corresponding Brodmann areas

should be considered rough estimates as well since all such efforts currently rely on the atlas generated by the sectioning of a single brain [69]; it is currently unknown how representative this brain is of population averages.

Source analysis of the Varimax S1T1 (P300) factor resulted in an RV of 9.6%. Transformation to Talairach space yield the coordinates (-26, -25, 22) and (27, -26, 21), roughly corresponding to Brodmann's Area 41 (the primary auditory cortex). Source localization of the S2T2 (Novelty P3) factor resulted in an RV of 3.7%. The Talairach coordinates of this solution are (-17, -10, 39) and (21, -11, 39). This corresponds roughly to Brodmann's area 24, namely the anterior cingulate sulcus. Finally, source localization of the S3T1 (frontal negativity) factor resulted in a 2.7% RV. The Talairach coordinates are (-32, 49, 2) and (37, 48, 1). This translates roughly to the frontal orbital cortex, in Brodmann's area 10. Note that the eye movement correction procedure may have distorted the topography of this component since it is centered near the eyes.

As for the Promax factors, the S1T1 (P300) factor produced an RV of 9.3%. Its coordinates of (-40, -44, 26) and (40, -46, 25) falls roughly within Brodmann's Area 40 at the temporo-parietal junction. These coordinates are quite close to the fMRI coordinates obtained in an oddball paradigm [50]: (-60, -32, 30), (-56, -48, 32) and (62, -34, 24). The S2T2 (Novelty P3) factor is modeled with an RV of 8.8%. Its Talairach coordinates are (-16, 3, 58) and (21, 2, 57) which roughly represents Brodmann's Area 6 of the supplementary motor area (SMA). Finally, the S3T1 (frontal negativity) factor has an RV of 8.9%. The coordinates of (-22, 64, 16) and (29, 62, 15) roughly correspond to Brodmann's Area 10 of the frontal poles.

The present results are inconsistent with the localization of the Novelty P3 to the superior temporal plane [55]. For comparison's sake, the Talairach coordinates for the fMRI novelty effect reported by Opitz et al. (1999) were used to seed a source solution for the present ERP data. The fit for the novel condition during the Novelty P3 period

reached an RV as low as 9.6%. We then proceeded further by fitting the same solution to the rare target data, achieving an RV that went as low as 6.1%. This result suggests that the source modeling might better reflect the P300 than the Novelty P3. Although Opitz and colleagues did not address this possibility in their Novelty P3 study, they did conclude in a separate paper [56], using the same dataset, that this activation corresponds to the P300 (to be fair, they report coordinates that differ by about two millimeters between the two conditions but this is negligible for the purposes of EEG localization or identification of Brodmann areas). It is not clear from their papers how they reconcile these conclusions.

The MUSIC-RAP analysis was conducted, resulting in a two dipole solution with an RV of 7.931%. Both dipoles met the 90% correlation threshold and were therefore modeled as single dipoles rather than as synchronous pairs. As seen in Figure 5, the first dipole was placed in the brainstem (-6 –20 1) and the second dipole was placed in the posterior cingulate (11 –65 27). The minimum norm solution, on the other hand, resulted in a very broad spread of activation that covered most of the lateral and inferior surface of the brain, including the brainstem.

4. DISCUSSION

This analysis suggests that factor decomposition methods provide a substantial benefit to source localization methods. Conventional source fitting procedures resulted in solutions similar to that previously reported [49] with only 30 channels, indicating the present solution is quite replicable across different montages and laboratories. Nonetheless, this solution lacks face validity, with the P300 sources being located in white matter and the Novelty P3 sources falling into primary motor cortex. Even taking depth indeterminacy (the inability of source analyses to distinguish between a deep point dipole or a diffuse surface generator) into account, a more superficial source for either of these components would not correspond to previous findings using other methodologies.

The solution produced by the Varimax rotation of the PCA appears more reasonable, but still suffer from face validity issues. The P300 factor was localized to the primary auditory cortex, a result consistent with the position of Opitz and colleagues but subject to concerns noted previously. The Novelty P3 factor was localized to the anterior cingulate, a not unreasonable location.

While the Promax rotation results appear much the same as the Varimax rotation results (see Figures 2 and 3), they produce notable changes in the source localization results. As expected, the P300 sources were localized to the TPJ (due to depth indeterminacy, the more superficial TPJ is part of the range of solutions while the deeper auditory cortex location is not). Although other potential sources have been cited as well, evidence is strongest for this location. The Novelty P3 solution shifted only to a modest degree from the Varimax solution (to the adjoining SMA). The SMA is within EEG's inherent 5-10 mm range of imprecision from the anterior cingulate, the more likely source based on the literature reviewed in the introduction. It would therefore appear that allowing the factors to correlate with each other, which is physiologically plausible, has yielded improvements in the face validity of the source localization analyses.

We therefore present this interpretation of the data thus far available. The strong source modeling fits obtained by Opitz and colleagues represent the P300, which our own data indicates is elicited by both rare target and rare novel stimuli. Further support for this supposition is the similar localization result obtained for the P300 using both EEG and MEG by another lab [70]. We further suggest that the strong fits obtained for the STG for the P300 by these two labs are due to its proximity to the TPJ, the more likely source site of the P300. If this is the case, it raises the question of why Opitz et al. obtained STG activation and no other fMRI activation. The STG activation could be due to refractory effects on the auditory cortex response to the frequent standards, as opposed to the rare targets and novels. Such a refractory effect has been observed in the auditory

N1 [54] which has been convincingly localized to the STG [62]. It is therefore possible that the STG activation corresponds to the N1, not the P300 or the Novelty P3. As for why activation of other regions such as the TPJ was not observed, presumably due to technical reasons, Opitz et al chose to scan only 56 mm, which is only about half the brain or so. Unfortunately, the authors did not indicate what portion of the brain was imaged so no further conclusions can be made on the subject. A more recent study on a 1.5T scanner reported widespread activations when the full head was imaged [39]. Thus, while the pioneering study by Opitz and colleagues demonstrates the promise of co-registering ERPs and fMRI data, it also shows the value of methods like PCA to first clarify the ERP componentry. Conversely, the widespread activations reported by Kiehl et al. are clearly not fully represented in the ERPs.

The apparent improvement in source localization provided by the PCA decomposition follows from the algorithms involved. When an equivalent dipole is fit to a dataset, an algorithm like BESA will seek to maximize the amount of variance it accounts for. To the extent that variance can be maximized by accounting for the variance of multiple components, the source solution will represent a weighted average of different sources [3,76]. An expert can address this by careful and systematic examination of a dataset, identifying time points and conditions that isolate components of interest from others. Such a process is often difficult to describe or reproduce.

PCA uses patterns of covariance to parcel out the variance in advance of the fitting procedure, using information derived from the spatial distribution, the time course, experimental effects, and individual differences. While the PCA procedure is available as a standard part of analysis packages such as BESA, these implementations typically do not take advantage of all four sources of covariance. These implementations also typically do not take advantage of rotational procedures like Promax that are necessary to obtain interpretable results [17]. In principle, components can thus be separated in a

more automatic fashion with less dependence on expert judgment, although statistics cannot fully replace expert judgment.

The utilization of all four sources of variance is likely the reason for the more plausible results yielded by PCA in comparison to MUSIC-RAP. Although posterior cingulate activation is sometimes seen in brain imaging studies of the oddball task and is therefore a potential generator site [cf., 46,48], the TPJ is a far stronger candidate for providing the bulk of the scalp-recorded P300 since it is the only activation area consistently observed in imaging studies of the oddball task, as described earlier. Likewise, the finding that TPJ lesions reduce the P300 give it a stronger claim [43,75]. Finally, the posterior cingulate activity was actually negative correlated with the amplitude of the P300 in a SPECT/ERP study [24].

The minimum norm indicated diffuse regions including the brainstem, which of course, is not a plausible source at all. While such widespread results could be consistent with the position of diffuse generator sites for the P300 and Novelty P3 [34], even these authors do not argue for synchronized firing by the entire brain. It seems likely that the results either reflect some issues with the minimum norm algorithm or that it was not suitable for this dataset.

With plausible source localization results for the Novelty P3 in hand, it is now possible to consider possible implications for interpreting this response. A source in the primary auditory cortex would have implied some type of sensory process, which would be unlikely given its relatively late onset. It would also have raised questions about why visual and somatosensory novel stimuli produce activity in the auditory cortex, given the polymodal nature of this response.

The present analyses suggest the Novelty P3 may arise from the supplementary motor area (SMA), or more likely from the adjoining anterior cingulate. Indirect support

for the anterior cingulate location is provided by the observation that the oddball response to rare targets includes a small Novelty P3 [66]. Most, but not all, of the oddball brain imaging studies cited earlier also found an activation in the anterior cingulate. A combined EEG/MEG study of the oddball response also suggested generators in both the TPJ and the anterior cingulate [8]. In any case, both the anterior cingulate and the SMA have particular roles in response selection [58] so the Novelty P3 could represent a response level process. Although there is general agreement on the attentional nature of the Novelty P3 response, the term "attention" is applied to a diverse set of processes, including response level processing [5].

The current results raise alternative explanations for age-related changes in this component. Young subjects display a shift from Novelty P3 to P300 activity with repeated exposures to novel stimuli while elderly subjects do not; this observation was interpreted as reflecting impairments in the ability of the elderly to form working memory templates of the novel stimuli [25]. Presumably, this hypothesis was inspired by findings that the frontal cortex plays a central role in working memory [64]. Since the source analyses of the Novelty P3 were not consistent with the area primarily implicated in working memory, the dorsolateral prefrontal cortex [30], it may be appropriate to consider alternative hypotheses (see Goldstein et al., 2002, for a discussion). If the Novelty P3 represents response-related activity, then this age-related change may reflect issues with response programming. For example, it is known that the elderly display more difficulties with maintaining response set shifts, mimicking the effects of frontal lobe lesions [57]. With the clues provided by the present report, it should be possible to formulate experiments to directly test these hypotheses.

Footnotes

1) The same conclusion was presented, although not interpreted, using a similar method called trilinear modeling [73]. This method is a type of three-mode PCA [44] which extends previous applications to ERP data [1,2,20,51]. It essentially consists of applying both steps of the spatiotemporal PCA as a single step. It has the drawback that it does not allow decisions like factor retention to be carried out in a stepwise fashion and it relies on the unrotated solution. See [17] for a discussion of rotation issues, as applied to ERPs.

This conclusion has also been made based on current source density (CSD) analyses [27]. This conclusion was undermined by two weaknesses. The first is that CSDs operate as a high pass spatial filter, eliminating widely distributed features like the P300 and possibly the Novelty P3. It is therefore unclear whether the CSD features illustrated in this report were in fact related to the Novelty P3 or the P300, or whether they instead represent minor features normally obscured by the two components. The second weakness is that visual inspection does not provide an objective evaluation of whether two proposed features are dissociable. The PCA of Spencer, Dien, and Donchin addressed both of these issues.

2) Another pair of studies [11,12] attempted to examine the novelty response but did not obtain main effects for novelty, just some interesting habituation trends. This different pattern of results may be due to issues with their stimulus set. They used the letters T, C, and X as their three stimuli, which do not appear to meet the requirement that the distractor stimulus be much more difficult to distinguish from the target than from the non-targets [14,38].

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Figure Legends

1) Dipole model of Novel-Rare difference wave in the 252-452 ms range. The three dipole pairs appear to correspond to the P300, the Novelty P3, and the Frontal Negativity.

2) PCA decomposition of the P300. The 2D scalp topographies are oriented with the nose facing up and represent the response to the Novel stimuli at 352 ms. The waveforms correspond to Pz. The top row represents the grand average data. The second and third rows correspond to the Varimax and Promax rotations of the PCA. For the PCA data, the first two columns describe the initial spatial PCA factor. The third column displays the result of the temporal PCA (the scalp topography does not change).

3) PCA decomposition of the Novelty P3. The 2D scalp topographies are oriented with the nose facing up and represent the response to the Novel stimuli at 328 ms. The waveforms correspond to Fz. The top row represents the grand average data. The second and third rows correspond to the Varimax and Promax rotations of the PCA. For the PCA data, the first two columns describe the initial spatial PCA factor. The third column displays the result of the temporal PCA (the scalp topography does not change).

4) Source localization results for the Varimax and Promax rotations of the P300, Novelty P3, and Frontal Negativity factors. The equivalent dipole locations are represented as white dots, superimposed on a representative MRI anatomical image (not from the study). The white box represents the Talairach coordinate system.

5) Source localization results for the oddball response using MUSIC-RAP and Minimum Norm algorithms. The time window from 250 to 350 ms. was analyzed for the grand average of the target rares minus the non-target frequents.