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Topography of the post-imperative negative variation in schizophrenic patients and controls obtained from high-resolution ERP maps

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The post-imperative negative variation (PINV) comprises a slow negative potential shift extending up to several seconds following a signaled task-relevant stimulus or response. This slow negativity is particularly intriguing, since it seems to be a component of event-related potentials which is found to be larger in amplitude in schizophrenics than in healthy subjects, whereas typically, amplitudes of such components are reduced in patient groups. In the latter case, differences may be due to higher intra-individual response variability and lower signal-to-noise ratio on the part of the patients. Obviously, such an interpretation cannot explain the PINV results. Furthermore, the occurrence of a PINV seems to be reliably related to the diagnosis of a schizophrenic disorder and other severe psychopathological conditions. It can be elicited repeatedly, and measured, independent of clinical judgment, objectively as well as non-invasively. Although frequently found in schizophrenic patients, the PINV is not a specific signature of schizophrenia but is also found in patients with major depressive disorders, and sometimes also in anxiety disorders [1–3], and in patients with obsessive thoughts [4]. Across diagnoses, [5] reported an increase of PINV amplitude from normal controls over neuroses and schizotypy to psychosis. As the PINV varies with the acuteness and severity of the illness [6–8], Timsit-Berthier [1] concluded that 'the PINV is not specific to a single diagnosis, but appears to be an extremely sensitive index of psychopathological morbidity' (p. 431).

In healthy subjects a type of PINV can be provoked by specific experimental conditions, implying, for instance, the introduction of stress during the interval between the warning and the imperative stimulus [9], a change in the contingency between the motor response and the offset of the imperative stimulus, implying control and predictability of control [10–13]. By varying experimental conditions across a series of studies, we found that the ambiguity in the match of samples (S1) and alternatives (imperative S2) in delayed-matching-to-sample tasks elicited a PINV in schizophrenics as well as in controls (compared to clear matching conditions), while working memory load induced by the variation of the signal stimulus from trial to trial, to which the imperative stimulus had to be matched, affected PINV amplitudes only in patients [14]. The PINV was negligible in schizophrenics and controls, whenever a motor response had to be withheld (in a go-nogo-

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paradigm; [15]), or was followed immediately by feedback about response adequacy [18] (Becker, unpublished data). We hypothesized that uncertainty about the appropriateness of one's preceding action constitutes a cognitive process contributing to the PINV and that patients suffer from a lower threshold for this uncertainty to be evoked.

The experimental variation of the PINV amplitude is not sufficient for our understanding of the nature of the phenomenon. From these results, it cannot be decided to what extent the group differences in PINV amplitude represent quantitative differences in the same process (sensitivity to performance uncertainty), or whether qualitatively different cortical processes contribute to the PINV in schizophrenics and controls. Analyzing the spatial distribution of the PINV might help to resolve this question. Earlier analyses of the three midline recordings (Fz, Cz, Pz referred to linked mastoids) consistently showed a frontal or frontocentral predominance of the PINV [19]. With recording sites over the two hemispheres and comparing the PINV amplitude to pre-trial baseline, the scalp distribution of the PINV was affected by the stimulus modality in schizophrenic patients as well as in controls, with more posterior predominance for visual, and more anterior predominance for auditory stimuli [17]. When the PINV was referred to the negativity preceding the imperative stimulus (CNV), group-specific distributions were found with a more symmetrical distribution in patients, but pronounced asymmetry with right-frontal predominance in controls. Spline interpolation and current source density analysis (CSD) of group- and condition-averages including 32 electrodes [16] verified more symmetrical PINV distribution with slightly left-frontal expression in patients, while controls exhibited a right-frontal, asymmetric PINV distribution. Thus, group-specific effects seemed to be underestimated and effects of conditions overestimated, if the PINV is related to pre-trial baseline. Modeling the PINV by means of a combination of spatial Principal Component Analysis (PCA) and dipole modeling [20] produced one component explaining the CNV, which suggested the continuation of the processes contributing to the CNV into the postimperative interval. This contribution might be described as 'delayed CNV resolution'. Additional principal components, however, indicated frontolateral sources that differed in symmetry between patients and controls. A component with group-specific topography points to qualitatively different contributions to the PINV in patients and in controls, that is, to at least one disease-specific meaning of the PINV.

In the most recent study we recorded the EEG from 64 channels (cap montage, plus additional electrodes for monitoring of vertical and horizontal eye movements) with a sampling rate of 100 Hz in 10 male schizophrenic patients and 10 controls matched for age and educational level. From the recording epoch 3 s baseline to 4.5 s postimperative interval, the PINV amplitude was determined for the interval 0.5–1.5 s following the imperative stimulus referred to pre-trial baseline. The PINV was provoked using the delayed-matching-to-sample task with auditory signal and imperative stimuli including ambiguous stimuli (adapted from [17]. The sample comprised 10 patients (2 female, 8 male, age 28.1 ± 7 (range 19–39) years) with a schizophrenic diagnosis: F20.0, $N = 8$; F20.1, $N = 2$. Comorbid diagnosis of substance dependence: $N = 3$. Duration of illness: 96 ± 132 weeks (range 8–442). Number of hospitalizations: 4.8 ± 3.3 (range 1–10). All patients were under standard ($N = 7$) or atypical ($N = 3$) neuroleptics (188.5 ± 91 mg/day CPZ equiv.), additional anticholinergics $N = 2$). Patients were compared to a group of 10 healthy subjects matched for sex and age to the patient group[1].

For every subject, the distribution of the sources of cortical activation was determined for PINV measured under conditions of ambiguous matching of auditory stimuli in the delayed-matching-to-sample task. The electric potential measured at the scalp surface cannot be directly related to the underlying brain activity, i.e. the spatial resolution is rather poor. In the absence of a reliable a priori source model (i.e. if many sources must be assumed to be simultaneously active), a method is required

[1] The data of one control subject could not be analyzed because of artifacts; results are based on $N = 9$ controls.

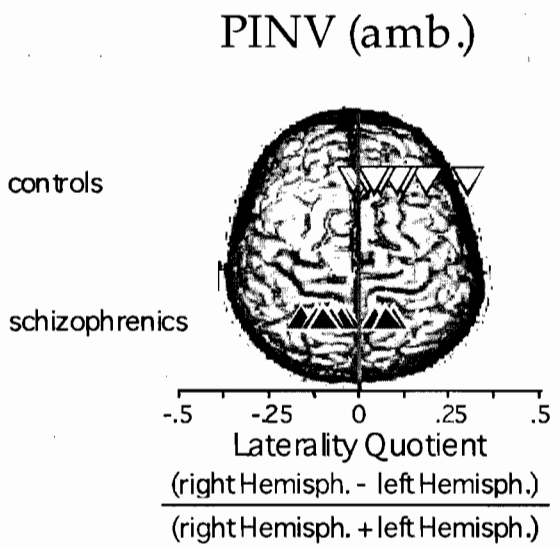

Fig. 1. Scattergram for the laterality quotient calculated from the deconvoluted measures of the PINV ('minimum norm') recorded under ambiguous conditions

which makes use of only the information contained in the data and yields the closest mapping of the measured potential to the underlying brain sources without a priori information. Such a solution can be obtained with the 'pseudo-inverse' or 'minimum norm method'. In the present study a distributed source solution was computed for 1384 dipole locations placed on four concentric shells with different radii in a spherical volume conductor. Each location contained three orthogonal dipoles (one radial and two tangential). For each of these dipoles a linear combination of the data was computed which was intended to filter out activity from just this dipole and to suppress activity from all the other ones.

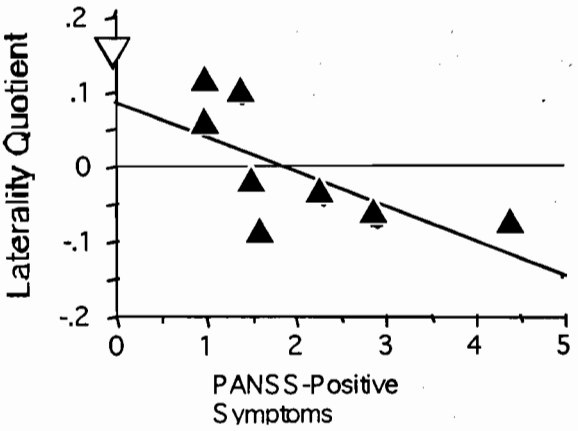

Fig. 2. Laterality quotient of the PINV (ambiguous condition) as a function of positive symptoms (average item score of the PANSS-P scale). The open downward triangle corresponds to the mean laterality quotient of controls.

Inspection of the 'minimum norm' maps indicated considerable inter-individual variability, which should call for caution in interpreting group averages. Comparing the individual maps revealed asymmetrical maps with right-hemispheric predominance of activity in more controls than patients, whilst symmetrical activity sources or left-hemispheric predominance was found in more patients than controls. For ambiguous matching conditions, the laterality quotient, calculated for potential maps and 'minimum norm' maps of pairs of corresponding recording channels over the left and right hemisphere[2], confirmed no clear asymmetry in the patient group (0.01 ± 0.03 for scalp potential, -0.03 ± 0.03 for MN) compared to a right-predominant asymmetry in the control group (0.15 ± 0.04 or 0.11 ± 0.03, respectively $F(1, 17) = 6.9$, $P < 0.02$ for scalp potentials, and 9.9, $P < 0.01$ for MN; see Fig. 1; positive values indicate larger right- than left-hemispheric activity). No significant effects were obtained for clear matching, and no differences in the mean PINV amplitudes were found between groups.

The correlation between the positive symptom ratings on the PANSS-P-scale and the laterality quotient of potential maps indicated reduced right-hemispheric predominance in patients to covary with increasing severity of positive symptoms ($r = 0.71$, $P < 0.05$) calculated for the patient group only; see Fig. 2.

The results obtained from high-resolution analysis confirmed a right-hemispheric activity focus in healthy subjects compared to reduced asymmetry and only slightly left-hemispheric activity focus during the post-imperative interval in schizophrenics. Increasing the number of elec-

[2] Difference of all right- minus all corresponding left-hemispheric electrodes divided by the sum of all right- and left-hemispheric electrodes.

trodes and determining the sources of activity not only uncovered the inter-individual variability of activity patterns but also allowed a first closer look at relationships with symptomatology: reduced right- and slightly left- predominant PINV was significantly related to a predominance of positive symptoms. Although the studies are not comparable, it is interesting to note that a negative correlation of PANSS-positive symptoms and right ear advantage in a dichotic listening task was reported by [21].

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