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Neuroimaging methods in affective neuroscience: Selected methodological issues

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Abstract: A current goal of affective neuroscience is to reveal the relationship between emotion and dynamic brain activity in specific neural circuits. In humans, noninvasive neuroimaging measures are of primary interest in this endeavor. However, methodological issues, unique to each neuroimaging method, have important implications for the design of studies, interpretation of findings, and comparison across studies. With regard to event-related brain potentials, we discuss the need for dense sensor arrays to achieve reference-independent characterization of field potentials and improved estimate of cortical brain sources. Furthermore, limitations and caveats regarding sparse sensor sampling are discussed. With regard to event-related magnetic field (ERF) recordings, we outline a method to achieve magnetoencephalography (MEG) sensor standardization, which improves effects' sizes in typical neuroscientific investigations, avoids the finding of ghost effects, and facilitates comparison of MEG waveforms across studies. Focusing on functional magnetic resonance imaging (fMRI), we question the unjustified application of proportional global signal scaling in emotion research, which can greatly distort statistical findings in key structures implicated in emotional processing and possibly contributing to conflicting results in affective neuroscience fMRI studies, in particular with respect to limbic and paralimbic structures. Finally, a distributed EEG/MEG source analysis with statistical parametric mapping is outlined providing a common software platform for hemodynamic and electromagnetic neuroimaging measures. Taken together, to achieve consistent and replicable patterns of the relationship between emotion and neuroimaging measures, methodological aspects associated with the various neuroimaging techniques may be of similar importance as the definition of emotional cues and task context used to study emotion.

Keywords: EEG; MEG; fMRI; average reference; sensor standardization; proportional global signal scaling; SPM of EEG/MEG distributed source estimations

Neuroimaging methods have been increasingly used to explore the neural substrate of emotion. Over the last decade, a multitude of studies utilized functional magnetic resonance imaging (fMRI) to indirectly reveal brain activity by measuring blood-flow-dependent signal changes in magnetic resonance (Murphy et al., 2003; Phan et al., 2004; Phelps, 2004). However, the inherent time lag of hemodynamic responses limits the temporal resolution of fMRI to reveal the dynamics of brain activity (Bandettini et al., 1992; Blamire et al., 1992). Recordings of the brain's magnetic and electrical fields provide data with high temporal precision needed to determine the brain dynamics of emotional processes. Availability of dense sensor electroencephalography (EEG; up to 256 channels) and magnetoencephalography (MEG;

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up to 275 channels) enable more adequate spatial assessment of electromagnetic fields thereby improving the ability of these measures to uncover brain sources. Thus, hemodynamic and electromagnetic neuroimaging measures provide complementary information regarding brain processes and progress may be expected in combining fMRI and EEG measures (Salek-Haddadi et al., 2003; Debener et al., 2005; Wang et al., 2006).

Studying emotional perception from the perspective of biphasic emotion theory, we utilized event-related potentials (ERPs), event-related magnetic field recordings (ERFs), and functional magnetic resonance imaging (fMRI) to reveal the brain dynamics and neural structures of the processing of emotional visual cues (Schupp et al., this volume; Kissler et al., this volume; Lang et al., this volume; Sabatinelli et al., this volume). In this research, methodological problems and challenges were encountered, unique to each neuroimaging method, with important implications for the interpretation of data, design of analyses, and comparison across studies. Specifically, we first discuss reasons for the adequate spatial assessment in event-related brain potential studies and highlight limitations associated with popular reference sites such as linked mastoid or earlobes. Next, we provide reasons and ways to implement sensor standardization in MEG research. In fMRI analyses, while proportional global signal scaling is routinely used, we report findings that violations in assumptions of this correction can dramatically impact statistical findings. None of these problems is specific to emotion processing and, indeed, points of concern raised by this review have been articulated repeatedly in cognitive neuroscience. However, we hope that illustration of these issues with specific examples from emotion research raises sensitivity to methodological issues in affective neuroscience. Finally, we describe a source spaced analysis of EEG/MEG data achieving electromagnetic data analyses with the same SPM (Statistical Parametric Mapping) routines as established for hemodynamic measures.

Event-related brain potentials and brain sources

An enduring problem inherent to event-related potential (ERP) research is the limitation to draw inferences about underlying brain sources. One challenge to determine more precisely neural sources in ERP research is the adequate spatial assessment of brain field potentials. Technological advances enable the routine recording of dense sensor ERPs up to 256 channels (Tucker et al., 2003), approaching the ideal of the reference-independent characterization of brain field potentials.

The difficulty to achieve a reference-independent characterization of brain field potentials and the reference dependency of sparse sampling reflects the biophysics of EEG signal generation. It is widely assumed that EEG represents signals meeting two requirements: First, because individual neuron activity generates small field potentials, activity has to be synchronous in thousands of neurons to allow for summation (Creutzfeld et al., 1966). Second, activity has to occur in spatially aligned neurons assuring that summation is effective (rather than cancellation as in closed fields; Lorente de No, 1947; Coles et al., 1990). It is for this reason that larger ERP components are considered to reflect predominantly excitatory postsynaptic potentials of cortical pyramidal cells. Neuronal activity is volume conducted through the scull to the scalp, where it can be recorded through surface sensors (Caton, 1875; Berger, 1929). Measuring brain potentials a few millimeters away from the source, the measured potential can be approximated by dipoles, with negligible contribution from multipole field potentials (Lutzenberger et al., 1987; Nunez, 1989). The dipolar nature of potentials measured at the head surface can be described as the superposition of the individual potentials of all active generators. Thus, assuming a complete coverage of the head surface (including the neck) and homogenous conductivity, the integral ERP activity would be zero. This logic underlies the calculation of the so-called average reference (Offner, 1950; Bertrand, 1985). Thus, after recording, the average reference can be computed by subtracting the mean of all sensors from each individual site. If the potentials at all body surface points would be known, an average reference transformation would provide a real inactive reference and thus complete reference independency of the EEG. However, EEG recordings according to the traditional international 10/20 system use a comparably small number of electrodes and even the international 10/10 system provides limited coverage of the head surface. Similarly, even though some researchers consider sensor arrays larger than 30 sensors as sufficient to calculate the average reference, the averaged potential across uncovered head surface areas may reveal residual mean activity leading to an inaccuracy of the average reference (Katznelson, 1981; Dien, 1998). Expanded EEG sensor head coverage (Tucker, 1993; Gevins et al., 1994) increasingly approximates the requirements of the average reference and the residual average activity approaches the expected zero potential. Simulation studies show that the step from a 10/20 system to a 128 whole head sensor recording approximately reduces the residual average reference activity by 50%. The improved coverage of inferior frontal, temporal, and occipital regions of 256 sensor arrays provides a further substantial reduction of the residual average reference activity (Junghöfer et al., 1999).

Residual average reference activity in regions not covered by electrodes can be estimated by extrapolation of the measured potential distribution. The compensation for residual average reference activity can approach a so-called ‘‘infinite’’ reference (Junghöfer et al., 1999; Yao, 2001). However, extrapolation of activity in uncovered areas is not unique even if physiological constraints about reasonable field propagation are taken into account and the extrapolation accuracy shrinks dramatically with an increasing integral of uncovered regions. For instance, international 10/20 system recordings are not sufficient for any reasonable extrapolation. Simulation studies demonstrate that a 128-sensor system allows compensation of roughly a third while a 256-sensor system can approximate more than the half of the residual average reference activity (Junghöfer et al., 1999).

A further mean to achieve a reference-free characterization of ERPs is to calculate the current source density (CSD; Perrin et al., 1987, 1989; Gevins et al. 1991), the negative second spatial derivative of the scalp voltage distribution. As the derivative of a constant value is zero, the CSD extracts the globally constant effect of a reference. The calculation of the CSD as well as the fundamentally equivalent methods ‘‘Laplacian’’ or ‘‘Cortical Mapping’’ (Junghöfer et al., 1997) are mathematically unique transformations compensating for the strong spatial lowpass filtering effect of the head as volume conductor — predominantly the ‘‘blurring’’ effect of the skull. These ‘‘deblurring’’ methods do not demand any a priori constraints or assumptions and are not affected by the ambiguity of the ‘‘inverse problem.’’ Thus, the CSD recommends itself as a reference-independent method to uncover local cortical generator sources and simulation studies demonstrate that progressively more details about cortical potential distribution can be obtained as spatial sampling is increased even beyond 128 channels (Srinivasan et al., 1996). In CSD solutions, a focal generator source is indicated by a sink/source pattern of inward/outward flow of current, which on the other hand reveals a more complicated distribution of multiple inward and outward currents in the case of activation of multiple adjacent generator sources. For instance, Junghöfer et al. (2001) used CSD to provide an increased spatial resolution of the early posterior negative (EPN) potential observed in emotion processing. Specifically, using the difference in evoked potentials of subjects viewing emotionally arousing or neutral pictures, the CSD revealed bilateral symmetric sources in occipital areas accompanied by right lateralized twin parietal sink sources (see Schupp et al., this volume). However the goodness of ‘‘deblurring’’ methods heavily depends on a sufficient spatial sampling ratio (Srinivasan et al., 1996; Junghöfer et al., 1997) as the sampling needs to meet the constraint of the Nyquist sampling theorem in order to avoid ghost effects consequent upon spatial aliasing. For scalp potential interpolation, CSD computation and ‘‘Cortical Mapping,’’ any choice of Green’s spline functions could be used. However, optimized spline functions can be derived from additional information such as physiological conductivity properties and estimated depth of generator structures as described in Junghöfer et al. (1997). A further requirement for applying CSD is a high signal-to-noise ratio because the CSD technique profoundly emphasizes high spatial frequencies and spurious findings may emerge by noisy data.

The calculation of inverse distributed source estimations such as the minimum-norm-least-square (MNLS; Hamalainen and Ilmoniemi, 1994) or low-resolution tomography (LORETA; Pascual-Marqui et al., 1994) provides further methods to achieve a reference-independent characterization of ERP potentials. These models use a large number of distributed test dipoles varying in strength to represent the scalp measured field potentials. The MNLS, as a linear estimation technique, is based on the assumption that the measured scalp potential distribution (**U**) at each point in time can be described as the product of a so-called leadfield matrix (**L**), specifying each electrode sensitivity to each of the distributed sources of the model head, and the generator activation $(\mathbf{G}) \rightarrow \mathbf{U} = \mathbf{L}\mathbf{G}$. In order to estimate the generator distribution $\mathbf{G} = \mathbf{L}^{-}\mathbf{U}$ the inverse of the leadfield matrix **L** has to be multiplied with the measured scalp potential distribution. However, this matrix inversion is only defined if the number of columns (given by the number of sensors in **U**) and rows (given by the number of sources in **G**) of **L** would be identical and **L** would have maximal rank. With distributed source models, the number of sources by far exceeds the number of sensors, and thus $\mathbf{L}^{-}$ has to be replaced by the pseudoinverse leadfield matrix $\mathbf{L}^{+}$ leading to $\mathbf{G} = \mathbf{L}^{+}\mathbf{U}$. In this case, the inverse equation is underdetermined and the inverse problem is ill posed, i.e., the scalp potential may be represented by an infinite number of solutions that could produce the identical measured field potentials. Thus, selection of the "most realistic" solution in distributed source models requires further constraints or criteria. In addition to representing the measured scalp field, the MNLS estimate uses as an additional criteria that the pseudoinverse multiplication is characterized by minimizing the mean power (least square) of the estimated current density of the sources. In contrast, LORETA selects the distributed source solution that is maximally smooth assuming that the higher spatial resolution of other solutions is usually not justified for EEG data. While the most important advantage of distributed source modeling is that these techniques do not depend on assumptions regarding location or number of brain generators, the assumptions introduced by these methods need to be considered providing limitations for the interpretation of the findings. Distributed source estimations considerably limit the detection of nearby focal sources and provide estimations of rather distributed neural generators. Thus, the nonuniqueness of the inverse estimation requires criteria that do not automatically reveal the correct solution, and, in the absence of independent further support, is probably best viewed in relation to broader anatomical regions rather then specific neural structures. While the spatial high pass filter characteristic of the CSD diminishes the impact of extended potential distributions of deeper neural activities and thus overestimates superficial sources, the MNLS and LORETA tend to explain activities in deeper structures by widely distributed superficial activities, an effect which can be compensated to some extent by depth weighting (Fuchs et al., 1994; Pascual-Marqui et al., 1994). Similar as CSD, inversely distributed source estimates demand a good signal-to-noise ratio because projecting electrophysiological data from two-dimensional (2D) signal space into 3D source space may lead to strongly magnified spatial variance.

Taken together, dense sensor arrays provide multiple avenues to achieve reference-independent characterization of electrophysiological recordings. Adequate spatial sampling is requested by these techniques and this may heavily impact the outcome of their application. As each method invokes unique assumptions, converging evidence across different analysis tools and complementary neuroimaging methods is particularly desirable. For instance, the early differential occipital negativity elicited by emotional compared to neutral pictures is revealed by brain maps based on the average reference, CSD sink/source patterns in occipito-temporo-parietal regions, and distributed posterior sources in minimum-norm solutions (cf. Fig. 2; Junghöfer et al., 2001; Schupp et al., 2006). Furthermore, fMRI results and electromagnetic recordings provide independent evidence for the increased activation of visual-associative structures by emotional cues amounting to converging evidence across several neuroimaging methods and types of analyses (cf., Figs. 4 and 5; Junghöfer et al., 2005a,b, 2006).

Sparse sensor sampling and the reference issue

As discussed above, sparse sampling of field potentials would seriously violate the assumption underlying the calculation of the average reference (Katznelson, 1981; Dien, 1998). Sparse sampling arrays provide a reference-dependent depiction of brain field potentials because EEG amplifier systems have the requirement to obtain voltage recordings as difference between two locations on the head or body surface. In the past, many researchers hoped to minimize the recording of brain activity from one recording site by choosing positions such as the linked earlobes, mastoids, or nose. The hope to approach monopolar recordings has been dubbed as "convenient myth" (Davidson et al., 2000, p. 33) or "EEG/ERP folklore" (Nunez, 1990, p. 25). Considering that electrical field potentials are volume conducted throughout the head, there is no site on the head surface showing a consistent zero activity across all possible brain sources. Specifically, depending on the location of brain sources, electrodes considered to represent an inactive reference may reveal substantial field potentials varying dynamically across time. To provide a potentially more intuitive analogy, consider temperature measurements obtained as difference between locations and compare effects to absolute (true) values. On a sunny day, the temperature may be 20 °C, 25 °C, and 30 °C in locations A, B, and C. Using A as reference, we measure for B and C temperature of 5 °C and 10 °C, respectively. Using B as reference, we obtain –5 °C and + 5 °C for locations A and C. Without information about the reference temperature, absolute temperatures are not achievable. It is for this reason that the choice of reference can have rather dramatic effects on the appearance of ERP recordings and thus, interpretation of ERP findings need to consider the choice of reference. Applying these issues to the field of emotion research, a large number of studies utilized visually presented stimuli and many of these studies relied on the popular linked mastoid reference when studying the processing of emotional pictures (Cuthbert et al., 2000; Schupp et al., 2000; Kemp et al., 2002; Pause et al., 2003; Amrhein et al., 2004; Carretie et al., 2004, 2005), emotional facial expressions (de Gelder et al., 2002; Holmes et al., 2003, 2005, Pourtois et al., 2004, 2005) or emotional words (Chapman et al., 1980; Bernat et al., 2001; Pauli et al., 2005). Other research utilized dense sensor recordings providing an improved description of the field potentials by calculation of the average reference in emotional picture (Junghöfer et al., 2001; Keil et al., 2002, 2005; Schupp et al., 2004a,b, 2006; Stolarova et al., 2006; Flaisch et al., 2005), emotional face (Batty and Taylor, 2003; Schupp et al., 2003a,b; Meeren et al., 2005), or emotional word processing (Skrandies et al., 2003; Ortigue et al., 2004; Herbert et al., 2006; Kissler et al., this volume).

In the following, significant effects of the reference choice (average reference vs. linked mastoids) are illustrated using data from a recent study in which subjects viewed a continuous stream of emotionally arousing and neutral pictures, each presented for 1 s (Junghöfer et al., 2003). Figure 1 illustrates the time course of anterior, posterior, and right inferior-lateral scalp potential activity using mid-frontal, mid-occipital, and occipito-temporal electrode sites. On the basis of the average reference, the occipital sensor (Fig. 1c) revealed a more negative potential for subjects viewing emotional compared to neutral cues. The relative negative difference component appeared sizable, developed with the falling slope of the P100 and was maximally pronounced around 220 ms. Polarity reversal was observed over anterior sensor sites as illustrated for a frontal sensor (Fig. 1a). Specifically, emotional pictures were associated with enhanced positivity compared to neutral items. A much different pattern of results emerged for the linked mastoid reference. Of most relevance, the relative difference potential "Emotional minus Neutral" appears small at the occipital sensor (Fig. 1d). Furthermore, frontal positivity effects of the difference potential are greatly amplified compared to the average reference recordings (Fig. 1b). These differences in the appearance of the effects of differential emotion processing are easy to explain: Mastoid sensors are most sensitive to generator sources in occipito-temporal brain regions engaged during processing of visual cues. Consistent with this notion, pronounced ERP activity for the right

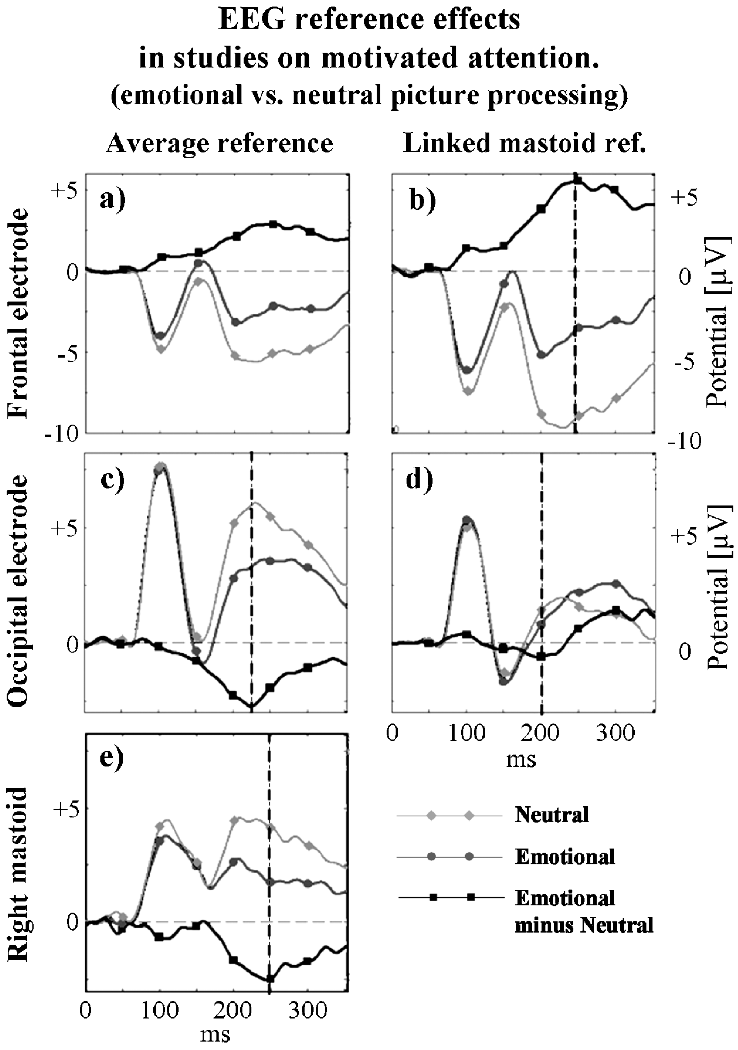

Fig. 1. While subjects viewed a continuous stream of emotionally arousing and neutral pictures, each presented for 1 s, ERPs were measured with a 128-sensor whole head EEG system. On the basis of an average reference (left row), emotional pictures evoke a relative negative ERP difference component (EPN) over occipital and occipito-temporal regions starting with the falling slope of the P100 and finding its maximum around 225 ms at occipital (c) and roughly 250 ms at occipito-temporal (mastoid) sites (e). If referenced to linked mastoids (right row) the strong negative difference component at the occipito-temporal mastoid sites is subtracted from all other electrodes strongly diminishing the posterior negativity at occipital leads (d) and significantly increasing the corresponding positive potential differences at frontal sites (b). The spreading brain activation from occipital to temporal areas leads to artificial latency shifts between posterior negativities and frontal positivities if referenced to linked mastoids.

mastoid site is revealed with the average reference (similar left mastoid activity is omitted for brevity). In contrast, the mean activity of both mastoids gets subtracted from all other sensors when using a linked mastoid reference, leading to a constant zero potential at the mastoids (Fig. 1e).

Brain potential maps (Fig. 2) further detail the effects of linked mastoids on the appearance of the ERP difference of emotional and neutral cues. Obviously, while the spatial characteristics of the potential distribution remain unaffected by choice of reference, the absolute magnitude of the

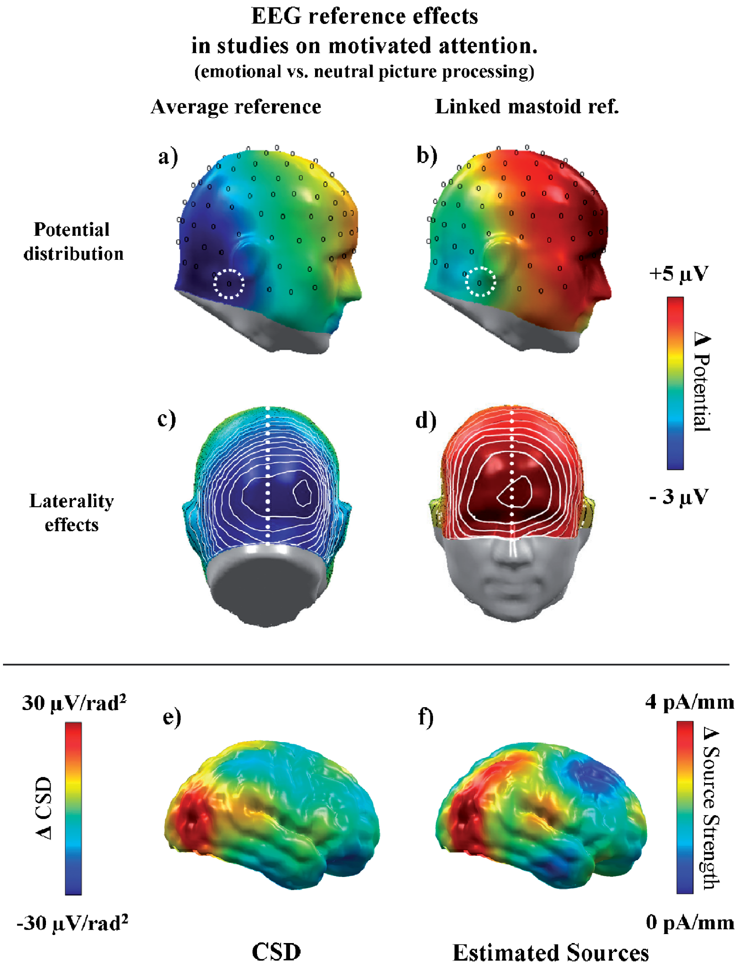

Fig. 2. Reference dependency of the EPN potential distribution at its maximum around 225 ms: The linked mastoid reference artificially converts the posterior (a) and right hemispheric dominant (c) EPN into an anterior (b) positivity without clear laterality effects (d). If based on the scalp potential distribution only, interpretations with respect to underlying generator structures are difficult. Additional information from reference-independent analysis techniques like the CSD (e) or the minimum-norm-least-square (f) or other neuroimaging methods such as fMRI (see Figs. 4 and 5) is needed.

potential characteristic depends entirely on the chosen reference location. In effect, with a mastoid reference (Fig. 2b) the ERP correlate of differential processing over distributed temporo-occipital areas is strongly suppressed if compared to the average reference (Fig. 2a), which in contrast reveals a pronounced differential occipital negativity for emotional pictures compared to neutral pictures.

In addition to such quite obvious spatial effects, the choice of reference may also have more subtle effects on the latency at which condition effects appear. For instance, on the basis of linked mastoid reference, latency differences between earlier negative posterior and later positive anterior potential differences in visual processing have been considered as evidence to reflect distinct generators in anterior/posterior brain regions (e.g. Bentin et al., 1996; Eimer, 2000). Similarly, in the example at hand, peak latency of emotional discrimination appears also to be distinctly later for the fronto-central positivity (around 245 ms;

Fig. 1b) compared to the residual occipital negativity (around 220 ms; Fig. 1d) if applying a linked mastoid reference. However, the different peak latencies might be attributed to electrical activity generated in occipito-temporal brain regions picked up by the mastoid sensors. Possibly reflecting the spread of brain activation from occipital to occipito-temporal brain regions, peak latency of emotional discrimination appears earlier at occipital sites (225 ms; Fig. 1c) and roughly 20 ms later at occipito-temporal electrodes such as the right mastoid (245 ms; Fig. 1e). Thus, neglecting the reference issue and the principle that voltage differences reflect the difference between bipolar sensor sites, the mastoid reference is suggestive of anterior/posterior latency differences by pushing peaks at sites more posterior than the mastoids to earlier latencies and peaks at more anterior sites to later latencies. In contrast, average reference montage provides a rather different view suggesting that mid-occipital and lateral occipital sensor sites have different peak latencies with regard to emotion discrimination. It is important to note that this example illustrates distinct latency effects for different reference choices only and should of course not be taken as evidence against early affect-driven difference activities in frontal brain areas.

In addition to latency effects and spatial effects in posterior–anterior direction, the choice of reference may also affect the appearance of hemispheric differences in emotion processing. With respect to affective processing of visual stimuli, the occipito-temporal areas of the right hemisphere often showed stronger effects of motivated attention for emotional pictures (Junghöfer et al., 2001) and faces (Schupp et al., 2004b) while the left hemisphere showed dominance for the processing of emotional words (Kissler et al., this volme). As shown in Fig. 2c, the right hemispheric dominance for emotional picture processing can be readily observed in the posterior negativity with average reference recording. However, forcing effects away from the occipito-temporal references, linked mastoids appear to sandwich difference effects from both sides to the frontal midline direction as illustrated by the lateral symmetric anterior positivity (Fig. 2d). Thus, the attenuated posterior negative difference potential observed for the linked mastoid reference may also affect findings of hemispheric dominance.

Summary

ERP recordings are increasingly used to reveal the brain dynamics in emotion processing. Dense sensor arrays provide multiple avenues to achieve the reference-independent characterization of field potentials and considerably improve the estimate of cortical brain sources. Caveats specific to each of these analyses need to be considered as well as the general principle that ERP field potentials reflect the superimposition of all active brain sources. However, limitations and shortcomings not withstanding, inference of brain sources appears possible and reasonable in particular when converging evidence is provided by other neuroimaging methods. The use of sparse sensor arrays imposes limitations with regard to the assessment of surface potentials. Active brain sites cannot be inferred and the reference issue needs to be considered when interpreting data and comparing across studies.

Event-related magnetic fields: effects of sensor standardization

The MEG detects weak magnetic fields generated by the flow of intracellular postsynaptic currents (Williamson and Kaufman, 1981; Hari and Forss, 1999) of pyramidal cells, which constitute two thirds of the neurons of the cerebral cortex (Creutzfeldt, 1995). It has been estimated that a small area of about 40 mm^2 including tens of thousand synchronously active neurons can yield a net dipole moment of about 10 nAm, which is strong enough to be detected extracranially by MEG (Hamalainen, 1993). While the EEG measures the electric potential of the secondary currents, the MEG measures the additive overlay of the weak magnetic fields of both primary and volume currents (Sarvas, 1987). MEG is principally sensitive to sources that are oriented tangentially to the skull, and much less sensitive to those oriented radially. Hence, MEG is mainly constrained to cortical areas that are bounded in the walls of fissural cortex and the amplitude of the measured MEG signal decreases rapidly as the source depth increases. MEG measures provide a reference-independent characterization of magnetic fields. Furthermore, being differentially sensitive to tangential and radial generator orientations, MEG provides a different view on neural generator sources compared to EEG. Combining EEG and MEG measures may therefore provide complementary evidence of neuronal emotion processing. However, results of ERP and ERF studies are difficult to compare because MEG analysis is traditionally predominantly performed in the generator source space while ERP analyses is most often based on measured sensor space subsequently extended to source space. The main reason for these different approaches is that a standardized alignment of magnetic field sensors in MEG is almost unachievable as sensor positions are fixed within the MEG scanner and can thus not be adjusted for individual head sizes and head shapes. In contrast, sensor positioning in EEG is usually standardized with respect to head landmarks (nasion, inion, vertex, and mastoids). Thus, standardized sensor positioning across different subjects is almost impossible for the MEG and even exact repositioning of a subject in the MEG scanner for a second measure is much harder to achieve compared to the EEG. Consequently, to allow within subject comparisons across different sessions, comparisons across different subjects, or comparisons across different MEG systems (e.g. magnetometer vs. gradiometer system), extrapolation of the individually measured fields onto a standard or target sensor configuration would be necessary. Techniques for such MEG sensor standardization have been developed and recommended (Hämäläinen, 1992; Numminen et al., 1995; Burghoff et al., 2000; Knösche, 2002) but, until now, did not find acceptance as standard application in MEG research. For instance, neither MEG manufacturer data analysis software (4D-Neuroimaging, VSM Medtech Ltd. or Elekta Neuromag Oy) nor the most popular commercial EEG/MEG analysis software programs (e.g., BESA® or CURRY®) include MEG sensor standardization techniques.

One reason that MEG sensor standardization is not routinely employed may be that MEG research often has the goal to use inverse modeling to localize brain activity. The application of inverse methods, like multiple equivalent current dipoles (ECD; Brazier, 1949; de Munck et al., 1988) or distributed source estimations like MNLS (Hämäläinen and Ilmoniemi, 1994) or LORETA (Pascual-Marqui et al., 1994), is based on individual head-sensor configuration without necessity of sensor standardization across sessions or individuals. However, except for special cases where the number of underlying sources involved in neural processing (ECDs) is fairly well known (Scherg and von Cramon, 1985) inverse source estimation is not unique, i.e., different generator distributions can lead to identical magnetic field measures (Helmholtz, 1853). The nonuniqueness of the inverse estimation, as well as the substantial enlargement of the signal space with transformation from the 2D ‘‘sensor space’’ into the 3D ‘‘source space’’ adds significant spatial variance and might eventually decrease statistical power compared to the analysis in the sensor space. Consequently and similar to the EEG, statistical analysis in MEG sensor space can be favorable if temporal aspects are the main focus of interest and regional localization of neural activities would be sufficient. Moreover, due to (i) the better signal-to-noise ratio, (ii) the undisturbed DC coupling, (iii) the reference independency, and (iv) the higher spatial resolution because of the less blurred topographies, MEG analysis in the sensor space may still offer some advantages compared to the EEG sensor space analysis. Furthermore, procedures for MEG sensor standardization have been already validated on the basis of simulated data or phantom measurements (Knösche, 2002).

MEG sensor standardization is based on the principle that a magnetic field distribution measured from some distance — the target sensor configuration — can be determined uniquely from a magnetic field distribution known at all sites of a closed surface enclosing all neural generators (Yamashita, 1982; Gonzalez et al., 1991). However, in reality the individual field is not known at all points of a closed surface but only at some points (the magnetometer or gradiometer positions) of a partial surface and thus, the accuracy of field extrapolation depends on an adequate spatial sampling (density of sensors), a sufficient coverage of the magnetic fields generated by neural activity and adequate extrapolation functions. Demands for dense sensor coverage are even higher in MEG compared to EEG because magnetic fields usually reveal higher spatial frequencies compared to the EEG, mainly a consequence of the low conductivity of the cranial bone strongly affecting EEG recordings. However, modern whole head MEG systems provide an adequate spatial sampling, as well as sufficient head coverage (Knösche, 2002). The extrapolation of the 2D ''sensor space'' onto a standard sensor configuration (forward solution) poses similar problems as the ''inverse solution'' in source modeling. In the same way as inverse methods try to minimize ambiguities by application of physiological constraints — e.g. information about reasonable source locations in the gray matter (Nunez, 1990) and orientations perpendicular to the gyri (Lorente de No, 1938) — extrapolation functions should take into account corresponding physiological constraints with regard to reasonable magnetic field propagation. An optimal extrapolation should thus estimate the ''most reasonable'' neural generator distribution explaining the magnetic field topography measured at an individual sensor configuration and use forward modeling to reveal the corresponding magnetic field at the standardized target positions. Similar to inverse modeling, different techniques to estimate neural sources (e.g., MNLS, LORETA) provide somewhat differing inverse solutions, extending in this case to differing extrapolations in the standardized target space. However, the important point is that the extrapolated 2D magnetic field distributions based on differing inverse solutions reveal much less variance compared to the variance in the 3D source space. Thus, estimation of the magnetic field in standardized sensor space may have increased statistical power compared to the analyses in ''source space.''

To illustrate the effects of MEG analyses with and without sensor standardization, we used whole head MEG data (275 channels) obtained during a classical conditioning experiment (Junghöfer et al., 2005a). Sensor standardization was achieved by the application of inverse/forward sensor extrapolations based on inverse MNLS estimations, which has been suggested as sensor standardization procedure in magnetocardiography (MCG) by Numminen et al. (1995) (see Knösche, 2002 for a similar procedure). In the alternative stream, data analysis was achieved without compensation for sensor positioning similar to previous MEG studies (Costa et al., 2003; Susac et al., 2004). Furthermore, to compare statistical power, the original sample ($n = 24$) was reduced to either 18 or 12 subjects. Figure 3 illustrates the statistical effects comparing CS+ and CS– (CS — conditioned stimulus) processing with paired t-tests for the auditory N1 peak (95–125 ms) and the original and reduced samples. Areas with statistically significant ($p < 0.01$) enhanced outgoing magnetic fields for CS+ compared to CS– stimulus processing are marked by ''+'' signs and areas with significantly enhanced ingoing fields are indicated by ''–''signs, respectively. The statistical maps reflect a tangential N1 dipole field with negative ingoing fields over centro-parietal regions and positive outgoing magnetic fields over inferior fronto-temporal regions. Obviously, sensor standardization of the same data is reflected by increased statistically significant sensor areas to detect classical conditioning effects of the N1 peak and the advantages of sensor standardization are distinctly more pronounced for smaller subject samples. In addition, although superficially similar, topographic differences emerge for the original sample in the topography of the effects. Sensor standardization is superior to detect conditioning effects over inferior temporal regions. Without sensor standardization, the ''effective sensor coverage'' is limited to areas covered by the majority of subjects.

These data suggest that MEG sensor standardization should be considered as standard routine in MEG sensor space analyses. Statistical power and ''effective sensor coverage'' was increased in the present example and there are reasons to suspect that standardization effects were rather underestimated in the present study. Specifically, effects of sensor standardization may become significantly stronger with MEG recordings using less sensors and smaller coverage compared to the 275 whole head VSM Medtech Ltd. system. Advantages are

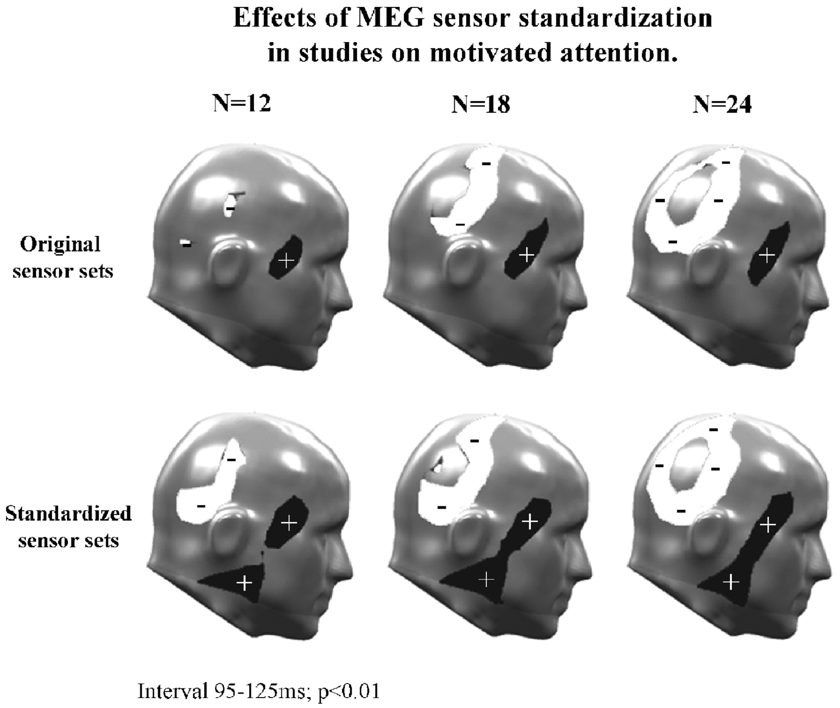

Fig. 3. Effects of sensor standardization for MEG sensor space data analysis. Statistical effects of paired *t*-tests comparing the processing of affectively conditioned CS+ and CS− tones with a 275-sensor whole head MEG are shown. Areas with statistically significant ($p < 0.01$) enhanced outgoing (+) and ingoing (−) magnetic fields of the auditory N1 peak (95—125 ms) are projected onto a model head. Sensor standardization leads to increased statistically significant sensor areas and widens the effective sensor coverage, in particular over inferior temporal regions. The advantages of sensor standardization are distinctly more pronounced for smaller subject samples.

not limited to the increased statistical power and "effective sensor coverage." Sensor standardization is a prerequisite for averaging across subjects or sessions in EEG and MEG research to avoid ghost effects as pure consequence of inconsistent sensor configuration. Furthermore, sensor standardization may facilitate comparison of MEG waveforms across studies.

Summary

As a consequence of both the nonuniqueness of the inverse solution as well as the higher dimensionality of the "source" compared to the "sensor space," statistical analysis in MEG "sensor space" can be favorable. However, sensor standardization is a necessary prerequisite for such an analysis. Three-dimensional extrapolation functions taking into account physiological constraints about reasonable magnetic field propagation provide a high goodness of extrapolation if they are based on adequate sensor density and sufficient head coverage. Sensor standardization significantly improves effect sizes in typical neuroscientific investigations, avoids the finding of ghost effects, and facilitates comparison of MEG waveforms across studies.

Functional magnetic resonance imaging: effects of proportional global signal scaling

ERP and ERF measures provide excellent temporal resolution but are limited with respect to determining the exact location of brain generators. In contrast, fMRI (Bandettini et al., 1992; Kwong et al., 1992; Ogawa et al., 1992) is an important method for determining the location of activated brain regions during emotion processing with much better spatial resolution. This method provides an indirect assessment of brain activity by measuring local concentration variations of oxygenated hemoglobin in the blood presumed to be mostly induced by synaptic events of neuronal activity (Logothetis et al., 2001; Raichle, 2001). However, utilizing this method in emotion research poses important challenges. Limbic and paralimbic target structures are notoriously difficult to assess and often require specific protocols. For instance, sampling of the amygdala is improved by acquiring thin coronal slices that minimize signal loss due to susceptibility artifacts (Ojemann et al., 1997; Merboldt et al., 2001). Similarly, a number of recommendations for an optimal assessment of blood oxygen level dependent (BOLD) activity in the orbitofrontal cortex also suffering from strong susceptibility artifacts are outlined by Kringelbach and Rolls (2004). In addition to such challenges in the assessment of neural target structures, methodological issues in data analysis may be also of concern when studying emotional processes. A still unresolved controversy is the use of proportional global signal scaling (PGSS) of BOLD signals in fMRI analysis.

Global variations of BOLD-fMRI signal are changes common to the entire brain volume and have been considered to reflect background activity rather than signal changes related to experimental manipulations (Ramsay et al., 1993). Consequently, global variations of the BOLD signal are commonly considered as nuisance effects, contributing unwanted sources of variance such as hardware scanner drifts, physiological movements, or pulsations. While agreeing on the fundamental necessity of global signal correction, discussion centered on the proper method of normalization, identifying global signal changes as either "additive" or "multiplicative" compared to the regional effects of interest (Fox et al., 1988; Friston et al., 1990; Arndt et al., 1996). However, normalization of global signal changes might turn into a confound, i.e. significantly changing the outcome of the analysis when the global signal is not orthogonal to the experimental paradigm (Andersson, 1997).

We recently explored reservations regarding the use of PGSS in the domain of emotion research comparing emotional and neutral pictures taken from the International Affective Picture System (IAPS, Lang et al., 2005). One specific concern was to consider the effects of emotional intensity. As suspected, the strong and distributed BOLD activations elicited by high-arousing emotional contents dominated the global signal variance violating the orthogonality assumption of global signal and experimental condition for high arousing emotional materials but not for low-arousing emotional contents. In line with previous reports (cf. Aguirre et al., 1998), this violation of the orthogonality assumption resulted in widely differing outcomes comparing two streams of fMRI analysis with and without global proportional signal scaling: As shown in Fig. 4, the unjustified application of proportional global signal scaling (PGSS) leads to an attenuated effect of emotional activation in structures with a positive correlation of local and global BOLD signal ("activation"; indicated by reddish colors). Omitting global proportional signal scaling, structures associated with pronounced BOLD signal activations when contrasting high-arousing and neutral picture conditions were apparent in uni- and heteromodal sensory processing areas in the occipital, parietal, and temporal lobe. Invariably, although still significant, application of PGSS was reflected by reduced effect sizes and cluster volumes. However, both streams of analysis also differed qualitatively, i.e., revealing significant findings in the analyses without PGSS, when focusing on structures with moderate effect sizes in the parieto-temporo-occipital cortex as well as limbic and paralimbic structures. Focusing on "deactivations," the use of global signal covariates augmented effects in structures with a negative correlation of emotional arousal and BOLD signal (indicated by bluish colors in Fig. 4a). Specifically, areas revealing significant deactivation in the analysis without PGSS, such as parietal, occipital, and temporal structures, revealed enlarged effect sizes and cluster volumes in the PGSS analysis. Furthermore, the PGSS analysis revealed significant deactivations not observed when omitting global signal covariates, especially left parietal and right hemispheric subcortical structures. As can be seen in Fig. 4b, analysis with and without PGSS appeared similar

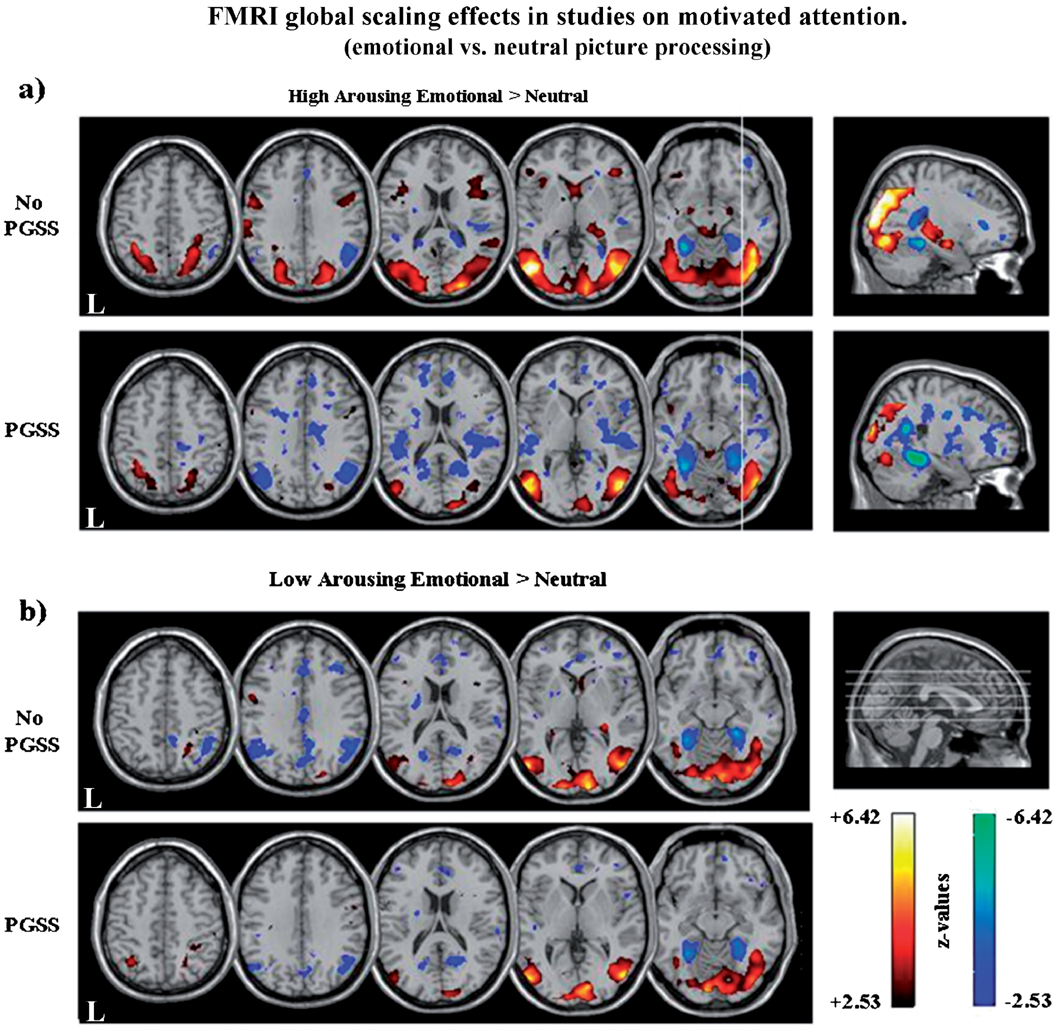

Fig. 4. Effects of MRI proportional global signal scaling (PGSS) in emotion research (random effect analysis; 21 subjects; $k = 20$; DF = 20). Significant BOLD signal differences contrasting high-arousing emotional (a) or low-arousing emotional (b) with neutral picture conditions are shown. Reddish colors indicate a stronger BOLD signal for the emotional stimuli compared to the neutral stimuli; bluish colors indicate stronger activations for neutral conditions compared to emotional picture conditions. The unjustified application of PGSS greatly distorts statistical findings in key structures implicated in emotional processing and might contribute to conflicting results in affective neuroscience fMRI studies, in particular with respect to limbic and paralimbic structures.

when comparing low-arousing emotional and neutral picture contents restricting the detrimental effects of unjustified global scaling to emotional stimuli of high intensity.

Emotional stimuli have been associated with activations in limbic and paralimbic structures (Morris et al., 1998; Vuilleumier et al., 2001; Hamann and Mao, 2002; Pessoa et al., 2002). However, results were rather inconsistent regarding the emotion-driven activation of these structures across studies (Davis and Whalen, 2001; Phan et al., 2002). The present data suggest that the unjustified use of global signal scaling might contribute to inconsistencies in findings. In contrast to the analysis omitting global scaling, the PGSS-based analysis failed to reveal significant activations in limbic and paralimbic regions for high-arousing emotional materials. It seems noteworthy that this effect was apparent for the amygdala, a key structure of emotional processing in current emotion theories (LeDoux et al., 2000; Lang et al., 2000; Lang and Davis, this volume). Thus, the unjustified application of global signal covariates appears to be a strong confound with regard to limbic and paralimbic structures, possibly contributing to inconsistencies in the literature. It appears likely that the untested use of global signal covariates impedes the generalization across studies, subject groups, and stimulus materials (Davis and Whalen, 2001; Phan et al., 2002; Wager et al., 2003). Particularly troublesome errors of interpretation might arise when comparing results of experimental conditions with and without significant global signal correlation and thus, this information should be provided in publications (Aguirre et al., 1998).

Summary

Taken together, this study demonstrated that the concerns and precautions questioning the standard use of PGSS in the cognitive domain also apply to emotion research. The unjustified application of PGSS in emotion research greatly distorts statistical findings in key structures implicated in emotional processing and might contribute to conflicting results in affective neuroscience fMRI studies, in particular with respect to limbic and paralimbic structures. Reiterating Aguirre et al. (1998), it is recommended to report the correlation of global signal and experimental condition when using PGSS and omit this confound in cases where the global signal and experimental condition show a significant relationship.

Distributed EEG/MEG source analysis with statistical parametric mapping

A current challenge for progress to determine the neural underpinnings of emotion processing is to integrate ERP/ERF and fMRI measures. In the present example, we provide an approach to analyze ERP/ERF data (Junghöfer et al., 2005a) that allows application of the statistical parametric mapping toolbox of SPM used for functional imaging (Friston et al., 1995). Please note that a similar approach will be implemented in future releases of SPM (www.fil.ion.ucl.ac.uk/spm). The idea behind this approach is that the distributed neural activity generating measurable scalp potentials or magnetic fields can be estimated by inverse distributed source methods like MNLS (Hamalainen and Ilmoniemi, 1984), LORETA (Pascual-Marqui et al., 1994), sLORETA (Pascual-Marqui, 2002; Liu et al., 2005), or even Beamformer techniques (Van Veen et al., 1997; Robinson and Vrba, 1999; Sekihara et al., 2001; Huang et al., 2004) and the resulting 3D volumes of estimated neural activity can be treated and analyzed in a similar fashion as fMRI volumes of BOLD activity. Thus, event-related single trial EEG or MEG data can be averaged across all time samples in an interval of interest, the underlying generator activity of this time interval can be estimated using inverse distributed source modeling, and these functional volumes of brain activity can then be submitted to the parametric analysis of SPM. The number of epochs in EEG or MEG studies does often outnumber the number of functional scans in fMRI examinations. However, the ratio is usually modest and state-of-the-art workstations can easily process this amount of data in reasonable time.

In order to demonstrate the practicability of this method, we will present a brief example where MEG data of 16 subjects who viewed a rapid serial visual presentation (RSVP; 333 ms per picture; no ISI) of 200 alternating aversive and neutral pictures (IAPS; Lang et al., 1999) were reanalyzed with this suggested method. As a first step, the event-related fields were edited on the basis of a method for statistical control of artifacts in high-density EEG/MEG measures (Junghöfer et al., 2000) which includes the extraction of globally noise contaminated epochs and interpolation of regional contaminations within trials. In a second step, the Tihkonov regularized MNLS with a regularization value of $\lambda = 0.05$ was calculated for the mean magnetic field in the EPN time interval (150—230 ms; see Fig. 1) for each artifact corrected epoch. As recommended by Hauk et al. (2002), a distributed source model with four concentric shells and evenly distributed sources in both tangential directions (2×350, 2×197,

2×87, and 2×21 dipoles per shell, no radial direction in MEG) was used. The 3D MNLS volumes of estimated neural source activity were than stored in a 3D voxel based file format (ANALYZE) with a field of view covering the whole inverse model head ($51 \times 51 \times 51$ voxel) and an isotropic voxel size of 4 mm (adapted to the smallest spatial distance of neighboring sources). In the following step, the functional MNLS volumes were spatially filtered by SPM (Friston et al., 1995) with an isotropic 20 mm full width maximum Gaussian kernel. The motivation for this spatial lowpass filtering of the MNLS estimations is the same as in fMRI data smoothing: The application of a Gaussian random field theory (as applied in SPM) is based on smooth Gaussian fields and smoothing will normalize the error distribution and ensure the validity of statistical tests. With respect to across-subject random effects analysis, smoothing allows some compensation for functional and anatomical differences between subjects. Afterwards, the experimental conditions were analyzed using the statistical parametric mapping toolbox SPM. Within this procedure, conditions were modeled with boxcar functions and condition effects were estimated according to the general linear model while the specific effect of interest (aversive versus neutral picture perception) was compared using a linear contrast. As second-level analysis, across-subject random effects analysis was performed on this contrast of interest. With respect to the visualization of the final calculated statistical parametric map, the spherical model head was coregistered onto the Montreal Neurological Institute (MNI) standard brain and functional results were superposed on it using the freely available software tool MRIcro (www.sph.sc.edu/comd/rorden/mricro). In the posterior regions of interest, the goodness of coregistration was high, but it was unsatisfying in anterior regions. Thus, regional spheres, realistic boundary element (BE; Cuffin, 1996), or finite element (FE; Weinstein et al., 2000) head models may be needed to explore activations in prefrontal regions.

The results obtained with this analysis are illustrated in Fig. 5, contrasting the differential processing of aversive compared to neutral pictures in the early posterior negativity (EPN-M) time interval (150–230 ms) and, for comparison, the hemodynamic correlate (BOLD) of the corresponding contrast (aversive vs. neutral picture processing; Junghöfer et al., 2005b). Although the same stimuli were used in both studies and picture presentation rate was identical, the comparison of both effects is somehow limited since different subjects have been investigated and even more important, different paradigms have been applied — block design in fMRI and alternating design in MEG. However, considering these methodological limitations, results demonstrate converging findings across both methods with respect to posterior brain regions. Both methods suggest that neural activity is elicited as function of emotional arousal in bilateral occipito-temporal and occipito-parietal areas, somewhat more pronounced on right hemispheric regions. In contrast, prefrontal activations revealed by fMRI are not readily apparent in MEG results which might be explained by the fact that the chosen isotropic spherical head model is less appropriate for prefrontal areas revealing strong conductivity inhomogenities and anisotropies (Wolters et al., 2006). Of course, due to the limited depth resolution of the MEG and the MNLS bias towards superficial sources, the MEG analysis did not reveal activations in subcortical structures like thalamus, hippocampus, or amygdale, which thus appear in the fMRI analysis only. A strong advantage of the statistical parametric mapping of ERP/ERF data is the possible consideration of additional covariates of interest like behavioral or autonomic measures.

Summary

Distributed EEG/MEG source analysis with statistical parametric mapping is one approach that uses common software routines across different neuroimaging measures. Applying the same analysis routines across fMRI, MEG, and EEG may help to demonstrate the convergence across measures. Furthermore, data processing of EEG/MEG measures using source localization procedures are usually performed within subject-related coordinate systems. Even if source localization is performed in standardized coordinate systems, the

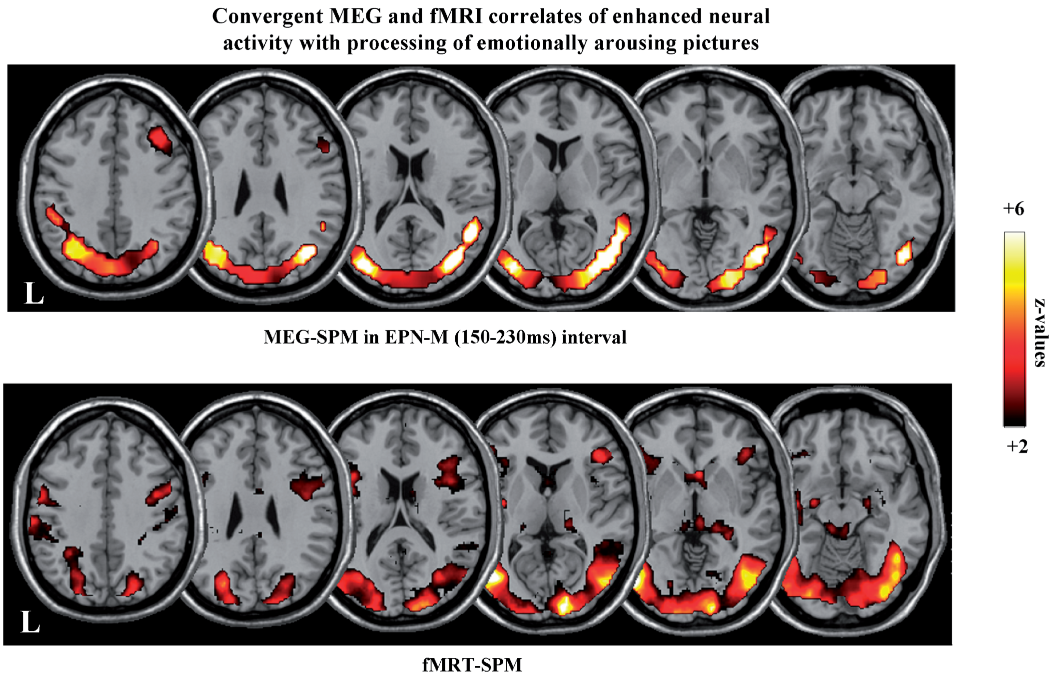

Fig. 5. Distributed EEG/MEG source analysis with statistical parametric mapping reveals convergent effects of increased blood flow and increased MEG source activity in the EPN time interval (150–230 ms) in subjects observing emotionally stimulating and emotionally neutral images.

interindividual variability of the "source space" can be considered to influence and bias results to some extend. This is even more important if results over subjects and/or different groups of subjects are compared. The use of SPM together with source analysis procedures opens the gate to nonlinear subject normalization methods — a widely used procedure in fMRI analysis — and therefore can be expected to significantly decrease spatial variance across subjects.

Conclusion

A current goal of affective neuroscience is to reveal the relationship between emotion and dynamic brain activity in specific neural circuits (LeDoux, 2000; Lang and Davis, this volume). In humans, noninvasive neuroimaging measures are of primary interest in this endeavor. The review raised specific methodological issues, which we encountered in our research, while neglecting many other issues deserving similar consideration. However, in our view, progress in the field of affective neuroscience is facilitated by the improvement and standardization of data acquisition and analysis, in particular regarding the goal to compare findings across studies. To achieve consistent and replicable patterns of the relationship between emotion and neuroimaging measures, methodological aspects associated with the various neuroimaging techniques may be similarly important as the definition of emotional cues and task context used to study emotion (Bradley, 2000).

Abbreviations

BOLD	blood oxygen level dependent
CS	conditioned stimulus
CSD	current source density
DC	direct current
ECD	equivalent current dipoles
EEG	electroencephalography
EPN	early posterior negativity
EPN-M	early posterior negativity (meg)

ERF	event-related magnetic field
ERP	event-related potential
FMRI	functional magnetic resonance imaging
IAPS	international affective picture system
LORETA	low-resolution tomography
MCG	magnetocardiography
MEG	magnetoencephalography
MNLS	minimum-norm-least-square
PGSS	proportional global signal scaling
RSVP	rapid serial visual presentation

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