BRAIN RESEARCH

Research Report

Subject's own name as a novel in a MMN design: A combined ERP and PET study

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ABSTRACT

With a view to elaborating a clinical tool to assess cognitive functions in brain-damaged patients, we had previously displayed characteristic patterns of ERPs (32 electrodes) in awake healthy persons in response to their own name (SON) presented as a novel in a passive oddball paradigm. In the present combined ERP and PET study, in an attempt to identify brain correlates of duration MMN and response to SON uttered by a familiar (FV) or an unknown voice (NFV), we used a block design protocol as close as possible to the aforementioned SON protocol. ERP data showed robust duration MMN and novelty P3 in response to SON similar to our previous results. The PET technique did not allow true MMN generators to be disclosed, but blocks with duration deviants elicited an increase of activation in the right temporal pole as compared with the control condition with no deviants, supporting the hypothesis of right hemispheric dominance in early sound discrimination. For SON contrasts, robust cerebral blood flow activation present over temporal, frontal and parietal cortices, in the hippocampus and in the precuneus could be associated with speech, novelty and self-recognition processing. Familiar and unfamiliar voices activated the prefrontal cortex differently, suggesting different retrieval processes, although corresponding ERP responses could not be differentiated.

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1. Introduction

Functional neuroimaging is providing new insights into cerebral activity in patients with brain damage. Measurements of cerebral metabolism and brain activation in response to sensory stimuli with PET, fMRI and electrophysiological methods provide information on the presence, degree and location of any residual brain function and are thus usable for predicting outcome in brain-damaged patients.

Past data have shown the effectiveness of event-related brain potentials (ERPs) notably mismatch negativity (MMN) (Fischer et al., 1999, 2004, 2006; Kane et al., 1996) and the P300 component (Guerit, 1999; Signorino et al., 1995), in predicting awakening and good outcome in comatose patients and in

assessing cognitive activity in unresponsive patients (Laureys et al., 2004b; Perrin et al., 2006).

The underlying novelty detection mechanisms require the incoming information to be compared with a relevant memory template (Rolls et al., 1982). The preservation of this processing in comatose patients can represent the ability to respond actively to novel events and more generally the ability to preserve some cognitive activity. The typical signature of novel stimuli eliciting the ERP response (novelty P3) involves their being infrequent, complex, nontarget stimuli, which are physically very different from other nontarget stimuli in the sequence (Courchesne et al., 1975).

Generally, the ERP paradigms used to predict awakening from coma have employed tone stimuli. Speech-evoked ERPs have shown significantly larger P3 amplitudes (Lew et al., 1999). Levy et al. found that human voice (as opposed to instrumental sounds) evoked a Voice-Sensitive Response (VSR) that is reminiscent of the novelty P3 with similar latency (Levy et al., 2001). They proposed that, because of their ecological salience, voices were always perceived as being categorically different. Under such an interpretation, the VSR might be a member of a family of components including the novelty P3, both being manifestations of general attention-orienting mechanisms (Alho et al., 1998; Escera et al., 1998, 2000). In a study including attentional modulation of the VSR, Levy et al. further showed that this voice-specific component was based on the significance of the stimuli rather than on their novelty relative to the acoustic context (Levy et al., 2003). In parallel, some electrophysiological studies have demonstrated that the phonological processing of vocal stimuli occurs far earlier than the latency of VSR (Beauchemin et al., 2006; Titova and Näätänen, 2001).

Among the various types of verbal stimuli that can be used to elicit a cognitive response in comatose patients the subject's own name (SON) appears to be particularly well-suited because it is assumed to have the same significance across all subjects, contrary to other words that might not have the same valence in all subjects. Previous studies have described the electrophysiological response to SON (Berlad and Pratt, 1995; Folmer and Yingling, 1997; Müller and Kutas, 1996). Using PET Gorno-Tempini et al. have described differential activations of multiple brain regions during the processing of proper names faces and object names during an explicit visual matching task (Gorno-Tempini et al., 1998). Recent studies have shown preserved ERP P3 responses to SON in minimally conscious patients (Laureys et al., 2004a; Perrin et al., 2006). In a recent fMRI study SON spoken by a familiar voice activated the primary auditory cortex in almost the same way in vegetative or minimally conscious state (Di et al., 2007).

The use of neuroimaging techniques in people with brain damage is methodologically complex, however, and needs careful quantitative analysis and interpretation based on our knowledge of the brain's functional organization in the healthy population. By providing information on the degree and location of any residual functions in unresponsive patients PET and fMRI are important tools for clinical research (Bernat, 2006; Giacino et al., 2006; Laureys et al., 2006; Owen et al., 2006; Schiff, 2006). A previous PET and ERP study (Perrin et al., 2005) assessed the brain areas involved in SON processing using a passive oddball study where response to SON was compared with response to other first names. The amplitude of the P3 component when hearing one's own name correlated with

regional cerebral blood changes in the right superior temporal sulcus, precuneus and medial prefrontal cortex, the latter being more correlated to the P3 for SON compared to other first names. Using fMRI Carmody and Lewis examined brain activation patterns to hearing SON in contrast to hearing the names of others. They claimed specific activation for one's own name in relation to the names of others in the left middle frontal cortex, middle and superior temporal cortex and cuneus (Carmody and Lewis, 2006). Using fMRI activation of the medial surface of the superior frontal gyrus when calling a subject's own name relative to calling the names of others had previously also been demonstrated (Kampe et al., 2003).

In a previous ERP study in healthy awake adults, we tested a passive oddball protocol with duration deviants, where SON was presented as a rare unattended (novel) stimulus. We showed that SON uttered by a familiar person elicits larger responses (in the late phase of novelty P3) and more sustained parietal activities (in the late slow waves) than when the speaker is unknown to the subject (Holeckova et al., 2006). This result confirms the intuitive idea that a familiar voice may induce an increased brain response due to its emotional dimension. Therefore this ERP protocol represents a valuable tool for testing residual cognitive functions in uncooperative patients, since it can be used to assess altogether pre-attentive response (MMN) and attention orienting (novelty P3) as well as higher cognitive functions (late slow waves).

The anatomical substrate of the response to SON as a novel stimulus incorporated into an MMN protocol is not well known. The functional neuroanatomy of novelty processing of pure sine tones and unique environmental sounds has been studied by combining ERP and fMRI (Opitz et al., 1999a). A novelty P3 was elicited while the fMRI responses showed bilateral foci in the middle part of the superior temporal gyrus. Subjects who attended to identifiable novel stimuli had additional fMRI activation in the right prefrontal cortex.

The objective of the present functional imaging PET study was to identify, in healthy awake adults, the topography of brain activation related to the occurrence of SON among the sequence of standard and deviant auditory stimuli that are delivered for MMN recording in passive oddball conditions. The stimuli were presented in a block design. PET data were acquired in four experimental conditions of auditory stimulation; S: standard tones only; SD: S+duration deviant tones; SDNFV: SD+SON uttered by an unfamiliar voice and SDFV: SD+SON uttered by a familiar voice. Five main contrasts were performed to assess regions activated by pre-attentive processing of deviant stimuli (SD–S), by hearing one's own name (SDNFV–SD and SDFV–SD) and specifically when the person calling you is familiar (SDFV–SDNFV) or unfamiliar (SDNFV–SDFV).

2. Results

2.1. Behavioral results

Although they were watching a silent movie and instructed to ignore the stimuli, all of the 10 subjects involved in this study reported they had been aware their own first name was randomly presented in SDNFV and SDFV conditions and six of them identified the familiar speaker.

Table 1 – Probability of stimuli in different experimental conditions

Experimental condition	Proportion of stimulus in condition			
	Standard	Deviant	SONNFV	SONFV
S	1			
SD	0.86	0.14		
SDNFV	0.82	0.14	0.04	
SDFV	0.82	0.14		0.04

Standard: tone of 800 Hz lasting 75 ms.
Deviant: tone of 800 Hz lasting 30 ms.
SONNFV: subject's own name uttered by unfamiliar voice.
SONFV: subject's own name uttered by familiar voice.

2.2. PET results

The different conditions of stimulation are described in Table 1. The results of inter-block contrasts are given in Table 2.

2.2.1. SD–S: the MMN contrast
In the context of electrophysiological procedures, the MMN EEG response represents the difference between deviant stimuli and standard stimuli. In this PET study increases of rCBF were evaluated by the parametric comparison of SD versus S blocks. The statistical analysis, in which the entire brain volume was considered, revealed a significant increase of activation for SD blocks minus S blocks in the anterior part of the right temporal lobe (temporal pole (TP)) outside the primary auditory cortex with Z=3.75 (Fig. 1A and Table 2).

2.2.2. SDNFV–SD: the SON contrast with unfamiliar voice
Cortical processing of novel stimulus (in these conditions subject's own name uttered by an unfamiliar voice) was assessed by contrasting images from the SDNFV blocks with images from the SD blocks.

This contrast resulted in activation in the left temporal lobe with two local maxima in the middle temporal gyrus (MTG) and superior temporal sulcus (STS) representing the largest

Table 2 – The PET results of comparisons between conditions

Contrast	Statistical values		Coordinates			Anatomical location		
	Cluster size	Z value	x	y	z	Structure	Side	BA
SD–S	86	3.75	34	−4	−38	TP	R	20
SDNFV–SD	29	3.81	76	−20	−6	MTG/STS	R	21
	72	3.75	−54	−6	−10	MTG/STS	L	21
	43	3.54	58	−66	32	TPJ	R	39
	21	3.44	−30	−2	−20	MTG	L	21
	12	3.31	36	34	8	TTG	R	41
	19	3.29	44	−4	−18	MTG	R	21
	6	3.19	8	−32	0	Hi	R	
	6	3.17	−46	26	−4	IFG	L	47
	3	3.13	−50	−26	−8	MTG/STS	L	21
SDFV–SD	319	4.31	60	−6	−8	MTG/STS	R	21
	144	4.10	−58	−66	34	TPJ–AG	L	39
	261	4.08	−42	22	−22	TP/STG	L	38
	211	4.06	36	16	−26	TP–STG	R	38
	297	3.98	−64	−38	2	MTG/STS	L	21
	86	3.75	6	58	26	SFG	R	10
	68	3.46	48	30	−6	IFG	R	47
	32	3.44	−44	−54	28	TPJ–GSM	L	40
	28	3.42	46	−64	48	TPJ–AG	R	39
	26	3.41	−58	−58	16	MTG/STS	L	21
	20	3.35	−54	−16	−32	TP–ITG	L	20
	21	3.33	2	−70	32	PrC	R	7
	24	3.30	−28	−6	−24	Hi	L	
	18	3.26	−44	12	−40	TP–ITG	L	20
SDFV–SDNFV	45	3.59	−48	46	−10	IFG	L	47
SDNFV–SDFV	62	3.68	40	−12	20	IFG	R	6
	39	3.52	56	6	26	IFG	R	44
	34	3.51	−36	−6	66	SFG	L	6

S: standard.
SD: standard+deviant (p=0.14).
SDNFV: standard+deviant (p=0.14)+subject's own name uttered by an unfamiliar voice (p=0.04).
SDFV: standard+deviant (p=0.14)+subjects' own name uttered by a familiar voice (p=0.04).
SD–S: MMN contrast.
SDNFV–SD: SON (novel) contrast with unfamiliar voice.
SDFV–SD: SON (novel) contrast with familiar voice.
SDFV–SDNFV: voice familiarity contrast.
SDNFV–SDFV: opposite (negative) voice familiarity contrast.
Z score indicates the magnitude of statistical significance. Localization is based on stereotactic coordinates system (Talairach and Tournoux, 1988) in the MNI space.

magnitude of blood flow changes in the mid/anterior part with Z=3.75, in the posterior part with Z=3.13 and in the middle temporal gyrus with Z=3.44. The activation in the right temporal lobe was found in the mid/anterior part of medial temporal gyrus (MTG) with Z=3.29, in the posterior part of MTG/STS with Z=3.81 and in the transverse temporal gyrus (TTG) with Z=3.31. In comparison to SD, SONFV also activated the left inferior frontal gyrus (IFG) with Z=3.17, the right temporal–parietal junction (TPJ) with Z=3.54 and the right hippocampus with Z=3.19 (Fig. 1B and Table 2).
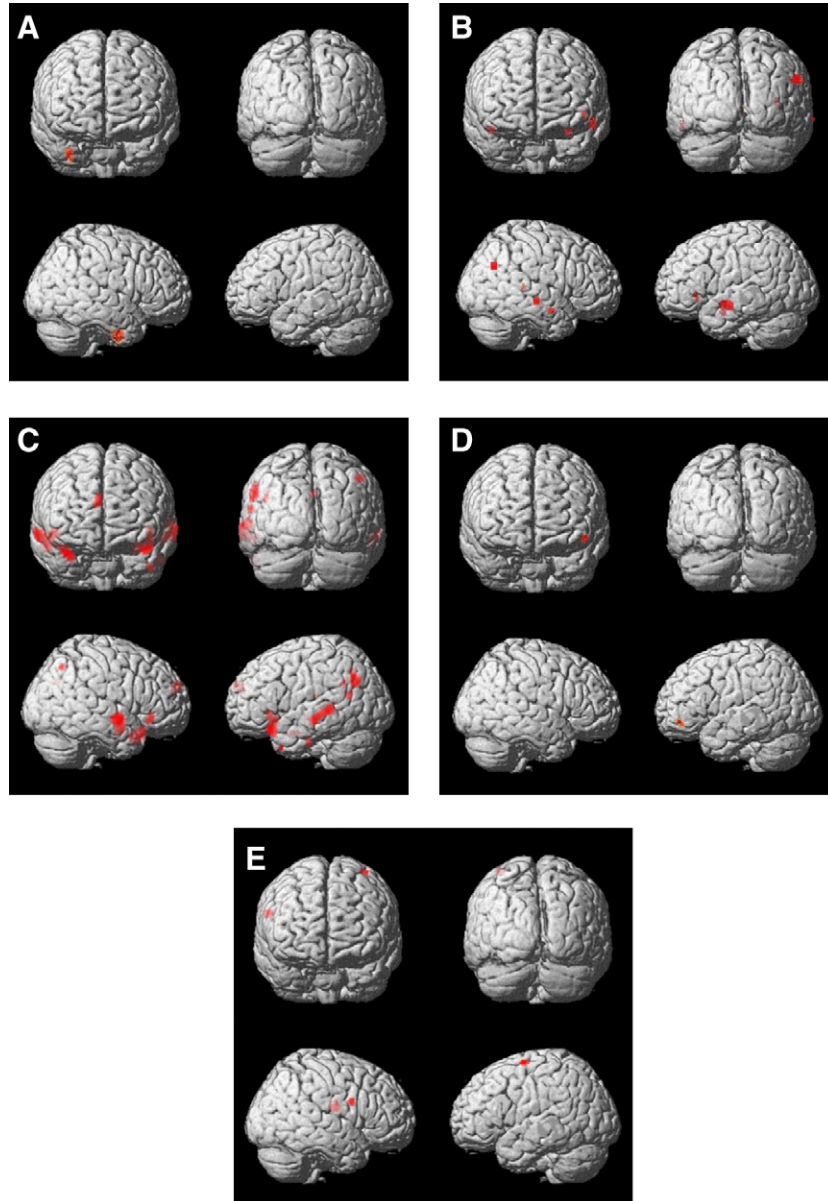

Fig. 1 – Anterior, posterior and lateral views of the thresholded (p<0.001) t-statistic maps projected on an MRI surface of the MNI template. A: MMN contrast: The contrast between SD and S blocks discloses a significant activation in the anterior part of the right temporal lobe outside the auditory primary cortex. B: Subject's own name contrast with unfamiliar voice: Increased hemodynamic response during passive sensation of subject's own name uttered by unfamiliar voice. The contrast between SDNFV and SD blocks shows a significant activation in temporal regions, in frontal regions, in the right temporal–parietal junction and in the right hippocampus. C: Subject's own name contrast with familiar voice: Increased hemodynamic response during passive sensation of subject's own name uttered by familiar voice more extensive than by unfamiliar voice. The contrast between SDFV and SD blocks shows a significant activation in temporal and frontal regions, in the bilateral temporal–parietal junction, in the left hippocampus and in the right precuneus. D: Voice familiarity contrast: Increased rCBF in the SDFV condition (subject's own name uttered by a familiar voice) as compared to the SDNFV condition (subject's own name uttered by a non-familiar voice) in the left lateral prefrontal cortex. E: Voice unfamiliarity contrast: Increased rCBF in the SDNFV condition (subject's own name uttered by a unfamiliar voice) as compared to the SDFV condition (subject's own name uttered by a familiar voice) in the fronto-opercular part of the right inferior frontal cortex and in the left superior frontal cortex.
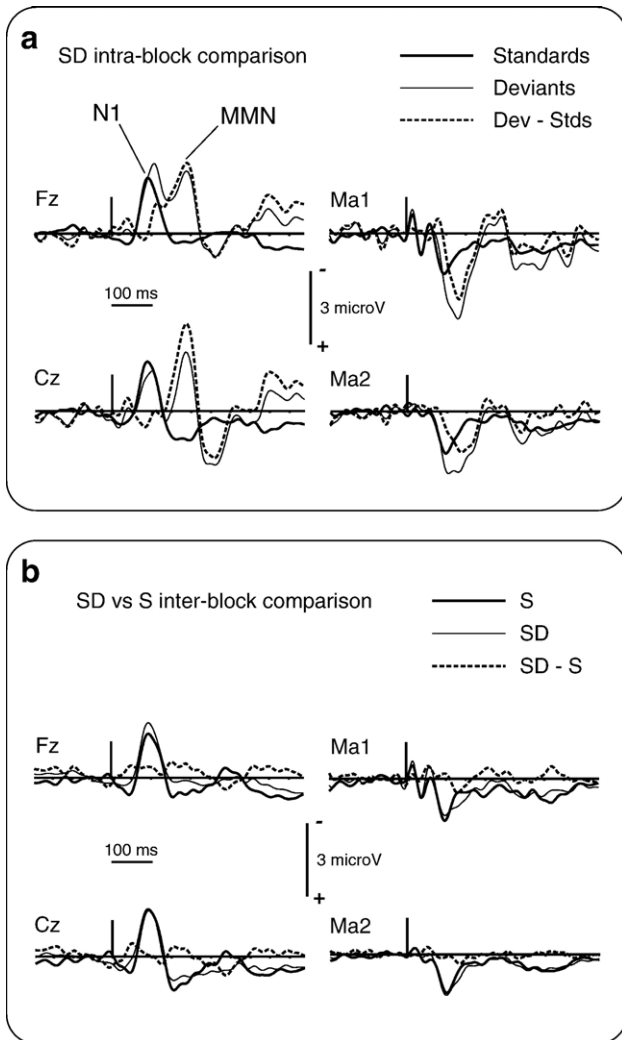
Fig. 2 – Grand average waveforms recorded at 2 midline electrodes (Fz, Cz) and 2 mastoids (Ma1, Ma2) for the 10 subjects. Above (a) the responses to standard and deviant tones inside the SD block are displayed, as well as their differences (intra-block comparison). Below (b) the responses to all stimuli in S blocks (standards alone) and their responses to all stimuli in the SD blocks (standards and deviants) are displayed, as well as their differences (inter-block comparison).

2.2.3. SDFV–SD: the SON contrast with familiar voice

Cortical processing of novel stimulus (in these conditions subject's own name uttered by a familiar voice) was assessed by contrasting images from the SDFV blocks with images from the SD blocks.

This contrast resulted in activation in the left temporal lobe with five local maxima. The activation was found in the posterior part of MTG/STS with two local maxima with $Z=3.98$ and $Z=3.41$, in the anterior part of superior temporal gyrus (STG) with two local maxima with $Z=4.08$ and 3.26 and in the anterior part of the inferior temporal gyrus (ITG) with $Z=3.35$. The activation in the right temporal lobe was found in the mid/anterior part of MTG/STS with $Z=4.31$ and in the anterior part of STG with $Z=4.06$. SONFV also activated the left TPJ with two local maxima with $Z=4.10$ and $Z=3.44$ and the right TPJ wit $Z=3.42$. The activation was found also in the right superior frontal gyrus (SFG) with $Z=3.75$ and in the right inferior frontal gyrus (IFG) with $Z=3.46$. In comparison to SD, SONFV also activated the right precuneus with $Z=3.33$ and the left hippocampus with $Z=3.30$ (Fig. 1C and Table 2).

2.2.4. SDFV–SDNFV: the voice familiarity contrast

Comparing familiar voice versus unfamiliar voice uttering the subject's own name revealed only one region where voice familiarity was associated with significant rCBF change located in the left IFG where activation was found with $Z=3.59$ (Fig. 1D and Table 2).

2.2.5. SDNFV–SDFV: the voice familiarity opposite contrast (unfamiliarity contrast)

Comparing unfamiliar and familiar voices uttering the subject's own name revealed activation in the fronto-opercular part of the right IFG with two local maxima with $Z=3.68$ and $Z=3.52$ and in the left SFG with $Z=3.51$ (Fig. 1E and Table 2).

2.3. ERP results

2.3.1. SD intra-block comparison

Between 31 and 43 deviants remained for analysis in SD blocks for each subject after artifact rejection (mean number: 36). Fig. 2a shows the grand average waveform across the 10 subjects at 4 selected electrodes, in response to the standards and to the deviants in the SD blocks, as well as the deviant minus standard subtraction. Standards and deviants elicited a large
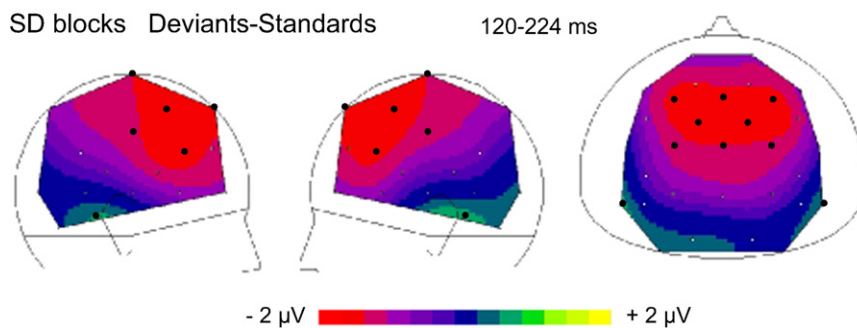

Fig. 3 – Mean scalp distribution of the difference potentials (deviant minus standard in SD blocks) at the MMN latency (120–224 ms). From left to right: right view, left view, top view. Fronto-central electrodes showing significantly negative potentials in this window, as well as mastoid electrodes showing significantly positive potentials are highlighted (black points).
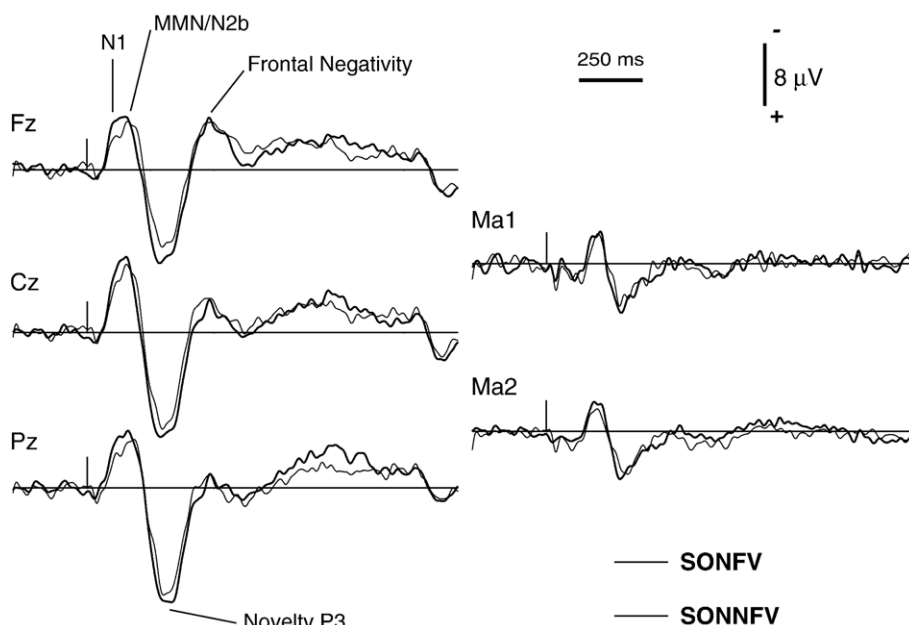
Fig. 4 – Grand average waveforms recorded at 3 midline electrodes and at both mastoids, in response to the subject's own name uttered by a familiar voice (novels in SDFV blocks) and by an unknown speaker (novels in SDNFV blocks).

N1 at 90 ms. In the difference grand average (Fig. 2a), fronto-central electrodes showed a negative maximum around 190 ms and the mastoids showed a positive maximum around 130 ms. The difference between standard and deviant responses was assessed at each sample time in the 450 ms following the stimulus onset, i.e. in a large interval covering the expected pre-attentive response (MMN) and a possible attention orienting response (P3a). Significant topographical differences ($p < 0.05$) were found in consecutive sample points from 120 ms to 224 ms post-stimulus. In the post-hoc permutation procedure, this 114 ms interval was highly significant, insofar as the maximum duration of consecutive significant measurements found by chance in 95% of the cases was less than or equal to 60 ms. The scalp distribution maps of the averaged potentials in this 120–224 ms window are displayed in Fig. 3. In the 120–224 ms window, the mean potential was found to be significantly negative in a large set of electrodes (unilateral t-test, at Fz, F3, F4, FC1, FC2: $p < 0.001$; at C3, C4, Cz: $p < 0.005$), highlighted on the maps in Fig. 3. In the 120–140 ms window surrounding the positive maximum at mastoids, the potential was found to be significantly positive (unilateral t-test at Ma1 and Ma2: $p < 0.001$). This topography of negative fronto-central potentials associated with a clear inversion at both mastoids

strongly suggests the presence of a MMN with bilateral temporal generators. After 224 ms, the responses to standards and to deviants showed no topographical difference, suggesting the absence of any P3a component at the group level.

Thus, the electrophysiological data in the SD block clearly suggest non-attentional detection of deviant stimuli without any attentional switching.

2.3.2. SD versus S inter block comparison

Fig. 2b shows the averaged responses to all stimuli in the S blocks (standards), in the SD blocks (standards and deviants undifferentiated), and their difference (inter-block difference). No significant topographical difference was found during the 450 ms period following stimulus onset. The maximum duration of consecutive significant measurements was 12 ms in actual data, when it was 50 ms in 95% of the cases after permutation. Moreover, in the 120–224 ms window where MMN was detected in the intra-block analysis reported above, the mean potential measured at frontal electrodes was not significantly negative (mean value at Fz, F3, F4, FC1, FC2: $-0.34 \mu V \pm 0.68$, unilateral t-test $p = 0.714$).

Thus, when considered globally, the electrophysiological response in the blocks with standards and deviants could not be

Table 3 – Responses to subject's own name uttered by the familiar voice (SONFV) and by an unknown voice (SONNFV): mean amplitude ± standard deviation (in μV, 9 subjects) of the potentials in time intervals around the peak latencies of the N1 and MMN/N2b components, in the 2 stages of novelty P3 (early and late nP3) and at the latency of the frontal negativity (FN)

	N1	MMN/N2b	Early nP3	Late nP3	FN
Time range of analysis (ms)	100–140	140–180	220–300	300–380	450–550
Site of measurement	Cz	Cz	Cz	Pz	Fz
SONFV	−8.27 ± 5.55	−8.82 ± 6.09	9.89 ± 9.51	12.87 ± 5.96	−5.23 ± 4.30
SONNFV	−5.63 ± 6.56	−7.45 ± 7.45	8.51 ± 9.97	11.84 ± 4.73	−5.38 ± 6.2

differentiated from the response in the blocks with standards alone, i.e. an MMN was not detected in the inter-block comparison.

2.3.3. Response to novel stimuli

One subject showed large eye movements at each presentation of his own name. For this subject, responses to novel stimuli could not be studied. For the nine other subjects, the number of accepted responses was between 8 and 15 for SONFV (in
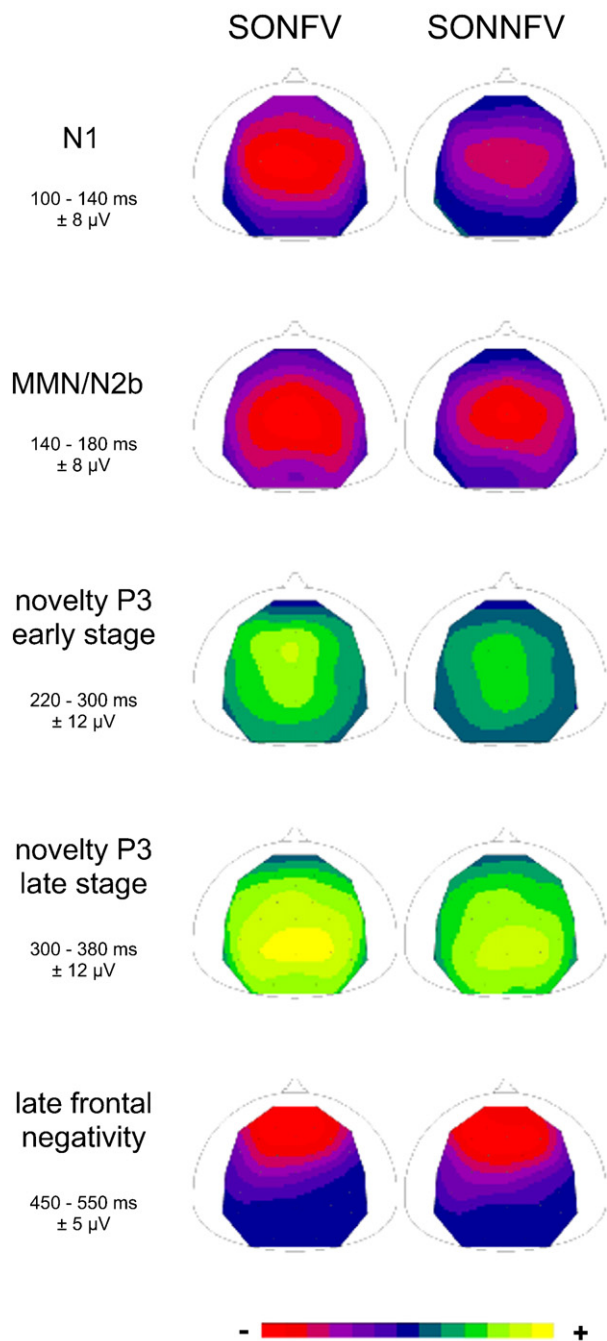

Fig. 5 – Mean scalp potential distribution of the responses to the own name uttered by a familiar voice (left column) and to the own name uttered by an unknown voice (right column), over the 100–140 ms (N1), 140–180 ms (MMN/N2b), 220–300 ms (early novelty P3), 300–380 ms (late novelty P3) and 450–550 ms (late Frontal Negativity) intervals.

average 13 accepted responses) and between 7 and 14 for SONNFV (in average 11 accepted responses). Fig. 4 displays the grand average of the responses to FV and NFV novels at the 3 midline electrodes and at both mastoids. In accordance with the results obtained in a previous study (Holeckova et al., 2006) these responses to the subject's own name presented as a novel stimulus showed a negative deflection (auditory N1 and MMN/N2b) followed by a huge central positivity (novelty P3) with two distinct maxima and later a frontal negativity (FN). Mean amplitudes around the maxima of the different waves (N1, N2b/MMN, early and late parts of the novelty P3 and frontal negativity) are displayed in Table 3. Scalp potential maps in these time intervals are shown in Fig. 5. Neither of the waves showed significantly different amplitude between the 2 novels (Student test). In the early (220–300 ms) and late (300–380 ms) stages of novelty P3, two-way ANOVA was performed on normalized data with the stimulus type (SONFV, SONNFV) and midline electrodes (Fz, Cz, Pz) as factors. In both intervals, no interaction was found between stimulus type and electrodes, suggesting similar topographies. In the late stage of novelty P3 (300–380 ms), a significant effect of electrodes was found ($F(2,16) = 10.281$, $p = 0.0014$; Pz larger than Cz: $p = 0.0072$ for FV and $p = 0.0278$ for NFV; Cz larger than Fz: $p = 0.0074$ for FV and $p = 0.0275$ for NFV), suggesting the presence of some parietal subcomponent in the late stage of novelty P3, as observed in our previous study. This P3b-like subcomponent was not significantly different between the two stimuli. In the 450–550 ms time range, the potentials were significantly negative at Fz for both novels (unilateral t-test: $p = 0.0033$ for FV, $p = 0.0159$ for NFV), and this late frontal negativity showed no difference between the two stimuli. The responses did not show any late parietal positivity accompanying the frontal negativity.

Thus, in spite of the small number of sweeps included in the analysis after artifact rejection, ERPs showed large and clearly identifiable components, reflecting similar sensory, attention-orienting, and higher cognitive processes for both types of vocal novel stimuli. Although the responses to the familiar voice were numerically larger than the responses to the unfamiliar voice (see Figs. 4 and 5 and Table 3), this difference was not statistically different.

3. Discussion

The purpose of this combined ERP and PET study was to identify brain areas activated by sound duration mismatch processes and by brain processing of SON uttered by either a familiar or an unfamiliar voice, in the framework of a mixed protocol including duration deviants and SON as a novel stimulus. SON was incorporated as a novel stimulus into an MMN protocol that we use in daily routines for the examination of comatose patients (Fischer et al., 2004). We added SON as a novel to evaluate attention orienting using this stimulus known to elicit a robust ERP response (Berlad and Pratt, 1995). We had previously shown that SON uttered by a familiar voice elicits a response different from that elicited by an unfamiliar voice in late latencies of novelty P3 and in the subsequent late slow waves (Holeckova et al., 2006).

In the present study, we simultaneously used two methods as different as ERP recording and PET data analysis. We had to

adapt our previous ERP protocol to the PET technique. For each subject we analyzed only those potentials recorded during CBF measurement, thus representing a relatively small number of stimuli.

3.1. MMN

In the standard electrophysiological MMN procedure, the response to standard stimuli is subtracted from the response to deviant stimuli and the difference discloses the MMN wave. Within SD blocks, we found a large difference wave with fronto-central negativity associated with a clear inversion at both mastoids, strongly suggesting the presence of MMN with temporal generators. This result confirms that our protocol is able to elicit robust pre-attentive mismatch processes and demonstrates that it is efficient even with a small amount of repetitions. In addition, the absence of any following P3a component clearly suggests the absence of any switch of attention after non-attentional detection of deviant stimuli.

In the PET block design, the MMN contrast (SD–S) revealed enhanced hemodynamic response in the anterior part of the right temporal lobe. Belin had shown that discrimination of sound duration involves a right fronto-parietal network and a network of regions such as the basal ganglia, cerebellum and right prefrontal cortex (Belin et al., 2002). A lateralization to the right anterior temporal lobe for infrequent duration change was found in a previous ERP source imaging study (Waberski et al., 2001). A lateralization to the right in the auditory secondary cortex for duration deviance was found also in an fMRI/MEG study (Kircher et al., 2004). Small activation in the anterior part of the right superior temporal gyrus was reported in an MMN–PET study (Müller et al., 2002) as well as in an MMN–fMRI study (Opitz et al., 1999b). In earlier studies deviant-related activation was right-hemisphere dominant among all the different feature deviancies that were studied (Alho et al., 1998; Opitz et al., 2002). The evidence for right anterior temporal activation in the MMN contrast supports the hypothesis of right hemispheric dominance in sound duration discrimination.

PET data analysis showed no activation in the supratemporal cortices, where the main generators of electric MMN were found (Alho, 1995). A previous MMN PET study, in which a "standard" condition was compared with a "frequency deviance" condition, did indeed show activation in the auditory cortex (Müller et al., 2002). Due to the tonotopic organization of the primary and secondary auditory cortices (Kaas and Hackett, 1998; Schönwiesner et al., 2002) the reported differences in activation might be explained by differences in sensory stimulation (Molholm et al., 2005). Such a confounding effect is unlikely to occur when using duration deviants. Activation was found in the primary auditory cortex in duration-deviant PET studies (Dittmann-Balcar et al., 2001; Schall et al., 2003) using duration increment protocols where the activation in the auditory cortex may be explained by the increment of energy rather than by deviant detection (Jacobsen and Schröger, 2003). In a recent fMRI study using standards of 75 ms and different sound duration decrements (Rinne et al., 2005) activation in the STS was elicited only with medium duration changes (25 ms).

Nor did we find any activation in the frontal region though several MMN imaging studies (Dittmann-Balcar et al., 2001; Müller et al., 2002; Schall et al., 2003) and human lesion studies (Alho et al., 1994) have demonstrated activation in the frontal cortex. It has been hypothesized that the pre-attentive change detection process in the temporal cortex is followed by frontal cortex activation thought to reflect a mechanism that directs attention towards the deviant stimulus and sets the stage for subsequent attentive processes (Giard et al., 1990; Rinne et al., 2000). This activity may be related to the generation of the P3a component (Escera et al., 1998). The lack of frontal activation in our PET results, in parallel with the absence of P3a response in ERP data, suggests that stimulus deviance did not reach a sufficient threshold to trigger attention orienting. In their fMRI study of sound duration decrements, Rinne et al. (2005) had to use a contrast testing inverse relationship between activation and the magnitude of sound change in order to be able to reveal inferior frontal cortex activation.

The fact that expected areas of MMN generators like supratemporal and frontal cortices were not disclosed by PET–MMN contrast could also be explained by the design of PET analysis. Mismatch occurred for only 14% of the stimuli presented in SD blocks, and in a ERP block contrast resembling the one used in PET analysis (inter-block analysis) no mismatch responses appeared. Accompanied neither by any detectable enhancement of sensory processes nor by any switch of attention, the mismatch processes occurring after rare deviants are likely to have been too discreet to be fully revealed in a block design PET experiment with poor temporal resolution, although they were manifest in the ERP paradigm (intra-block analysis).

3.2. Subject's own name as a novel

In the present study the subject's own name was presented as a novel stimulus in two experimental conditions: in SDFV (subject's own name uttered by a familiar voice) and in SDNFV (subject's own name uttered by an unfamiliar voice).

In both the SDNFV and SDFV blocks the electrophysiological response to the subject's own name presented as a novel stimulus attested robust attention-orienting mechanisms (MMN/N2b followed by a large novelty P3). In spite of the absence of any active task, the novelty P3 showed a clear parietal subcomponent in its late stage, which may be associated with stimulus categorization (Friedman et al., 2001; Gaeta et al., 2003). The subsequent late frontal negativity may be related to some "familiarity" processing (Mecklinger, 2000) triggered by the SON considered as an item already known by the subject.

In the PET data, in both SON/novelty contrasts (with an unfamiliar voice: SDNFV–SD and with a familiar voice: SDFV–SD) we found activation in the temporal and frontal regions, in the hippocampus and in the temporo-parietal junction. As can be seen in Fig. 1 and in Table 2, activation in theses regions was more extensive with a familiar voice than with an unfamiliar voice. In the SDFV–SD contrast other regions such as the medial prefrontal cortex, temporal pole bilaterally and precuneus were activated (Fig. 1 and Table 2). Thus, the activations found in the contrast with an unfamiliar voice were replicated in the contrast with a familiar voice, with some modulation being due to the familiarity of the voice. We shall consider common activations as the correlate of SON/novelty processing.

Our PET results can be interpreted from different, but not exclusive angles.

First, they may be interpreted by the neural network engaged in novelty detection. Various studies show that novelty is a broad concept that includes a number of separable processes and brain regions. There is converging evidence from neuroimaging studies (Kiehl et al., 2001; Müller et al., 2002; Opitz et al., 1999a) and from ERP studies (Alho et al., 1998; Gaeta et al., 2003; Yago et al., 2003) that novelty processing activates a large cortical and subcortical network including the temporal, parietal and frontal regions, irrespective of stimulus modalities.

Brain imaging studies (Kiehl et al., 2001; Müller et al., 2002; Opitz et al., 1999a) have indicated the contribution of a fronto-temporal network to auditory novelty detection and suggest that the superior temporal regions are involved in novelty detection, whereas the prefrontal cortex is engaged in related subsequent processing. Consistent with previous studies using environmental novel sounds (Opitz et al., 1999a), digital noises (Kiehl et al., 2001) or complex novel sounds (Müller et al., 2002) our results showed that novel stimuli (in our case SON) activate widespread areas in the superior temporal regions bilaterally. Additional prefrontal activation in the fMRI–ERP study by Opitz was strongly related to ERP N4-like negativity in response to identifiable novels in attended conditions (Opitz et al., 1999a). In our study, SON represents an identifiable novel even if it is presented in a passive condition, and our results are consistent with Opitz's results with identifiable novels, i.e. a novelty P3 followed by subsequent late frontal negativity in ERP results and the activation of the prefrontal cortex.

Bilateral frontal lobe injury has been shown to reduce attention to novel stimuli and to reduce the amplitude of the novelty P3 response to novel stimuli in different modalities (Knight, 1984) The IFG is known to be bilaterally involved in attention-orienting, executive and working memory functions (Cabeza and Nyberg, 2000). Damage to the frontal lobe may prevent the generation of a signal indicating that a novel event requires additional attention (Baudena et al., 1995; Daffner et al., 1998). ERP findings in the present study, as well as in the previous one (Holeckova et al., 2006), confirmed that SON attested robust attention-orienting, categorization and memory updating responses. Larger activation in the frontal regions for SDFV-SD than for SDNFV-SD contrasts suggests that the familiar voice might capture attention more easily than an unfamiliar voice and that it demands additional processing. This is in accordance with the observation by Escera et al. (2003) that indicated that the attention-orienting mechanism in passive conditions could be stronger for highly identifiable novel stimuli.

Consistent with human lesion studies (Knight, 1996) and intracranial recordings (Halgren et al., 1995) that suggested hippocampal involvement in novelty processing, we also obtained hippocampal activation for SON as a novel.

In spite of passive conditions in our study, the novelty P3 showed a clear parietal subcomponent in its late stage, in agreement with data from Yago et al. (2003) and Friedman et al. (2001). This posterior aspect of novelty P3 represents an instance of the P3b component. Human lesion studies have suggested that the temporal–parietal junction may be an important contributor to P3b potentials (Knight and Nakada,

1998). Accordingly, in parallel with ERP results showing P3b in response to SON, PET results showed cortical activation in the temporal–parietal junction.

Second, bilateral temporal and frontal activations by SON may be related to speech and voice recognition processing. Speech recognition has been associated with the left temporal structures since the days of Wernicke. A recent PET study confirmed this left lateralization for phonetic stimuli (Terva-niemi et al., 2000). The processing of paralinguistic aspects of vocal processing (e.g. the speaker's gender, age, emotional state) tends to be associated with activation of the right temporal structures (Belin et al., 2004; Schirmer and Kotz, 2006).

We observed activation by SON in the left middle/anterior and posterior MTG/STS regions (BA 21). These data are consistent with studies proposing an anterior–posterior stream of speech processing in the left temporal lobe (Binder et al., 2000; Rimol et al., 2005).

We also observed activation by SON in the right temporal regions. Previous studies (von Kriegstein and Giraud, 2004) showed that recognizing voices in blocks of sentences spoken by different speakers activated the right anterior STS irrespective of voice familiarity and that the right posterior STS displayed stronger responses to unfamiliar voices. Right temporal activation by SON is in agreement with the recent demonstration by Belin (Belin and Zatorre, 2003) suggesting that this region plays an important role in the representation of individual voices and acoustic properties of voices and is concerned with voice identity, i.e. showing adaptation to speaker identity. In our study, we observed enhanced response in the right anterior and posterior MTG/STS. We propose that the right temporal MTG/STS is activated not only during explicit recognition of different speakers but may be also activated during implicit recognition of voice in passive task conditions. Some lesion studies have shown a loss of function in unfamiliar voice discrimination with damage to either the left or the right temporal lobe (Van Lancker et al., 1988).

In a third aspect, activation in SON contrasts may be interpreted in terms of self-recognition. We observed activation in the right temporal–parietal junction (BA 39 and 40) for SDNFV–SD and bilaterally for SDFV–SD contrasts. These regions were assessed in studies of self-recognition and self-representation and they showed greater activation in response to hearing one's own name (Carmody and Lewis, 2006). It has also been shown that a signal such as calling a person's name activates the paracingulate cortex and temporal poles bilaterally (Kampe et al., 2003). Furthermore, hearing one's own name presented among other first names, with different probabilities, correlated with regional cerebral blood changes in the right superior temporal sulcus, precuneus and medial prefrontal cortex. The latter is more correlated to the P3 for the SON compared to other first names (Perrin et al., 2005). In our study, activation of the precuneus and medial prefrontal cortex was found only in SDFV–SD contrast. Moreover, the bilateral temporal pole activation observed in SDFV–SD contrast may be related to person identification. A few neuroimaging studies (Gorno-Tempini et al., 1998; Grabowski et al., 2003; Nakamura et al., 2001) showed that the anterior temporal lobe is critical for face and person recognition. It has been proposed that the anterior temporal lobe is necessary to, but not

specialized, in person recognition (Olson et al., 2007). It has been suggested that the right temporal pole is a storehouse (Nakamura et al., 2001) of personal episodic memories, whereas the left anterior temporal lobe is more associated with semantic memories. Activations in the temporal pole for SDFV–SD novel contrast may reflect the retrieval of person-specific memories.

In short, the subject's own name presented as a novel stimulus in a non-verbal stimulation stream activated regions that could be related to novelty processing as well as linguistic auditory processing, voice and person discrimination, working memory or self-recognition. For technical and ethical reasons, our PET protocol could not include additional conditions with other types of novel sounds (e.g. other names or non-speech sounds). Without any direct comparison with such stimuli, is not possible to ascertain exactly to what extent the SON-related activations were specific to novelty, speech or self processing.

3.3. Voice familiarity

ERP responses to SON uttered by familiar or unfamiliar voices showed no significant differences. In a recent study on electrophysiological markers of voice familiarity, Beauchemin et al. (2006) found enhanced MMN and P3a to vowels infrequently uttered by a familiar voice as compared to vowels infrequently uttered by an unknown voice, both rare stimuli being embedded among frequent vowels uttered by another unknown voice. Their results suggest that voice recognition plays a role in pre-attentive discrimination processes. In our studies (the present one and the previous one; Holeckova et al., 2006), we considered the responses to complex vocal stimuli (own names) uttered by a familiar and by an unknown voice, presented with a very low probability among non-vocal stimuli. Thus we tested the interaction between voice familiarity and cognitive processes such as attention orienting and stimulus categorization. As suggested by Escera et al. (2003), semantic analysis of significant sounds may occur after a transitory switch of attention toward the eliciting stimuli. In our previous paradigm (Holeckova et al., 2006), three different novels (a non-vocal stimulus, SON uttered by an unknown voice and SON uttered by a familiar voice) were presented altogether in 5 successive blocks of 500 stimuli, with a probability of 0.02 each. This resulted in 50 repetitions of each novel stimulus, with a mean interval of 30 s between identical novels and only 10 s in average between different novels. In this context, SON uttered by a familiar person as compared with SON uttered by an unknown person elicited larger response amplitudes in the late phase of novelty P3 (after 300 ms), and a larger parietal positive component at the latency of the late slow waves. In the present study, SONs uttered by the familiar and unfamiliar voices were presented with a probability of 0.04 (i.e. an interval of 15 s between 2 identical novels), in separate blocks about 10 min apart. Although the novelty P3 was numerically larger for the familiar voice, the responses to familiar and unfamiliar voices showed no significant difference. Moreover, no late parietal positivity was observed in response to either voice. In both studies, identification of a familiar speaker was not explicitly required. In the previous study, with different voices randomly presented in the same block, implicit voice recognition could happen at each occurrence of a vocal stimulus and we associated a larger parietal component of novelty P3 with specific stimulus categorization and larger late parietal positivity with specific recollection processes. In contrast, in the present study, where the two voices were presented in separate blocks, implicit recognition may not have systematically occurred. The P3 and late frontal negativity were found not to be different between the two voices, suggesting equivalent stimulus categorization. As a matter of fact, when asked after the recording session, four subjects among 10 said not to have really identified the familiar person.

Whereas ERP responses to SON uttered by the familiar and unfamiliar voices showed no significant differences, both PET contrasts that highlight specific voice processing ("familiarity": SDFV–SDNFV and "unfamiliarity": SDNFV–SDFV) showed small but significant frontal activation with some hemispheric asymmetry. For the "familiarity" contrast, the left inferior frontal region (BA 47) (in the vicinity of the human voice-related area) was activated, and for the "unfamiliarity" contrast, mainly right frontal regions were activated in the fronto-opercular part of the right inferior frontal cortex, with a small additional activation in the left superior prefrontal cortex. The differential contribution of the left and right prefrontal cortices may be explained by different memory processing when hearing a familiar or an unknown voice.

In the familiarity contrast, activation of the left frontal pole may be associated with retrieval and recall of the familiar voice. In a PET study it had been shown that the left frontal pole and right temporal pole were activated during discrimination of familiar voices in blocks of sentences spoken by different speakers (Nakamura et al., 2001). The value of rCBF in the left frontal pole and right temporal pole correlated with the subjects' correct identification rates of familiar voices. Nakamura hypothesized that if the right temporal pole is the storehouse, the function of the left frontal pole would be to access the storehouse for retrieval of memory of familiar voices.

Furthermore, the own name uttered by a familiar voice could integrate vocal emotion. Emotional comprehension is supposed to be mediated by bilateral mechanisms. The left IFG would be associated with retrieval and integration of emotions (Schirmer and Kotz, 2006) and would be involved in the retrieval of memories (Fletcher and Tyler, 2002) and may reflect retrieval efforts. The familiar voice in our protocol could have required some retrieval effort in order to be fully recognized.

In the unfamiliar voice contrast, activation of the right frontal regions may be associated with recognition processing, which could be related to the verification and evaluation of an unknown voice.

Moreover, one of the regions in the fronto-opercular part of the right inferior frontal cortex which was more activated by the unfamiliar voice than by the familiar voice coincides with areas that were found in several studies to be associated with auditory attention (Bushara et al., 1999; Lewis et al., 2000; Rees et al., 1997; Voisin et al., 2006). Although their attention should not have been engaged by any voice recognition task, the subjects may have shown more attention to the stimuli, in an effort to recognize the unknown voice.

Lastly, our hemodynamic results showed specific voice familiarity processing even when the subjects were not required to explicitly differentiate or fully recognize the voices. In the blocks where the unknown voice was presented, attention may have been slightly more sustained. In the blocks where the familiar voice was presented, a small region in the left prefrontal cortex was activated, which could be related to emotional significance and to retrieval efforts to recognize the familiar voice. These highly cognitive, probably sustained, activities following attention-orienting processes were probably not time-locked to the stimuli; they could not be highlighted in ERP responses to novel stimuli.

4. Conclusion

Our PET data combined with ERP results confirm that SON presented as a novel stimulus in a sequence of standard and deviant auditory stimuli delivered for MMN recording in a passive oddball condition generates robust cerebral blood flow activation over the temporal, frontal and parietal cortices, in the hippocampus and in the precuneus.

Nevertheless our PET data indicate that different neuronal networks are active in post-detection novelty treatment representing the different higher-level treatment of SON uttered by familiar and unfamiliar voices, probably depending on the proportion of novel information carried by a stimulus and representing the different meaning-based operations.

Brain correlates of hearing one's own name and specifically when the person calling you is familiar could be assessed by cerebral blood flow activation. SON therefore appears to be a valuable tool for testing the residual cognitive functions in uncooperative patients (Di et al., 2007).

Controversially, due to the poor temporal resolution of PET, the block design used did not allow a thorough evaluation of the brain regions activated by mismatch duration processing. In presence of rare duration deviants we found enhanced hemodynamic activation only in the anterior part of the right temporal lobe. Duration deviant processing may be better studied by electrophysiological recordings in which specific ERP responses are elicited by duration deviants.

5. Experimental procedures

5.1. Subjects

Ten healthy right-handed male volunteers participated in the study (aged 20–47 years, mean age 28 years). Informed written consent was obtained from each subject prior to the experiment. All subjects were paid for their participation. The protocol was approved by the local ethics committee.

5.2. Procedure and stimuli

Regional cerebral blood flow (rCBF) and scalp potentials (EEG) were recorded simultaneously while the subjects laid in the PET scanner. The subjects were instructed to watch a silent movie projected on a mirror placed in their visual field and not to pay attention to sound stimuli.

Auditory stimuli were presented binaurally through inserted earphones at an intensity of 65 dB HL using Presentation software (Neurobehavioral Systems). Four auditory experimental conditions (S, SD, SDFV and SDNFV) were in turn randomly applied four times each (Table 1), spaced by rest periods of at least 10 min. In the S condition, only standard tones were presented. In the SD, SDFV and SDNFV conditions, as in a classical oddball paradigm, 14% of the standards were replaced by deviant tones, each deviant being systematically preceded by at least two standards. The standard and deviant stimuli were spectrally rich tones with a main frequency of 800 Hz and two harmonic partials (1600 Hz and 2400 Hz with respective amplitudes at -6 dB and -12 dB). Their durations were 75 ms for the standards and 30 ms for the deviants, including 5 ms rise and fall times for both. Stimulus onset asynchrony was 610 ms. In the SDFV and SDNFV conditions, vocal novel stimuli were randomly included ($p=0.04$). In the SDFV condition, the novel (SONFV) was the subject's own name uttered by a voice well-known to the subject (voice of a spouse, a relative or a friend). In the SDNFV condition, the novel stimulus (SONNFV) was the subject's own name uttered by an unknown voice. Subjects were aware that the familiar voice was recorded, but they were not aware of the presentation of this voice during experimental procedure. These vocal stimuli were digitally recorded using CoolEdit (Syntrillium software). For each subject, both speakers were of the same gender (3 male speakers, 7 female speakers). The SONNFV stimulus was adjusted so that the 2 vocal stimuli (SONNFV and SONFV) had the same intensity and duration. Name duration was on average 538 ms (min=379 ms and max=654 ms). The interval between the onset of a SON stimulus and the onset of the following tone stimulus was set to 1220 ms whatever the duration of SON.

For each of the four conditions, stimulation and EEG recording started about 1 min before the beginning of rCBF measurement and lasted 4 min. In the SDFV and SDNFV blocks, no vocal stimulus was presented during the first minute, so that the first novel stimulus never appeared before rCBF measurement started. Markers for the starting and ending of CBF measurement were put manually into the EEG file.

5.3. PET rCBF measurement

The data were acquired with a Siemens Exact ECAT HR+ (CPS Corp, Knoxville) PET scanner. The subject's head was immobilized with a thermoplastic mask attached to the scanner bed and molded to fit the individual head shape. A plastic cannula was placed in the left cubital vein to administer the PET tracer. The regional cerebral blood flow was measured using the $[^{15}O]H_2O$ bolus injection technique. For each scan, approximately 330 MBq $[^{15}O]H_2O$ were injected using an automatic injector system. The interval between injections was 10–11 min. During this interval, the $[^{15}O]H_2O$ activity in the brain decayed to a background level that was at most 5% of the peak counts of the previous scan. A bolus of about 10–20 ml of 0.9% sodium chloride solution over a period of 50 s was administered. After administration of $[^{15}O]H_2O$, the measurements lasted 60 s and started only shortly before the rise of the head curve which corresponds to the first

detectable change in blood flow. For each of the four conditions, stimulation and EEG recording started about 1 min before the beginning of CBF measurement and lasted 4 min (see Procedure and stimuli). Each 60-s PET acquisition were reconstructed with a filtered back projection technique with a Hanning filter (cut-off at 0.5 cycles/pixel) leading to a 3D volumic measure of rCBF consisting in 63 transverse planes (2.42 mm thick) of 128x128 voxels (2.1×2.1 mm^2 each).

5.4. Image analysis

The data were analyzed with SPM 99 (Welcome Department of Cognitive Neurology: http://w.w.w.fil.ion.ucl.ac.uk/spm). PET activation volumes for each subject were realigned to the first scan. After realignment, all images were spatially normalized using the SPM99-PET rCBF template of the MNI from ICBM consortium. Subsequent normalization images were smoothed with a low pass Gaussian filter ($12 \times 12 \times 12$ mm at FWHM). Global flow differences were normalized voxel by voxel to a mean of 50 ml/100 mg/min by proportional scaling. Voxel-based statistical analyses performed with SPM99 were based on group effects.

The resulting t-map of contrast between SD–S, SDNFV–SD, SDFV–SD, SDFV–SDNFV and SDNFV–SDFV conditions were thresholded at the voxel-wise level of $p<0.001$ (uncorrected for multiple comparison). Clusters of voxels exceeding the threshold level were considered as significant and reported in table. For readability, t-score were transformed into the unit normal distribution [SPM(Z)].

5.5. EEG recording

Thirty-one Ag/AgCl scalp electrodes were manually put in place following the extended International 10–20 System, and fixed by means of EC$_2$ electrode cream Pactronic (Grass Product Group). The reference electrode was placed on the tip of the nose, the ground electrode on the forehead. One bipolar EOG derivation was recorded from 2 electrodes placed on the supraorbital and infraorbital ridges of the right eye. Electrode impedance was kept below 5 kΩ. The signal was amplified (bandpass 0.3–100 Hz), digitized (sampling frequency 1024 Hz) and stored for off-line analysis, using a Micromed System 98 EEG recording system.

5.6. EEG analysis

Off-line analysis of event-related potentials (ERPs) was performed using the ELAN Pack processing software developed at Inserm U 821.

For each subject, we analyzed only the potentials recorded during CBF measurement. Four periods of about 1 min were thus analyzed in each of the four auditory conditions, including about 400 stimuli (56 deviants in the SD condition, 16 novel stimuli in the SDFV and SDNFV conditions). Responses to standard and deviant tones were analyzed in sweeps of 600 ms, including 100 ms before the stimulus. Epochs of 1400 ms including 200 ms before the stimulus were averaged for the FV and NFV novels.

Epochs contaminated by eye movements and other artifacts were automatically rejected, using a customized software that rejects responses sticking out of a template computed around the median response to each type of stimulus in each block. The width of the template was ±5 standard deviations of the responses around the median. The responses showing more than 20 consecutive sampling points out of the template for standard and deviant responses and the responses showing more than 50 consecutive points out of the template for the novels were excluded from the analysis.

After averaging, a 30-Hz low-pass digital filter was applied (bidirectional Butterworth, 6th order).

EEG analysis of S and SD blocks looked for two objectives. The first one was, classically, to highlight the MMN component. In the SD blocks, responses to the deviant stimuli were therefore compared with the standard responses obtained after exclusion of the standard stimuli immediately following a deviant (SD intra-block comparison). The mismatch response was obtained from the subtraction of the response to standards from the response to deviants. The second aim, in parallel with PET data analysis, was to highlight any global topographical difference between the responses in the S and in the SD conditions. We thus also compared the response to standard stimuli in the S blocks with the overall response to standards and deviants in the SD blocks (S versus SD inter-bock comparison).

To globally assess topographical differences between two conditions, we used an exact statistical method for comparing maps, rooted in permutation test theory, proposed by Karniski (Karniski et al., 1994). The topographical maps obtained from the 31 scalp electrodes were first normalized as recommended by McCarthy and Woods (McCarthy, 1985). The difference measure consisted then in computing the sum across electrodes of squared values of paired t-tests at each electrode (Karniski et al., 1994). At each sampling point, performing all possible permutations between the conditions in the initial data sets provided a distribution of the difference measure, thus making it possible to assess the statistical significance of the measure obtained in actual data (Edgington, 1987). In order to take multiple comparisons into account in the time interval of interest and thus to assess the actual significance of time intervals of apparent significant differences, we used an ad hoc procedure proposed by Blair and Karniski (1993) and inspired by Guthrie and Buchwald (1991). This procedure compares the number of consecutive sampling points showing a significant difference measure (i.e. the number of consecutive points with a probability less than 0.05 to show no difference) with the distribution of the maximum number of such consecutive points obtained by chance, i.e. through all the permutations between the conditions. For 10 subjects, the number of permutations is 1024.

The peaks of the ERPs (N1, MMN/N2b, novelty P3, FN) were identified in the grand average responses. Amplitudes of the components of interest were determined for each subject as the mean value within a time interval around the peaks. Statistical significance of these components was assessed, when necessary, using unilateral t-tests comparing their amplitude to zero. Differences in novelty P3 scalp distributions between the two novels were assessed in the interactions between the ANOVA factors stimulus type and electrode sites after amplitude normalization (McCarthy, 1985). The Greenhouse–Geisser correction of the degrees of freedom was applied.

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