CORTEX 47 (2011) 659–673

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Research report

Are left fronto-temporal brain areas a prerequisite for normal music-syntactic processing?

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ARTICLE INFO

Article history:
Received 29 July 2009
Reviewed 28 October 2009
Revised 5 January 2010
Accepted 7 April 2010
Action editor Stefano Cappa
Published online 1 May 2010

Keywords:
Music
Language
Syntax
ERAN
ELAN
Brain lesions

ABSTRACT

An increasing number of neuroimaging studies in music cognition research suggest that "language areas" are involved in the processing of musical syntax, but none of these studies clarified whether these areas are a prerequisite for normal syntax processing in music. The present electrophysiological experiment tested whether patients with lesions in Broca's area ($N = 6$) or in the left anterior temporal lobe ($N = 7$) exhibit deficits in the processing of structure in music compared to matched healthy controls ($N = 13$). A chord sequence paradigm was applied, and the amplitude and scalp topography of the Early Right Anterior Negativity (ERAN) was examined, an electrophysiological marker of musical syntax processing that correlates with activity in Broca's area and its right hemisphere homotope. Left inferior frontal gyrus (IFG) (but not anterior superior temporal gyrus – aSTG) patients with lesions older than 4 years showed an ERAN with abnormal scalp distribution, and subtle behavioural deficits in detecting music-syntactic irregularities. In one IFG patient tested 7 months post-stroke, the ERAN was extinguished and the behavioural performance remained at chance level. These combined results suggest that the left IFG, known to be crucial for syntax processing in language, plays also a functional role in the processing of musical syntax. Hence, the present findings are consistent with the notion that Broca's area supports the processing of syntax in a rather domain-general way.

1. Introduction

In 2001, Maess et al. (2001) stated that "Musical syntax is processed in Broca's area", and suggested that this region may "process syntactic information that is less language-specific than previously believed". More precisely, the authors reconstructed the sources of the magnetic equivalent of the Early Right Anterior Negativity (ERAN), a component of the event-related potential (ERP) elicited by harmonically unexpected chords and taken as an index for early music-syntactic processing (Koelsch et al., 2000; Koelsch, 2009). Most intriguingly, the dipoles of the mERAN (i.e., the ERAN recorded with magnetoencephalography – MEG) were localised in Broca's area (inferior Brodman area 44), a brain region known to be

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doi:10.1016/j.cortex.2010.04.007

involved in syntactic analysis in language (Friederici, 2006; Grodzinsky and Santi, 2008), and its right hemisphere homotope. The present electroencephalography (EEG) study aimed to strengthen the proposition of Maess et al. (2001) by testing whether lesions in left fronto-temporal brain regions lead to deficits in music-syntactic processing.

During the past 10 years, a series of studies has referred to the neuroanatomical and functional parallels of syntax processing in music and language (for reviews, see Koelsch, 2005; Patel, 2008). Music, like language, is a progression of perceptually discrete elements (e.g., chords and words) that are arranged according to specific rules (e.g., harmonic and morphosyntactic principles) to form meaningful sequences (e.g., musical phrases and sentences; Lerdahl and Jackendoff, 1983; Patel, 2003; Koelsch and Siebel, 2005). We effortlessly acquire implicit representations of these syntactic systems by mere exposure during early childhood (Koelsch et al., 2003; Kuhl, 2004; McMullen and Saffran, 2004; Oberecker et al., 2005; Tillmann et al., 2000), and automatically access this knowledge to smoothly and accurately integrate successively incoming chords and words, and to predict forthcoming elements when listening to music or speech.

Neuroimaging studies have suggested that these parallels of syntax processing in music and language map onto a partly common neural architecture. Broca's area has been associated with syntactic and hierarchical processing in language (e.g., Grodzinsky and Santi, 2008; Friederici et al., 2006; Makuuchi et al., 2009; for a review see Grodzinsky and Friederici, 2006). For example, the neural generators of the language-related Early Left Anterior Negativity (ELAN), an ERP component evoked by word-category errors in sentences (Neville et al., 1991; Friederici et al., 1993; Hahne and Friederici, 1999; Lau et al., 2006) have been localised in Broca's area and its right hemisphere homologue (Friederici et al., 2000; Knösche et al., 1999; additional sources of the ELAN were found in the anterior superior temporal gyrus – aSTG bilaterally). As mentioned above, the dipoles of the music-related ERAN were also located in the left and right inferior frontal gyrus (IFG; Maess et al., 2001), in fact, close to those of the ELAN. Likewise, functional magnetic resonance imaging (fMRI) studies yielded activations in the IFG and the aSTG during the presentation of both music-syntactic irregularities (Koelsch et al., 2002a, 2005a; Tillmann et al., 2003, 2006; Krumhansl, 2004; Minati et al., 2008), or syntactically incorrect sentences (Brauer and Friederici, 2007; Friederici et al., 2003; Rüschemeyer et al., 2005), although activations were mostly bilateral with right-hemispheric weighting during the processing of music, and were clearly left-dominant during the processing of language. These findings led to the assumption that syntax processing in music and language may partly overlap in fronto-temporal brain areas, particularly in the language-dominant left hemisphere (Patel, 2003).

However, neither MEG nor fMRI are able to ultimately clarify whether these brain regions are a prerequisite for syntax processing. MEG source localisation has to face the ambiguity of the inverse problem, and fMRI results usually reflect correlations between brain activations and an assumed function resulting from the subtraction of two conditions. In other words, such data may indicate an involvement of the IFG and aSTG, even if these are not obligatory to syntax processing, thus rendering it premature to conclude that these areas are crucial for the processing of musical and/or linguistic syntax. This question can be resolved by testing whether the respective functions are disrupted in patients with lesions in these brain areas.

In the language domain, numerous lesion studies prove the necessity of the left inferior frontal and the left anterior temporal lobe for linguistic syntax processing (Friederici and Kotz, 2003; Stowe et al., 2005). For example, Broca's aphasics exhibit deficits in comprehending semantically reversible passives such as "*The boy was kissed by the girl.*" which can only be correctly understood when relying on syntactic information (Caplan and Futter, 1986; Caplan et al., 1996; Caramazza and Zurif, 1976; Davis et al., 2008). Likewise, patients with left anterior temporal brain lesions exhibit marked deficits in comprehending complex morphosyntactic structures (Dronkers et al., 1994; Grossman et al., 1998). Further evidence comes from ERP studies showing that the ELAN (indexing initial phrase-structure building in sentences) disappears if left fronto-lateral or left anterior temporal brain areas are damaged (Friederici et al., 1998, 1999; Friederici and Kotz, 2003; Kotz et al., 2003), suggesting the necessity of these left hemispheric brain regions for fast syntactic procedures during language processing.

In the music domain, the clinical literature on music-syntactic processing is restricted to four behavioural case studies (for an overview, see Stewart et al., 2006) that do not, however, yield a precise spatial localisation of the perturbed functions, because they tested either split-brain patients (Tramo and Bharucha, 1991) or patients with bilateral lesion configurations (Peretz, 1993; Peretz et al., 1994; Tramo et al., 1990). A recent study included patients with a homogeneous syntactic comprehension deficit in language, but with variable lesion sites in the left hemisphere, not always including Broca's area or temporal regions (Patel et al., 2008). Therefore, it is currently unknown whether left inferior frontal and left anterior temporal brain structures are relevant for the processing of syntax in music.

The present EEG study was designed to fill this gap and tested whether patients with lesions encompassing the left IFG (Broca's area) or the left aSTG exhibit deficits in the processing of musical structure. Special care was taken that either the IFG or the aSTG but not both structures were lesioned, to allow a possible dissociation of their function. No patients with similarly circumscribed lesions in the homotope right-hemispheric areas were tested.[1] The ERAN was used as an electrophysiological marker for intact or disrupted music-syntactic processing. It was hypothesised that both patient groups would exhibit a reduced amplitude and/or a topography shift of the ERAN, as well as behavioural deficits in detecting music-syntactically irregular chords (compared to healthy controls). Such a result would provide direct evidence for the necessity of the left inferior frontal and the left anterior temporal lobe in musical syntax processing.

[1] Patients with circumscribed lesions of the right IFG or right aSTG show up only rarely in clinical settings, most probably because they do not develop those massive (language) deficits as patients with comparable left hemispheric lesions. For example, no patient with focal right IFG lesion and spared aSTG was found among the more than 2000 records of our data base.

2. Method

2.1. Participants

2.1.1. Patients

Because the particular aim of this experiment was the localisation of music-syntactic functions, all patients were chosen according to lesion site, not according to functional deficits (for a reverse approach, see Patel et al., 2008). Two patient groups were studied. The first lesion group comprised six patients (one woman) with lesions encompassing the left IFG including the pars opercularis and the pars triangularis (but sparing the left aSTG). The second lesion group contained seven patients (two women) with lesions in the left anterior temporal lobe including the aSTG and the planum polare (but sparing the left IFG). Heschl's gyrus was intact in all patients (see Fig. 1 and Table 1), and all of them reported to have normal hearing. Eleven patients were right-handers and two were ambidextrous according to the Edinburgh Handedness Inventory (Oldfield, 1971). They had a mean age of 52.5 (IFG) and 54.71 years (aSTG). Both groups had suffered their lesion (of varying aetiology) an average of 7 years before the present study, ranging from .58 to 10.42 years in IFG patients, and from 4.17 to 8.92 years in aSTG patients. Mean education was 10 (IFG) and 11.43 years (aSTG). Mean time of formal musical training (mostly during adolescence) was 1.67 (IFG) and 2 years (aSTG; see top of Table 2 for details). All patients were able to understand the instructions of the experiment as affirmed with the Token Test (a screening for receptive deficits in aphasics; Huber et al., 1993).

2.1.2. Matched controls

For each patient, one healthy control subject matched in gender, age (mean: 53.62 years), handedness, school education (mean: 10.77 years), and years of formal musical training (mean: 1.85 years) was recruited for the experiment (see bottom of Table 2). All control participants reported to have normal hearing. An analysis of variance (ANOVA) with the fixed factor Group (healthy controls *vs* IFG patients *vs* aSTG patients) indicated that the three experimental groups did not differ with respect to nonverbal intelligence ($p > .156$; assessed with the third subtest of the L-P-S or L-P-S 50+ by Horn, 1983; Sturm et al., 1993) and short-term memory (STM, $p > .235$; assessed with the block span forward by Wechsler, 1987). It was only in the working memory test (WM; block span backward by Wechsler, 1987), that the controls scored higher than both patient groups [$F(2,21) = 3.76$, $p < .041$], as confirmed by post-hoc two-samples *t*-tests [controls *vs* IFG patients: $t(16) = -1.98$, $p < .021$; controls *vs* aSTG patients: $t(16) = -1.91$, $p < .075$; IFG *vs* aSTG patients: $t(10) = -.90$, $p > .388$]. Consequently, differences in behavioural performance or electrophysiological effects cannot be attributed to the intelligence level or STM capacity of the patients and controls, whereas WM capacity must be considered when interpreting the results. Informed consent according to the Declaration of Helsinki was obtained from each participant prior to the experiment which was approved by the local Ethical Committee.

2.2. Stimulus material

Participants were presented with two chord sequences transposed into all twelve major keys, resulting in 24 different stimuli (Fig. 2; for the evaluation of these stimuli in healthy students, see Koelsch and Sammler, 2008). The chord functions of the initial five chords were identical in both sequence types (regular and irregular): dominant [V]–tonic [I]–subdominant [IV]–supertonic [II]–dominant [V] (left panel of Fig. 2). The final chord function was a tonic chord [I] in regular sequences, and a *double dominant* [II^{3+}] in irregular sequences (right panels of Fig. 2). The tonic chord is the most regular and expected chord at the final position of these sequences, according to the theory of harmony (Piston, 1948/1987; Schönberg, 1969). The *double dominant* is music-

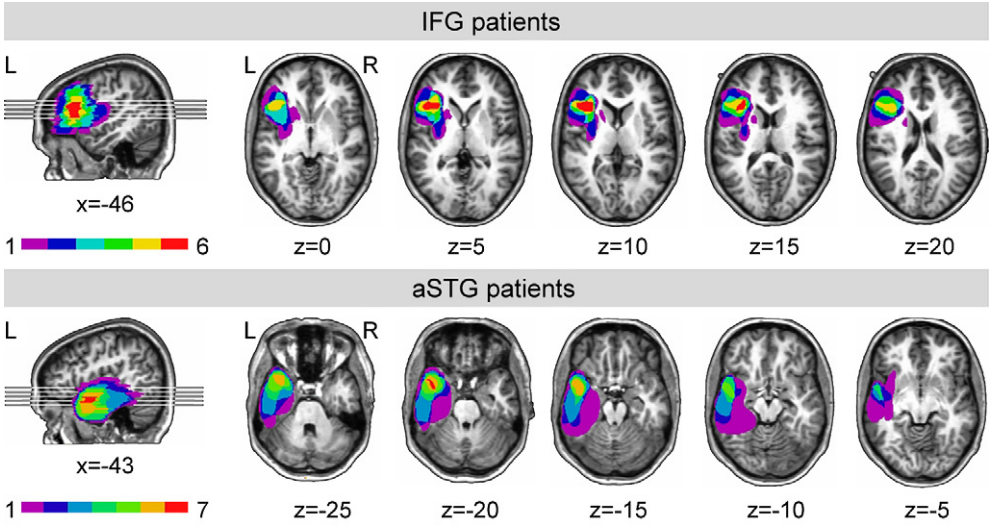

Fig. 1 – Overlay of the lesions of the IFG (top) and the aSTG patients (bottom). Each row depicts five brain slices of a standard brain (Talairach and Tournoux, 1988). The colour code indicates the number of patients with lesions in the given area (purple = 1 patient, red = all patients of the group).

Table 1 – Description of the lesions for each individual patient with IFG or aSTG lesions. Aetiology: IS = ischemic stroke, CH = cerebral haemorrhage, T = tumour resection, TBI = traumatic brain injury, HE = herpes encephalitis. Time since brain injury: years; months. + = unequivocal lesion; (+) = likely lesion; – = no lesion.

Lesion sites	IFG patients						aSTG patients						
	S.C.	B.K.	R.G.	A.G.	P.S.	M.S.	H.N.	I.P.	R.B.	S.H.	B.R.	N.L.	E.S.
Aetiology	IS	IS	CH	T	IS	IS	TBI	HE	T	TBI	IS	T	HE
Lesion onset (yrs; mon.)	10;5	9;9	8;0	7;11	5;9	0;7	8;7	8;6	6;2	8;11	5;2	7;8	4;2
IFG, pars opercul.	+	+	+	+	+	+	(+)	–	–	(+)	–	–	–
IFG, pars triangul.	(+)	+	+	+	+	+	–	–	–	–	–	–	–
IFG, pars orbitalis	(+)	+	+	+	+	+	–	–	–	–	–	–	–
Inf. precentr. gyr.	–	+	–	–	–	+	–	–	–	–	–	–	–
Anterior insula	+	+	–	(+)	+	+	–	–	–	–	–	–	–
STG, anterior part	–	–	–	(+)	–	–	+	+	+	+	+	+	+
STG, middle part	–	–	–	–	–	–	+	–	+	+	–	+	+
Heschl's gyrus	–	–	–	–	–	–	–	–	–	–	–	–	–
MTG, anterior part	–	–	–	–	–	–	+	–	+	+	–	+	+
MTG, middle part	–	–	–	–	–	–	+	–	+	+	–	+	+
Temporal pole	–	–	–	–	–	–	(+)	+	+	+	–	+	+

syntactically less expected in this context. Auditory modelling of the chord sequences by means of the IPEM toolbox (Leman et al., 2005) affirmed that perceived differences between the final regular and irregular chords as well as the resulting ERAN could not be due to acoustic factors like pitch or pitch class repetition, sensory dissonance, and roughness (for more details, see Koelsch and Sammler, 2008). Hence, brain responses elicited by these stimuli largely represent music-syntactic processing, not sensory deviance detection (for a discussion on the inter-relationship between music-syntactic and acoustic deviance, see Bharucha and Stoeckig, 1987; Bigand, 2003; Koelsch et al., 2007).

Sound files of the sequences were generated using Cubase SX 2.0 (Steinberg Media Technologies, Hamburg, Germany) with grand piano sound (Steinberg, The Grand). A second sound file of each sequence was created containing one chord played by a deviant instrument (bells, VST sound a1), to provide the participants with an easy detection task (see below). The presentation time of all chords was 500 msec, except the critical final chords which lasted 1000 msec and were followed by a 500 msec pause. Across the experiment, participants listened to 192 regular and 192 irregular sequences as well as 48 sequences containing a deviant instrument (equiprobably at any of the six chord positions).

Table 2 – Personal and neuropsychological data of the patients and matched controls. Gender: F = female, M = male. Handedness: R = right, A = ambidextrous. School education: years. Musical training: accumulated years of playing an instrument. Token Test (language comprehension): number of mistakes (age corrected). L-P-S (nonverbal intelligence): T-values. Block span forward/backward (nonverbal short-term and working memory): percentages. Bold values indicate a performance below the norm range. Behavioural data of patient R.B. could not be assessed due to severe illness.

Lesion sites	IFG patients						aSTG patients						
	S.C.	B.K.	R.G.	A.G.	P.S.	M.S.	H.N.	I.P.	R.B.	S.H.	B.R.	N.L.	E.S.
Age	63	56	63	45	22	67	57	57	50	62	52	57	49
Gender	F	M	M	M	M	M	M	M	M	F	M	M	F
Handedness	R	R	R	R	A	R	R	R	A	R	R	R	R
School education	8	10	12	8	10	12	12	12	12	10	12	12	10
Musical training	0	0	4	4	0	2	2	0	0	0	12	0	0
Token Test	2	0	0	0	2	3	0	0	–	0	0	0	3
L-P-S	**35**	52	54	48	55	46	44	59	–	**38**	44	59	55
Block span	27/**5**	27/92	58/**10**	50/**2**	95/93	88/67	98/70	27/70	–	27/22	71/55	85/70	71/92
	Healthy controls												
	G.M.	H.L.	V.G.	M.F.	L.G.	K.G.	K.G.	T.W.	L.R.	V.M.	F.T.	H.A.	G.P.
Age	63	55	61	44	22	66	57	55	51	64	54	56	49
Gender	F	M	M	M	M	M	M	M	M	F	M	M	F
Handedness	R	R	R	R	R	R	R	R	R	R	R	R	R
School education	8	10	10	10	10	12	12	12	12	10	12	12	10
Musical training	6	0	3	0	0	4	0	6	1	4	0	0	0
Token Test	0	0	0	0	0	0	0	0	0	0	0	0	0
L-P-S	47	48	55	60	55	52	52	59	59	50	58	58	57
Block span	27/45	71/55	98/97	93/92	76/75	77/67	85/92	90/97	90/55	95/85	90/92	85/92	50/92

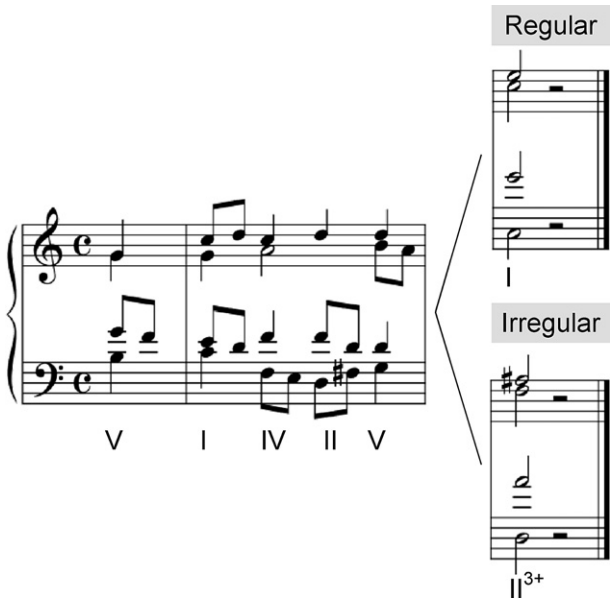

Fig. 2 – Examples of the chord sequences employed in the present experiment. The functions of the first five chords were identical in both sequence types (left panel). The final regular chord was a tonic [I], the final irregular chord a double dominant [II^{3+}] (upper and lower right panels; see also the "polyphonic" stimulus set in Koelsch and Sammler, 2008).

Regular and irregular sequences were pseudo-randomly intermixed. Consecutive sequences always had a different tonal key and not more than 3 sequences of the same type followed each other.

2.3. *Procedure*

Participants sat in a comfortable chair in a soundproof cabin. Stimuli were presented via loudspeakers at a comfortable volume using Presentation 0.53 (Neurobehavioral Systems, Inc., Albany, Canada). The EEG session was divided into two blocks (see also Koelsch and Sammler, 2008). In the first block, participants looked at a fixation cross while listening to the stimuli. If they felt able to continue, a second block was added to gain more trials. Both blocks were identical, except that a silent movie (without subtitles, reduced to 1/4th of its original size in order to avoid eye movement artefacts) was presented during the second run to make the experiment more appealing, and to decrease the incipient tension of the face muscles, leading to a higher signal-to-noise ratio of the data (for similar approaches, see Koelsch and Sammler, 2008; Poulin-Charronnat et al., 2006). All participants completed both blocks, brain potentials did not differ between blocks (see Results section). Listeners were not informed about the regular and irregular sequence endings to avoid electric brain responses that would be elicited in an explicit discrimination task (e.g., the N2b or P300) and confound ERPs related to implicit musical structure building (i.e., the ERAN that is elicited even without being informed about the music-syntactic irregularities; Koelsch et al., 2002b). To control whether participants attended to the music, they were asked to press a button whenever they detected one of the infrequently occurring deviant instruments. This task was unrelated to music-syntactic processing and trials containing such a timbre deviant did not enter the data analysis. The experiment had a duration of approximately 30 min.

To test whether participants were able to explicitly perceive harmonic irregularities, a post-hoc behavioural test was conducted at least 2 days after the EEG measurement. Participants were asked to discriminate chord sequences with regular and irregular endings as presented during the EEG experiment (Fig. 2), and to press a right- or left-hand button, without time constraints. To familiarise participants with the test, they received training with 10 randomly presented chord sequences (50% irregular). If necessary, the training was repeated once (in 2 patients and 2 controls). Error feedback was given during the training but not during the main test. The actual test comprised 48 regular and 48 irregular sequences that were presented in pseudo-random order via headphones (Sennheiser HD 202) in a silent room using Presentation 0.53 (Neurobehavioral Systems, Inc., Albany, Canada). The test had a duration of approximately 10 min.

2.4. *EEG data acquisition and analysis*

The EEG was recorded with 30 Ag/AgCl electrodes placed according to the extended international 10–20 system (cf., Sharbrough et al., 1991). The electrode positions were: FP1, FP2, AF7, AF8, AF3, AF4, AFZ, F7, F8, F3, F4, FZ, FT7, FT8, FC3, FC4, T7, T8, C3, C4, CZ, CP5, CP6, P7, P8, P3, P4, PZ, O1, O2. Left mastoid (M1) served as reference; an additional electrode was placed on the right mastoid bone (M2) and the tip of the nose for off-line re-referencing. The ground electrode was located on the sternum. Horizontal and vertical electrooculograms (EOG) were bipolarly recorded from electrodes placed on the outer canthus of each eye, as well as above and below the right eye. Impedances were kept below 5 kΩ. Signals were amplified with two synchronised PORTI-32/MREFA amplifiers (Twente Medical Systems International B.V., Enschede, NL) and digitised with a sampling rate of 250 Hz.

EEP 3.2 (ANT-software) was used to re-reference the data to linked mastoids, and to filter the data using a .4-Hz highpass filter (fir, 3465 points). Further processing steps were carried out using EEGLAB 5.03 (Delorme and Makeig, 2004) in Matlab 7.1.0. Data were cut into epochs of −2700 to 1000 msec relative to the onset of the final chord. Epochs containing strong muscle artefacts, electrode drifts, or technical artefacts were manually rejected. Non-rejected epochs were subjected to an Independent Component Analysis. Components reflecting eye movement, blink, and muscle artefacts or extensive alpha activity were removed. Afterwards, the data were filtered with a 25-Hz lowpass filter (fir, 277 points), and rejected [1] for threshold (±55 μV), [2] for linear trends (±50 μV in a 400 msec gliding window), [3] for improbable data [±5 *SD* range (for a single channel) or ±3 *SD* range (for all channels) of the mean probability distribution], [4] for abnormally distributed data [±6 *SD* range (for a single channel) or ±3 *SD* range (for all channels) of the mean distribution of kurtosis values], and [5] by visual inspection (to eliminate small blinks and drifts that were not rejected by the automatic procedures). Non-rejected

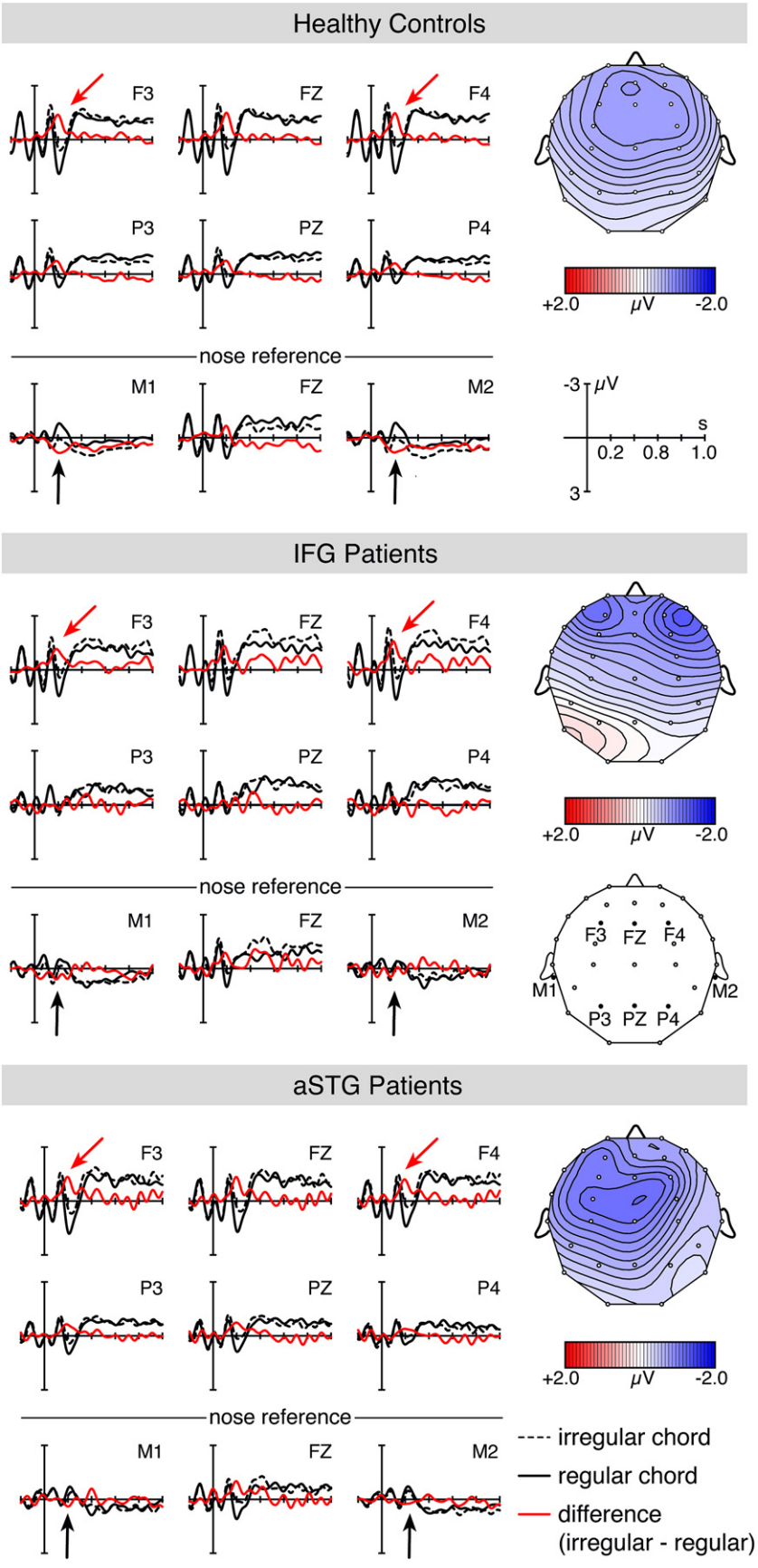
Healthy Controls
F3
FZ
F4
P3
PZ
P4
nose reference
M1
FZ
M2
+2.0
μV
-2.0
-3 μV
s
0.2
0.8
1.0
3
IFG Patients
F3
FZ
F4
P3
PZ
P4
nose reference
M1
FZ
M2
+2.0
μV
-2.0
F3
FZ
F4
M1
M2
P3
PZ
P4
aSTG Patients
F3
FZ
F4
P3
PZ
P4
nose reference
M1
FZ
M2
+2.0
μV
-2.0
irregular chord
regular chord
difference
(irregular - regular)

Table 3 – ANOVAs of Chord × Hemisphere × AntPost for healthy controls and both patient groups. Bold values indicate significant results.

Effect	Healthy controls		IFG patients		aSTG patients	
	$F(1,12)$	p-value	$F(1,5)$	p-value	$F(1,6)$	p-value
Chord	38.47	**<.0001**	9.38	**<.029**	65.69	**<.0001**
Chord × Hemisphere	.00	>.964	5.46	<.067	3.16	>.126
Chord × AntPost	30.89	**<.0001**	32.06	**<.003**	17.36	**<.007**

epochs were averaged in a time window from 0 to 1000 msec relative to the onset of the final chord with a −200 to 0 msec baseline. An average of 246 trials was included for each participant (mean ± *SD* of healthy controls: 256.92 ± 54.76, IFG patients: 183.67 ± 49.46, aSTG patients: 279 ± 55.06), that means, a sufficient number to obtain reliable effects.

For the statistical analysis, mean amplitudes were calculated for each condition in a time window from 150 to 250 msec after onset of the final chord for four Regions of Interest (ROIs): left anterior (AF3, F3, F7, FC3, FT7), right anterior (AF4, F4, F8, FC4, FT8), left posterior (C3, T7, CP5, P3, P7), and right posterior (C4, T8, CP6, P4, P8). To test whether the irregular chords elicited an ERAN in patients and controls, ANOVAs for repeated measures with the within-subject factors Chord (regular [I] *vs* irregular [II^{3+}]), Hemisphere (left *vs* right), and AntPost (anterior *vs* posterior) were calculated on these mean amplitude values separately for each patient group and healthy controls. The data of the two blocks (fixation cross *vs* silent movie) were pooled because ANOVAs with the factors Chord, Hemisphere, AntPost and Block did not reveal a significant interaction of Chord × Block in any of the three groups (p's > .310). To test group differences, an ANOVA for repeated measures with the within-subject factors Chord, Hemisphere, AntPost and the between-subjects factor Group (healthy controls *vs* IFG patients *vs* aSTG patients) was computed.

2.5. Post-hoc behavioural test

To evaluate whether the participants performed above chance level (50%), hit rates were subjected to one-sample *t*-tests with the test value 50 in each patient group and in healthy controls. Performance differences between patients and controls were analysed with an ANOVA for repeated measures with the within-subject factor Chord (regular [I] *vs* irregular [II^{3+}]) and the between-subjects factor Group (healthy controls *vs* IFG patients *vs* aSTG patients).

3. Results

3.1. EEG experiment

Participants detected on average 98.96% of the deviant instruments (hits corrected by false alarms: healthy controls: 99.08%, IFG patients: 98.61%, aSTG patients: 99.03%), showing that they attended to the musical stimuli and reliably identified the deviant timbre. An ANOVA with the between-subjects factor Group (healthy controls *vs* IFG patients *vs* aSTG patients) showed that patients and controls performed similarly in this non-syntactic timbre task (no main effect of Group: $p > .861$).

Fig. 3 depicts the electric brain responses to final regular and irregular chords separately for healthy controls and each patient group. In all groups, the irregular chords elicited an ERAN peaking around 200 msec with a frontal scalp distribution (see red arrows in Fig. 3). When re-referenced to the nose electrode, the ERAN inverted polarity at mastoid leads (see black arrows in Fig. 3) indicating that this ERP effect is not an N2b (the N2b does not invert polarity and has a less anterior scalp distribution; Schröger, 1998; Näätänen et al., 2007). Notably, in IFG patients, the ERAN was more frontally distributed and appeared to be more strongly right lateralised compared to the effects in healthy controls and the aSTG patients, who exhibited a non-lateralised negativity (see Fig. 3).

Three-way ANOVAs with the factors Chord, Hemisphere, and AntPost revealed main effects of Chord and an interaction of Chord × AntPost in the control and both patient groups, indicating that irregular chords elicited a negativity with anterior scalp distribution irrespective of group or lesion site (mean of all ROIs ± *SEM* in healthy controls: $\Delta = -.76 \pm .12$ μV; IFG patients: $\Delta = -.55 \pm .18$ μV; aSTG patients: $\Delta = -.67 \pm .08$ μV). In IFG patients, a marginally significant interaction of Chord × Hemisphere was found ($p < .068$), demonstrating a trend of a right lateralisation of the effect in this group (left: $\Delta = -.40 \pm .16$ μV; right: $\Delta = -.72 \pm .22$ μV; see Table 3 for statistical values). Healthy controls and aSTG patients exhibited non-lateralised effects (Chord × Hemisphere: p's > .126).

Likewise, a four-way ANOVA with the factors Chord, Hemisphere, AntPost, and Group (healthy controls *vs* IFG patients *vs* aSTG patients) revealed a main effect of Chord [$F(1,23) = 64.82$, $p < .0001$], and an interaction of Chord × AntPost [$F(1,23) = 79.14$, $p < .0001$]. Moreover, significant three-way interactions of Chord × AntPost × Group [$F(2,23) = 4.54$, $p < .022$] and Chord × Hemisphere × Group [$F(2,23) = 5.18$, $p < .014$] were found. To further elucidate these interactions, three analogous four-way ANOVAs were computed in which

Fig. 3 – Electrophysiological responses to regular (solid line) and irregular final chords (dotted line) plotted for healthy controls (upper panel), patients with IFG (middle panel) or aSTG lesions (lower panel). Irregular chords elicited an ERAN (see red line and red arrows) in all groups. Likewise, a polarity inversion was observed at mastoid leads in all groups when the data were re-referenced to the nose electrode (see black arrows pointing to electrodes M1 and M2). The topography maps show the scalp distribution of the ERAN in a time window from 150 to 250 msec after onset of the final chord (referenced to linked mastoids). In patients with IFG lesions, the ERAN was distributed significantly more anteriorly and was more strongly right lateralised than in the healthy controls or in patients with aSTG lesions. The scalp distribution in controls and aSTG patients did not significantly differ from one another.

the factor Group was systematically reduced to two levels (i.e., IFG patients *vs* controls, aSTG patients *vs* controls, and IFG *vs* aSTG patients; see Table 4 for statistical values). These analyses showed that the ERAN was indeed more anteriorly distributed and more strongly right lateralised in patients with IFG lesions compared to controls (interaction of Chord × AntPost × Group: $p < .035$; interaction of Chord × Hemisphere × Group: $p < .045$), and compared to patients with lesions in the aSTG (Chord × AntPost × Group: $p < .014$; Chord × Hemisphere × Group: $p < .015$; see topography maps in Fig. 3). The scalp topography did not differ between aSTG patients and controls (no interaction of Chord × AntPost × Group or Chord × Hemisphere × Group: p's $> .104$). These findings underline that the scalp topography of the ERAN was particularly different in the IFG patients.

To make sure that these results in the IFG patients were not predominantly due to patient M.S. who had acquired his lesion considerably more recently (7 months prior to testing) than the other IFG and aSTG patients (>4 years; see Table 1), analogous ANOVAs were computed excluding M.S.'s data set (see below for a separate analysis of M.S.'s data). These analyses revealed virtually identical results [IFG patients *vs* healthy controls: Chord × Hemisphere × Group: $F(1,16) = 7.38$, $p < .016$, Chord × AntPost × Group: $F(1,16) = 6.76$, $p < .020$; IFG patients *vs* aSTG patients: Chord × Hemisphere × Group: $F(1,10) = 10.87$, $p < .009$, Chord × AntPost × Group: $F(1,10) = 10.91$, $p < .009$], indicating that the scalp topography of the ERAN remains specific even in patients with older left IFG lesions.

Interestingly, in none of the patient groups the overall ERAN amplitude was significantly reduced compared to controls (no significant interaction of Chord × Group: p's $> .365$; see Table 4). To test whether this result was possibly due to a recovery of the ERAN since lesion onset (i.e., to clarify whether the ERAN amplitude increased with time since brain injury) one-sided Pearson correlations were calculated between lesion onset and the ERAN amplitude (average of frontal ROIs), separately for each patient group. As depicted in Fig. 4A, a strong correlation between lesion onset and ERAN amplitude was found in the IFG patients [$r(4) = -.726$, $p < .052$; $R^2 = .53$, indicating a large effect size, Bortz and Döring, 2003], demonstrating that left IFG lesions with recent onset are more likely to reduce the ERAN amplitude than older lesions. A similar, but considerably weaker and non-significant trend was observed if patient M.S. was excluded from the analysis [$r(3) = -.369$, $p > .270$], suggesting that the ERAN amplitude is less prone to changes in more chronic lesions. No correlation (not even a trend) was found in patients with lesions in the aSTG [$r(5) = +.007$, $p > .494$; Fig. 4B].

3.2. *Post-hoc behavioural test*

All participants expressed great uncertainty about the distinction between regular and irregular final chords, reflected in relatively low hit rates (healthy controls: 61.29%; IFG patients: 54.69%; aSTG patients: 58.16%). Nevertheless, controls and also the aSTG patients performed significantly above the 50% chance level [controls: $t(11) = 4.84$, $p < .002$, aSTG patients: $t(5) = 3.24$, $p < .024$; one-sample *t*-tests], whereas patients with lesions in the left IFG performed at chance level ($p > .242$), even if patient M.S. was excluded from the analysis ($p > .137$). However, no significant differences were found between patients and controls (no main effect of Group: $p > .256$).

To test whether the behavioural performance was modulated by general cognitive abilities, one-sided Pearson correlations were computed across all participants between hit rates and nonverbal intelligence [$r(22) = .042$, $p > .424$), working memory [$r(22) = .049$, $p > .410$], and STM [$r(22) = -.54$, $p > .402$]. No significant relations were found, indicating that the discrimination performance did not depend on these general cognitive functions.

To test whether the behavioural performance increased with time since brain injury (like the ERAN amplitude), one-tailed Pearson correlations were calculated between lesion onset and hit rates, separately for each patient group. As depicted in Fig. 4C, a correlation between lesion onset and discrimination performance was found in patients with IFG lesions [$r(4) = .628$, $p < .091$, $R^2 = .40$, indicating a medium to large effect size, Bortz and Döring, 2003]. This result mirrors the correlation found for the ERAN amplitude (see above) in that more recent lesions were associated with weaker sensitivity for music-syntactic irregularities than older lesions. Again, a similar but considerably weaker and non-significant trend was found if patient M.S. with the most recent lesion was excluded from the analysis [$r(3) = .344$, $p > .285$], suggesting that the behavioural performance is more stable in chronic lesions. No correlation (not even a trend) was found in patients with aSTG damage [$r(4) = .020$, $p > .485$; Fig. 4D].

3.3. *Single case analysis of patient M.S.*

The correlation between the EEG, behavioural data and the time since lesion onset in IFG patients suggested a likely impact of recovery over time, therefore, perhaps obscuring deficits that occur only for a short time after brain injury. As patient M.S. had acquired his lesion (Fig. 5) only 7 months prior to testing (making a complete recovery of music-syntactic functions less likely than in the other patients with lesions older than 4 years) M.S.'s data were analysed separately and compared as a single case with the data of the remaining IFG patients and healthy controls. No such analysis was conducted in aSTG patients because none of these individuals had a recent lesion.

The ERAN amplitude of patient M.S. (mean: $\Delta = -.16\ \mu V$) was significantly lower than the one observed in the other IFG patients [mean: $\Delta = -1.06\ \mu V$, $t(5) = -4.49$, $p < .012$; one-sample *t*-test with test value $-.16$; see Fig. 6A]. Moreover, M.S.'s ERAN amplitude was also significantly smaller than the one in healthy controls [mean: $\Delta = -.96\ \mu V$, $t(12) = -6.28$, $p < .0001$]. The ERAN amplitudes of the IFG patients with older lesions and of healthy controls did not differ as indicated by a non-significant interaction of Chord × Group in an ANOVA with the factors Chord, Hemisphere, AntPost, and Group [$F(1,16) = .13$, $p > .720$].

The behavioural performance of patient M.S. (hits: 44.79%) was at chance level (assessed with a binomial test: $p > .820$) and significantly weaker than the performance of the other IFG patients [mean of hits: 56.67%, $t(4) = 3.31$, $p < .04$;

Table 4 – ANOVAs of Chord × Hemisphere × AntPost × Group/LesionSite. Bold values indicate significant results.

	IFG patients versus healthy controls		aSTG patients versus healthy controls		IFG patients versus aSTG patients	
	$F(1,17)$	p-value	$F(1,18)$	p-value	$F(1,11)$	p-value
Chord	36.30	**<.0001**	63.60	**<.0001**	41.78	**<.0001**
Chord × Group	.86	>.365	.26	>.616	.35	>.567
Chord × Hemisphere	4.90	**<.041**	2.76	>.114	.15	>.707
Chord × Hemisphere × Group	4.69	**<.045**	2.92	>.104	8.34	**<.016**
Chord × AntPost	67.24	**<.0001**	39.25	**<.0001**	52.61	**<.0001**
Chord × AntPost × Group	5.26	**<.035**	.76	>.394	8.55	**<.015**

one-sample t-test with test value 44.79; see Fig. 6B], and healthy controls [mean of hits: 61.29%, $t(11) = 7.07$, $p < .0001$]. No significant difference was found between the other IFG patients and healthy controls [$t(15) = -1.08$, $p > .299$; two-samples t-test]. These combined results suggest that the ERAN amplitude and the ability to detect harmonically irregular chords are impaired in early stages after left IFG injury, but might have reached normal levels several years later (despite a still abnormal scalp distribution of the ERAN; see above).

4. Discussion

The present study investigated whether left inferior frontal and left anterior temporal brain areas (known to be crucial for syntax processing in language) are a prerequisite for normal syntax processing in music. Patients with lesions including the left IFG or left aSTG as well as healthy controls were tested in a chord sequence paradigm. The behavioural performance in detecting harmonically irregular chords, and the ERAN (an

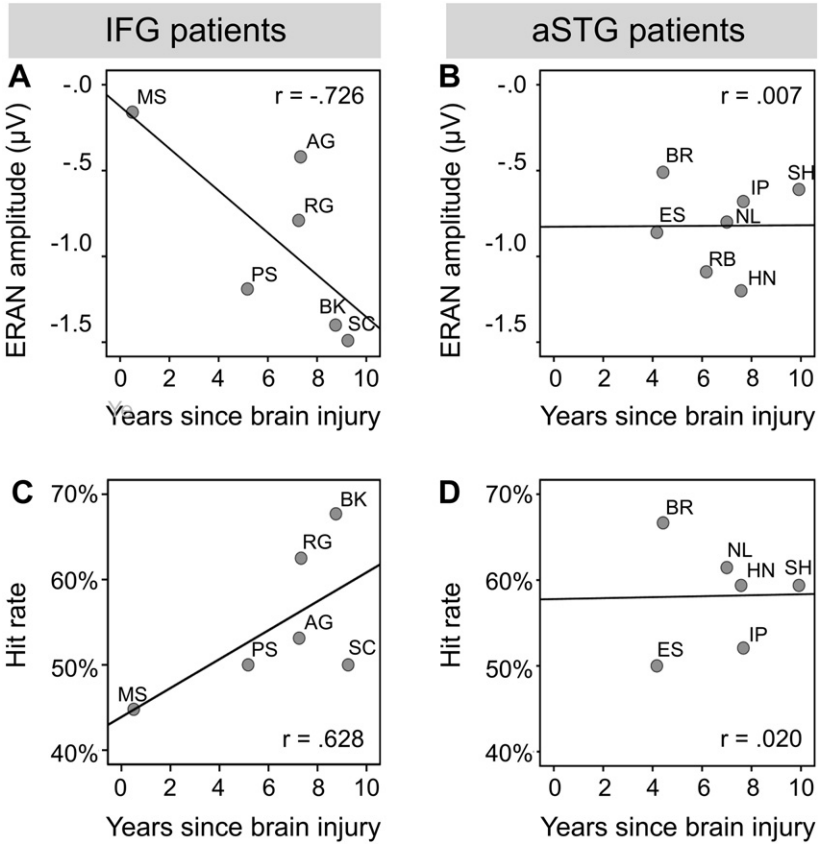

Fig. 4 – Correlation of lesion onset, ERAN amplitude and behavioural discrimination performance. In patients with IFG lesions, the ERAN amplitude (average of the frontal ROIs) increased linearly (i.e., became more negative) with time since brain injury (A). Likewise, performance in explicitly discriminating chord sequences with regular and irregular endings increased with time since lesion onset in IFG patients (C). These correlations lost their significance if patient M.S. (with the most recent lesion) was excluded from the analysis. No correlations were found in patients with aSTG lesions (B and D). Patient R.B. is missing in D because he did not participate in the behavioural experiment due to severe illness.

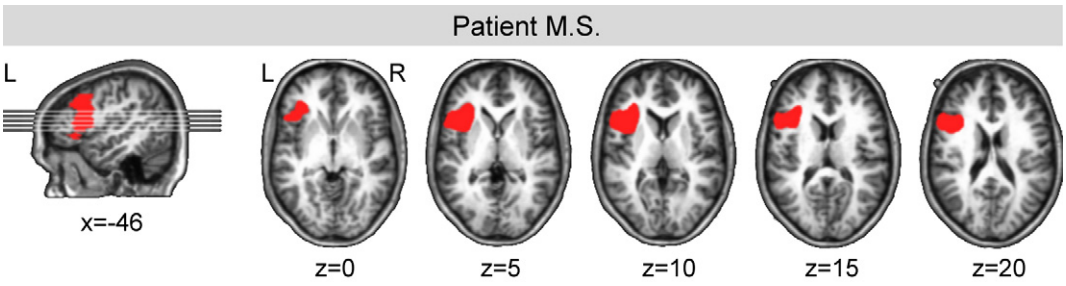

Fig. 5 – Reconstruction of the lesion of patient M.S. mapped onto a standard brain (Talairach and Tournoux, 1988; see Fig. 1 for group data).

ERP component reflecting early processing of music-syntactic irregularities) served as indicators for intact or disrupted processing of musical structure.

Interestingly, the average amplitude of the ERAN and the overall behavioural discrimination performance were not significantly reduced at group level, neither in left IFG patients, nor in left aSTG patients compared to controls (but see below for other indices of left IFG involvement in music-syntactic processing). There may be two reasons for this finding: the dynamic interplay between left and right-hemispheric structures and a likely impact of recovery on the present data. First, prevailing imaging studies (Maess et al., 2001; Koelsch et al., 2005a; Tillmann et al., 2003, 2006) describe the left IFG and left aSTG as two constituents of a larger bilateral and most likely right-dominant network of structures involved in music-syntactic processing. Therefore, it is to be expected that lesions to one of these (perhaps subordinate) constituents will result in subtle deficits rather than a dramatic breakdown of the system. Second, it appears plausible that (originally predominant) right-hemispheric structures might easily compensate for these deficits after brain injury, perhaps obscuring initially impaired functions. As patients were tested an average of 7 years after brain injury (for the recovery of amusic behavioural deficits within 6–12 months after brain damage, see Schuppert et al., 2003), it is well conceivable that the present data reflect an already recovered ability to process musical syntax (see below for corresponding evidence). Future studies with more recent or temporary lesions as induced by Transcranial Magnetic Stimulation (Walsh and Pascual-Leone, 2003) could circumvent such recovery processes.

4.1. *The role of the left IFG in musical syntax processing*

Despite these considerations, the present study yielded two main findings in support of a functional role of the left IFG in music-syntactic processing. First, the scalp topography of the ERAN in IFG patients differed significantly from the one observed in healthy controls and aSTG patients, still four years and later after brain injury. Second, the ERAN amplitude as well as the behavioural discrimination of regular and irregular chord functions was significantly impaired in a single case with a subchronic IFG lesion (patient M.S.), and seemingly modulated by the time since injury of the left IFG (as indicated by the data from the patients with older brain lesions).

The scalp topography of the ERAN was significantly more frontally distributed and more strongly right lateralised in the IFG patients than in controls, suggesting a modified weighting of the different network constituents in these patients. The stimulus material employed in the present experiment evoked non-lateralised effects in controls, suggesting a balanced involvement of left and right hemisphere generators in a healthy elderly population. Similar non-lateralised

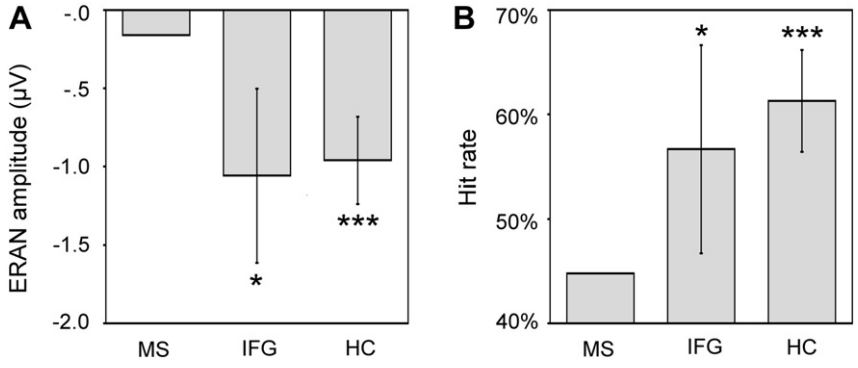

Fig. 6 – ERAN amplitude (A) and behavioural discrimination performance (B) in patient M.S. with a lesion onset of 7 months, compared to IFG patients with lesions older than 4 years (IFG), and healthy controls (HC). Error bars indicate the borders of the 95% confidence interval. Asterisks indicate the significantly smaller ERAN amplitude and weaker performance of patient M.S. compared to IFG patients and healthy controls. $^{*}p < .05$, $^{***}p < .001$.

early negativities have been repeatedly reported by recent ERP studies, mostly when harmonically complex stimulus material was used like in the present experiment (for a review, see Koelsch, 2009). The persistent topography shift in IFG patients still four years after brain injury might reflect a greater predominance of the right-hemisphere generators of the ERAN compared to healthy controls, due to the breakdown of the left hemisphere units and/or a shift of the function to the contralesional hemisphere (for similar inter-hemispheric shifts during aphasia recovery see, e.g., Schlaug et al., 2008 [Patient #1]; Saur et al., 2006; Thiel et al., 2006). Because the scalp distribution of the ERAN in aSTG patients did not significantly differ from that of controls (both groups exhibited non-lateralised effects), it is unlikely that the topography shift observed in the IFG patients is merely an effect of weaker signal quality over the ipsilesional compared to the contralesional hemisphere.

In the absence of longitudinal data, it is difficult to ascertain whether the topography shift of the ERAN (despite normal ERAN amplitude) represents a general sufficiency of right-hemispheric structures for music-syntactic processing, or post-lesional reorganisation and recovery. However, for two reasons it may be speculated that the data are more consistent with a structural and functional reorganisation of music-syntactic processing. First, as a group, patients with lesions in the left IFG showed chance level performance in the discrimination of regular and irregular sequence endings, contrary to healthy controls and the patients with aSTG lesions. Although no significant group differences were found (most presumably due to a floor effect)[2] and any interpretation must therefore remain speculative, this result fits with the assumption that the neural network underlying music-syntactic processing is slightly less sensitive to irregular chords if its left frontal constituent is lesioned. Second, a progressive recovery of music-syntactic processing fits with the correlations between the ERAN amplitude, the discrimination performance, and the time since lesion onset (although this assumption should be further tested in a longitudinal study). Corroboratingly, the IFG patient M.S. with the most recent lesion (7 months prior to testing, i.e., in a subchronic stage of recovery) exhibited a significantly smaller ERAN amplitude and a weaker sensitivity to harmonic irregularities than patients with lesions older than four years. Moreover, his behavioural and amplitude values differed significantly from those of healthy controls, whereas no such difference was found between controls and IFG patients with older lesions. This finding cannot be attributed to general cognitive deficits of M.S. who scored normally (sometimes even slightly higher than the other groups) in intelligence, WM and STM tests (Table 2). The combined results suggest that the ERAN may regain strength and perceptual sensitivity may increase over the years, finally even reaching normal levels as in healthy controls, perhaps through a compensatory up-regulation of right-hemispheric activity as suggested by the abnormal distribution of the ERAN in chronic lesions (see above). Overall, the finding that both the ERAN amplitude and the behavioural measures were deficient in early stages after IFG injury, and increased with time since lesion onset, conjointly suggest that the left IFG may be originally necessary (although most likely not sufficient) for normal music-syntactic processing, but that its dysfunction may have been gradually compensated for in our patients.

Taken together, the ERAN was extinguished in one IFG patient tested 7 months post-stroke. Patients with chronic left IFG lesions showed an ERAN, which was, however, significantly differently distributed than in controls. Moreover, behaviourally, patients failed to perceive harmonic closure, although the data suggest that the sensitivity to harmonic irregularities may gradually recover over the years. These combined findings are consistent with the notion that the left IFG, as part of a larger bilateral processing network, is functionally relevant for the processing of musical syntax, and that initial deficits might recover over the years. The former observation is in keeping with a series of previous MEG (Maess et al., 2001) and fMRI studies (e.g., Koelsch et al., 2002a, 2005a; Tillmann et al., 2003, 2006) reporting bilateral fronto-temporal brain activations related to the processing of harmonic irregularities, consistently encompassing the left IFG. Future studies may be devoted to the functional relevance of the right IFG for music-syntactic processing.

4.2. *The role of the left aSTG in musical syntax processing*

Contrary to our predictions, music-syntactic processing was unimpaired in patients with left aSTG lesions. Their ERAN amplitude and scalp topography did not differ from that in healthy controls; they were able to explicitly detect harmonic irregularities, and none of these measures correlated with time since brain injury. These results can be interpreted in two ways: They may either demonstrate that the left aSTG is not involved in the processing of musical syntax, or they may reflect the compensation for, or recovery of, its function.

The first interpretation seems to conflict with the neuroimaging literature that consistently reported activations in the left or bilateral aSTG when comparing the processing of harmonically distantly and closely related items in melodies or chord sequences (Koelsch et al., 2002a, 2005a; Krumhansl, 2004; Tillmann et al., 2006). However, due to the coarse temporal resolution of fMRI, it remains unclear whether the aSTG brain activation actually reflects the processes underlying the ERAN or other effects observed in the ERP for the processing of harmonic structure. Furthermore, while fMRI identifies the brain structures that are involved in a cognitive function, lesion data determine cerebral regions that are crucial for a given task. Consequently, it may be suggested that the aSTG activations in fMRI studies do not reflect harmonic structure building as indicated by the ERAN *per se*,

[2] A floor effect is indicated by the surprisingly low hit rate of the healthy elderly control group (61.29%), making it difficult to statistically capture group differences. Healthy students (aged 20–35 years) normally exhibit an average performance of 76% correct with these stimuli (Koelsch et al., 2007). This difference between young and elderly participants relies most likely on reduced task-relevant resources like working memory or attentional capacities with increasing age, not necessarily on reduced syntactic processing resources (because young as well as elderly healthy participants show an ERAN, once more underlining the importance of testing implicit processing as in the current EEG experiment).

but represent related processes in the service of music perception, for instance melodic processing (e.g., Patterson et al., 2002), or structural integration and the processing of meaning as reflected by the N5 (Koelsch et al., 2000; Steinbeis and Koelsch, 2008).

On the other hand, the influence of compensation cannot be dismissed either, particularly when considering the left aSTG as only one, perhaps subordinate, constituent of a bilateral fronto-temporal network whose breakdown may have been compensated for by the remaining constituents of the circuit 4 years and later after brain injury (see above; Schuppert et al., 2003). Taken together, based on the present data, the function of the left aSTG in music-syntactic processing must remain suggestive in the way formulated above.

4.3. *Overlap of musical and linguistic syntax processing*

The present findings speak for a functional relevance of the left IFG for musical syntax processing, as proposed by Maess et al. (2001). This result deserves specific attention, in the context of the notion of a domain-general role of Broca's area in syntax processing, e.g., in music and in language. Previous lesion studies have established the necessity of the left IFG for syntax processing in language (for reviews, see Drai and Grodzinsky, 2006; Friederici and Kotz, 2003; Grodzinsky, 2000; Stowe et al., 2005). Notably, Friederici et al. (1998, 1999) showed that the ELAN, an ERP component thought to reflect early syntactic procedures in language (analogous to those reflected by the ERAN in music, Koelsch, 2009) crucially depends on the integrity of the left inferior frontal lobe, because lesions in this region lead to an extinction of the ELAN. Importantly, lesion sites of the patients that participated in these language studies were highly similar to those of our patients. Taken together, left inferior frontal brain damage has thus been associated with a complete extinction of the ELAN (assessed about 1.25 years after brain injury; Friederici et al., 1998, 1999), a significant reduction of the ERAN amplitude 7 months after lesion onset (patient M.S.), as well as an abnormal scalp topography of the ERAN still 4 years after left IFG injury. Consequently, the left inferior frontal lobe appears to represent a neural substrate of syntax processing that is shared by music and language (although this assumption should be further tested using a within-subject design). Such an interface may at least partly account for recently observed interactions between musical and linguistic syntax processing (Fedorenko et al., 2009; Koelsch et al., 2005b; Slevc et al., 2009; Steinbeis and Koelsch, 2008), enhanced linguistic syntax processing in musically trained subjects (Jentschke et al., 2005; Jentschke and Koelsch, 2009), or deficient music-syntactic processing in individuals with language disorders in the syntax domain (Jentschke et al., 2008; Patel et al., 2008). Moreover, this conclusion would be in line with the proposed domain-general role of left frontal brain areas in syntactic processing (Patel, 2003, 2008) specifically the processing of syntactic hierarchies in different domains (Bahlmann et al., 2009; Fadiga et al., 2009; Makuuchi et al., 2009; Friederici et al., 2006; Tettamanti and Weniger, 2006).

When considering the entire network supporting music-syntactic processing, regions of overlap between music and language may not be confined to the left IFG. Another likely candidate is the right IFG frequently associated with the processing of musical structure (Koelsch et al., 2002a, 2005a; Tillmann et al., 2003, 2006; Krumhansl, 2004) or pitch working memory (Zatorre et al., 1994), and the processing of prosody in connected speech (Friederici and Alter, 2004; Meyer et al., 2002, 2004), and also the posterior portion of the STG, which is viewed as an area of auditory-motor integration (Hickok et al., 2003). Data from imaging studies in music (Koelsch et al., 2002a, 2005a; Tillmann et al., 2006) and language (Friederici et al., 2003; Rüschemeyer et al., 2005) indeed suggest a domain-general role of posterior temporal and parietal brain areas during syntax processing, opening a field for future studies.

5. Conclusion

The present study suggests that the left IFG is relevant (but not sufficient) for the generation of the ERAN, i.e., for the processing of syntactic irregularities in rule-based harmonic sequences, complementing the vast literature on the predominance of the right frontal cortex in music processing (Koelsch et al., 2005a; Tillmann et al., 2006; Zatorre et al., 1992, 1994). Given that previous studies have established the necessity of the left inferior frontal lobe for the processing of syntactic structures in language (Davis et al., 2008; Friederici and Kotz, 2003), in space (Bahlmann et al., 2009), and lately also in action (Fazio et al., 2009), the current finding is compatible with the notion that Broca's area supports the processing of syntactic structure in a rather domain-general way.

Acknowledgements

We wish to thank Prof. Dr. D. Y. von Cramon for kindly providing the patients, Anne-Kathrin Franz for patient recruitment, Sylvia Stasch for help with data acquisition, Sebastian Seiffert for advice in lesion segmentation, Dr. Derek V. M. Ott and Dr. Christoph Preul for help with lesion localisations, and Dr. Sebastian Jentschke for helpful comments on the data analysis.

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