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Ictal fear depends on the cerebral laterality of the epileptic activity

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ABSTRACT – Glascher and Adolph (2003) proposed that both amydalae are specialized for fear, but that the right one is a fast, short, and relatively automatic fear processor, whereas the left one is more detail-oriented and perceptual-cognitive. According to this model, early ictal fear should occur more often in cases with a right temporal lobe epileptic focus. Several authors have tried to find a hemispheric specialization for ictal fear, but have not reached the power to attain a statistically significant effect of focus side. In this study, using previously published cases of unilateral epileptic focus causing early ictal symptoms of fear, we found 144 cases, of which 98 had a right hemisphere focus (68%) and 46 having left hemisphere focus (32%, $p < 0.0005$). Several control variables were assembled to verify possible alternative explanations of the main effect.

Key words: ictal fear, lateralization, hemispheric specialization, approach/avoidance

In rodents, monkeys and man, lesions of the amygdala are well known to dampen the fear response, with bilateral lesions having a major effect and unilateral lesions in either hemisphere having a significant but milder effect (Anderson and Phelps 2001, Blair *et al.* 2005, Kalin *et al.* 2001, Labar and Ledoux 1996, Vuilleumier *et al.* 2004). Zald (2005) reviewed the functional imaging literature on emotional processing by the amygdalae. His assessment of the results from the 26 studies reviewed led him to several important conclusions: 1) the two amydalae seem equally responsive to aversive stimuli or representation of aversion; 2) these stimuli need not be processed consciously; 3) the amygdalar response habituates quickly. In their review of 54 functional brain imaging studies of the amygdalae, Baas *et al.* (2004) conclude that there is usually slightly more activation of the left amygdala, and that this activation asymmetry is not particularly related to emotional valence of the stimuli or task. More recent studies have yielded similar results (Das *et al.* 2005, Noesselt *et al.* 2005, Van Reekum *et al.* 2007).

The absence of asymmetry of emotional amygdalar processing in functional imaging studies and the absence of laterality findings in much of the lesion literature could be explained by two factors. Firstly, intense experience of fear is not induced or observed in the functional imaging or lesion studies, but rather participants are required to perceive fear (in situations, faces, etc.). Likewise in the studies of lesioned humans, tests of the hypothesis of a dampened fear response use very mild stimuli, no doubt for ethical

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reasons. Secondly, these techniques might not have the temporal resolution required to identify lateralized processing, which would be related to the fast onset, emotionally significant component of true fear.

Glascher and Adolph (2003) proposed that both amygdalae are specialized for fear (a statement which is compatible with the functional imaging literature), but that the right one is a fast, brief, and relatively automatic fear processor whereas the left one is a more detail-oriented, perceptual-cognitive processor. There are several lines of evidence which can support or refute this proposal, namely functional brain imaging studies with very high temporal resolution (*e.g.* magnetoencephalography), EEG and ERP studies, studies of lesioned patients, depth electrode studies of epileptic patients, and studies of the side of the focus in ictal fear in epileptics.

Moses and colleagues (2007) reported a magnetoencephalographic study of induced (automatic) fear in normal humans. They found that the right amygdala presented a stronger and earlier response (at 270 ms), a full and significant 30 ms before the left amygdala response. Tomarken *et al.* (1990) and Wheeler *et al.* (1993) found that fear- and disgust-inspiring stimuli elicited greater right than left activation on EEG. In a study on facial musculature involved in the expression of emotions, Coan *et al.* (2001) found that the muscular contractions that form a facial expression of fear produced less left frontal activity than did those forming a happy facial expression. Patients with right amygdala lesions have a greater insensitivity to fear-invoking stimuli than patients with left amygdala lesions (Glascher and Adolph, 2003).

Gloor et *al.* (1982) noted that stimulation of the right amygdala caused more intense fear than stimulation of the left amygdala. Early ictal manifestations can reflect activation of the hemisphere in which the epileptic focus is located, especially if spiking is observed (Aghakhani *et al.* 2004). Ictal fear is one of the most common emotional manifestations associated with aura or early ictus. In temporal lobe epileptics, ictal fear is estimated to occur in 10 to 35% of cases (Devinsky *et al.* 1989). The localization of the epileptic focus leading to ictal fear is commonly in the temporal lobe. Several multiple case studies have been published on ictal fear, the majority of which did not find a lateralization effect for this epileptic manifestation (Biraben *et al.* 2001, Mintzer *et al.* 2002, Sazgar *et al.* 2003, Sengoku *et al.* 1997, Strauss *et al.* 1982), although one found a right lateralization (Bartolomei *et al.* 2002). One possible explanation is that these studies lacked power (maximum number of patients was 16). Another explanation would be a lack of control of other, potentially confounding variables.

The amygdala is considered to be the most important component of the fear response, and if there is a hemispheric specialization specifically related to the fear response, then that asymmetry should be found, at least, in the amygdalae. However, it is widely recognized that the fear response is generated in a widely distributed brain network involving the frontal lobe, the insula, the cingulate gyrus and many other systems including the hypothalamus (see Milad *et al.* 2006 for a review). Concerning epileptic manifestations of fear, clinicoscientific workup of patients suggests that amygdalar foci are indeed those most closely associated with early ictal fear (Bartolomei *et al.* 2002, Biraben *et al.* 2001, Cendes *et al.* 1994, Takeda *et al.* 2001); however, foci thought to be located in the cingulate gyrus, insula or frontal lobe, based, among other things, on depth electrode investigation, can also generate early ictal fear (Bartolomei *et al.* 2002, Biraben *et al.* 2001, Isnard *et al.* 2004, 2005). Pre-ictal or early ictal behavioural manifestations such as hallucinations (Lüders *et al.* 1998) or fear (Bartolomei *et al.* 2002) seem to occur during the period when the focal area starts to become active.

The present study aimed to determine hemispheric specialization for early ictal fear, using a larger data base and more control of potentially confounding variables, and based upon a review of published case reports. If Glascher and Adolph's (2003) proposal of hemispheric asymmetry of processing of fear is correct, then ictal fear should result more often from a right hemisphere epileptic focus than a left one. The present study proposes a review of published cases of early ictal fear. Based on Holmes and colleagues (2001), we set our inference tests at 50% probability of occurrence of right versus left foci.

Method

We sought in the literature, cases presenting early ictal anxiety, fear or panic attacks associated with a unilateral epileptic focus. We used Google scholar, pubmed and psyclit search engines with the search terms "anxiety", "fear", "panic" and "epilepsy". However, most of the published cases presenting early ictal fear could not be found using this technique because ictal fear was not the principal reason for their publication and thus, was not in the web-searchable components (key words, titles, abstracts). Our laboratory has been collecting published case reports on other, related topics for 15 years, and thus most of the cases presented in this article were found in our own filing cabinets!

The inclusion criteria were; a unilateral epileptic focus and the presence of the target symptom of interest: early ictal anxiety, fear or panic attacks. The exact deployment of the fearful behavior was not always described within the time frame of the abnormal electrical manifestations in the case reports. Such cases were not excluded because we felt it could be safely assumed that the particular behavior usually occurs during the aura or early part of the seizure (Bartolomei *et al.* 2002). It has consistently been found that the focal area determined by scalp EEG, might be, and often is, hypoperfused interictally and even ictally. However, spiking observed ictally on the scalp EEG has consistently been found to correspond to increased perfusion in the

brain area under which the spiking is observed (Kuhl *et al.* 2004, Rougier *et al.* 1999. Yoshinaga *et al.* 2004). Furthermore, the focus area of interictal spiking is highly predictive (> 90%) of the focus area of subsequent ictal spiking (Blume *et al.* 1991, Stefan *et al.* 1987). Consequently, in the present study, spikes on the scalp EEG were considered to be epileptic activation of the hemisphere, more specifically during the aura or early part of the ictus, and spiking was an inclusion criterion. In other words, abnormal, slow activity without spiking was an exclusion criterion. We included cases presenting seizures and a lesion only if the target symptom could clearly be attributable to the epileptic focus (the expression of fear had to be exclusively during the aura or early ictus and spiking had to be present on the EEG, etc.). We did not exclude cases with only interictal determination of the focus site because interictal spikes on scalp EEG are 90% predictive of findings on ictal scalp EEG (Holmes *et al.* 2000). However, because ictal EEG increases the precision of both the localization of the focus and the timing of the fearful behavior relative to scalp EEG changes, we systematically coded each case as comprising ictal determination of the focus or not, in view of control analyses to follow.

When a unilateral epileptic focus is established, it remains possible, and even quite common, that epileptic EEG abnormality may later spread to the contralateral hemisphere, *i.e.*, may secondarily "generalize". In these cases, there is an increased risk of the target manifestation (fear) occurring only when the hemisphere contralateral to the focus is paroxysmal, thus defeating the justification of the main research hypothesis. As a consequence, when the author(s) of the report described the case as "generalizing", this was noted and coded for subsequent statistical analysis. The presence of a lesion was also considered a control variable as were gender, age, hand writing preference, lobar localization and extension of the focus, intensity of fear (anxiety, fear or panic), type of fear (reactive *versus* sham), presence of cognitive symptoms, neurological symptoms, and treatment efficacy – subdivided into pharmacological *versus* surgical treatment.

These control variables were quantified and assessed statistically to make sure that: 1) the target symptom (early ictal fear) was caused by neural activation at the epileptic focus; 2) the epileptic focus was unilateral; 3) there was no concurrent explanation of the main effect of focus side.

Our exclusion criteria were; 1) bilateral foci; 2) a non-ictal target symptom; 3) the absence of an EEG; 4) an ictal functional imaging (fMRI or SPECT) indicating hyperperfusion in the hemisphere contralateral to the focus or hypoperfusion in the hemisphere of the focus.

Results

Tables 1 and *2* present the 144 cases of ictal anxiety, fear or panic caused by a unilateral epileptic focus, collected for analysis with a brief description of some of their most important features.

Of the 144 cases of ictal fear due to a unilateral epileptic focus, 98 had a right focus (68%) and 46 had a left focus (32%). Ictal fear resulted significantly more often from a right than a left focus ($Chi^2 = 18.8$, $p < 0.0005$).

Secondary analysis of potential contaminants

Each case was coded for several possible intervening variables. Gender was of interest because, in an MRI study, women have been found to present less hemispheric specialization for fear than men (Williams *et al.* 2005). Age could be a contaminating variable because juvenile patients could be less lateralized than middle-aged patients. Diffuse, bilateral cortical damage associated with normal advanced age could also bias the results. After analysis, none of these variables was found to be significantly related to focus side. Hand writing preference was important because as many as 30% of left handers show an inverted hemispheric specialization (Rasmussen and Milner 1977). Interestingly, four of the six non-right handers had a left focus whereas 33 of the 48 right handers had a right focus ($Chi^2 = 2.9$, $p = 0.087$).

Lobar localization of the focus was noteworthy because of the well established involvement of the amygdalae in the expression of fear (see the introduction). This variable was coded for each lobe separately as 1) presence of focus in a particular lobe and 2) absence. In the present sample, there were 25 cases of frontal epileptic focus (17.4%), 119 cases of temporal lobe focus (82.6%), 19 cases of parietal epileptic focus (13.2%), 11 cases of occipital epileptic focus (7.6%), and only one case of cingulate epileptic focus. None of the lobar localizations was particularly related to focus side, nor was the focus extension (determined as the number of lobes forming the epileptic focus). Multivariate prediction of focus side, by lobar localization of the focus, was also far from significance as determined with multinomial (non-parametric) multiple regression analysis ($Chi^2 = 4.0$, $p = 0.41$). The focus-side effect was significant even in cases presenting an exclusively non-temporal (thus non-amygdalar) lobe focus ($Chi^2 = 5.76$, $p = 0.016$, $n = 21$), 16 cases presenting a right hemisphere focus and five presenting a left hemisphere focus.

Other control variables were identified because of their potential effect on the accuracy of the determination of the epileptic focus. Mere interictal determination of the epileptic focus instead of a more precise ictal determination could add noise, even though abnormal interictal EEG is highly predictive of ictal EEG (Holmes *et al.* 2000). This variable was not related to focus side. Intracranial EEG is considered more precise in determining the epileptic focus than scalp EEG. Intracranial versus scalp EEG was not related to focus side. Generalizing seizure rather than a seizure remaining focal (this determination is usually based on scalp EEG) could add noise to the determination of the focus, or to the synchrony between the target

Table 1. Cases of ictal anxiety, fear or panic due to a unilateral epileptic focus.

Age of the patient	Gender	Hand preference	Locus of the epileptic focus	Ictal determination of focus side	Intracranial focus determination	Generalizing epileptic scalp EGG activity reported	Intensity of fear symptom	The ictal fear symptom is sham	Abnormal CT scan/MRI reported	Abnormal neurological exam. reported	Cognitive impairments reported	Anticonvulsants were ineffective	Lobectomy was effective	Presence of hallucination noted	Bibliographic reference
21	M		L-tp	X		X	1	X	N	N					Alajouanine *et al.* 1955
32	F		R-p	X			2	X	Y	N		Y	Y		Alemayehu *et al.* 1995
14	F		R-tp	X	X	X	4	X	Y			Y	Y		Alemayehu *et al.* 1995
1	F		R-t	X		X	2	X	Y	N		Y	Y	X	Andermann *et al.* 1999
3	F	R	R-ftp		X		3	X	Y	N	X				Bancaud *et al.* 1970
9	M	R	R-t			X	2	X	Y						Bancaud *et al.* 1989
16	F	R	R-t	X	X	X	2	X	N						Bancaud *et al.* 1994
12	F	R	L-t	X	X		2	X	N						Bancaud *et al.* 1994
4	F	R	R-t		X	X	2	X	Y						Bancaud *et al.* 1994
22	M	R	R-t	X	X	X	1	X	N					X	Bancaud *et al.* 1994
6	M	R	R-t	X	X	X	2	X	N					X	Bancaud *et al.* 1994
16	F	R	L-t	X	X		2	X	N					X	Bancaud *et al.* 1994
2	F	R	R-t	X	X	X	2	X	N					X	Bancaud *et al.* 1994
12	F	R	R-fpo	X	X	X	3	X	Y						Bartolomei *et al.* 2002
14	F		L-fo		X		2	X	Y						Bartolomei *et al.* 2005
7	F		R-ft		X		3	X	N						Bartolomei *et al.* 2005
20	M	R	R-f		X		2	X	N						Bartolomei *et al.* 2005
14	F	L	L-t	X	X		3	X	N						Biraben *et al.* 2001
12	M	L	L-t	X	X		3	X	Y						Biraben *et al.* 2001
19	F	L	R-f	X	X		3	X	Y						Biraben *et al.* 2001
12	F	L	L-t	X			3	X	Y						Biraben *et al.* 2001
37	F		R-t	X		X	3	X	Y						Biraben *et al.* 2001
7	F	R	L-tp	X	X		2				X			X	Blanke *et al.* 2005
11			L-to	X			2		N			Y	Y	X	Blume *et al.* 1991
6			R-tpo	X			2		N			Y	Y	X	Blume *et al.* 1991
68	M	R	R-ftp				2	X	N	N				X	Blume *et al.* 1992
13	F	R	R-fp	X	X		2		N			Y	Y	X	Blume *et al.* 1992
8	F		L-t	X			2		Y	N		Y	N	X	Caplan *et al.* 1991
13	M	R	L-t			X	1	X		N		N	ND		Cavenar and Haris 1979
8	M		R-f	X		X	2	X	N	N		Y	Y		Chang *et al.* 1991
27	F		L-ft			X	1	X	N			N	ND		Dantendorfer *et al.* 1995
17			R-ft				2	X							DeRomanis 1962
3	F		R-t	X	X		3	X	N	N		Y	Y		Devinsky *et al.* 1989
25	M		L-t				4	X	Y						Edlund *et al.* 1987
39	F	R	R-t				4	X		N					Edlund *et al.* 1987
14	F		R-t				2		N			Y	Y	X	Ellis 1989

Table 1 (suite).

Age of the patient	Gender	Hand preference	Locus of the epileptic focus	Ictal determination of focus side	Intracranial focus determination	Generalizing epileptic scalp EGG activity reported	Intensity of fear symptom	The ictal fear symptom is sham	Abnormal CT scan/MRI reported	Abnormal neurological exam. reported	Cognitive impairments reported	Anticonvulsants were ineffective	Lobectomy was effective	Presence of hallucination noted	Bibliographic reference
10	M	R	R-t			X	2			N				X	Epstein 1979
30	M	R	R-t	X		X	2	X	N	N	X	Y	Y		Fiol 1988
83	F		R-t				2	X	Y	N				X	Forster 1978
5	F		R-o	X			1	X							Gallet *et al.* 1986
8	F		L-o			X	2			N		N	ND	X	Gastaut 1982
23	F		L-t			X	2	X				N	ND		Gauthier-Smith 1980
32	M	R	R-t	X			2		N	N		N	ND	X	Gillig *et al.* 1988
32	M		R-t	X	X		1								Gloor *et al.* 1982
19	F		R-t	X			3	X						X	Gloor *et al.* 1982
29	F	L	R-ft			X	2		N					X	Hansen and Brodtkorb 2003
10	M	R	R-p				2	X		Y	X	Y	N		Hecaen *et al.* 1956
3	F	R	R-tp	X		X	3	X	N	N		Y	Y		Henriksen 1973
3	M		R-t				3	X							Hermann and Chhbria 1980
3	M		R-t			X	3	X							Hermann and Chhbria 1980
37	M		R-t				2	X	Y	Y				X	Hierons and Saunders 1966
5	M		L-ft	X			3		Y					X	Huppertz *et al.* 2002
14	F		R-t				2		N	N					Ide *et al.* 2000
6	M		L-t	X			2	X	N	N		N	ND		Inthaler *et al.* 1991
23	F	R	R-tp				1	X						X	Kamiya and Okamoto 1982
20	F	R	L-t	X	X		2		Y	N	X	Y	Y	X	Kanemoto 1997
66	F		R-p				4	X	Y	N					Kellner *et al.* 1996
14	F		R-ft	X			4	X	N			N	ND		Laidlaw and Khin Maung 1993
17	F	R	L-t	X		X	4		Y			N	ND	X	Lambert *et al.* 2002
8	M	R	R-f	X			3		Y		X	Y	Y	X	La Vega-Talbot *et al.* 2006
34	F		R-t				1	X	N	N	X				Lawrie *et al.* 1993
57	F		R-po	X			3		N		X			X	Leker *et al.* 1996
54	F	R	R-t	X			2	X	Y						Loddenkemper *et al.* 2004
49	M	R	L-t	X			1	X	Y						Loddenkemper *et al.* 2004
53	F	R	R-t	X		X	2	X	Y						Loddenkemper *et al.* 2004
4	M		L-ft	X	X		3	X		N		Y	Y		Lombroso 2000
32	F	R	R-t	X		X	2	X	Y						Luciano *et al.* 1993
22	M		R-t	X			3	X	N					X	Macrae 1954
10	F		R-t	X	X	X	2	X	N	N		Y	Y		McLachlan and Blume 1980
12	F	R	L-t	X			4	X	N	N		N	ND		McNamara and Fogel 1990
37	F	R	R-t	X			2	X		N					Mesulam 1981
33	F	R	L-t	X			1	X							Mesulam 1981
38	M	R	R-t				3	X	Y	Y					Mesulam 1981

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27	F	R	R-f	X		X	2	X	N					X	Mesulam 1981
			L-t	X			2	X	N						Mintzer and Lopez 2002
			L-t	X			2	X	N						Mintzer and Lopez 2002
			L-t	X	X		2	X	Y						Mintzer and Lopez 2002
			R-t	X	X		2	X	Y						Mintzer and Lopez 2002
			R-t	X	X		2	X	Y						Mintzer and Lopez 2002
			R-t	X			2	X	Y						Mintzer and Lopez 2002
			L-f	X			2	X	Y						Mintzer and Lopez 2002
			L-t	X			2	X	Y						Mintzer and Lopez 2002
24	M		R-t	X	X	X	3	X		N		Y	Y	X	Montplaisir *et al.* 1981
24	F		L-t			X	1	X							Oana 1998
50	M		L-t			X	2							X	Onuma 2000
12	F		L-t	X			2	X	N			N	ND		Pegna *et al.* 1999
45	F		R-t				2	X	N	N		N	ND		Pilo 1990
40	M	R	R-t	X		X	2	X	N	N					Ramchandani and Riggio 1992
10	F		R-t	X			2		N	N					Reami *et al.* 1991
40	F		L-t	X			3	X	N	N		N	ND		Reid *et al.* 1988
12	F	R	R-t			X	3					Y	Y	X	Remillard *et al.* 1983
4	M	R	R-t	X		X	2	X	Y			Y	Y	X	Reutens *et al.* 1997
48	M		R-t				2	X						X	Roth and Harper 1962
56	F	R	L-t	X			4	X	N	N		N	ND		Saegusa *et al.* 2004
7	F		R-to				2		N		X	Y	Y	X	Salanova *et al.* 1992
15			R-to				2		Y			Y	Y	X	Salanova *et al.* 1992
16	F		R-t	X		X	2	X	Y			Y	Y		Sazgar *et al.* 2003
16	M		R-t	X			4	X	Y			N	ND		Sazgar *et al.* 2003
20	F		R-t	X			2	X	Y						Sazgar *et al.* 2003
9	F		R-t	X			4	X	Y			Y	Y		Sazgar *et al.* 2003
20	F		R-ft	X			2	X	Y			Y	Y	X	Sazgar *et al.* 2003
17	M		R-t				2	X							Senanayake 1990
19	F		R-tp				2								Senanayake 1990
17	F		R-t				2							X	Senanayake 1990
15	M		R-t				2							X	Senanayake 1990
18	M		R-t				2							X	Senanayake 1990
18	M		R-tp				2							X	Senanayake 1990
17	F		R-t				2							X	Senanayake 1990
14	M		R	X			2	X							Sengoku *et al.* 1997
35	F		R	X			2	X						X	Sengoku *et al.* 1997
24	M		R	X			2	X						X	Sengoku *et al.* 1997
9	M		R				2	X						X	Sengoku *et al.* 1997
9	M	R	L-ft	X		X	2	X	N	N		N	ND		Shuper and Goldberg-Stern 2004
7	F		R-t				2					N	ND		Snyder 1958

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Age of the patient	Gender	Hand preference	Locus of the epileptic focus	Ictal determination of focus side	Intracranial focus determination	Generalizing epileptic scalp EGG activity reported	Intensity of fear symptom	The ictal fear symptom is sham	Abnormal CT scan/MRI reported	Abnormal neurological exam. reported	Cognitive impairments reported	Anticonvulsants were ineffective	Lobectomy was effective	Presence of hallucination noted	Bibliographic reference
9	M		R-p				1	X				N	ND		Snyder 1958
83	M	L	L-to	X			2		Y	Y				X	Spatt and Mamoli 2000
25	F	R	L-t			X	4	X	N	N		N	ND	X	Spitz 1991
53	F		L-t				2	X							Stefan *et al.* 2003
42	F		R-t				2	X							Stefan *et al.* 2003
43	F		R-t				2		Y			Y	Y	X	Stefan *et al.* 2004
36	F	R	L-t	X			4	X			X	N	ND		Stern and Murray 1984
14	F	R	R-t	X	X		3		Y			Y	N	X	Stevens 1990
25	F	R	L-t		X		2	X		N		Y	Y	X	Takeda *et al.* 2001
21	F	R	R-o	X			3	X	N	N	X	N	ND	X	Thomas *et al.* 1991
61	M		L-t				4	X	Y	Y					Tucker *et al.* 1986
19	F		R-t				4	X	N	N		N	ND		Tucker *et al.* 1986
16	M		R-t			X	1	X	N	N		N	ND	X	Valli *et al.* 1999
10	M		R-c				2	X	N	N		N	ND		Vetrugno *et al.* 2005
42	M		R-t				4	X	Y			N	ND		Volkow *et al.* 1986
4	M		L-p	X		X	3	X	N	N	X	N	ND		Wakai *et al.* 1994
31	M	R	R-ft				4		N	N		N	ND		Warneke *et al.* 1976
17	F		L-t			X	2	X	Y			Y	Y		Weil 1956
32	F		R-t				2	X	Y	Y					Weil 1956
19	F	R	R-t			X	4	X		N					Weilburg *et al.* 1987
35	M	R	R-ft	X			4	X	Y			N	ND	X	Weilburg *et al.* 1993
16	F	R	R-t	X	X		3		N			Y	Y	X	Weingarten *et al.* 1977
12	F		R-t	X	X		1	X	Y	N		N	ND	X	Wieser 1980
11	F		L-t				2	X	N						Williams 1956
15	F		R-t				2	X							Williams 1956
19	F		R-t				2		N					X	Williams 1956
			L-f				2	X	N						Williamson *et al.* 1985
9	F	R	L-ft	X			3	X	Y		X	Y	Y		Yamada *et al.* 2005
12	F	R	L-t	X		X	3	X	N	N					Zappoli *et al.* 1983
9	F		R-f				3		N	N		N	ND	X	Zwijnenburg *et al.* 2002

M: male; F: female; R: right; L: left; f: frontal; p: parietal; t: temporal; o: occipital; c: cingulate; 1: anxiety; 2: fear; 3: intense fear, terror; 4: panic attack; Y: yes; N: no; ND: not done.

symptom and the unilateral epileptic activity on EEG. The "generalizing" nature of the seizure was often hard to determine with the information contained in the articles. Only cases reported as "generalizing" by the author(s) were coded as generalizing (n = 40), and only cases specified by the author(s) as non-generalizing were coded as such (n = 11). There were 51 cases thus characterizable. This variable (generalizing versus non-generalizing), fell far short of significantly modulating focus side ($Chi^2 = 0.23$, $p = 0.63$).

The presence of a lesion (always on the side of the focus in the present data base) could bias the main finding by decreasing the probability of the target symptom resulting from the ictal activity. A positive neurological examination showing signs of chronic hemianopia, loss of sensation in one hemibody, etc., is a potential manifestation of the

Table 2. Chi^2 analyses of frequencies of patients in relatively more methodologically "sound" subgroups.

Subgroup	n	Proportion of RH foci	Chi^2	p
Cases seizure-free and without fear after lobectomy	28	79%	9.1	0.002
Cases with no evidence reported of generalization	104	70%	17.0	0.000
Cases without findings or mention of cognitive deficits	131	69%	18.3	0.000
Cases with depth electrode investigation	31	68%	3.9	0.048
Cases with a normal neurological examination	44	66%	4.5	0.035
Cases not attributing the fear to a specific external stimulus or to another internal state (e.g., hallucination)	108	66%	10.7	0.001
Cases with intense fear or panic	47	66%	4.8	0.029
Cases with normal imaging	54	67%	6.0	0.014
Cases with an ictal determination of the focus site	81	62%	4.5	0.035

presence of a lesion and could thus similarly bias the main result. The presence of cognitive symptoms could also be representative of chronic cerebral damage. In principle, these three variables are extremely important because lesions and activational foci are expected to have opposite effects on the target symptom. These variables were not significantly related to focus side. Chronic psychiatric comorbidity could also bias the result because of a potential fudging effect on the hemispherically-specialized functioning of the brain. This variable was not related to focus side.

Treatment efficacy was also of interest because a lack of efficacy of anticonvulsants leaves open the eventuality that the target symptom is not a consequence of the epileptic activity. This variable (n = 60) was related to focus side ($Chi^2 = 4.35$, $p = 0.037$). The treatment-resistant subgroup had a higher proportion of right hemisphere foci (77%) than did the subgroup of good responders (48%). This appears counter-intuitive at first glance, but becomes understandable when one considers that of the 29 anticonvulsant-resistant patients, 28 were subsequently lobectomized -after which convulsions and fear symptoms disappeared. It remains to be explained why the 31 cases treated effectively with anticonvulsants were at chance for focus side. One explanation could consist of the following: cases effectively treated with anticonvulsants could have been published earlier -when clinical investigation of epilepsy was less precise. This indeed tended to be the case: the correlation between (efficacy/inefficacy of anticonvulsants and date of publication was R(eta) = 0.8, p = 0.067, with the effectively treated cases having been published earlier. We have no explanation of this association, except perhaps sampling artefact. However, the association itself does explain the absence of a focus side effect in the effectively treated cases. Treatment efficacy as a whole (good *versus* bad outcome, whether the patient was treated with anticonvulsants only or with lobectomy) was unrelated to focus side.

The intensity of the ictal fear manifestation was also analyzed. This variable was coded for increasing intensity as 1) anxiety (n = 14); 2) fear (n = 83); 3) intense fear or terror (n = 29); 4) panic attacks (n = 18), and was not statistically related to focus side.

Presence of an event (hallucination or fear-inducing objective situation) causing the ictal fear could add noise to the determination of hemispheric specialization of ictal fear. Indeed, such an event could arise from a focus in the left hemisphere and serendipitously cause the patient to report a feeling of fear. In this study, there were 108 patients in whom it seemed clear that the fear was not precipitated by any particular event (hallucination, social situation, etc.). These patients were termed cases of "sham fear". There were 23 patients who expressed fear as a direct consequence of a hallucination. A further six cases expressed fear of an external event such as a crowd, fear of the ictus itself, etc. These 29 patients were termed cases of "reactive fear". The Chi^2 test of the interaction between type of fear (sham/reactive) and focus side was far from significance (n = 137).

Among the "sham fear" group, 26 patients had ictal hallucinations which they did not consider fearful. A test of interaction between side of focus and type of hallucination (benign/fear inspiring) was carried out on the entire cohort of patients with ictal hallucination (n = 49). That interaction fell short of significance ($Chi^2 = 3.79$, $p = 0.052$). The trend was for the "benign" cases to more often present a right focus.

Best case analysis of the focus side effect

Although only one control variable significantly explained the focus side effect (anticonvulsant therapy efficacy), the large size of the sample reviewed here allows for a different statistical test of the focus-side effect. Various analyses can be carried out on subsets of cases presenting less contaminated or less complicated profiles or simply a better quality of the determination of the side of focus or of the supposed timing (early ictal) of the manifestation of fear. To this end we carried out a series of analyses, of which we report in *table 2*, those that comprised sufficiently large samples.

The intersections between these subsamples did not yield an increase in the right hemisphere focus prevalence effect.

Discussion

The results of this investigation strongly support Glascher and Adolph's (2003) proposal of different contributions of each hemisphere to the processing involved in fear. As a whole, the numerous analyses carried out in the present study all support a right hemisphere focus prevalence of 62 to 79%, each estimate except one, being statistically significant. The lower end of the estimate range can easily be explained by noise anywhere along the inferential steps upon which rest the oriented hypothesis. Examples of such errors would be errors of assignation of the fear-producing focus to the correct hemisphere or errors of assignation of the fear symptoms to the focus. In addition, we could have made erroneous inferences of neural activation of the focus during the fear symptom in some cases. That determination of side of focus is an imperfect art is attested to by: 1) inconsistency of focus determination in repeated scalp recordings (Yoshinaga *et al.* 2004); 2) incongruence of metabolic imaging, functional imaging, surface and depth EEG (Stefan *et al.* 1987); 3) persistence of seizures in lobectomized patients, at least 16%, in outcome studies (see McIntosh *et al.* 2001 for a meta-analysis of the outcome studies) and 11% in the present data set. That assignation of fear symptoms can be incorrectly assigned to the epileptic aura or ictus is suggested by the facts that; 1) there are cases in the literature (excluded from the present review) in whom fear symptoms were initially thought to be ictal (including those based on EEG), and in whom, after in depth investigation, those symptoms were no longer thought to be related to the actual ictus (Alsaadi and Vinter Marquez 2005); 2) persistence of seizures in patients treated with anticonvulsants (McCorrya and Chadwicka 2004) (48% in the present set of cases). Finally, although ictal spiking is correlated with increased perfusion as measured by SPECT and fMRI, the correlation is not perfect (Kuhl *et al.* 2004, Rougier *et al.* 1999, Yoshinaga *et al.* 2004). In short, in our judgment, considering the numerous technical and methodological sources of error in estimating hemispheric specialization using ictal phenomena, the right focus prevalence observed here is remarkably high.

Ictal fear probably consists essentially of a primitive (non-perceptual, non-cognitive), fast-onset, highly transient, activation of the right amygdala and/or its relevant surrounding network in the right hemisphere, as proposed by Glascher and Adolph (2003). The briefness of the phenomenon would explain why cases with rapidly diffusing ictal activity would manifest the right hemisphere focus prevalence nearly as much as those cases with a focus limited to one hemisphere: the fear is generated in the earliest moment of the ictus, while later components of the ictus are unrelated to the symptoms of fear. This account also explains why lesion studies and functional imaging studies of the fear response have typically not observed hemispheric asymmetry. This study could not establish that the right hemisphere prevalence of fear-inducing foci is significantly modulated by any of the following variables: ictal *versus* interictal determination of the focus, inclusion or not of intracranial investigation of the epilepsy, lobar location or extension of the focus, successful *versus* unsuccessful surgical treatment, neurological or cognitive deficits, gender, age, or intensity of the fear.

What remains to be done is to apply an appropriate imaging technique (as in Moses *et al.* 2007) to both baseline resting frontal asymmetry (individual differences in temperament) and specific amygdalar response patterns to induced fear, in real time. After all, temperament, or behavioral style ought to consist of stable, complex, distributed networks of brain systems (beyond the frontal EEG in the alpha band), interacting with a variety of events occurring in the environment. □

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