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Emotional reactivity and neuropsychological assessment in ten cases of ablated temporal lobe tumors

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ABSTRACT

Aim: Emotional reactivity (ER) and neuropsychological (Np) status were investigated in a case series of patients that underwent a surgical ablation of temporal lobe tumors (TLT).

Methods: Ten patients (6 females, 4 males) who had undergone surgical ablation of TLT and 10 controls matched for age and gender were recruited. ER was tested using International Affective Picture System (IAPS); Clinical Global Impression evaluated behavioral disturbances, affective symptoms and emotional involvement/reaction to the pathological condition. Np assessment was carried out using well established measures; anatomopathological, neuroradiological and clinical data were also collected.

Results: Patients showed more positive valence and higher arousal upon viewing neutral images compared to controls. To a lesser extent, the same pattern was observed with socially pleasant images. No affective symptoms were observed at CGI-BP evaluation. Arousal to negative images, with or without social involvement, revealed a moderately strong relationship with the patient's subjective emotional appraisal of the consequences of the illness.

Conclusion: We observed an optimistic emotional environment perception and a detachment from the pathological condition related to lowered emotional involvement and reactivity to negative emotional cues. This pattern of emotional reactivity leads to the hypothesis of an effective coping strategy development to a severe pathological condition.

1. Introduction

Emotional reactivity can be considered an early rapidly-evoked response to an emotionally salient stimulus, the starting point of the emotional experience and regulation (Nock, Wedig, Holmberg, & Hooley, 2008; Thompson, 1994). Emotional regulation after the evaluation and monitoring of emotional reactions, leads to subsequent modifications in the perception of feeling behavior as part of the individual's coping style, eliciting adaptive responses. Emotional dysregulation impairs functioning and quality of life with a significant role in psychopathology, chiefly in mood disorders (Morris, Bylsma, & Rottenberg, 2009; Rottenberg & Johnson, 2007).

Patients with highly malignant and rapidly progressive temporal lobe tumors (TLT) face an illness that severely challenges their survival, so that they frequently experience mood and emotional status alterations that affect their quality of life.

These aspects not only depend on patients' premorbid personality, but are also likely to be conditioned by the anatomical and pathological features of the TLT. As a matter of fact, the tumor itself, as well as the subsequent surgical treatment, provokes neurocognitive impairment influencing quality of life and survival (Johnson, Sawyer, Meyers, O'Neill, & Wefel, 2012; Meyers, Hess, Yung, & Levin, 2000), and interacting with mood and emotional status (Chelune, 1991; Duffau et al., 2000; Rausch, 1985).

The interactions among emotional processing, cognitive impairment and behavioral responses are not however completely understood

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Table 1
Demographic and clinical data.

Case number	gender	age	side affected	histologic examination	grade	residual	insula	hypothalamus	hippocampus	thalamus	cingulate cortex	amygdala	history	Neurogical status
1	F	69	Left	Glioblastoma	4	No	I	Ni	I	Ni	Ni	I	Amnesia	Amnesia
2	M	51	Left	Glioblastoma	4	Yes	I	I	I	I	Ni	I	Seizure	Asymptomatic
3	M	32	Left	Astrocytoma	2	No	Ni	Ni	I	Ni	Ni	I	Seizure	Asymptomatic
4	F	43	Right	Astrocytoma	3	Yes	I	Ni	I	Ni	Ni	I	Seizure	Seizure
5	M	31	Right	Oligodendroglioma	2	No	I	Ni	Ni	Ni	Ni	Ni	Seizure	Asymptomatic
6	M	58	Right	Glioblastoma	4	Yes	I	Ni	I	Ni	Ni	I	Dysarthria, dizziness, ataxia	Asymptomatic
7	M	65	Left	Gliosarcoma	4	No	I	Ni	I	Ni	Ni	I	Asymptomatic	Asymptomatic
8	M	56	Left	Oligodendroglioma	3	No	Ni	Ni	Ni	Ni	Ni	Ni	Seizure	Asymptomatic
9	F	60	Right	Glioblastoma	4	Yes	I	Ni	Ni	Ni	Ni	Ni	Facial palsy	Facial palsy
10	F	69	Right	Glioblastoma	4	Yes	I	Ni	Ni	I	I	Ni	Aphasia, facial palsy	Aphasia, facial palsy

I : involved. **Ni**: not involved.

(Ledoux, 2002).

The neural underpinnings of emotional reactivity and regulation have been recently studied, particularly by using neuroimaging techniques (Kohn et al., 2014) suggesting that the site and the side of the lesion affecting structures belonging to the limbic system is crucial (Lindquist, Wager, Kober, Bliss-Moreau, & Feldman Barret, 2012). Right temporal lobectomy has been shown to cause alterations in emotional reactivity **(**Morris, Bowers, Williamson, & Heilman, 2017**).** The electrical stimulation of specific brain areas and the evidence provided by the results of cerebral lesions allow to hypothesize the role played by the main limbic areas. Subcortical structures such as hypothalamus seem to be relevant in the arousal activation provoked by emotional stimuli. Neocortical structures, primarily insula, are thought to act as tonic controller and emotional reactivity modulator, conferring an emotive valence to the stimuli (Calder, Lawrence, & Young, 2001).

Emotionally salient stimuli confer a relevant evolutionary contribution to the subject survival capturing attention and being processed in terms of arousal (i.e. intensity of evoked emotion) and valence (i.e. degree of pleasantness) (Ni et al., 2011). The insula, a brain structure involved in cognitive, affective and regulatory functions which include enteroceptive awareness together with emotional responses and empathic processes, is sensitive to prominent events. Its function lies in signaling such events for additional processing and initiating the appropriate behavior. The "salience network", formed by the anterior insula and the anterior cingulated cortex segregates the most relevant internal and external stimuli in order to guide behavior (Menon & Uddin, 2010). Human anterior insular cortex plays a part in emotional awareness, in the conscious experience of emotions as well as in the understanding of the emotional state of others (Gu, Hof, Friston, & Fan, 2013).

Among the corticolimbic structures that are responsible for emotion regulation, the amygdala plays a central role in the network, being responsible for appraisal of emotional stimuli. Negative emotional pictures seem to activate the amygdala, lateral prefrontal cortex and occipital-temporal areas while positive pictures provoke activation of the left nucleus accumbens (Meseguer et al., 2007). Increased connectivity between the insula and the right amygdala may generate excessive positive feedback, in that both regions are involved in the appraisal of emotional stimuli. Emotionally salient pictures have been shown to activate an emotional network, including amygdala, medial prefrontal cortex, orbitofrontal cortex, and occipito-temporal areas. The amygdala is actively involved in the processing and transmission of information concerning the valence (positive or negative) of the stimuli in order to adapt behavior. Both organic and functional alterations of the network engaging the amygdala in the elaboration of a suitable behavior through the emotional processing can provoke pathological responses (Janak & Tye, 2015).

On the basis of these considerations we used the International Affective Picture System (IAPS) paradigm (Lang, Bradley, & Cuthbert, 1999), a widely used measure of emotional reactivity, to obtain an emotion-processing measure that we could relate to the neuropsychological status and the behavioral regulation (Ciuffini, Stratta, & Marrelli, 2018).

The aim is the study of the interactions among emotional processing, neurocognitive impairment and behavioral responses in a series of cases of patients that had undergone surgical ablation of temporal lobe tumors.

2. Methods

2.1. Subjects

Patients affected by surgically ablated TLT, consecutively referring to the Clinical Neurophysiology Unit were taken into consideration for the study.

Patients with a history of psychiatric symptoms previous or

coexisting with the onset of tumor and unable to provide an informed consent were excluded from the study. For this purpose, a careful evaluation was made by a senior psychiatrist (PS), on the basis of more than thirty years of clinical experience, by means of the clinical approach, quantified using the Clinical Global Impression Scale (CGI) severity of illness.

Ten right-handed patients (4 females, 6 males, mean age 53.4 years SD 14) were eventually admitted to the study. 10 healthy subjects were recruited as healthy controls among those accompanying the outpatients (6 females and 4 males) matched for age (mean age 48.7, sd 11.2) with the clinical sample.

Demographic and clinical data of the patients are shown in Table 1. Informed consent was obtained from all participants. The research procedure was reviewed and approved by the ethical committee of the University of L'Aquila (Italy) (Institutional Review Board code 14249/9.5.2016).

2.2. Clinical assessment

The Clinical Global Impression (CGI) – Bipolar Version (Spearing, Post, Leverich, Brandt, & Nolen, 1997) severity was used to evaluate behavioral disturbances and affective symptoms. The Clinical Global Impression (CGI) (Guy, 1976) was also used to evaluate a nuclear symptom a priori defined as emotional involvement and reaction to the pathological condition along a 1–7 Likert scale: 1 physiological adjustment to the index disorder - 7 extreme emotional disengagement and lack of insight.

2.3. Emotional reactivity

The assessment was carried out using the International Affective Picture System (IAPS) paradigm (Lang et al., 1999; Lang, 1980; Lang, Bradley, & Cuthbert, 1997), which represents the most widely used instrument to measure emotional reactivity. It consists in a set of static images based on a dimensional model of emotion (Jayaro, de la Vega, D´ıaz-Mars´a, Montes, & Carrasco, 2008).

Ninety color pictures were chosen from IAPS (Lang, Bradley, & Cuthbert, 2005) depicting events with different affective valence, i.e. unpleasant, pleasant and neutral events. Unpleasant and pleasant events were also distinguished in pictures involving or not involving social human conditions: e.g. mother-child or familial interactions for pleasant pictures or outcomes of violence for the negative ones with social involvement; landscape scenes or flowers for pleasant pictures or snakes, contamination or pollution for the negative ones without social involvement. Neutral images consisted of pictures of furniture or appliances. For each of the five categories 18 images were shown.

The emotional evaluation of pictures was rated on the basis of valence and arousal. The valence rating instructions were "Rate how unpleasant or pleasant the image makes you feel using a 1–9 Self-Assessment Manikin (SAM) valence scale (1 = very unpleasant, 5 = neutral, 9 = very pleasant)". The arousal rating instructions were "Rate how emotionally intense or arousing the image makes you feel using a 1–9 scale SAM arousal scale (1 = calm, 5 = somewhat aroused, 9 = excited)".

The SAM valence scale consisted of a cartoon-type figure in which nine human emotional expressions, ranging from smiling and happy to frowning and unhappy, were presented. The SAM arousal consisted of another cartoon-type figure with nine expressions ranging from calm and relaxed to excited and wide-eyed.

Stimuli presentation and response recording were managed using custom software (Superlab 4.0 for Windows).

The subjects were tested individually in a dimly lit room. They were seated in front of a 15-inch computer monitor at a distance of 50 cm. During the test session, subjects were instructed that a series of 90 trials would be presented, and that for each trial they would be asked to rate the valence and arousal of that picture.

Trials started with a 2 s. full-screen presentation of one picture. The order of neutral, pleasant and unpleasant with or without social involvement picture presentation was randomized for each subject. Then, after a 1 s. black screen, a display containing a smaller version of the same picture (located in the upper part) and the SAM valence scale (located in the lower part) was presented (Bradley and Lang, 1994; Lang, 1980).

This display remained visible until the participant's response, or for 3 s. After the participants' valence rating, another display was presented in which the SAM valence scale was substituted by the SAM arousal scale. Similarly, the display remained visible until the participant responded or for 3 s. Both valence and arousal ratings were made on a nine-point scale by pressing one of the keys of the PC keyboard labeled from 1 to 9.

If the subjects did not respond within 3 s, an omission was recorded. Those who showed more than 5% of omitted responses were excluded from the two samples and not considered in the analysis. No subjects in our study were excluded for this reason.

2.4. Neuropsychological assessment

All the patients underwent a NP assessment in order to investigate the global cognitive status, memory, language, executive functions and apraxia. The battery included Mini Mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975), Rey Auditory Verbal Learning Test (RAVLT) (Hays, Emmons, & Lawson, 1993), Benton Visual Retention Test (BVRT) (Benton, 1945), Raven's Progressive Matrices (RPM) (Raven, 1938), Verbal Fluency Test (VFT) (Lezak, 1995), Sentence Construction Test (SCT) (Kaszniack, Garron, Jacob, Bergen, & Huckan, 1979), Digit Span Test (DST) (Blankenship, 1938), Weigl Test (WT) (Weigl, 1941), Scrawl Discrimination Test (SDT) (Spinnler & Tognoni, 1987) and Apraxia Test (AT) (De Renzi, 1989). MMSE and RPM scores were corrected by age and educational level (Table 2).

2.5. Statistical analysis

To avoid the normality issues in the data set non-parametric statistic was chosen. Mann-Whitney *U* test was used for between group comparisons of IAPS indexes. Correlation analysis between IAPS and Np assessment was performed using non parametric Spearman rho. SPSS Statistics for Windows, version 24 (IBM Corp., Armonk, NY, USA) was used for the statistical analysis.

3. Results

In five of the subjects the left temporal lobe was affected while in the other five the right one. The earliest referred symptom reported by five patients was a seizure while three reported a neurological deficit (case 6: dysarthria and ataxia; case 9: facial palsy, case 10: aphasia and facial palsy). Case 1 showed an evident clinical Np impairment and one patient (case 7) was asymptomatic. The neurological examination at the moment of the evaluation for the study showed a neurological deficit in three patients (case 1: amnesia; case 9: facial palsy, case 10 aphasia, facial palsy). Six patients were treated with chemio/radiation therapy following assessment. One patient continued to present seizures and was given antiepileptic therapy (levetiracetam 2000 mg/die). The remaining patients were asymptomatic and did not undergo antiepileptic or psychopharmacological treatment.

All patients underwent post-surgical brain Magnetic Resonance Imaging (MRI) performed with 3 T scanner. We acquired multiplanar T1, T2, DWI and Flair sequences; T1 sequences were repeated after intravenous administration of contrast medium. At the moment of the evaluation 5/10 had a residual of the disease defined as no residual enhancement, near-total resection as having a thin rim enhancement of the resection cavity only, and subtotal resection as having a residual nodular enhancement.

Table 2
Overview of the neurocognitive assessment.

Test	Description	Score range
MMSE	To measure cognitive impairment	0–30 age and educational level corrected
RAVLT	To measure short-term auditory verbal memory, rate of learning, learning strategies, retroactive and proactive interference, presence of confabulation and confusion in memory processes	0–75
BVRT	To measure visual memory, perceptual processing, encoding, storage and retrieval	0–22
RPM	Intelligence test	0–36 age and educational level corrected
VFT	To measure verbal fluency both phonetic and semantic	n. of elements in 60 s
Letter		
Cathegory		
SGT	To measure grammatical and syntactic skills	n. of elements in 10 min
DST	To measure short-term memory	0–7
Forward		0–7
Backward		
WT	To measure executive functions (selection, crop rotation and categorization of stimuli)	0–15
SDT	To measure the categorical thinking	0–15
AT	To measure ideational and ideomotor apraxia	0–6

MMSE: Mini Mental State Examination, **RAVLT**: Rey Auditory Verbal Learning Test, **BVRT**: Benton Visual Retention Test, **RPM**: Raven Progressive Matrices, **VFT**: Verbal Fluency Test, **SCT**: Sentences Generation Test, **DST**: Digit Span Test, **WT**: Weigl Test, **SDT**: Scrawls Discrimination Test, **AT**: Apraxia Test.

On the basis of MRI, the main structures thought to be relevant for the purpose of this study were coded as involved or not involved. Insula was involved in 8/10 patients, amygdala in six, hypothalamus in one, thalamus in two, cingulated cortex in one, hippocampus in six. The histologic examination identified five glioblastomas, two astrocytomas, two oligodendrogliomas and one gliosarcoma. Six tumors were at grade IV of the WHO classification of brain tumors, two at grade III and two at grade II (Kleihues, Burger, & Scheithauer, 1993).

The neurological examination at the moment of the evaluation for the study showed a neurological deficit in three patients (case 1: amnesia; case 9: facial palsy, case 10 aphasia, facial palsy). Six patients (case 1, 2, 6, 7, 9, 10) were treated with chemio/radiation therapy following assessment. One patient (case 4) continued to present seizures and was given antiepileptic therapy (levetiracetam 2000 mg/die). The remaining patients were asymptomatic and did not undergo antiepileptic treatment.

Preliminary comparisons of IAPS scores between right and left temporal lobe tumor patients showed no differences, the two groups were therefore collapsed. The between-group comparisons versus controls showed higher mean arousal and valence ratings for neutral pictures in the clinical sample (Mann-Whitney U 5.00 and 3.00 respectively, $p < .0005$). The valence for pleasant pictures with social involvement was significantly higher for the clinical group than controls (Mann-Whitney U 20.00, $p < .05$); a trend toward significance was instead found for the arousal ($p < .10$) (Table 3).

The IAPS arousal reached the statistical significance for correlations between unpleasant images and MMSE and RAVTL (rho = .73 and 0.76), as well as socially unpleasant images and SGT (rho = .65), DST forward (rho = .70) and AT (rho = -.70).

The IAPS valence reached the statistical significance for correlations between neutral images and AT (rho = -0.70), socially pleasant IAPS images and SGT (rho = .83), DST forward (rho = .90), DST backward (rho = .64), SDT (rho = .81) and AT (rho = -0.70) (Table 4).

As regards psychopathological evaluation, no classical affective symptoms have been observed, all the patients having CGI-BP evaluations within 1–2 range (normal, not ill – minimally ill). As regards CGI evaluation of emotional involvement and reaction to the pathological condition, moderately strong correlations with arousal of unpleasant and socially unpleasant images were observed, although, statistical significance was not reached due to limited sample size (rho = -0.56 and rho = -.54, $p < .10$: i.e. the higher emotional disengagement, the lower arousal from emotionally unpleasant images). No significant correlations were found with the Np evaluation.

4. Discussion

To the best of our knowledge this is the first study examining both ER and Np status in patients with ablation of TLT related to the clinical

Table 3
Mean (± SD) picture arousal ratings, as a function of group (10 individuals with tumors vs. 10 gender and age matched healthy controls) and pictures valence (socially pleasant, pleasant, neutral, unpleasant and socially unpleasant).

Arousal					
	socially pleasant	*pleasant*	*neutral*	*unpleasant*	*socially unpleasant*
Tumor group	7.10 ± 2.30	6.84 ± 1.49	5.04 ± 1.14	4.75 ± 1.38	3.78 ± 1.34
Control group	6.50 ± 1.35	6.78 ± 1.27	2.70 ± .69	4.66 ± 1.54	4.33 ± 1.33
Mann-Whitney U	26.50	45.50	5.00	44.50	41.00
p	NS	NS	< .0005	NS	NS
Valence					
	socially pleasant	*pleasant*	*neutral*	*unpleasant*	*socially unpleasant*
Tumor group	7.48 ± 2.18	7.51 ± .84	5.52 ± .96	4.02 ± 1.79	3.25 ± 1.35
Control group	6.51 ± 1.30	6.79 ± 1.24	3.27 ± .89	3.64 ± 1.14	3.16 ± 1.11
Mann-Whitney U	20.00	31.00	3.00	43.00	46.50
p	< .05	NS	< .0005	NS	NS

Table 4
Spearman rho correlations among IAPS indexes and cognitive performances in individuals with ablated temporal lobe tumors (values are reported as mean ± SD).

	MMSE 24.10 ± 5.74	RAVLT 16.50 ± 13.49	BVRT 18.10 ± 4.30	RPM 25.20 ± 9.52	VFT Letter 17.90 ± 12.18	VFT category 36.20 ± 21.52	SGT 3.40 ± 2.01	DST forward 9.10 ± 4.17	DST backward 6.40 ± 4.90	WT 11.40 ± 4.06	SDT 30.20 ± 1.81	AT 1.20 ± .42
Neutral A			.52	.53								−.52
Neutral V								.50		.52		**−.70***
Unpleasant A	**.73***	**.76***			.55	.55	.52					
Unpleasant V		.58										−.52
Pleasant A			.59	.60							.58	−.61
Pleasant V								.56			.60	−.52
Socially Unpleasant A	.56				.51	.51	**.65***	**.70***	.59			**−.70***
Socially Unpleasant V												−.52
Socially Pleasant A			.60				.56	.59			**.71***	−.61
Socially Pleasant V		.57				.57	**.83****	**.90§**	**.64***		**.81****	**−.70***

Only correlation coefficients higher than 0.51 are reported.
*p < .05; ** p < .005; § p < .0005 (2-tailed).
A = Arousal; V = Valence.

status. The main result is that the patients gave a more positive valence and showed higher arousal towards neutral images. Socially pleasant images also showed a similar pattern, although to a lesser extent. Arousal to negative images, with or without social involvement, showed a moderately strong relationship with the subjective emotional involvement in the evaluation of illness consequences. In other words, we observed a sort of detachment from the pathological condition (an illness causing severe effects on a patient's quality of life with potentially fatal consequences) which is related to lower emotional involvement and reaction to negative stimulations. A tentative explanation of the correlation pattern reported between IAPS and some NP tests (MMSE, RAVLT, and AT) could suggest the involvement of other functionally connected brain areas co-working with the limbic system, such as a dysexecutive syndrome (i.e. lower apraxia test score) that could favor higher arousal and valence.

Diano et al. (2017) showed that exposure to emotional stimuli lead to dynamic changes of the amygdala and recruitment of brain networks. This report highlights the role of the interaction between emotions and anatomically distributed dynamic networks with a structure-function relationship. A dysfunction of frontal-limbic brain circuitry can be hypothesized in lesion of the temporal lobe. The involvement of limbic system may well generate an emotional dysregulation with consequent impairment in functioning of patients with TLT ablation. Because of its role in mood regulation and emotion processing, functional or structural amygdala alterations can have a substantial role in the modulation of the cerebral network likely involved in psychiatric disorders as well (Garrett & Chang, 2008). If so, studies addressing amygdala functionality and emotion reactivity in neurologic illnesses and in psychiatric disorders are warranted.

In a study of patients with amygdala damage using IAPS, a lack of arousal gradient across negative, but not positive stimuli, was observed. However, the patients correctly recognized and categorized both positive and negative features of the stimuli (Berntson, Bechara, Damasio, Tranel, & Cacioppo, 2007). The result was replicated in a subsequent report by the same research group (Berntson et al., 2011) also reporting that insular lesions showed reduced arousal to both negative and positive stimuli. On the other hand, Funayama, Grillon, Davis, and Phelps (2001) observed normal arousal to negative pictures in patients with unilateral temporal lobectomies, but reduced startle potentiation to the negative pictures in the patients with right hemisphere damage. These relative lack/reduction of emotional arousal and startle potentiation to negative stimuli may be partially in agreement with the trend toward reduced emotional involvement we observed.

The subjects in our study, hit by a severe illness, give a more pleasant valence together with higher arousal to neutral cues. Moreover, the lower reactivity to negative emotional cues is related to less emotional involvement, so that their apparent indifference to their illness can derive from an abnormal processing of emotional cues instead of an anosoagnosia.

Speculatively, the pattern of emotional reactivity we observed can help to cope with a severe pathological and disabling condition avoiding an emotional breakdown. Similar behavior is for instance a marker of social anxiety, where a psychological distress and impairment avoidance is present (Aldao, Nolen-Hoeksema, & Schweizer, 2010; Kashdan et al., 2013). On the contrary, the kind of emotional reactivity actually seems to confer some degree of resistance to a relevant psychological distress, a coping strategy to a severe pathological condition. Whether emotion regulation can be categorized as healthy or unhealthy depends therefore on its contextual adaptive meaning (Kashdan, Young, & Machell, 2015).

Limitations of the study have to be considered. The sample size is relatively small, but sufficient for a case series study to experiment a new investigation paradigm. The study must therefore be replicated in a larger sample taking into account different groups categorized by gender, tumor type, localization of the ablation. Evaluation of community functionality, quality of life and follow-up assessment must also

be considered. Furthermore, inclusion of objective measurements of the emotional response, such as skin conductance and heart rate, to obtain a comprehensive model of emotional evaluation is appropriate. Our study can however be of heuristic value for further investigations.

Ethical statement

All patients signed a written informed consent to participate after receiving a comprehensive explanation of the study procedures and goals. Approval of the study protocol was obtained from the Local Ethic Committee.

Role of the funding source

No economic source was interested.

Declaration of Competing Interest

Authors report no financial relationships with commercial interests.

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