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Pinpointing regional surface distortions of the amygdala in patients with spider phobia

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Abstract

The amygdala is a key brain structure involved in emotional processing, especially fear. Neuroimaging studies in patients with phobias have revealed alterations in amygdala reactivity and volumes. Here, we investigated the shape composition of the amygdalae to explore if patients with spider phobia show local morphological differences as compared to healthy controls. Magnetic resonance imaging data was analyzed from 20 female spider phobic patients and 20 age-matched healthy controls. Amygdala shape was quantified using a surface-based mesh modeling method (FIRST). Differences in amygdala topography were most prominently located over the basolateral and central nuclei of the left, but not right amygdala. These differences were further related to the severity of spider phobic symptoms and were independent of age, years of education or duration of illness. The present results point to focal amygdala distortions in spider phobic patients. Due to anomalies within the amygdala, spider phobia might be characterized by a deregulation in both an initial amplified fear response during exposure to spiders as well as a subsequent impaired down-regulation of the elicited fear response.

Keywords: Spider phobia, amygdala, shape, volume

Introduction

Spider phobia is a disease characterized by abnormal and automated fear reaction towards spiders [3]. Theories about the etiology of phobic fear suggest that the enhanced fear response in phobic patients results from a systematically biased interpretation of the danger associated with the feared stimulus [5]. Öhman's theory presumes that in healthy subjects, after encountering a phobia-relevant stimulus, an affective response is elicited through automatic and rapid evaluation of the stimulus, which initiates a sequence of controlled processing procedures. In phobic patients, these controlled mechanisms are suggested to be overridden by the automatic and exaggerated affective response [34].

Indeed, deregulation of emotional processes is one of the core clinical characteristics of spider phobia [16,23] and several neurobiological studies have suggested that the pathophysiology of spider phobia involves brain circuits sub-serving emotion regulation processes, encompassing fronto-limbic brain regions [24,42]. Amongst them, the amygdala has been suggested to play a role in a wide range of emotional processes which include: the perception and experience of emotional states, emotional learning and formation of emotional memories and emotion regulation [4,7,15,22,48,53,63].

Studies on amygdala morphology have revealed that the amygdala complex is not a homogenous structure and comprises sub-groups of specialized nuclei: a) the cortico-medial group with the cortical and medial nuclei, b) the central nucleus, and c) the basolateral group with the accessory basal, basal and lateral nuclei [2,31,32]. The amygdala is presumed to be implicated in the processing of sensory information through extensive connections that receive inputs from several brain areas [32]. Although the functional specialization of the amygdaloid nuclei in humans remains vague, evidence from animal studies suggest distinctive roles of different amygdaloid nuclei, with for example the central nucleus playing a crucial role in reflexive, conditioned responses to aversive stimuli and the basolateral complex playing a key role in voluntary behavior based on emotional episodes [25]. Furthermore, it has been suggested that the basolateral complex of the amygdala plays a key role in mediating the memory-enhancing effect of emotional arousal [44]. However, although animal studies are useful to identify the role of different amygdala nuclei in fear processes, it may not be applicable to humans [28].

Although specific phobias are one of the most prevalent mental disorders in the general population [1,55], it has received limited attention in structural brain imaging, so far. It has been

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argued that not only disturbances in amygdala function, but also in its structure might contribute to emotional dysfunction in individuals with anxiety disorders [11,21,47,50]. Though there is extensive literature on differences of amygdala activation in fear and phobias [6,9,13,56,62], to our knowledge, there is no study published on amygdala surface properties in specific phobia. We decided to compare the amygdala shape composition, because volumetric analyses do not account for the different amygdala subdivisions and thus not showing in which part changes are occurring. If only the total volume of the amygdala is estimated, it cannot be determined whether potential volume differences are diffuse and covering the whole amygdala or whether it is localized to specific regions. Since the amygdala has been shown to be an important structure in the generation of fear reactions and consists of several specialized nuclei, the aim of this study was to advance the knowledge about anatomical differences within the amygdala of phobic patients by focusing on differences in surface constitution compared to healthy controls.

Methods

Subjects

Participants were recruited by advertisements and were screened by a structured interview to exclude history of psychiatric or neurological illness. Age in the control group was matched with those in the patient group. Only women (in whom specific phobias are much more prevalent [19]) were included into the analysis in order to reduce variation due to gender effects. Because participant's handedness might influence the lateralization or symmetry of the amygdalae [57], only right-handed participants (assessed by the Edinburgh Handedness Inventory [35]) were included into the study. The often-observed co-morbidities make it difficult to directly attribute structural abnormalities to the disease. Therefore, participants were excluded from the study for the following reasons: a) any neurological problem, b) psychiatric diseases, other than spider phobia in patients, and c) medical conditions that could influence the results of the study. We further exluded participants that were taking any medication acting on the cerebral nervous system or using hormonal contraceptives. Written informed consent was obtained from all participants prior to the investigation. Finally, twenty spider phobic patients and twenty healthy controls were entered into the analysis. The study was conducted in accordance with the principles of the Declaration of Helsinki [41] and approved by the ethics committee of the Canton of Bern, Switzerland (161/07).

Clinical assessment

Diagnosis of spider phobic disease in patients was made according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) [3], using a computer-based structured clinical interview (DIA-X) [65], which is based on the Composite International Diagnostic Interview (CIDI) [45]. Asking patients retrospectively about the first appearance of phobic symptoms assessed information about age at onset of the illness. The duration of illness was defined as the time between onset of spider phobic symptoms and scan acquisition. Patients were screened with a questionnaire for DSM-IV disorders (SKID II) [20] and healthy controls were screened by the Symptom Checklist by Degoratis (SCL-90-R) [18]. In all participants, spider phobic symptoms were assessed more specifically with the Spider Phobia Questionnaire (SPQ) [27] and the Fear of Spiders Questionnaire (FSQ) [58].

Data acquisition

Structural magnetic resonance images were collected on a 3T Siemens Magnetom Trio Scanner (Erlangen, Germany). T1-weighted structural scans for subcortical analysis were acquired using modified driven equilibrium Fourier transform (mdeft) sequence [12] with the following parameters: repetition time (TR)=7.92msec, echo time (TE)=2,48msec, field of view (FOV) =256x256mm, voxel size=1x1x1mm and 910msec inversion time (Ti) for an optimal contrast-to-noise ratio [12].

Amygdala shape analysis

Automated amygdala segmentation and vertex analysis were performed using the FIRST module of FSL (FSL v4.1.9; available on: http://www.fmrib.ox.ac.uk/fsl). FIRST is an automatic, surface based segmentation tool that is used to analyze shape differences of subcortical brain structures [37]. First, the structural images were brain extracted using BET (brain extraction tool, [51]) and then registered to the MNI152 standard space using global affine transformation. The registration was then refined using a subcortical mask to improve the joint alignment of the subjects' amygdalae. Afterwards, a deformable model was fitted to the images in native space, based on a Bayesian shape and appearance model. The model is derived using a training set consisting of 336 brain scan training set and was then transferred to standard space using affine registration. The shapes of the amygdalae are then expressed as a mean with modes of variation (principal components). Finally, a boundary correction was used to determine which boundary voxels belonged to the amygdala [52]. To determine these voxels, the algorithm requires the number of iterations as input, which was set to 80, according to the recommendations of Patenaude and his colleagues [37]. For more technical details on subcortical segmentation with FIRST, see Patenaude's Thesis [36].

To test for local shape differences between groups, a vertex-wise analysis was finally performed in standard space in order to account for differences in brain size. The statistics were calculated using general linear model (GLM) and corrected for multiple comparisons using false discovery rate (FDR). To test for local shape differences between groups, a vertex-wise analysis was finally performed in standard space in order to account for differences in brain size. More in detail, in a vertex-wise analysis a single vertex point (sing-Vtx) [that describes a scalar in a 3D topological space] is compared to a "reference"

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vertex point of a template (temp-Vtx). In this step, vertex points belonging to each separated set of amygdala of each subject are projected onto the surface of a template. A distance between these two points is subsequently estimated. If the resulted distance is positive then the sing-Vtx lays outside the surface of the template; if the resulted distance is negative then the sing-Vtx lays inside the surface of the template.

To clarify whether the severity of the disease or the disease duration has an effect on specific amygdala nuclei, separate correlation analyses were performed within the patient group.

Statistical analyses

Statistical analyses of clinical scores and demographics were conducted using R (version 2.14.1, http://www.r-project.org). Group differences in demographic and clinical characteristics were analyzed with unpaired t-tests. All tests were two-tailed and a probability of less than 0.05 was considered significant.

Results

Subject characteristics

As seen in **Table 1**, spider phobic patients and healthy controls differed significantly in clinical scores with regard to spider phobic symptoms. The two groups did not differ significantly with respect to demographic variables and other clinical scores, except the number of years of education (t_{38}=2.48; p=0.02). To rule out this potential confound, a separate vertex analysis with level of education as covariate was conducted.

Table 1. Demographic and clinical characteristics of the patients and their control group.

	Patients (n=20)		Controls (n=20)			
Characteristics	**Mean**	**SD**	**Mean**	**SD**	**t**	**p**
Age	29.9	11.3	27.1	5.9	-0.98	0.33
Years of education	13.1	1.9	14.6	2.0	2.47	0.02
Age at onset	6.7	3.3	--	--	--	--
Duration of illness (years)	22.2	13.01	--	--	--	--
Handedness scores	9.7	0.6	9.8	0.4	0.65	0.52
SPQ	21.6	4.3	6.1	3.8	-11.99	0.00
FSQ	79.7	11.6	14.7	18.9	-12.55	0.00

SPQ: Spider Phobia Questionnaire; FSQ: Fear of Spiders Questionnaire

Amygdala surface properties

In **Figure 1**, statistical multivariate F statistic maps based on Pillai's Trace indicate regions of structural differences in spider phobic patients relative to healthy controls, with high F-values indicating regions of considerable structural differences. The F-values are color-coded from 2 to 5 with significant differences shown as green/blue and red regions indicating no statistical significance. Surface deformations were restricted to regions in the approximate vicinity of the basolateral complex and the central nucleus of the left amygdala. There were no significant surface differences of the right amygdala between patients and controls.

In order to facilitate the view of these results the shape of the bilateral amygdala are overlaid and projected onto an axial slice of the standard space (**Figure 2**). In the same **Figure 2** the quality of the segmentation performed by FSL/FIRST is displayed for two representative patients. The anatomical location of the amygdala is shown on an axial slice of these patients that

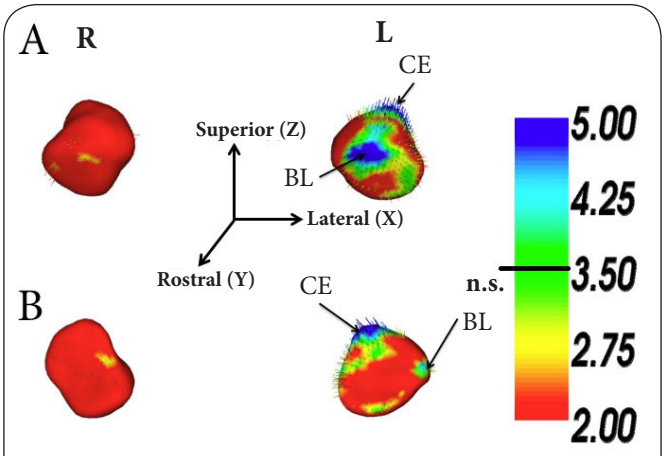

Figure 1. Amygdala statistical maps with F-values indicating structural differences between individuals diagnosed with spider phobia and healthy controls rendered on reference amygdalae. The colors indicate the statistical strength of the difference. Regions in blue/green correspond to the parts of the amygdala that are larger in controls than in patients. The color bar on the right indicates the vertex-wise F-statistic values, corrected for multiple comparisons by False Discovery Rate. (**A**) ventral view; (**B**) dorsal view; CE: central nucleus; BL:basolateral complex encompassing the accessory basal, basal and lateral nuclei. The little arrows pointing outwards in the figure indicates increased shape in controls as compared to a template. The level of significance is indicated by a line in the colorbar.

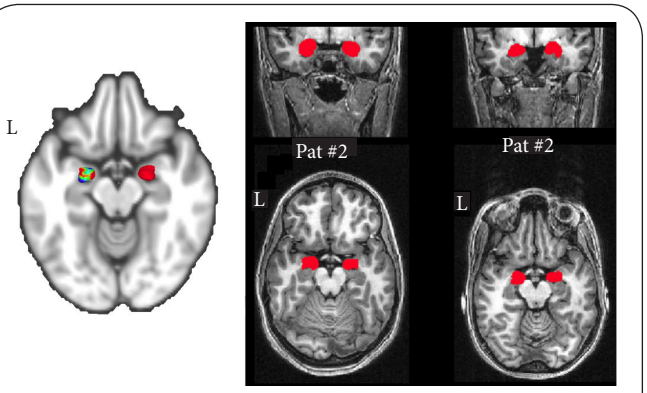

Figure 2. Projection of the surface as shown on **Figure 1** on a axial slice of the standard brain. The quality of the segmentation performed by FSL/FIRST is displayed for two representative patients. The anatomical location of the amygdala is shown on an axial slice of these patients that also includes the filled contour of the segmentation (in red).

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also includes the filled contour of the segmentation (in red). The regions of the amygdala that are larger in controls as compared to patients (see **Figure 1**) were additionally found to lie outside the reference amygdala (i.e., template). This finding is represented on **Figure 1** by the little arrows pointing outwards. The differences in the shape of the amygdala between patients and controls can additionally be expressed as changes in the volume of the amygdala. Patients showed significant smaller left amygdala volumes as compared to controls (Left Amygdala controls: volume=1802.6±162.1 and pat: volume=1649.7±198.9; t_{38}=2.66; p=0.01). No significant differences were observed for the right amygdala (Right Amygdala controls: volume=1708.8±235.2 and pat: volume=1654.0±374.4; t_{38}=0.58; p=n.s.). Unfortunately, it is not possible to further delineate the segmentation results to the nuclei level.

Effect of age, symptom severity and duration of illness

To rule out potential factors that could affect the amygdala surface constitution, correlational analysis between surface-based mesh modeling and age, SPQ score, FSQ score and duration of illness were conducted. Within the whole population, regional differences in the vicinity of the basolateral and central nucleus of the left but not right amygdala significantly correlated with the severity of phobic symptoms (**Figure 3**). Age did not account for differences in amygdala shape in both the patient and control groups. Within the phobic sample, duration of illness was not associated with the surface constitution of both amygdalae.

The overlap of both the statistical maps (from group comparison as shown in **Figure 1** and from symptom severity correlation as shown in **Figure 3**) is visualized on **Figure 4** by the blue regions. The red background shows all remaining regions that do not overlap between both statistical maps. This overlap was constructed by logical conjunction (i.e., AND) of p<0.05 values in both statistical maps. The total number of vertex-points of the overlapping region is 159 out of 229 vertex points in the group comparison and 202 in the correlation analysis.

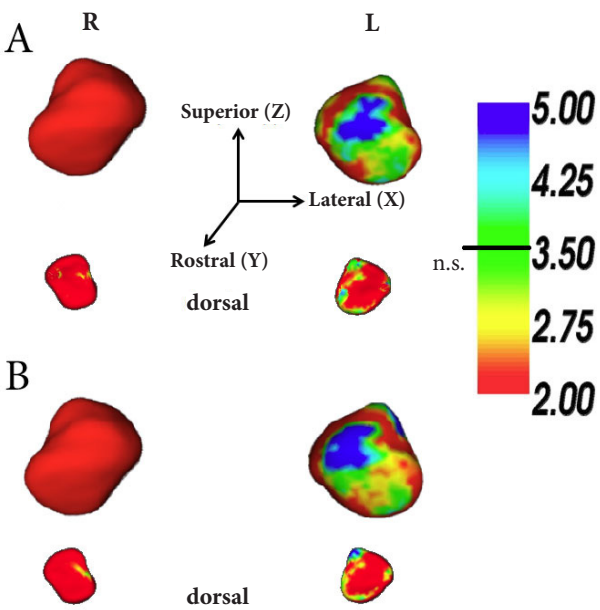

Figure 3. Correlations of symptom severity with amygdala surface of the whole population. The colors on the surface of the mesh display the significance of the variation in symptom severity that can be attributed to the regression of surface and symptom severity. The color bar depicts the calculated F-values for the analysis of variance. Higher F-values (blue/green) indicates loci of significant correlation, whereas lower F-values indicate no significant correlation. (**A**) correlation with scores on the Spider Phobic Questionnaire; (**B**)correlation with scores on the Fear of Spiders Questionnaire.The ventral and the dorsal view is shown for each correlation.

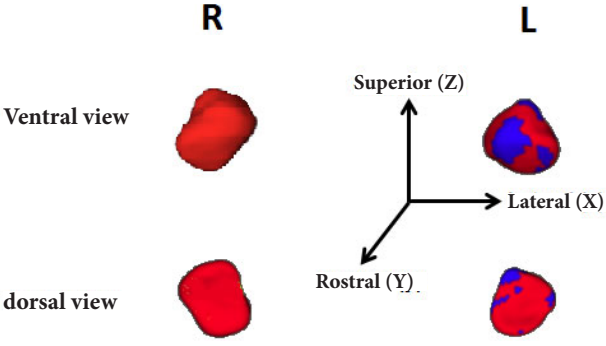

Figure 4. Overlap of both the statistical maps (from group comparison as shown in **Figure 1** and from symptom severity as shown in **Figure 3**) is visualized by the blue regions. The red background shows all remaining regions that do not overlap between both statistical maps.

Discussion

We evaluated shape differences of the amygdala between patients diagnosed with spider phobia and healthy comparison subjects. The current study demonstrates decrements localized in regions in the vicinity of the basolateral and central nuclei in patients with spider phobia. These sub-regional alterations were associated with symptom severity. Moreover, results could not be attributed to years of education nor ageor duration of illness. Therefore, the observed differences in left amygdala topography over distinct nuclei in our patient group might be linked to disorder-related amplified fear responses during phobic situations.

Theories about the etiology of phobic fear suggested that laterality differences may account for innate versus conditioned fearful stimuli, with the left amygdala playing a greater role in response to innate fearfully stimuli such as spiders [**14**]. Evidence for this hypothesis stems from neuroimaging studies investigating the habituation phenomenon which demonstrated greater and more sustained activation of the

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left amygdale [39,64,66]. In patients, the observed structural differences in the left amygdala could reflect impairments in top-down cognitively mediated processing. Our findings of left-lateralized differences suggest that the two amygdalae do not perform entirely equivalent functions. Evidence from a functional imaging study suggest, that activation of the left amygdala is strongly correlated with the fear response [38]. Hence, the right amygdala may have a general role during the initial automatic reaction, whereas the left amygdala could be more specifically involved in a more differentiated emotional reaction [33,66].

Apart the lateralization of fear responses, animal studies suggest that the basolateral nucleus is critically involved in fear memory [17,43] or in the consolidation of information that leads to phobic avoidance and constitutes a genetic predisposition to acquire specific phobias [25]. Because the amygdala integrates the information related to fear and strong emotions and sends outputs via the central nucleus for automatic arousal and via the basolateral nucleus for more active aspects of coping [29], atrophies in these regions may lead to phobic diseases. Importantly, the central nucleus have been suggested to be involved in many of the phobic symptoms and may exert modulatory influences upon hypothalamus and brainstem, mediating autonomic reactions which are characteristic of fear behavior [8,10,30,40].

Beyond animal studies, Sheline and colleagues [49] found a decrease in the size of both basolateral nuclei in patients with depression, attributing these volume losses to neuronal degeneration as a result of hypercortisolemia which may occur by the amplified activity of the amygdala. In phobic patients, the hyperactivity of the amygdala has been proposed to result from a lack of cortical inhibition by the prefrontal cortex, which sends dense projections to the amygdala primarily through GABAergic neurons [54]. The basal nucleus of the amygdala receives inputs from the hippocampus and prefrontal cortex and might integrate these signals to regulate the fear response [32,61]. Thus, there might occur an uncoupling of prefrontal inhibition of the amygdala in phobic patients that triggers extreme amygdala responses. Though, this uncoupling might be further supported by the observered structural deficits within the amygdala.

Altogether, it is still unclear whether morphological alterations of the amygdala constitute a state characteristic of the disorder or a trait marker. Multiple mechanisms could account for the occurrence of behavioral symptoms, functional differences and morphological features. The interplays between these factors are largely unknown. Though, phobic diseases could be driven by a genetic polymorphisms x environment interaction, modulated by molecular processes that lead to the expression of adaptive changes and phobic diseases. Furthermore, the microstructural determinants of group differences in amygdala morphology are unknown, as is the extent to which differences in surface properties relate to abnormalities in the underlying nuclei of the amygdala.

It is not trivial to provide a conclusive meaning of what the measure of surface morphology generally captures. Intuitively, the measure of shape morphology as compared to a simple volumetric investigation offers a more detailed view of the investigated region of interest. In fact, volumetric changes alone could result from two totally different regions that share no or few geometrical properties (i.e., like a sphere and a cube; or a cube and a torus). Shape analysis additionally provides a micro-architectonic description of local deviations of a region of interest from a template. In the present study both, the volume and the shape of the left amygdala were found to be significant different in patients as compared to healthy controls. The measure of volume alone represents just a simple number while the shape analysis additionally provides detailed information on how and where the surface of the amygdala might be deformed. The assessment of deformation can be understood as a non-linear method that may capture morphological changes and that goes beyond conventional linear voxel vise analysis of volume. Moreover, volume changes in the left amygdala alone describe uniquely a global feature while shape analysis additionally captures regional properties within the left amygdala. The observed volumetric changes in the patients left amygdala are not due to a general reduction in volume as compared to healthy controls: shape analysis locates the significant deviations in distinct nuclei of the left amygdala. This is the major insight that in the present study was uniquely obtained through the shape analysis.

Nonetheless, there are a few studies investigating morphological properties such as in hippocampal and enthorinal cortex of elderly [60], mild cognitive impairment and Alzheimer's disease [59] and hippocampal gender differences in puberty [46]. All these investigations are based on FSL/FIRST as described in [37].

There are some limitations of the study that need to be taken into account. Focusing only on single brain regions does not recognize that phobia is a disorder encompassing multiple brain regions sub-serving phobic fear. Furthermore, the standard resolution of structural imaging at 3T does not allow a reliable localization of structural alterations within specific amygdala cell groups. The relative sensitivity of magnetic resonance imaging in detecting amygdala damage, compared to histological analysis has so far not been established. The precise identification of amygdala nuclei requires histological investigation. It needs to be clarified that the labeling of the amygdala nuclei in this study was based on information obtained from a brain atlas [31]. Furthermore, the possibility remains that surface distortions also reflect atrophies in nuclei that are not represented on the surface of the amygdala. The modest number of subjects in each group (n=20) raises the possibility of a type II statistical error. Moreover, sex differences may also have an influence on amygdala structure [26]. As we only analyzed data from females, results can't be generalized.

Overall, the findings provide initial evidence for structural

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amygdala abnormalities as an element in the pathophysiology of phobic diseases. Our findings further illuminate the need to treat the amygdala as a heterogeneous structure. The documented findings might be clinically relevant as localized alterations might be reversible by pharmacotherapy or psychotherapy, which should be addressed in future studies. Although future prospective longitudinal research is required to establish structure-function relationship and neural mechanisms underlying phobic diseases, this study highlights the importance of the amygdala as a potentially important neural substrate.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Authors' contributions	AF	MSF	HS	TD	WS	RW	DJD	LMS
Research concept and design	--	--	--	--	--	--	✓	✓
Collection and/or assembly of data	--	✓	--	--	--	--	--	--
Data analysis and interpretation	--	✓	--	--	--	--	--	--
Writing the article	✓	✓	--	--	--	--	--	--
Critical revision of the article	✓	✓	✓	✓	✓	✓	✓	✓
Final approval of article	✓	✓	✓	✓	✓	✓	✓	✓
Statistical analysis	--	✓	--	--	--	--	--	--

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