

# Proximity alert! Distance related cuneus activation in military veterans with anger and aggression problems



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## ABSTRACT

Problems involving anger and aggression are common after military deployment, and may involve abnormal responses to threat. This study therefore investigated effects on neural activation related to threat and escapability among veterans with deployment experience. Twenty-seven male veterans with anger and aggression problems (Anger group) and 30 Control veterans performed a virtual predator-task during fMRI measurement. In this task, threat and proximity were manipulated. The distance of cues determined their possibility for escape. Cues signaled impending attack by zooming in towards the participant. If Threat cues, but not Safe cues, reached the participants without being halted by a button press, an aversive noise (105 dB scream) was presented. In both the Threat and the Safe condition, closer proximity of the virtual predator resulted in stronger activation in the cuneus in the Anger versus Control group. The results suggest that anger and aggression problems are related to a generalized sensitivity to proximity rather than preparatory processes related to task-contingent aversive stimuli. Anger and aggression problems in natural, dynamically changing environments may be related to an overall heightened vigilance, which is non-adaptively driven by proximity.

## 1. Introduction

Anger and aggression are feelings and behaviors involving the intent to harm a perceived threat (Anderson and Bushman, 2002). Disproportional anger and impulsive aggression can cause serious problems and danger to the individual and other people. Anger and aggression problems may occur after military deployment (Elbogen et al., 2010; Reijnen et al., 2015) due to the serious impact of a deployment (MacManus et al., 2015). These problems tend to persist over a long period of time, and can develop even after a substantial period of time after deployment (Heesink et al., 2015).

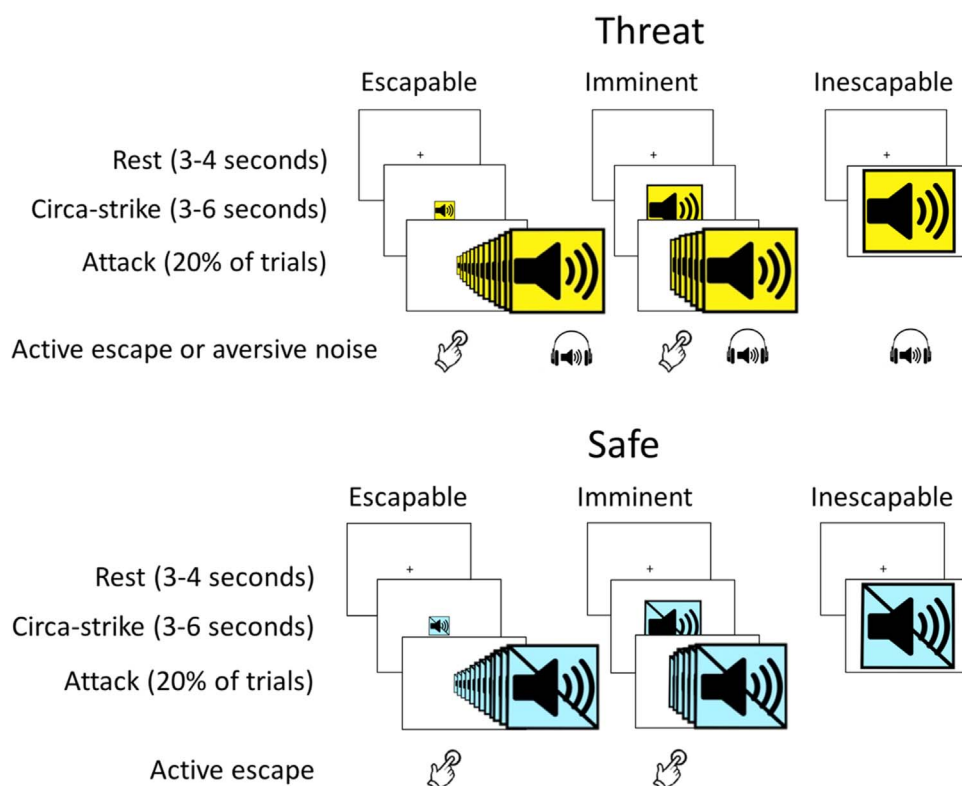
Heightened anger and aggression have been linked to a lowered threshold of perceiving situations as threatening (Novaco and Chemtob, 2002). Animal research shows that distance is an important feature in risk assessment (Blanchard et al., 2011). When a possible threat is observed, a survival mode is activated, involving behavior ranging from freeze or flight when the threat is at a distance, to fight when threat is close by and more imminent (Blanchard et al., 2005). In humans, similar behavior in response to threat has been reported (Blanchard et al.,

2001). In threatening situations, humans tend to respond faster (Nieuwenhuys et al., 2012) and show increased response preparation in anticipation of avoidable threat (Gladwin et al., 2016a).

The fight-response in animals is mediated by a neural circuit including the amygdala, the hypothalamus and the periaqueductal gray (PAG; for review see Blanchard et al., 2005). This system appears to be involved with the response to threat in humans as well (Hermans et al., 2013). In fMRI studies using threat paradigms, a shift was found from prefrontal activity during avoidable and distant threat, to brainstem activity (periaqueductal gray; PAG) during unavoidable, proximal threat (Coker-Appiah et al., 2013; Mobbs et al., 2009, 2007). Furthermore, exposure to threat is associated with activation in brain areas implicated in anxiety (Gold et al., 2015).

The Fear-And-Escape Task was developed to investigate the response to threat in interaction with distance (Montoya et al., 2015). The task consists of a virtual predator in which the chance to escape the virtual predator varies with distance: it can be easily escapable, imminent (chance-level escapable) or inescapable. Further, threat is manipulated by using two predators, only one of which is associated with

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**Fig. 1.** Outline of the Fear-and-Escape Task (FAET). The task consists of 3 blocks of 29 trials. The Threat condition consists of 5 Escapable trials, 5 Imminent trials and 4 Inescapable trials. In 20% of the Escapable and Imminent (escapable at chance-level) trials the cue attacked the participant by rapidly increasing in size. This could be halted by pushing a button. When this was not done in time, a highly aversive noise was presented. The procedure was exactly the same in the Control condition, only without the threat of the aversive noise.

**Table 1**  
Description of the Anger group and the Control group.

	Anger group (N = 27) Mean (SD)	Control group (N = 30) Mean (SD)	Statistics
Age	36.37 (6.54)	34.53 (7.59)	$t(1,55) = 0.97, ns$
Education	4.22 (0.64)	4.2 (0.81)	$t(1,55) = 0.11, ns$
Number of deployments	2.07 (1.17)	2.37 (1.25)	$t(1,55) = -0.91, ns$
Frequency of aggressive behavior			
Verbal	4.44 (1.55)	0.3 (0.99)	$t(1,55) = 12.15, p < 0.001$
Physical	2.22 (1.65)	0.00 (0.00)	$t(1,55) = 7.39, p < 0.001$
STAXI-2			
State Anger	23.33 (10.08)	15.20 (0.76)	$t(1,55) = 4.41, p < 0.001$
Trait Anger	22.44 (6.88)	12.13 (2.47)	$t(1,55) = 7.68, p < 0.001$
Aggression Questionnaire			
Physical aggression	29.26 (7.10)	18.47 (4.55)	$t(1,55) = 6.91, p < 0.001$
Verbal aggression	15.41 (3.99)	11.3 (1.54)	$t(1,55) = 5.23, p < 0.001$
Anger	24.26 (5.47)	11.17 (2.49)	$t(1,55) = 11.83, p < 0.001$
Hostility	24.04 (7.22)	11.87 (3.41)	$t(1,55) = 8.27, p < 0.001$

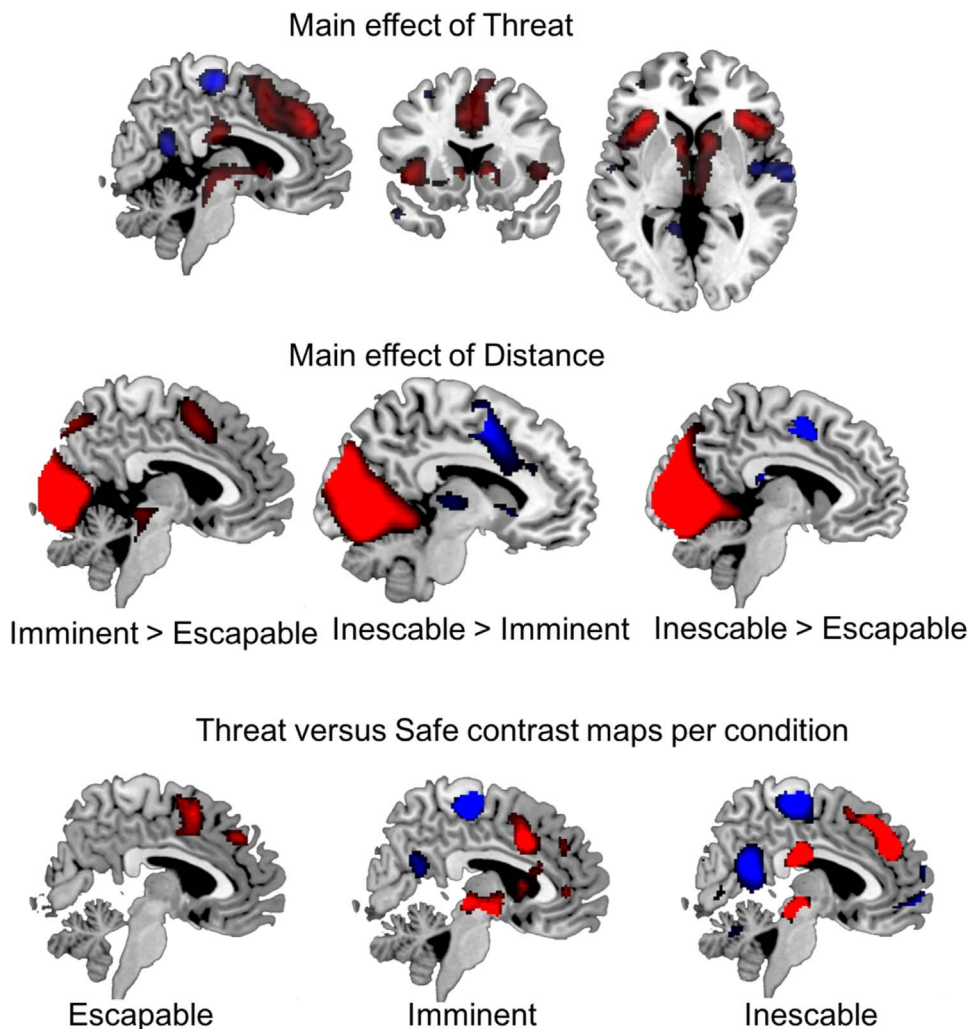
**Table 2**  
Behavioral data from the FAET.

Condition	Attempted escapes (SD)		Succeeded escapes (SD)	
	Anger	Control	Anger	Control
<b>Escapable</b>				
Threat	100% (0.0)	100% (0.0)	100% (0.0)	100% (0.0)
Safe	100% (0.0)	100% (0.0)	100% (0.0)	99% (6.1)
<b>Imminent</b>				
Threat	91% (14.9)	87% (20.7)	43% (29.0)	46% (28.3)
Safe	89% (16.0)	89% (16.0)	27% (33.4)	34% (29.7)

Note. Significant differences were found in succeeded escapes in the Imminent Threat condition compared to the Imminent Safe condition (Wilcoxon Signed Rank test,  $p < 0.01$ ). Mann-Whitney  $U$  tests revealed no significant differences between the two groups (all  $p$ 's  $> 0.234$ ).

an aversive stimulus. The task shows a deactivation of the default mode network (parietal and prefrontal regions) and stronger activation within the midbrain due to threat imminence using a virtual predator (Montoya et al., 2015). This suggests that a shift from planning to impulsive (flight-fight) behavior takes place when threat approaches.

Reactions to threat, such as aggressive behaviors, can be adaptive and result in appropriate defensive responses, but aggression may also be dysfunctional. In individuals with aggression problems, stronger reactivity towards stressful or aversive stimuli has been reported (Patrick, 2008). For instance, individuals scoring high on aggressiveness react to avoidable threat with increased response preparation (Gladwin et al., 2016a). Furthermore, violent behavior in military veterans is associated with hyperarousal symptoms (Taft et al., 2015), also indicating stronger threat reactivity. Aggressive behavior in youths low in psychopathic traits is also linked to exaggerated activity in the PAG (White et al., 2016). In patient populations at risk for impulsive aggression (e.g., Intermittent Explosive Disorder (IED) and borderline personality disorder) heightened amygdala reactivity was found during



**Fig. 2.** Brain activation during onset of the cues. The statistical map is overlaid on a template brain in MNI-space, thresholded at  $p < 0.05$ , FWE-corrected ( $t = 4.49$ ).

the presentation of emotional faces compared to control participants (Coccaro et al., 2007; McCloskey et al., 2016; New et al., 2007). Again, this stronger reaction to aversive stimuli indicates a stronger reactivity to threat in anger and aggression.

The aim of the current neuroimaging study was therefore to investigate whether veterans suffering from anger and aggression problems, relative to veterans without these problems, show different neural responses to threat-related effects, as measured using the Fear-and-Escape Task (FAET). Based on the above literature, the primary hypothesis is that the anger group will show stronger activation reflecting the shift from escapable to inescapable threat. Further, differences between the two groups on the neural response to both threat and proximity were tested, as these factors may also play a role in abnormal responses to threat and perceived risk which may lead to aggressive behavior.

## 2. Materials and methods

### 2.1. Participants

Twenty-seven male veterans with anger and aggression problems were included. All participants were right-handed and had normal or corrected-to-normal vision. They were recruited via their psychologists/psychiatrists at the Military Mental Health Care Institute and via advertisements in the waiting room and newsletters for veterans. Additionally, 30 control veterans without anger and aggression problems were included. Inclusion criteria for the Anger group were based

on the four research criteria for impulsive aggression described by Coccaro (2012): 1) Verbal or physical aggression towards other people occurring at least twice weekly on average for one month; or three episodes of physical assault over a one year period; 2) the degree of aggressiveness is grossly out of proportion; 3) the aggressive behavior is impulsive (not premeditated); 4) the aggressive behavior causes either distress in the individual or impairment in occupational or interpersonal functioning (Coccaro, 2012). Inclusion criteria for the Control group were 1) no current DSM-IV diagnosis; 2) no history of pathologic aggressive behavior.

All participants signed an informed consent before participation after a complete written and verbal explanation. The Ethics Committee of the University Medical Center Utrecht, The Netherlands, approved this study. This study was carried out in accordance with the Declaration of Helsinki.

### 2.2. Measures

#### 2.2.1. Interview and questionnaires

All participants were screened for psychiatric diagnoses according to the DSM IV (American Psychiatric Association, 2013) using the MINI interview (Van Vliet et al., 2000). Anger and Aggression were measured using the Dutch version of the State-Trait Anger Expression Inventory revised (STAXI-2; Hovens, Rodenburg, and Lievaart, 2015) and the Dutch version of the Aggression Questionnaire (Meesters et al., 1996).

**Table 3**

Task effect threat onset.

Region	Side	x	y	z	n voxels	Center of mass, t or F
<i>Main effect of Threat onset</i>						
<i>Threat &gt; Safe</i>						
Insula	L	−32	24	−2	694	9.60
Insula	R	40	24	−2	793	9.55
Frontal superior medial cortex	R	6	40	38	351	7.10
Cingulum mid	L	0	−18	30	270	6.26
Caudate	R	12	12	2	66	6.01
Supramarginal gyrus	R	58	−42	28	231	5.88
Caudate	L	−8	10	2	50	5.83
Thalamus	R	2	−22	−6	154	5.83
Cingulum mid	R	2	12	46	467	5.75
Supramarginal gyrus	L	−56	−42	30	162	5.59
Frontal mid	R	30	50	20	67	5.19
Superior frontal cortex	R	14	10	66	23	4.94
<i>Safe &gt; Threat</i>						
Hippocampus	L	−26	−24	−16	1125	−8.11
Hippocampus	R	28	−16	−18	699	−7.98
Supplementary motor area	R	6	−22	64	513	−7.26
Thalamus	L	0	−24	20	1707	−6.79
Superior frontal cortex	L	−18	34	48	602	−6.42
Thalamus	R	18	−28	12	1735	−6.44
Middle temporal gyrus	L	−58	−6	−8	191	−6.27
Angular gyrus	R	50	−62	24	264	−5.91
Postcentral gyrus	L	−54	−6	26	287	−5.70
Inferior orbitofrontal cortex	L	−38	36	−16	48	−5.44
Lingual gyrus	R	24	−58	−8	46	−5.31
Precentral gyrus	R	44	−16	58	166	−5.29
Insula	L	−36	−12	12	39	−5.13
Cerebellum	L	−14	−50	−20	39	−5.03
Superior medial frontal cortex	L	−8	64	18	85	−4.83
Middle occipital gyrus	R	42	−76	14	41	−4.79
Middle occipital gyrus	L	−42	−74	8	32	−4.72
Postcentral gyrus	R	46	−26	48	61	−4.74
<i>Main effect of Distance</i>						
Calcarine cortex	R	2	−76	4	26253	573.18
Supplementary motor area	R	4	8	50	2696	74.96
Postcentral gyrus	L	−38	−18	50	3497	56.44
Thalamus	R	24	−24	−2	153	45.01
Insula	R	34	24	6	238	28.48
Inferior frontal gyrus	L	−48	30	0	454	27.56
Precentral gyrus	L	−56	6	28	71	25.35
Insula	L	−30	20	4	290	24.92
Precuneus	R	22	−40	14	122	24.52
Insula	L	−42	0	12	131	23.36
Cerebellum	R	22	−50	−26	114	22.26
Posterior cingulum	L	−18	−42	12	81	20.37
Caudate	R	12	16	0	72	19.36
Caudate	L	−10	18	−2	37	19.60
Midbrain	R	2	−46	−26	77	16.99
Midbrain	R	2	−26	−10	173	17.71
Cingulum mid	R	2	−22	24	218	18.24
Middle frontal gyrus	L	−32	38	32	55	16.74
Inferior frontal gyrus	R	56	30	0	28	15.34
<i>Imminent &gt; Escapable</i>						
Calcarine cortex	R	2	−76	8	19475	30.56
Hippocampus	L	−20	−26	−4	171	8.64
Thalamus	R	22	−26	−2	184	8.55
Middle frontal gyrus	L	−32	−4	52	957	6.43
Supplementary motor area	R	12	6	54	1630	6.44
Brainstem	R	2	−26	−10	281	5.87
Insula	L	−36	16	4	29	4.75
<i>Escapable &gt; Imminent</i>						
Inferior occipital cortex	R	32	−90	−6	420	−21.78
Inferior occipital cortex	L	−30	−88	−10	303	−18.97
Middle occipital gyrus	L	−46	−68	26	838	−8.82
Angular cortex	R	54	−64	28	399	−7.30
Superior medial frontal	L	−8	56	32	27	−4.71

**Table 3 (continued)**

Region	Side	x	y	z	n voxels	Center of mass, t or F
<i>cortex</i>						
<i>Inescapable &gt; Imminent</i>						
Lingual cortex	R	2	−70	4	15468	20.10
Inferior frontal gyrus	L	−48	30	0	682	7.41
Inferior frontal gyrus	R	54	30	0	75	5.54
Middle frontal gyrus	L	−44	18	44	64	5.32
Middle temporal gyrus	L	−48	−56	22	24	4.75
<i>Imminent &gt; Inescapable</i>						
Cingulum mid	L	−2	0	44	2931	−11.97
Postcentral cortex	L	−42	−20	50	3152	−10.59
Inferior occipital cortex	R	30	−90	−6	437	−8.18
Insula	R	34	24	6	315	−7.50
Precentral cortex	L	−56	6	28	103	−6.96
Insula	L	−40	2	12	209	−6.78
Putamen	L	−24	20	4	458	−6.61
Cerebellum	R	20	−50	−26	128	−6.33
Caudate	R	12	16	2	177	−6.12
Thalamus	L	−8	−18	6	268	−6.13
Cingulum mid	R	2	−22	24	347	−6.00
Midbrain	R	4	−48	−26	95	−5.42
Middle frontal gyrus	L	−30	36	30	82	−5.33
Thalamus	R	10	−18	8	21	−4.70
<i>Inescapable &gt; Escapable</i>						
Lingual gyrus	R	2	−72	6	22824	31.82
Hippocampus	R	24	−26	−4	113	7.96
Superior parietal cortex	L	−20	−60	54	167	5.77
<i>Escapable &gt; Inescapable</i>						
Inferior occipital cortex	R	32	−90	−6	543	−23.83
Inferior occipital cortex	L	−30	−88	−10	399	−21.86
Postcentral cortex	L	−46	−22	50	1224	−8.45
Precuneus	R	22	−40	14	224	−6.99
Supplementary motor area	L	−4	4	52	318	−6.89
Posterior cingulum	L	−18	−42	12	147	−6.35
Midbrain	R	2	−44	−26	109	−5.76
Angular cortex	R	48	−70	36	64	−5.82
Rolandic operculum	L	−40	−2	12	60	−5.49
Insula	R	32	22	12	34	−5.11
Thalamus	R	10	−24	20	103	−5.14
Thalamus	L	−6	−26	20	47	−5.02
Caudate	L	−14	18	22	158	−5.15
<i>Interactions: Threat × Distance</i>						
Hippocampus	L	−28	−22	−12	295	20.48
Postcentral cortex	R	64	−16	36	127	19.90
Hippocampus	R	30	−18	−16	130	18.88
Inferior parietal cortex	L	−52	−22	42	189	18.11
Amygdala	L	−26	−2	−20	65	16.74
Postcentral cortex	R	48	−28	50	122	15.83
Anterior cingulum	R	16	32	−4	20	15.61
Middle temporal gyrus	L	−50	−68	0	64	15.31
Insula	L	−34	−2	14	30	15.57
Precentral cortex	L	−36	−12	62	43	15.13
Supplementary motor area	R	2	−20	64	45	14.73
Postcentral cortex	L	−38	−34	54	29	14.38
<i>Escapable, Threat &gt; Safe: no suprathreshold voxels</i>						
<i>Escapable, Safe &gt; Threat: no suprathreshold voxels</i>						
<i>Imminent, Threat &gt; Safe</i>						
Insula	L	−32	22	−2	481	6.77
Inferior orbitofrontal cortex	R	34	24	−6	206	6.16
Thalamus	R	4	−8	−8	28	5.11
Cingulum mid	L	0	14	40	56	4.82
<i>Imminent, Safe &gt; Threat</i>						
Supplementary motor area	R	4	−22	64	210	−5.68
<i>Inescapable, Threat &gt; Safe</i>						
Insula	R	40	26	0	453	7.87
Insula	L	−32	24	0	352	7.58
Superior medial frontal cortex	R	6	42	36	159	6.50
Cingulum mid	R	2	−18	28	189	6.23
Thalamus	R	2	−24	−6	40	5.26

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Table 3 (continued)

Region	Side	x	y	z	n voxels	Center of mass, t or F
Superior medial frontal cortex	R	4	34	48	28	4.87
Inescapable, Safe > Threat						
ParaHippocampal_R	R	30	−18	−18	1226	−8.34
Supplementary motor area	R	6	−22	66	648	−6.90
Superior temporal cortex	L	−54	−2	−10	681	−6.62
Thalamus	L	−12	−12	0	2669	−8.54
Rolandic operculum	R	38	−22	26	5146	−7.11
Middle occipital gyrus	L	−40	−68	18	1864	−6.13
Inferior frontal gyrus	R	50	40	8	133	−5.88
Middle frontal gyrus	L	−22	24	50	710	−5.89
Middle temporal gyrus	R	48	−62	10	1224	−5.77
Insula	L	−36	−8	10	185	−5.66
Postcentral cortex	L	−52	−16	34	559	−5.64
Postcentral cortex	L	−38	−32	48	294	−5.29
Caudate	L	−22	−2	24	101	−5.12
Middle occipital gyrus	R	26	−74	34	123	−5.12
Superior parietal cortex	R	24	−52	58	121	−5.03
Inferior orbitofrontal cortex	R	18	34	−4	26	−5.01
Inferior frontal gyrus	L	−48	36	10	39	−5.00
Inferior orbitofrontal cortex	L	−38	36	−16	27	−4.97
Superior medial frontal cortex	L	−8	66	22	97	−4.98
Caudate	R	20	6	24	26	−4.77
Superior parietal cortex	L	−24	−52	60	24	−4.68

Note. Table shows anatomical region, MNI coordinates of the center of the cluster, and *F* or *t*-values for the main effect of Threat onset, Distance and the interaction effect of Threat × Distance. Clusters with more than 0.10 proportion overlap were combined. Clusters consisting of at least 20 voxels are reported. All analyses are conducted at the voxel-level, whole-brain *p*-value < 0.05, FWE-corrected.

### 2.2.2. Fear-and-Escape Task

A virtual-predator task, the Fear-and-Escape Task, (FAET; Montoya et al., 2015) was used. An outline of the task is depicted in Fig. 1 (for a complete description of the task see Montoya et al., 2015). The task consists of a Threat condition and a Safe condition, indicated by a yellow and a blue pictogram, respectively. The pictograms were presented either at a small size, of full-screen divided by 16 (in the escapable condition), full-screen divided by 2 (in the imminent condition) or at actual full-screen size (in the inescapable condition). The sizes visually represented distance. The duration of presenting these pictograms was randomized and counterbalanced across conditions and lasted 3, 4.5 or 6 s. The pictograms in the escapable and imminent conditions could increase in size ('Attack'), visually nearing the participant. During this Attack, participants could press a button to halt this approach. If this was not done in time and the pictogram reached full size in the Threat condition, an aversive noise (AN) in the form of a female scream at 110 dB for the duration of 1 s, was presented through MR-compatible headphones. The large picture (full-screen size) in the Threat condition could also be followed by the AN in 20% of the trials, however this could not be prevented (unavoidable). The trials in the Safe condition were never followed by the AN, but participants were requested to also push the button when these cues increased in size. Between trials, a resting phase, indicated by a black fixation cross, displayed for 3 or 4 s. The durations were randomized and counterbalanced between conditions.

### 2.2.3. fMRI acquisition and preprocessing

Using a 3T magnetic resonance imaging scanner (Philips Medical System, The Netherlands) 622 functional images were acquired during the task. A two-dimensional echo planar imaging-sensitivity encoding (EPI-SENSE) sequence was used with the following parameters: voxel size = 4 mm isotropic; repetition time (TR) = 1400 ms; echo time (TE)

= 23 ms; flip angle = 70°; 4 mm slice thickness; field of view (FOV) 208 × 119 × 256 mm; 30 slices; SENSE-factor *R* = 2.4 (anterior-posterior). For within subject registration, a T1-weighted image (200 slices; TR = 10 ms; TE = 3.8 ms; flip angle = 8°; FOV = 240 × 240 × 160 mm, matrix of 304 × 299) was used. The images were obtained in a single run with a duration of 14 min and 30 s.

All fMRI data was preprocessed using statistical parametric mapping (SPM8; Wellcome Trust Center for Neuroimaging, [www.fil.ion.ucl.ac.uk](http://www.fil.ion.ucl.ac.uk)), and visualized using hiro3 (Gladwin et al., 2016b). Preprocessing started with motion-correction of the functional scans to the first dynamic scan and slice-time correction to the middle slice. Next, the anatomical scan was coregistered to the mean functional scan. Subsequently, the structural scan was segmented and normalization parameters were estimated. Using these normalization parameters, all volumes were normalized to a standard brain template (MNI) and resliced at 2.0 mm isotropic voxelsize. Smoothing (8.0 mm full width at half maximum Gaussian kernel) was applied to the normalized functional volumes.

### 2.2.4. Statistical analyses

Mann-Whitney U Tests were used to test whether the groups show differences in the proportion of attempted and successful escapes, and for the difference scores between the Threat and Safe condition. Furthermore, it was tested whether the two conditions, Threat and Safe, differ in attempted and successful escapes using a Wilcoxon Signed Rank Test.

General Linear Models (GLM) were used to model BOLD-responses to various events. Six trial types were distinguished: Threat-Escapable, Threat-Imminent, Threat-Inescapable, Safe-Escapable, Safe-Imminent and Safe-Inescapable. In the first-level GLM, the following regressors were used: six for the onsets of each trial type, six for the trial-offsets, four for the attacks of each relevant trial type, one for the AN-onset and one for the responses. Due to previous found activation in response to trial-offsets (Klumpers et al., 2010), these were also modeled, but where not of interest in the current study. Furthermore, to reduce variance due to noise caused by movement and drifts in the signal, realignment parameters and a discrete cosine transform high-pass filter (1/128 Hz cut-off frequency) were entered into the analyses. Maps of the regression coefficients for the model were computed for each participant.

Effects on activation at stimulus onset were tested using a full-factorial 2 × 2 × 3 ANOVA design (Anger/Control × Threat/Safe × Escapable/Imminent/Inescapable) with group as between-subjects factor and the conditions as within-subjects factors. A threshold of *p* < 0.05 family-wise error (FWE)-corrected was used in all contrasts. Small volume corrections were applied for regions of interest (ROIs), *p* < 0.05, FWE-corrected. The ROIs used were based on the findings in Montoya et al. (2015) in the placebo condition, and included the anterior insular cortices, dorsal anterior cingulate cortices and the midbrain.

## 3. Results

### 3.1. Demographics

Demographic information is depicted in Table 1. The groups did not significantly differ on age, education and number of deployments. The anger and aggression measures all showed a significant difference between the groups.

### 3.2. Behavioral data

Table 2 shows the behavioral results of the FAET. Participants succeeded in escape more often in the Imminent Threat condition compared to the Imminent Safe condition (Wilcoxon Signed Rank test, *p* < 0.01). The data thus indicate that participants were motivated to avoid the aversive scream. Mann-Whitney *U* tests revealed no



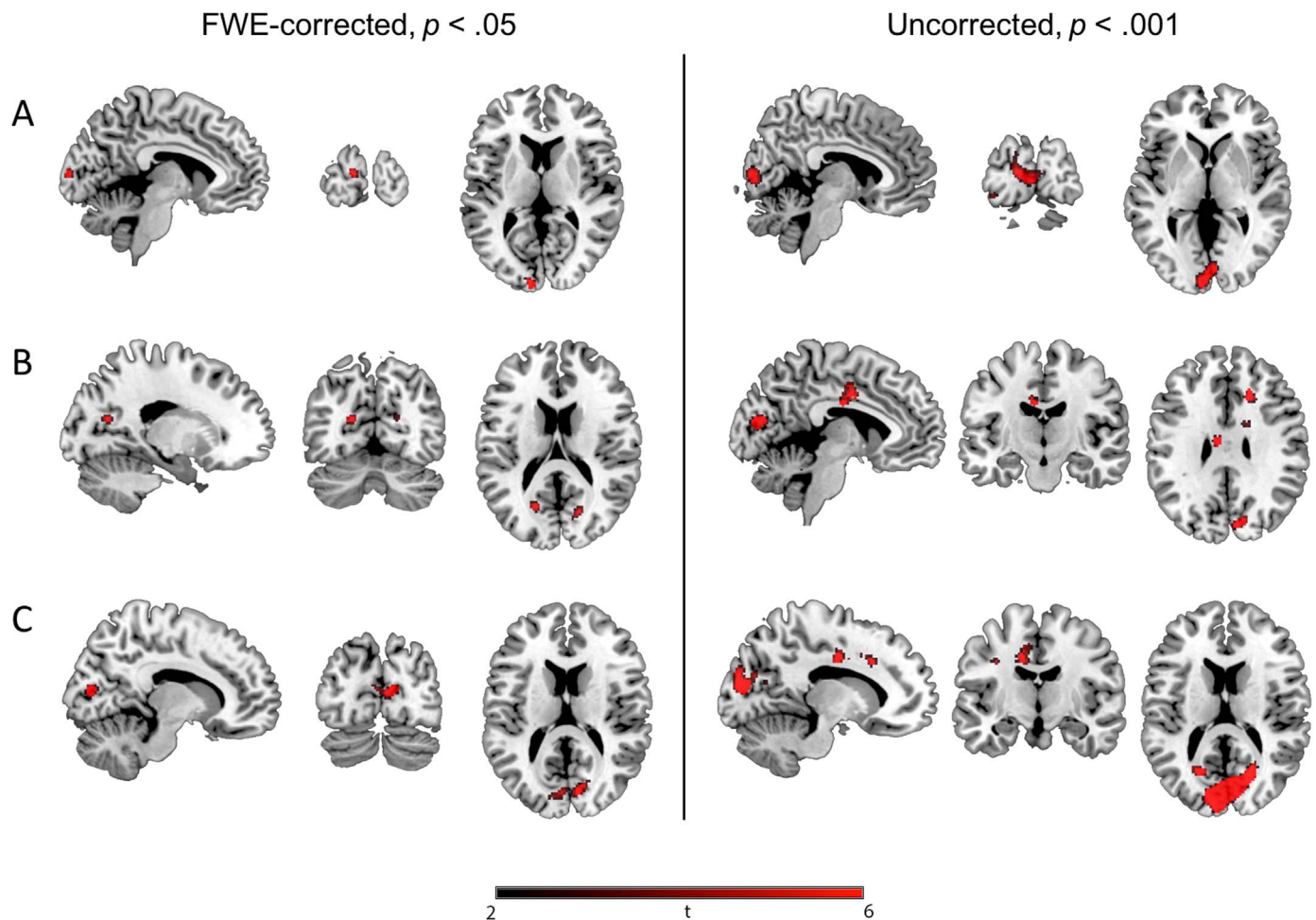


Fig. 3. A) Stronger activation in imminent versus escapable stimuli in the Anger group compared to the Control group. B) Stronger activation in inescapable versus imminent stimuli in the Anger group compared to the Control group. C) Stronger activation in inescapable versus escapable stimuli in the Anger group compared to the Control group.

significant differences between the two groups (all  $p$ 's > 0.234). Furthermore, the difference between the two conditions in proportion attempted escapes and succeeded escapes did not differ between the two groups (Mann-Whitney  $U$  test,  $p = 0.557$  and  $p = 0.434$ , respectively).

### 3.3. fMRI results

#### 3.3.1. Task effects

The Threat versus Safe contrast revealed a comparable pattern to that described by Montoya et al. (2015), see Fig. 2 and Table 3. Several regions, among which the hippocampus, insula and the supplementary motor cortex, were active during observation of the threat-indicating stimulus compared to the control stimulus, many of them part of the salience network. Furthermore, deactivation was found in regions that are part of the default mode network, such as prefrontal and parietal cortices.

The main effect of Distance is also shown in Fig. 2 and Table 3. Results show stronger activation in the occipital cortex during the onset of cues in the Imminent versus the Escapable condition, in the Inescapable versus the Imminent condition, and the Inescapable versus the Escapable condition.

The interaction between Threat and Distance is shown in Fig. 2 and Table 3. Stronger activation during Threat cues was found in the insula, brainstem and the cingulum, whereas deactivation of the supplementary motor area was found.

#### 3.3.2. Group effect

The Group\*Threat and the Group\*Threat\*Distance interaction

revealed no significant results. Small volume correction within the ROI based on the activation found in Montoya et al. (2015) in the control (placebo) condition also showed no significant differences between the Anger and the Control group on these contrasts.

The Group\*Distance interaction revealed significant differences with peaks at the right calcarine cortex ( $x=8, y=-80, z=10$ ) and the left occipital superior cortex ( $x=-8, y=-96, z=10$ ). T-tests revealed that the occipital superior cortex was more active in the Anger group compared to the control group during viewing of inescapable stimuli versus escapable stimuli (Fig. 3 and Table 4). Furthermore, the cuneus was more active in the Anger group compared to the control group during viewing of imminent stimuli versus escapable stimuli. Fig. 3 and Table 4 show these effects.

### 4. Discussion

The current study used the Fear-And-Escape Task (FAET) to determine abnormal neural responses to threat related to anger and aggression in military veterans. The main finding was the significantly stronger activation in the cuneus in the Anger group compared to the Control group with increasing proximity. The cuneus is involved in motivated attention (Bradley et al., 2003), which facilitates the perceptual processing of motivationally relevant stimuli or stimulus features (Edmiston et al., 2013; Lang et al., 1998; Lee et al., 2014; Satpute et al., 2015). The stimulus size indicates proximity, and therefore makes stimuli more salient. Motivated attention refers to the attentional processing of motivationally relevant stimuli or stimulus features, such as proximity. The size of the stimuli not only reflects saliency, it also

**Table 4**  
Interaction effect of Group and Distance.

Region	Side	x	y	z	n voxels	Peak, T	p
<i>Imminent &gt; Escapable</i>							
Cuneus	L	−8	−96	8	57	5.65	< 0.05, FWE-corr.
	L	−8	−96	8	230	5.65	< 0.001
Cuneus	R	4	−84	6	84	3.87	< 0.001
Inferior occipital gyrus	L	−30	−84	−8	45	3.76	< 0.001
	L	−36	−92	−12	same cluster	3.28	< 0.001
Lingual gyrus	L	−14	−92	24	1	3.10	< 0.001
<i>Inescapable &gt; Imminent</i>							
Sub-gyral	L	−20	−66	16	7	4.70	< 0.05, FWE-corr.
Precuneus	R	18	−70	18	2	4.52	< 0.05, FWE-corr.
Sub-gyral	L	−20	−66	16	1431	4.70	< 0.001
Precuneus	R	18	−70	18	same cluster	4.52	< 0.001
Cuneus	R	12	−76	24	same cluster	4.39	< 0.001
Cingulate gyrus	L	−10	−8	40	256	3.98	< 0.001
	L	−8	−10	32	same cluster	3.89	< 0.001
	L	−14	0	34	same cluster	3.17	< 0.001
Cingulate gyrus	R	18	26	30	78	3.83	< 0.001
Fusiform	L	−22	−44	−18	76	3.55	< 0.001
Cingulum mid	L	−16	−34	42	44	3.44	< 0.001
	L	−10	−38	48	same cluster	3.31	< 0.001
Cingulate gyrus	R	14	4	28	17	3.32	< 0.001
	R	16	−4	32	same cluster	3.18	< 0.001
Fusiform	L	−22	−32	−22	9	3.31	< 0.001
Cingulate gyrus	R	12	−38	26	6	3.27	< 0.001
Cerebellum	L	−6	−46	−24	3	3.24	< 0.001
Fusiform	R	28	−54	−18	3	3.22	< 0.001
Extra-nuclear	L	−30	−28	24	1	3.20	< 0.001
<i>Inescapable &gt; Escapable</i>							
Cuneus	R	8	−80	10	216	5.62	< 0.05, FWE-corr.
Cuneus	L	−6	−82	14	same cluster	4.89	< 0.05, FWE-corr.
Cuneus	R	8	−80	10	2084	5.62	< 0.001
Cuneus	L	−6	−82	14	same cluster	4.89	< 0.001
	L	−4	−92	14	same cluster	4.38	< 0.001
Cingulate gyrus	L	−12	−8	34	145	3.90	< 0.001
	L	−14	0	36	same cluster	3.33	< 0.001
Inferior occipital gyrus	L	−30	−84	−8	33	3.88	< 0.001
Cingulate gyrus	L	−14	18	34	54	3.74	< 0.001
Precentral gyrus	L	−36	−12	34	32	3.48	< 0.001
Cingulate gyrus	R	18	26	32	19	3.45	< 0.001
Fusiform	L	−28	−72	−10	4	3.34	< 0.001
Cerebellum	L	−6	−66	−6	12	3.31	< 0.001
Cingulate gyrus	L	−12	6	38	4	3.29	< 0.001
Extra-nuclear	L	−32	−28	24	8	3.25	< 0.001
Sub-gyral	L	−36	−66	10	9	3.25	< 0.001
Sub-gyral	R	24	−52	38	5	3.22	< 0.001
Hippocampus	L	−30	−28	−12	4	3.21	< 0.001
Fusiform	R	30	−50	−18	1	3.14	< 0.001
Inferior occipital gyrus	L	−34	−92	−12	1	3.14	< 0.001
Sub-gyral	L	−38	−24	−10	1	3.14	< 0.001

Note. Table shows anatomical region, MNI coordinates and T-values for the main effect of Threat onset. All analyses are conducted at the voxel-level, both whole-brain  $p$ -value < 0.001 and < 0.05, FWE-corrected.

reflects threat. A larger cue can attack and is harder to escape from. This might be perceived as more threatening by the Anger group leading to more extensive processing of stimulus features. Proximity thus appears to evoke increased motivated attention in the Anger group. This may be related to the fundamental role distance plays in defensive responses to threat (Fanselow, 1994; Mobbs et al., 2007). Future study is needed to determine whether the group by proximity effect reflects a more general tendency to be vigilant towards stimuli or features relevant for defensive responses, in particular those such as proximity that have a “hard-wired” relationship to defensive responses. If so, aggression in the complex, dynamic environment of daily life could be related to attention that is automatically biased towards threat-relevant signals, which could increase the likelihood of false positives in the detection of actual threat.

Further, the results confirmed that the paradigm activates a similar pattern in this population as shown by Montoya et al. (2015): Proximal and escapable threat activated areas that are part of the salience network, and deactivated areas that are part of the default mode network,

in line with the literature on the threat system (McNaughton and Corr, 2004). The overall effect of anticipatory threat was thus replicated, but this effect did not differ between the anger group and the control group. This contrasts with previous studies in patients with anger and aggression problems, which show increased reactivity to facial threat stimuli in passive viewing paradigms (Coccaro et al., 2007; McCloskey et al., 2016; New et al., 2007). This might indicate that the processing of anticipated threat is not affected in veterans with anger and aggression problems. Further, military personnel is required to respond differently compared to civilians in similar situations. This might also explain the different results in reactivity to threat. Whether unanticipated threat is affected or not in anger and aggression, needs to be explored in future studies.

Visual threat processing has been studied in anxiety, with studies among others showing that in anxiety, perception of threat is increased (Bar-Haim et al., 2007; Fox et al., 2001; Sussman et al., 2016). A perceptual bias toward potential threat in anxiety is also seen in the current sample. However, anticipatory processing in threat has been found

to showed no differences with regard to visual stimuli in anxiety disorder compared to controls (Mills et al., 2014). These corresponding results might be explained by the high overlap between aggression and anxiety (Pinna et al., 2016).

The stimuli used in the current task were clearly differentiable task-contingent threat and safe cues, without any ambiguity. Differences in response to threat associated with aggression problems might be more related to a hostile attribution bias, in which in particular ambiguous situations are more easily coded as threatening (Anderson and Bushman, 2002). Indeed, increased partner violence was found in military veterans who interpret all kinds of situations in an overly hostile manner (Taft et al., 2015). Perception also plays a role in the effect of deployment on the brain: the neural coupling between the amygdala and the insula/dorsal anterior cingulate cortex in deployed veterans is mainly influenced by perceived threat rather than by actual threat exposure (van Wingen et al., 2011). Whether reactivity to ambiguous situations is indeed distinctly different from non-ambiguous threat reactivity in veterans with an aggression disorder, should be addressed in future research.

Note however that the Anger group might also be more impulsive relative to the control group, and it is not possible to disentangle effects of impulsivity. Furthermore, the experienced anger during the task was not measured, thus, it could not be tested whether subjective feelings of anger influenced the activation.

Since the participants in this study were all male veterans, generalization of the results to females, other professions, or civilians, is difficult. However, anger and aggression are common problems that are not only reported within military veterans. For instance, heightened anger has also been described in police personnel (Meffert et al., 2008). The results from this study therefore have a wider significance beyond the current sample. Threat-related motivated attention in dynamically changing situations involving threat could play a role in other populations as well. Future research could focus on whether training can reduce increased motivated attention in anger and aggression. Decreasing this attention might lead to fewer situations perceived as provocative or threatening. Furthermore, when patients recognize these situations earlier, it might lead to more appropriate behavior.

In conclusion, while no differences related to anticipatory threat were found, individuals with anger and aggression showed a sensitivity to proximity of the virtual predator. Future research is needed to confirm whether anger and aggression are related to abnormal responses to fundamental stimulus features such as proximity in threatening contexts, as opposed to more contingent forms of threat. Moreover, the role of ambiguity in contingent threat remains an important direction for future research. Such research might help to develop methods for clinical interventions aimed at reducing aggression-related threat reactivity.

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