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# The Fine Line Between 'Brave' and 'Reckless': Amygdala Reactivity and Regulation Predict Recognition of Risk

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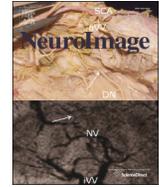


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## The fine line between ‘brave’ and ‘reckless’: Amygdala reactivity and regulation predict recognition of risk



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### ABSTRACT

**Background:** High sensation-seekers (HSS) pursue novelty even at the cost of self-harm. When challenged, HSS are less anxious, show blunted physiological (cortisol, startle) and neurobiological (prefrontal-limbic) responses, and devalue aversive outcomes. Here, we investigate how these features interact under conditions of physical danger, in distinguishing between adaptive and maladaptive approaches to risk.

**Methods:** We recruited a cohort of individuals who voluntarily sought out recreational exposure to physical risk, and obtained serial cortisol values over two time-locked days. On the ‘baseline’ day, we scanned subjects’ brains with functional and structural MRI; on the ‘skydiving day,’ subjects completed a first-time tandem skydive. During neuroimaging, subjects viewed cues that predicted aversive noise; neural data were analyzed for prefrontal-limbic reactivity (activation) and regulation (non-linear complexity), as well as cortical thickness. To probe threat perception, subjects identified aggression for ambiguous faces morphed between neutral and angry poles.

**Results:** Individuals with prefrontal-limbic meso-circuits with less balanced regulation between excitatory and inhibitory components showed both diminished cortisol/anxiety responses to their skydives, as well as less accurate perceptual recognition of threat. This impaired control was localized to the inferior frontal gyrus, with associated cortical thinning. Structural equation modeling suggests that sensation-seeking is primarily mediated via threat-perception, which itself is primarily mediated via neural reactivity and regulation.

**Conclusions:** Our results refine the sensation-seeking construct to provide important distinctions (brain-based, but with endocrine and cognitive consequences) between the brave, who feel fear but nonetheless overcome it, and the reckless, who fail to recognize danger. This distinction has important real-world implications, as those who fail to recognize risk are less likely to mitigate it.

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### Introduction

For any organism, novelty provides both potential benefits as well as potential costs: an animal that ventures out of known territory may find a new source of food, yet it may also expose itself to predation. As such, evolutionary selection may have favored a spectrum of novelty-seeking behavior within a species, as different circumstances make different attitudes towards risk more or less adaptive.

‘Sensation-seeking,’ in humans, is a personality construct characterized by the pursuit of novelty, even at the risk of increased social, financial, or physical harm (Zuckerman, 1994). High sensation-seekers

(HSSs) have received clinical attention because they are more likely than low sensation-seekers (LSSs) to engage in personally and socially destructive behavior such as drug abuse (Dennhardt and Murphy, 2013; Ersche et al., 2013; Marvel and Hartmann, 1986; Zuckerman, 1986), gambling (Estevez et al., 2013; Harris et al., 2013; Stanton et al., 2001), and promiscuity (Newcomb et al., 2011; Stanton et al., 2001). However novelty seeking, as a character trait, may also be disproportionately represented among populations (e.g., emergency room physicians, surgeons (Hojat and Zuckerman, 2008), firemen (Levenson, 1990), bomb squad technicians) that our society tends to view as altruistic, and even heroic. Here, we hypothesize that individuals who pursue a dangerous activity with full awareness of its risks (‘the brave’), versus those who pursue the same activity blind to its risks (‘the reckless’), are not simply two sides of the same coin, culturally distinguished post hoc simply by virtue of whether their impact is ultimately pro or anti-social. Rather, they represent qualitatively

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heterogeneous approaches to risk, which are neurobiologically, physiologically, and cognitively distinct.

Human and animal studies have established that threat assessment is regulated by a control circuit, with the amygdala and prefrontal regions providing dominant excitatory and inhibitory components, respectively (Phelps and LeDoux, 2005). From a control systems perspective, a healthy prefrontal-limbic circuit should be sufficiently flexible to respond to environmental threat, yet sufficiently constrained to efficiently return to baseline following perturbation. Because flexibility and constraint of the circuit affect the dynamics of the hemodynamic time-series, characterization of these dynamics can be used to quantify circuit-wide regulation. Theoretical work by ourselves (Rădulescu and Mujica-Parodi, 2014) and others (for review, see Bullmore et al., 2009; Gisiger, 2001; He et al., 2010) demonstrate that when control systems are optimized for both responsiveness and homeostasis, signal outputs are self-similar or *fractal*, with time-series that follow a power law for both excitatory and inhibitory nodes, balanced at a critical point between order and complexity (see Methods section). As circuits become increasingly dysregulated, signal complexity for affected nodes deviates from that critical point (Rădulescu and Mujica-Parodi, 2014), as observed in trait anxiety (Tolkunov et al., 2010), schizophrenia (Rădulescu et al., 2012), autism (Lai et al., 2010), epilepsy (Daneshyari and Kamkar, 2010), and aging (Suckling et al., 2008). Different brain states (He, 2011) and disorders may each reflect distinct regulatory circuit dynamics. However, the unique signature for each brain state and disorder derives from the specific circuit, feedback function (e.g., positive versus negative, strength, lag), and node affected, as well as whether deviation from the critical point shifts towards greater or lesser complexity (Rădulescu and Mujica-Parodi, 2014).

This study was designed to test whether one hallmark feature of HSS—reduced response to threat (De Pascalis et al., 2007; Joseph et al., 2009; Kruschwitz et al., 2012)—is predicted by prefrontal-limbic dysregulation, via its effect on threat perception. We recruited a cohort of first-time tandem skydivers—individuals who all willingly chose recreational exposure to physical risk. The study consisted of two testing days ('baseline' and 'skydive'), between 7 and 14 days apart, and time-locked to control for diurnal variability. On the baseline day, we obtained functional and structural MRI as well as personality measures. On the skydiving day, the subject jumped from 4 km (13,000 ft). On both testing days, subjects provided serial endocrine (cortisol, epinephrine, beta endorphin, testosterone) measurements and self-reported levels of state anxiety and euphoria. Neuroimaging data were analyzed for prefrontal-limbic reactivity (fMRI activation in anticipation of aversive bursts of loud white noise) and system-wide regulation (power spectrum scale invariance, a measure of signal complexity), as well as cortical thickness. We measured threat perception using a separate signal-detection task, in which subjects were asked to identify affect-valence for ambiguous faces morphed by degrees between neutral and angry expressions. Structural equation modeling mapped the relationship between sensation-seeking and neural, endocrine, and cognitive measures.

## Methods

### Participants

The Institutional Review Board at Stony Brook University approved this study; all participants provided informed consent. Thirty (12 female) healthy adults between the ages of 18 and 48 ( $M = 24.69 \pm 7.27$ ) participated in the primary study; an additional  $N = 22$  (2 female) healthy adults between the ages of 18 and 46 ( $M = 22.45 \pm 7.48$ ) participated in a pilot fMRI-skydiving study reported in Appendix A. Participants were recruited from individuals who contacted Skydive Long Island (Calverton, NY) to schedule their first-time skydives. Potential participants were screened for drug usage, neurological/psychiatric histories, and MR exclusion criteria. Participants

provided information regarding age, gender, height and weight, and filled out questionnaires designed to measure different measures of personality related to risk aversion. These questionnaires included the NEO Personality Inventory (PAR, Lutz FL), Perceived Stress Scale (Cohen et al., 1983), Attitudes Towards Risk Questionnaire (Franken et al., 1992), State-Trait Anxiety Inventory (STAI: Mind Garden, Menlo Park, CA), and the Sensation-Seeking Scale (Zuckerman and Link, 1968). For the primary study, trait anxiety scores ranged from 20 to 53 ( $M = 33.07 \pm 7.11$ ) while sensation-seeking scores ranged from 16 to 35 ( $M = 24.85 \pm 4.68$ ); and detailed subject information for the pilot study is provided in Appendix A.

### fMRI task

Pilot testing, in an independent sample of  $N = 22$  first-time tandem skydivers, established that fear peaked in anticipation of—rather than in response to—the jump, and that cortisol response to that anticipatory period correlated with amygdala activation in response to fearful faces (see Appendix A). Therefore, for this study we used a neuroimaging task previously shown to elicit subjective threat anticipation, with associated activation of the amygdala and insula (Carlson et al., 2011). The *Anticipation of Aversive Events Task* consisted of a 20 trial block design, in which each trial consisted of a 1000 ms cue (red  $\otimes$  for 'aversive,' blue  $\odot$  for 'benign'), followed first by a 16 s countdown, and then by a 1000 ms auditory stimulus. Aversive cues predicted a burst of 100 dB white noise, while benign cues predicted a burst of 55 dB white noise. Inter-trial intervals were jittered between 4000 and 8000 ms, during which time subjects viewed a white fixation cross on a black screen. Total task time was 8 min.

### MRI acquisition and analysis

Subjects were scanned on 3 T Siemens Trio ( $N = 18$ ) or Philips ( $N = 12$ ) MRI scanners at the Stony Brook University SCAN Center using 12-channel SENSE parallel head coils (post-hoc analyses, the results of which are provided in Appendix A, show that the use of two scanners did not significantly impact our results). Data were acquired using 232 T2\*-weighted echo planar single-shot images covering the whole brain with the following parameters: TR = 2500 ms, SENSE factor = 2, TE = 22 ms, Flip angle = 83°, Matrix dimensions =  $96 \times 96$ , FOV =  $224 \times 224$  mm, Slices = 36, Slice thickness = 3.5 mm, Gap = 0. Standard pre-processing procedures were performed using the Statistical Parameter Mapping software (SPM5), including image realignment corrections for head movements, slice-timing corrections for order of slice acquisition, normalization to standard  $2 \times 2 \times 2$  mm MNI space, and spatial smoothing with a Gaussian FWHM 6 mm filter. Using the general linear model in SPM5, first-level single-subject statistical maps were created from contrasts (17 s anticipatory cue block that combined 1 s cue plus 16 s countdown, for aversive versus benign conditions) and auditory events (0 s, for aversive versus benign conditions). At the second-level, cortisol reactivity values for each of the three time-periods were included as regressors of interest.

To quantify circuit-wide regulation via the degree of complexity in the signal, we calculated its power spectrum scale invariance (PSSI) using parameters that we previously optimized for fMRI time-series (Rubin et al., 2013). Outputs that are self-similar or *fractal* have frequency spectra  $S(f)$ , which follow a power law:  $S(f) \propto f^{-\beta}$ , with the critical point between order and complexity defined by  $\beta = 1$  (*pink noise*) (Gisiger, 2001). Shifts towards greater chaos or greater persistence are defined as towards  $\beta = 0$  (*white noise*) or  $\beta = 2$  (*brown noise*) respectively. Using modeling and simulations of a prefrontal-limbic meso-circuit, we previously have shown that control systems with balanced excitatory and inhibitory components produce outputs with PSSI closer to pink noise, whereas control systems with less effective inhibitory feedback produce PSSI closer to white noise (Rădulescu and Mujica-Parodi, 2014).

For PSSI analyses, we used the full 232-point pre-processed time series, which included all conditions. For each voxel, we calculated the power spectral density as the squares of the Fourier transformation amplitudes of the linearly detrended time series. From the power spectral density we computed the scaling parameter  $\beta$  by plotting the power spectrum on a log–log scale and estimating the slope by applying a linear fit to the data in the 0.06–0.2 Hz range (Tolkunov et al., 2010). The scaling parameter  $\beta$  was then averaged for each of the limbic regions of interest (ROI; bilateral *amygdala, insula, anterior cingulate, hippocampus, superior frontal gyrus* and *inferior frontal gyrus*) defined anatomically using the Wake Forest University Pick-Atlas (Maldjian et al., 2003). In order to test the robustness of the ROI results, we also conducted unbiased voxel-wise statistics and calculated PSSI using a different frequency range, 0.01–0.1 Hz, used in the scale-free fMRI literature (He, 2011; He et al., 2010). For both analyses, we performed regressions, taking individual PSSI images as a dependent variable, and the cortisol reactivity to skydive as an independent variable in SPM. The confirmatory voxel-wise analysis was done in SPM and corrected for multiple comparisons using a cluster-extent correction method (AFNI 3dClustSim) at ROI-corrected  $p$  (alpha) < 0.05. This yielded ROI-specific minimum cluster sizes at  $p$  threshold of .05 (Monte-Carlo simulation = 10,000 iterations: minimum cluster size for the amygdala = 155.8; hippocampus = 195.6; insula = 134.2; anterior cingulate cortex = 310.2; superior frontal gyrus = 210.3; inferior frontal gyrus = 222.3).

#### Cortical thickness analysis

$T_1$ -weighted structural magnetic resonance imaging in the same 3 T scanner was collected on the control day. We performed cortical reconstruction and volumetric segmentation with the Freesurfer image analysis suite (<http://surfer.nmr.mgh.harvard.edu/>). The technical details of these procedures are described in prior publications (Dale et al., 1999; Desikan et al., 2006; Fischl and Dale, 2000; Fischl et al., 1999, 2002). Briefly, image processing includes motion correction and averaging of multiple volumetric  $T_1$  weighted images, removal of non-brain tissue using a hybrid watershed/surface deformation procedure, automated Talairach transformation, segmentation of the subcortical white matter and deep gray matter volumetric structures, intensity normalization, tessellation of the gray matter white-matter boundary, automated topology correction, and surface deformation following intensity gradients to optimally place the gray/white and gray/cerebrospinal fluid borders at the location where the greatest shift in intensity defines the transition to the other tissue. Once the cortical models were complete, a number of deformable procedures were performed for further data processing and analysis including surface inflation, registration to a spherical atlas which utilized individual cortical folding patterns to match cortical geometry across subjects, parcellation of the cerebral cortex into units based on gyral and sulcal structures, and creation of surface based data including maps of curvature and sulcal depth. This method uses both intensity and continuity information from the entire three dimensional MR volume in segmentation and deformation procedures to produce representations of cortical thickness, calculated as the closest distance from the gray/white boundary to the gray/cerebral spinal fluid (CSF) boundary at each vertex on the tessellated surface. The maps are created using spatial intensity gradients across tissue classes and are therefore not simply reliant on absolute signal intensity. The maps produced are not restricted to the voxel resolution of the original data and are thus capable of detecting submillimeter differences between groups. Procedures for the measurement of cortical thickness have been validated against histological analysis (Rosas et al., 2002) and manual measurements (Kuperberg et al., 2003; Salat et al., 2004). Freesurfer morphometric procedures have been demonstrated to show good test–retest reliability across scanner manufacturers (Han et al., 2006; Reuter et al., 2012). Following these procedures, we derived mean thickness of the inferior frontal gyrus (IFG) in each individual.

We performed a bivariate correlation analysis between the thickness and the PSSI values of the IFG, controlling for the effects of age, gender, and intracranial volume (Ge et al., 2002; Tisserand et al., 2004; Welborn et al., 2009).

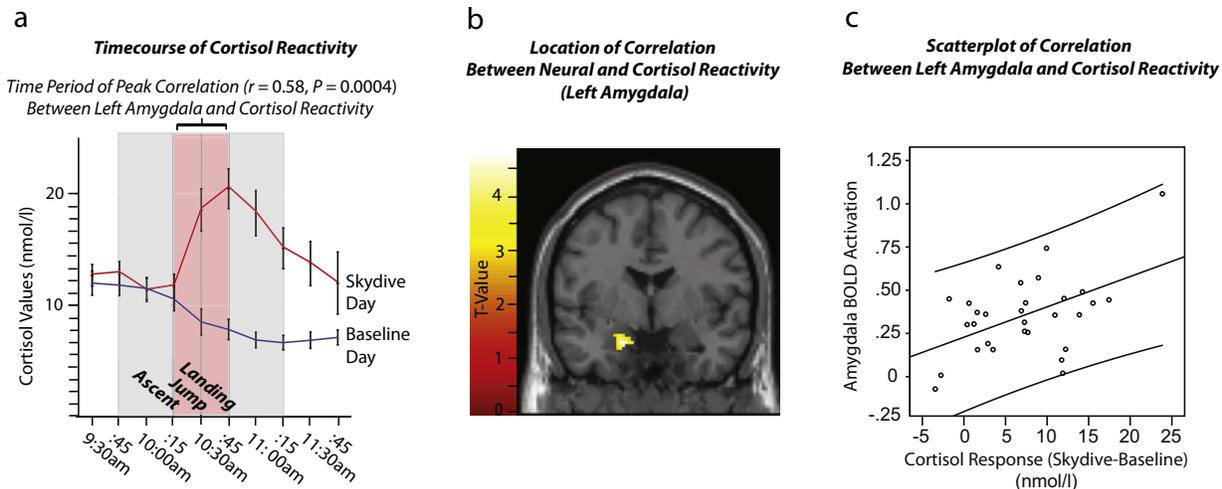
#### Challenge and endocrine sampling

The entire protocol took place over two separate highly controlled time-locked days, between 7 and 14 days apart (counter-balanced for order). On each day participants awoke at 6:30 am and ate a standardized breakfast at 8:00 am, after which they were not permitted to eat, drink (other than water), or to participate in physical exercise until the completion of cortisol acquisition. Participants provided ten 6 cm<sup>3</sup> saliva samples via the passive drool method. Saliva collection began at 9:15 am and subsequently occurred in sequential 15 minute intervals between 9:30 am and noon. Subjects boarded the plane at 10:15 am, ascended to an altitude of 4 km (13,000 ft.) over 15 min, and jumped at 10:30 am. All subjects were in free-fall for one full minute, under the canopy for 4 min, and landed at 10:35 am. Samples were frozen at –20 °F and subsequently assayed via radioimmunoassay with a Coat-A-Count Cortisol Kit (Siemens Medical Solutions Diagnostics, Los Angeles, CA). Cortisol time-courses were individually baseline-corrected for diurnal variability using cortisol values sampled following an identical (time-locked) protocol to the skydiving day, but without the skydive. Self-report values of state anxiety (Spielberger State-Trait Anxiety Scales; Mind Garden, Menlo Park, CA) and euphoria/pleasurable excitement (see Appendix A) were obtained at six time points (9:00 am, 10:25 am, 10:45 am, 11:15 am, 1:00 pm, and 3:30 pm) on both days. Plasma levels, assayed for epinephrine,  $\beta$ -endorphins, and testosterone, were collected four times: during the baseline day at 9:15 am, and during the skydive day at 9:15 am, immediately upon landing, and 1 h after landing.

#### Behavioral testing of threat perception

On the fifteen-minute plane ride leading up to the jump, subjects completed our *Ambiguous Threat Detection Task*, which we have previously shown to be responsive to stress (DeDora et al., 2011). The Ambiguous Threat Detection Task was designed to quantify the amount of signal/noise required for decision-making, dissociating perceptual and cognitive components. Three male faces, taken from the Ekman Pictures of Facial Affect, were morphed between neutral (0% angry) and angry (100% angry) poles, ranging from 20–80% angry over 10% intervals. Subjects were presented with a series of images, and instructed to indicate whether each face was ‘neutral’ or ‘aggressive’ as quickly as possible without sacrificing accuracy. Each morphed face was perceptually occluded with a filter of 15% Gaussian white noise (Photoshop CS 2 Version 9.02, Adobe Inc., San Jose, CA), ranging from a signal-to-noise ratio of 0% to a signal-to-noise ratio of 100%. Each trial started with a 1500 ms period of dynamic visual white noise. Over the course of 5250 ms (35 iterative images each, with 150 ms duration, displayed at 6.67 Hz), a grainy, pixilated image gradually was transformed into a face. The instruction to work as quickly as possible without sacrificing accuracy meant that subjects made their decisions as soon as they were the first able to detect a visually coherent image; thus, response time identified the transition point in perceptual signal/noise. To provide environmental isolation, all subjects completed the task while wearing a head-mounted display (nVisor SX60, NVIS Inc, Reston, VA) connected to a laptop computer. The task was programmed and run using E-Prime software version 1.2 (Psychology Software Tools, Inc, Sharpsburg, PA).

Canonical perceptual experiments in psychophysics (Newsome et al., 1990) have shown that one sensitive way to probe subtle features



**Fig. 1.** Anticipatory amygdala reactivity correlates with cortisol reactivity in anticipation of a first-time tandem skydive. (a) The challenge elicited marked cortisol increases ( $F(1, 28) = 28.92, p = .000001$ ). Shaded areas refer to the three time-periods compared: *early anticipation*, *late anticipation* to *early recovery*, and *late recovery*. Pink area reflects the timeframe for which anticipatory left amygdala reactivity of aversive > benign contrast predicted cortisol reactivity ( $F = 14.19, p = .001$ ). (b) fMRI activation map showing correlation was maximal at  $-18, -2, -22$  extending into the basolateral (7 voxels) and superficial (29 voxels) amygdala: ( $r = .58, p = .0004$ ). (c) Scatterplot for correlation between superficial amygdala ROI and anticipatory cortisol response ( $r = .50, p = .005$ ), with 95% confidence interval.

of decision-making is by using parameters of a sigmoidal fit:

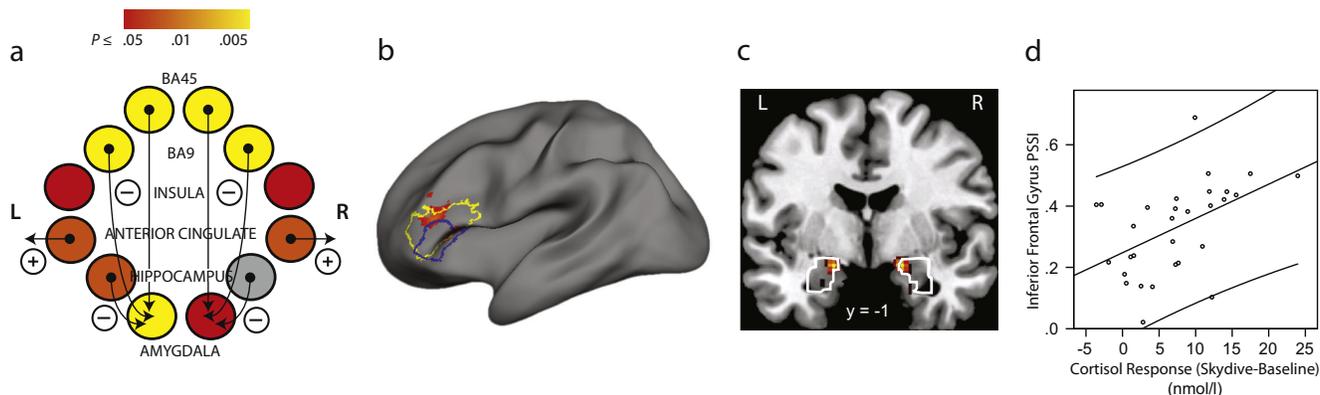
$$f(x) = \frac{1}{1 + \exp\left(\frac{x_{half} - x}{\sigma}\right)}$$

The inflection point of the psychometric curve,  $x_{half}$ , identifies the transition point at which subjects are the first able to detect threat among stimuli whose affect-valence was ambiguous, while  $\sigma$  provides the slope, or discriminability, between threatening and non-threatening stimuli. Each subject's behavioral responses to 20–80% angry faces were fit with the above sigmoid function using Igor PRO 6.32A (WaveMetrics, Inc.; Lake Oswego, OR), generating an inflection point  $x_{half}$  for each subject. Group statistics were then performed upon individual subjects'  $x_{half}$  values, to determine whether individual variability in subjects' physiological responses to jumping out of a plane were linked more generally to their thresholds for threat perception.

## Results

### Validation of challenge

Skydive and baseline days showed marked cortisol differences (Repeated-measures ANOVA:  $F(1, 28) = 28.92, p = .000001$ ). As per Fig. 1a, Bonferroni-corrected paired t-tests revealed that these started during the anticipatory period 15 min prior to the jump that, because of the 20 minute delay in salivary bioavailability (Kirschbaum and Hellhammer, 1994), was sampled at landing (skydive day: 18.57 nmol/l,  $SE = 1.13$ ; baseline day: 8.78 nmol/l,  $SE = 1.13$ ;  $t(28) = 5.9, p = .000001$ ), and peaked during the jump itself, sampled 20 min post-jump (skydive day: 21.21 nmol/l,  $SE = 1.7$ ; baseline day: 8.45 nmol/l,  $SE = .9$ ;  $t(28) = 7.9, p = .000000005$ ). Cortisol response in anticipation of the jump positively correlated with pre-jump epinephrine ( $r = .71, p = .00002$ ), self-reported anxiety ( $r = .3, p = .02$ ), and negatively correlated with self-reported euphoria ( $r = -.3, p = .05$ ). Thus, the



**Fig. 2.** Correlation of limbic power spectrum scale invariance (PSSI) with anticipatory cortisol response. (a) System-wide regulation, particularly the inferior frontal gyrus (Brodmann area 45) and the amygdala, correlated with reactivity to the skydive, showing less balanced regulation at baseline for participants who produced less anticipatory cortisol response. Arrows denote excitatory (+) and inhibitory (-) influence, with prefrontal and hippocampal areas providing predominately inhibitory outputs to the amygdala (Critchley et al., 2003; Phelps and LeDoux, 2005), and the anterior cingulate providing predominately excitatory outputs to the autonomic nervous system (Critchley et al., 2003). (b) Averaged PSSI values of the inferior frontal gyrus (yellow) and the amygdala were used in the correlation analyses. We confirmed these results with a voxel-wise method at cluster-extent ROI corrected  $p < 0.05$  (red). In the inferior frontal gyrus, the higher PSSI values were predicted by the greater mean cortical thickness (blue):  $r = .65, p = .00003$ , (c) while in the amygdala, maximally correlated voxels were located at superficial nuclei that interact primarily with the orbitofrontal cortex (the amygdala anatomical mask is outlined; an arbitrary threshold applied to the corrected result to emphasize the effect). (d) Scatterplot for the inferior frontal gyrus PSSI and the cortisol response ( $r = .54, p = .003$ ) with 95% confidence interval.

**Table 1**

Stepwise (backward) linear regression shows that biological variables predict cortisol response to skydive with greater accuracy than self-reported measures of personality.

ANOVA regression						Predictors
Model	R(square)	Sum of squares	Mean square	F	Sig.	Cortisol response to skydive
1	0.65	787.30	52.49	1.38	0.3	a, b, c, d, e, f, g, h, i, j, k, l, m, n, o
2	0.65	785.58	56.11	1.61	0.21	g, d, k, f, m, c, b, e, j, i, l, n, o
3	0.65	781.87	60.14	1.85	0.14	d, k, f, m, c, b, e, j, i, l, n, o
4	0.64	774.87	64.57	2.10	0.09	k, f, m, c, b, e, j, i, l, n, o
5	0.64	768.22	69.84	2.40	0.06	f, m, c, b, e, j, i, l, n, o
6	0.64	765.72	76.57	2.79	0.03	m, c, b, e, j, i, l, n, o
7	0.63	753.16	83.69	3.15	0.02	c, b, e, j, i, l, n, o
8	0.59	704.81	88.10	3.17	0.02	b, e, j, i, l, n, o
9	0.57	686.21	98.03	3.59	0.01	h, e, j, i, l, n, o
10	0.56	669.93	111.66	4.17	0.007	e, j, i, l, n, o
11	0.51	613.58	122.72	4.36	0.007	j, i, l, n, o
12	0.47	570.45	142.61	4.94	0.005	i, l, n, o
13	0.44	523.71	174.57	5.89	0.004	l, n, o
14	0.4	478.27	239.14	7.90	0.002	n, o

Predictor labels		
a	NEO openness	Self-report variables
b	NEO extraversion	
c	NEO neuroticism	
d	STAI trait-anxiety	
e	Perceived stress	
f	Attitudes towards risk I	
g	Attitudes towards risk II	
h	Sensation-seeking: thrill and adventure seeking	
i	Sensation-seeking: disinhibition	
j	Sensation-seeking: experience seeking	
k	Sensation-seeking: boredom susceptibility	
l	Age	Biological variables
m	Sex	
n	L amygdala reactivity (activation)	
o	L BA45 (inferior frontal gyrus) regulation (PSSI)	

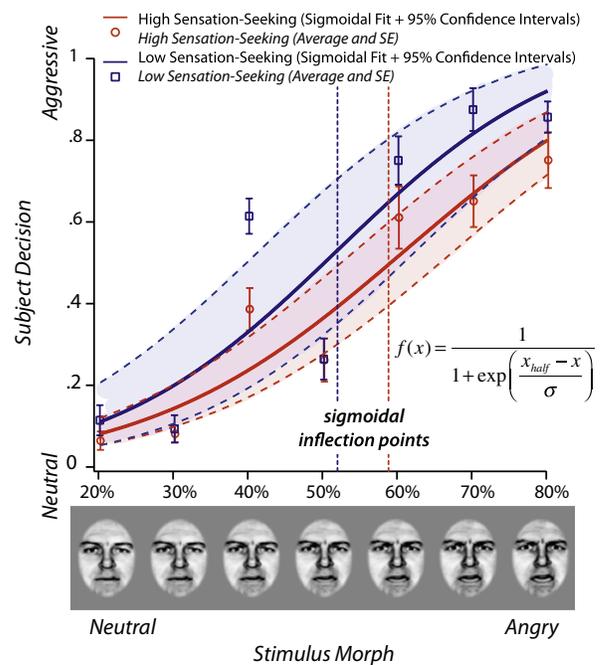
skydiving was successful at activating the hypothalamic–pituitary–adrenal axis in a manner that was both acute, as well as specific to fear.

*Prefrontal-limbic reactivity (fMRI activation)*

To reduce multiple comparisons, cortisol samples were first combined into three general timeframes: *early anticipation* (–75 min to –45 min. pre-jump), *late anticipation to early recovery* (±30 min pre/post-jump), and *late recovery* (+45 min to +75 min post-jump). This approach allowed us to identify a general time frame for the effect that could be subsequently examined over shorter intervals. Cortisol reactivity regressors for each of the three time-periods identified greater left amygdala activation for the aversive > benign anticipatory cue contrast (Fig. 1) during the period of peak cortisol response, the *late anticipation to early recovery* period ( $t(28) = 4.52, r = .65, P_{\text{peak}} = .00005, P_{\text{SVC}} = .03, k = 36, \text{peak voxel (MNI): } -18, -2, -22; \text{average: } r = .58, p = .0004$ ). Using extracted mean regressor value from this cluster, we confirmed that the amygdala activation continued to correlate with the cortisol response to the challenge (two-tailed Partial correlation:  $r = .41, p = .02$ ), even after controlling for trait anxiety, body mass index (Mujica-Parodi et al., 2009b), and removing one individual with amygdala, cortisol, and self-reported pre-jump anxiety values >2 SD above the mean. Breaking down the *late anticipation to early recovery* period by individual time-points showed that the strongest relationship occurred during the anticipatory period 30 min prior to the jump (two-tailed Pearson correlation:  $r = .56, p = .001$ ).

*Prefrontal-limbic regulation (fMRI power spectrum scale invariance)*

Based upon previous results for trait anxiety implicating dysregulation of specific components of the prefrontal-limbic circuit (Tolkunov et al., 2010), average power spectrum scale invariance (PSSI) values were extracted for the anatomically defined (Maldjian et al., 2003)



**Fig. 3.** Sensation seekers show heightened thresholds for threat detection when viewing faces morphed between neutral and angry expressions ( $F(1) = 5.23, p = .03$ ). The theoretical mid-point between neutral and angry poles (i.e., maximum ambiguity) was 50%. Statistically clustering subjects by sensation-seeking, individuals who were relatively low sensation seekers first identified the faces as aggressive just above this mid-point, at 51.95% angry ( $SE = 2.23$ ). In contrast, relatively high sensation seekers failed to perceive faces as aggressive until faces were 58.76% angry ( $SE = 1.98$ ).

bilateral amygdala, hippocampus, anterior cingulate, insula, superior frontal gyrus (Brodmann Area 9), and inferior frontal gyrus (Brodmann Area 45) regions of interest. Even after controlling for trait anxiety, system-wide limbic regulation correlated with cortisol response for the same anticipatory – 30 min. pre-jump time-period (Fig. 2). Stepwise (forward and backward) linear regression identified the left inferior frontal gyrus as most strongly contributing to the variance ( $r = .54, p = .003; F(1,28) = 8.95, p = .006$ ). These results were confirmed with follow-up voxel-wise statistical analyses. PSSI values of the amygdala (left hemisphere,  $t(28) = 2.92, p_{\text{peak}} = 0.003$ ; right hemisphere,  $t(28) = 2.87, p_{\text{peak}} = 0.004$ ) and the left inferior frontal gyrus ( $t(28) = 3.15, p_{\text{peak}} = 0.002$ ) showed significant positive correlation with cortisol reactivity at a cluster extent-corrected ROI-corrected  $p < 0.05$ .

*Prefrontal regulation and cortical thickness*

We then investigated whether our prefrontal-limbic regulation (PSSI) values correlated with gray matter volumetric variability across individuals. Individuals with closer-to-optimal regulation in the inferior frontal gyrus had greater cortical thickness for that same region, lateralized to the left side (two-tailed Pearson correlation:  $r = .65,$

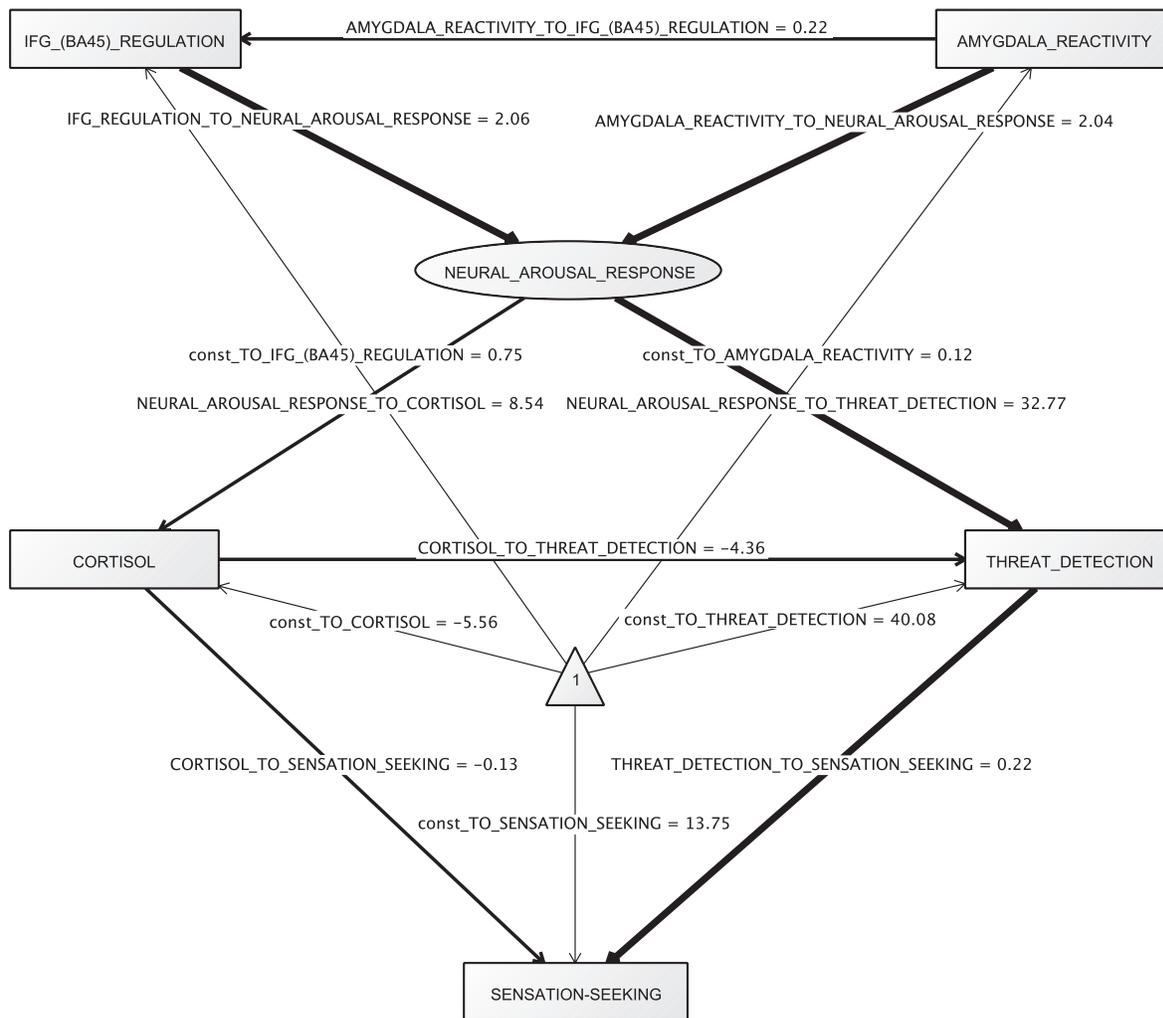
$p = .00003$ ; Fig. 2b). The association was not attributable to age (two-tailed Pearson partial correlation:  $r = .003, p = .99$ ).

*Prediction of cortisol response*

Amygdala reactivity and prefrontal regulation each explained approximately one quarter of the variance in participants' cortisol reactivity to the skydive. A multiple regression that included both of these accounted for 40% of the variance in their responses to the skydive ( $r = .63, SE = 5.5; F(2,27) = 7.9, p = .002$ ). A multiple regression that included both of these ( $\beta_{\text{amygdala}} = .37, \beta_{\text{IFG}} = .3$ ), in addition to age ( $\beta_{\text{age}} = .22$ ), accounted for 44% of the variance in their responses ( $r = .66, F = 5.9, p = .004$ ). As shown by Table 1, stepwise (backward) linear regression compared 14 models, which yielded an adjusted  $p = .004$ . Thus, models with biological measures (amygdala reactivity, prefrontal regulation, and age) provided greater reliability than models with self-report measures (including sensation-seeking) in predicting a subject's subjective and cortisol responses to the first-time skydive.

*Sensation-seeking and threat perception*

To simplify interpretation, we performed a k-mean cluster analysis ( $k = 2$ ) on the sensation-seeking scores to separate the skydivers into



**Fig. 4.** Structural equation modeling suggest sensation-seeking is primarily mediated via threat perception, which itself is primarily mediated via amygdala reactivity and prefrontal regulation. Fit parameters (SRMR = 0.0552, CFI = 0.9255) confirmed that the model provided a good fit to the data using established cutoffs of SRMR ≤ 0.08, CFI ≥ 0.90. Rectangles represent manifest variables, circles represent latent variables, and triangles represent normalization constants.

(relatively) higher sensation-seeking (rHSS;  $\mu = 27.71 \pm 2.26$ ,  $N = 17$ ) and (relatively) lower sensation-seeking (rLSS;  $\mu = 20.87 \pm 2.75$ ,  $N = 15$ ) groups, which were subsequently compared. Even among a group of risk-takers, rHSS showed less anticipatory anxiety in the minutes prior to the jump, as demonstrated by blunted baseline-corrected cortisol response (rHSS:  $\mu = 3.33$ ,  $SE = .73$ ; rLSS:  $\mu = 13.23$ ,  $SE = .83$ ;  $F(1) = 5.02$ ,  $p = .04$ ) and less self-reported state anxiety (rHSS:  $F(1) = 3.70$ ,  $p = .08$ ).

Our hypothesis that this diminished response to threat—a signature of HSS (De Pascalis et al., 2007; Joseph et al., 2009; Kruschwitz et al., 2012)—would be associated with a heightened threshold for threat perception, was supported by behavioral results on the Ambiguous Threat Detection Task, taken during the same 15 minute window preceding the skydive. As shown in Fig. 3, we found significant differences between groups for the inflection point—that is, the point at which individuals transitioned, from perceiving stimuli as neutral, to perceiving stimuli as aggressive ( $F(1) = 5.23$ ,  $p = .03$ ). For our morphed images, the theoretical mid-point between neutral and angry poles (i.e., maximum ambiguity) was 50%. Individuals who were rLSS first identified the faces as aggressive just above this mid-point, at 51.95% ( $SE = 2.23$ ). In contrast, rHSS failed to perceive faces as threatening until they were 58.76% ( $SE = 1.98$ ) aggressive. Importantly, this difference in judgment on the part of rHSS was not due to impulsivity, or making decisions with less information than rLSS. In fact, rHSS took slightly longer to make a decision, and therefore (because images gradually emerged out of the white noise) were making their judgments about an image that was less perceptually distorted (rHSS:  $\mu = 1622$  ms,  $SE = 29$  ms; rLSS:  $\mu = 1524$  ms,  $SE = 34$  ms;  $F(1) = 4.9$ ,  $p = .04$ ). Moreover, just as there were no differences in baseline cortisol between the two groups ( $F(10,18) = .64$ ,  $p = .76$ ), the behavioral differences between these two groups of risk-takers were apparent only during challenge. At baseline, the groups responded equivalently in detecting threat ( $\mu = 53.56\%$ ,  $SE = 1.15\%$ ;  $F(1) = .02$ ,  $p = .883$ ), an effect that was unrelated to previous exposure to the stimuli with respect to order between the skydive and baseline days (skydive  $\rightarrow$  baseline:  $F(1) = .06$ ,  $p = .81$ ; baseline  $\rightarrow$  skydive: ( $F(1) = 1.47$ ,  $p = .24$ ).

### Structural equation modeling

To provide a more integrated conceptual organization of how the neural (based upon stepwise linear regression), cortisol/fear, and cognitive measures fit together with the sensation-seeking trait, we conducted structural equation modeling of the dominant results, using *Omega/OpenMx* (Boker et al., 2011). Modeling used five manifest variables: amygdala reactivity (*aversive > benign activation*), IFG/Brodman Area 45 regulation (PSSI), cortisol response (*baseline-corrected late-anticipation to early recovery-period*), threat-detection (*inflection-point*), and sensation-seeking, which we normalized for mutual comparison. We created one latent variable, *neural arousal response*, which comprised both reactivity and regulation. Cognitive inputs were defined both by baseline brain features, as well as by stress-induced cortisol response, which can acutely affect the brain and thus cognition (Butts et al., 2011; Lupien and McEwen, 1997; Mujica-Parodi et al., 2009b). Endocrine and cognitive components were designated as inputs to the psychological construct, “sensation seeking,” to assess their relative importance in defining self-reported personality.

Fit parameters (Standardized Root Mean Square Residual, SRMR = 0.0552, Comparative Fit Index, CFI = 0.9255) confirmed that the model provided a good fit to the data using established cutoffs of  $SRMR \leq 0.08$ ,  $CFI \geq 0.90$  (Hu and Bentler, 1999). As per Fig. 4, variance in sensation-seeking was accounted for more by an increased threshold for threat-detection (.22) than by blunted cortisol (.13). Variance in threat-detection was accounted for more by the neural arousal response (32.77) than by cortisol (4.36). Finally, the neural arousal response was affected roughly equally by amygdala reactivity (2.04) and prefrontal regulation (2.06). Taken together, our model suggests that a brain-

based cognitive deficit in perception of threat leads to a trait tendency towards sensation-seeking—a differential pattern seen even within a sample of risk-takers.

### Discussion

Animal studies show that the tendency to seek novelty at the expense of caution is primarily biological in nature, strongly heritable, and a function of dopaminergic pathways in the limbic and reward circuits (Ballaz et al., 2008, 2013; Stead et al., 2006). Indeed, our linear regression demonstrated that neurobiological measures were more reliable than psychological self-report in predicting the fear response.

These neurobiological measures suggest that individuals less responsive to the very real risks inherent in jumping out of a plane were not ‘super-regulators,’ but rather showed dysregulation of the prefrontal-limbic meso-circuit symmetric to that seen in highly trait anxious individuals. To compare our prefrontal-limbic regulation results across a wider spectrum of fear reactivity, we normalized<sup>1</sup> across a larger sample of  $N = 96$  participants scanned with fMRI (Rădulescu and Mujica-Parodi, 2014). These included a separate sample of  $N = 65$  (Mujica-Parodi et al., 2009a), for which we assessed trait anxiety via the State-Trait Anxiety Inventory (STAI min/max = 21–67;  $M = 38 \pm 10$ ), this article’s sample of  $N = 30$  first-time tandem skydivers (STAI min/max = 20–53;  $M = 33.07 \pm 7.11$ ), as well as a single case study of a bomb squad technician working in support of Navy SEAL missions. Individuals at the middle of the spectrum—those who showed low trait anxiety and a robust fear/cortisol response to their skydives—were in the pink noise (optimally balanced) range for both excitatory and inhibitory components of the prefrontal-limbic system. In contrast, individuals at the extreme ends of the fear-reactive spectrum (either exceptionally trait anxious, or else exceptionally non-responsive to the skydive) had prefrontal-limbic PSSI shifted towards white noise. This may indicate that the same prefrontal-limbic circuit is dysregulated in different ways that produce deficits in risk assessment with distinct clinical features.<sup>2</sup> Or, it may mean that the inferior frontal gyrus is not simply inhibitory, but also plays a more complex, if equally critical, role in threat-assessment (e.g., acting as a comparator or filter). Future work, using control systems approaches to probe the dynamics of the circuit in greater detail, will explicitly address this question.

<sup>1</sup> Interpretation of PSSI across studies is complicated by the fact that this type of analysis has developed in parallel within the physics and physiology literatures, but with slightly different methods and notations that profoundly impact meaning of the results. Within the physics literature, PSSI is typically calculated from the raw time-series, whereas in the physiology literature, PSSI is typically calculated from the first-derivative of the raw time-series. The derivative shifts  $\beta$  by a constant, such that  $\beta_{derivative} = \beta_{raw} + 2$ . Moreover, PSSI is sometimes defined as  $S(f) \propto f^{-\beta}$  (for which  $\beta$  for white, pink, and brown noise are defined as 0, +1, +2 respectively) and sometimes defined as  $S(f) \propto f^{\beta}$  (for which  $\beta$  for white, pink, and brown noise are defined as 0, -1, -2 respectively). Unfortunately, these discrepancies can mean that smaller  $\beta$  can refer to greater complexity following one set of conventions, and lesser complexity following another. Thus, for this comparison, we recalculated PSSI identically across both more (LSS) and less (HSS) reactive populations, using definitions provided in the above Methods section.

<sup>2</sup> Our PSSI analyses suggest that dysregulation of the prefrontal-limbic system is present both in populations for which threat perception thresholds are abnormally high (high sensation-seekers) as well as abnormally low (high trait anxiety). This (seemingly counter-intuitive) symmetry is common for dysregulatory disorders in physiology. For example, both Type 1 and Type 2 diabetes are caused by dysregulation of the same (excitatory) glucose-(inhibitory) insulin control circuit. However, in Type 1 diabetes, the pancreas produces insufficient insulin (causing a *feedforward* dysregulation); whereas, in Type 2 diabetes, insulin fails to trigger a subsequent decrease in glucose (causing a *feedback* dysregulation). Thus, the two metabolic disorders are caused by *different types of dysregulation of the same circuit*. As with the symmetry we see at the extreme ends of our threat response spectrum, Type 1 and 2 diabetics show both clinical similarities (since glucose levels are elevated in both, symptoms associated with hyperglycemia are present in both), as well as clinical presentations that can appear to be opposites of one another (e.g., because insulin is linked to fat production, Type 1 diabetics show abnormally low body fat, whereas Type 2 diabetics show abnormally high body fat). Future work will be needed to probe the prefrontal-limbic circuit with system identification techniques (coupled differential equations that describe the entire circuit), in order to establish the self-interacting dynamics by which the system evaluates threat.

Both ends of the fear-reactive spectrum had PSSI differences that specifically implicated the amygdala and inferior frontal gyrus (Brodmann area 45). The amygdala is the primary excitatory component of the control system regulating emotional arousal. Within it, the most significant association between the PSSI values and cortisol responses was observed in bilateral superficial nuclei that are anatomically and functionally linked with the orbitofrontal cortex (Bach et al., 2011; Zald et al., 2014). We found that individuals who showed less amygdala reactivity in response to threat also showed a blunted cortisol response to the jump. This result was robust, replicating across not only our primary study ( $N = 30$ ), but also our pilot study ( $N = 22$ ), using different tasks (passive viewing of fearful faces, anticipation of aversive noise) designed to activate the same prefrontal-limbic system. This amygdala activation appears to reflect efficiency of interaction with the prefrontal cortex network, most likely via direct synaptic connections with the orbitofrontal cortex. The inferior frontal gyrus, on the other hand, is a prefrontal region implicated in affect processing (Yamasaki et al., 2002), suppression of emotion (Depue et al., 2007; Vanderhasselt et al., 2013), and response inhibition (Aron et al., 2003; Sagaspe et al., 2011), mediated by its extensive connection with other prefrontal cortical regions (Croxson et al., 2005). The present results, showing a positive association between chaotic PSSI of the prefrontal cortex and cortical thinning, suggest that less-effective control may be linked to cortical structure, as per models of this control circuit linking complexity and connectivity (Rădulescu and Mujica-Parodi, 2014).

Psychological constructs, by definition, aim to generalize over complex phenomena. While the individual variability we observed in response to challenge shares some similarities to commonly held features of 'sensation-seeking,' there were also areas of divergence. First, contrary to the Optimal Level of Arousal hypothesis that HSS are behaviorally self-medicating to compensate for lower basal levels of arousal ((Zuckerman, 1994), but see also (Carrol et al., 1982)), the relationships seen between sensation-seeking, prefrontal-limbic, cortisol, threat-detection, and state anxiety variables were evident specifically in response to physical danger, but not at baseline. Second, the more reckless aspects of HSS have often been conceptually linked to impulsivity (Zuckerman, 1993, 1996), which would be consistent with our observed cortical thinning and impaired prefrontal regulation. However, our behavioral results showed that rHSS's failure to perceive threat was not due to impulsive decision-making, since those who had the highest threshold for threat-detection also waited for the most information. Finally, HSS is thought of as not only including diminished sensitivity to threat, but also increased capacity for reward (Zuckerman, 1994). However, our results showed that individuals with greater sensation-seeking had suppressed anxiety and cortisol in response to the jump, rather than showing heightened euphoria or blood  $\beta$ -endorphin levels ( $p > .1$ ).

The ability to accurately evaluate risk (i.e., 'good judgment') has been associated in non-human primates with social dominance, showing an endocrine signature of lower basal cortisol levels as well as greater testosterone response to challenge (Virgin and Sapolsky, 1997). While basal cortisol levels were equivalent across subjects, males who showed prefrontal regulation closest to the critical point also showed the largest plasma testosterone increases in response to the jump (Repeated-Measures ANOVA:  $F = 6.001$ ,  $p < 0.03$ ,  $N = 19$ ). Thus, one area for future investigation is whether optimal prefrontal regulation may be an important neural feature of social dominance.

Novelty-seeking can lead to addiction, participation in dangerous recreational activities, and sociopathy, but the willingness to take risks may also lead to outstanding acts of human achievement and altruism for the greater good. From a clinical perspective, therefore, it matters not only whether an individual avoids or embraces risk, but also whether the response to risk is adaptive or maladaptive. In this context, we define 'adaptive' response to risk as one that permits taking appropriate safeguards: that is, which includes both an accurate recognition of risk, as well as the ability to avoid being paralyzed by fear. From

this perspective, our experiment was unique. Previous studies have compared populations that are predominantly approach-oriented (HSS) to populations that are predominantly avoidance-oriented (LSS). In contrast, each of the subjects recruited to this study had already independently contacted a local skydiving school to schedule his or her first tandem-skydive. Skydiving is a high-risk recreational sport, with a non-trivial risk of fatality. This fact was reinforced frequently during the brief training that preceded the jumps, as well as by the legal waiver that all participants signed, which released the skydiving school from responsibility in the event of the participant's death (the waiver listed an impressive variety of means by which death might occur, including plane engine failure, parachute failure, tandem-master error, and failure by the participant to follow instructions). The fact that—in spite of these warnings—they all chose to follow through with the jump, indicates that our study was of a population that would all be considered approach-oriented. What distinguished them, therefore, was not their willingness to take risks, but rather how they responded to the experience: whether or not they recognized the risks, and appropriately felt afraid.

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### Disclosures

The authors declare no financial conflicts of interest.

### Appendix A. Supplementary data

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.neuroimage.2014.08.038>.

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